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A genomic approach to interneuron diversity and the emergence of an epileptic brain.

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Table of contents

Notes

This thesis has been co-supervised by the International School for Advanced Studies in Trieste, Italy and the University Marie Curie in Paris, France. The work described in this dissertation was carried out in Trieste, Italy, between October 2004 and October 2007, under the direction of Prof. Enrico Cherubini and Prof. Stefano Gustincich and in the "Cortex et Epilepsie" lab in Paris, France, between November 2007 and August 2008 under the direction of Prof. Richard Miles. All work reported here, with the exception of the electrophysiological experiments (carried out by Caroline Le Duigou), and the morphological studies on epileptic network (carried out by Nicole Chemaly and Lucia Wittner), arises from my own experiments. All statistical analysis of the gene expression experiments on somastostatin-containing interneurons was performed by Remo Sanges, who also performed the normalization of GeneChip data in the epileptic network study. The work will be included in the following works in preparation:

Motti D, Le Duigou C, Eugene E, Chemaly N, Wittner L, Lazarevic D, Krmac H, Sanges R, Stupka E, Cherubini E, Gustincich S, Miles R. Gene expression changes associated with the emergence of an epileptiform activity after focal injection of kainic acid into the mouse hippocampus. *In preparation*

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The following study (under submission) arises from a collaborative project not included in the present thesis:

Valen E, Pascarella G, Chalk A, Maeda N, Sano H, Kojima M, Kawazu C, Murata M, Nishiyori H, Marstrand TT, Tang MHE, Krogh A, Winther O, Lazarevic D, **Motti D**, Arakawa T, Kawai J, Wells G, Daub G, Harbers M, Hayashizaki M, Gustincich S, Sandelin A, Carninci P. Genome-wide detection and analysis of hippocampus core promoters using DeepCAGE. (Under submission)

Abbreviations

GABA: gamma-aminobutyric acid

GABARs: GABA receptors

EPSPs: Excitatory Postsynaptic Potentials

IPSPs: Inhibitory Postsynaptic Potentials

mRNA: messenger ribonucleic acid

PCR: polymerase chain reaction

CNS: central nervous system

NSC: Neural Stem Cells

SOM: Somatostatin

GAD: Glutamate Decarboxylase

GIN: GFP-expressing Inhibitory Neurons

RT-PCR: Reverse Transcription – Polymerase Chain Reaction

MTLE: Mesial Temporal Lobe Epilepsy

EEG: Electroencephalogram

HS: Hippocampal Sclerosis

IPI: Initial Precipitating Event

KA: Kainic Acid

WT: Wild Type

Abstract

The hippocampus is an archicortical region involved in functions including memorisation and spatial navigation. These operations depend on complex synaptic interactions involving both excitatory and inhibitory signaling between hippocampal neurones. Changes in the balance of excitatory and inhibitory systems may result in pathological conditions such as epilepsy. Understanding the properties of hippocampal cells and networks at multiple levels and in both physiological and pathological conditions is thus an important task for research on the healthy and diseased brain.

Genomic tools provide access to an essential level of organisation, that of gene expression and regulation in hippocampal cells. They may serve as a marker to study how a cell population responds to a physiological stimulus or identify genes specific to a defined cell type. Genetic approaches are also used to examine how gene expression is changed during pathological conditions and may help identify novel processes or molecules thus providing new pharmacological targets.

In the first part of my thesis, microarray analysis of gene expression was used to compare patterns of gene expression in a subfamily of Somatostatin containing hippocampal interneurons and principal glutamatergic excitatory cells. GABAergic interneurons constitute a heterogeneous group while pyramidal cells are probably a rather homogeneous population. Interneurone diversity is important for the function hippocampal networks, and this genomic analysis will help understand this diversity.

I found significant differences in genes expressed in interneurones and pyramidal cell populations. Protein products of differentially expressed genes are mainly involved in transport and signalling, together with some proteins coding for neurotransmitter receptors and channels and a cluster of transcription factors. Although these data need to be confirmed with RT PCR and immunocytochemical experiments, further work is necessary to identify genes involved in the development of the distinct phenotypes, in the control of different physiological properties or for use as cell type markers.

The second part of my thesis examined changes in gene expression during the establishment of an epileptic network after intra-hippocampal injection of kainic acid. Many genes were changed with different time courses and spatial localisation with respect to the injection site. The altered genes are often involved in immune and inflammation responses but also in cell death and growth processes. Some genes coding for proteins that control cellular excitability and

neuronal communication were also changed. The major implication of inflammatory and immune processes is consistent with previous work on animal models of epilepsy or human epileptic tissue. I confirmed changes in some individual genes with qPCR analysis.

My work suggests that kainate injection changes the expression of early response genes near the lesion at 6hrs, but also induces distinct alterations at distant sites in contralateral hippocampus. A maximum number of changed genes was identified during the latent phase at 15 days after kainate injection but before the emergence of spontaneous seizures. At 6 months, recurrent spontaneous seizures have emerged and changes in gene expression are limited to the area near the lesion.

The progression of epilepsy in this animal model was confirmed with EEG and slice records and anatomical work was done to characterize the time course of cell death and fibre degeneration. Alterations in gene regulation correspond quite well to these electrical and anatomical data. Furthermore immuno-histochemical stains for specific proteins produced by differentially regulated genes revealed their expression by proliferating astrocyte precursors and by activated astroglial cells that were differentially localized in the two hippocampi.

In conclusion multiple different processes are triggered with different spatial patterns and timing during the emergence of an epileptic network. However, during the expression of recurrent seizures, few genes are changed except at sites surrounding the sclerotic lesion.

Introduction

1. The Hippocampus

1.1 Structural Organization

The hippocampus is one of best characterized brain structures, since its layered organization (Andersen, Bliss et al. 1971) is especially suitable for anatomical and physiological studies. In his book "*De Humano Foetu liber*" (Rome, 1564) Giulio Cesare Aranzi (1529-1589) named this brain structure "hippocampus" after the sea horse monster of Greek mythology (in Greek *hippo* means "horse" and *kampos* means "sea monster") due to a distinctive, curved shape that he likened to the famous mythological beast. The resemblence of the hippocampus to the horns of a ram, prompted another name - "cornu arietis" later changed by René Croissant de Garengeot (1688-1759) to "cornu ammonis" because of the ancient Egyptian god of Theba Amun who was presented as a ram headed man, or a ram headed sphinx. The shape of the hippocampus is maintained across the range of mammalian species, from hedgehog to human.
Ramon y Cajal (1852-1934) made major advances in understanding the microscopic structure of the nervous system, using a modification of the Golgi (1843-1926) staining method, which completely stains a small proportion of cells. His discoveries on the cellular architecture of the hippocampal formation and its regional subdivisions remain a keystone of present day knowledge of the hippocampus as part of the archicortex.
The hippocampus plays a major role in some forms of learning and memory (Kandel 2001). Deep structures of the temporal lobe, including the hippocampus (Amaral and Witter 1989), are involved in the storage of long-term traces in humans and other mammalian species (Milner, Squire et al. 1998; Eichenbaum, Dudchenko et al. 1999; Kim and Baxter 2001; Burgess, Maguire et al. 2002). The rodent hippocampus is involved in spatial navigation and some hippocampal cells called "place cells" respond specifically with a high rate of firing when the animal moves through a specific location in an environment (O'Keefe 1983).
The hippocampus also has a high seizure susceptibility (Green 1964). Many human epilepsies originate in the temporal lobe and these seizures are often the most difficult to control with

anti-epileptic drugs. The hippocampus is especially vulnerable to ischemic and anoxic insults and parts of the hippocampal formation, particularly the enthorinal cortex, are prime targets for the pathology associated with Alzheimer's disease.

Anatomically, the hippocampus is an elongated structure located on the medial wall of the lateral ventricle, whose longitudinal axis forms a semicircle around the thalamus. Figure 1 shows the location of the hippocampal formation in the rat brain. With a layered organisation, cutting the hippocampus across its transverse, septo-temporal axis, results in a familiar structure well preserved in all slices with this orientation. The hippocampus proper and its neighbouring regions, the dentate gyrus (DG), subiculum and enthorinal cortex, are collectively termed the "hippocampal formation". Cajal divided it into four regions or "cornu ammonis" areas CA1-CA4 based on the size and appeareance of neurons. CA1 and CA3 are the largest zones, CA4, or the hilus, corresponds to the initial part of CA3 and in rodents the CA2 region is small. While CA1 represent a small-celled distal region, CA3 and CA2 fields are equivalent to a larger-celled region closer to dentate gyrus. Evenmore CA1 and CA3 present a clear connectional difference that will be discussed in the next section. The CA2 field was originally defined as a zone of large cells like CA3 but that did not receive innervation like the CA1. In CA3 area Lorente de Nó (1934) identified 3 subareas by anatomical position: CA3a (the bend of the CA3), CA3b (the ventral portion between the bend and the lateral end of the DG) and CA3c (the portion incapsulated by the blades of the DG). Pyramidal cell somata are arranged in a layer, the *stratum pyramidale,* in all these regions. Other identified layers include *stratum oriens,* the site of pyramidal neuron basilar dendrites, *stratum radiatum*, and *stratum lacunosum-moleculare* where the apical dendrites of pyramidal cells are radially oriented. The principal cells of the dentate gyrus, granule cells, possess only apical dendrites.

2. The Hippocampal circuitry

2.1 Fibres inputs, outputs and internal connexions

The main input to the hippocampus is the perforant path. It originates in the enthorinal cortex, mainly in layers II and III, but also in layers IV and V. It passes through the subicular complex and terminates mainly in the dentate gyrus, making synapses on granule cells.

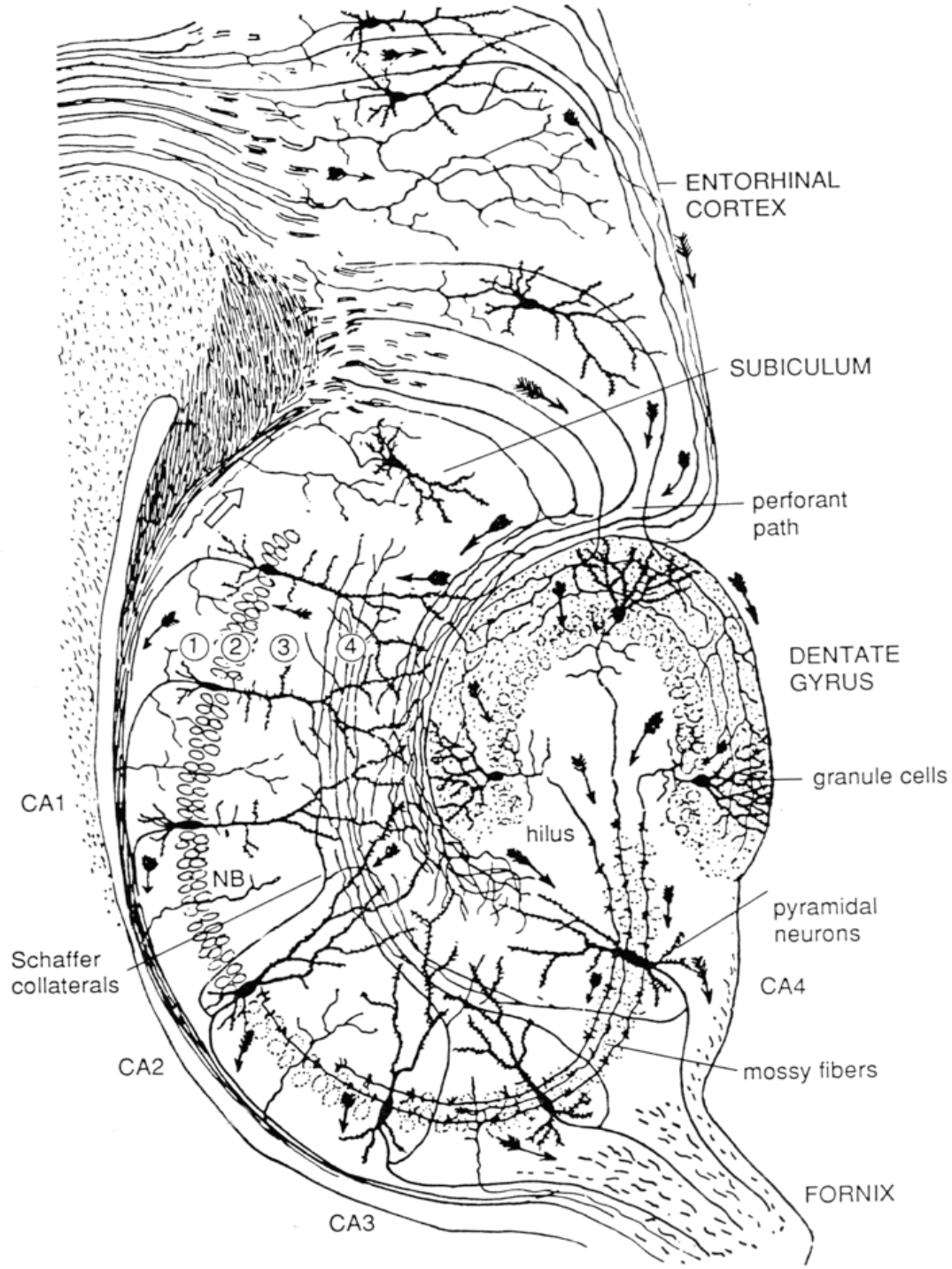

Fig. 1. NEURONAL ELEMENTS OF THE HIPPOCAMPAL FORMATION. Labelled areas include the subiculum, part of the enthorinal cortex, the fornix, the dentate gyrus and the region CA1 to CA4. The hippocampus *proper* is divided into *stratum oriens* (1), *stratum pyramidal*e (2; cell bodies drawn as ovals), *stratum radiatum* (3) and *stratum lacunosummoleculare* (4). (Modified from Ramón y Cajal, 1911)

The distinctive unmyelinated axons of the granule cells, the mossy fibres (MF), give rise to large *en passant* swellings and terminal expansions on CA3 principal neurons or mossy cells seen as giant boutons at the electron microscopic level. These presynaptic swellings adapt very well to specialized postsynaptic elements present on proximal dendrites of CA3 principal cells, called *thorny excrescences*. The MF synaptic complex contains multiple active zones (up to 50) associated with postsynaptic densities. In addition MF make synaptic contacts with GABAergic interneurons present in the *hilus* and in the CA3 area and these represent the majority of all MF connections. These have either the shape of small boutons or filopodial extensions. Differences in morphology between MF terminals at principal cells and interneurons may account for the distinct functional properties of these synapses which appear to be regulated in a target specific way. The axons of CA3 pyramidal cells ramify locally and also form Schaffer collaterals which contact CA1 pyramidal neurones. CA1 pyramidal cells project to the subiculum and the deep layers of enthorinal cortex. .

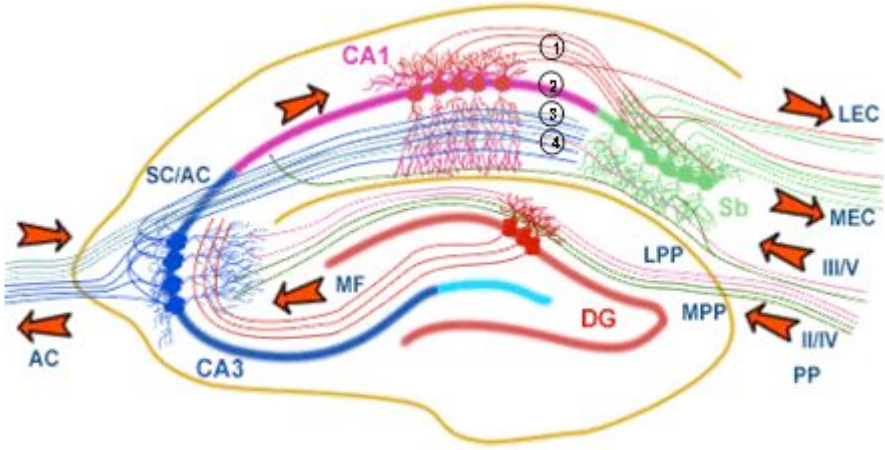

Fig. 2. THE HIPPOCAMPAL NETWORK. Hippocampus forms a uni-directional network with inputs from the Entorhinal Cortex (EC) that forms connection with the Dentate Gyrus (DG) and CA3 pyramidal neurons via the perforant path (PP-split into lateral and medial, LPP and MPP respectively). CA3 neurons receive also input from the DG via the Mossy Fibres (MF). They send axons to the CA1 pyramidal cells via the Schaffer Collateral Pathway (SC) as well as to CA1 cells in the controlateral hippocampus via the Associational Commissural Pathway (AC). CA1 neurons also receive inputs directly from the PP and send axons to the Subiculum (Sb). These neurons in turn send the main hippocampal output back to the EC forming a loop.

Thus, neuronal signals entering the entorhinal cortex from a specific cortical area can traverse the complete tri-synaptic hippocampal circuit before returning to the cortical area from which they originated.

Commissural associative fibres connect mainly CA3 pyramidal neurons of ipsi- and contralateral hippocampi, *via* the fornix. CA3 pyramidal cells also make synapses with their neighbouring

cells via axon collaterals. The simultaneous activation of these connections may be involved in generating epileptiform activity, characterised by synchronised and rhythmic firing in the CA3 cell population (Miles and Wong 1986; Traub and Miles 1991). These connections may contribute to the initiation of seizures in this region when convulsive drugs are applied (Ben-Ari and Cossart 2000). Physiologically, the recurrent associative network in the CA3 region may contribute to the associative memory recall (Nakazawa, Quirk et al. 2002)

2.2 Synaptic Transmission

Most synaptic contacts between neurons are made between synaptic *boutons*, either at an axon terminal or along (*en passant*) axons of a presynaptic neuron, and finger-like processes, or spines, of postsynaptic dendrites (axo-dendritic synapses). Synaptic contacts may occur also between axon terminals and soma (axo-somatic), between two axons (axo-axonic) and between dendrites (dendro-dendritic synapses).

Chemical synapses operate via the release of neurotransmitters from presynaptic nerve terminals. Once released, neurotransmitters diffuse in the synaptic cleft and bind to selective membrane proteins (receptors) present on the postsynaptic membrane in close opposition to presynaptic release sites. The bind of the transmitter to the receptors induces the opening of ion channels and electrical changes in the postsynaptic cells. The resulting depolarizing or hyperpolarizing voltage changes (the excitatory postsynaptic potentials or EPSPs and the inhibitory postsynaptic potentials or IPSPs) move the membrane potential towards or away from action potential threshold, respectively. IPSPs usually reduce cell excitability. The reduction in excitability may result from (either or both) a shift in membrane potential towards negative values or by a reduction in membrane resistance (also known as a shunting effect). An inhibitory current can be elicited by the inflow of negative charged ions or by the outflow of positive charges through ligand or voltage-activated channels. In the adult brain, GABA is the main inhibitory neurotransmitter (Sivilotti and Nistri 1991; Kaila 1994) and glutamate (Glu) is the major excitatory transmitter (Storm-Mathisen 1977; Roberts and Sharif 1981). Ionotropic receptors for Glu were first classified, on the basis of their most effective agonists, as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate or N-methyl-D-aspartate (NMDA). These receptors not only bind neurotransmitter but also open a membrane channel permeable to Na^+, K^+ and sometimes Ca^{++} (Ascher and Nowak 1986). Calcium in turn can activate different signaling pathways. GABA activates ionotropic receptors permeable to Cl^-

and to a lessser degree to HCO_3^- (Bormann, Hamill et al. 1987; Schofield, Darlison et al. 1987; Polenzani, Woodward et al. 1991).

The second major class of post-synaptic receptor has been termed metabotropic because they do not form ion channels but are indirectly linked to ion channels through GTP-binding proteins (G-proteins). The nature of the ion channels and of the G-protein interaction determines the functional effects of metabotropic transmission. Eight distinct metabotropic receptors which operate via several distinct intracellular signalling cascades have been identified for glutamate: mGluR1-8 (Schoepp and Conn 1993; Pin and Duvoisin 1995). Their activation tends to induce a post-synaptic excitation often by the suppression of specific K-channels. Activation of mGluRs expressed on axon terminals enhances transmitter release. G-coupled receptors for GABA, known as $GABA_B$ receptors (Hill and Bowery 1981; Wilkin, Hudson et al. 1981; Kaupmann, Huggel et al. 1997), inhibit neurones via inward rectifying K^+ conductances (Gage 1992; Mott and Lewis 1994; Misgeld, Bijak et al. 1995) or by suppressing voltage-sensitive Ca^{2+} conductances (Kamatchi and Ticku 1990) and they may reduce transmitter release when expressed at pre-synaptic sites.

3. Cellular components of the Hippocampus

3.1 Major neuronal types in the hippocampus

Pyramidal cells, which account for about 90% of hippocampal neurons, are a rather uniform cell population with homogenous morphology. They are named for their somatic shape and possess apical and basal dendrites. Pyramidal cells are excitatory and liberate the neurotransmitter glutamate (Storm-Mathisen 1977; Roberts, J. et al. 1981).

In contrast, inhibitory interneurons, which form about 10% of hippocampal neurons constitute a heterogeneous population of cells (Freund and Buzsaki 1996) and liberate the transmitter γ-aminobutyric acid (GABA). They play a critical role in controlling communication between pyramidal neurones and the balance between excitation and inhibition, a critical factor in hippocampal function. Interneurons are distributed across all layers of the hippocampus and have a highly variable morphology. They differ from pyramidal cells in their active and passive membrane properties. For instance, pyramidal cells accommodate (during a steady current

pulse the firing is not maintained but decline with time) while interneurons usually do not accommodate and can fire at frequencies up to 400 Hz with little reduction in frequency (Lacaille 1991). This may be due to major differences in transcript expressions for distinct subunits of voltage-gated K^+ channels. Kv3.1 and Kv 3.2 would be preferentially expressed in basket cell interneurons while Kv4.2 and Kv4.3 in pyramidal cells (Martina, Schultz et al. 1998). The resting membrane potential of pyramidal cells and interneurons also differs being in interneurons 10-15 mV more depolarized. Moreover, in comparison with principal cells, interneurons exhibit a higher input resistance (Morin, Beaulieu et al. 1996; Cauli, Audinat et al. 1997; Savic, Pedarzani et al. 2001). These differences seem to depend on the differential expression of pH-sensitive leak potassium channel TASK, a subtype of KCNK channel that regulates resting membrane potential and input resistance. TASK channel subunits 1 and 3 seem to be more highly expressed in pyramidal cells than in interneurons (Taverna, Tkatch et al. 2005).

Pyramidal cells and interneurones also differ in peptide composition, neurotransmitter receptor subunit expression and neurotransmitter release mechanisms (Buzsaki 2001). Further studies and novel techniques may uncover additional differences between these two classes of neurons. Global gene expression profiling for instance (see *Section 6*) may provide a useful strategy for identifying different neuronal subtypes (Mott and Dingledine 2003; Markram, Toledo-Rodriguez et al. 2004). Microarray mRNA expression analysis has been used to compare the cellular heterogeneity of excitatory and inhibitory neurons in different brain areas (Sugino, Hempel et al. 2006) including the CA1 region of the hippocampus (Kamme, Salunga et al. 2003).

Hippocampal function is thought to depend on the balance between synaptic excitation and inhibition and changes in this balance may lead to aberrant activities including seizures. Differences in the expression of subunits for Glu and GABA receptors may thus be finely tuned to generate appropriate and different behaviours of pyramidal cells and interneurons. Differences in subunit composition have been examined by immunohistochemistry (Macdonald and Olsen 1994; Pickard, Noel et al. 2000), by combined patch – single cell PCR studies (Martina, Schultz et al. 1998; Taverna, Tkatch et al. 2005) and by work on mRNA expression profiles (Telfeian, Tseng et al. 2003). However, without full information on differences in genes expressed by these two cell types, knowledge of factors underlying distinct physiologies and diversities will remain incomplete.

3.2 Glial Cells

Glial cells comprise two major subclasses: microglia and macroglia with different origins, morphology and function. While glial were thought to support and maintain neurones, recent evidence suggests their involvement in synaptic transmission and modulation of neuronal excitability as well as other further functions that remain to be clarified.

3.2.1 Microglia

Microglial cells, which are distributed throughout the CNS, form about 20% of brain glial cells (Lawson, Perry et al. 1990). They have a myeloid origin, deriving from bone marrow precursor cells (Ling and Wong 1993) and form a resident, stable population of innate immune cells whose phenotype seems to represent an adaptation of the monocyte and macrophage cells of the blood to a neural environment.

In normal brain, microglial phenotype is downregulated and characterized by a low expression of the CD45 leukocyte antigen. Microglia normally have no phagocytitotic or endocytotic activity and proteins that induce or mediate typical macrophage functions are poorly expressed or absent (Kreutzberg 1996). Normal levels of neuronal activity apparently act to maintain this inactivate microglial cell phenotype via neurotrophin signalling (Neumann, Misgeld et al. 1998; Wei and Jonakait 1999) as well as neurotransmitter and peptide levels (Hetier, Ayala et al. 1991; Delgado, Carlin et al. 1998). It has recently been suggested that neurons signal directly to microglia, in cell-to-cell fashion, with an inhibitory signal involving the membrane glycoprotein OX2 (Hoek, Ruuls et al. 2000; Wright, Puklavec et al. 2000).

A wide range of injuries can quickly transform resting microglia to an activated state in which they act as the main immune effector cells of the brain (Gehrmann, Matsumoto et al. 1995). Microglial activation or "maturation" involves a stereotyped sequence of steps including proliferation, expression of new molecules and movement to the injury site. This response can be induced via direct interaction with pathogens and microbial structures (Medzhitov and Janeway 2000) or may involve membrane receptors for different cytokines liberated in the CNS during inflammation (Aloisi 2001). Microglia also respond quickly to increases in potassium, due to their expression of a unique palette of potassium channels, in this way providing a feedback from a cell-firing dependant increase in extracellular potassium (Gehrmann, Mies et al. 1993).

When activated, microglia has phagocytic capacity and secretes multiple signalling molecules including pro- and anti-inflammatory cytokines (i.e. IL-1, TNF-α, INF-γ), chemokines (i.e. IL-8, MIP-1 and RANTES) and prostanoids (i.e. PGD_2 and PGE_2). These factors stimulate and

modulate humoral and cell mediated immune responses, recruit and regulate T-cell responses and also have cytotoxic actions (for a review see Aloisi 2001).
Beside the resident population in many types of neuroinflammatory, neuroinfectious or neurodegenerative processes, recruitment of new cells from the bone marrow occurs (Davoust, Vuaillat et al. 2008) leading to a renewal of the microglial population (Lassmann, Schmied et al. 1993; Flugel, Bradl et al. 2001; Priller, Flugel et al. 2001). In vitro studies suggested a role from astrocytes (see next section) in the differentiation of the bone marrow derived progenitors into microglial cells (Schmidtmayer, Jacobsen et al. 1994; Sievers, Parwaresch et al. 1994).

3.2.2 Macroglia

Macroglia are a large cell class including oligodendrocytes and astrocytes. They originate, as do neurones, from the differentiation of multipotent neural stem cells (NSCs).
Oligodendrocytes, located in white matter, act primarily to form myelin (Bunge 1968) an insulation of modified plasma membrane that surrounds myelinated axons. They govern the speed and efficacy of axonal impulse conduction and so are essential to CNS function.
Astrocytes were thought to support neuronal function by supplying essential substrates and removing toxic substrates, but recent data suggests they are intimately involved in the neurogenesis occuring in restricted brain regions of adult mammals including the hippocampus (Doetsch and Scharff 2001; Song, Stevens et al. 2002). Astrocytes can retain stem cell like properties (Doetsch 2003) and induce differentiation in adult neural stem cells (Song, Stevens et al. 2002) or direct differentiation in neuronal cell types (Berninger, Costa et al. 2007).
Another interesting role for astrocytes is as a third partner, with pre- and post-synaptic elements in the structural and functional organization of synapses. Porter and colleagues have shown that astrocytes express receptors and respond to several neurotransmitters including glutamate (Porter and McCarthy 1996; Porter and McCarthy 1997) and GABA (Kang, Jiang et al. 1998; Araque, Martin et al. 2002). Astrocytes modulate also neurotransmission by controlling ambient transmitter levels with glutamate transporters and instruct the development, maintenance and recovery of synapses.
Synaptic stimuli from neurones can evoke astrocytic responses including increases in intracellular Ca^{2+} and release of "gliotransmitter". Self propagating waves of Ca^{2+} signals are reported to spread long distances to other glial cells via gap junctions or ATP signals (Newman 2001). Reciprocally, reports suggest that astrocytes can release glutamate (Bezzi, Carmignoto et al. 1998; Araque, Li et al. 2000; Pasti, Zonta et al. 2001; D'Ascenzo, Fellin et al. 2007; Fellin, D'Ascenzo et al. 2007) or D-Serine, an endogenous ligand for NMDA receptors (Mothet, Pollegioni et al. 2005) and depolarize neurones in several regions including hippocampus (Hassinger, Atkinson et al. 1995). Studies also suggest that a potentiation of hippocampal synaptic transmission induced by repetitive inhibitory cell firing may depend on glutamate release

from nearby astrocytes (Kang, Jiang et al. 1998). These results confirm that astrocytes have a real role in synaptic transmission.

4. Interneurons of the hippocampus

4.1 Overview

Since the anatomical studies of Ramón y Cajal (1911) and Lorente de Nó (1934) on the hippocampal cortex, it has been clear that the morphology and connectivity of local circuit neurons are heterogeneous while those of principal seem to be more uniform.

The term interneuron was originally used to describe invertebrate cells that were neither input nor output neurons. As the concept of synaptic inhibition developed (Eccles 1964), it came to be used as a synonym for inhibitory cells with short axons. These cells were seen to play an essential role in the regulation of local circuit excitability, while principal cells, with long axons, were considered as channels to project information to distant brain regions. The continued emergence of functional, biochemical and anatomical data on principal and inhibitory cells has revealed exceptions to this definition such that the original views on interneurons are clearly an oversimplification. Glutamatergic cells make synapses locally as well as at a distance, and GABAergic cells can make synapses at a distance as well as locally. Thus the short axon cells of Golgi, non pyramidal cells of Ramón y Cajal and Lorente de Nó, and inhibitory interneurons of Eccles may be identical but they are far from the full story.

For this work, 'non-principal cells' of the hippocampus may be a sufficiently simple and accurate term to describe GABAergic local circuit inhibitory cells, even while recognizing that some of these cells may have long-range extra-hippocampal or commissural projections. At the same time, glutamatergic neurons such as the mossy cells which have a purely local connectivity are not considered to be interneurons. Since most, if not all, non-principal cells use GABA as a transmitter (Freund and Buzsaki 1996), the definition "GABAergic non-principal cells" appears to be the most adequate for hippocampal interneurons.

With a unifying criterion established, attention has turned to a search for how to classify GABAergic non-pyramidal cells, with a goal of constraining interneuron diversity into a manageable number of precisely defined and non-overlapping subgroups. The different approaches to this goal will be described in detail.

4.2 Towards a classification of the interneurons

The problem of a classification of interneurones remains to be completely resolved. Ideally a combination of functional, chemical and anatomical markers should permit separation of hippocampal GABAergic cells into neat sub-populations. Multiple schemes have been proposed: they vary from 10-20 classes defined in terms of morphology and neurochemistry (Freund and Buzsaki 1996; McBain and Fisahn 2001; Maccaferri and Lacaille 2003; Somogyi and Klausberger 2005) to suggestions that while groups exist, interneurons may be difficult to classify when anatomy, physiology and the expression of receptors for modulating transmitters are all taken into account (Mott, Turner et al. 1997; Parra, Gulyas et al. 1998).

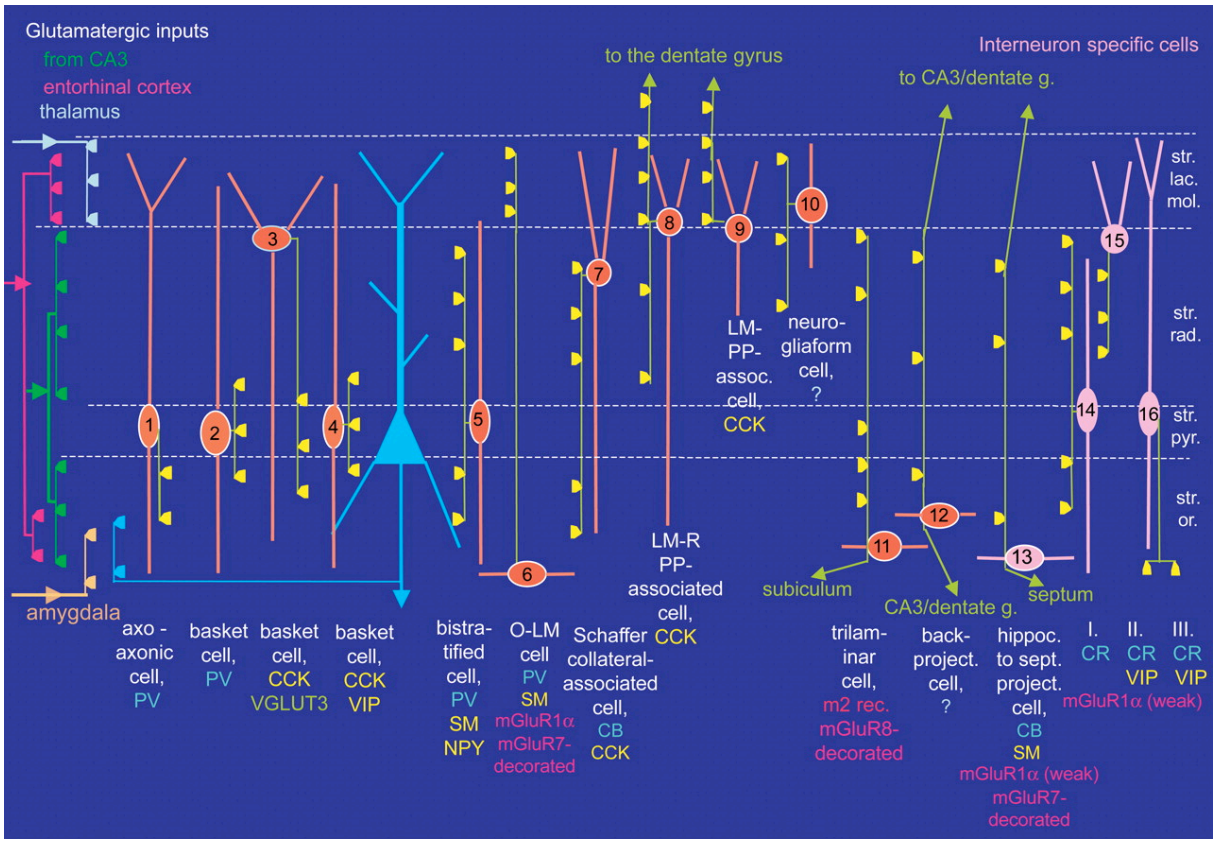

Fig. 3. INTERNEURONS IN THE CA1 AREA OF THE HIPPOCAMPUS. Somata and dendrites of interneurons innervating pyramidal cells are shown in orange, those innervating other interneurons are shown in pink. Axons are green and the main termination zone of GABAergic synapses are shown in yellow. Molecular cell markers in combination with the axonal patterns help the recognition and characterisation of each class. Further data may lead to lumping of some classes and to the identification of additional cell types. CB, calbindin; CR, calretinin; LM-PP, lacunosum-moleculare–perforant path; LM-R-PP, lacunosum-moleculare–radiatum–perforant path; m2, muscarinic receptor type 2; NPY, neuropeptide tyrosine; PV, parvalbumin; SM, somatostatin; VGLUT3, vesicular glutamate transporter 3. (Somogyi and Klausberger 2005)

Interneurons illustrate the wider problem of the definition of a cell type. There are both theoretical and practical difficulties in such a definition. The criteria to define a cell type are not universally accepted, but also conclusions must sometimes be based on small data-sets using

partial criteria. Furthermore we should recognize that variability does, and perhaps must, exist within a single cell population (Aradi, Santhakumar et al. 2002; Foldy, Aradi et al. 2004) even though it can complicate cell classification.

The following sections provide an overview of a different interneuron features used in classification schemes (see Maccaferri and Lacaille 2003). It is probable that measurements of many parameters should permit a given cell to be clustered with similar cells in a region of parameter space corresponding to a *cell type*. Experimentally only a few parameters may be available, so it is important to establish which partial measures can best situate a cell correctly within its class, in a cortical area, across areas or across species. Progress towards this goal may be most rapid in simple cortical areas such as the CA1 region of the hippocampus (Somogyi and Klausberger 2005).

4.2.1 Morphological classification

The idea that neurones with different shapes have distinct roles in the cortex was implicit in the early work of Ramón y Cajal and was elegantly elaborated by Janos Szentagothai (1975). A differential and highly selective location of synaptic terminals made by short axon cells on all target neurones suggests that different cells may have specific and distinct functional roles (Ramon y Cajal 1893; Szentagothai 1975). Indeed, interneuron anatomy alone provides insights into how different cell types contribute within hippocampal circuits, by relating the somatodendritic location to the layer specificity of synaptic input and the axonal projections to the postsynaptic target domain.

Based on Golgi staining Ramon y Cajal (1893) and Lorenté de No (1934) distinguished ~20 different types of hippocampal interneurons. Distinct cell types were first described according to features of their axonal or dendritic processes (e.g. basket cell, horizontal cell and stellate cell). Labelling techniques can now reveal the entire dendritic and axonal processes of recorded cells (Buhl, Halasy et al. 1994). The large number of interneuron types was matched by an equally rich terminology including both classical descriptions such as basket cells and new terms emphasizing different aspects of interneuron anatomy (Gulyas, Miles et al. 1993). The postsynaptic target domain has been highlighted for the 'axo–axonic cells', which innervate the axon initial segment of pyramidal cells (Buhl, Halasy et al.1994). The site of layers containing the soma and axonal processes is noted in the names of O-LM cells (oriens–lacunosum moleculare, Freund and Buzsáki 1996), P-LM cells (pyramidale–lacunosum moleculare, Oliva, Jiang et al. 2000) and O-OR bistratified cells (oriens–oriens and radiatum, Maccaferri, Roberts et al. 2000). For long-range projecting interneurons, the origin and target brain regions were embedded in the terminology, as for hippocampo–septal neurons. Other names have emphasized the orientation of interneuron dendrites, as in stellate cells, and the vertical or horizontal cells of

stratum oriens, as well as the nearby excitatory synapses on post-synaptic sites such as the Schaffer-collateral associated interneurons.

However, without a universal nomenclature the same type of interneuron has been named differently by different investigators (e.g. horizontal cells in McBain, DiChiara et al. 1994, and O–LM cells in Maccaferri, Roberts et al. 2000; vertical cells in McBain, DiChiara et al. 1994, and basket or bistratified cells in Buhl, Halasy et al. 1994). There is a strong need for an accepted interneuron vocabulary as was pointed out very recently by the foundation of The Petilla Interneuron Nomenclature Group (PING) a representative group of researchers that provided a set of terms to describe the anatomical, physiological and molecular features of GABAergic interneurons of the cerebral cortex (Ascoli, Alonso-Nanclares et al. 2008). Despite the descriptive power of an accurate anatomical characterization, the role of an interneuron in an active brain network is also crucially shaped by its functional properties which must, therefore, be included in its definition.

4.2.2 Functional classification

Interneurons are not completely defined by their anatomy. Cells with a similar morphology may have widely varying electrical and molecular properties. The first physiological descriptions were based on action potential firing patterns, and again different investigators made different classifications : accommodating or non-accommodating, bursting, fast-spiking cells and regular-spiking cells (Lacaille, Mueller et al. 1987; Traub, Miles et al. 1987; Kawaguchi and Hama 1988). More recently, interneurons have been divided according to their steady-state or initial responses to stimuli, or spontaneous firing pattern, distinguishing for instance between cells that fired in a regular, irregular or clustered fashion (Parra, Gulyas et al. 1998). Such classifications are useful, but as for the morphology, few studies have attempted to demonstrate that discrete classes exist rather than a continuum.

Furthermore, firing patterns result from a combination of the activities of numerous voltage-gated conductances. The proteins responsible have distinct somato-dendritic expression patterns in different interneurons. During firing their effects overlap in time, to impart subtle characteristics to action potential timing and waveform. So, while practically useful, this classification may become problematic with the large number of membrane channels known to contribute to the distinct electrical activity of inhibitory neurons (Vinet and Sik 2006). Another physiological basis for interneuron classification derives from the nature of transmission at afferent excitatory synapses. In particular the facilitation or depression of EPSPs, recorded in experiments on connected pairs of neurons, during repetitive afferent

activation is suggested as a useful descriptive criterion. However, the utility of such schemes can be questioned, since single axons can transmit information in a target-specific manner (Maccaferri, Toth et al. 1998; Scanziani, Gahwiler et al. 1998).

4.2.3 Neurochemical classification

Differences in chemical markers expressed by interneurons, determined with immuno-histochemical tools, have provided data for classification schemes. Even while no single marker defines a specific interneuron type, neuropeptides and Ca-binding protein distribution has been especially useful to distinguish cell types (Freund and Buzsaki 1996).

Interneurons all contain GABA (Storm-Mathisen, Leknes et al. 1983), and the GABA-synthesizing enzymes GAD65 and GAD67 (Ribak 1978). Specific interneuron populations contain different peptides, including somatostatin, cholecystokinin (CCK) and substance P, or Ca^{2+}-binding proteins, such as calbindin, parvalbumin and calretinin, (Somogyi, Hodgson et al. 1984). These markers have been used to produce a neurochemical classification which may also imply functional differences (Freund and Buzsaki 1996; Baraban and Tallent 2004). Parvalbumin, calbindin or calretinin expression seems to discriminate between interneurons with different dendritic geometry, postsynaptic target selection and synaptic input density (Gulyas, Megias et al. 1999). However, morphologically defined interneurons may co-exist in a single neurochemically identified subgroup. For example, O–LM, O–bistratified, P–LM and radiatum–lacunosum moleculare (R– LM) interneurons of the CA1 hippocampal subfield are all immunoreactive for somatostatin (Katona, Acsady et al. 1999; Maccaferri, Roberts et al. 2000; Oliva, Jiang et al. 2000; Losonczy, Zhang et al. 2002). Similarly, parvalbumin is expressed by basket and axo–axonic cells (Kosaka, Katsumaru et al. 1987; Klausberger, Magill et al. 2003) as well as at lower levels in the soma and dendrites but not terminals of O–LM cells (Maccaferri, Roberts et al. 2000; Losonczy, Zhang et al. 2002). Furthermore distinct markers may be expressed in morphologically similar interneurons with different functional properties. Basket cells for instance express parvalbumin or CCK (Freund 2003). Therefore, a combined neurochemical and anatomical classification will be more useful than a scheme based on either one of these parameters. Addition of physiological properties results in further overlap since for instance somatostatin-expressing neurons exhibit a high degree of electrophysiological variability (Ma, Hu et al. 2006).

Recent *in vivo* data suggest a functional approach based on axonal and dendritic anatomy, chemical markers and cellular firing pattern during population activities such as theta oscillations and sharp waves may be useful. Parvalbumin-positive basket cells, axo–axonic cells and somatostatin-containing O–LM cells fired in distinct patterns (Klausberger, Magill et al. 2003). More data is needed on further cell types, but these results suggest that specific types of interneuron are selectively recruited for distinct functions in different brain states.

4.3 Functional role of interneurons

Many principles of interneuron function were first defined in the hippocampus, especially the dentate gyrus (Freund and Buzsaki 1996). This work suggested that GABA-releasing hippocampal interneurons act to regulate the activity of principal cells. Recent evidence indicates that interneurons may also be intimately involved in the generation and control of rhythmic brain activities. Their highly divergent network connectivity, the existence of interneurons that specifically target other interneurons and the complex inhibitory cell firing patterns due to specific distributions of voltage-gated currents are finely tuned to permit inhibitory interneurons to regulate network oscillations. Perisomatic interneurons in particular exert a strong control on pyramidal cell population discharges, and thus cognitive operations, (Freund 2003). The diverse yet precise connectivity of different types of interneurons (Ramon y Cajal 1893; Lorente de Nó 1934) enables them to carry out multiple tasks.

Interneurons are excited by synaptic input from several sources both intrinsic and extrinsic to the hippocampus (Lacaille, Mueller et al. 1987; Kawaguchi and Hama 1988; Freund and Buzsaki 1996; Oliva, Jiang et al. 2000) which exhibit various activity-dependent plasticity (Losonczy, Zhang et al. 2002). Gulyas, Megias et al. (1999) studied differences in excitatory innervation of CA1 interneurons containing parvalbumin, calretinin and calbindin. Both parvalbumin and calretinin interneurons received synapses from all strata, while calbindin cells were excited primarily by Schaffer collaterals in stratum radiatum. This suggests calbindin cells are activated by feed-forward circuits, while parvalbumin and calretinin containing cells receive both feed-forward excitation from the Schaffer collaterals, entorhinal fibres and thalamic afferents, and feed-back excitation by CA1 recurrent collaterals. Activity-dependant plasticity at synapses that excite interneurons appears to differ from synapses that excite principal cells (Maccaferri and McBain 1996; McBain, Freund et al. 1999).

Several evidences revealed that inhibitory interneurons of the hippocampus are interconnected by electrical synapses. An electrical synapse is a mechanical and electrically conductive junction between two cells woth a narrow gap between pre- and postsynaptic cell known as a gap junction. Dendrodendritic gap junctions between interneurons are frequently seen in areas CA1 and CA3 (Kosaka and Hama 1985) and in the dentate gyrus (Kosaka 1983). Several types of gap junction–coupled interneurons have been identified (Katsumaru, Kosaka et al. 1988; Fukuda and Kosaka 2000). The structural proteins comprising gap junctional channels are called connexins. Single-cell RT-PCR experiments has revealed the presence of mRNA encoding for connexin 36 (Cx36) in interneurons (Venance, Rozov et al. 2000). Furthermore, although

electrical coupling between pairs of interneurons was abundant in the CA3 and in the dentate areas of wild-type mice, it was absent in cells of Cx36 knockout mice (Hormuzdi, Pais et al. 2001).

The functions of electrical coupling between hippocampal interneurons are not yet well understood. Many studies have focused on the possibility that gap junctions play a role in generating or modulating synchronous oscillations or seizure-like activity (Draguhn, Traub et al. 1998; Hormuzdi, Pais et al. 2001; Traub, Draguhn et al. 2002; Buhl, Harris et al. 2003).

4.4 Molecular and genetic variety of interneurons

Recent technical developments, including single-cell reverse transcriptase polymerase chain reaction (RT-PCR), *in vivo* labelling and other molecular biological methods now permit a molecular approach to interneuron diversity (Meyer, Katona et al. 2002; Blatow, Rozov et al. 2003; Monyer H 2004). The generation of transgenic mice expressing fluorescence in parvalbumin positive interneurons allowed Meyer and colleagues to study electrical coupling between these cells. They showed an interesting developmental regulation of the presence and strength of electrical coupling in distinct brain areas (Meyer, Katona et al. 2002). Blatow and collagues used the same animals to identify a new subclass of PV positive interneurons that differed physiologically from the fast-spiking interneurones which also express parvalbumin. These distinct Multipolar Bursting cells (MB) also express calbindin while fast-spiking cells do not (Blatow, Rozov et al. 2003). Can this approach determine whether interneurons should be divided into discrete classes, or rather considered as a continuum of different neurons?

The acceptance of distinct anatomical classes of interneurons has been facilitated by the evident functional differences between cells that for instance target different somato-dendritic domains of pyramidal cells. At the molecular level, some markers are expressed only by certain interneuron types. However, it seems clear that no single marker defines a single anatomical or electrical interneuron sub-type, but rather multiple markers must be analysed. At the electrical level, the diversity might seem arbitrary, probably due to the lack of defined functions for the different behaviours. The class-versus-continuum issue can probably only be resolved objectively by studies that examine variations in gene expression.

The electrical diversity of neocortical interneurons results from the somato-dendritic pattern of expression of distinct ion-channels as well as neuronal form. Ion-channel gene expression seems to correlate with interneuron physiology falling into three clusters according to expression of different calcium-binding proteins (Markram, Toledo-Rodriguez et al. 2004). The correlation between expression profiles and electrical phenotypes, constraints in co-

expression profiles and the 'flip' of entire expression profiles into opposing electrical phenotypes, suggest that expression of distinct combinations of just a few transcription factors, may define a finite number of distinct interneuron classes (Toledo-Rodriguez, Blumenfeld et al. 2004; Toledo-Rodriguez, Goodman et al. 2005). Recent work in this field suggests the *Lhx* and *Dlx* families of transcription factors are especially important. Ghanem and colleagues have shown that different enhancers of the *Dlx1* and 2 locus (*i12b* and *URE2*) are expressed in distinct subsets of cortical interneurons (Ghanem, Yu et al. 2007). Zhao and colleagues have provided new detail on how Lhx6 controls the specification and development of interneurons (Zhao, Flandin et al. 2008).

So, most interneurons probably belong to distinct electrical, morphological and molecular classes. Detected diversity is much less than that expected for a continuum of electrical types with more than 100 available ion-channel genes. This points to strong constraints on diversity which can be studied with molecular and genetic tools, permitting perhaps a resolution of the class-versus-continuum debate for interneurons.

This work has already begun with the use of transgenic animals to examine molecular variability of interneurons. The use of knock out mice has already helped understand links between the chemical content of GABAergic interneurons and their network functions (Deans, Gibson et al. 2001; Hormuzdi, Pais et al. 2001). At a practical level, transgenic mice now permit easy visualisation of specific interneuronal subfamilies (Oliva, Jiang et al. 2000; Meyer, Katona et al. 2002) greatly facilitating classification studies.

5. Temporal Lobe Epilepsy

5.1 Epilepsy

The hippocampus is vulnerable to anoxia and ischemia and it is affected early in the pathology associated with Alzheimer's disease. The hippocampal formation also has an especially low threshold for certain forms of epilepsy (Green 1964). The word "Epilepsy" derives from the greek *Epilambanein,* meaning "to take hold of" or "to seize". A seizure corresponds to a sudden abnormally synchronous neuronal activity at one or more brain regions. The clinical characteristics of the seizure depend on the regions involved.

5.2 Epileptic Syndromes

Multiple epileptic syndromes exist and together affect ~1% of the world population (McNamara 1999). The incidence in developed countries is ~50/100.000 persons per year. The incidence is higher in infants and elderly people and also in non developed countries (MacDonald, Cockerell et al. 2000; Sander 2003; Forsgren, Beghi et al. 2005).

Epileptic syndrome classsification has evolved over the years. Systems were published in 1969 and 1981, then again in 1985 and 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (TFCT-ILAE 1981; TFCT-ILAE 1989). The 1969 / 1981 classification was based exclusively on clinical and electro-encephalographic criteria. The more recent classification of 1985 / 1989 also takes the presumed origins of the pathology into account. The first system made a major distinction between focal, or partial, seizures, generalized convulsive seizures and generalized non convulsive seizures, also known as absence seizures. The second classification introduced idiopathic, symptomatic and cryptogenic syndromes.

Partial seizures originate in a defined unilateral region, known as the epileptic *focus.* Often the focus of partial epilepsies is located inside the temporal lobe (66%), but frontal (25%) and more rarely occipital (3%) and parietal (2%) epileptic foci also occur (Semah, Picot et al. 1998). Generalized seizures involve abnormal activity which seems to originate simultaneously in extended cortical and sub cortical regions of both hemispheres.

Idiopathic syndromes occur in the absence of an evident, organic cerebral lesion, while for symptomatic syndromes a focal or diffuse lesion can be detected, usually by non-invasive imaging. Cryptogenic lesions differ from idiopathic syndromes but no lesion can be detected.

5.3 Etiology of epilepsies

Some epilepsies are inherited, while others are induced by acquired factors which create a lesion. Epileptic syndromes with Mendelian genetics are rare, so most syndromes with an inherited component probably involve multiple genes as well as interactions with environmental factors. Genetic epilepsies corresponding to idiopathic syndromes account for ~30% of cases (Hauser, Annegers et al. 1993; Jallon, Loiseau et al. 2001). Acquired epileptic syndromes due to events such as cranial traumas, developmental malformations, post-infections lesions or tumours are

collectively termed symptomatic and account for ~25% of patients (Hauser, Annegers et al. 1993; Jallon, Loiseau et al. 2001).

5.3.1 Symptomatic syndromes

Multiple external factors contribute to the etiology of an epileptic syndrome. Some anomalies of cortical development, often with a genetic component, are associated with severe and drug-resistant epilepsies (Benlounis, Nabbout et al. 2001; Guerrini and Carrozzo 2001; Guerrini and Carrozzo 2002). If the malformation is focal, a partial epileptic syndrome may result (Barkovich, Kuzniecky et al. 2001).

Two broad classes of malformation produce an epileptic brain: defects in neuronal migration, or errors in cortical organization. Neuronal migration syndromes include the lissencephalies, where the cortex has a smooth rather than a sulcated phenotype and heterotopias of the grey substance, where groups of neurons are abnormally situated and localized. Heterotopias may be sub-cortical (or laminar) band heterotopias also known as "double cortex" syndromes (Barkovich, Guerrini et al. 1994) and periventricular heterotopias.

While symptomatic epilepsies are considered acquired, recent data suggested they may have a significant genetic component. Specific syndromes have been linked to mutations in genes coding for proteins associated with the cytoskeleton including Filamin1 (FLN1; (Sheen, Dixon et al. 2001; Guerrini, Mei et al. 2004), Doublecortin (Dclx) (des Portes, Pinard et al. 1998) or reelin which is associated with the extracellular matrix.

Cortical organization errors associated with epileptic syndromes include different dysplasias, polymicrogyrias and schizencephalia. Of them, focal cortical dysplasia is the most frequent cause of intractable epilepsy in children. It corresponds to a cortical cellular expansion with grey matter less differentiated than white matter, a disorganised laminar architecture and glial and neuronal abnormalities including the presence of abnormally large balloon cells (Palmini, Najm et al. 2004).

A distinct group of factors in the etiology of epileptic syndromes are those that induce convulsions in childhood which are succeeded by adult onset epilepsy. They include CNS infections such as viral encephalitis and bacterial meningo-encephalitis (Annegers, Hauser et al. 1988). Cerebral febrile affections occuring at ages up to five years old may induce febrile convulsive sizures in genetically predisposed persons (Maher and McLachlan 1995; Camfield and Camfield 2002).

Brain tumours may induce epileptic syndromes (Cascino 1990; Smith, Hutton et al. 1991). Most frequently they include oligodendrogliomas, astrocitomas, meningiomas, metastasis and glioblastomas of frontal central cortex. Cranial trauma may induce a post-traumatic epilepsy (Annegers, Hauser et al. 1998). Seizures typically appear at one week to two years after the trauma (Willmore 1992; Pohlmann-Eden and Bruckmeir 1997) usually without a chronic state. In the elderly, a stroke may trigger an epileptic syndrome (Loiseau, Loiseau et al. 1990), usually within two years, and more frequently for ischemic than hemorrhagic accidents.

5.3.2 Idiopathic Syndromes: channelopaties.

Hippocrate in 400 B.C may have been the first to note that epileptic syndromes could be inherited. Patterns of transmission of distinct syndromes differ and genetic variation may have a major impact on treatment response, prognosis and consequences.

Mutations in more than 70 genes have now been linked to epileptic syndromes or other episodic cortical dysrhythmias. Many of these genes code for membrane ion channels involved in the transmission of the nerve impulse or the control of neuronal excitability, recalling the necessity for a balance between brain excitation and inhibition for normal function. Other genes with quite different functions have also been linked to distinct epileptic syndromes. They include transcription factors regulating early development and plasticity as well as structural proteins and those related to the cytoskeleton.

These “epilepsy” genes have usually been identified starting from linkage analysis and then genetic DNA sequencing in order to discover the pathological mutation, to functional assays to show how the mutation affects network properties (George 2004). Since many of them code for proteins that form or are associated with voltage-gated or receptor-operated membrane channels these conditions have been termed “channelopathies”. They include both regulatory and pore-forming subunits of voltage gated channels as well as receptors for neurotransmitters and neuromodulators (Noebels 2003).

Inherited Epilepsies

Syndrome (OMIM No.)	Chromosomal Locus	Gene	Gene Product
BNFC			
BNFC type 1 (121200)	20q13.2	*KCNQ2*	Voltage-gated potassium channel, α subunit
BNFC with myokymia (606437)	20q13.2	*KCNQ2*	Voltage-gated potassium channel, α subunit
BNFC type 2 (121201)	8q24	*KCNQ3*	Voltage-gated potassium channel, α subunit
Benign familial neonatal infantile seizures (607745)	2q24	*SCN2A*	Voltage-gated sodium channel, α subunit
Febrile seizures			
GEFS+ type 1 (604233)	19q13.1	*SCN1B*	Voltage-gated sodium channel, β_1 subunit
GEFS+ type 2 (604233)	2q24	*SCN1A*	Voltage-gated sodium channel, α subunit
GEFS+ type 3 (604233)	5q31.1-q33.1	*GABRG2*	$GABA_A$ receptor, γ_2 subunit
Febrile seizures associated with afebrile seizures (604233)	2q24	*SCN2A*	Voltage-gated sodium channel, α subunit
Severe myoclonic epilepsy of infancy, Dravet syndrome (607208)	2q24	*SCN1A*	Voltage-gated sodium channel, α subunit
Intractable childhood epilepsy with frequent generalized tonic-clonic seizures	2q24	*SCN1A*	Voltage-gated sodium channel, α subunit
Familial febrile convulsions type 4 (604352)	5q14	*MASS1*	Monogenic audiogenic seizure-susceptible gene
ADNFLE			
ADNFLE type 1 (600513)	20q13.2-q13.3	*CHRNA4*	nAChR, α_4 subunit
ADNFLE type 2 (603204)	15q24	?	?
ADNFLE type 3 (605375)	1q21	*CHRNB2*	nAChR, β_2 subunit
Absence epilepsy			
Childhood absence epilepsy type 1 (600131)	8q24	?	?
Childhood absence epilepsy type 2 and febrile seizures (607681)	5q31.1-q33.1	*GABRG2*	$GABA_A$ receptor, γ_2 subunit
Childhood absence epilepsy type 3 (607682)	3q27.1*	*CLCN2*	Voltage-gated chloride channel
Juvenile absence epilepsy (607631)	3q27.1*	*CLCN2*	Voltage-gated chloride channel
Myoclonic epilepsy			
Autosomal dominant juvenile myoclonic epilepsy (606904)	5q34-q35	*GABRA1*	$GABA_A$ receptor, α_1 subunit
Juvenile myoclonic epilepsy (606904)	3q27.1*	*CLCN2*	Voltage-gated chloride channel
Juvenile myoclonic epilepsy (606904)	2q22-2q23	*CACNB4*	Voltage-gated calcium channel, β_4 subunit
Myoclonic epilepsy of Unverricht and Lundborg (254800)	21q22.3	*CSTB*	Cystatin B
Myoclonic epilepsy of Lafora (254780)	6q24	*EPM2A*	Protein tyrosine phosphatase (laforin)
Benign adult familial myoclonic epilepsy (601068)	8q24	?	?
Other epilepsy syndromes			
Epilepsy with grand mal seizures on awakening (607628)	3q27.1*	*CLCN2*	Voltage-gated chloride channel
Autosomal dominant lateral temporal lobe epilepsy (600512)	10q24	*LGI1*	Leucine-rich gene, glioma inactivated
X-linked infantile spasm syndrome, West syndrome (308350)	Xp22.13	*ARX*	Aristaless-related homeobox gene
X-linked infantile spasm syndrome, West syndrome (308350)	Xp22.13	*STK9*	Serine/threonine kinase 9

Abbreviations: ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BNFC, benign familial neonatal convulsions; GABA, γ-aminobutyric acid; GEFS+, generalized epilepsy with febrile seizures plus; nAChR, nicotinic acetylcholine receptors; OMIM, Online Mendelian Inheritance in Man database (available at: http://www.ncbi.nlm.nih.gov/Omim/); question mark, unknown.
*Indicates the cytogenetic location was refined (database available at: http://genome.uscs.edu).

Fig. 4: MAJOR INHERITED EPILEPTIC SYNDROMES AND GENES ASSOCIATED. In the table in the picture are listed the major syndrome associated with a genetic inheritance, in the second column the chromosomal loci candidate or demonstrated to be linked to the pathology. In the third and fourth columns are listed the different genes associated, in case of mutation, to the distinct syndromes

1) *Na^+ channels*: mutations in several subunits of Na+ channels have been linked to epileptic syndromes (Grieco, Afshari et al. 2002). Three different genes (Scheffer and Berkovic 1997) have been associated with the syndrome $GEFS^+$, generalized epilepsy with febrile seizures plus, first described by Scheffer and Berkovic (1997). Mutations in an alpha subunit, SCN1A (Escayg, MacDonald et al. 2000; Escayg, Heils et al. 2001; Wallace, Scheffer et al. 2001) have been characterized (Spampanato, Escayg et al. 2001; Lossin, Wang et al. 2002; Cossette, Loukas et al. 2003; Lossin, Rhodes et al. 2003; Spampanato, Escayg et al. 2003). Some of

these mutations are associated with a gain in function probably leading to neuronal hyperexcitability while paradoxically others seem to induce a loss-of-function but evidences have been reported that the loss of function is specific to inhibitory PV positive interneurones (Ogiwara, Miyamoto et al. 2007). Distinct alpha-subunit mutations (SCN2A; (Sugawara, Tsurubuchi et al. 2001) and beta sub-unit mutations (SCN1B) associated with $GEFS^+$ (Wallace, Wang et al. 1998) have not yet been functionally characterized. Sodium channel mutations are associated with other syndromes including SCN1A mutations that cause trafficking problems linked to severe myoclonic epilepsy of infancy (Claes, Del-Favero et al. 2001; Fujiwara 2006).

2) *K^+ channels*: Many distinct subunits participate in voltage-gated family K^+ channels assemblies, and in consequence many combinatorial possibilities of the subunit proteins exist. As yet, few of them have been associated with inherited epileptic disorders. Mutations of KCNA1 affecting channel assembly, targeting or kinetics (Rea, Spauschus et al. 2002) are linked to temporal lobe epilepsies. For this gene too, different mutations have been linked with distinct pathologies - some KCNA1 mutations are associated with neuromyoatonia (Zuberi, Eunson et al. 1999; Eunson, Rea et al. 2000). Another mutation in the subunit KCNAB2 may be associated with the 1p36 deletion syndrome (Heilstedt, Burgess et al. 2001) that has an epileptic phenotype, but the association is not yet proven (Kurosawa, Kawame et al. 2005).
Mutations in the genes KCNQ2 and KCNQ3 were discovered by cloning material from patients with a benign familial neonatal convulsion syndrome (Charlier, Singh et al. 1998; Singh, Charlier et al. 1998; Leppert and Singh 1999). These genes, members of the Q family, named for the link between KCNQ1 and the congenital cardiac long Q-T syndrome, coassemble in different ways. They generate persistent voltage and transmitter-modulated currents, first known as M-currents, since they are blocked by muscarine. Activation of Q-family currents reduces neuronal excitability and suppresses repetitive firing (Wang, Pan et al. 1998). Mutations in KCNQ2 and KCNQ3 induce a loss-of-function but as other inhibitory influences on neuronal excitability predominate; this pathology recedes after few weeks of life. These two genes both expressed in pyramidal cells of neocortex and hippocampus (Saganich, Machado et al. 2001) and KCNQ2 is expressed in inhibitory neurons (Cooper, Harrington et al. 2001). Novel mutations associated with this benign epileptic syndrome are still being discovered (Tang, Li et al. 2004; Li, Li et al. 2008; Sadewa, Sasongko et al. 2008).

3) *Ca^{2+} channels*: Changes in internal calcium concentration act as a trigger for many biological processes including neurotransmitter release, excitation-contraction coupling and gene expression. Relations between subunit mutations and inherited epilepsies are therefore somewhat different for voltage-gated Ca^{2+} channels and for Na^+ or K^+ channels. Changes in the biophysical properties of Ca^{2+} channels modify synaptic strength and promote aberrant synchronies. Several spontaneous mice mutants exhibit epileptic syndromes linked to mutations in proteins coding for Ca^{2+} channels subunits and have been associated with absence-type seizures. Mutants in CACNA1A, coding for the α1a subunit are detected in mice strains including *totterer, leaner, rocker, roller*. Mutations in CACNB4 are associated with the *lethargic* mouse phenotype, in CACNA2D2 coding for the α2δ subunit in the mouse *ducky*, and in the γ2 Ca channel subunit coded by CACNG2, in *stargazer* and *waggler* mice exhibit absence seizures as well as ataxia (Burgess and Noebels 1999; Crunelli and Leresche 2002).
Ca channel mutations underlying human inherited epilepsies are less frequent but have been detected for the α1 (Jouvenceau, Eunson et al. 2001) and β4 subunits (Escayg, De Waard et al. 2000). Mutations in the CACNA1H gene, coding for T-type voltage-gated Ca channel have been linked to Childhood absence epilepsy (CAE). In two studies, fifteen distinct mutations have been described (Chen, Lu et al. 2003; Heron, Phillips et al. 2004).

4) *Cl^- channels*: Chloride channels gated by voltage are involved directly and indirectly in inhibitory processes, both by hyperpolarizing cells directly and also by contributing to internal Cl^- levels which affect the polarity of GABAergic signalling. The CLCN2 gene codes for a chloride channel widely expressed by pyramidal, interneurones and astrocytes (Sik, Smith et al. 2000) that contributes to Cl- homeostasis by a voltage-sensitive inwardly rectifying chloride conductance (Staley 1994). Mutations in this channel have been linked to an idiopathic generalized epilepsy syndrome with seizures of diverse phenotype (Haug, Warnstedt et al. 2003). In families with mutations in this gene, the epileptic phenotypes do not always segregate as true monogenic traits, suggesting that modifier genes contribute to the phenotype.

5.3.3 Idiopathic Syndromes: mutations on not-channel genes.

Genes coding for neurotransmitter receptors and other aspects of synaptic function have been linked to epileptic syndromes.

1) *GABA transmission*: GABA receptors are receptor-operated channels, permeable to chloride and bicarbonate, that mediate synaptic inhibition in higher brain regions. Mutations of the γ2 subunit, coded by the gene GABRG2 are associated with $GEFS^+$, the same syndrome linked with SCN1A mutations (Baulac, Huberfeld et al. 2001; Wallace, Marini et al. 2001). Mutations in GABRA1, which codes for the α1 subunit, have been related to an adolescent epileptic syndrome, Juvenile myoclonic epilepsy (Cossette, Liu et al. 2002).
Genes that affect GABA release, synthesis and recapture could be associated with epiletic phenotypes. Probably the best known example is that of mutations in GAD65, one of the two isoforms of the enzyme involved in GABA synthesis (Kash, Johnson et al. 1997).

2) *Glu transmission*: Mutations of genes associated with glutamatergic neurotransmission and linked to epileptic syndromes include one in GluRB, the gene conding the βsubunit of the glutamate receptor, (Brusa, Zimmermann et al. 1995) as well as a mutation of the transporter EEAT1 that removes glutamate from the active zone (Sepkuty, Cohen et al. 2002), and a deficiency of EEAT2, a distinct glutamate transporter (Tanaka, Watase et al. 1997).

3) *Ach transmission*: Mutations of two different subunits of a neuronal nicotinic receptor have been linked to an epileptic syndrome termed Autosomal dominant nocturnal frontal lobe epilepsy. They concern the gene CHRNA4 that codes for the α4 subunit (Steinlein, Mulley et al. 1995; Hirose, Iwata et al. 1999; Tenchini, Duga et al. 1999) and CHRNB2 which codes for the β2 subunit (De Fusco, Becchetti et al. 2000).

Many knockout mice of genes involved in the physiology of synaptic transmission and electrical activity possess an epileptic phenotype. Genes include those coding for proteins expressed at the synapse and involved in transmitter mobilization and release such as the SNARE and RAB proteins as well as vesicle-associated proteins. Other genes whose deletion or mutation is associated with epileptic syndromes include those involved in cellular proliferation, migration and other developmental processes. This family of proteins also includes transcription factors (see for review Noebels 2003). These developmental errors often correspond to different forms of dysplasia where neurones are misplaced in focal or band patterns.

Genetic variations have been linked even to symptomatic epilepsy syndromes. Epileptic syndromes of Mendelian inheritance with a single altered gene are clearly a minority. With a complex genetic equilibrium involving multiple genes as well as changes in protein function or expression induced by external factors, subtle genetic and genomic variations may contribute to a wider range of epileptic syndromes than presently admitted.

5.4 Mesial Temporal Lobe Epilepsy - MTLE

The focal site for seizures in partial epileptic syndromes is often located in the temporal lobe. Mesial Temporal Lobe Epilepsies (MTLE) account for ~60% of the adult human epilepsies (Bancaud 1987; Semah, Picot et al. 1998). While they are often seen as a single syndrome, several types of epilepsies with different properties arise from the temporal lobe. In humans, such epilepsies typically emerge in adolescence, but may often be traced to an initial precipitating event (IPI) of childhood, such as a febrile seizure, hypoxia, trauma, intracranial infection, partial onset status-epilepticus, brain tumors and strokes. Pharmaco-therapy may be effective, and usually involves multiple molecules often with different targets. In many patients, however, the efficacy of anti-epileptic drugs is reduced with time.
Pharmacoresistant epilepsies affect 20% of patients with partial epilepsies; (Hauser 1992). In these cases, a unilateral removal of seizure-generating circuits of the hippocampus and amygdala may be an effective treatment (Gloor 1991; Engel, Williamson et al. 1997). Physiological work on resected tissue demonstrates an abnormal hyperexcitability of dentate granule cells and hippocampal pyramidal neurons (Schwartzkroin 1986; Masukawa, Higashima et al. 1989).

5.4.1 Semiological remarks and histological features

Epilepsies of the mesial temporal lobe are diagnosed principally from electroencephalogram (EEG) records and functional magnetic resonance images (fMRI). They show:

- Temporal seizures arise in the temporal lobe, especially the hippocampus/amygdala.
- An intercritical pathological EEG activity is generated in focal areas between seizures.
- Hippocampal volume is reduced (de Lanerolle, Brines et al. 1992)

Resected human tissue has permitted work on the causes of the reduction in volume. It reflects a hippocampal sclerosis corresponding to a selective neuronal loss accompanied by a gliosis in the CA3 and CA1 areas (Babb, Lieb et al. 1984; Engel 1992). Synaptic contacts are reorganised in sclerotic human temporal lobe. The best example is from the dentate gyrus where mossy fibres sprout and form aberrant synapses with nearby granule cells (Sutula, Cascino et al. 1989). While CA1 and CA3 are reduced in size, the area of the dentate gyrus sometimes increases, with a dispersion of granule cells, and even an abnormal giant morphology and an ectopic location (Houser, Miyashiro et al. 1990). It is difficult to determine whether these changes in the dentate are a cause or a consequence of either repeated seizure activity or of the sclerotic neuronal loss in the CA3 region.

One major problem in studies on patients lies in relating such pathological changes to an initial injury such as a febrile seizure. Tissues become typically available many years later after a *latent* period between the IPI and the onset of recurrent seizures. Severe prolonged insults like prolonged febrile convulsions may lead to a shorter latency period (VanLandingham, Heinz et al. 1998). There is also a period of several years during which seizures can be controlled by pharmacotherapies (Berg, Langfitt et al. 2003) before they become pharmacoresistant. The mechanisms underlying the delayed emergence of recurrent seizures in MTLE have not yet been completely resolved.

5.4.2 Hippocampal Sclerosis

Hippocampal sclerosis (HS), with neuronal loss and glial proliferation, was first associated with temporal lobe epilepsies by Bouchet and Cazauvieilh in 1825. More than 50% of pyramidal cells in the CA1 and CA3 areas and the hilus may die, resulting in a severe atrophy. Both temporal lobes are usually affected but one side is almost always more sclerosed than the other hemisphere (Margerison and Corsellis 1966). CA2 pyramidal cells and dentate granule cells are much less affected, and dentate granule cells may disperse and take abnormal morphologies (Houser, Miyashiro et al. 1990; Houser 1992; Lurton, Sundstrom et al. 1997; Mathern, Babb et al. 1997). Mossy fibre axons of dentate granule cells re-organize, probably in response to the loss of their targets in CA3. Aberrant and pro-epileptic connections are formed with the dendrites of nearby dentate cells (Mathern, Babb et al. 1997).

The existence of a causal association between hippocampal sclerosis and temporal lobe seizures remains unclear. In patients sclerosis usually preceeds the emergence of seizures, but it is mild or even absent in some patients. In contrast, sclerosis does not necessarily lead to mesial temporal lobe seizures.

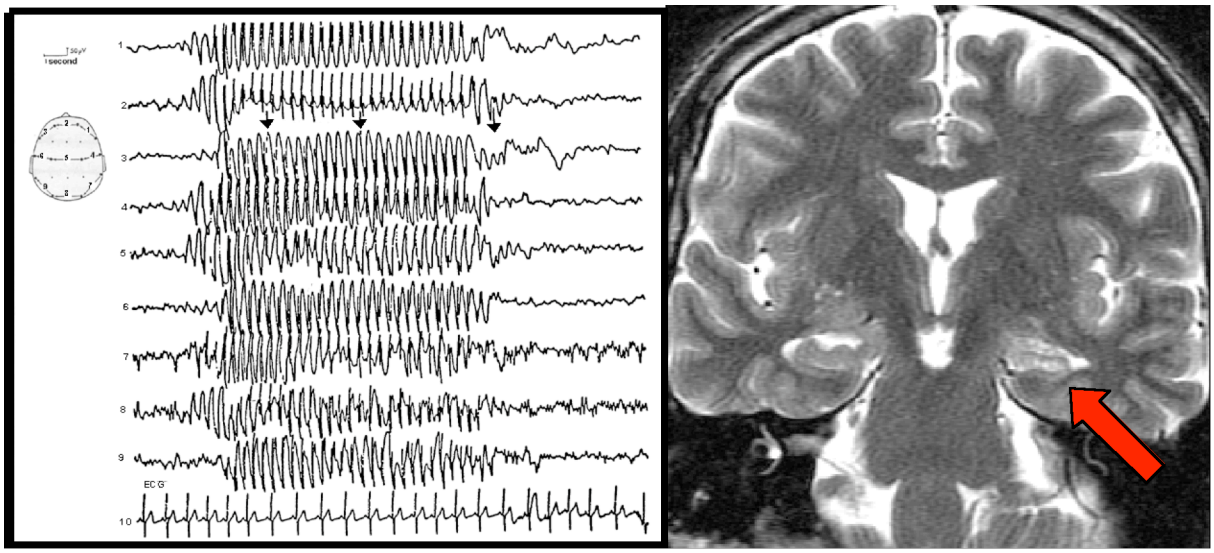

Fig.5: TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS. On the left panel EEG recordings showing aberrant electrical activity in a patient affected by Temporal Lobe Epilepsy. On the right panel MRI of brain in an epileptic patient, presenting evidence of Hippocampal Sclerosis marked by the red arrow.

Very similar patterns of cell loss are described in geriatric patients with neurocognitive impairments and dementia (Dickson, Davies et al. 1994; Vinters, Ellis et al. 2000). Morphometric studies on sclerosis in *post mortem* or surgically removed tissue has shown major differences in the form, extent and severity of scerosis in epileptic patients. Marguerison and Corsellis (1996) detected a pattern of cell death involving primarily the hilus and CA3c region. Bruton (1988) proposed three categories: classic sclerosis, total sclerosis and sclerosis limited to CA3c-hilus (Bruton 1988). The limited sclerosis accounts for about 5 % of cases, with the majority following a classical pattern of cell death in the hilus, CA3 and CA1 regions. Neuronal death and gliosis is detected, to a lesser extent, in extra-hippocampal regions including the entorhinal cortex and the amygdala in about 60% of cases (Yilmazer-Hanke, Wolf et al. 2000; Bocti, Robitaille et al. 2003). Typical anti-epileptic surgery removes the amygdala as well as the regions of hippocampal cell death (Gloor 1991; Wieser 1998).

5.4.3 Natural history of MTLE

Patients with mesial temporal lobe epilepsies tend to share a similar history (Mathern, Babb et al. 1996; Engel, Williamson et al. 1997) with a common progression of clinical features that reinforces the notion of a disease that evolves over a long time period:

1) *IPI.* In patients with MTLE, it is often possible to identify a childhood incident, frequently associated with a convulsion or status-epilepticus. Both external insults and innate conditions may be involved but careful studies on the progression from such an incident to adolescent seizures are rare. Febrile seizures are the most common precipitant but not all such events lead eventually to adult epilepsies. Infant hypoxia, brain trauma and intracranial infection also act as precipitants. A distinct genetic background may be associated with either the predisposition to childhood convulsions or to an enhanced susceptibilty for the development of either hippocampal sclerosis or adult epilepsy.
Kunz et al (2000) have related a specific mitochondrial dysfunction to the susceptibility for MTLE (Kunz, Kudin et al. 2000). Evidence has also grown for a role of inflammatory processes in the development of pro-epileptic circuits (Vezzani and Granata 2005) and Crespel and colleagues have suggested that such processes may be activated both by the initial precipitating episode and during the formation of a glial scar (Crespel, Coubes et al. 2002). Some gene polymorphisms may be related to the susceptibility to develop adult seizures. Preliminary data supports associations with polymorphisms in genes coding for the GABAB1 receptor (Gambardella, Manna et al. 2003), prodynorphin (Stogmann, Zimprich et al. 2002; Gambardella, Manna et al. 2003) and members of the Interleukin 1 pathway (Kanemoto, Kawasaki et al. 2000),

2) *Latent period*: There may be a delay, of weeks to many years, between the IPI and the emergence of recurrent seizures. The processes occuring during this latent period remain to be fully characterized. Possibly interictal activity, which may be limited to the hippocampus, is generated before recurrent seizures that propagate to extra-hippocampal sites. Such activity could induce further cell death and so contribute to a progressive evolution of the sclerosis, (Saukkonen, Kalviainen et al. 1994; Mathern, Pretorius et al. 1995; Mathern, Pretorius et al. 1995; Lombardo, Kuzniecky et al. 1996; Pitkanen, Tuunanen et al. 1998). Other processes that presumably occur during this period include the formation of novel connections, formation and

evolution of populations of activated glial cells, the generation of new neurons perhaps in sites outside the dentate and changes in inhibitory synaptic function. These processes will be discussed in the following sections.

3) *Emergence of recurrent seizures*: After a delay, recurrent seizures may last for several tens of seconds. They are initiated in the hippocampal formation and propagate to extra-hippocampal sites. Initially seizures may be controlled with paharamcotherapy, but later they become pharmacoresistant (Engel, Williamson et al. 1997). Seizure frequency can vary from several per day to monthly and it may vary according to hormonal or emotional factors.

5.4.4 Animal models of MTLE

Physiological and molecular mechanisms underlying the development of temporal lobe epilepsies after an initial convulsion cannot be followed in experiments on humans. Studies on mechanisms can be performed in animal models of the syndrome which should mimic the human condition as closely as possible.

1) *Kindling models*: A spontaneously epileptic state is induced after several weeks of daily electrical stimulation of moderate intensity. This process was first described by Grahame Goddard (Goddard 1967; Goddard, McIntyre et al. 1969). The amygdala and hippocampus have especially low thresholds, but other brain structures are also susceptible to kindling (McNamara, Bonhaus et al. 1985; Racine, Mosher et al. 1988; Sutula, He et al. 1988). The kindling procedure does not mimic status epilepticus, but probably does engages similar plastic processes to those of epileptogenesis. Discharges generated during kindling are not equivalent to a status-epilepticus and it is difficult to identify a latent phase (McNamara 1984). A single prolonged stimulation of the perforant pathway (Olney, deGubareff et al. 1983; Sloviter 1983) may also generate spontaneous, persistent seizures (Lothman, Bertram et al. 1990; Bertram 1997; Mazarati, Wasterlain et al. 1998) associated with a severe sclerosis of the dentate gyrus (Sloviter 1983; Sloviter, Dean et al. 1996) and mossy fibre sprouting.

2) *Hyperthermia and hypoxia models*: Two models mimic conditions that induce seizures in infants. A heating protocol can induce prolonged febrile seizures in young rodents (Baram,

Gerth et al. 1997). Spontaneous seizures emerge in the following weeks (Dube, Richichi et al. 2006) but are not associated with a classical hippocampal sclerosis even though there is some cell loss (Toth, Yan et al. 1998; Bender, Dube et al. 2003; Dube, Yu et al. 2004). Changes are reported in the Ih current (Chen, Aradi et al. 2001; Santoro and Baram 2003) which indirectly affects GABAergic signalling (Chen, Baram et al. 1999; Chen, Ratzliff et al. 2003). The association between these changes and spontaneous seizure activity remains to be established (Baram, Eghbal-Ahmadi et al. 2002).

Neonatal hypoxia may be a precipitating factor for adult seizures (Bergamasco, Benna et al. 1984; Volpe 1994). Jensen and colleagues developed a model (Jensen, Applegate et al. 1991) in which a perinatal hypoxia of 15 min duration induced seizures in young rats (P7 to P15) but activities were not maintained and hippocampal sclerosis did not develop in adult animals.

3) *Neurotoxin injection*: Lesions that mimic hippocampal sclerosis are induced by focal or systemic injection of neurotoxic or convulsant substances. Cell death and gliosis is followed by the emergence of an epileptic phenotype after several weeks or months.

Kainic Acid (KA) is an agonist at a family of glutamatergic receptors. Systemic injection of KA generates a status-epilepticus and induces severe cell loss in the hippocampus, some cortical regions, lateral septum and amygdale, and mossy fibre sprouting (Ben-Ari, Tremblay et al. 1981; Olney, Collins et al. 1986). Spontaneous, recurrent seizures emerge after a latent phase of several weeks (Ben-Ari, Tremblay et al. 1981; Lothman and Collins 1981; Zaczek and Coyle 1982). Partial seizures are initiated in the hippocampal formation and rapidly generalize to frontal cortical areas.

Pilocarpine, a muscarinic receptor agonist, induces a similar epileptic phenotype to KA. Systemic injection induces a status-epilepticus (Cavalheiro 1995). A bilateral sclerosis is induced in the hippocampus and other limbic structures with a severe cell loss and a moderate gliosis (Honchar, Olney et al. 1983; Turski, Cavalheiro et al. 1983; Cavalheiro, Leite et al. 1991; Cavalheiro 1995). Mossy fibre sprouting occurs as does dispersion of the dentate structure (Mello, Cavalheiro et al. 1993). Recurrent seizures emerge after a latent period of 1-6 weeks. Seizures arise in either hippocampus, and become generalized to involve wide frontal regions over time (Leite, Bortolotto et al. 1990; Cavalheiro, Leite et al. 1991).

Intra hippocampal injection of tetanus or botulinum toxin has been used to create another animal model of temporal lobe epilepsy (Mellanby, George et al. 1977). These toxins inhibit transmitter release by proteolitic cleavage of the presynaptic protein synaptobrevin (Schiavo, Benfenati et al. 1992). While their injection does not induce a status-epilepticus, in the days

after injection epileptiform activity emerges in the hippocampus and evolves towards recurrent seizures which generalize (Hawkins and Mellanby 1987; Jefferys, Borck et al. 1995; Finnerty and Jefferys 2002). Cell loss is limited to CA1 region and does not always occur (Mellanby, George et al. 1977). The seizure state tends to be transient, expressed over a restricted period of several months. Presumably seizures do not induce further cell loss in this model, and it is suggested that adaptive changes in GABAergic circuits underly the cessation of spontaneous seizures (Whittington and Jefferys 1994).

5.4.5 Intrahippocampal injection of Kainic acid

In the first studies using Kainic acid to produce epileptic animals, Ben-Ari and colleagues, made focal intra-amygdaloid rather than systemic injections (Ben-Ari and Lagowska 1978; Ben-Ari, Lagowska et al. 1979). Focal injections produce a unilateral and spatially restricted cellular lesion (Magloczky and Freund 1993; Suzuki, Junier et al. 1995). This restricted cellular damage also permits separation of local and distant effects of both cell death and epileptiform activity.

The status epilepticus induced by focal KA injection lasts up to 24 hours (Ben-Ari 1985; Ben-Ari and Cossart 2000). During this phase pyknotic neurons appear in the hilus and the CA1 and CA3 regions exclusively in the injected hemisphere (Suzuki, Junier et al. 1995). Le Duigou showed that during status epilepticus, cellular activity was almost abolished near the injection site, and epileptiform discharges were generated at distant sites (Le Duigou, Wittner et al. 2005).

After one week, cell death is observed close to the injection site (Bouilleret, Ridoux et al. 1999). After 3-4 weeks pyramidal cells of the CA1 and CA3c regions of the injected hippocampus have largely disappeared (Riban, Bouilleret et al. 2002) and some specific types of interneurons are also lost (Magloczky and Freund 1993; Bouilleret, Loup et al. 2000). Over the same period, the dentate gyrus becomes enlarged, granule cells disperse (Suzuki, Junier et al. 1995; Bouilleret, Ridoux et al. 1999; Knuesel, Zuellig et al. 2001), and mossy fibres sprout to establish novel contacts in the subgranular molecular layer of the dentate gyrus and stratum oriens of ipsilateral hippocampus. Mossy fibre sprouting may sometimes even extend to the contalateral hippocampus (Bouilleret, Ridoux et al. 1999). Gliosis, as evident in an increased

number of GFAP positive cells, occurs over a similar time period in the dentate gyrus as well as in the CA3 and CA1 regions.

While morphological changes occur over a period from days to months after KA injection, physiological alterations detected by EEG traces evolve more slowly and with a delay. Up to 3-4 weeks only sporadic interictal events occur. They may evolve to short discharges but seem to be limited to the injected hippocampus and there is no behavioural correlate. In the chronic state after 4 weeks, EEG records show interictal and recurring seizure activity. Seizures are associated with immobilization or convulsive behaviours. Both the unilateral sclerosis and the recurrent seizures persist and, in this respect, the KA injection model is similar to the human MTLE syndrome (Magloczky and Freund 1993; Magloczky and Freund 1995).

5.4.6 Comparison of the different animal models

Comparison of different animal models for MTLE must consider both physiological and anatomical changes, including hippocampal sclerosis. All models except for kindling and tetanus toxin injection induce an initial status epilepticus. However, factors other than the status epilepticus may contribute to the emergence of a chronic epileptic syndrome. It is not easy to identify an equivalent of the latent period in the kindling model, where all discharges are induced by direct stimulation. The presence of a latent phase in an animal model may provide insights into the evolution of factors in the exacerbation of the lesion (Bragin, Engel et al. 1999; Bragin, Wilson et al. 2000; Riban, Bouilleret et al. 2002). The efficiency of the different models for induction of recurrent spontaneous seizures varies. Seizures induced by systemic KA and by Tetanus toxin may tend to disappear with time. Furthermore, focal injection of convulsants such as KA or pilocarpine clearly induces a unilateral sclerosis, whereas systemic injection tends to affect both hippocampi to a similar extent. In conclusion, consideration of all factors suggests that focal pilocarpine or KA injection produce a syndrome most similar to human MTLE.

5.5 Molecular Mechanisms of MTLE

While the sequence of anatomical and physiological changes associated with the emergence of mesial temporal lobe epilepsies are relatively clear, the molecular mechanisms remain to be clarified. Understanding at this level will be crucial, both to identify causal relations and eventually to develop new therapies. It seems important to establish for instance whether seizures cause cell death or whether a hippocampal sclerosis is crucial for the emergence of an epileptic brain. In animal models, can changes induced by convulsants be separated into pro-epileptic factors and homeostatic mechanisms that act to counter epileptogenesis? Does the synaptic reorganization induced by cell death promote aberrant discharge patterns or might it act to stabilize hippocampal excitability? Here, recent progress on understanding molecular factors and putative mechanisms for the genesis of the chronic epileptic phenotype will be reviewed.

5.5.1 Cell loss

The initial event during the evolution of hippocampal sclerosis is a massive, selective cell death. After a convulsant is injected, neurons die either by necrosis or by activation of apoptotic programmes both of which are triggered by a massive Ca^{2+} entry (Pollard, Charriaut-Marlangue et al. 1994; Fujikawa, Shinmei et al. 2000).

Oliva et al visualised morphological changes in dendrites of EGFP-Somatostatin positive O-LM interneurons during the early stages of cell death due to KA application (Oliva, Lam et al. 2002). Indeed intereneurones seem to be more sensitive to cell death induced by KA and pilocarpine and death ensues within hours (Bouilleret, Ridoux et al. 1999; Bouilleret, Loup et al. 2000; Dinocourt, Petanjek et al. 2003). Patterns of interneuron death are not uniform: interneurones of the hilus are most susceptible (Leranth and Ribak 1991; Obenaus, Esclapez et al. 1993; Sloviter, Dean et al. 1996; Buckmaster and Dudek 1997; Sloviter, Zappone et al. 2003) then CA1 interneurones while CA3 interneurones are resistant (Bouilleret, Loup et al. 2000; Cossart, Dinocourt et al. 2001; Kobayashi and Buckmaster 2003; Sloviter, Zappone et al. 2003).

Distinct subtypes of interneurons are differentially susceptible, with SOM-containing cells of the CA1 region being especially sensitive (de Lanerolle, Kim et al. 1989; Magloczky and Freund 1995; Buckmaster and Jongen-Relo 1999; Cossart, Dinocourt et al. 2001; Wittner, Magloczky et al. 2001; Dinocourt, Petanjek et al. 2003; Kobayashi and Buckmaster 2003). Parvalbumin-containing interneurones are differentially sensitive: basket cells survive while axo-axonic cells tend to die (Cossart, Dinocourt et al. 2001; Dinocourt, Petanjek et al. 2003). Patterns of death of Calretinin and Calbindin containing interneurons vary according to their location (Bouilleret, Ridoux et al. 1999; Bouilleret, Loup et al. 2000). The differential susceptibility of distinct types of interneurone may depend on changes in internal Ca^{2+} according to their expression of distinct KA (Cossart, Esclapez et al. 1998; Frerking, Malenka et al. 1998; Cossart, Epsztein et al. 2002) or Ca^{2+}-permeable AMPA receptors (Koh, Geiger et al. 1995; Leranth, Szeidemann et al. 1996).

Two different mechanisms with distinct kinetics induce pyramidal cell death after KA treatment: necrotic death occurs first due to excitotoxic processes initiated by an increase in intracellular Ca^{2+} (Choi, Maulucci-Gedde et al. 1987; Fujikawa, Shinmei et al. 2000) and activation of the apoptotic pathway induces death which occurs with a slower time course (Pollard, Charriaut-Marlangue et al. 1994). In the hilus and the CA3 region, KA or pilocarpine induce an almost complete death of pyramidal cells (Riban, Bouilleret et al. 2002). Pyramidal cell loss in the CA1 regions may reach 60% of the total, in the subiculum 20-30% (Knopp, Kivi et al. 2005) but granule cells of the dentate gyrus and CA2 pyramidal cells are preserved (Covolan, Ribeiro et al. 2000). KA is reported to induce a reduction in expression of the GluR2 subunit in CA3 and hilar pyramidal cells. AMPA receptors lacking this subunit are Ca^{2+} permeable (Pellegrini-Giampietro, Gorter et al. 1997) which may exacerbate susceptibility to necrotic or apoptotic processes. In contrast, reduction of the Ca-binding protein calbindin (Nagerl, Mody et al. 2000) or increased mGluR4 expression (Lie, Becker et al. 2000) may be an adaptive response.

Some studies have provided evidence for cell death contralateral to focal KA injection including a decreased expression of calbindin in the CA1 region, and changes in the peptides CCK and neuropeptide Y (Bouilleret, Loup et al. 2000; Arabadzisz, Antal et al. 2005). During hippocampal sclerosis, changes in expression have also been noted for molecules that induce or regulate cell death. Proteins including IL-1RA (receptor for Interleukin 1) or TNF may be upregulated in homeostatic fashion to aid neuronal survival (Liu, D'Amore et al. 1993; Bruce, Boling et al. 1996; Panegyres and Hughes 1998), while growth factors including GDNF and

aFGF may act to reduce seizure frequency and so enhance neuronal survival (Cuevas, Revilla et al. 1994; Martin, Miller et al. 1995; Cuevas and Gimenez-Gallego 1996).

5.5.2 Fibre sprouting

Death of post-synaptic target neurons can induce reactive sprouting of pre-synaptic axons and the establishment of novel synaptic contacts (Scheff, Benardo et al. 1977; Nadler, Perry et al. 1981; Frotscher and Zimmer 1983). Mossy fibre sprouting has been especially well studied since mossy fibre terminals have high levels of the metal zinc, which is detected by the Timm's stain. Axons of the dentate granule cells sprout following the loss of hilar cells. They occupy and form synapses in novel regions including the inner molecular layer of the dentate gyrus (Frotscher and Zimmer 1983; Sutula, He et al. 1988) and the CA3 stratum oriens. Sprouting is first detected at 5 days after KA injection, peaks at about 3 weeks and may persist up to 18 months after the lesion (Cavazos, Golarai et al. 1991; Cavazos, Golarai et al. 1992).
Novel synaptic terminals are formed with the spines of granule cells and with inhibitory interneurons including basket cells (Ribak and Peterson 1991; Buckmaster, Zhang et al. 2002; Cavazos, Zhang et al. 2003). Physiological studies have shown that these new connections are functional (Tauck and Nadler 1985; Wuarin and Dudek 1996; Lynch and Sutula 2000; Wuarin and Dudek 2001).
Axons of CA1 pyramidal cells also sprout into previously non-innervated regions after KA treatment. Axon collaterals extend to the CA1 stratum lacunosum-moleculare and radiatum where they presumably form new excitatory synapses with other CA1 pyramidal cells and also into the subiculum (Perez, Morin et al. 1996; Esclapez, Hirsch et al. 1999; Morin, Beaulieu et al. 1999; Cavazos, Jones et al. 2004). The establishment of recurrent connections in the dentate and CA1 regions (Deuchars and Thomson 1996) creates novel feedback mechanisms that may contribute to epileptiform behaviours (Smith and Dudek 2001; Smith and Dudek 2002; Sadewa, Sasongko et al. 2008).
Several molecules, including cytokines and growth factors, have been identified as stimulators of axonal sprouting and guidance factors. Brain derived neurotrophic factor (BDNF) and basic Fibroblast growth factor (bFGF) induce sprouting *in vitro* (Lowenstein and Arsenault 1996). The expression of both BDNF (Ernfors, Bengzon et al. 1991; Isackson, Huntsman et al. 1991; Zafra, Lindholm et al. 1992) and bFGF (Humpel, Lippoldt et al. 1993; Follesa, Wrathall et al.

1994; Simonato, Molteni et al. 1998) are upregulated in several different seizure models. The first discovered neuronal growth factor (NGF) is involved since its inhibition decreases axonal outgrowth (Holtzman and Lowenstein 1995; Van der Zee, Rashid et al. 1995). Gall and Isackson (1989) first described NGF upregulation in epilepsy, and this has been repeatedly confirmed (Zafra, Hengerer et al. 1990; Ballarin, Ernfors et al. 1991).

Evidence for a sprouting process for inhibitory axons is contradictory. An increase in GAD-positive terminals was detected in the dentate of rat epilepsy models (Houser 1992; Gruber, Greber et al. 1993) and in the subiculum of tissue from epilepsy patients (Arellano, Munoz et al. 2004), but other work found no consistent change (Wittner, Magloczky et al. 2001; Wittner, Eross et al. 2005). It is likely that inhibitory cell axonal sprouting differs between regions and between different types of interneurons.

5.5.3 Cellular excitability

Neuronal expression of both voltage-gated and receptor-operated channels is changed in animal models of epilepsy.

Three sodium channel subunits, Scn2a1, Scn8a and Scn1b are upregulated after pilocarpine treatment (Ellerkmann, Remy et al. 2003) and may contribute to neuronal hyperexcitability. In contrast the subunit Scn2a1 is reported to be downregulated in the sclerotic zones of tissue obtained from patients (Lombardo, Kuzniecky et al. 1996). An increase in expression of the Ca^{+}-channel subunit Cacna1c has been detected in activated astrocytes (Westenbroek, Bausch et al. 1998). Upregulation might be associated with an increased neuronal excitability, but existing evidence suggests that the Cacna1a subunit is rather downregulated following KA treatment (Vigues, Gastaldi et al. 1999).

A reduced expression or efficacy of K^{+} channel subunits would also have pro-epileptic consequences. Bernard and colleagues described changes in the Kcnd2 and Kcnb1 subunits as "acquired channelopathies" after pilocarpine treatment (Bernard, Anderson et al. 2004). Both a transcriptional down-regulation and a post-translational reduction in efficacy of dendritic conductances due to alterations in phosphorylation by ERK for Kcnd2 and PKC for Kcnb1 were detected (Bernard, Anderson et al. 2004; Misonou, Mohapatra et al. 2004).

In the kainate model, Shah and colleagues (Shah, Anderson et al. 2004) showed a down-regulation of HCN1 and 2, hyperpolarization-activated, cyclic nucleotide-gated channels

underlying the h-current which generates a depolarization when cells are hyperpolarized. Changes in the expression of these two subunits have also been noted in human tissue (Brewster, Bender et al. 2002).

These modifications may alter intrinsic neuronal properties so as to produce a hyperexcitable pro-epileptic phenotype as reported for subicular pyramidal cells after KA-treatment (Wellmer, Su et al. 2002).

Changes are also reported in the expression of molecules associated with chemical synaptic transmission. Glutamate receptor subunit expression is altered by treatment with KA or pilocarpine. GluR1 and GluR2/3 expression is upregulated both in human tissue and animal models (Babb, Mathern et al. 1996; Mathern, Pretorius et al. 1998). There is also evidence for altered phosphorylation or redux modulation of GluR subunits (Lieberman and Mody 1999; Sanchez, Wang et al. 2000; Rycroft and Gibb 2004).

The expression of the metabotropic receptors mGluR1 and 5 is reduced in pyramidal cells (Akbar, Rattray et al. 1996; Tang, Lee et al. 2001) of KA-treated animals. In contrast astrocytic expression of mGluR5 is increased (Ulas, Satou et al. 2000) and in human tissue mGluR 2, 3, 4 and 8 subunits are upregulated on astrocytes (Tang and Lee 2001).

Changes in gene expression or protein regulation can also affect ambient levels of extracelluar glutamate. Thus, the neuronal glutamate transporters EAAT3 and 1 are upregulated in granule cells and CA3 pyramidal cells while EAAT2 is downregulated in astrocytes of the CA1 region and hilus in human tissue (Mathern, Mendoza et al. 1999). In KA-treated mice the murine homologue of the transporter EAA1, GLAST, is upregulated in CA3 and hilus after status epilepticus (Nonaka, Kohmura et al. 1998), while EACC1 (homologue to EAAT3) and GLT1 (homologue to EAAT2) seem to be downregulated (Simantov, Crispino et al. 1999).

Changes in expression of GABA receptor subunits also occur in human tissue and animal models of epilepsy. Expression is often downregulated in sclerotic regions (Schwarzer, Tsunashima et al. 1997; Fritschy, Kiener et al. 1999; Bouilleret, Loup et al. 2000), but increases have been reported for the α1 and α2 subunits in temporal lobe epilepsy patients (Loup, Wieser et al. 2000). Interestingly the α5 subunit of GABA-A receptors is downregulated in CA1 pyramidal cells (Houser and Esclapez 1996) since this subunit is specific for extra-synaptic GABA receptors (Mody 2001; Semyanov, Walker et al. 2004). $GABA_B$ receptor subunits Gabbr1 and Gabbr2 are downregulated in the CA1 and CA3 areas of KA-treated animals (Straessle, Loup et al. 2003). Changes have also been described in molecules associated with GABA-A receptors including the structural proteins gephyrin (Kumar and Buckmaster 2006) and dystrophin (Knuesel, Zuellig et al. 2001).

5.5.4 Neurogenesis

The subgranular zone of the dentate gyrus is one of the two areas of rodent brain where adult neurogenesis is maintained (Altman and Das 1965; Kuhn, Dickinson-Anson et al. 1996). Progenitor cells of this area develop a granule cell morphology (Cameron, Woolley et al. 1993; Seki and Arai 1993). Seizures trigger proliferation of precursor cells of the sub-granular zone (Parent, Yu et al. 1997; Thom, Sisodiya et al. 2002; Crespel, Rigau et al. 2005). Parent and colleagues showed that pilocarpine treatment stimulates differentiation of these proliferating cells into young granule cells (Parent, Yu et al. 1997). This process may be related to granule cell dispersion. Newly differentiated neurons also migrate to CA3 where they form novel connections that may contribute to epileptogenesis (Scharfman, Goodman et al. 2000).

Neuronal proliferation in the dentate is induced by status epilepticus not only in a KA-treated hippocampus but also in the contralateral non-injected hippocampus even in the absence of cell death (Kralic, Ledergerber et al. 2005). On the contralateral side, the newly generated elements differentiate largely into dentate granule cells and to a lesser extent into astrocytes. In contrast most cells in the injected hippocampus are GFAP-positive suggesting they remain trapped as astrocytes. The effects of spontaneous recurrent seizures on cellular proliferation and differentiation are much smaller than those of convulsant injection.

Differential expression of several markers for neurogenesis and astrogliosis has been described:

The identity of cascades of signalling pathways that control cell proliferation and differentiation is still being clarified. Markers for proliferative cells (PCNA), for new born neurons (DCX and PSA-NCAM) and for newly generated glial cells (GFAP) have been examined in KA-treated animals (Ledergerber, Fritschy et al. 2006). The basic Fibroblast Growth Factor (bFGF) is upregulated in and around the proliferative zone following seizures (Humpel, Lippoldt et al. 1993; Bugra, Pollard et al. 1994; Ballabriga, Pozas et al. 1997; Gomez-Pinilla, Dao et al. 1997). *In vitro* studies suggest that bFGF may be involved in the differentiation of neural precursors towards a neuronal phenotype, rather than in cellular proliferation (Basilico and Moscatelli 1992). Further work is clearly needed on reciprocal interactions between seizures and the proliferation and differentiation of neuronal and glial progenitor cells.

5.5.5 Inflammatory response and glia activation

It has become increasingly clear that different types of glial cells contribute to the development of MTLE. Experimental and clinical studies have associated inflammatory processes and epileptogenesis (Billiau, Wouters et al. 2005; Vezzani and Granata 2005; Gorter, van Vliet et al. 2006; van Gassen, de Wit et al. 2008). A gene profiling study from Gorter and colleagues has described a significant activation of immune responses during the latent period before seizure emergence (Gorter, van Vliet et al. 2006).

Microglial cells are associated with brain immune responses and after seizures these cells are activated: they proliferate, their morphology and gene expression change (Niquet, Ben-Ari et al. 1994; Represa, Niquet et al. 1995). Microglia is also activated by infection and fever which are among the most frequent precipitating events for MTLE. Activated glial cells secrete molecules including cytokines, neurotoxic substances, chemokines, growth factors (Giulian 1993; Chao, Hu et al. 1995) which have rapid effects on neurones but also initiate structural and genetic changes occuring over a longer time scale. The complement system, part of the immune system, is activated in epileptic human tissue (Jamali, Bartolomei et al. 2006) and seems to be differentially expressed during different phases of epileptogenesis in animal models (Gorter, van Vliet et al. 2006; Aronica, Boer et al. 2007)

Astrocytes are also activated after convulsant injection in animal models. Although it is unclear whether cell death or electrical activity of the status epilepticus is the effective stimulus, they proliferate as well as they change their shape and gene expression. Astrocyte activation stimulates precursor cell production. There is evidence that neuronal precursors move towards an astrocytic phenotype at sclerotic sites (Ledergerber, Fritschy et al. 2006) even though astrocyte-like cells are a precursor element for newly generated neurones (Berninger, Costa et al. 2007). Astrocytes may aid granule cell migration in the dentate gyrus (Crespel, Coubes et al. 2002) and it is suggested that astrocyte proliferation after seizures serves to repopulate sclerotic regions (Borges, McDermott et al. 2006), but the maintained presence of a glial scar suggests the process remains incomplete (Crespel, Coubes et al. 2002).

Astrocyte activation also affects electrical properties. Sodium channel expression is increased, and events similar to action potentials can be generated (O'Connor, Sontheimer et al. 1998). Astrocytes become more sensitive to glutamate (Seifert, Schroder et al. 2002) and participate

in the inflammatory response by releasing NFkB in models of epilepsy (Lerner-Natoli, Montpied et al. 2000). Calcium imaging studies suggest that astrocytes may even generate slow, coupled oscillations in internal calcium and membrane potential (Wang, Lou et al. 2006; Jourdain, Bergersen et al. 2007; Winship, Plaa et al. 2007)

Changes in intracellular Calcium in astrocytes may liberate neuroactive molecules like glutamate (Bezzi, Carmignoto et al. 1998), interleukins and growth factors. Among them, bFGF, IL-2 and TNF-α may modulate cellular excitability or increase seizure susceptability by alternative pathways (Nistico and De Sarro 1991; Liu, D'Amore et al. 1993; De Sarro, Rotiroti et al. 1994; Probert, Akassoglou et al. 1995; Liu and Holmes 1997; Yuhas, Shulman et al. 1999). Other liberated growth factors, like aFGF and GDNF (Martin, Miller et al. 1995; Cuevas and Gimenez-Gallego 1996), may counteract these effects by decreasing seizure intensity and duration.

The timing and consequences of activation of diverse types of glial cell during the development of an epileptic brain remains a vital subject for further work.

5.5.6 Transcription activity and conclusion

Changes in gene expression are clearly involved in the proliferation and differentiation of new cells and modify the physiology of existing cells. Presumably they are orchestrated by cell-specific transcription factors activated sequentially during the process of epileptogenesis.

Early-response genes which are upregulated in the hippocampus during status epilepticus include c-fos, EGR-1 and EGR-2 (Ben-Ari 2001; Rakhade, Yao et al. 2005). Elliott and colleagues described changes in the basic helix-loop-helix (bHLH) transcription factors (Elliott, Khademi et al. 2001) while altered expression is also described for ICER (Porter, Lund et al. 2008), p53, MDM2 (Engel, Murphy et al. 2007), NFkB (Lubin, Ren et al. 2007) and REST (Spencer, Chandler et al. 2006). Upregulation of transcription factors is known to induce cascades of activities leading eventually to gene transcription, as exemplified by the induction of CREB and the pro-inflammatory gene COX-2 (Lee, Dziema et al. 2007). The role of these factors in the establishment of an epileptic brain remains to be assessed.

In a typical case of MTLE an initial insult acts as a precipitating event often inducing a status epilepticus. The complex cascade of events that follows is not completely understood. The effects of neuronal cell death and glial cell activation, the involvement of inflammatory and

immune responses, the modifications of synaptic connectivity and the expression of voltage-gated and receptor-operated channels combine but it remains difficult to separate causes and effects, pro-epileptic responses and anti-epileptic homeostatic mechanisms. A molecular or genetic approach offers a distinct way to characterize how a healthy brain evolves into a pathological network.

6 Genomic tools to approach the complexity of the brain

6.1 Gene Expression Analysis

Molecules of mRNA are the products of transcription of the genetic heritage of a cell. A quantitative and qualitative description of transcribed mRNA in a cell gives a vision of its state and the activity of its genes. As precursors of translated proteins, changes in mRNA molecules determine the future proteome. Changes in gene expression have classically been analyzed by Northern blot and RT-PCR and by more advanced methods including differential display and SAGE (serial analysis of gene expression). While these techniques have identified novel differentially expressed genes (Kozian and Kirschbaum 1999), they are restricted to a limited number of genes. Larger-scale studies on gene expression have been enabled by microarray technology which permits the parallel analysis of thousands of genes in a single assay. These techniques include oligonucleotide microarrays (Lockhart, Dong et al. 1996) and cDNA microarrays (Schena, Shalon et al. 1995; Schena, Shalon et al. 1996).

6.1.1 Microarrays and DNA-Chips

Micro-arrays consist of miniaturised hybridisation assays that permit analysis of thousands of nucleic acid fragments. Nucleic acid sequences, or “probes”, are immobilised on an array and fluorescently labelled “target” samples are hybridized against the array. Fluorescent signals related to the quantity of hybridized target are read by a detection system for analysis. cDNA microarrays consist of preformed nucleic acid sequences immobilized onto several thousand spots of several µm diameter on a glass wafer support. The cDNAs usually consist of clones

amplified by polymerase chain reaction (PCR) from a collection of transcripts. DNA-chips, in contrast, are produced by proprietary technologies (Gene Chip®, Affymetrix). Oligo-nucleotides of 20-25 base pairs are synthesized and spotted directly onto a solid support by photolithography (Watson, Mazumder et al. 1998).

For gene expression analysis with spotted arrays, mRNA samples are converted into labelled populations of target nucleic acids. These populations consist of complex collections of many thousands of fragments which are labelled with fluorescent dyes, such as the cyanines Cy3 and Cy5. The use of more than one dye permits comparison of two or more samples on the same microarray. In GeneChip® RNA molecules are directly labelled and hybridized on the Chips. With a high reproducibility across chips, single channel analysis may be the better choice. In either case, labelled fragments form duplexes with immobilized complementary probes. The number of duplexes reflects the number of each specific fragment in the target. Two or more differently labelled samples can be hybridised simultaneously, and from measurements on the distinct fluorescent signals the relative abundance of specific sequences can be determined.

6.2 Gene expression profile studies in brain

Neurons are among the most actively transcribing cells of an organism. Even while neuronal shape, connectivity, intercellular communication and electrical activity are richly diverse, it is thought that neuronal cell types should share physiological properties, morphology or molecular markers. The characterization of such families remains however incomplete. It is suggested that gene expression profiles may offer an unbiased framework for neuronal classification (Mott and Dingledine 2003; Markram, Toledo-Rodriguez et al. 2004). The basic assumption is that the complete profile of genes transcribed by a cell underlies the highly specialized phenotype while in a neuron defines its physiological properties. During the transition to disease states, such as epilepsy, changes in gene profile seem likely to accompany pathological alterations to the normal features of a neuronal cell type. Thus gene expression profile studies have been used to answer question on both physiological and pathological conditions. The complexity of the brain makes such work both interesting and challenging.

6.2.1 Gene expression profile analysis and brain.

Most genomic approaches to the brain have examined specific regions (Sandberg, Yasuda et al. 2000; Zhao, Lein et al. 2001; Zirlinger and Anderson 2003) where tissue heterogeneity may average important signals from different or minority cell types. A better comprehension of neuronal taxonomy from gene expression profile may be achieved by first separating functionally distinct cell types. There are technical difficulties with this approach: cells of interest may constitute a small minority of the total or may share features with cells from different subclasses making recognition complex. Gene expression profiles of single cells have often been compared to electrophysiological features (Monyer and Markram 2004; Yano, Subkhankulova et al. 2006). Such approaches based on genetic material from a single cell have been used for some time (Eberwine, Yeh et al. 1992), but technical problems persist. A single cell yields small amounts of mRNA and one may still ask whether sufficient material can be reliably obtained from a single cell. Nevertheless, following such an approach, Kamme and colleagues have found that interneurons and pyramidal cells of the CA1 region of the hippocampus express specific subsets of different genes (Kamme, Salunga et al. 2003). Paradoxically, they also revealed differences in gene profile within the putatively homogenous pyramidal cell population.

Technical advances aid such work. Laser capture microdissection (Emmert-Buck, Bonner et al. 1996) permits RNA to be obtained from small groups of single cells and methods for PCR-based amplification of small quantities of RNA improve continuously (Eberwine, Yeh et al. 1992; Luo, Salunga et al. 1999). Specific subsets of neurons can now be recognized in tissue from transgenic animals made by fusing fluorescent proteins with molecules specific to a given cell type (Feng, Mellor et al. 2000; Oliva, Jiang et al. 2000; Chattopadhyaya, Di Cristo et al. 2004; Lopez-Bendito, Sturgess et al. 2004). Application of cell sorting techniques such as Fluorescent activated cell sorting (FACS) or Laser capture microdissection has permitted the analysis of gene expression profiles of isolated groups of homogeneous cells (Arlotta, Molyneaux et al. 2005; Sugino, Hempel et al. 2006). Gustincich and colleagues used such a transgenic animal to examine gene expression in catecholaminergic neurons of the retina, a retinal cell type (Gustincich, Contini et al. 2004). Sugino and colleagues, exploited several transgenic mice to compare gene expression in twelve different inhibitory and excitatory cell types from different brain regions (Sugino, Hempel et al. 2006).

In conclusion, mcroarray analysis of gene expression is becoming an increasingly useful tool to examine cellular heterogeneity in the brain as better techniques are applied to the separation of functional neuronal families.

6.2.2 Gene expression profile analysis in epilepsy.

Microarray technology has also been used to explore modifications in gene expression during changes and pathologies of the brain such as development (Geschwind, Ou et al. 2001; Mody, Cao et al. 2001) ischemia (Matzilevich, Rall et al. 2002) and aging (Lee, Weindruch et al. 2000; Jiang, Tsien et al. 2001) as well as disorders including Alzheimer's disease (Ginsberg, Hemby et al. 2000), multiple sclerosis (Whitney, Becker et al. 1999; Lock, Hermans et al. 2002) and schizophrenia (Mirnics, Middleton et al. 2000; Hakak, Walker et al. 2001).
Characterization of gene expression in epileptic tissue obtained from patients or from animal models of epilepsy may suggest novel therapeutic targets. In one early study, gene expression in sclerotic human hippocampus obtained after operations on pharmacoresistant patients was compared with that in control or lesioned hippocampi (Becker, Chen et al. 2002). They found that 21 genes were differentially regulated. A closed examination of a subset of these revealed that two (ataxin-3 and glial fibrillary acid protein: GFAP) were upregulated while one (calmodulin) was down regulated. Differentially regulated genes were classed as neuronal- or glial- specific, or as for calmodulin, related to a structural modification rather than to a change in the expression of a specific cell type. Jamali and colleagues made expression profile analysis on genes expressed in the entorhinal cortex of epileptic patients (Jamali, Bartolomei et al. 2006). They linked six genes to human MTLE: a serotonin receptor (HTR2A), a neuropeptide Y receptor type 1 (NPY1R), a protein (FHL2) associating with the KCNE1 (minK) potassium channel subunit and with presenilin-2 and three immune system-related proteins (C3, HLA-DR-gamma and CD99).
In contrast to work on tissues obtained from epileptic patients, animal models offer the possibility to follow changes in gene expression at several time points during epileptogenesis. These works demonstrate immediate genetic effects of several precipitating factors. Thus, the pro-epileptic effects of traumatic brain injury on hippocampal gene expression has been examined at 1 hr, 4-8 hrs and 1 day after the damage (Matzilevich, Rall et al. 2002; Long, Zou et al. 2003). Matzilevich and colleagues found that about 6% of 8.800 identified transcripts

were differentially expressed. These transcripts were involved in oxidative stress, metabolism, inflammation, structure and cellular signaling. Long and coworkers found that the expression of 253 genes was altered: 106 increased, 147 decreased. Most up-regulated genes were involved in cell homeostasis and calcium signaling, downregulated genes coded for mitochondrial enzymes, metabolism, and structural proteins, while genes coding for proteins involved in inflammatory reactions were both up and down regulated. Comparison of the effects of KA treatment on gene expression in parietal cortex on the day of injection and one day later (Tang, Lu et al. 2002) revealed 186 differentially expressed genes mostly involved in inflammation.

Distinct changes in genetic profile occur during the latent phase in the dentate gyrus of rat 14 days after treatment (Elliott, Khademi et al. 2001). Lukasiuk, Kontula and Pitkanen used amygdala kindling in the rat and analysed the effects in microarray analysis of hippocampal and temporal lobe tissue at delays of 1, 4 and 14 days. Pooling mRNA from both ipsi-lateral and contralateral hippocampi provided evidence for a complex network of gene expression with changes specific to the different time points (Lukasiuk, Kontula et al. 2003). They identified 282 genes whose expression changed during epileptogenesis: 87 hippocampal and 207 temporal lobe transcripts. 13 genes were common to both structures, but only four genes (all expressed sequence tags) changed in the same direction at the same time in both regions.

Similar time points were combined in a hippocampal kindling model by Gorter and coworkers with a regional analysis that compared changes in CA3, the entorhinal cortex and the cerebellum (Gorter, van Vliet et al. 2006). Gene expression changed even in the unstimulated cerebellum. The largest changes occurred for genes associated with immune responses, such as cytokines, complement factors and interleukins, and these changes were maintained for several months after stimulation. Genes associated with synaptic transmission, including the GABA-A receptor subunits α5 and δ, tended to be downregulated during both the acute and latent phase.

These studies led to the identification of several epilepsy candidate genes, and had great importance in giving more insights in the complex networks of events that lead from a first injury to the establishment of an epileptic brain.

Methods and Results

- ***Different patterns of gene expression in Somatostatin-containing interneurons and pyramidal cells of the hippocampus***

Different patterns of gene expression in Somatostatin-containing interneurons and pyramidal cells of the hippocampus

In preparation

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Introduction

Hippocampal neurons can be broadly divided into pyramidal cells and interneurons. Pyramidal cells liberate glutamate to excite post-synaptic neurons while interneurons release GABA which inhibits principal cells and other inhibitory cells. Even though GABAergic interneurons form a minority of about 10% of hippocampal neurons, they are diverse in terms of their anatomy, their expression of neuropeptide co-transmitters and Ca-binding proteins as well as in neurophysiological properties (Ramon y Cajal 1893; Freund and Buzsaki 1996).

Attempts made to classify interneurons according to these criteria (Freund and Buzsaki 1996; Parra, Gulyas et al. 1998) have been only partially satisfactory (Parra, Gulyas et al. 1998; McBain and Fisahn 2001). It remains a challenge to find a classification scheme that encompasses anatomical, physiological, pharmacological, developmental and phylogenetic aspects of the interneuron phenotype in the face of novel molecular data. A promising approach may involve a systematic analysis of the expression of large numbers of molecules. Recent work has used techniques including RT PCR (Toledo-Rodriguez, Goodman et al. 2005) and gene profile expression derived from microarray systems (Sugino, Hempel et al. 2006) to explore the molecular composition of distinct groups of GABAergic cells.

Such molecular approaches to interneuron classification may be usefully combined with the recent development of transgenic techniques for identification of subsets of interneurons. In these animals, enhanced green fluorescent protein (EGFP) is coupled to a promoter that controls the expression of a specific peptide or calcium binding protein (Monyer and Markram 2004). Oliva *et al.* (2000) have used this technique to generate transgenic mice that express EGFP under the control of the regulatory sequence of the gene coding for the Glutamate Decarboxylase 1 protein (67 KDa, *Gad1* or *Gad67*). EGFP was found, in one transgenic mouse strain, to be expressed in hippocampal and neocortical interneurons containing Somatostatin. This strain has been named GIN for GFP-expressing Inhibitory Neurons. These GFP-expressing cells seem not to express (Oliva et al, 2001) other markers such as Calbindin (CB) and Neuropeptide Y (NPY) that are present in some SOM-expressing hippocampal interneurons (Kohler, Eriksson et al. 1987; Toth and Freund 1992). They did not express parvalbumin (PV) or calretinin (CR), but systematically expressed the "a" spliced form of the metabotropic glutamate receptor 1 (mGluR1a, Oliva et al. 2000).

The identification of fluorescent EGFP-positive cells of GIN mice has facilitated anatomical and physiological studies on this subset of GABAergic cells. The axon of nearly all EGFP positive cells with somata in *stratum oriens* of the CA1 region projects to *stratum lacunosum-moleculare* (O-LM; Oliva *et al.* 2000). Multiple physiological studies have also been made on O-LM interneurons both before and after the emergence of the GIN mouse strain (Lacaille, Mueller et al. 1987; Lacaille and Williams 1990; McBain, DiChiara et al. 1994; Maccaferri and McBain 1996; Maccaferri, Roberts et al. 2000; Maccaferri and Lacaille 2003; Maccaferri 2005).

In this study, I used microarray techniques to compare gene expression of EGFP+ fluorescent interneurons from the GIN mouse strain and non-fluorescent CA1 pyramidal cells. These cell types were sorted on the basis of their fluorescence after dissection with laser capture microscopy (Oliva, Jiang et al. 2000). This work identified 443 differentially expressed genes: 260 of them were more highly expressed by interneurons and 183 genes were expressed at higher levels in pyramidal cells. The differentially expressed genes included several proteins involved in tramission of nerve impulse or modulation of synaptic activity, as well as 37 transcription factors or genes associated with transcription regulation which displayed distinct expression patterns.

Materials and Methods

All experiments were carried out in accordance with the European Community Council Directive of 24 November 1986 (86/609EEC) and were approved by local authority veterinary service.

Dissociation of hippocampal neurons

Experiments were performed on wild-type FVB mice and GIN mice, aged P15-P20 (GIN mice: Jackson Laboratories, Maine, USA; (Oliva AA Jr 2000). Animals were decapitated after anaesthesia induced by intraperitoneal injection of urethane (2 g/Kg body weight) and both hippocampi were dissected.

Several different procedures were tested to optimise the stability and quantity of RNA that could be isolated from GFP-positive interneurons and pyramidal cells of the hippocampus. The first procedure used a fluorescence activated cell sorter to sort fluorescent interneurones from pyramidal cells. Hippocampi were placed in ice-cold phosphate buffer solution (PBS) and cut into small pieces (~2x2 mm) with a scalpel blade, removing white matter as far as possible to facilitate cell dissociation. These pieces were then put in a Falcon tube containing 5 ml of cold EBSS (Earle's Balanced Salt Solution: 10X EBSS, Sigma, St Louis, MO, USA; 7.5% $NaHCO_3$; 1M HEPES, Sigma, St Louis, MO, USA; 0,35g/ml of Glucose; pH adjusted to 7.4 with 1N HCl). This solution was briefly washed with 5 ml of a Digestion Solution (137 mM NaCl, 5mM KCl, 7 mM, Na_2HPO_4, 25 mM HEPES, 4.2 mM $NaHCO_3$, 200 mM Kynurenic Acid, pH adjusted to 7.4). It was then replaced by 5 ml of the same solution containing 20 U/ml papain (Worthington Biochemical Co., Freehold, NJ). Papain was pre-activated by incubation at 37°C for 30 min in the presence of 1 mM L-cysteine and 0.5 mM EDTA. After adding activated papain, 250 µl DNAseI was added to the digestion solution and the tube was gently agitated at 37°C for 20 min. The digestion medium was then removed and the contents washed briefly in EBSS. An additional wash (5 min at 4°C) was then performed with 5ml of EBSS containing 500 µl of 1% Ovomucoid Inhibitor (Worthington Biochemical Co, Freehold, NJ) and 1% BSA (Sigma, St Louis, MO, USA). This inhibitor was then removed, the tissue was briefly washed in EBSS before treating the tissue again with 750 µl of dissection buffer and 250 µl of DNAse in EBSS. Hippocampi were mechanical triturated with fire-polished glass pasteur pipettes in this solution before centrifugation at 1000 rpm for 5

min. Pelletted cells were then resuspended in 2 ml of extracellular solution or RNAlater (Qiagen, Chatsworth, CA, USA).

Fluorescence Activated Cell Sorting

Fluorescence Activated Cell Sorting was done in collaboration with Dr. Myrza Suljagic using a FACSCalibur System (BD Biosciences, Franklin Lakes, NJ USA) kindly provided by Prof. Oscar Burrone at the Centre for Genetic Engineering and Biotechnology in Trieste. Resuspended cells were diluted with PB and the solution was passed through the machine. Fluorescence acquisition and data analysis were performed with CellQuest Pro Software (BD Biosciences, Franklin Lakes, NJ USA). Sorted cells were collected in 50 ml Falcon Tubes.

Laser Capture Microdissection

As an alternative approach, we used laser capture microdissection to separate EGFP+ interneurons and CA1 pyramidal cells according to C. Vlachouli *et al*; manuscript in preparation. For these experiments, brains were dissected and incubated in 1X Zinc Fix (BD Biosciences, Franklin Lakes, NJ USA) in H_2O treated with Diethyl Pyrocarbonate (DEPC, Sigma, St Louis, MO, USA) solution for 6 hours. After fixation, brains were exposed overnight to a 1X Zinc Fix + 30% sucrose solution. They were then included in section medium Neg-50 (Richard Allan scientific, Kalamazoo, MI, USA) and placed on an isopentane layer (Sigma, St Louis, MO, USA) that had been frozen in liquid nitrogen. Blocks of tissue were placed in a freezing cryostat (Microm International, Walldorf, Germany) and maintained at -21°C for 30 min. Frontal sections of whole brain were then cut at a thickness of 16 μm and transferred to Superfrost Plus glass slides (Menzel-Glaser, Menzel GmbH & co KG, Braunschweig, Germany). EGFP-positive interneurons cells were identified in unstained tissue using a Zeiss P.A.L.M. LCM microscope (Carl Zeiss Inc., Germany). Sections were air dried for 2 min and fluorescent cells were microdissected, collected in adhesive caps (PALM Microlaser Technologies GmbH, Bernried, Germany) and their mRNA was rapidly extracted.

Pyramidal cells were collected using similar procedures in experiments on FVB wild type mice, aged P15-P20. Pyramidal cell bodies were recognised by applying a modified Nissl stain protocol to coronal sections. Cells of the pyramidal layer were identified on dry sections, microdissected, collected and mRNA was rapidly extracted.

Modified Nissl Staining

A modified rapid Nissl staining was needed to reduce the possibility that sections dried during the time between cryostat cutting and use of the laser capture microdissector (C.Vlachouli, personal comunication). Slices on glass slides were washed for 30sec in PBS 1X and stained for 10 min in a Cresyl Violet solution (0.5X Cresyl Violet, 1% Acetic Acid, 0.04X Sodium Acetate in nuclease-free H_2O). They were then passed through PBS, 70% EtOH, and 95% EtOH for 30 s in each solution. Laser micro-dissection was then performed.

RNA extraction and probe synthesis

mRNA from EGFP-positive interneurons and pyramidal cells was extracted, isolated, purified and amplified with the μMACS SuperAmp kit (Miltenyi Biotec, Bergisch Gladbach, Germany) according to manufacturer's protocol (C. Vlachouli *et al*.; manuscript in preparation). GlobalPCR product was purified with the High Pure PCR Product Purification Kit (Roche diagnostics GmbH, Mannheim, Germany) and the DNA concentration of samples was measured with ND-1000 spectrophotometer (Nanodrop technologies, Wilmington, DE, USA). For hybridization on two microarray slides (SISSA1/SISSA2), 350 ngm of globalPCR were labelled with μMACS SuperAmp kit with added Klenow Fragment (20 units, Fermentas Inc., Glen Burnie, MD, USA) and 25nmol cy3-dCTP (GE Healthcare, UK) according to manufacturer's protocol. When labelled, the probe was purified with Illustra CyScribe GFX Purification kit (GE Healthcare, UK). Dye incorporation and DNA concentration were measured with a ND-1000 spectrophotometer.

For total hippocampus hybridizations, animals were decapitated and tissue removed into ice-cold PBS 1X in DEPC-treated H_2O. Hippocampi were dissected in RNAse free conditions and placed in Eppendorf containing 1 ml TRIzol (Invitrogen, Carlsbad, CA, USA). Total RNA

was isolated according to the manufacturers instructions. Samples were treated to avoid genomic contamination with 2 units of RNAse-free DNAse (2 units/µl; Ambion, Austin, TX USA) for 15 min at 37°C. Total RNA was further purified with RNeasy Mini Kit (Qiagen, Chatsworth, CA, USA). The quality of purified RNA quality was assessed using an Agilent 2001 Bioanalyzer (Agilent, Palo Alto, CA, USA) and quantified with a ND-1000 spectrophotometer (Nanodrop technologies, Wilmington, DE, USA). In hybridization experiments, 10 µg of purified RNA were used.

Standard RNA processing for microarray experiments

For hybridization on two microarray slides (SISSA1/SISSA2), 10 µg of Universal mouse reference RNA (Stratagene, La Jolla, CA, USA) was mixed with 5 µl of Random Primers (Concentration, Manufacturer) and 2 µl of smart T7-24 primer.

After 5 min at 70°C, 4 µl of 5X First Strand Buffer, 2 µl of DTT (both reagents from Invitrogen, Carlsbad, CA, USA), 2 µl of amino allyl dUTP-dNTPs, 1 µl of SuperScript II (Invitrogen, Carlsbad, CA, USA) and 0.5 µl of RNAse Out (Invitrogen, Carlsbad, CA, USA) were added to this pre-mix. The reaction mix was incubated for 2 hours at 37°C and for 5 min at 70°C to inactivate the enzyme. After adding 1 µl of 0.5M EDTA pH 8.0 and 10 µl 1M NaOH, the reaction was performed at 70°C for 10 min before adding 20 µl of 1M HEPES. The standard probe was precipitated at 4°C for 30 min by adding 3M NaOAc to a final concentration of 0.3M, 1 µl of Linear Acrylamide (Ambion, Austin, TX, USA), 150 µl of Nuclease Free H_2O and 150 µl of Isopropanol. Samples were centrifuged for 30 min at 15000xg, isopropanol was removed and pellets washed with 70% EtOH. They were re-suspended in 4.5 µl of Nuclease Free H_2O and 4.5 µl of 0.1M $NaHCO_3$ and incubated for 15 min at RT. Cy5 dye (GE Healthcare, UK) in 2 µl of DMSO was then added and coupling was done overnight at RT. The coupling reaction was quenched with 4.5 µl of 4M hydroxyamine incubated at RT in the dark for 15 min before adding 35 µl of 100mM NaOAc pH 5.2. The labelled probe was purified with PCR purification kit (Qiagen, Chatsworth, CA, USA). Dye incorporation and DNA concentration were measured with an ND-1000 spectrophotometer.

Microarray hybridization

Before hybridization, SISSA1/SISSA2 slides were incubated for 1 hr at 55°C in 0.2X SSC (Ambion, Austin, TX USA) buffer filtered through a 0.22 μm filter, washed in distilled water and centrifuged at 2000 rpm for 5 min. For each slide pair, ~2 μg of probe were mixed with 2 μg of standard RNA probe together with 1.3 μl of 3.5 mg/ml Salmon Sperm (Sigma, St Louis, MO, USA), 1.3 μl of 1 mg/ml Cot-1 mouse (Invitrogen, Carlsbad, CA, USA), 6.6 μl of PolyA and 6.6 μl of 11.8 mh/ml tRNA (Sigma, St Louis, MO, USA). Sample volume was brought to 150 μl with distilled H_2O, before adding 150 μl of 2X formamide-based hybridization buffer (Genisphere, Hatsfield, PA, USA) pre-heated to 65°C for 10 min. Slides were mounted on a GeneMachines Hyb4 Microarray Station (Genomic Solutions, MI, USA) and after pre-heating to 80°C for 10 min. 150 μl of the sample was pipetted onto each slide. Hybridization was achieved with the sequence: 65°C for 2 hr, 55°C for 2 hr and 44°C for 12 hr. Slides were washed 5 times with 2X SSC + 0.2 SDS at 65°C, 5 times with 2X SSC at 55°C, and 5 times with 0.2 SSC at 42°C. Each wash included 10s of flowing solution, and 30s at holding temperature. Before scanning, slides were centrifuged at 2000 rpm for 10 min in the dark.

Analysis of expression profile data

Slides were scanned with a GenePix Personal 4100A microarray scanner (Molecular Devices Corporation, CA, USA). Pre-processing, including slide reading and intra- and inter-array normalization, was done independently for each group. Loading, normalization and statistical analysis were done with the LIMMA package from BioConductor or statistical computing in the R programming environment (Gautier L 2004). Normalization within arrays was done with the function “normalizeWithinArrays” based on the LOWESS algorithm: “normalizeWithinArrays(RG,method="loess",bc.method="normexp",offset=50)”.
Normalization between arrays was done with the function “normalizeBetweenArrays” based on the quantile method: “normalizeBetweenArrays(MA,method="quantile")”.
After loading and normalization, all signals were merged before statistical analysis. Our hybridization design permitted two distinct types of analysis: a) to compare single cell or tissue RNA levels to a control (universal mouse RNA): similar to the ’single-channel

hybridization'; b) to compare RNA expression levels between two different cell types or tissues, using the same reference (universal mouse RNA) for both hybridizations. All statistical analyses were done using the eBayes function of the LIMMA package. Filters used are the widely accepted: fold change ≤ log2 (-1) or fold change ≥ log2 (1) (corresponding to a ± 2 fold change on a linear scale) and corrected p-value ≤ 0.05.

Heatmaps were generated by submitting gene lists to the MultiExperiment Viewer program (Institute for Genomic Research, Rockville, MD, USA; www.tigr.org). Fold Changes for each experiment compared the sample to the Standard Reference and were then normalized to perform Hierarchical Clustering (Eisen, Spellman et al. 1998) based on Euclidean Distance. Gene Ontology analysis was performed using tools for annotating gene lists available at DAVID Bioinformatics Resources: http://david.abcc.ncifcrf.gov/ (Dennis, Sherman et al. 2003).

Results

Dissociation and FACS analysis of EGFP positive cells.

Data was obtained from mice of the GIN strain at P10-P15. The optimum cell dissociation protocol (see methods section) was based on papain rather than trypsin or pronase digestions. Microscopic observation of dissociated cells plated onto a poly-lysine coated petri suggested that up to 10^6 cells of healthy appearance based on a Trypan Blue vitality test (data not shown) could be obtained from the hippocampi of 4 animals.

We first attempted to separate fluorescent interneurons and non-fluorescent pyramidal cells with a fluorescence activated cell sorting machine (Herzenberg, Sweet et al. 1976), which analyzed the fluorescence and size of cells passed through it. Parameters measured were Forward Scattering (FSC-H) which reflects cell size, Side Scattering (SSC-H) related to cell shape and Green (FL1-H) or Red (FL2-H) fluorescence signals. The same analysis was performed on dissociated hippocampal cells from WT animals as a control.

We first used a resuspension media containing RNAlater (Qiagen, Chatsworth, CA, USA). However, analysis of FSC-H and SSC-H signals (Fig. 1A) suggested that while this solution preserved RNA, it also induced a significant cell shrinkage. Signals from tissue dissociated from WT or GIN animals were dispersed due to cell bodies and debris and a high percentage of data points were close to the lowest levels of detection. We then switched to a standard extracellular solution which permitted detection of two distinct cell populations in both EGFP and WT animals. These cell groups showed different levels of Forward Scattering, with more cells in a group with a lower FSC-H.

Cell shrinkage induced by RNAlater was associated with a loss of fluorescence evident in plots (Fig. 1B) of green fluorescence (FL1-H) against forward scattering (SSC-H)). It revealed an accumulation of cells at the lowest levels of fluorescence with detection thresholds set between 10^1 and 10^2 to exclude detection of cells from WT samples. Comparing specific and aspecific fluorescent signals by plotting red (FL2-H) against green fluorescence (FL1-H) revealed a specific green signal in a population of selected cells.

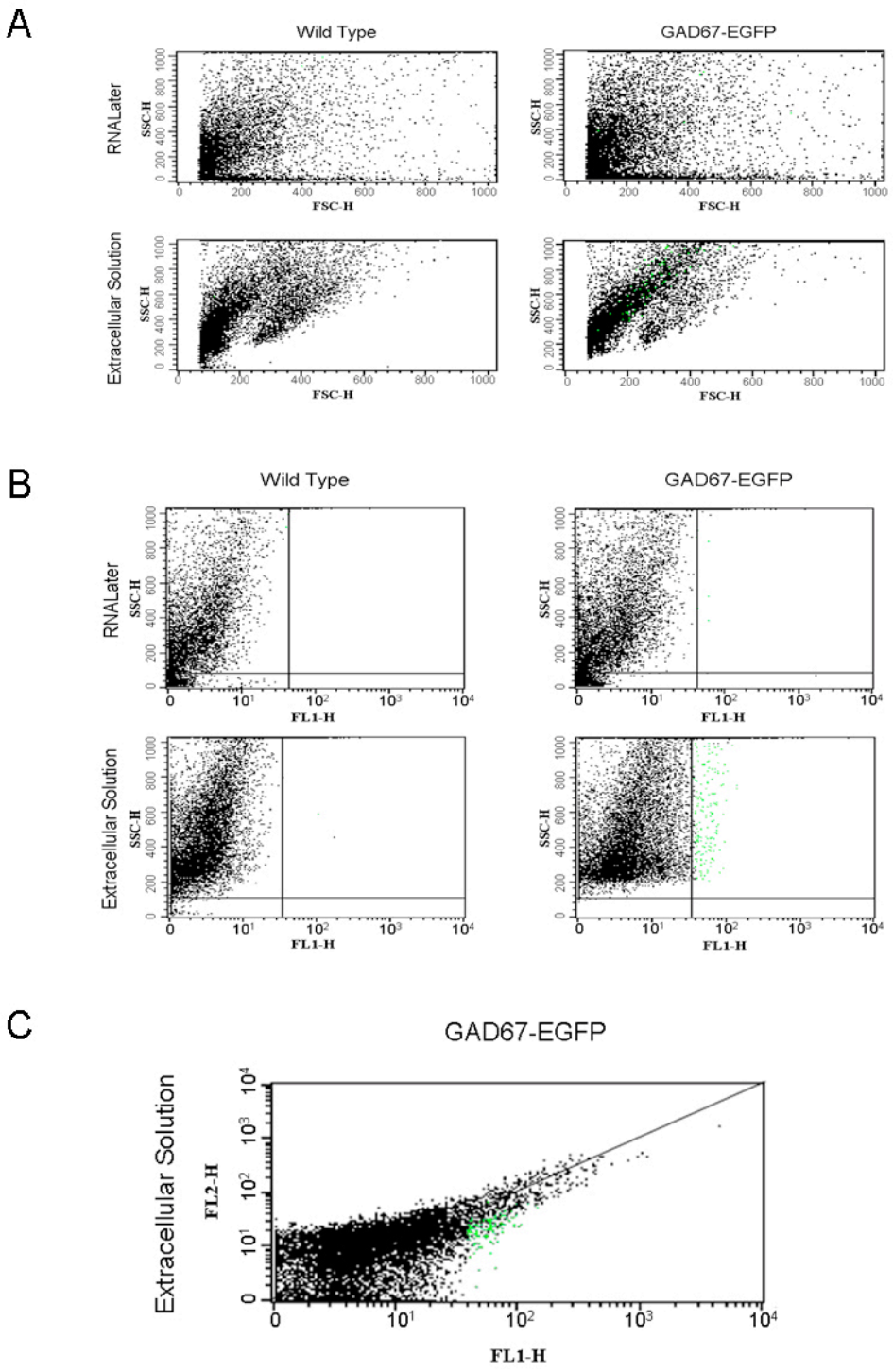


Fig.1: FACS ANALYSIS OF DISSOCIATED CELLS FROM WILD TYPE AND GIN MICE HIPPOCAMPI. Each panel compares Side Scattering (SSC) to Forward Scattering (FSC). 1A, there was signal dispersion from cells resuspended in RNAlater, while two populations, in terms of size and shape, were evident for cells resuspended in fresh extracellular solution. 1B, comparison of green fluorescence (FL1) with respect to SSC (1B) revealed no difference between wild type and GFP positive cells when RNAlater was used, and the signal accumulation near threshold levels is suggestive of a large cellular shrinkage. Cells from GIN and WT mice resuspended in extracellular solution showed different levels of fluorescence, permitting isolation of up to 10^4 cells with fluorescence higher than a set threshold (1B). Isolated cells are shown as green spots in all graphs. The specific fluorescence is evident in comparisons of FL1 and FL2 (1C).

Using this threshold, 0.5 - $1*10^4$ cells could be sorted from a suspension of about 10^6 dissociated cells derived from the hippocampi of two GIN mice. This represents 0.9 - 1.2 % of the number of cells analyzed. It is consistent with estimates that EGFP positive interneurons of GIN mice account for ~1% of hippocampal neurons (Oliva et al, 2000).
All fluorescent cells fell into the population of smaller cells based on FSC-H values and most of them showed high SSC-H values. However, isolated cells were collected from the sorter in a volume of ~50 ml of PBS which was too large for further steps towards gene profiling. We therefore searched for an alternative method to distinguish between EGFP-positive interneurons and pyramidal cells.
We next used laser capture microscopy to collect mRNA from fluorescent interneurons and from pyramidal cells. In this technique, a laser beam precisely cuts small areas of tissue and focal laser pulses can then be used to catapult cut tissue into a collection tube (Emmert-Buck, Bonner et al. 1996).

Slice preparation.

GIN mice, aged P15-P20 were sacrificed, and their brains dissected in RNAse-free conditions. Brains included in cutting medium were then frozen in isopentane and cut at a cryostat in 16 μm thick slices. Due to the nature of the tissue, and given the lack of fixation (to preserve RNA integrity) slices were immediately moved under the microscope to perform Laser Capture Dissection. In order to identify the pyramidal layer and collect pyramidal cells slices were stained with Cresyl Violet before laser capture. Nissl staining protocol was modified to be faster in order to avoid drying of slices and RNA degradation..

Laser Capture Dissection.

Cells of tissue derived from GIN animals were selected on the basis of their fluorescence and the location of their soma in the *stratum oriens* of the CA1 region. In each experiment ~300 EGFP positive cells were collected from the sections. While axonal projection patterns could not be determined, most of these fluorescent cells probably corresponded to O-LM interneurons. For comparison, about 300 pyramidal cells were dissected from the *stratum pyramidale* of CA1 and CA3 regions of tissue from same animals.

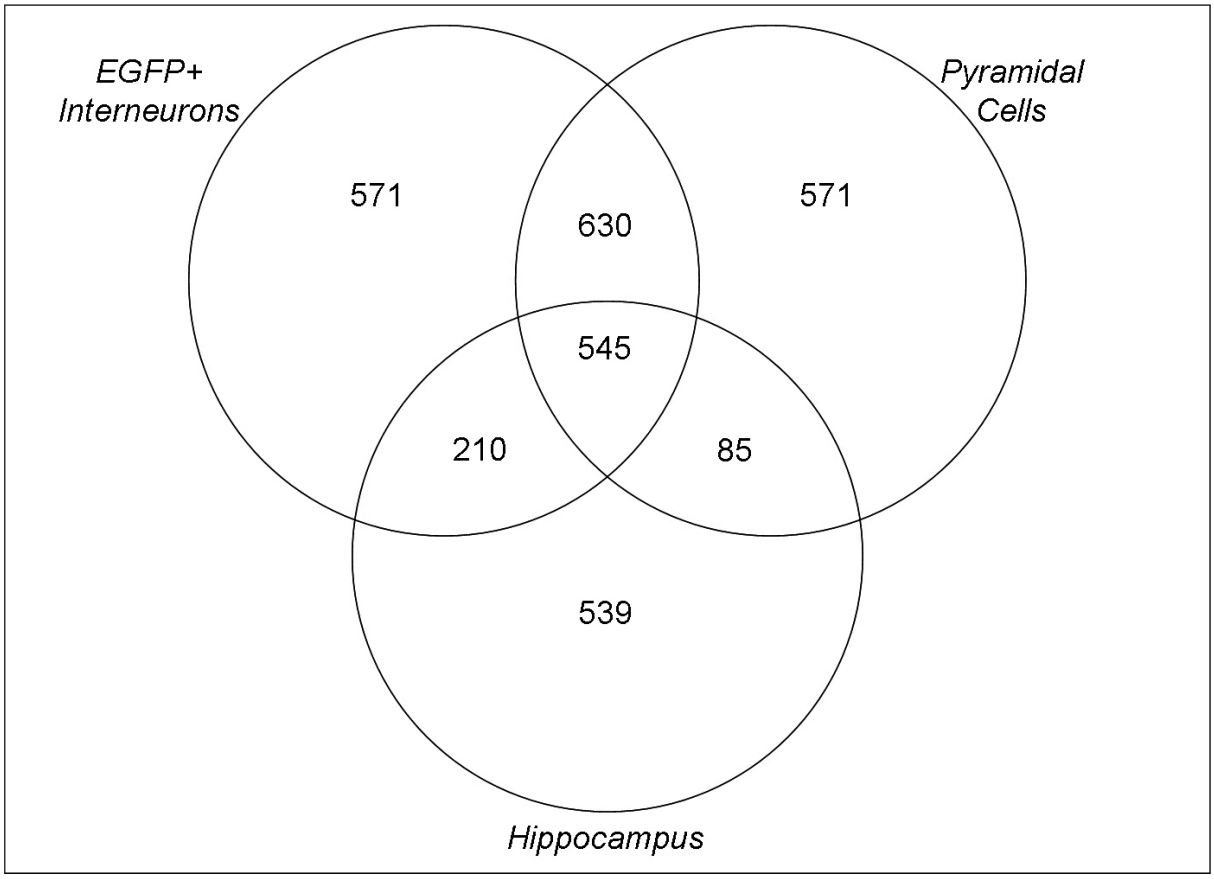


Fig.2: STATISTICAL ANALYSIS OF DIFFERENTIALLY EXPRESSED PROBES. Three distinct microarray hybridizations were done on EGFP+ Interneurons, Pyramidal Cells and total Hippocampus. Each sample was hybridized against a reference RNA. Statistical analysis identified transcripts differentially expressed between the single sample and the reference RNA. In the circles are reported the numbers of transcripts passing the statistical analysis for sample type. In the intersected areas the number of transcripts shared between the different analyses.

RNA extraction and hybridization.

Samples from these cells were processed for mRNA extraction and amplification with μMACS SuperAmp kit (Miltenyi Biotec, Bergisch Gladbach, Germany) which uses magnetic beads to specifically isolate messenger RNA. This RNA was then amplified, labelled with fluorofores and hybridized on home-made microarrays. The same analysis was performed on total hippocampal mRNA extracted from isolated hippocampi of GIN animals. The arrays used were home-spotted with the FANTOM 2 collection of mouse transcripts (Okazaki, Furuno et al. 2002); (FANTOM international Consortium). We chose ~14 000 well characterized and non-redundant transcripts from ~60 000 transcripts in the collection. Genes

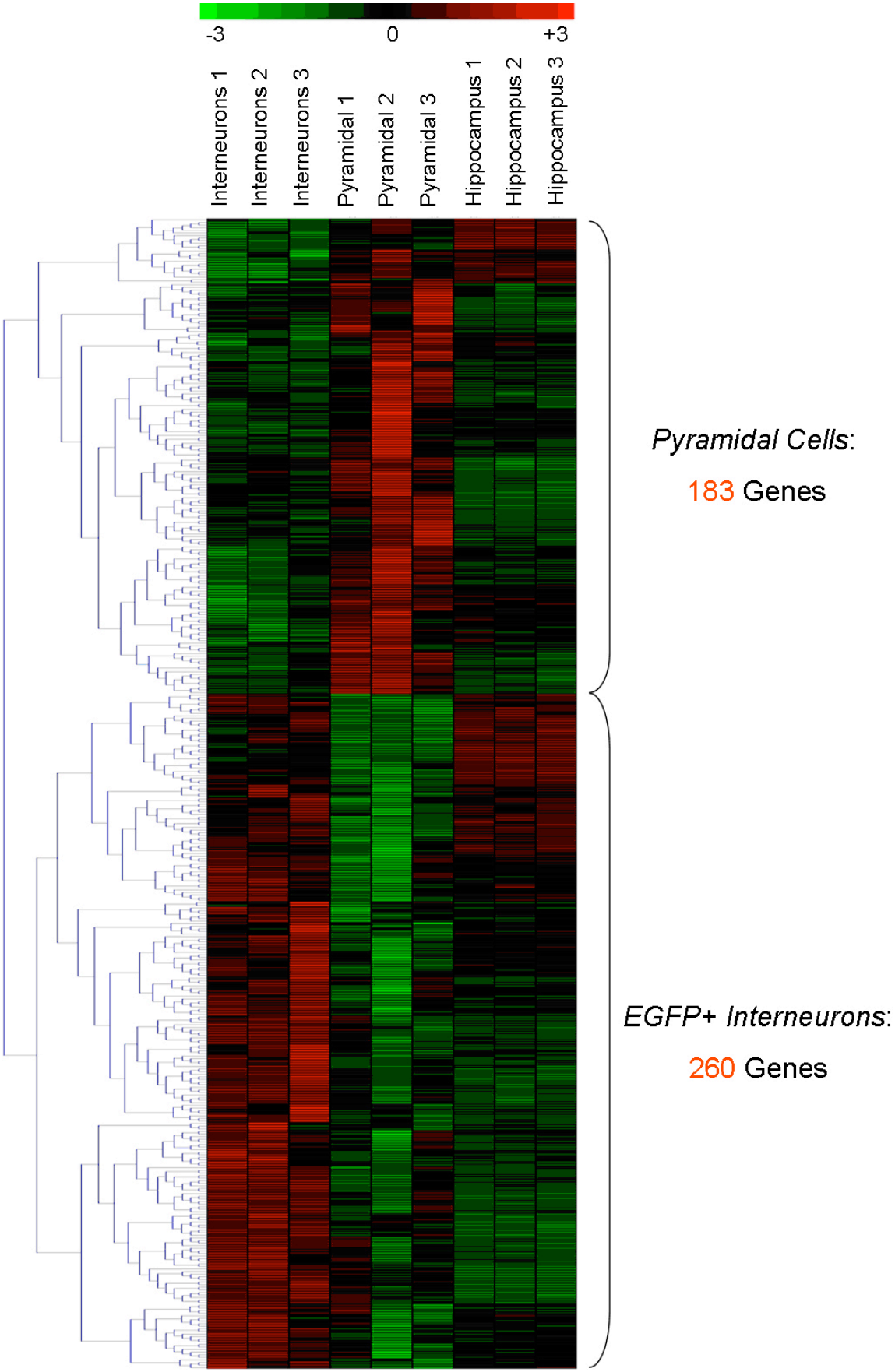
were represented in triplicate and the whole collection was printed on two slides which were both hybridized in each experiment. Hybridizations were repeated three times for each cell population, and were always hybridized against a standard universal mouse reference RNA sample.

Differentially expressed genes.

Fig.2 shows the number of transcripts in EGFP-positive interneurons, identified pyramidal cells and total hippocampal tissue that were differentially expressed with respect to reference RNA. After application of threshold procedures described in the methods, we detected 1956 transcripts expressed by interneurons, 1831 by pyramidal cells, and 1379 transcripts by the total hippocampal tissue. As shown in Fig. 2, some of these transcripts were common to the different groups. For example, 1175 probes, differentially expressed with respect to reference RNA, were common to both EGFP+ cells and pyramidal cells.

We next attempted to separate genes that were expressed differently by EGFP-positive interneurons and pyramidal cells. Data from the two populations were reanalysed using a Bayesian algorithm to identify statistically significant differences. After filtering according to p-values and Log-fold changes (see methods) we detected 443 genes that were differently expressed in these two cell groups. In the heatmap shown in Fig.3, where slots are coloured according to expression levels with respect to the reference for each experiment, two major clusters were detected corresponding to the different cell types. It shows 260 transcripts were more represented in EGFP positive interneurons, and 183 had higher expression levels in pyramidal cells.

Fig.3, next page: HEATMAP OF GENES DIFFERENTIALLY EXPRESSED BETWEEN SOM-CONTAINING INTERNEURONS AND PYRAMIDAL CELLS. Each slot represents the differential expression of the gene in the row as Fold Change in logarithmic scale between the cell type/tissue in the column and the Reference. The gradient goes from green to red. Two main clusters of genes were identified: those overrepresented in the interneuronal population (260) and those overrepresented in the pyramidal cells (183)


-3
0
+3
Interneurons 1
Interneurons 2
Interneurons 3
Pyramidal 1
Pyramidal 2
Pyramidal 3
Hippocampus 1
Hippocampus 2
Hippocampus 3
Pyramidal Cells:
183 Genes
EGFP+ Interneurons:
260 Genes

Association of differentially expressed genes with Gene Ontology terms.

We examined associations of differentially expressed genes with *cellular component, molecular function* and *biological process* terms of the Gene Ontology database. 400 of 443 transcripts were present in the database for mice. 328 of them were clustered for association with one or more terms after application of a threshold p-value, ≤ 0.05, provided by the clustering analysis (http://david.abcc.ncifcrf.gov/; (Dennis, Sherman et al. 2003) .

More than half of the differentially expressed genes were associated with *cytoplasmic compartment* and *intracellular region* from the *cellular component* terms.

Of *molecular function* terms, more than 10% of differentially expressed genes (52 transcripts) were associated with *nucleotide binding.*

The most differentially expressed was the gene Rab3b, a member of the Rab family, more highly expressed in interneurons with a log-fold change of 3.1. Rabs are GTP-binding proteins involved in regulating membrane traffic (Darchen and Goud 2000; Deneka, Neeft et al. 2003) and Rab3b is one of four Rab proteins implicated in exocytosis (Touchot, Chardin et al. 1987; Matsui, Kikuchi et al. 1988; Zahraoui, Touchot et al. 1989).

Pyramidal cells showed a higher representation of the Transient receptor potential cation channel, subfamily C, member 4 associated protein (Trpc4ap) from the molecular component terms. This gene is expressed in the brain (Soond, Terry et al. 2003) and recent data suggests polymorphisms exist which may be associated with a susceptibility to Alzheimer's Disease (Poduslo, Huang et al. 2008).

Among the *biological process* terms, multiple differentially expressed genes were associated wih *transport* activity and *signal transduction*. Of 57 genes related to these functions, 36 were more highly expressed in interneurons and 21 more expressed in the pyramidal cells. These genes included a differential expression of $GABA_A$ receptor subunits with α4, δ and γ2 (Gabra4, Gabrd and Gabrg2) more highly expressed in interneurons and the θ subunit (Gabraq) more expressed in pyramidal cells.

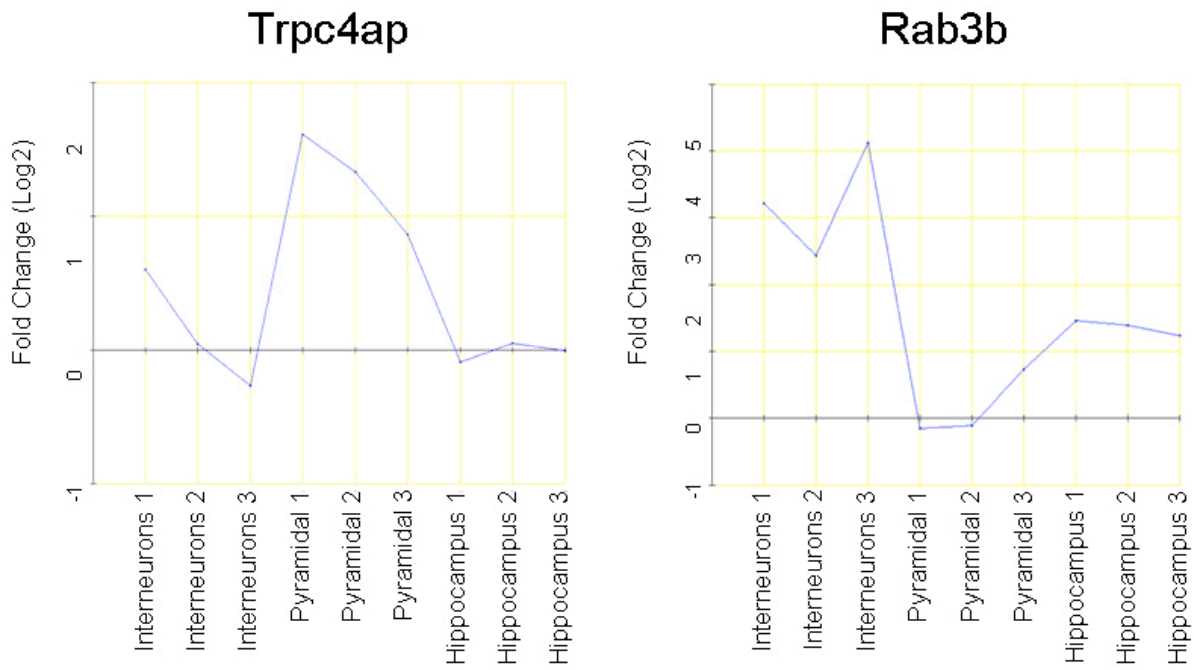


Fig.4 : Differential expression in all hybridizations of genes associated with *molecular function: nucleotide binding*. Rab3b was more highly expressed by EGFP+ interneurons than by pyramidal cells according to fold-changes between the different cell types and Standard RNA in all hybridizations. In contrast Trpc4ap is more highly expressed by pyramidal cells.

Among the genes that may be involved directly in the determination of the distinct phenotypes of interneurons and pyramidal cells, we also detected differences in the expression of transcription factors (TF). Thus differentially expressed TFs may form a "*fingerprint*" to recognize and classify cell types. From *biological process* terms corresponding to differentially expressed genes, a subset of 37 genes was associated with *Regulation of gene expression.* As shown in the heatmap of Fig. 5, 13 of them were more highly expressed in pyramidal cells and 24 were more highly represented in the subset of EPFP-positive GABAergic neurons.

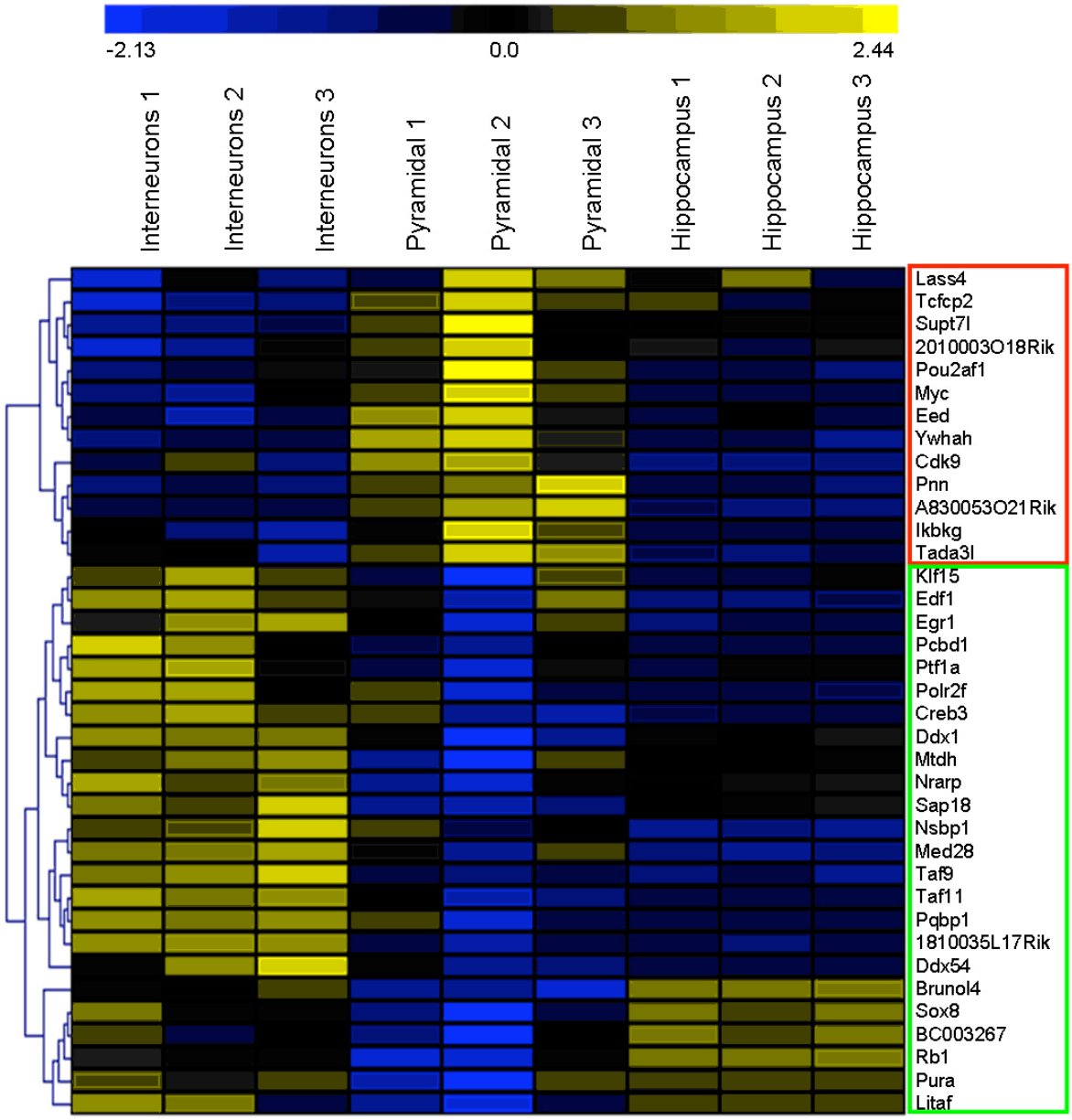


Fig.5: HEATMAP OF DIFFERENTIALLY EXPRESSED GENES ASSSOCIATED WITH *REGULATION OF GENE EXPRESSION*. Each slot represents the differential expression of the gene in the row as Fold Change in logarithmic scale between the cell type/tissue in the column and the Reference. The genes in the red box are more highly expressed in pyramidal cells, and those in the green box are more highly represented in SOM containing interneurons.

Discussion

We have analyzed differences in gene expression by CA1 pyramidal cells and a subset of hippocampal interneurons labelled with green fluorescent protein in the GIN mice (Oliva, Jiang et al. 2000). These cells seem to correspond to a subpopulation of interneurons that express somatostatin (SOM). The somata of cells that we analysed were located in the *stratum oriens* of the CA1 region and it seems likely that they correspond to the O-LM group of interneurons whose axon projects to the *stratum lacunosum-moleculare*. Using gene arrays based on the FANTOM collection, we detected differential expression of 443 mRNA transcripts, with 260 species more represented in EGFP-positive interneurons, and 183 more highly expressed in pyramidal cells.

Technical issues.

The combination of fluorescence activated cell sorting and microarray analysis has been used to determine differential gene expression in neurons (Arlotta, Molyneaux et al. 2005; Marsh, Minarcik et al. 2008). We found that resuspension of dissociated cells in RNAlater medium to preserve genetic material caused a significant cell shrinkage which seriously reduced fluorescent signals. Fluorescent cell sorting was achieved in extracellular solution with no added RNAlater. It permitted the separation of a population of green fluorescent cells (FL1-H reading > $10^{1,2}$). Our yields were ~5000 fluorescent cells per hippocampus. However after collection cells were suspended in a solution of 50 ml, too large for mRNA preparation. We therefore turned to laser capture techniques to dissect EGFP positive cells from hippocampal slices (Lefebvre d'Hellencourt and Harry 2005; Yao, Yu et al. 2005; Sugino, Hempel et al. 2006). Pyramidal cells were collected in a similar way after staining tissue with a rapid variant of the cresyl violet Nissl stain to identify the location of pyramidal cell somata. Tissue fixation, cell harvest and RNA purification have been previously optimized for LCM-based gene expression profiling (C. Vlachouli; PhD thesis *in preparation*).

Microarray experiments were performed by hybridizing RNA from the two cell populations as well as from total hippocampus against a standard reference RNA. This permitted identification of differences in transcript expression in the two cell types. The differences in gene expression should be confirmed with single cell or Real Time PCR data. Immuno-histochemistry with antibodies raised against specific gene products of mRNA species showing distinct expression

patterns in pyramidal cells and O-LM interneurons may identify additional specific markers for these interneurons.

Contribution to the molecular basis for the distinct phenotype of O-LM interneurons.

Our data may contribute to the problem of the classification of GABAergic interneurons (Maccaferri and Lacaille 2003). They provide a gene profile for a well-characterized class of hippocampal interneuron and reveal several interesting differences in gene expression between these cells and pyramidal neurons of the same region. We should note that our data was obtained from ~300 cells of either type lumped together so masking possible variability in genes expressed by cells of the same group. A similar approach has been used to characterize parvalbumin positive (Meyer, Katona et al. 2002) and parvalbumin and calbindin-positive GABAergic cells (Blatow, Rozov et al. 2003).

The O-LM group of interneurons has a distinct somatic site, axonal arborisation pattern and dendritic morphology from CA1 pyramidal cells. O-LM cell expression of Ca-binding proteins may be diverse (Parra, Gulyas et al. 1998), but they consistently express the peptide somatostatin (Oliva, Jiang et al. 2000) and type I metabotropic glutamate receptors (van Hooft et al, 2000). Firing behaviour and the properties of afferent excitatory synapses differ between O-LM interneurons and CA1 pyramidal cells (Ali and Thomson 1998). These differences in phenotype presumably derive in part from differential gene expression between the two cell types. Our data revealed that large numbers of genes were differentially expressed, although they did not include those coding for Ca-binding proteins, neuropeptides or mGluRs. In fact we could not provide data for well known differentially expressed genes described for these cells (Oliva, Jiang et al. 2000) like Somatostatin or mGluR1 because they are not present in our transcripts database. Instead we detected differences in genes associated with *biological process, cellular component* or *molecular function* terms from the Gene Ontology classification.

As expected, many differentially expressed genes were associated with the *cytoplasmic compartment* of the *cellular component* division of the Gene Ontology. In terms of *molecular function*, genes associated with *nucleotide binding* were more strongly expressed in the EGFP-psotive intereneurons. They included the gene coding for Rab3b (higher than 8 times difference in expression) which has been implicated in vesicular exocytosis (Touchot, Chardin et al. 1987; Matsui, Kikuchi et al. 1988; Zahraoui, Touchot et al. 1989). In contrast pyramidal cells showed a higher expression of Trpc4ap (Soond, Terry et al. 2003). Differentially expressed genes associated with terms from the *biological process* division of the Gene Ontology numbered 57, and included those related to *transport* activity and *signal*

transduction. Three $GABA_A$ receptor subunits α4, δ and γ2 (Gabra4, Gabrd and Gabrg2) were more highly expressed by interneurons and the θ subunit (Gabraq) was more expressed in pyramidal cells. The gene coding for the pre-synaptic protein Synaptotagmin I was expressed at higher levels in EGFP-positive interneurons than in CA1 pyramidal cells.

Interestingly we detected differences in 37 genes associated with *Regulation of gene expression* with 13 transcripts more highly expressed in CA1 pyramidal cells and 24 detected at higher levels in O-LM interneurons. The expression of distinct combinations of such genes, including transcription factors, may define specific classes of interneurons by controlling the expression of cytoplasmic and membrane proteins that distinguish their phenotype from that of pyramidal cells (Toledo-Rodriguez, Blumenfeld et al. 2004; Toledo-Rodriguez, Goodman et al. 2005).

- ***Gene expression changes associated with the emergence of epileptiform activity after injection of kainic acid into the mouse hippocampus.***

Gene expression changes associated with the emergence of epileptiform activity after injection of kainic acid into the mouse hippocampus.

In preparation.

Dario Motti, Caroline Le Duigou, Emmanuel Eugène, Nicole Chemaly, Lucia Wittner, Dejan Lazarevic, Helena Krmac, Remo Sanges, Elia Stupka, Enrico Cherubini, Stefano Gustincich and Richard Miles.

Introduction

Disease processes involve changes in expression and function of many proteins that may contribute to the pathology as well as to participate in adaptive responses. Gene profiling techniques assays permit simultaneous measurements of changes in the expression of thousands of genes. Importantly, gene expression studies using micro-arrays have helped identifying molecular defects associated with human diseases including cancer, asthma and neurodegeneration (Karp, Grupe et al. 2000; Lock, Hermans et al. 2002; van 't Veer, Dai et al. 2002).

Gene profile studies on the epilepsies have been facilitated by the availability of living brain tissue after surgery on patients with pharmacoresistant syndromes. Following these studies, human temporal lobe epilepsies have been associated with changes in the immune and complement systems (Jamali, Bartolomei et al. 2006; Aronica, Boer et al. 2007) as well as with altered glial function (Ozbas-Gerceker, Redeker et al. 2006). While such micro-array data from human tissue is valuable, there are some difficulties in its interpretation. First, adequate control tissue is hard to obtain. Second, changes in gene expression may differ between sclerotic regions, sites of neuronal cell death and glial activation, and the regions that generate aberrant population activities (Arion, Sabatini et al. 2006; Jamali, Bartolomei et al. 2006). Third, at the time of their surgery, patients may have experienced seizures over 10-20 years. Therefore, adaptive changes may have occured in response to both pathological changes underlying the epilepsy and prolonged treatments with anti-epileptic drugs (Tang, Glauser et al. 2004; Aronica, Boer et al. 2007).

Animal models of the epilepsies may provide solutions to some of these problems. Kindling is a widely used animal model that closely mimics temporal lobe epilepsies (Goddard 1967; Gorter, van Vliet et al. 2006), In these experimental settings, repetitive stimulation of the hippocampus or the amygdale initiates spontaneous seizures over days or weeks. Temporal lobe epilepsies can be also mimicked by the application of convulsants such as pilocarpine or kainic acid (Ben-Ari, Lagowska et al. 1979; Becker, Chen et al. 2003). These convulsants initiate a prolonged status epilepticus, with a cell death pattern that is similar to human hippocampal sclerosis. Interestingly, spontaneous, recurrent seizures emerge after a period of several weeks. In both animal models control tissue is readily available. Regions of sclerosis and those generating epileptiform activity can be identified and analyzed separately, if

needed. Furthermore, gene expression changes can be followed during the evolution of the disease.

Animal models might also offer insights into the nature of the stimuli responsible for the emergence of an epileptic brain. Between convulsant injection and the emergence of spontaneous recurrent seizures, the hippocampus engages in a prolonged epileptic activity (Pitkanen, Nissinen et al. 2002; Williams, Hellier et al. 2007), During this period some neurones die (Sater and Nadler 1988; Magloczky and Freund 1993), expression and distribution of cell surface receptors and channels change (Misonou, Mohapatra et al. 2004; Shah, Anderson et al. 2004; Epsztein, Represa et al. 2005), different cohorts of glial cells are activated (Vezzani and Granata 2005; Wetherington, Serrano et al. 2008), immune and inflammatory responses are triggered (Andersson, Perry et al. 1991; Vezzani and Granata 2005) and novel aberrant synaptic circuits are formed (Sutula, He et al. 1988; Patrylo and Dudek 1998). How these events are related and how they are associated with the emergence of seizures is only partially clear.

In an attempt to clarify some of these questions we used gene profile technology, in association with EEG recordings and anatomy, to examine the progression towards recurrent seizures in mice treated with kainic acid (KA). Experiments were performed at three different time points corresponding to three different phases of progression of the model: 6 hours after injection (corresponding to the initial status epilepticus), 15 days after injection (corresponding to the latent phase) and 6 months after the injection (corresponding to the establishment of a recurrent epileptic activity).

In our experimental settings, KA was injected into one hippocampus (Bouilleret, Ridoux et al. 1999; Le Duigou, Wittner et al. 2005). In a former work we showed differential involvement of the ventral and dorsal part of both the injected and the contralateral hippocampus in the electric activity (Le Duigou, Wittner et al. 2005). Therefore experiments were performed separately in the injected area (Ipsilateral Dorsal area), in the ventral part of the same hippocampus (Ipsilateral Ventral area) and in the dorsal (Contralateral Dorsal area) and ventral area (Contralateral Ventral area) of the hippocampus contralateral to the injected one.

As we shall show, focal intracranial KA application may allow separation of several stimuli that may be involved in the emergence of an epileptic brain.

Both the injected and the contralateral hippocampi participate in a status epilepticus which lasts for several hours after KA injection. In contrast, cell death occurs exclusively in the injected hippocampus and is most evident near the injection site in the dorsal hippocampus. Axonal degeneration and the consequent de-afferentation is strongest near the site of KA

injection but also occurs in the ventral injected hippocampus and at mirror sites in the contralateral non-injected hippocampus. We therefore compared changes in gene expression in the dorsal and ventral injected hippocampus and in the dorsal and ventral contralateral hippocampus. The cell specificity and regional distribution of selected genes was further examined with immuno-histochemical techniques.

Materials and Methods

Intrahippocampal KA injection

Experiments were performed on adult C57BL/6J male mice (Janvier, Le Genest Saint Isle, France), weighing 30-35g and housed in a 12 hours light-dark controlled cycle. All experiments were performed in accordance with the European Committee Council Directive of November 24, 1986 (86/89/EEC) and with INSERM guidelines. Male mice aged 2-3 months were anaesthetized with 4% chloral hydrate (120 ml/kg; Sigma, St Louis, MO, USA) and 4% urethane (1000 ml/kg; Sigma, St Louis, MO, USA,) and placed in a stereotaxic frame. Injections were made by a stainless steel cannula of outside tip diameter 0.28 mm connected to a 500 nl microsyringe (Hamilton, Fisher Labosi, France). A volume of 50 nl kainic acid (Sigma, St Louis, MO, USA) dissolved at 20 mM in 0.9% NaCl was injected into the right dorsal hippocampus (Bouilleret, Ridoux et al. 1999). Control animals were prepared identically and injected with the same volume of 0.9% NaCl solution. Injections were made at the stereotaxic coordinates: anterior-posterior = -1.8 mm, medial-lateral = - 1.8 mm, dorsal-ventral = - 1.8 mm with respect to the bregma. These coordinates correspond to an apical dendritic site in the CA1 region of dorsal hippocampus. After recovery from anaesthesia, animals displayed behavioural signs of status epilepticus, specifically maintained turning movements.

EEG recordings

EEG records were made using nickel/chrome wire electrodes of external diameter 200 µm. Bipolar records were made using two wires twisted together from (1) a site near the position of kainate injection in the right, dorsal hippocampus, (2) the equivalent site in the contralateral hippocampus, (3) a ventral site in the injected right hippocampus and (4) a mirror ventral site in the non-injected contralateral hippocampus. AP = - 3,28 mm, L = +/- 3 mm, P = - 2.8 mm. Monopolar records were made bilaterally from the parieto-occipital cortex. A monopolar reference electrode was implanted in the cerebellum and a neutral

electrode above the olfactory cortex. EEG electrode connectors were fixed to the skull with dental cement. Animals were housed singly after implanting EEG electrodes. EEG signals were recorded during sessions of duration 3-4 hrs typically in the afternoon during the period from 1 day to 6 months after KA-injection. EEG signals were amplified with a 24-channel system (Medelec, Oxford Instruments, Abingdon UK) and acquired to a computer at 1024 Hz and 22-bit resolution. Signals were filtered between 0.5 and 500 Hz. Recordings were made by Caroline Le Duigou and Nicole Chemaly at the INSERM U739 lab in Paris, France.

Morphology

Cell death and fibre degeneration was studied using Nissl Staining and the Fink-Heimer silver impregnation technique (Fink and Heimer 1967). For Fink-Heimer impregnation animals were perfused intracardially with cold ACSF followed by 100 ml of fixative containing 4% paraformaldehyde and 15% saturated picric acid dissolved in 0.1M phosphate buffer (PB). The brains were removed and 100 µm thick sections were cut with a Vibratome and washed in PB. After impregnation, sections were washed in PB, mounted on gelatine coated slides and covered with DePeX (Laboratoire DBH, France). As well as cell bodies, degenerating axons and synaptic terminals are coloured black by this silver-staining technique. Fink-Heimer staining experiments were conducted by Lucia Wittner.

Preparation of tissue for RNA extraction

After decapitation both hippocampi, the injected ipsilateral and the contralateral one, were dissected in cold PBS 1X in DEPC-treated (Sigma, St Louis, MO, USA) H_2O under RNAse free conditions. Each hippocampus was divided into a ventral and a dorsal part which were placed in an Eppendorf containing 1 ml of TRIzol (Invitrogen, Carlsbad, CA, USA), frozen and packed in dry ice and then sent to Trieste, Italy, where samples were stored at -80°C before former treatments. In the end for each mouse we obtained four areas: ipsilateral dorsal (ID, close to where kainate was injected), ipsilateral ventral (IV), contralateral dorsal (CD) and contralateral ventral (CV)

RNA extraction and probe synthesis

Total RNA was isolated according to the TRIzol Reagent Protocol provided by the manufacturer. To avoid genomic contamination samples have been treated with 2 units of RNAse free DNAse (2 units/µl; Ambion, Austin, TX USA) for 15 min at 37°. Total RNA was further purified with RNeasy Mini Kit (Qiagen, Chatsworth, CA, USA). RNA quality was assessed using an Agilent 2001 Bioanalyzer (Agilent, Palo Alto, CA, USA), samples with an R.I.N. index (RNA Integrity Number) higher than 8 were considered good and used for following hybridizations. Samples were then quantified with a ND-1000 spectrophotometer (Nanodrop technologies, Wilmington, DE, USA). 500 ng of Total RNA from each sample were used as a template to generate biotinylated cRNA following the protocol from Illumina Total Prep Amplification Kit (Agilent, Palo Alto, CA, USA).

Hybridization and scanning

Sample labelling, hybridization to arrays and image scanning were carried out as described in the Affymetrix Expression Analysis Technical Manual. cRNA was hybridized to Affymetrix murine 430A 2.0 gene chips which analyze the expression level of approximately 14,000 well-characterized mouse genes. Chips were scanned with a laser Agilent 3000 Scanner. Image analysis was performed with GeneChip® Operating Software. WT samples for dorsal and ventral hippocampus were hybridized in double. For each time points 2 samples for each area from Kainate injected mice were hybridized, together with one sample per area from NaCl injected mice.

Analysis of expression profile data

Expression levels were calculated with the Bioconductor (Gautier L 2004) collection of packages in the R programming environment for statistical computing. They were calculated using the RMA function (Irizarry, Hobbs et al. 2003) in the 'Affy' package with default parameters which make use of the quantile normalization. To extract changes in gene

expression each single time point was compared to the wild type sample and to the NaCl-injected control of the same area. Genes were considered as "changing" if both values of expression in the kainate treated samples were outside the range covered by the expression levels of the two wild type samples and the NaCl controls for the very same time point and area. "Changing" genes were then filtered by Fold Change (in logarithmic scale): in order to be included in downstream analysis a gene should have fold change (Kainate injected vs. WT AND Kainate injected vs. NaCl) $\leq \log2(-1)$ or fold change $\geq \log2(1)$ (which is a fold change of ± 2 on a linear scale). Exceptions were included if fold change in respect to Wild Type or NaCl was ≤ -0.98 or ≥ 0.98 with the Fold Change in respect to the other value (either NaCl or WT) was ≤ -1.2 or ≥ 1.2 accordingly with the former one.

When more than one probe for a single gene was found differentially regulated in one area/time point, only the highest Fold Change was taken in consideration. We never find probes screening for the same gene moving in opposite direction during the analysis (for instance one probe upregulated and another downregulated).

Gene Ontology profiles were performed with GenMAPP 2.0 (http://www.genmapp.org) analysis software. The lists of selected genes for each area and time point were submitted together with the list of all the probes contained in our reference Chip: the murine 430 A 2.0 as a background. Ontology terms were considered only if Z-Score was higher than 1.96 (corresponding to a p-value ≤ 0.05).

Real Time Experiments

To validate some of the changes that were detected with Affymetrix Chips, real-time quantitative PCR analysis was performed using RNA obtained from injected mice at 6 hours after the injection extracted and treated in the same way as those used in the array experiments. For each gene that was chosen Forward and Reverse Primers were designed with the Beacon Designer™ 6.0 (PREMIER Biosoft International, Palo Alto, CA, USA). To design the primers, the transcripts' sequences extracted from Ensembl (www.ensembl.org) were submitted to the program together with the following criteria: avoiding cross homology, primer length between 18 and 25 bp, product length between 75 and 200 bp and Tm between 58°C and 62°C. The transcripts' sequences were also processed with Mfold v3.2 (Zucker M., Nucleic Acids Res., 2005) to evaluate the secondary structure of the transcripts, to avoid

primers to anneal to unreachable positions. The analysis was performed with the default criteria except for: annealing reaction 60°C, Na^+ concentration 50 mM and Mg^{++} concentration 5 mM. The genes selected and the relative primers are: **Isl1** (Forward Primer: 5'-ATTGTCCAACCACCATTTCACTG-3', Reverse Primer: 5'-GATTACACTCCGCACATTTCAAAC-3'), **Lcn2** (Forward Primer: 5'-ACGACAACATCATCTTCTC-3', Reverse Primer: 5'-ATGCTCCTTGGTATGGTG-3'), **Trpm7** (Forward Primer: 5'-CTTGGAACAGGCTATGCTTGATG-3', Reverse Primer: 5'-TGAGATGGAACAACATTGGATTGG-3'), **P2ry12** (Forward Primer: 5'-ATTCACAGAAGAACACTCAAGG-3', Reverse Primer: 5'-TTGACACCAGGCACATCC-3'), **Hspa1b** (Forward Primer: 5'-TTCGTGGAGGAGTTCAAG-3', Reverse Primer: 5'-GTGATGGATGTGTAGAAGTC-3'), **Hes5** (Forward Reverse: 5'-GAGATGCTCAGTCCCAAG-3', Reverse Primer: 5'- AAGGCTTTGCTGTGTTTC-3'), **Gad2** (Forward Primer: 5'-GGCTCTGGCGATGGAATC-3', Reverse Primer: 5'-GACTATGCTCTGATGTGAACG-3'). As housekeeping genes we tested with Real Time PCR the levels of transcription of **Actb** (Forward Primer: 5'-TGGGTATGGAATCCTGTGGCATC-3', Reverse Primer: 5'-GTGTTGGCATAGAGGTCTTTACGG-3') and **Gapdh** (Forward Primer: 5'-AGAAGGTGGTGAAGCAGGCATC-3', Reverse Primer: 5'-CGAAGGTGGAAGAGTGGGAGTTG-3'). All of the samples were run in duplicate. Real Time Experiments were performed on tissues from three distinct injected mice. All RNAs were diluted at the lowest concentration and 1 µg of it was used for the reaction of Reverse Transcription, together with 4 µl of 5x iScript Select reaction mix and 1µl of iScript reverse transcriptase from the iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, CA, USA). The final volume was adjusted with Nuclease Free H_2O to 20 µl. The mix was kept for 5' at 25°C to allow primer annealing. Reverse Transcription was performed at 42°C for 50', followed by 5' at 80°C to inhibit the enzyme. 250 ng of cDNA per sample were mixed with 10 µl of 2X iQ Supermix (Bio-Rad Laboratories, Hercules, CA, USA), and specific primers to a final concentration of 250 nM in 20 µl of final volume (reached with Nuclease Free H_2O) to perform the Real Time PCR experiments. Time monitoring of PCRs was performed using the iQ5 Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA). The mixture was incubated for 30' at 43°C, for Reverse Transcription, then heated to 95°C for 3'for initial denaturation. Following PCR reaction included the following cycling conditions: 41 cycles of denaturation at 95°C for 20sec, annealing at 60°C for 20sec and extension at 72°C for 30sec. Fluorescence was measured by a triple acquisition mode at 72°C after each

cycle. Primer dimers' presence and specific/non-specific products ratio were detected by measuring a melting curve after the amplification by holding the temperature at 55°C for 1' followed by a gradual increase in temperature to 95°C at a rate of 0.05°C/s. Analysis of data was performed using the iQ5 Optical System Software v2.0.

Immunofluorescence

To evaluate whether changes in gene expression correspond to changes in protein expression we performed immunofluorescence analysis on Vimentin and GFAP, genes we identified as differentially regulated during the latent phase of progression of the pathology and that are related to proliferation of astroglial cells. Kainate-injected mice and NaCl-injected control mice where perfused transcardially with 50 ml of PFA 4% in 1X PBS. Brains where extracted and put in PFA 4% for one hour of post fixation, then washed 3 times in 1X PBS, 15' minimum per wash, and incubated in 30% in 1X PBS Sucrose solution overnight. After overnight incubation at 4°C the brains where frozen in dry ice and sectioned at a cryostat: 50 µm horizontal sections were collected in Prolong Gold Antifade Reagents (Invitrogen, Carlsbad, CA, USA). To avoid non specific binding sections were incubated in TBS plus 0.5% Triton X100 (Roche Diagnostics, France) for 1 hour at room temperature. Sections were incubated with primary antibody overnight at 4°C. All antibodies where diluted 1:1000 in TBS+. After incubation with the primary antibody sections were washed three times for 1 hour per wash with 0.1M PB at room temperature and incubated with Cy2-conjugated anti-chicken, Cy3-conjugated anti-rabbit and Cy5-conjugated anti-mouse secondary antibody (Jackson Immuno Research, West Grove, PA; diluted 1:1000 in TBS+) for 4 hours at room temperature. Antibody against Vimentin (anti-Vim; polyclonal chicken; Abcam, Cambridge, UK), Glial Fibrillary Acidic Protein were used (anti-Gfap; monoclonal rabbit; Promega, Madison, WI, USA) and NeuN (anti-NeuN; Chemicon, Temecula, CA, USA)

Results

Experimental Settings

Adult C57BL/6J mice, aged 2-3 months were anaesthetized and placed in a stereotaxic frame. Then 50 nl of KA or 0.9% NaCl was injected into the right dorsal hippocampus, the apical dendritic site in the CA1 region of dorsal hippocampus (for coordinates see *Materials and Methods*) (Bouilleret, Ridoux et al. 1999). After recovery from anaesthesia, animals displayed behavioural signs of status epilepticus, specifically maintained turning movements. Mice were then sacrificed at different time points and in different ways due to the specific experiment. A total of 80 mice were injected, 31 died during or immediately after surgery.

Analysis of EEG recordings.

To evaluate short-term electric activity, EEG recordings were made from dorsal and ventral sites in both injected and non-injected hippocampus for 24 hrs after KA injection. A distinct large, slow EEG activity emerged first close to the injection site at 2-3 hrs after KA-injection. This activity grew in size and complexity with time and spread throughout both hippocampi (see Fig.1). Propagation occurred from dorsal to ventral regions of the injected hippocampus, then to ventral and dorsal regions of contralateral non-injected hippocampus. At 5 hrs after the injection all regions of both hippocampi participated in a status epilepticus which persisted for up to 24 hrs after injection.

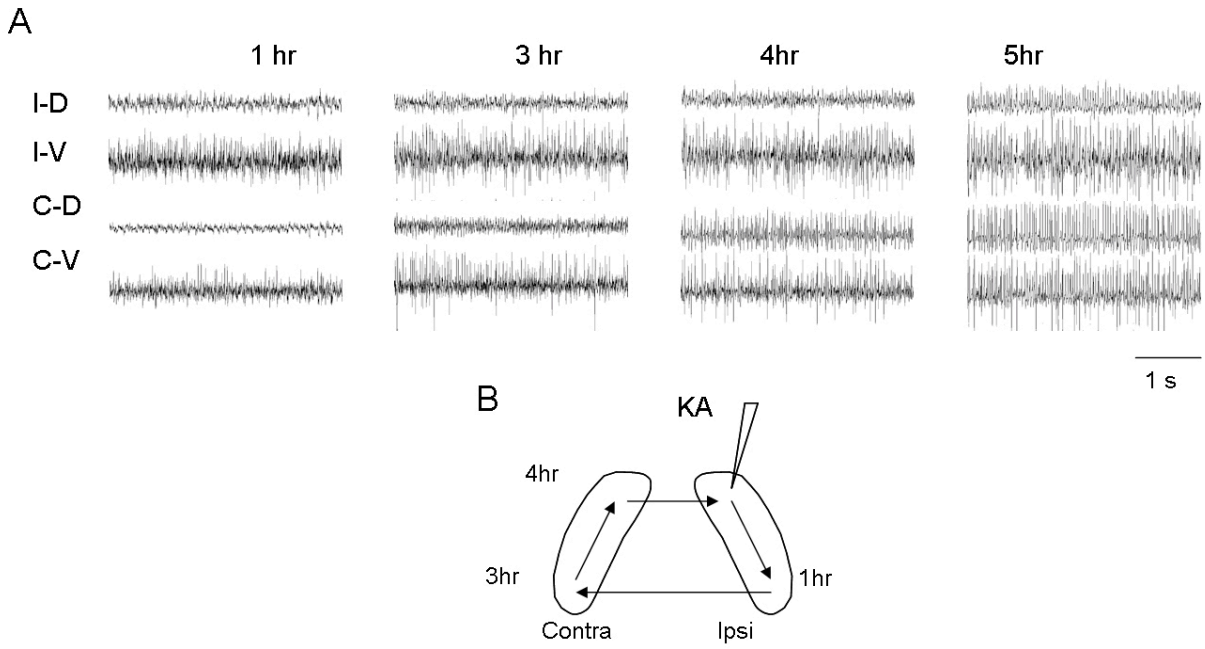


Fig.1: EEG RECORDINGS AT EARLY STAGES. In panel A EEG recordings taken from the injection site (I-D), the ventral part of the same hippocampus (I-V) and the dorsal and ventral area of the contralateral hippocampus show propagation of the electrical activity starting from I-V through to all of the evaluated areas following a scheme represented in panel B. At 5 hours after the injection all of the areas participate to the status epilepticus.

In long term recordings made 3 to 4 days after KA injection, no epileptiform activity was detected. Simple bilateral spike and wave activities emerged over the next two weeks. More complex sequences of recurring, bilateral epileptiform activities were observed at 3-4 weeks. Electrographic tonic-clonic seizures with few clear behavioural correlates were detected in records made from this time-point up to 10 months after KA-injection. The seizure initiation usually seemed to be localised to the KA-injected hippocampus but in some cases seizures appeared to emerge from the non-injected hemisphere (Fig. 2).

These data show that both dorsal and ventral portions of both ipsilateral injected and contralateral non-injected hippocampus participated in the status epilepticus provoked by KA-injection. They suggest that further epileptiform activity was absent until 2-3 weeks later when spike and wave discharges and occasional tonic-clonic seizures were established.

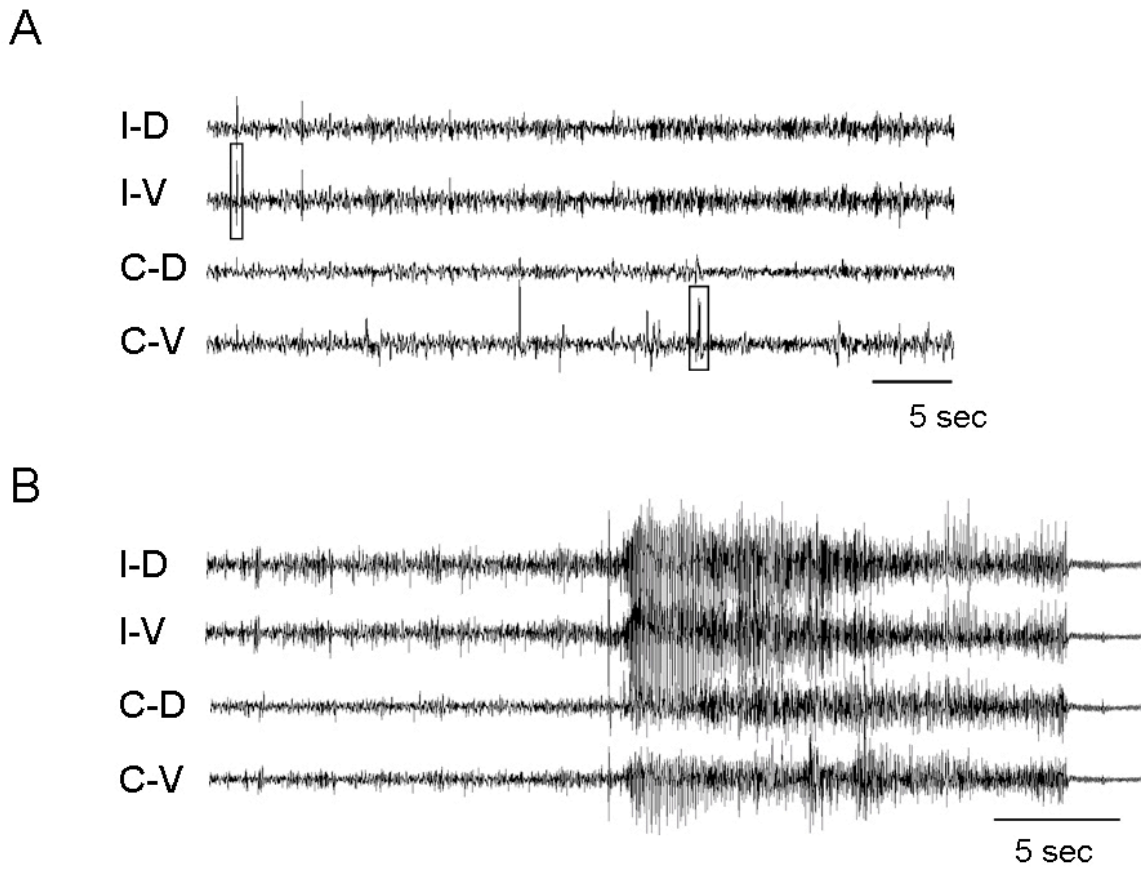


Fig.2: EEG RECORDINGS DURING LATENT AND CHRONIC PHASE. In panel A recordings from the four different areas from a few days to 3 to 4 weeks after the injection show no epileptic activity. Bilateral spikes may be observed that are highlighted in the boxes. In panel B are shown recordings from hippocampi of mice 6 months after the injection. Bilateral epileptic activity is observed starting from both the injected and the contralateral hippocampus.

Analysis of cell death

Previous work on KA-injected animals suggests that a significant pyramidal cell death occurs in the CA1, CA3 and hilar regions (Le Duigou, Wittner et al. 2005). We performed Nissl staining which confirmed a severe cell loss around the injection site in dorsal hippocampus at 4 weeks. There was a lesser cell loss at the ventral injected hippocampus but no cell death could be detected in dorsal or ventral regions of contralateral hippocampus. Cell loss were revealed by the disappearance of cell bodies in the hilar region and the thickening of the pyramidal layer in tha CA1 region.

Then we performed Fink-Heimer staining, a procedure that shows both dead cells and degenerating fibres. To this purpose we examined hippocampi from three different KA-

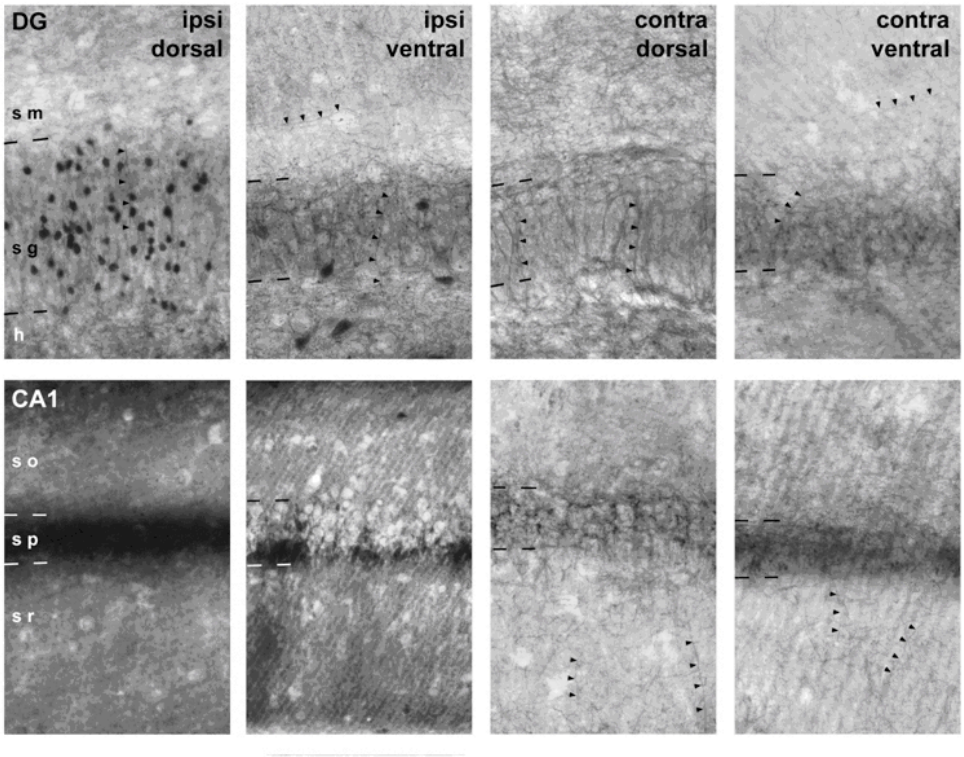
injected animals at 6-8 days after injection when fibre degeneration should be maximal. Mice were anesthetized and perfused with ACSF. Brains were then extracted and cut in slices 100 µm thick that were than processed for Fink-Heimer impregnation. Both cell death and fibre degeneration were estimated semi-quantitatively from the dentate gyrus, CA1, CA3 and subiculum of sections prepared from the middle regions of dorsal and ventral injected hippocampus and from dorsal and ventral non-injected hippocampus.

At 6-8 days after injection we detected a profound cell loss in dorsal injected hippocampus and a less extensive cell loss in ventral regions of this hippocampus. Cell death was largest in the CA1 and CA3 regions while some black-staining somata were evident in the dentate gyrus and in the subiculum. In the non-injected hippocampus, less than 0.1% black-staining cell bodies were detected. In contrast, fibre degeneration was apparent in both somatic and dendritic regions of both dorsal and ventral sites from the contralateral hippocampus. The extent of degeneration was similar in the dentate gyrus, subiculum and in the CA1 and CA3 regions. Contralateral fibre degeneration was less than that detected in the ipsilateral KA-injected hippocampus where diffuse Fink-Heimer staining of fibre-like elements was most strong in dorsal CA1 and in subicular regions close to the injection site.

These data suggest that cell death is limited to the injected hippocampus and is most severe near the dorsal injection site. At 6-8 days after injection, fibre degeneration is not limited to those sites but is also evident in dorsal and to a lesser extent ventral hippocampus. This degeneration is presumably correlated with a partial de-afferentation of contralateral cells.

In summary, these data show that epileptiform activity, both interictal-like and ictal-like events induced by tetanic stimulation, is not limited to the KA-injected hippocampus. All regions participated in the initial status epilepticus. Cell death was maximal in dorsal, evident in ventral injected hippocampus, but absent from both dorsal and ventral contralateral hippocampus. Fibre degeneration, and presumably partial de-afferentation, was maximal in dorsal and ventral injected hippocampus but was also detected in dorsal and to a lesser extent ventral contralateral hippocampus. These data allowed some comparative procedures to examine the relative influence of status epilepticus, cell death and de-afferentation on gene expression changes leading eventually to the establishment of an epileptic hippocampus.

A



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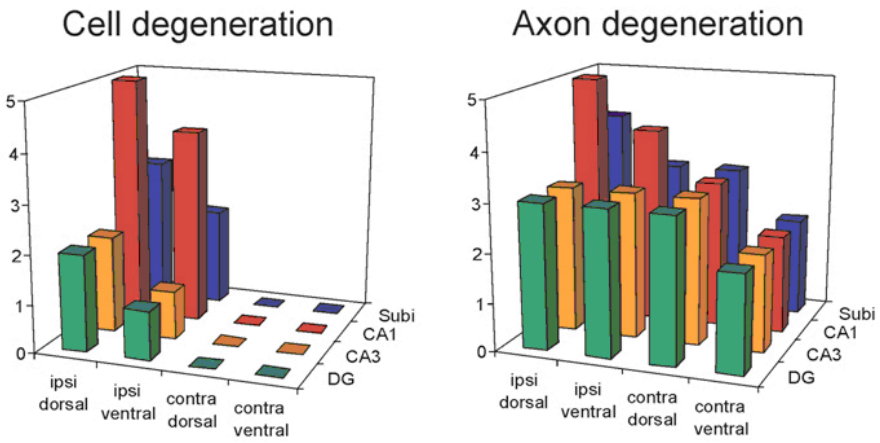


Fig.3: FINK-HEIMER STAINING. In panel A pictures taken from Dentate Girus (DG) and CA1 regions (CA1) of dorsal and ventral areas of both hippocampi in mice 6 to 8 days after injection with dead cells stained with Fink-Heimer silver impregnation technique. We observe an accumumalation of dead cells in *stratum granulosum* of DG and *stratum pyramidale* of CA1 in the area close to the site of injection (Ipsi dorsal) and to a less extent in a more distal site of the same hippocampus (Ipsi ventral). No sign of dead cells is present in the contralaterl hippocampus.
In panel B a graphical representation of the level of cell and axon degeneration in the four areas and different sites (Subiculum, CA1, CA3 and Dentate Gyrus) 6 to 8 days after kainate injection measured after Fink-Heimer staining.

Analysis of gene expression profile: experimental protocol.

We examined changes in gene expression using the Affymetrix murine 430A 2.0 gene chips which analyzes the expression level of approximately 14,000 well-characterized mouse genes. Mice were injected as described before. Two KA-injected and one NaCl-injected were sacrificed at three different time point after the injection: 6 hours, 15 days and 6 months. Together with these, two WT mice were sacrificed with the same procedure. Hippocampi were dissected in nuclease-free condition. Both hippocampi were divided in two so changes could be compared in the dorsal ipsilateral hippocampus (the injection site) as well as the ventral ipsilateral hippocampus and the dorsal and ventral contralateral regions of the non-injected hippocampus. Tissue samples included the dentate gyrus, areas CA1 and CA3 as well as the subiculum.

Following treatment included RNA precipitation (following TRIzol protocol provided by the manufacturer) and purification (with the RNeasy Mini Kit from Qiagen, Chatsworth, CA, USA). RNA quality was assessed using an Agilent 2001 Bioanalyzer (Agilent, Palo Alto, CA, USA): only samples with an RNA Integrity Number (R.I.N.) higher then 8 were used to perform the analysis. 500 ng of Total RNA from each sample were used as a template to generate biotinylated cRNA following the protocol from Illumina Total Prep Amplification Kit (Agilent, Palo Alto, CA, USA).

After overnight hybridization, Chips were scanned. Image files were then processed to obtain raw data as CEL files. These were then processed for normalization, and expression levels were calculated through Bioconductor (Gautier L 2004).

From gene expression levels, two threshold procedures were used to define differentially expressed genes so that up- or down-regulated from kainate-treated animals differed from both wild-type animals and from animals injected with NaCl.

Analysis of Gene expression profiles: summary of results

Fig. 4 shows the tempo/spatial distribution of genes altered by kainate-treatment: not considering overlapping, a total of 1563 genes resulted differentially expressed in at least 1 time and 1 space point (the complete list is in the *Supplementary Table* section).

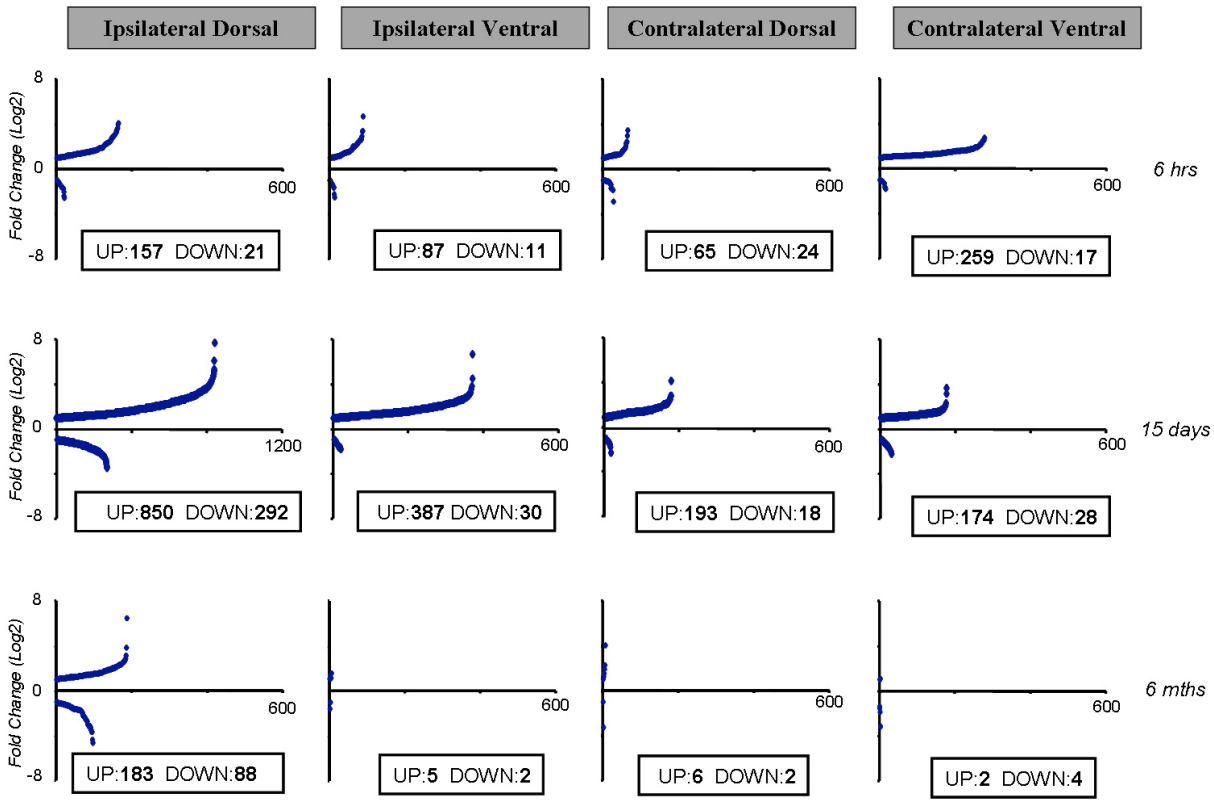


Fig.4 : TEMPORAL AND SPATIAL DISTRIBUTION OF DIFFERENTIALLY EXPRESSED GENES AFTER KA INJECTION. In the graphs are reported the number of genes differentially regulated for each area at the three different time points. In each graphs on x-axe are reported the number of genes, on y the Fold Change in logarithmic scale. Below each graphs the number of Up- or Down-regulated genes are shown.

In summary we found that:

6 hours after injection:

- Neglecting overlap, a total of 507 genes were changed.
- Near the injection site in dorsal ipsilateral hippocampus, 157 genes were upregulated and 21 genes down-regulated.
- The region with the largest number of changed genes was the contralateral non-injected ventral hippocampus with 276 genes up-regulated and 16 genes down-regulated.
- Interestingly, the composition of these two groups of genes was rather different: 150 of 178 genes changed (84%) in the dorsal ipsilateral hippocampus were

unchanged in contralateral ventral hippocampus and 90% of 276 genes changed in the contralateral ventral area were unchanged in the dorsal ipsilateral samples.

- A smaller number of genes was changed in the dorsal contralateral (89 genes) and ventral ipsilateral areas (98 genes). They were mostly similar to genes changed close to the injection site, with a percentage of overlapping of 57% for the ipsilateral ventral and 43% for the contralateral ventral area.

Therefore, we can conclude that at 6 hours after the injection a common pattern of expression was induced by kainate in dorsal and ventral ipsilateral as well as dorsal controlateral hippocampi. Surprisingly, a specific and large transcriptional response was present in the controlateral ventral hippocampus.

15 days after injection:

- This is the time point with the largest number of changed genes: 1218.
- In the ipsilateral dorsal hippocampus 850 genes were up-regulated and 292 genes were down-regulated (a total of 1142 genes).
- In the ventral ipsilateral hippocampus 417 genes changed their expression with 95% of them common with the dorsal ipsilateral region.
- In contralateral dorsal hippocampus the expression of 211 genes was changed with, again, 98% genes common to the expression at the site of injection.
- In contralateral ventral hippocampus, changes occurred in the expression of 202 genes, of which 26% differed from those changed in the dorsal ipsilateral hippocampus.

We noticed a colocalization of changes in areas close to the site of injection, with 186 genes in common to the ipsilateral dorsal, ipsilateral ventral and contralateral dorsal areas. Among these, only 32 (17%) were present in one or more of the areas at 6 hours. A smaller overlapping has been reported with the contralateral ventral area, however the amount of specific genes is much less significant than at 6 hours with 47 (23%) genes differentially expressed only in this area. Among them 21 (44% of the specific ones) were common to the controlateral ventral specific pattern at 6 hours.

6 months after injection:

- At this time point a total of 276 genes changed their expression.

- Nearly all the changed genes were located in the ipsilateral dorsal injected hippocampus (271 / 292 or 93%). A relatively high proportion of these genes were down-regulated.
- Six to eight genes were changed in each of the other regions. In total, 10 of these genes differed from those altered in the dorsal ipsilateral region (4 in the IV, 4 in the CD and 2 in the CV).

In conclusion 6 months after the injection of kainate almost all of the gene expression changes we identified were confined to the site of the injection, while the other areas account for a very small amount of changes and most of them overlap with changes in the ipsidorsal site.

Comparison of the time course and spatial location of gene expression provided some insights into the structure of changes induced by kainate-treatment. With twelve different time/space points, 2^{12} or 4096 different combinations of changed or unchanged expression were possible. We found that 134 different patterns of expression existed.
Interestingly, more than half of these genes (n=911 of 1563; 58%) were changed only at a single site and at a single time point with the most evident groups being:
- 545 genes were only changed at 15 days in ipsilateral dorsal hippocampus
- 178 genes changed exclusively in contralateral ventral hippocampus at 6 hours.

Several temporal and spatial patterns were evident in the 681 genes that were altered at multiple time points. For these genes, maximal changes were detected at:
- the ipsilateral dorsal injection site at 6hrs (n=58 genes)
- at 15 days (n=471 genes)
- at 6months (n=53 genes).

The size of these changes in expression often followed a similar spatial order. The same gene showed the largest change in expression at the dorsal site of injected hippocampus, the next largest in ventral ipsilateral hippocampus, then in dorsal contralateral hippocampus and the smallest change occurred in ventral contralateral regions.

A fourth set of genes showed maximal changes at 6hrs in the contralateral ventral hippocampus (n=53). Asmaller number of different patterns associated with smaller numbers

of genes were also detected (n=42). Most clusters consisted of groups of upregulated genes, however a downregulation was detected most often (41 out of 53 genes) in the cluster of genes that changed at 6 months in ipsilateral hippocampus where were down-regulated.

Analysis of Gene expression profiles: Correlation and verification of Affymetrix gene profile data with data from RT-PCR

We decided to compare data on changes in gene expression determined by micro-array analysis with those estimated by real-time PCR analysis to define the accuracy of our methods.

Three mice where injected with KA as previously described. 6 hours after injection they were sacrificed and tissue samples from the four different areas where collected in RNAse free conditions. RNA samples were collected from three wild type mice following the same procedure. RNA was extracted, purified and checked for good quality (see *Materials and Methods*). RNA samples where then used to perform quantitative analysis for seven transcripts where the chip analysis had reported a large change in expression at 6 hours after the injection in at least one site: *Lcn2* (log-fold changes of 5.28, 4.64, 4.80, 2.55 between KA-treated and WT tissue from ipsilateral dorsal, ipsilateral ventral area, contralateral dorsal area and contralateral ventral areas respectively), *Hspa1b* (3.98, 2.61, 2.94, 1.64), *Trpm7* (0.35, 0.02, -0.13, 1.95), *Gad2* (0.15, 0.46, -0.57, 2.48), *Hes5* (-1.42, -1.19, -1.13, -0.99), *P2ry12* (-2.17, -2.54, -2.01, -0.63) and *Isl1* (-2.18, -0.03, -2.92, 0.97) as well as two housekeeping genes *Actb* and *Gapdh* for calibration.

Results showed that, overall, the direction of the change in expression detected with the q-PCR technique agreed with that predicted by the micro-array work in 22 of 28 cases. Comparative values were best fitted with a linear relation of the form: qPCR value = 0.57*(Affymetrix value) – 0.86 ($r^2 = 0.48$). As shown in Fig. 5, the data for changes in gene expression determined from the two techniques agree relatively well, with the array measurements rather more sensitive than those made with q-PCR. Fig. 5 also presents a Table comparing the more significant fold-changes for up- and down-regulated genes from the array analysis and corresponding values from qPCR experiments.

A

Probe	Gene	Area	GeneChip Fold Change	qPCR Fold Change
1427747_a_at	Lcn2	Ipsilateral Dorsal	5.286875474	2.58695503
1427747_a_at	Lcn2	Contralateral Dorsal	4.800379683	2.36447272
1427126_at	Hspa1b	Ipsilateral Dorsal	3.980084941	1.64262066
1456010_x_at	Hes5	Ipsilateral Dorsal	-1.426888946	-3.92980454
1431724_a_at	P2ry12	Ipsilateral Ventral	-2.541444925	-0.35845677
1450723_at	Isl1	Contralateral Dorsal	-2.918052288	-3.82903056

B

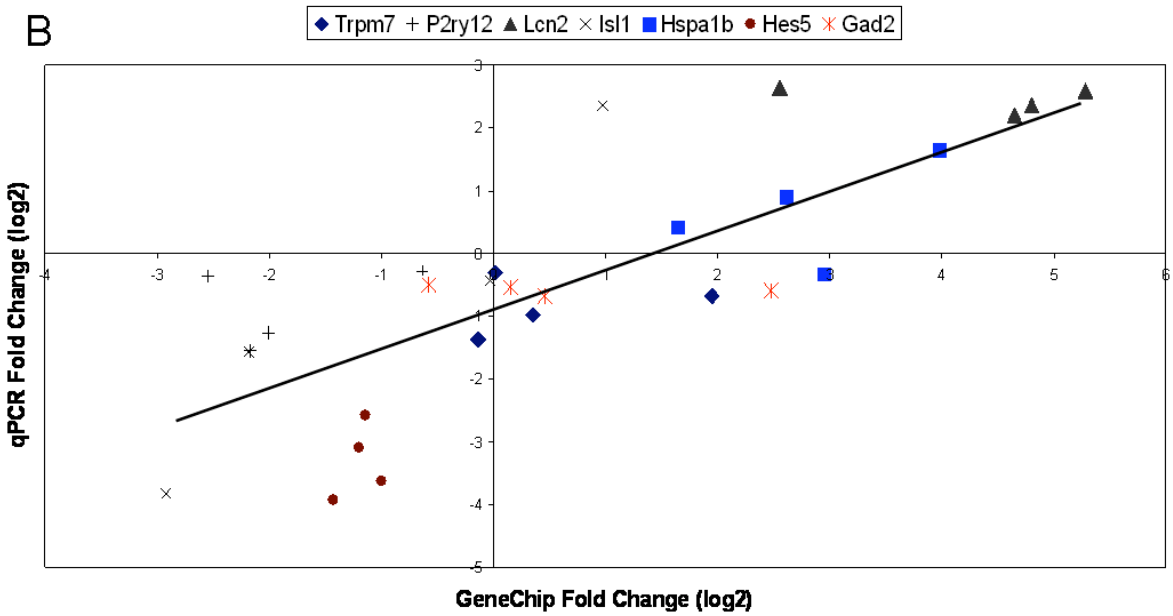


Fig. 5: CORRELATION BETWEEN GENECHIP ANALYSIS AND qPCR EXPERIMENTS. Real Time PCR experiments were performed for 7 genes differentially expressed in the four areas at 6 hours after injection. In tab A are reported the Fold Changes for the GeneChip analysis and for the qPCR for 6 representative highly variable points. In graph B all of the results of qPCR experiments were plotted against the corresponding Fold Changes according to Gene Expression Profiling for a total of 28 points. 21 out of 28 points show a good agreement between the results of the two techniques. The approximate linear correlation represented in the plot is: qPCR value = 0.57*(Affymetrix value) – 0.86

Analysis of Gene expression profiles: Gene Ontology terms

The identity of genes whose expression changed provided clues on the time course and nature of pathological processes initiated by KA-treatment.

For a general view of the time course of processes intervening between KA-injection and the emergence of an epileptic brain, we examined associations of groups of altered genes with

terms from the Gene Onthology system. As a first approach, we compared genes from injected and from contralateral hippocampus at all three time points pooling together genes from the dorsal or ventral areas. List of genes where submitted to GenMAPP (http://www.genmapp.org) and analysed. Gene Ontology terms were sorted according to Z-score and percentage of number of altered genes associated/number of genes present on the Chip associated.

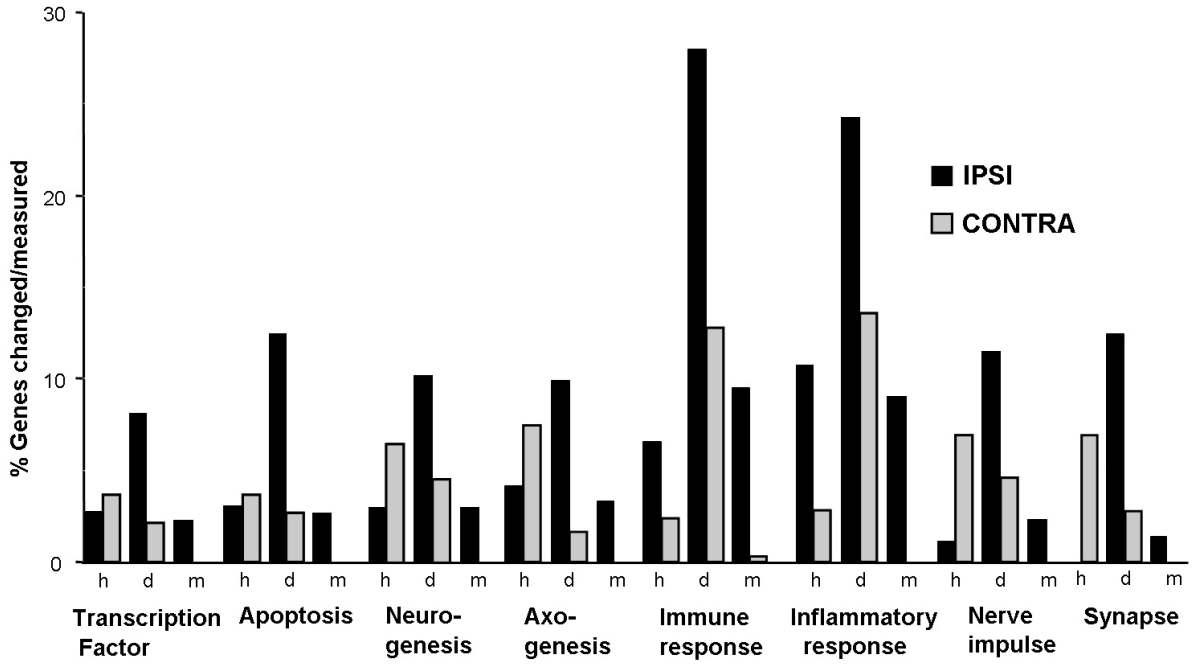


Fig. 6: CHANGES IN GENE EXPRESSION ASSOCIATED WITH GENE ONTOLOGY TERMS The graph shows the number of genes changed as a percentage of the number measured for 8 GO terms. Plots are made for each GO term, at each time point (6hr, 15 days and 6 months) for tissue from injected (IPSI) and from contralateral hippocampus (CONTRA).

Data for some of the most highly associated terms is shown in Fig. 6. We noted that:

- *Inflammatory* and *Immune responses* were the terms with the highest proportion of genes whose expression was changed. At 6 hours ~10% of the genes were altered in the ipsilateral hippocampus, less than 5% in the contralateral. At 15 days there are more than 20% of them differentially expressed in the injected side with a consistent 12% in the contralateral. Changes were still detected at 6 months in the area near the injection site.
- Up to 10% of the genes associated with *transcription factor activity* present on the Chip changed after KA injection. These alterations were initiated at the 6 hr time

point, at 15 days increased just in the injected side where some changes were maintained until 6 months.

- Genes associated with both *neurogenesis* and *axogenesis* were more affected at contralateral sites at the 6 hr time point, but maximum activity occurred ipsilaterally to the injection site at 15 days.
- Similar results were found for genes associated with *apoptosis*. .
- Terms associated with *nerve impulse transmission* and *synaptic function* also showed early activity in the contralateral hippocampus. These reached a maximum in the injected site of the hippocampus at 15 days but only minor alterations persisted at 6 months.

Analysis of Gene expression profiles: Identification of gene clusters.

We also examined the composition of smaller clusters of genes with similar spatial and temporal patterns and directions of altered expression. Fig. 7 shows a graphical representation of the differential expression in the clusters we identified:

1. *Genes upregulated **only** at 15 days **at least** in the ipsilateral dorsal site*. The largest of these clusters consisted of genes upregulated at the ipsilateral dorsal injection site, at 15 days. This cluster consisted of 850 genes with a majority (594 genes) changing only at this time point and 346 changing only at this site. Many of these genes participate in inflammatory processes such as interferon (*Ifi47* or *Isgf3g*) and other cytokines (*Tnfrsf13b, Il10ra* and *Cxcr6*), while others are associated with apoptosis (*Casp1*, *Casp7* and *Casp8*). Genes associated with the extracellular matrix composition (*Expi*, *Col20a1* and *Mmp19*) may participate in the development of the glial scar associated with neuronal death. Genes upregulated in other areas at this time point included caspases, chemokines, cytokines and receptors pointing to a wider activation of inflammation, cell death and sclerotic processes during the latent phase.
2. *Genes upregulated at both 15 days and 6 months **at least** in the ipsilateral dorsal site* after KA-treatment were considered separately. Usually these genes were upregulated to a lesser extent at the later time point. These were often correlated with GeneOntology terms similar to those described in the former cluster. Interestingly we

also identified 7 genes participating in the complement cascade (*C3ar1*, *C5ar1*, *C4b*, *C1qa*, *C1qb*, *C1qc* and *C3*) a process implicated in the progression towards seizures (Jamali, Bartolomei et al. 2006; Aronica, Boer et al. 2007) present in this cluster. 31 of these genes were also showing alteration at 6 hours still in the injection area. This subset includes the gene *Ctla2a* which codes for a protein related to inflammation. The fold changes detected for this gene were 3.06, 2.07 and 1.38 fold at 6 hrs, 15 days and 6 months respectively. This process seems reduced with time even though the number of genes that changed did not. Vimentin, a marker of radial astroglial cells (*Vim*: 1.49, 2.78 and 1.84) and the brain-derived neurotrophic factor (*Bdnf*: 1.49, 2.9 and 1.9) were also present in this subset.

3. *Genes downregulated at 6 months **only** in the ipsilateral dorsal site*. In the ipsilateral hippocampus at 6 months the highest ratio of downregulated genes compared to the upregulated ones. So we considered as a separate cluster the downregulated genes in this area/time point (88 genes). Most of these genes were already downregulated at 15 days but to a lesser extent. They included transcription factors (i.e. genes related to neurogenesis *Isl1* and *Neurod6)* and genes associated with neuronal signalling (*Trpv4* and *Rab20)*. Of these, three potassium channel genes (*Kcnh2*, *Kcnq5* and *Kcne2*) were downregulated at both 15 days and 6 months. Genes belonging to this downregulated cluster also coded for proteins involved in the establishment and maintenance of the architecture of brain tissue. These included three collagen subunits (*Col9a3*, *Col6a3* and *Col8a1*), Claudin 1 and 2 and the protein *Tjp3* which are involved in the formation of tight junctions (Eum, Andras et al. 2008; Van Itallie, Holmes et al. 2008; Xu, Kausalya et al. 2008). Downregulation of Claudin 8 during kindling has been described by Lamas et al (2002). The presence of these genes at the injection site suggests that after KA-treatment and neuronal death, the extracellular matrix undergoes long-term changes consistent with the formation of a glial scar.
4. *Genes differentially expressed **only** at 6 hours **only** in the contralateral ventral area*. Our differential analysis of dorsal and ventral regions of both injected and contralateral hippocampi permitted identification of changes at different distances from the site of KA-injection. We noted a cluster of 178 genes selectively changed at

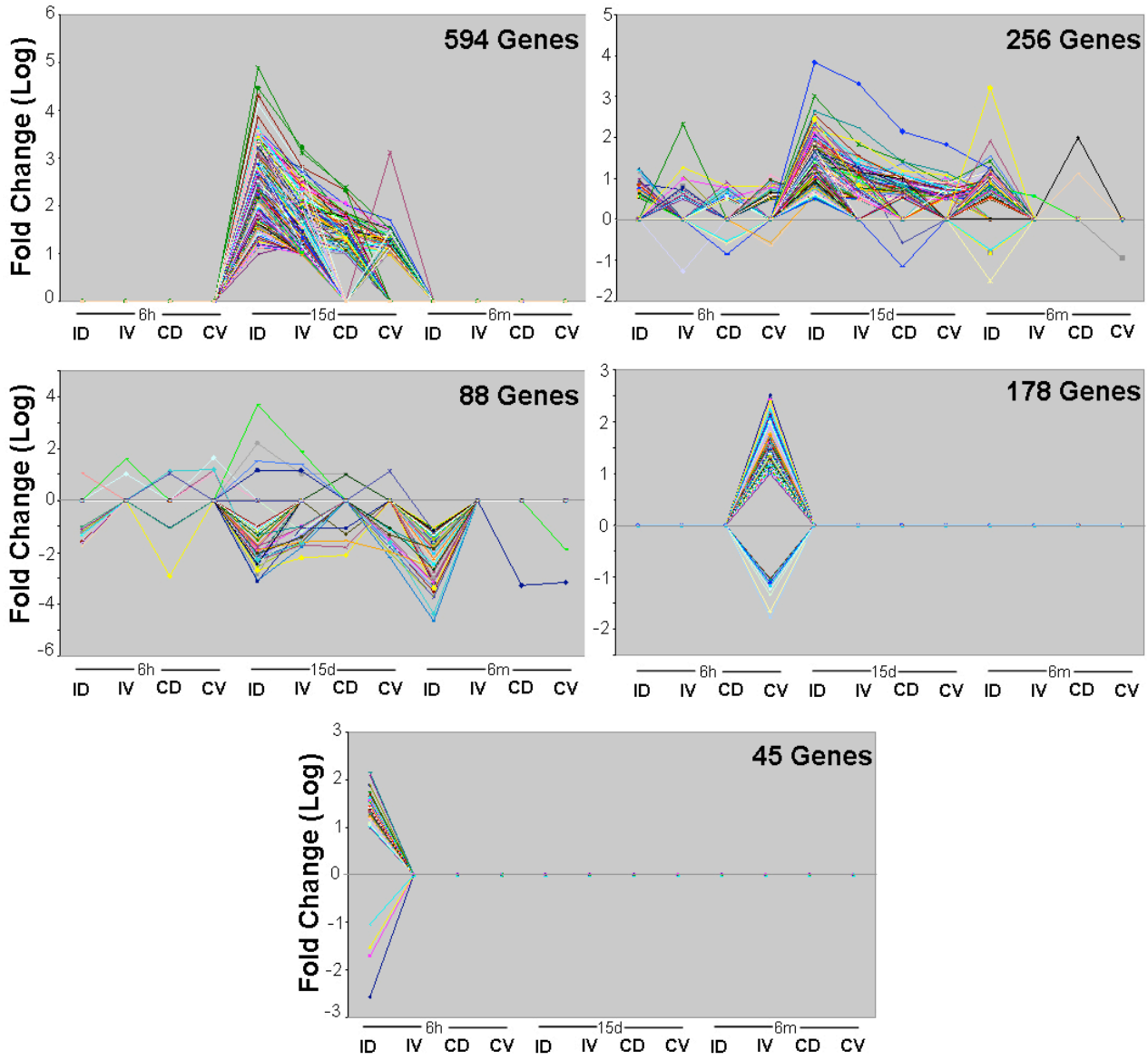


Fig. 7: CLUSTERS OF GENE EXPRESSION CHANGES. In the graphs are represented 5 clusters of common patterns of expression including most of the changes we identified. For each time point and area (x; ID= ipsilateral dorsal, IV=ipsilateral ventral, CD= contralateral dorsal, CV=contralateral ventral) the Fold Change is plotted (y). Different lines and colors indicate different genes. One single condition per cluster was used to filter the genes. Cluster 1: genes upregulated just at 15 days. Cluster 2: genes upregulated at 15 days and at more time point. Cluster 3: genes downregulated at 6 months in ID. Cluster 4: genes differentially regulated only in CV at 6 hours. Cluster 5: genes differentially regulated only in ID at 6 hours

the contralateral ventral site at 6 hrs after injection. These genes were mostly moderately up-regulated with fold changes in the range -2 to +2.5. They included genes associated with transcription and protein synthesis (*Pa2g4*, *Chd4* or *Nr2c2)* genes coding for regulators of chromatin assembly (*Smarcc1* and *Smarca*) and four factors that initiate translation (*Eif3s10*, *Eif4g1*, *Eif4a1* and *Eif5b*). Possibly these

genes are induced by activity associated with the status epilepticus since the Fink-Heimer silver stain revealed subsequent little cell death or fibre degeneration in this zone.

5. *Genes differentially regulated **only** at 6 hours **only** in the ipsilateral dorsal area*. A smaller cluster consists of genes (n=45) with medium changes in expression limited to the injection site during status epilepticus. These early responding genes included *Fos*, *Jun* and *JunB* as well as some Kruppel-like transcription factors (members 4, 6 and 9). The *Klf* family is involved in multiple processes including lymphocyte proliferation and differentiation, as well as apoptosis (Good and Tangye 2007; Britschgi, Trinh et al. 2008; Pearson, Fleetwood et al. 2008). The presence of these genes, with *Il6,* a factor associated with the pathogenesis of neurodegeneration during the development of an epileptic phenotype (Fassbender, Rossol et al. 1994; De Simoni, Perego et al. 2000) as well as the chemokines *Ccl7* and *Ccl11* suggest that the KA-treatment induces a rapid proliferation and activation of glial and microglial cells.

Analysis of Gene expression profiles: Neurotransmitter receptors and voltage-gated channels.

Genes coding for membrane proteins associated with synaptic signalling and cellular excitability showed only moderate changes. Five GABA-receptor subunits were differentially regulated.

- *Gabrg1*was downregulated (-1.2) and *Gabrg2* upregulated (1.18). at 15 days in the injected site.
- *Gabra1* and *Gabrb3* were moderately upregulated in the Contralateral Ventral area at 6 months (fold-chages of 1.27 and 1.58 respectively).
- Surprisingly, the subunit *Gabra6*, thought to be expressed only in the cerebellum (Kato 1990; Luddens, Pritchett et al. 1990) was detected at three different sites (ID, 1.74; CD, 1.85; CV, 1.02) at 6 months after the injection.

Expression changes were detected for four glutamate receptor subunits:

- *Gria3* was upregulated at 6 hours in the CV area (fold-change of 1.29)
- *Gria1*, *Grim1* and *Grik1* were moderately downregulated at 15 days in close to the site of KA-injection. Possibly these changes resulted from a dilution effect related to neuronal loss in the area.

The polypeptide 1 of the alpha nicotinic receptor (*Chrna1*) was up-regulated at both 15 days and 6 months in the injected area.

The strongest changes in genes coding for membrane channels controlling cellular excitability were observed for potassium channel subunits. Fig. 8 shows complex temporal and spatial patterns of up- and down regulation detected for genes of this family.

- Five genes (*Kcnk4*, *Kcnmb2*, *Kctd2*, *Kcnq2* and *Kcnab2)* were downregulated in the injected site of the dorsal hippocampous at 15 days.
- *Kcnq5* was down-regulated at 15 days in the injection site as well as in ipsilateral ventral and contralateral dorsal areas. At 6 months it was still downregulated in the ipsilateral dorsal site.
- *Kcne2* was downregulated at 15 days in both injected hippocampus and in contralateral ventral area with an increased down-regulation (fold-change of -4.65) at 6 months in the ipsilateral dorsal hippocampus.
- *Kcne1l* was the only K-channel subunit up-regulated at all four sites at 15 days especially (maximum fold-change of 4.67) in the ipsilateral dorsal where it also remained upregulated at 6 months.

Analysis of gene expression profiles: Transcription Factors.

A large number of differentially expressed genes were transcription factors. Expression changed significantly for 74 of them. Changes were detected at 6 hrs after KA-treatment for *Jun*, *Fos* and *Fosb.* While these changes were not unexpected, the largest alterations were detected for the transcription factor *Atf3* which is related to neuronal protection and known to be upregulated by KA-treatment (Francis, Dragunow et al. 2004). This transcription factor was upregulated at both 6 hrs and at 15 days. *Stat3,* a transcription factor involved in microglia activation (Fielding, McLoughlin et al. 2008; Huang, Ma et al. 2008), was upregulated at all time points in the injected area, underlying perhaps a persistent microglial activation to promote the inflammatory process.

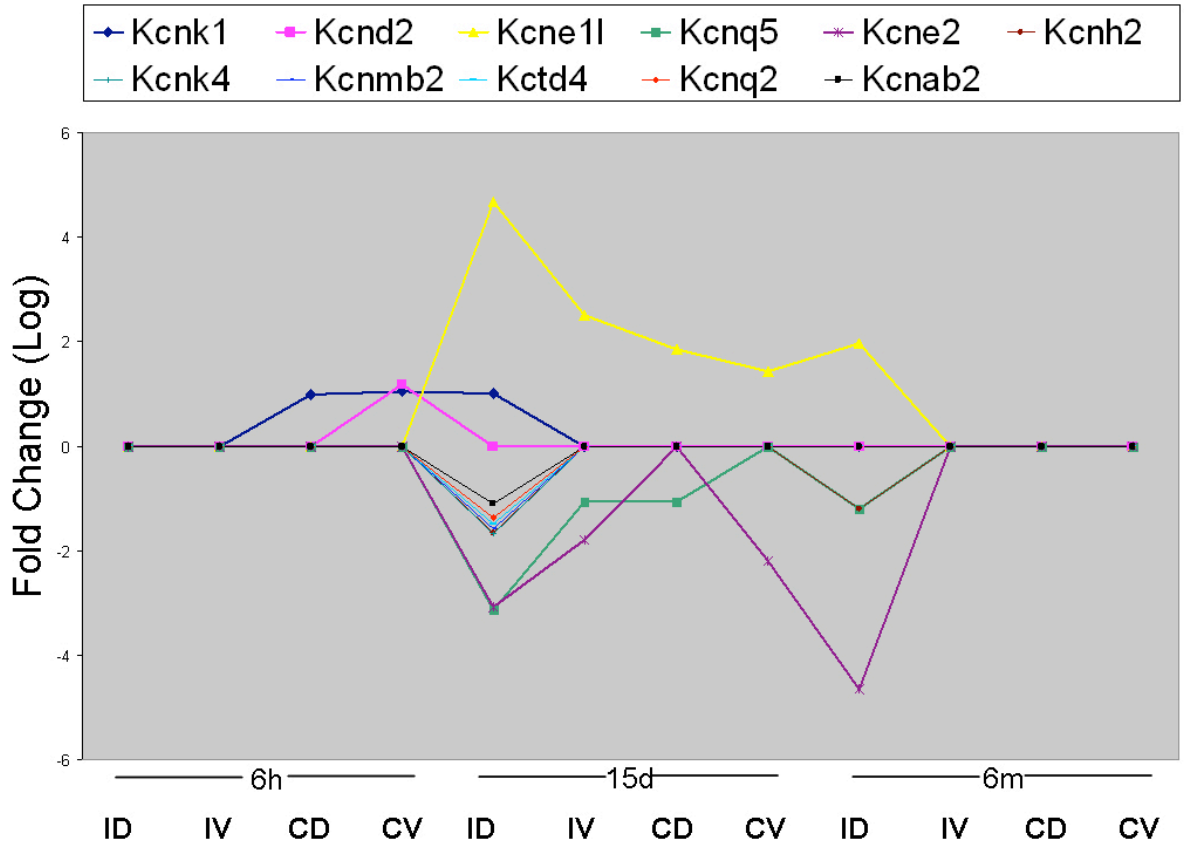


Fig. 8: TEMPORAL PATTERN OF DIFFERENTIAL EXPRESSION OF K CHANNELS. Fold Change of gene expression alteration expressed as a function of time points and areas (ID= ipsilateral dorsal, IV=ipsilateral ventral, CD= contralateral dorsal, CV=contralateral ventral) for subunits of K+ channels reported in the legend.

Many of the changes in transcription factor expression detected at 15 days after KA-treatments also seem likely to be involved in the orchestration of inflammatory responses. They include the interferon-related factors (*Irf7* and *Irf8*), as well as *Mef2c* or *Fli1*. Other identified regulatory genes have been associated with cellular proliferation and differentiation. The transcription factor *Satb2,* involved in the specification of a neuronal phenotype (Szemes, Gyorgy et al. 2006; Alcamo, Chirivella et al. 2008) was strongly downregulated at 15 days in the injected area as was *Lhx9* (Molle, Pere et al. 2004).

Some others transcription factors with altered expression limited to the ipsilateral dorsal site of the hippocampus showed alteration at 15 days persistant at 6 months. They were typically downregulated, including *Dlx1* and *Dlx5*, which form part of a family of transcription factors associated with interneuronal differentiation and migration (Anderson, Eisenstat et al. 1997) via inhibitory actions on axonal and dendritic growth (Cobos, Borello et al. 2007).

Suppression of *Dlx1* results in a loss of interneurons and induces seizures (Cobos, Calcagnotto et al. 2005).

Immuno-histochemical exploration of cell-type specificity of changes in selected genes.

While micro-array data from brain homogenates obtained from KA-treated animals provide evidence that a number of identified transcripts are up- or down regulated, they did not allow identifying the cells in which gene expression was changed. We therefore turned to immunohistochemistry to try to link gene profile data with cell types and their localisation within the hippocampus.

Glial cell activation is a key process induced by KA-treatment (refs) as confirmed by our micro-array data. We traced this process using antibodies that recognize vimentin and Glial Fibrillary Acidic Protein, two intermediate filament proteins expressed in astrocytes. Vimentin is expressed in both early and late developmental stages, but GFAP is only present in mature astrocytes (Eng 1988; Eliasson, Sahlgren et al. 1999). Both vimentin and GFAP are enhanced in reactive gliosis and after seizures (Lin and Cai 2004; Pekny and Nilsson 2005). Our gene profile data revealed a major up-regulation of *Vim* and *Gfap* at 15 days in all areas which persisted at 6 months near the injection site. We also detected *Vim* up-regulation at 6 hrs in both dorsal and ventral injected hippocampus. Astrocyte, or radial glial cell, activation in the hippocampus also contributes to neurogenesis (Doetsch and Scharff 2001; Song, Stevens et al. 2002; Doetsch 2003; Berninger, Costa et al. 2007) and synaptic activity (Porter and McCarthy 1996; Porter and McCarthy 1997; Kang, Jiang et al. 1998; Araque, Martin et al. 2002).
Fig. 9 shows immuno-staining experiments to explore the identity of elements expressing *Vim* and *Gfap* in hippocampal tissue from KA-treated animals at 15 days after injection. The neuronal marker NeuN let us identify changes in neuronal architecture including the loss of CA1 and hilar cells as well as the dispersion of dentate granule cells.

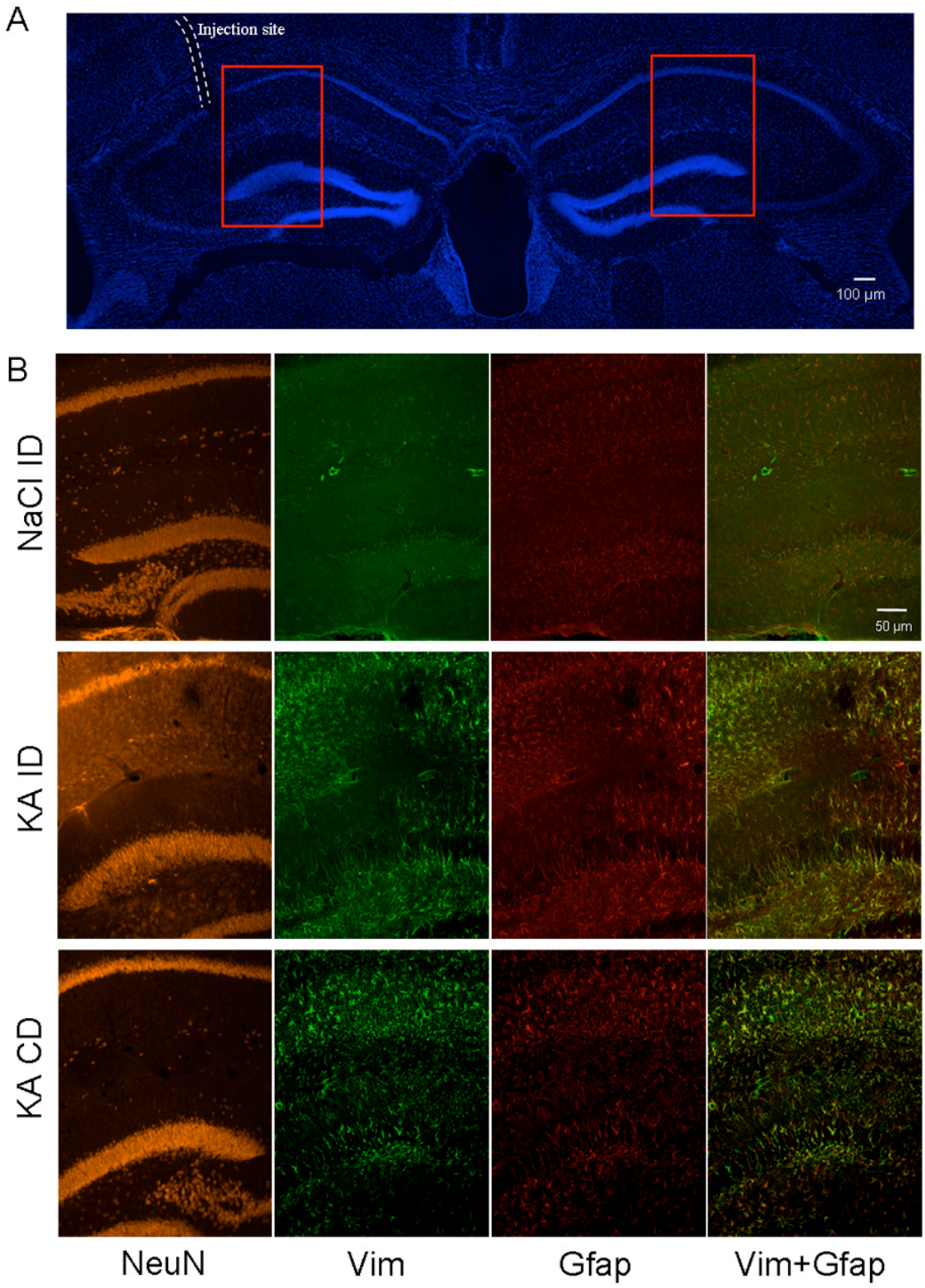
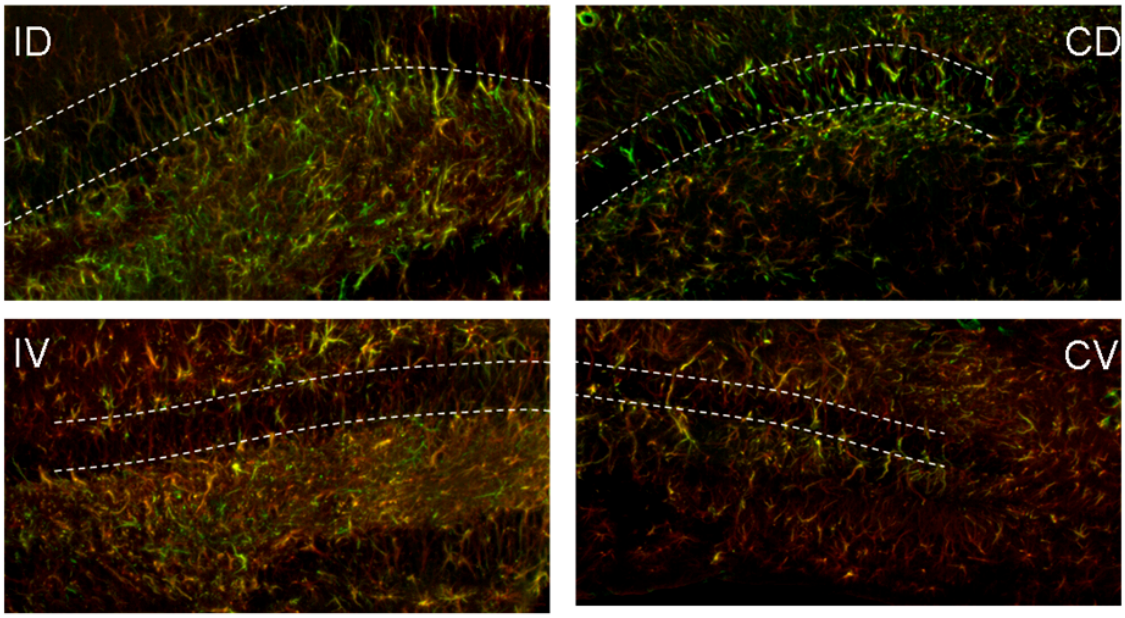


Fig. 9: IMMUNOSTAINING FOR PROTEINS ASSOCIATED WITH EARLY AND MATURE ASTROCYTES. A shows DAPI staining of both ipsilateral and contralateral hippocampi at 15 days after KA-injection. The injection site is shown and red squares indicate regions shown at greater magnification in B. B, shows stains for *NeuN* (orange) to indicate neurons, *Vim* (green), and *Gfap* (red) and the final overlay column (*Vim* + *Gfap)* shows their co-expression. The rows show tissue from the Ipsilateral Dorsal of NaCl-injected (first row) and KA-treated animals (second row) and from the contralateral site of the KA-treated animal (third row).

Immuno-staining for Vimentin and GFAP proteins revealed that KA-treatment induced a consistent increase in cells expressing Vim alone or both Vimentin and GFAP. The increase was larger in injected than in contralateral site of the hippocampus. It was most evident in the dentate, but also in the stratum radiatum of the CA1 region. Neither Vimentin nor GFAP staining was detected with NeuN in neuronal somatic layers. Comparison of dorsal and ventral regions of injected and contralateral hippocampus revealed differential staining patterns.

A



B

	ID	IV	CD	CV
Vim	**2.78**	2.45	1.67	1.49
Gfap	**2.12**	1.803	1.56	1.252

Fig. 10: VIM+ and GFAP+ CO-EXPRESSION IN THE DENTATE REGION OF KA-TREATED MICE. A shows immunofluorescence for Vimentin (green) and GFAP¨ (red) in the Dentate Gyrus at 15 days after KA-injection for tissue from ipsilateral dorsal, ID, contralateral dorsal, CD, ipsilateral ventral, IV and contralateral ventral CV regions. The granule cell layer is outlined with white dots. B shows log fold-changes from the array work for *Vim* and *Gfap* at 15 days. Red highlights the zone of maximal upregulation.

The highest density of Vim+ cells was detected in the dentate region of ipsilateral dorsal hippocampus with a significant co-localization with Gfap+ elements. Staining levels were lowest in tissue from contralateral ventral hippocampus, but colocalization of Vim+ and Gfap+ elements was consistently higher in ventral rather than in dorsal regions.

There was also a consistent difference in the localization of differentially immuno-positive elements (see Fig. 10). Vim+ cells were typically detected in the hilus, especially of dorsal injected hippocampus where most of them were Vim+/Gfap- while Vim+/Gfap+ elements tended to increase in ventral injected hippocampus. In contralateral hippocampus however Vim+ cells were strictly confined to the granular and subgranular zones of the dentate gyrus, regions classically associated with neuronal progenitor cells.

Discussion

The data on the identity of genes that change expression after KA-treatment shows some similarities to previous gene-chip work on epilepsy models. Our protocol based on intra-hippocampal KA injection permitted comparison of tissue from both injected and non-injected hippocampus. In this way we aimed to dissect relations between the genetic changes involved in epileptogenesis and the distinct stimuli, including the initial status epilepticus, cell death and the ensuing deafferentation as well as gliosis. Our data provided evidence for changes in a large number of genes (n=1563, see Figs 4 and *Supplementary Table*). The major classes of genes changed were involved in immune responses and inflammation, in cell death and cell growth. Many distinct spatio-temporal patterns of up- and down regulation were evident in our data, but a clear temporal sequence of changes in gene expression was evident:

- Early changes, at 6hrs after KA-treatment, included several transcription and growth factors.
- The largest numbers of altered genes involved with immune and inflammatory responses were detected at 15 days
- There was a limited number of persistent changes in genes coding for proteins that control cellular excitability and neuronal communication. However, most persistent changes were limited to tissue near to the KA-injection site and also concerned genes linked to inflammatory and immune responses.

Technical points:

To perform our study we used a common, well annotated array (mouse 430A2.0 from Affymetrix) containing thousands of genes, although not the entire transcriptome. Analyses were performed separately on four different areas: dorsal and ventral regions of injected and contralateral hippocampus for three time points each.

The number of animals used could have been larger, but we are encouraged that our results were similar to previous studies (Tang, Lu et al. 2002; Lukasiuk, Kontula et al. 2003; Gorter,

van Vliet et al. 2006). Furthermore, they were confirmed by measurements on some of the same genes using q-PCR (Fig. 5) and on their protein products using immunohistochemistry (Figs. 9 and 10). EEG records made from a larger animal sample could also have permitted correlation of genetic changes with the time from the most recent seizure (Gorter, van Vliet et al. 2006).

Our relatively large tissue samples yielded good quantities of genetic material but dictated a coarse spatial resolution. More detailed studies comparing tissue from smaller regions such as the sclerotic CA1 region and the non-sclerotic dentate gyrus should give more precise information. An increased number of time points might permit a better temporal mapping of genetic processes during the progression towards an epileptic brain. It would specifically permit verification of genes whose expression was altered at a single site and single time-point (178 genes for contralateral ventral tissue at 6 hrs and 545 genes from ipsilateral dorsal tissue at 15 days). While our immunohistochemical work begins to link changed genes to specific cell types (*Vim* and *Gfap* in Figs. 9 and 10), micro-array analysis does not provide such data. Cell specificity may be especially important in the epilepsies since neuronal death and glial proliferation implies that the cellular provenance of the material studied can change. The size of this shift in cell numbers has been derived from the CA1 region of patients with temporal lobe epilepsy (Lee, Dziema et al. 2007). In sclerotic tissue 95% of CA1 cells were of glial origin, while only 56 % of CA1 cells were glial in non-sclerotic tissue. Such a 'neuronal dilution' effect might bias data towards an upregulation of genes associated with glial cells. Our data and other studies (Hendriksen, Datson et al. 2001; Tang, Lu et al. 2002; Lukasiuk, Kontula et al. 2003) report an upregulation of such genes, but we noted no systematic artefactual down-regulation of genes associated with neurons.

Differential changes in gene expression resulting from focal KA-injection:

We defined some of the stimuli contributing to the development of chronic epileptiform activities with EEG records and anatomy. All regions participated in the status epilepticus at the first 6 hr time point used in array analysis (Fig. 1). The strongest activity was recorded from ventral regions of contralateral and injected hippocampus. Slice work (Le Duigou, Wittner et al. 2005) suggests that at this time, some cells near the KA-injection site are depolarized to potentials where they no longer discharge. Nissl and Fink Heimer stains made at 8 days after KA-injection (Fig. 3A) let us define the extent of cell death and fibre

degeneration before the second time point at 15 days. Cell death was maximal in the ipsilateral dorsal region, moderate in ipsilateral ventral regions and effectively absent in contralateral hippocampus. Fibre degeneration was detected in dorsal contralateral hippocampus as well as in both regions from the injected hippocampus. Slice records from hippocampal tissue obtained from KA-treated animals at latencies corresponding to the 6 month chronic time point reveal that interictal-like activity is preserved *in vitro* and occurs spontaneously in slices from both the ipsilateral and the controlateral side after KA-injection (Le Duigou, Bouilleret et al. 2008). Seizure-like activity could be induced by tetanic stimulation in both ipsilateral and contralateral hippocampus. Spontaneous interictal activity was rarely detected and tetanic stimuli rarely induced seizures in the region of maximal sclerosis in dorsal ipsilateral hippocampus.

There is a very good correlation between kainite-induced changes in gene expression and electrical and anatomical modifications. Genes up- and down-regulated in the ipsilateral dorsal cluster at 6 hours presumably correspond to those activated in early stages of neuronal death and to those involved in inflammatory and immune responses. In contrast those genes changed in the contralateral ventral cluster at 6 hours (largely moderate changes) may correspond more closely to changes induced by the epileptiform activity and exclude genes involved in neuronal death. The largest gene cluster centred on the ipsilateral dorsal hippocampus at the 15 day time point included those coding for proteins associated with the inflammatory and immune responses. There was little evidence for a cluster centred on dorsal contralateral hippocampus at 15 days where relatively pure responses to de-afferentation might have been expected, however genes induced by de-afferentation seem likely to also have been strongly activated in ipsilateral hippocampus. At this time point genes associated with the growth of neuronal processes and with neurogenesis were activated in tissue from both injected and non-injected hippocampus. At six months a single gene cluster was apparent in dorsal injected hippocampus with a few isolated genes still active in other regions. This cluster, with a strong down-regulated component, consisted of genes that were also detected at earlier time points together with some novel transcripts. There was a significant contribution of genes related to inflammation as noted in previous gene profile analyses of the epilepsies (Lukasiuk, Kontula et al. 2003; de Lanerolle and Lee 2005; Hunsberger, Bennett et al. 2005; Gorter, van Vliet et al. 2006). These may be related to the persistence of a glial scar (Crespel, Coubes et al. 2002) as well as other secondary inflammatory responses.

Microglial activation and immune / inflammatory responses

As already mentioned, the gene profile approach does not allow to link altered gene expressions with particular cell types. We are completing an immunohisto-chemical approach to this question as shown in Figs. 9 and 10 data on *Vim* and *Gfap*. Even so, several of the processes that change according to Gene Ontology associations can be linked to specific cell types.

Inflammatory processes and immune responses, are strongly upregulated in seizure-evoked animal models of hippocampal epilepsies as well as in epileptic patients, (Billiau, Wouters et al. 2005; Vezzani and Granata 2005; Gorter, van Vliet et al. 2006; van Gassen, de Wit et al. 2008). They involve microglial cells. After seizures these cells are activated which involves changes in cell number, morphology and gene expression (Niquet, Ben-Ari et al. 1994; Represa, Niquet et al. 1995). When activated, microglia secrete modulators of inflammation including cytokines and chemokines (Giulian 1993; Chao, Hu et al. 1995) which contribute to the induction of apoptosis (Margerison and Corsellis 1966; Magloczky and Freund 1993; Pollard, Charriaut-Marlangue et al. 1994; Fujikawa, Shinmei et al. 2000; Ben-Ari 2001).

We obtained evidence for a global up-regulation of genes associated with microglial signalling in both injected and contralateral hippocampus during the latent period. However at the time point corresponding to the emergence of chronic seizures, changes in expression of these genes became restricted to the injection site. This restriction may result from specific chemokines and trophic factors that maintain immune cells at this site in an active state.

Astrocyte proliferation, neurogenesis and growth.

Astrocytes are also activated in epileptic brain (Ernfors, Bengzon et al. 1991) and can be linked to a distinct set of Gene Ontology terms that we found were altered. They are involved in precursor cell proliferation and differentiation and secrete trophic factors that encourage cell growth (Song, Stevens et al. 2002). We detected an upregulation of genes coding for markers of precursor and mature astrocytes (Vimentin and GFAP, Figs 9 and 10) as well as secreted growth factors including members of the *Bdnf*, *Gmfa*, *Fgf* and *Tgf*'s families. Some of these factors, including *bdnf*, are known to modify neuronal excitability (Bariohay, Tardivel et al. 2008). Astrocytes may act as a third modulatory element at synapses involving

several neuro-transmitters (Porter and McCarthy 1996; Porter and McCarthy 1997; Kang, Jiang et al. 1998; Araque, Martin et al. 2002) and can also themselves release neurotransmitters in some conditions (Bezzi, Carmignoto et al. 1998; Araque, Li et al. 2000; Pasti, Zonta et al. 2001; D'Ascenzo, Fellin et al. 2007; Fellin, D'Ascenzo et al. 2007).

Our immunofluorescence data (Figs. 9 and 10) verified the Affymetrix data suggesting an upregulation of the genes *Vim* and *Gfap* also providing an insight into the cellular and regional specificity of their protein products. Vimentin is a marker for precursor cells while mature astrocytes express both Vimentin and GFAP. We found an increase in precursor radial glial-like elements (Gfap-/Vim+) in dorsal regions of both injected and contralateral hippocampus. Contralaterally, *Vim* and *Gfap* were confined to the subgranular zone of the dentate region, the traditional site for neurogenesis, but in injected hippocampus these cells were much more widely expressed.

The question of an increased neurogenesis in an epileptic brain remains controversial (Parent, Yu et al. 1997; Scharfman, Goodman et al. 2000; Fahrner, Kann et al. 2007). Our data suggest that hippocampal neuronal precursor cells receive distinct stimuli, but it remains unclear whether they favour production of stable new neurons. Some data suggests that newly generated elements mostly differentiate into astrocytes near the injection site but that the rate of neurogenesis is higher contralaterally (Kralic, Ledergerber et al. 2005; Ledergerber, Fritschy et al. 2006). Other work suggests daughter elements of radial glial cells can differentiate into neurons (Berninger, Costa et al. 2007). Probably precise patterns of precursor production depend on distinct niche conditions and different stimuli operating in the various environments. Our immuno-staining data supports this possibility suggesting that precursor proliferation and differentiation may even vary at distant sites of the same area in the same hippocampus.

Comparison with gene profile studies on animal models and human epileptic tissue

Genomic approaches based on a microarray analysis of epileptic tissue from MTLE patients are confined to the chronic phase of the pathology and often to sclerotic tissue (Becker, Chen et al. 2002; de Lanerolle and Lee 2005; Arion, Sabatini et al. 2006; Jamali, Bartolomei et al. 2006; Ozbas-Gerceker, Redeker et al. 2006). Several features of these results are consistent with our data. There is a consensus on changes in genes associated with glial cells, including

gfap, as well as inflammatory and immune responses, especially activation of the complement system and interleukins (de Lanerolle and Lee 2005; Jamali, Bartolomei et al. 2006). The predominance of changes in genes associated with glial cells led de Lanerolle and colleagues to emphasize an active astrocytic role in icto-genesis. They suggested this might emerge from a loss of K^+ buffering capacity due to down regulation of aquaporins. We found that *Aq4* was downregulated at 6hrs and became progressively more so with time. Changes in expression of genes coding for receptor and voltage-operated channels tended to be related to GABAergic transmission and to K^+ conductances (Arion, Sabatini et al. 2006; de Lanerolle and Lee 2005; Jamali, Bartolomei et al. 2006). We were also able to detect changes in K-channel subunits (Fig. 8) and a differential regulation, but in the opposite direction, of *Gabrb3* and *Gabrg2* subunits as in sclerotic human temporal lobe (Arion, Sabatini et al. 2006).

The use of animal models of epilepsy based either on convulsant treatment inducing a status epilepticus or on kindling stimulation has permitted to follow gene profile changes to the chronically epileptic state. The first studies identified changes in genes coding for structural and especially inflammatory processes at early time points (Elliott, Khademi et al. 2001; Matzilevich, Rall et al. 2002; Tang, Lu et al. 2002; Long, Zou et al. 2003). Elliott and colleagues focussing on transcription factors described a down-regulation of Hes5, a gene that we detected and that is involved in neurogenesis. As in the present case, pooling data from ipsilateral and contralateral hippocampis, Lukasiuk and colleagues (Lukasiuk, Kontula et al. 2003) provided evidence for activation of genes coding for transcription factors, cytokines structural proteins and immune processes. Gorter and colleagues (Gorter, van Vliet et al. 2006) performed possibly the most complete gene expression study on a kindling model of epilepsy analyzing tissue from CA3 hippocampal region, entorhinal cortex and cerebellum at acute, latent and chronic phases of the progression of this model toward recurrent seizures. Our derivation of Gene Ontology terms associated with the three time points reveals several similarities, although our data describes a lower level of changes in voltage-gated channels during the chronic phase and we did not detect a down-regulation of terms associated with synaptic transmission during the acute phase.

Genes associated with chronic epileptiform activity.

At six months after KA-injection, few genes were altered at sites distant from the original injection and few of them are involved in synaptic transmission or membrane excitability. The most intriguing of them was the GABA receptor subunit Gabra6 which was found to be upregulated exclusively at 6 months after KA-injection. Immunostaining is needed to determine which cells express this subunit which was previously thought to be present only in the cerebellum (Kato 1990; Luddens, Pritchett et al. 1990).

What does our data mean for the contribution of long-term genetic alterations to the chronic epileptic state? Possibly seizures are generated exclusively from the sclerotic region. This seems to contradict our slice work suggesting that seizures could be initiated by tetanic stimuli applied to both ipsilateral and contralateral sites. Furthermore interictal-like activity was generated by slices from both injected and non-injected hippocampus. Alternatively, changes in genes controlling neuronal electrical activity and synaptic transmission were diluted by tissue volume or glial proliferation to levels below our detection criteria. Finally, it may be that the genetic changes needed to produce an epileptic brain are terminated at the 6 month time point. This could be the case, if for example, circuit reconfiguration that involves the establishment of aberrant synaptic connections depends on the activation of genetic pathways for axonal and dendritic growth and synapse formation during a limited period. Our data show that genes associated with these processes were activated in regions other than dorsal ipsilateral hippocampus at the 15 day time point.

Conclusions and Perspectives

In the work done for this thesis, I used a genomic approach consisting of expression profile analysis with microarray technology to study genetic differences between a defined set of hippocampal interneurons and CA1 pyramidal cells and also to examine the time course of genetic changes involved in the emergence of an epileptic brain after intra-hippocampal injection of the convulsant kainic acid.

Gene profiling studies on interneuron diversity.

A two channel microarray technology was used to examine gene expression of EGFP-positive hippocampal interneurons from the GIN strain of mice (Oliva, Jiang et al. 2000) which correspond to the O-LM inhibitory cells containing somatostatin and sending an axon to innervate distal dendrites of CA1 pyramidal cells. We compare gene expression of EGFP-positive cells and CA1 pyramidal cells after sorting using on the basis of fluorescence or of a modified fast-Nissl stain combined with laser capture technology.

Comparison of expression levels for more than 10 000 transcripts represented on these arrays revealed specific differences between EGFP+ cells and pyramidal cells. A group of 443 transcripts was differentially expressed between the two different cell types; 260 of them at higher levels in the O-LM interneurons and 183 significantly more highly expressed in CA1 pyramidal cells. The Gene Ontology notation suggested that many of the genes with differential expression were involved in the processes of *signal transduction* and *transport*. Some genes coding for neurotransmitter receptors and ion channels were also differentially expressed and these genes together with those involved in signal transduction and transport may contribute to the neurophysiological difference between these different cell types.

Further experiments using qPCR experiments or immuno-histochemistry are needed to confirm the identity of differentially regulated transcripts. Either a conclusive identification of genes specific to this subset of Somatostatin-containing O-LM cells or just differentially expressed between hippocampal interneurons and pyramidal cells would be of interest. A complete characterization of the genetic profile of different sets of hippocampal GABAergic

neurons will be extremely useful to progress with the question of the complexity and diversity of this cell population (Ascoli, Alonso-Nanclares et al. 2008).
More precisely targeted experimental work would be useful to pursue the functional effects of some of the proteins found to be differentially expressed by SOM interneurons and CA1 pyramidal cells. For instance how does the differential expression of the *Rab3b* protein contribute to the differences in physiological properties of the two cell types? One possibility would be to use selective intrabodies (Zita, Marchionni et al. 2007) as molecular tools to suppress function of this gene *in vivo*. Alternatively, *Rab3b* might be targeted with RNA interference techniques (RNAi) at the level of mRNA degradation and subsequent inhibition of protein synthesis (Ramos, Bai et al. 2006). Further tests of electrical activity of perhaps and synaptic transmission may help identifying how *Rab3b* contributes to distinct functions of the two cell types.

We also noted with interest that a number of transcription factors were differentially expressed in the two cell types. None of these regulatory elements have previously been linked with specification of interneurons or pyramidal cells. Possibly knock-out or RNAi experiments might help define a differential role for these molecules during neuronal development.

A conclusive validation of the gene array technology might have been provided if it showed a differential expression of genes coding for proteins known to be differentially expressed by the two cell types. Unfortunately neither the gene coding for somatostatin nor for the *a* splice variant of mGluR1 (Oliva, Jiang et al. 2000) were present in the arrays used in this work. However it seems clear that the combined use of laser capture technology and gene profile analysis can reveal sensitive differences in gene expression by distinct interneuron cell populations and principal cells of hippocampus and cortex (Sugino, Hempel et al. 2006).

A necessary further step in this work will be to compare profiles of differentially expressed genes with anatomical, immunostaining and especially electrophysiological data. It may even be possible eventually to perform expression profile experiments on single neurones (Subkhankulova and Livesey 2006; Yano, Subkhankulova et al. 2006), in conjunction with patch clamp recording. Such studies might provide data on the variability of genetic properties of different cells within an identified interneurone population. Physiological studies suggest that O-LM interneurons have diverse excitable properties (Minneci, Janahmadi et al.

2007). So are Somatostatin containing Interneurons part of a unique class? Single cell gene expression profiles from these cells could highlight differences and similarities between the neurons and clarify whether they form a genomically homogeneous population.

Gene profiling studies on dynamic changes in a model of an epileptic syndrome.

In the second part of the work, I used the well characterized Affymetrix GeneChip technology.(430A 2.0 chip, ~14 000 transcripts) to analyse gene expression changes occurring at 6 hours, 15 days and 6 months after KA-injection into the hippocampus. These time points correspond to the initial status epilepticus, the latent phase, and the stable expression of spontaneous recurrent seizures in this mouse model of temporal lobe epilepsy. I identified large numbers of transcripts that were differentially regulated in a number of different patterns over the three different time points. As expected, the profiles of differentially expressed genes suggested multiple processes were activated during the progression towards an epileptic brain including immune and inflammatory responses, as well as cell growth and neurogenesis were activated during the progression towards an epileptic brain. Changes detected with the array studies were concordant with controls using qPCR and immunohistochemistry to measure changes in expression of gene and of coded proteins.

Inflammatory processes were still engaged, exclusively at sites near KA-injection, even after a delay of six months. The role of these persistent changes remains unclear but they are consistent with recent findings in both animal models of epilepsy and in tissue obtained from epileptic patients (de Lanerolle and Lee 2005; Ozbas-Gerceker, Redeker et al. 2006; Aronica and Gorter 2007). Further studies are needed to ask whether this persistent inflammation is an epi-phenomenon related to the cell death of hippocampal sclerosis, or a crucial factor in the emergence of recurrent seizures. Interestingly, inflammation-associated genes are activated after convulsant-induced status epilepticus and ischemia-induced neuronal loss (Simon, Cho et al. 1991; Stoll, Jander et al. 1998; Lee, Grabb et al. 2000) which may not lead to an epileptic brain. A careful comparison of gene expression changes in epileptic and ischemic tissue may permit identification of similarities and difference in the activation of the immune system by the two stimuli.

It would be especially useful to compare in ischemic and epileptic animals the degree of activation of the complement cascade (Jamali, Bartolomei et al. 2006; Aronica, Boer et al.

2007). Furthermore, injection of complement factors induces cell death and seizures in the rat (Xiong, Qian et al. 2003). Further studies using KO or RNAi techniques may help identifying the roles of specific components of the immune system in the generation of the epileptic network (Einav, Pozdnyakova et al. 2002).

My gene array analysis identified many transcripts associated with microglia and astrocytes as well as large numbers of genes that could not be definitively attributed to a specific cell type. Immunostaining work (i.e. for Vimentin and GFAP) may help clarify the cell-type and regional distribution of gene changes. An alternative approach to this question might be to pursue gene profile studies on purified cell populations obtained from epileptic animals at different time points. In this sense the FACS technology used to separate EGFP+ hippocampal interneurons, together with astrocyte or microglial-specific fluorescent markers could prove useful. It might permit to detect neuron-specific changes more sensitively than from whole-tissue homogenates by avoiding fractional changes in cell types resulting from 'glial dilution'.

The effects of KA-injection on gene expression by EGFP+ neurons from GIN mice could be followed with this technique. In fact this cell group seems to be particularly vulnerable to excitotoxic insults (Oliva, Lam et al. 2002) and they are among the first cells to die during the development of the epileptic network (Dinocourt, Petanjek et al. 2003). Studies on EGFP+ cells may permit a clarification of genes and pathways activated in KA-induced cell death.

Epilepsy is a disease of aberrant and hypersynchronous neuronal electrical activity. I identified a set of genes, in the contralateral ventral region, that were probably activated by epileptiform activity during the status epilepticus and were not related to neuronal death. At the 15 days time point, changes were detected in many transcripts related to glial cell activation. During the persistent phase of recurrent seizure expression, there were few changes in neuron-associated genes outside the initial injection site. Are seizures initiated exclusively from sites of profound neuronal death? Or might seizures arise from changes in neuronal connectivity due to genes controlling growth processes activated at the intermediate time point? Gene profile analysis at more intermediate time points might better define growth processes. Further EEG studies on sites for seizure initiation would also be useful to define sites for a more precise gene profile analysis to improve understanding on the links between changes at these sites and the initiation of recurrent seizures.

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Supplementary Tables

Tab.1 : Differentially expressed genes between EGFP+ Somatostatin-containing interneurons and pyramidal cells of the hippocampus. Fold Changes is expressed in logarithmic scale. Positive values represent genes more represented in the interneuronal population, negative values genes more represented in pyramidal cells. Genes are listed in order of Fold Change (Log2).

Symbol	*Name*	*Fold Change (Log2)*	*p-value*
Rab3b	RAB3B, member RAS oncogene family	3.106	0.00012
Aldoc	Aldolase 3, C isoform	3.084	0.00001
Ndufa12	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12	2.899	0.00002
Rabac1	Rab acceptor 1 (prenylated)	2.898	0.00012
Ptgds	Prostaglandin D2 synthase (brain)	2.820	0.02538
Nap1l5	Nucleosome assembly protein 1-like 5	2.647	0.00102
Cox4i1	Cytochrome c oxidase subunit IV isoform 1	2.528	0.00284
Wdr5	WD repeat domain 5	2.522	0.00066
Slc25a4	Solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 4	2.483	0.00015
Trf	Transferrin	2.432	0.00002
Apoe	Apolipoprotein E	2.412	0.00256
Uqcrb	Ubiquinol-cytochrome c reductase binding protein	2.394	0.01115
Stx8	Syntaxin 8	2.392	0.00020
Ndufb8	NADH dehydrogenase (ubiquinone) 1 beta subcomplex 8	2.390	0.00258
Tmem160	Transmembrane protein 160	2.359	0.00001
1700001L19Rik	RIKEN cDNA 1700001L19 gene	2.353	0.00002
Cxx1c	CAAX box 1 homolog C (human)	2.353	0.00000
1810046J19Rik	RIKEN cDNA 1810046J19 gene	2.207	0.00003
Syt1	Synaptotagmin I	2.199	0.00000
EG628161	Predicted gene, EG628161	2.152	0.00237
Cmtm5	CKLF-like MARVEL transmembrane domain containing 5	2.138	0.00009
Rps2	Ribosomal protein S2	2.102	0.00112
Prr8	Proline rich 8	2.084	0.01651
Rpl35	Ribosomal protein L35	2.081	0.00712
2900011O08Rik	RIKEN cDNA 2900011O08 gene	2.052	0.01361
Bcl2l13	BCL2-like 13 (apoptosis facilitator)	2.045	0.00009

Cdh13	Cadherin 13	2.040	0.00038
Prdx2	Peroxiredoxin 2	2.032	0.00073
1500032D16Rik	RIKEN cDNA 1500032D16 gene	2.025	0.02405
Vtn	Vitronectin	2.020	0.00505
Pqbp1	Polyglutamine binding protein 1	2.000	0.00906
Kctd20	Potassium channel tetramerisation domain containing 20	1.983	0.00002
Ldhb	Lactate dehydrogenase B	1.979	0.03275
Hint1	Histidine triad nucleotide binding protein 1	1.972	0.00004
Snrpd2	Small nuclear ribonucleoprotein D2	1.958	0.00066
Ddx1	DEAD (Asp-Glu-Ala-Asp) box polypeptide 1	1.957	0.00002
Cox5a	Cytochrome c oxidase, subunit Va	1.950	0.02387
Nme1	Expressed in non-metastatic cells 1, protein	1.942	0.00007
Atp5g3	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 3	1.937	0.00160
Lrrc4	Leucine rich repeat containing 4	1.896	0.01658
Serpine2	Serine (or cysteine) peptidase inhibitor, clade E, member 2	1.871	0.00304
Tmem121	Transmembrane protein 121	1.866	0.00118
Pnoc	Prepronociceptin	1.823	0.00102
Ap1m2	Adaptor protein complex AP-1, mu 2 subunit	1.816	0.00001
Ndrg4	N-myc downstream regulated gene 4	1.816	0.01028
Hspe1	Heat shock protein 1 (chaperonin 10)	1.814	0.00035
Crct1	Cysteine-rich C-terminal 1	1.807	0.00160
H2-Ke2	H2-K region expressed gene 2	1.799	0.00002
Litaf	LPS-induced TN factor	1.798	0.00051
2310003F16Rik	RIKEN cDNA 2310003F16 gene	1.797	0.00035
Ik	IK cytokine	1.766	0.00662
Ppa2	Pyrophosphatase (inorganic) 2	1.766	0.00632
Alkbh6	AlkB, alkylation repair homolog 6 (E. coli)	1.756	0.00502
Gap43	Growth associated protein 43	1.752	0.00612
Dpp10	Dipeptidylpeptidase 10	1.750	0.00313
Spcs1	Signal peptidase complex subunit 1 homolog (S. cerevisiae)	1.748	0.00002
Nrarp	Notch-regulated ankyrin repeat protein	1.743	0.00008
Gabrg2	Gamma-aminobutyric acid (GABA-A) receptor, subunit gamma 2	1.741	0.00177
Rpl28	Ribosomal protein L28	1.730	0.02605
Snap25	Synaptosomal-associated protein 25	1.726	0.01060

Ube1dc1	Ubiquitin-activating enzyme E1-domain containing 1	1.714	0.00191
Hmox2	Heme oxygenase (decycling) 2	1.701	0.00020
Zcchc12	Zinc finger, CCHC domain containing 12	1.688	0.00002
Ndufa8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8	1.664	0.00647
Ndrg2	N-myc downstream regulated gene 2	1.662	0.01527
Mrpl36	Mitochondrial ribosomal protein L36	1.652	0.00001
Pappa	Pregnancy-associated plasma protein A	1.637	0.00030
Gabrd	Gamma-aminobutyric acid (GABA-A) receptor, subunit delta	1.632	0.00014
Atp5f1	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit b, isoform 1	1.631	0.00102
Nsg1	Neuron specific gene family member 1	1.621	0.00041
Kctd6	Potassium channel tetramerisation domain containing 6	1.599	0.00021
Shc4	SHC (Src homology 2 domain containing) family, member 4	1.594	0.00240
Phpt1	Phosphohistidine phosphatase 1	1.586	0.02504
LOC100043341	Similar to ribosomal protein L35a	1.576	0.00062
Slitrk5	SLIT and NTRK-like family, member 5	1.576	0.00012
1700021F05Rik	RIKEN cDNA 1700021F05 gene	1.575	0.00072
EG328451	Predicted gene, EG328451	1.568	0.00065
Taf11	TAF11 RNA polymerase II, TATA box binding protein (TBP)-associated factor	1.558	0.02047
Arl6ip5	ADP-ribosylation factor-like 6 interacting protein 5	1.555	0.00447
Csrp1	Cysteine and glycine-rich protein 1	1.553	0.04443
Lsm11	U7 snRNP-specific Sm-like protein LSM11	1.541	0.03542
Pcnxl2	Pecanex-like 2 (Drosophila)	1.538	0.00502
B630005N14Rik	RIKEN cDNA B630005N14 gene	1.529	0.02277
Atp5b	ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit	1.521	0.00662
Pick1	Protein interacting with C kinase 1	1.518	0.00035
Akap13	A kinase (PRKA) anchor protein 13	1.508	0.00040
Hnt	Neurotrimin	1.505	0.03273
BC031853	CDNA sequence BC031853	1.504	0.04232
0610006I08Rik	RIKEN cDNA 0610006I08 gene	1.503	0.01003
Cox6a1	Cytochrome c oxidase, subunit VI a, polypeptide 1	1.498	0.00557
Arpc2	Actin related protein 2/3 complex, subunit 2	1.497	0.03731
Grtp1	GH regulated TBC protein 1	1.479	0.03905
Anp32a	Acidic (leucine-rich) nuclear phosphoprotein 32 family, member A	1.475	0.02003
Ecgf1	Endothelial cell growth factor 1 (platelet-derived)	1.474	0.00165

Grik1	Glutamate receptor, ionotropic, kainate 1	1.467	0.00643
Gpx3	Glutathione peroxidase 3	1.453	0.00073
Praf2	PRA1 domain family 2	1.451	0.01228
Ptf1a	Pancreas specific transcription factor, 1a	1.451	0.00102
Ndufa1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1	1.450	0.00765
Tmem91	Transmembrane protein 91	1.447	0.04597
1810035L17Rik	RIKEN cDNA 1810035L17 gene	1.444	0.00001
Mrpl46	Mitochondrial ribosomal protein L46	1.443	0.00021
Magee1	Melanoma antigen, family E, 1	1.439	0.00096
Pigc	Phosphatidylinositol glycan anchor biosynthesis, class C	1.421	0.03058
Mlc1	Megalencephalic leukoencephalopathy with subcortical cysts 1 homolog (human)	1.419	0.01868
Rps6	Ribosomal protein S6	1.418	0.04888
Psmd12	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 12	1.411	0.00194
Pdcd6	Programmed cell death 6	1.410	0.00823
Gas6	Growth arrest specific 6	1.394	0.00031
Spast	Spastin	1.394	0.00662
Flywch2	FLYWCH family member 2	1.389	0.03273
6330577E15Rik	RIKEN cDNA 6330577E15 gene	1.383	0.00294
Gse1	Genetic suppressor element 1	1.382	0.00001
2810487A22Rik	RIKEN cDNA 2810487A22 gene	1.380	0.01569
Hsdl1	Hydroxysteroid dehydrogenase like 1	1.379	0.00418
Ndufa11	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 11	1.372	0.04063
2310003H01Rik	RIKEN cDNA 2310003H01 gene	1.367	0.00732
Trappc4	Trafficking protein particle complex 4	1.367	0.00001
Pura	Purine rich element binding protein A	1.361	0.02605
Cend1	Cell cycle exit and neuronal differentiation 1	1.353	0.04658
Yipf1	Yip1 domain family, member 1	1.351	0.00355
1500005A01Rik	RIKEN cDNA 1500005A01 gene	1.348	0.00012
3321401G04Rik	RIKEN cDNA 3321401G04 gene	1.348	0.00179
Nsg2	Neuron specific gene family member 2	1.345	0.00095
Plxdc2	Plexin domain containing 2	1.344	0.00447
Nell2	NEL-like 2 (chicken)	1.342	0.01998
BC003267	CDNA sequence BC003267	1.340	0.03731
Rmnd1	Required for meiotic nuclear division 1 homolog (S. cerevisiae)	1.339	0.01424

2310014G06Rik	RIKEN cDNA 2310014G06 gene	1.330	0.02515
Acsbg1	Acyl-CoA synthetase bubblegum family member 1	1.325	0.00038
Fto	Fat mass and obesity associated	1.313	0.00026
1700016H13Rik	RIKEN cDNA 1700016H13 gene	1.309	0.01334
Nsbp1	Nucleosome binding protein 1	1.306	0.00847
Ddx24	DEAD (Asp-Glu-Ala-Asp) box polypeptide 24	1.305	0.00008
Mtdh	Metadherin	1.304	0.00692
G6pc3	Glucose 6 phosphatase, catalytic, 3	1.301	0.00921
Sdhb	Succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	1.300	0.01527
Snrpn	Small nuclear ribonucleoprotein N	1.300	0.00293
Hook2	Hook homolog 2 (Drosophila)	1.299	0.01960
C330019L16Rik	RIKEN cDNA C330019L16 gene	1.295	0.04531
2810468N07Rik	RIKEN cDNA 2810468N07 gene	1.291	0.00360
Egr1	Early growth response 1	1.291	0.01541
Ndufb5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5	1.288	0.04489
Rtcd1	RNA terminal phosphate cyclase domain 1	1.288	0.00160
Tm2d2	TM2 domain containing 2	1.286	0.00177
Ppp1r11	Protein phosphatase 1, regulatory (inhibitor) subunit 11	1.284	0.02206
Neurl2	Neuralized-like 2 (Drosophila)	1.278	0.03273
1810021J13Rik	RIKEN cDNA 1810021J13 gene	1.273	0.03201
Gtpbp1	GTP binding protein 1	1.262	0.03275
Rps11	Ribosomal protein S11	1.262	0.01445
Vamp8	Vesicle-associated membrane protein 8	1.260	0.01685
Mel13	Melanoma nuclear protein 13	1.256	0.04574
Polr2f	Polymerase (RNA) II (DNA directed) polypeptide F	1.253	0.01969
Sfxn5	Sideroflexin 5	1.247	0.01497
Mea1	Male enhanced antigen 1	1.244	0.00732
Selm	Selenoprotein M	1.244	0.02996
Timp4	Tissue inhibitor of metalloproteinase 4	1.239	0.02806
Rgs16	Regulator of G-protein signaling 16	1.237	0.02432
A930017N06Rik	RIKEN cDNA A930017N06 gene	1.235	0.01317
BC049635	CDNA sequence BC049635	1.230	0.00882
Sdha	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	1.229	0.00347
Mgat5b	Mannoside acetylglucosaminyltransferase 5, isoenzyme B	1.228	0.01926

BC003266	CDNA sequence BC003266	1.227	0.00357
OTTMUSG00000007209	Predicted gene, OTTMUSG00000007209	1.225	0.00329
Mobkl1b	MOB1, Mps One Binder kinase activator-like 1B (yeast)	1.224	0.00263
Vcp	Valosin containing protein	1.223	0.00904
Orc5l	Origin recognition complex, subunit 5-like (S. cerevisiae)	1.220	0.00626
Tpo	Thyroid peroxidase	1.210	0.00511
Dolk	Dolichol kinase	1.207	0.00038
Gabra4	Gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 4	1.204	0.04632
Ubxd2	UBX domain containing 2	1.204	0.00329
Sap18	Sin3-associated polypeptide 18	1.203	0.01974
4930520K10Rik	RIKEN cDNA 4930520K10 gene	1.197	0.01876
Rbmx2	RNA binding motif protein, X-linked 2	1.196	0.02084
Bnip2	BCL2/adenovirus E1B interacting protein 1, NIP2	1.195	0.00606
Rnaseh2c	Ribonuclease H2, subunit C	1.189	0.00904
Adpgk	ADP-dependent glucokinase	1.185	0.00256
Taf9	TAF9 RNA polymerase II, TATA box binding protein (TBP)-associated factor	1.185	0.00026
Cldn5	Claudin 5	1.184	0.02873
2310004L02Rik	RIKEN cDNA 2310004L02 gene	1.183	0.03770
Ptprk	Protein tyrosine phosphatase, receptor type, K	1.178	0.00662
A230065H16Rik	RIKEN cDNA A230065H16 gene	1.177	0.01060
Klhl22	Kelch-like 22 (Drosophila)	1.176	0.02382
Mark2	MAP/microtubule affinity-regulating kinase 2	1.174	0.00727
Stt3b	STT3, subunit of the oligosaccharyltransferase complex, homolog B (S. cerevisiae)	1.170	0.00607
Tmem176b	Transmembrane protein 176B	1.170	0.01497
Arl4d	ADP-ribosylation factor-like 4D	1.168	0.02515
Ddx54	DEAD (Asp-Glu-Ala-Asp) box polypeptide 54	1.165	0.01455
Actr10	ARP10 actin-related protein 10 homolog (S. cerevisiae)	1.155	0.00665
Edf1	Endothelial differentiation-related factor 1	1.155	0.01651
Mir16	Membrane interacting protein of RGS16	1.155	0.00447
Polr2k	Polymerase (RNA) II (DNA directed) polypeptide K	1.155	0.00170
Pcbd1	Pterin 4 alpha carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear factor 1 alpha (TCF1) 1	1.152	0.03875
Tor2a	Torsin family 2, member A	1.150	0.00360
Med11	Mediator of RNA polymerase II transcription, subunit 11 homolog (S. cerevisiae)	1.148	0.02504
Gclm	Glutamate-cysteine ligase , modifier subunit	1.143	0.01424

Sbds	Shwachman-Bodian-Diamond syndrome homolog (human)	1.142	0.01317
2610204K14Rik	RIKEN cDNA 2610204K14 gene	1.141	0.01334
Myo18b	Myosin XVIIIb	1.140	0.02101
Uxt	Ubiquitously expressed transcript	1.140	0.01186
Hspa4	Heat shock protein 4	1.135	0.00923
Itm2b	Integral membrane protein 2B	1.135	0.02382
Alkbh2	AlkB, alkylation repair homolog 2 (E. coli)	1.134	0.01880
Tmem79	Transmembrane protein 79	1.134	0.01614
Rb1	Retinoblastoma 1	1.132	0.03985
Shmt1	Serine hydroxymethyltransferase 1 (soluble)	1.125	0.00268
8430415E04Rik	RIKEN cDNA 8430415E04 gene	1.124	0.01960
Atp6v1c1	NA	1.120	0.01614
0610007L01Rik	RIKEN cDNA 0610007L01 gene	1.118	0.01614
Gstm4	Glutathione S-transferase, mu 4	1.115	0.01444
Rbm16	RNA binding motif protein 16	1.115	0.00171
Rtn3	Reticulon 3	1.114	0.01250
Serpinb12	Serine (or cysteine) peptidase inhibitor, clade B (ovalbumin), member 12	1.114	0.03623
A230056P14Rik	RIKEN cDNA A230056P14 gene	1.112	0.03229
Psmd11	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 11	1.108	0.02625
Nat2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	1.103	0.01674
Kin	Antigenic determinant of rec-A protein	1.098	0.00906
Ncam1	Neural cell adhesion molecule 1	1.098	0.01681
Adipor1	Adiponectin receptor 1	1.095	0.02402
1300010M03Rik	RIKEN cDNA 1300010M03 gene	1.093	0.02382
Klf15	Kruppel-like factor 15	1.087	0.02405
Rhoj	Ras homolog gene family, member J	1.087	0.00102
AW209491	Expressed sequence AW209491	1.084	0.02630
ENSMUSG00000053412	Predicted gene, ENSMUSG00000053412	1.084	0.04715
Cort	Cortistatin	1.083	0.02651
1810029B16Rik	RIKEN cDNA 1810029B16 gene	1.082	0.03273
2700078K21Rik	RIKEN cDNA 2700078K21 gene	1.080	0.02013
Ube2z	Ubiquitin-conjugating enzyme E2Z (putative)	1.079	0.03996
Mrpl14	Mitochondrial ribosomal protein L14	1.075	0.02686
5430433E21Rik	RIKEN cDNA 5430433E21 gene	1.074	0.00662

Bicd1	Bicaudal D homolog 1 (Drosophila)	1.072	0.01873
Ssu72	Ssu72 RNA polymerase II CTD phosphatase homolog (yeast)	1.071	0.00662
Gabarapl1	Gamma-aminobutyric acid (GABA(A)) receptor-associated protein-like 1	1.070	0.00713
Enpp2	Ectonucleotide pyrophosphatase/phosphodiesterase 2	1.064	0.04117
2410002F23Rik	RIKEN cDNA 2410002F23 gene	1.058	0.02010
Med28	Mediator of RNA polymerase II transcription, subunit 28 homolog (yeast)	1.046	0.00647
Rufy3	RUN and FYVE domain containing 3	1.044	0.02286
1110034G24Rik	RIKEN cDNA 1110034G24 gene	1.040	0.02126
5830471E12Rik	RIKEN cDNA 5830471E12 gene	1.040	0.00330
Aktip	Thymoma viral proto-oncogene 1 interacting protein	1.040	0.02120
Ergic2	ERGIC and golgi 2	1.037	0.00331
Cox11	COX11 homolog, cytochrome c oxidase assembly protein (yeast)	1.036	0.02126
Tmem119	Transmembrane protein 119	1.035	0.01685
Immt	Inner membrane protein, mitochondrial	1.029	0.02286
C230093N12Rik	RIKEN cDNA C230093N12 gene	1.024	0.02155
Brunol4	Bruno-like 4, RNA binding protein (Drosophila)	1.021	0.00287
Creb3	CAMP responsive element binding protein 3	1.021	0.03996
Pigy	Phosphatidylinositol glycan anchor biosynthesis, class Y	1.021	0.00643
Sephs1	Selenophosphate synthetase 1	1.021	0.01042
Sdk1	Sidekick homolog 1 (chicken)	1.019	0.04794
Slc2a5	Solute carrier family 2 (facilitated glucose transporter), member 5	1.019	0.02534
Thumpd2	THUMP domain containing 2	1.019	0.03388
Gabpb2	GA repeat binding protein, beta 2	1.018	0.03717
Cdc123	Cell division cycle 123 homolog (S. cerevisiae)	1.017	0.04051
Sox8	SRY-box containing gene 8	1.016	0.01630
Mcts2	Malignant T cell amplified sequence 2	1.013	0.00662
Gpr83	G protein-coupled receptor 83	1.010	0.02387
Usp4	Ubiquitin specific peptidase 4 (proto-oncogene)	1.010	0.01317
Nt5c3l	5'-nucleotidase, cytosolic III-like	1.008	0.02899
Kel	Kell blood group	1.002	0.00500
Stom	Stomatin	-1.004	0.01251
Clrn1	Clarin 1	-1.006	0.01725
Slc6a19	Solute carrier family 6 (neurotransmitter transporter), member 19	-1.006	0.01732
C030048H21Rik	RIKEN cDNA C030048H21 gene	-1.010	0.03024

Saps2	SAPS domain family, member 2	-1.012	0.02510
ENSMUSG00000051848	Predicted gene, ENSMUSG00000051848	-1.027	0.01012
Wdr89	WD repeat domain 89	-1.027	0.00529
Crkrs	Cdc2-related kinase, arginine/serine-rich	-1.029	0.03024
Eif4h	Eukaryotic translation initiation factor 4H	-1.038	0.01275
C330006K01Rik	RIKEN cDNA C330006K01 gene	-1.039	0.00355
E130116L18Rik	RIKEN cDNA E130116L18 gene	-1.041	0.00505
Ikbkg	Inhibitor of kappaB kinase gamma	-1.043	0.02899
Lass4	Longevity assurance homolog 4 (S. cerevisiae)	-1.044	0.04880
Ddx21	DEAD (Asp-Glu-Ala-Asp) box polypeptide 21	-1.045	0.04629
Ankrd13a	Ankyrin repeat domain 13a	-1.047	0.01651
Ckap5	Cytoskeleton associated protein 5	-1.050	0.04593
Fzd2	Frizzled homolog 2 (Drosophila)	-1.050	0.01831
P4ha1	Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha 1 polypeptide	-1.053	0.00578
Flnc	Filamin C, gamma (actin binding protein 280)	-1.054	0.03985
Lamp2	Lysosomal-associated membrane protein 2	-1.057	0.01359
BB031773	Expressed sequence BB031773	-1.060	0.04084
Cd44	CD44 antigen	-1.062	0.01399
Adam23	A disintegrin and metallopeptidase domain 23	-1.065	0.01998
Cnot1	CCR4-NOT transcription complex, subunit 1	-1.071	0.00278
Pik3cd	Phosphatidylinositol 3-kinase catalytic delta polypeptide	-1.073	0.04113
2810408A11Rik	RIKEN cDNA 2810408A11 gene	-1.084	0.04084
Bat1a	HLA-B-associated transcript 1A	-1.086	0.02382
Dtl	Denticleless homolog (Drosophila)	-1.088	0.02013
BC005537	CDNA sequence BC005537	-1.093	0.03090
Mmp19	Matrix metallopeptidase 19	-1.098	0.02886
Tspan31	Tetraspanin 31	-1.098	0.01501
Ddx6	DEAD (Asp-Glu-Ala-Asp) box polypeptide 6	-1.102	0.04632
Usp7	Ubiquitin specific peptidase 7	-1.104	0.00826
Wdr82	WD repeat domain containing 82	-1.106	0.00009
Ccr9	Chemokine (C-C motif) receptor 9	-1.110	0.01361
Tradd	TNFRSF1A-associated via death domain	-1.113	0.02496
2210038L17Rik	RIKEN cDNA 2210038L17 gene	-1.114	0.03514
Fbln2	Fibulin 2	-1.115	0.02376

Akap8	A kinase (PRKA) anchor protein 8	-1.117	0.02758
Sdccag3	Serologically defined colon cancer antigen 3	-1.117	0.03486
Cct7	Chaperonin subunit 7 (eta)	-1.125	0.01764
Polb	Polymerase (DNA directed), beta	-1.129	0.00594
Scd2	Stearoyl-Coenzyme A desaturase 2	-1.130	0.01974
Trpc4ap	Transient receptor potential cation channel, subfamily C, member 4 associated protein	-1.142	0.00076
Abcc9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	-1.143	0.01651
Ube2c	Ubiquitin-conjugating enzyme E2C	-1.145	0.01518
Ampd2	Adenosine monophosphate deaminase 2 (isoform L)	-1.151	0.02571
Chrna1	Cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)	-1.153	0.04872
2900005J15Rik	RIKEN cDNA 2900005J15 gene	-1.154	0.03388
Gtpbp4	GTP binding protein 4	-1.156	0.01329
Pde4dip	Phosphodiesterase 4D interacting protein (myomegalin)	-1.157	0.01317
Loxl2	Lysyl oxidase-like 2	-1.158	0.01361
Fasn	Fatty acid synthase	-1.167	0.00768
Snd1	Staphylococcal nuclease and tudor domain containing 1	-1.174	0.03875
Dcakd	Dephospho-CoA kinase domain containing	-1.176	0.02084
Shroom2	Shroom family member 2	-1.188	0.01488
4930423O20Rik	RIKEN cDNA 4930423O20 gene	-1.189	0.00307
A630033H20Rik	RIKEN cDNA A630033H20 gene	-1.190	0.04172
Cdk9	Cyclin-dependent kinase 9 (CDC2-related kinase)	-1.191	0.00854
Eed	Embryonic ectoderm development	-1.196	0.02126
Ammecr1	Alport syndrome, mental retardation, midface hypoplasia and elliptocytosis chromosomal region gene 1 homolog (human)	-1.197	0.00164
Lrrc40	Leucine rich repeat containing 40	-1.197	0.00854
Dync1i2	Dynein cytoplasmic 1 intermediate chain 2	-1.199	0.02390
AI847670	Expressed sequence AI847670	-1.203	0.04627
Fat1	FAT tumor suppressor homolog 1 (Drosophila)	-1.204	0.01680
Masp1	Mannan-binding lectin serine peptidase 1	-1.204	0.04758
Rrm2	Ribonucleotide reductase M2	-1.204	0.02084
Adsl	Adenylosuccinate lyase 1	-1.206	0.00751
Traf2	Tnf receptor-associated factor 2	-1.209	0.01361
Sec16a	SEC16 homolog A (S. cerevisiae)	-1.217	0.01003
Higd2a	HIG1 domain family, member 2A	-1.218	0.02449
Shmt2	Serine hydroxymethyltransferase 2 (mitochondrial)	-1.219	0.00847

Xcr1	Chemokine (C motif) receptor 1	-1.219	0.00505
Supt7l	Suppressor of Ty 7 (S. cerevisiae)-like	-1.220	0.02191
Pou2af1	POU domain, class 2, associating factor 1	-1.222	0.02913
Thtpa	Thiamine triphosphatase	-1.226	0.01596
2600001M11Rik	RIKEN cDNA 2600001M11 gene	-1.227	0.00258
Cttn	Cortactin	-1.242	0.00320
Armc7	Armadillo repeat containing 7	-1.247	0.00447
Ptpn7	Protein tyrosine phosphatase, non-receptor type 7	-1.253	0.02126
Nmral1	NmrA-like family domain containing 1	-1.256	0.02730
Tcfcp2	Transcription factor CP2	-1.256	0.00512
Ercc6	Excision repair cross-complementing rodent repair deficiency, complementation group 6	-1.265	0.04062
LOC100039419	Similar to translation initiation factor eIF-2 gamma subunit	-1.265	0.02651
Pole	Polymerase (DNA directed), epsilon	-1.266	0.00683
Trim2	Tripartite motif protein 2	-1.278	0.01152
2010003O18Rik	RIKEN cDNA 2010003O18 gene	-1.279	0.03655
C230021P08Rik	Riken cDNA C230021P08 gene	-1.280	0.02387
4930550G17Rik	RIKEN cDNA 4930550G17 gene	-1.281	0.00472
Lbr	Lamin B receptor	-1.282	0.01547
Ift172	Intraflagellar transport 172 homolog (Chlamydomonas)	-1.284	0.02158
Rint1	RAD50 interactor 1	-1.287	0.00727
1200009F10Rik	RIKEN cDNA 1200009F10 gene	-1.294	0.00662
Pisd	Phosphatidylserine decarboxylase	-1.305	0.01630
EG433144	Predicted gene, EG433144	-1.306	0.04157
Actn4	Actinin alpha 4	-1.307	0.02842
Spint1	Serine protease inhibitor, Kunitz type 1	-1.310	0.00015
A930005I04Rik	RIKEN cDNA A930005I04 gene	-1.311	0.00505
Rabl2a	RAB, member of RAS oncogene family-like 2A	-1.314	0.02515
4833442J19Rik	RIKEN cDNA 4833442J19 gene	-1.315	0.04489
B3gntl1	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase-like 1	-1.315	0.00842
Pnn	Pinin	-1.315	0.00330
Hpx	Hemopexin	-1.331	0.01619
Ptbp1	Polypyrimidine tract binding protein 1	-1.332	0.02899
D330001F17Rik	RIKEN cDNA D330001F17 gene	-1.335	0.02382
P2ry4	Pyrimidinergic receptor P2Y, G-protein coupled, 4	-1.338	0.00076

Cd300a	CD300A antigen	-1.344	0.02473
Rgs11	Regulator of G-protein signaling 11	-1.347	0.01441
Fer1l3	Fer-1-like 3, myoferlin (C. elegans)	-1.358	0.00337
Slit3	Slit homolog 3 (Drosophila)	-1.366	0.00443
Ccr4	Chemokine (C-C motif) receptor 4	-1.370	0.01314
H2-Bl	Histocompatibility 2, blastocyst	-1.375	0.00529
Adh4	Alcohol dehydrogenase 4 (class II), pi polypeptide	-1.376	0.04734
B230340J04Rik	RIKEN cDNA B230340J04 gene	-1.388	0.00305
Npy2r	Neuropeptide Y receptor Y2	-1.401	0.01894
Gnl2	Guanine nucleotide binding protein-like 2 (nucleolar)	-1.422	0.00061
Mtr	5-methyltetrahydrofolate-homocysteine methyltransferase	-1.433	0.00007
2210010N04Rik	RIKEN cDNA 2210010N04 gene	-1.436	0.00447
Abcb6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	-1.451	0.01359
Rbpj	Recombination signal binding protein for immunoglobulin kappa J region	-1.452	0.04573
Tmem16f	Transmembrane protein 16F	-1.452	0.01596
Thnsl1	Threonine synthase-like 1 (bacterial)	-1.472	0.01567
Lss	Lanosterol synthase	-1.487	0.02787
Cep135	Centrosomal protein 135	-1.491	0.00284
LOC100043000	Similar to ribosomal protein L3	-1.510	0.04673
Adss	Adenylosuccinate synthetase, non muscle	-1.515	0.03760
Efha1	EF hand domain family A1	-1.520	0.00491
ENSMUSG00000051848	Predicted gene, ENSMUSG00000051848	-1.525	0.02144
Gulp1	GULP, engulfment adaptor PTB domain containing 1	-1.536	0.00152
Cdc37	Cell division cycle 37 homolog (S. cerevisiae)	-1.537	0.00936
Gabrq	Gamma-aminobutyric acid (GABA-A) receptor, subunit theta	-1.540	0.01361
Tada3l	Transcriptional adaptor 3 (NGG1 homolog, yeast)-like	-1.552	0.00027
A430005L14Rik	RIKEN cDNA A430005L14 gene	-1.553	0.04798
Myc	Myelocytomatosis oncogene	-1.573	0.03436
4632417N05Rik	RIKEN cDNA 4632417N05 gene	-1.574	0.02198
2900046G09Rik	RIKEN cDNA 2900046G09 gene	-1.594	0.00028
2200002D01Rik	RIKEN cDNA 2200002D01 gene	-1.599	0.02913
Lgals3	Lectin, galactose binding, soluble 3	-1.601	0.01411
Rps6kb2	Ribosomal protein S6 kinase, polypeptide 2	-1.603	0.00041
Ddx46	DEAD (Asp-Glu-Ala-Asp) box polypeptide 46	-1.610	0.00034

Asah3	N-acylsphingosine amidohydrolase (alkaline ceramidase) 3	-1.619	0.00015
Tbc1d5	TBC1 domain family, member 5	-1.628	0.02651
Cdca8	Cell division cycle associated 8	-1.639	0.01541
Pfn4	Profilin family, member 4	-1.645	0.00031
6030405A18Rik	RIKEN cDNA 6030405A18 gene	-1.660	0.00031
Ppp2r3a	Protein phosphatase 2 (formerly 2A), regulatory subunit B", alpha	-1.665	0.04658
9.13E+15	Hypothetical 9130022E09	-1.672	0.00031
Rpsa	Ribosomal protein SA	-1.687	0.00491
Dctn2	Dynactin 2	-1.709	0.02013
Rqcd1	Rcd1 (required for cell differentiation) homolog 1 (S. pombe)	-1.711	0.01614
Sdf2	Stromal cell derived factor 2	-1.723	0.01366
Spire1	Spire homolog 1 (Drosophila)	-1.786	0.01250
Acp6	Acid phosphatase 6, lysophosphatidic	-1.794	0.00029
Ly6e	Lymphocyte antigen 6 complex, locus E	-1.797	0.03775
Thap6	THAP domain containing 6	-1.803	0.01317
Lamb1-1	Laminin B1 subunit 1	-1.805	0.00330
Tanc1	Tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1	-1.809	0.00004
Serinc3	Serine incorporator 3	-1.817	0.00375
Soat1	Sterol O-acyltransferase 1	-1.818	0.00692
4930435E12Rik	RIKEN cDNA 4930435E12 gene	-1.901	0.01685
Tbce	Tubulin-specific chaperone e	-1.922	0.00022
Ubxd5	UBX domain containing 5	-1.953	0.00665
9130016M20Rik	RIKEN cDNA 9130016M20 gene	-1.964	0.00243
C030019F02Rik	RIKEN cDNA C030019F02 gene	-1.984	0.00364
Alas2	Aminolevulinic acid synthase 2, erythroid	-1.997	0.01301
Jazf1	JAZF zinc finger 1	-1.997	0.00712
Ywhah	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	-2.005	0.01187
Pfas	Phosphoribosylformylglycinamidine synthase (FGAR amidotransferase)	-2.071	0.00411
Polr2e	Polymerase (RNA) II (DNA directed) polypeptide E	-2.096	0.01588
Cyb5r1	Cytochrome b5 reductase 1	-2.131	0.00360
Rbm10	RNA binding motif protein 10	-2.215	0.01685
Ftsj3	FtsJ homolog 3 (E. coli)	-2.228	0.00002
Stac3	SH3 and cysteine rich domain 3	-2.311	0.00000
Ncl	Nucleolin	-2.398	0.00026

Il13ra2	Interleukin 13 receptor, alpha 2	-2.560	0.00000
Sgta	Small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	-2.580	0.00002
Tmed9	Transmembrane emp24 protein transport domain containing 9	-2.614	0.00038
Slc38a6	Solute carrier family 38, member 6	-2.739	0.00078
A930016O22Rik	RIKEN cDNA A930016O22 gene	-2.790	0.00066
AI118078	Expressed sequence AI118078	-2.912	0.00239
Kcnab1	Potassium voltage-gated channel, shaker-related subfamily, beta member 1	-2.929	0.00240
A830053O21Rik	RIKEN cDNA A830053O21 gene	-3.009	0.00000
E430029J22Rik	RIKEN cDNA E430029J22 gene	-3.245	0.00000

Tab.2 : Differentially expressed genes in mouse hippocampus after focal injection of kainic acid. In the 12 columns on the right are reported the fold changes for each area and time point. Fold Changes are in logarithmic scale (base 2). ID= Ipsilateral Dorsal, IV= Ipsilateral Ventral, CD= Contralateral Dorsal, CV= Contralateral Ventral. 6h= 6 hours after the injection, 15d= 15 days after the injection, 6m= 6 months after the injection. The "-" symbol means that for that area at that time point the specific gene is not showing significant change or that change is present also in the NaCl injected controls, therefore it was not considered in further analysis. Genes are listed in alphabetical order.

Aff ID	*Gene*	*Gene name*	*ID 6h*	*IV 6h*	*CD 6h*	*CV 6h*	*ID 15d*	*IV 15d*	*CD 15d*	*CV 15d*	*ID 6m*	*IV 6m*	*CD 6m*	*CV 6m*
1434719_at	A2m	alpha-2-macroglobulin	-	-	-	-	3.17	2.31	1.55	-	1.59	-	-	-
1421839_at	Abca1	ATP-binding cassette, sub-family A (ABC1), member 1	-	-	-	-	1.90	1.2	-	1.17	-	-	-	-
1449588_at	Abca4	ATP-binding cassette, sub-family A (ABC1), member 4	-	-	-	-	-1.5	-	-	-	-2.7	-	-	-
14164-3_at	Abcb1-	ATP-binding cassette, sub-family B (MDR/TAP), member 1-	-	-	-	1.11	-	-	-	1.08	-	-	-	-
1419759_at	Abcb1a	ATP-binding cassette, sub-family B (MDR/TAP), member 1A	-	-1.2	-	-	-	-	-	-	-	-	-	-
1418872_at	Abcb1b	ATP-binding cassette, sub-family B (MDR/TAP), member 1B	-	-	-	-	1.50	-	-	-	-	-	-	-
1449818_at	Abcb4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	-	-	-	-	1.28	-	-	-	-	-	-	-
1428988_at	Abcc3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	-	-	-	-	1.95	1.4	1.01	-	-	-	-	-
1419748_at	Abcd2	ATP-binding cassette, sub-family D (ALD), member 2	-	-	-	-	1.53	-	-	-	-	-	-	-
1416315_at	Abhd4	abhydrolase domain containing 4	-	-	-	-	1.00	-	-	-	-	-	-	-
1416863_at	Abhd8	abhydrolase domain containing 8	-	-	-	-	1.27	-	-	-	-	-	-	-
1428146_s_at	Acaa2	acetyl-Coenzyme A acyltransferase 2 (mitochondrial 3-oxoacyl-Coenzyme A thiolase)	-	-	-	-	-	-	-	-	-1.5	-	-	-
1449827_at	Acan	aggrecan	-	-	-	-	3.06	-	-	-	1.41	-	-	-
1417994_a_at	Accn1	amiloride-sensitive cation channel 1, neuronal (degenerin)	-	-	-	-	1.25	-	-	-	-	-	-	-
1427-34_at	Ace	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	-	-	-	-	-1.1	-	-	-	-1.5	-	-	-
1422715_s_at	Acp1	acid phosphatase 1, soluble	-	-	-	1.14	-	-	-	-	-	-	-	-
1451828_a_at	Acsl4	acyl-CoA synthetase long-chain family member 4	1.2	-	-	1.02	1.58	-	-	-	-	-	-	-
1416871_at	Adam8	a disintegrin and metallopeptidase domain 8	1.89	-	-	-	-	-	-	-	-	-	-	-
145-716_at	Adamts1	a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1	1.09	-	-	-	1.42	-	-	-	-	-	-	-
1451932_a_at	Adamtsl4	ADAMTS-like 4	-	-	-	-	1.28	-	-	-	-	-	-	-
1455462_at	Adcy2	adenylate cyclase 2	-	-	-	-	-1.01	-	-	-	-	-	-	-
14563-7_s_at	Adcy7	adenylate cyclase 7	-	-	-1.1	-	2.42	1.5-5	1.26	-	-	-	-	-
1423427_at	Adcyap1	adenylate cyclase activating polypeptide 1	-	-	-	-	1.89	-	-	-	1.67	-	-	-
1451914_a_at	Add2	adducin 2 (beta)	-	-	-	1.37	-	-	-	-	-	-	-	-

1426574_a_at	Add3	adducin 3 (gamma)	-	-	-	1.09	-	-	-	-	-	-	-	-
1448318_at	Adfp	adipose differentiation related protein	-	-	-	-	-	1.07	-	-	-	-	-	-
145-214_at	Adora2b	adenosine A2b receptor	-	-	-	-	-0.98	-	-	-	-	-	-	-
1422335_at	Adra2c	adrenergic receptor, alpha 2c	-	-	-	-	-	-	-	1.01	-	-	-	-
1416645_a_at	Afp	alpha fetoprotein	1.08	-	-	-	3.75	1.69	1.47	-	-	-	-	-
1438651_a_at	Agtrl1	angiotensin receptor-like 1	-	-	-	-	1.71	1.02	-	-	-	-	-	-
1425576_at	Ahcyl1	S-adenosylhomocysteine hydrolase-like 1	-	-	-	1.37	-	-	-	1.54	-	-	-	-
1452217_at	Ahnak	AHNAK nucleoprotein (desmoyokin)	-	-	-	-	1.04	-	-	-	-	-	-	-
14182-4_s_at	Aif1	allograft inflammatory factor 1	-	-	-	-	3.08	2.28	1.64	-	-	-	-	-
14197-6_a_at	Akap12	A kinase (PRKA) anchor protein (gravin) 12	1.73	-	-	-	-	-	-	-	-	-	-	-
1455151_at	Akap9	A kinase (PRKA) anchor protein (yotiao) 9	-	-	-	1.15	-	-	-	-	-	-	-	-
1448894_at	Akr1b8	aldo-keto reductase family 1, member B8	-	-	-	-	2.07	1.06	-	-	1.38	-	-	-
1419136_at	Akr1c18	aldo-keto reductase family 1, member C18	-	-	-	-	-1.86	-	-	-	-	-	-	-
1448789_at	Aldh1a3	aldehyde dehydrogenase family 1, subfamily A3	-	1.09	-	-	-	-	-	-	-	-	-	-
1434987_at	Aldh2	aldehyde dehydrogenase 2, mitochondrial	-	-1	-	-	-	-	-	-	-	-	-	-
1419115_at	Alg14	asparagine-linked glycosylation 14 homolog (yeast)	-	-	-	-	-	-	-	-	-	-	-	-1.6
1437728_at	Alkbh5	alkB, alkylation repair homolog 5 (E. coli)	-	-	-	1.76	-	-	-	-	-	-	-	-
1418266_at	Alox12b	arachidonate 12-lipoxygenase, 12R type	-	-	-	-	-1.70	-	-	-	-	-	-	-
1452-16_at	Alox5ap	arachidonate 5-lipoxygenase activating protein	-	-	-	-	1.58	-	-	-	-	-	-	-
1416835_s_at	Amd1	S-adenosylmethionine decarboxylase 1	-	-	-	1.07	-	-	-	-	-	-	-	-
1422573_at	Ampd3	AMP deaminase 3	-	-	-	-	1.25	-	-	-	-	-	-	-
1427-44_a_at	Amph	amphiphysin	-	-	-	-	-1.29	-	-	-	-	-	-	-
145-717_at	Ang	angiogenin, ribonuclease, RNase A family, 5	-	-	-	-	1.69	1.35	-	-	-	-	-	-
141713-_s_at	Angptl4	angiopoietin-like 4	2.78	2.55	-	-	-	-	-	-	-	-	-	-
1419421_at	Ank1	ankyrin 1, erythroid	-	-	-	-	-1.83	-	-	-	-	-	-	-
1436998_at	Ankrd43	ankyrin repeat domain 43	-	-	-	-	-2.02	-	-	-	-	-	-	-
1454736_at	Ankrd57	ankyrin repeat domain 57	-	-	-	-	-	-	-	-	-1.2	-	-	-
1419-91_a_at	Anxa2	annexin A2	-	1.03	-	-	1.58	1.03	-	-	1.05	-	-	-
146-33-_at	Anxa3	annexin A3	-	-	-	-	2.42	1.65	1.29	-	-	-	-	-
1424176_a_at	Anxa4	annexin A4	-	-	-	-	1.79	-	-	-	-	-	-	-
1425567_a_at	Anxa5	annexin A5	-	-	-	-	1.26	-	-	-	-	-	-	-
145-915_at	Ap3b1	adaptor-related protein complex 3, beta 1 subunit	-	-	-	1.63	-	-	-	-	-	-	-	-
1431946_a_at	Apba2bp	amyloid beta (A4) precursor protein-binding, family A, member 2 binding protein	-	-	-	-	1.41	-	-	-	1.3	-	-	-

14218-3_at	Apbh	androgen-binding protein eta	-1.5	-	-	-	-	-	-	-	-	-	-	-
142-957_at	Apc	adenomatosis polyposis coli	-	-	-	-	-	-	-	-	-	-	1.23	-
1439214_a_at	Api5	apoptosis inhibitor 5	-	-	-	1.18	-	-	-	-	-	-	-	-
142-382_at	Apob48r	apolipoprotein B48 receptor	-	-	-	-	1.32	-	-	-	-	-	-	-
1451755_a_at	Apobec1	apolipoprotein B editing complex 1	-	-	-	-	1.93	1.25	-	-	-	-	-	-
141747-_at	Apobec3	apolipoprotein B editing complex 3	-	-	-	-	1.14	-	-	-	-	-	-	-
1417561_at	Apoc1	apolipoprotein C-I	-	-	-	-	1.23	-	-	-	-	-	-	-
1418-69_at	Apoc2	apolipoprotein C-II	-	-	-	-	1.95	1.34	-	-	-	-	-	-
14162-3_at	Aqp1	aquaporin 1	-1.6	-	-	-	-2.3	-1.6	-	-1.6	-3.5	-	-	-
1425382_a_at	Aqp4	aquaporin 4	-	-	-	-	2.51	1.36	1.34	1.34	1.6	-	-	-
1418687_at	Arc	activity regulated cytoskeletal-associated protein	1.64	-	-	-	-	-1	-	-1.4	-	-	-	-
1423743_at	Arcn1	archain 1	-	-	-	-	-	-	-	-1	-	-	-	-
1421134_at	Areg	amphiregulin	1.83	-	-	-	1.15	-	-	-	-	-	-	-
1438661_a_at	Arf2	ADP-ribosylation factor 2	-	-	-	1.11	-	-	-	-	-	-	-	-
1451526_at	Arhgap12	Rho GTPase activating protein 12	-	-	-	-	-1.15	-	-	-	-	-	-	-
1427522_at	Arhgap2-	Rho GTPase activating protein 2-	-	-	-	1.02	-	-	-	-	-	-	-	-
1419296_at	Arhgap4	Rho GTPase activating protein 4	-	-	-	-	1.38	-	-	-	-	-	-	-
1423194_at	Arhgap5	Rho GTPase activating protein 5	-	-	-	1.09	-	-	-	-	-	-	-	-
1451867_x_at	Arhgap6	Rho GTPase activating protein 6	-	-	-1.9	-	-1.4	-	-	-	-	-	-	-
1436-97_x_at	Arhgap9	Rho GTPase activating protein 9	-	-	-	-	1.63	-	-	-	-	-	-	-
1426454_at	Arhgdib	Rho, GDP dissociation inhibitor (GDI) beta	-	-	-	-	2.02	1.45	1.17	-	-	-	-	-
1431-24_a_at	Arid4b	AT rich interactive domain 4B (Rbp1 like)	-	-	-	1.19	-	-	-	-	-	-	-	-
142-973_at	Arid5b	AT rich interactive domain 5B (Mrf1 like)	1.35	-	-	1.52	-	-	-	-	-	-	-	-
1416226_at	Arpc1b	actin related protein 2/3 complex, subunit 1B	-	-	-	-	2.74	1.81	1.48	1.26	1.49	-	-	-
145128-_at	Arpp21	cyclic AMP-regulated phosphoprotein, 21	2.48	-	-	-	1.92	-	-	-	1.69	-	-	-
1425232_x_at	Arr3	arrestin 3, retinal	-	-	-	-	3.07	-	-	-	2.42	-	-	-
1416942_at	Arts1	type 1 tumor necrosis factor receptor shedding aminopeptidase regulator	-	-	-	-	1.09	-	-	-	-	-	-	-
145--42_at	Arx	aristaless related homeobox gene (Drosophila)	-	-	-	-	-1.29	-	-	-	-	-	-	-
1422153_a_at	Asb11	ankyrin repeat and SOCS box-containing protein 11	-	-	-	-	2.6	-	-	-	2.15	-	-	-
1418472_at	Aspa	aspartoacylase (aminoacylase) 2	-	-1.6	-	-	-	-	-	-	-	-	-	-
142-959_at	Asph	aspartate-beta-hydroxylase	-	-	-	-	1.27	-	-	-	-	-	-	-
1449363_at	Atf3	activating transcription factor 3	3.38	2.45	1.98	1.47	1.87	1.34	-	-	-	-	-	-
14212-5_at	Atm	ataxia telangiectasia mutated homolog (human)	-	-	-	-	1.25	-	-	-	-	-	-	-
1451388_a_at	Atp11b	ATPase, Class VI, type 11B	-	-	-	1.17	1.34	-	-	-	-	-	-	-

1455136_at	Atp1a2	ATPase, Na+/K+ transporting, alpha 2 polypeptide	-	-	-	-	1.11	-	-	-	-	-	-	-
1422--9_at	Atp1b2	ATPase, Na+/K+ transporting, beta 2 polypeptide	-	-	-	-	1.76	-	-	1.44	-	-	-	-
142-4-2_at	Atp2b2	ATPase, Ca++ transporting, plasma membrane 2	-	-	-	2.52	-	-	-	-	-	-	-	-
1423598_at	Atp8a1	ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	-	-	-	-	-	-	-	1.2	-	-	-	-
142-946_at	Atrx	alpha thalassemia/mental retardation syndrome X-linked homolog (human)	-	-	-	2.16	-	-	-	-	-	-	-	-
143-487_at	Auh	AU RNA binding protein/enoyl-coenzyme A hydratase	1.24	-	-	-	-	-	-	-	-	-	-	-
1423586_at	Axl	AXL receptor tyrosine kinase	-	-	-	-	1.61	-	1.05	-	-	-	-	-
1424459_at	Aytl2	acyltransferase like 2	-	-	-	-	1.01	-	-	-	-	-	-	-
1427511_at	B2m	beta-2 microglobulin	-	-	-	-	1.98	1.44	-	-	-	-	-	-
145-53-_at	B3galt1	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	-	-	-	1.19	-	-	-	-	-	-	-	-
142-852_a_at	B3gnt2	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2	-	-	-	1.4	-	-	-	-	-	-	-	-
142-994_at	B3gnt5	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	2.28	1.52	-	-	1.84	-	-	-	1.23	-	-	-
1418-14_a_at	B4galt1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	-	-	-	-	-	-1	-	-	-	-	-	-
1416673_at	Bace2	beta-site APP-cleaving enzyme 2	-	-	-	-	1.07	-	-	-	-	-	-	-
1449311_at	Bach1	BTB and CNC homology 1	1.04	-	-	1.45	-	-	-	-	-	-	-	-
1422452_at	Bag3	Bcl2-associated athanogene 3	1.59	1.3	1.24	-	1.75	-	-	-	1.52	-	-	-
1435128_at	Baiap2	brain-specific angiogenesis inhibitor 1-associated protein 2	-	-	-	-	-1.43	-	-	-	-	-	-	-
1424951_at	Baiap2l1	BAI1-associated protein 2-like 1	-	-	-	-	-	-	-	-	-1.7	-	-	-
14275-9_at	Baiap3	BAI1-associated protein 3	-	-	-1.7	-	2.99	-	-2.3	-	-	-	-	-
142-975_at	Baz1b	bromodomain adjacent to zinc finger domain, 1B	-	-	1.06	-	-	-	-	-	-	-	-	-
1422741_a_at	Bbx	bobby sox homolog (Drosophila)	-	-	-	1.21	-	-	-	-	-	-	-	-
14194-6_a_at	Bcl11a	B-cell CLL/lymphoma 11A (zinc finger protein)	-	-	-	-	-1.88	-	-	-	-	-	-	-
1419--4_s_at	Bcl2a1a	B-cell leukemia/lymphoma 2 related protein A1a	1.45	-	-	-	3.78	3.06	2.12	-	-	-	-	-
142-887_a_at	Bcl2l1	Bcl2-like 1	-	-	1.3	-	-	-	-	-	-	-	-	-
1418133_at	Bcl3	B-cell leukemia/lymphoma 3	-	-	-	-	1.53	-	-	-	1.27	-	-	-
145-381_a_at	Bcl6	B-cell leukemia/lymphoma 6	1.13	-	-	-	-	-	-	-	-	-	-	-
1422168_a_at	Bdnf	brain derived neurotrophic factor	1.49	1.23	-	1.47	2.9	-	-	-	1.9	-	-	-
1452451_at	Bean	brain expressed, associated with Nedd4	-	-	-	-	-1.10	-	-	-	-	-	-	-
14164-5_at	Bgn	biglycan	-	-	-	-	2.86	1.41	1.23	-	1.52	-	-	-
145-624_at	Bhmt	betaine-homocysteine methyltransferase	-	-	-	-	-	-	-	-	-1.7	-	-	-
1456-88_at	Birc4	baculoviral IAP repeat-containing 4	-	-	-	1.31	-	-	-	-	-	-	-	-
1424278_a_at	Birc5	baculoviral IAP repeat-containing 5	-	-	-	-	2.02	-	-	-	-	-	-	-
145178-_at	Blnk	B-cell linker	-	-	-	-	2.47	1.77	1.74	-1	1.19	-	-	-
1419616_at	Bmpr2	bone morphogenic protein receptor, type II (serine/threonine kinase)	-	-	-	1.76	-	-	-	-	-	-	-	-

1424921_at	Brd4	bromodomain containing 4	-	-	-	-	2.61	2.01	1.28	-	-	-	-	-
145224-_at	Brunol4	bruno-like 4, RNA binding protein (Drosophila)	-	-	-	-	-1.12	-	-	-	-	-	-	-
1422755_at	Btk	Bruton agammaglobulinemia tyrosine kinase	-	-	-	-	2.20	1.4	-	-	-	-	-	-
1424-46_at	Bub1	budding uninhibited by benzimidazoles 1 homolog (S. cerevisiae)	-	-	-	-	1.50	-	-	-	-	-	-	-
145-846_at	Bzw1	basic leucine zipper and W2 domains 1	-	-	-	1.41	-	-	-	1.34	-	-	-	-
1422772_at	C1galt1	core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1	-	-	-	-	1.12	-	-	-	-	-	-	-
1417381_at	C1qa	complement component 1, q subcomponent, alpha polypeptide	-	-	-	-	2.69	2.17	1.62	1.35	1.06	-	-	-
1417-63_at	C1qb	complement component 1, q subcomponent, beta polypeptide	-	-	-	-	2.93	2.52	1.79	1.55	1.16	-	-	-
14494-1_at	C1qc	complement component 1, q subcomponent, C chain	-	-	-	-	3.15	2.34	1.84	1.72	1.08	-	-	-
1425176_at	C1ql3	C1q-like 3	-	1.02	-	1.64	-	-	-	-	-1.1	-	-	-
1417--9_at	C1r	complement component 1, r subcomponent	-	-	-	-	1.62	-	-	-	-	-	-	-
1423954_at	C3	complement component 3	-	-	-	-	3.58	3.13	1.38	1.16	1.56	-	-	-
1419483_at	C3ar1	complement component 3a receptor 1	1.47	-	-	-	3.59	2.49	1.87	1.56	-	-	-	-
1418-21_at	C4b	complement component 4B (Childo blood group)	-	-	-	-	2.34	1.91	1.34	-1	2.17	-	-	-
142219-_at	C5ar1	complement component 5a receptor 1	1.64	-	-	-	1.31	-	-	-	-	-	-	-
1418432_at	Cab39	calcium binding protein 39	-	-	-	1.01	-	-	-	-	-	-	-	-
1436-3-_at	Cachd1	cache domain containing 1	-	-	-	-	-0.99	-	-	-	-	-	-	-
142-442_at	Cacna1s	calcium channel, voltage-dependent, L type, alpha 1S subunit	-	-	-	-	2.47	-	-	-	-	-	-	-
1449999_a_at	Cacna2d1	calcium channel, voltage-dependent, alpha2/delta subunit 1	-	-	-	1.15	-	-	-	-	-	-	-	-
1452-89_at	Cacnb4	calcium channel, voltage-dependent, beta 4 subunit	-	-	-	1.56	-	-	-	-	-	-	-	-
1418922_at	Cadm3	cell adhesion molecule 3	-	-	-	-	-1.18	-	-	-	-	-	-	-
1451499_at	Cadps2	Ca2+-dependent activator protein for secretion 2	-	-	-	-	-2.11	-	-	-	-	-	-	-
1448738_at	Calb1	calbindin-28K	-	-	-	-	-	-	-1.3	-	-	-	-	-
1422639_at	Calcb	calcitonin-related polypeptide, beta	-	-	-	-	-	-1	-	-	-	-	-	-
1424768_at	Cald1	caldesmon 1	-	-	-	1.51	-	-	-	-	-	-	-	-
1424713_at	Calml4	calmodulin-like 4	-1.3	-	-	-	-	-1.2	-	-1.8	-2.6	-	-	-
14176-4_at	Camk1	calcium/calmodulin-dependent protein kinase I	-	-	-	-	1.13	-	-	-	-	-	-	-
1452-5-_at	Camk1d	calcium/calmodulin-dependent protein kinase ID	-	-	-	-	-1.96	-	-	-	-	-	-	-
1424633_at	Camk1g	calcium/calmodulin-dependent protein kinase I gamma	-	-	-	-	-1.44	-	-	-	-	-	-	-
1455869_at	Camk2b	calcium/calmodulin-dependent protein kinase II, beta	2.39	-	1.3	-	2.19	-	-	-	-	-	-	-
1418954_at	Camkk1	calcium/calmodulin-dependent protein kinase kinase 1, alpha	-	-	-	-	-1.21	-	-	-	-	-	-	-
14238-2_at	Camkv	CaM kinase-like vesicle-associated	-	-	-	-	-1.38	-	-	-	-	-	-	-
1423222_at	Cap2	CAP, adenylate cyclase-associated protein, 2 (yeast)	-	-	-	1.16	-	-	-	-	-	-	-	-

145-355_a_at	Capg	capping protein (actin filament), gelsolin-like	-	-	-	-	2.73	2.5	1.46	1.45	-	-	-	-
1448348_at	Caprin1	cell cycle associated protein 1	-	-	-	-	-	-	-	1.01	-	-	-	-
145396-_a_at	Capzb	capping protein (actin filament) muscle Z-line, beta	-	-	-	-	-	-	-	1.18	-	-	-	-
1428485_at	Car12	carbonic anyhydrase 12	-	-	-	-	-	-	-	-	-1.1	-	-	-
1449434_at	Car3	carbonic anhydrase 3	-	-	-1.2	-	-1.1	-	-	-	-	-	-	-
1418-94_s_at	Car4	carbonic anhydrase 4	-	-	-	-	-1.32	-	-	-	-	-	-	-
1427482_a_at	Car8	carbonic anhydrase 8	-	-	-	-	1.24	-	-	-	1.21	-	-	-
1422825_at	Cartpt	CART prepropeptide	-	-	-	-	4.83	2.56	-1.2	-	1.96	-	-	-
1449265_at	Casp1	caspase 1	-	-	-	-	1.84	-	-	-	-	-	-	-
1449297_at	Casp12	caspase 12	-	-	-	-	1.72	-	-	-	1.43	-	-	-
1449839_at	Casp3	caspase 3	-	-	-	1.06	1.02	-	-	1.12	-	-	-	-
1449591_at	Casp4	caspase 4, apoptosis-related cysteine peptidase	-	-	-	-	2.88	1.33	-	-	-	-	-	-
1448659_at	Casp7	caspase 7	-	-	-	-	1.10	-	-	-	-	-	-	-
1424552_at	Casp8	caspase 8	-	-	-	-	1.84	-	-	-	-	-	-	-
1449145_a_at	Cav1	caveolin, caveolae protein 1	-	-	-	-	1.81	-	-	-	1.29	-	-	-
1455886_at	Cbl	Casitas B-lineage lymphoma	-	-	-	1.63	-	-	-	-	-	-	-	-
1423287_at	Cbln1	cerebellin 1 precursor protein	-	-	-	-	-1.79	-	-	-	-	-	-	-
1418778_at	Ccdc1-9b	coiled-coil domain containing 1-9B	-	-	-	-	-1.58	-	-	-	-	-	-	-
1428-66_at	Ccdc12-	coiled-coil domain containing 12-	-	-	-	-	-1.12	-	-	-	-	-	-	-
1427951_s_at	Ccdc28a	coiled-coil domain containing 28A	-	-	-	-	-1.04	-	-	-	-	-	-	-
1424186_at	Ccdc8-	coiled-coil domain containing 8-	-	-	-	-	1.55	-1	-	-	-	-	-	-
1452332_at	Ccdc85a	coiled-coil domain containing 85A	-	-	-	-	-1.48	-1.1	-	-	-	-	-	-
145477-_at	Cckbr	cholecystokinin B receptor	-	-	-	-	-2.08	-	1.1	-	-	-	-	-
1417789_at	Ccl11	small chemokine (C-C motif) ligand 11	1.35	-	-	-	-	-	-	-	-	-	-	-
1419282_at	Ccl12	chemokine (C-C motif) ligand 12	-	2.19	-	-	5.05	3.22	2.42	-	-	-	-	-
142-38-_at	Ccl2	chemokine (C-C motif) ligand 2	1.85	-	-	-	1.21	-	-	-	-	-	-	-
1419561_at	Ccl3	chemokine (C-C motif) ligand 3	3.66	3.36	2.02	-	4.16	3.51	-	1.76	-	-	-	-
1421578_at	Ccl4	chemokine (C-C motif) ligand 4	-	1.96	1.55	-	1.85	-	-	-	-	-	-	-
1418126_at	Ccl5	chemokine (C-C motif) ligand 5	-	-	-	-	3.86	2.52	1.85	-	-	-	-	-
1417266_at	Ccl6	chemokine (C-C motif) ligand 6	-	-	-	-	3.39	2.6	1.53	1.25	-	-	-	-
1421228_at	Ccl7	chemokine (C-C motif) ligand 7	1.56	-	-	-	-	-	-	-	-	-	-	-
1419684_at	Ccl8	chemokine (C-C motif) ligand 8	-	-	-	-	-	-	-	-	1.51	-	-	-
1448898_at	Ccl9	chemokine (C-C motif) ligand 9	2.73	1.4	1.4	-	3.59	2.43	2.11	1.6	-	-	-	-
141791-_at	Ccna2	cyclin A2	-	-	-	-	1.19	-	-	-	-	-	-	-

1416-76_at	Ccnb1-rs1	cyclin B1, related sequence 1	-	-	-	-	1.34	-	-	-	-	-	-	-
145-92-_at	Ccnb2	cyclin B2	-	-	-	-	1.40	-	-	-	-	-	-	-
145374-_a_at	Ccnl2	cyclin L2	-	-	-	-	-	-	-	1.11	-	-	-	-
1422259_a_at	Ccr5	chemokine (C-C motif) receptor 5	-	-	-	-	3.82	2.54	1.78	1.3-9	1.09	-	-	-
1425658_at	Cd1-9	CD1-9 antigen	-	-	-	-	1.97	-	-	-	-	-	-	-
1417268_at	Cd14	CD14 antigen	3.23	2.44	1.6	-	2.73	1.89	1.46	1.14	-	-	-	-
1424-93_x_at	Cd151	CD151 antigen	-	-	-	-	1.26	-	-	-	-	-	-	-
1421547_at	Cd18-	CD18- antigen	-	-	-	-	2.94	1.81	1.32	-1	-	-	-	-
1419769_at	Cd22	CD22 antigen	-	-	-	-	2.03	1.42	1	-	-	-	-	-
1449991_at	Cd244	CD244 natural killer cell receptor 2B4	-	-	-	-	1.35	-	-	-	-	-	-	-
1419714_at	Cd274	CD274 antigen	-	-	-	-	1.33	-	-	-	1.15	-	-	-
1428-18_a_at	Cd3--d	Cd3--D antigen	-	-	-	-	2.44	1.84	1.38	-	-	-	-	-
1427994_at	Cd3--lf	CD3-- antigen like family member F	-	-	-	-	1.77	1.17	-	-	-	-	-	-
145-513_at	Cd33	CD33 antigen	-	-	-	-	1.65	1.17	-	-	-	-	-	-
14192-6_at	Cd37	CD37 antigen	-	-	-	-	2.91	2.03	1.44	1.23	-	-	-	-
145-136_at	Cd38	CD38 antigen	-	-	-	-	1.83	-	-	-	-	-	-	-
1419178_at	Cd3g	CD3 antigen, gamma polypeptide	-	-	-	-	1.35	-	-	-	-	-	-	-
142376-_at	Cd44	CD44 antigen	2.31	-	-	-	4.45	1.84	2.74	1.36	3.11	-	-	-
14273-1_at	Cd48	CD48 antigen	-	-	-	-	3.85	2.29	2.11	-	1.21	-	-	-
1418353_at	Cd5	CD5 antigen	-	-	-	-	1.27	-	-	-	-	-	-	-
146-218_at	Cd52	CD52 antigen	-	-	-	-	4.39	3.8-6	2.38	2.17	1.5	-	-	-
1448617_at	Cd53	CD53 antigen	-	-	-	-	2.53	1.76	1.44	-	-	-	-	-
141871-_at	Cd59a	CD59a antigen	-	-	-	-	-	-	-	-	-1.6	-	-	-
1449193_at	Cd5l	CD5 antigen-like	-	-	-	-	3.60	2.44	1.42	1.33	-	-	-	-
1449164_at	Cd68	CD68 antigen	-	-	-	-	3.89	2.72	2.15	1.8	1.15	-	-	-
1449926_at	Cd7-	CD7- antigen	-	-	-	-	1.51	-	-	-	-	-	-	-
1426112_a_at	Cd72	CD72 antigen	-	-	-	-	3.45	2.02	1.34	-	-	-	-	-
1425519_a_at	Cd74	CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	-	-	-	-	1.02	-	-	-	-	-	-	-
1422875_at	Cd84	CD84 antigen	-	-	-	-	4.12	2.77	-	1.48	-	-	-	-
1449858_at	Cd86	CD86 antigen	1.63	-	-	-	3.65	2.0-6	2.24	1.49	1.04	-	-	-
1416-66_at	Cd9	CD9 antigen	-	-	-	-	1.54	1.39	-	-	-	-	-	-
1419589_at	Cd93	CD93 antigen	-	-	-	-	1.29	1.02	-	-	-	-	-	-
1425662_at	Cdadc1	cytidine and dCMP deaminase domain containing 1	-	-	-	-	-1.31	-	-	-	-	-	-	-

1448314_at	Cdc2a	cell division cycle 2 homolog A (S. pombe)	-	-	-	-	1.71	-	-	-	-	-	-	-
1428-92_at	Cdc5l	cell division cycle 5-like (S. pombe)	-	-	-	1.26	-	-	-	-	-	-	-	-
1452-4-_a_at	Cdca3	cell division cycle associated 3	-	-	-	-	1.44	-	-	-	-	-	-	-
14168-2_a_at	Cdca5	cell division cycle associated 5	-	-	-	-	2.48	1.64	-	-	-	-	-	-
1432-22_at	Cdgap	Cdc42 GTPase-activating protein	-	-	-	-	-0.98	-	-	-	-	-	-	-
1422-52_at	Cdh8	cadherin 8	-	-	-	-	-1.35	-	-	-	-	-	-	-
1421124_at	Cdk5r1	cyclin-dependent kinase 5, regulatory subunit (p35) 1	-	-	1.05	-	-	-	-	-	-	-	-	-
1421679_a_at	Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)	-	-	-	-	1.59	1.04	1.28	1.09	-	-	-	-
1417649_at	Cdkn1c	cyclin-dependent kinase inhibitor 1C (P57)	-	-	-	-	-1.5	-	-	-	-1.8	-	-	-
1424143_a_at	Cdt1	chromatin licensing and DNA replication factor 1	-	-	-	-	1.13	-	-	-	-	-	-	-
1418982_at	Cebpa	CCAAT/enhancer binding protein (C/EBP), alpha	1.24	-	1.61	-	1.9	1.51	-	-	-	-	-	-
145-842_a_at	Cenpa	centromere protein A	-	-	-	-	1.50	-	-	-	-	-	-	-
1427161_at	Cenpf	centromere protein F	-	-	-	-	1.36	-	-	-	-	-	-	-
1425639_at	Centa2	centaurin, alpha 2	-	-	-	-	1.81	-	-	-	-	-	-	-
145247-_at	Cep35-	centrosomal protein 35-	-	-	-	-1	-	-	-	-	-	-	-	-
1452242_at	Cep55	centrosomal protein 55	-	-	-	-	1.82	-	-	-	-	-	-	-
1449317_at	Cflar	CASP8 and FADD-like apoptosis regulator	-	-	-	-	1.05	-	-	-	-	-	-	-
1424528_at	Cgref1	cell growth regulator with EF hand domain 1	1.42	1.15	-	-	-	-	-	-	-	-	-	-
1449227_at	Ch25h	cholesterol 25-hydroxylase	-	-	-	-	3.50	2.21	-	-	-	-	-	-
1436343_at	Chd4	chromodomain helicase DNA binding protein 4	-	-	-	2.01	-	-	-	-	-	-	-	-
1451537_at	Chi3l1	chitinase 3-like 1	-	-	-	-	2.83	1.03	-	-	1.39	-	-	-
1419764_at	Chi3l3	chitinase 3-like 3	-	-	1.18	-	-	-	-	-	-	-	-	-
1416456_a_at	Chia	chitinase, acidic	-	-	-	-	-1	-	-	-	-1.4	-	-	-
1427573_at	Chic1	cysteine-rich hydrophobic domain 1	-	-	-	1.37	-	-	-	-	-	-	-	-
1428574_a_at	Chn2	chimerin (chimaerin) 2	-	-	-	1.53	-	-	-	-1	-	-	-	-
1418852_at	Chrna1	cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)	-	-	-	-	2.99	-	-	-	1.55	-	-	-
14274-1_at	Chrna5	cholinergic receptor, nicotinic, alpha polypeptide 5	-	-	-	-	-1.74	-	-	-	-	-	-	-
1421267_a_at	Cited2	Cbp/p3---interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	1.34	-	-	-	-	-	-	-	-	-	-	-
1429976_at	Clasp2	CLIP associating protein 2	-	-	-	-	-1.06	-	-	-	-	-	-	-
1417852_x_at	Clca1	chloride channel calcium activated 1	-	-	-	-	2.00	-	-	-	-	-	-	-
146-259_s_at	Clca2	chloride channel calcium activated 2	-	-	-	-	2	-	-	-	1.05	-	-	-
143727-_a_at	Clcf1	cardiotrophin-like cytokine factor 1	-	-	-	-	1.82	-	-	-	1.17	-	-	-
1437932_a_at	Cldn1	claudin 1	-	-	-	-	-	-	-	-	-2.4	-	-	-

1417231_at	Cldn2	claudin 2	-	-	-	-	-2.1	-1.4	-	-1.7	-3.4	-	-	-
1421366_at	Clec5a	C-type lectin domain family 5, member a	-	-	-	-	2.26	1.09	-	-	-	-	-	-
142-699_at	Clec7a	C-type lectin domain family 7, member a	-	-	-	-	5.29	4.48	2.82	2.31	1.15	-	-	-
1416656_at	Clic1	chloride intracellular channel 1	-	-	-	-	2.06	1.36	1.09	-	-	-	-	-
1429574_at	Clic3	chloride intracellular channel 3	-	-	-	-	-	-	-	-	-1.2	-	-	-
1448316_at	Cmtm3	CKLF-like MARVEL transmembrane domain containing 3	-	-	-	-	1.60	-	-	-	-	-	-	-
1451114_at	Cmtm6	CKLF-like MARVEL transmembrane domain containing 6	-	-	-	-	1.25	-	-	-	-	-	-	-
146-253_at	Cmtm7	CKLF-like MARVEL transmembrane domain containing 7	-	-	-	-	1.88	1.16	-	-	-	-	-	-
1419517_at	Cnih3	cornichon homolog 3 (Drosophila)	-	-	-	-	1.31	-	-	-	1.5	-	-	-
1417917_at	Cnn1	calponin 1	-	-	-	-	1.26	-	-	-	-	-	-	-
1426724_at	Cnn3	calponin 3, acidic	-	-	-	-	1.31	-	-	-	-	-	-	-
142-739_at	Cntn3	contactin 3	1.01	-	-	-	-	-	-	-	-	-	-	-
1437782_at	Cntnap2	contactin associated protein-like 2	-	-	-	-	-2.17	-	-	-	-	-	-	-
1419-44_at	Cntnap4	contactin associated protein-like 4	-	-	-	-	-1.88	-	-	-	-	-	-	-
1423285_at	Coch	coagulation factor C homolog (Limulus polyphemus)	-	-	-	1.02	-	-	-	-	-	-	-	-
1418599_at	Col11a1	procollagen, type XI, alpha 1	-	-	-	-	1.67	-	-	-	2.32	-	-	-
1427986_a_at	Col16a1	procollagen, type XVI, alpha 1	-	-	-	-	1.33	-	-	-	1.14	-	-	-
1421698_a_at	Col19a1	procollagen, type XIX, alpha 1	-	-	-	-	-2.72	-	-	-	-	-	-	-
1423669_at	Col1a1	procollagen, type I, alpha 1	-	-	-	-	-	1.16	-	-	-	-	-	-
1425234_at	Col2-a1	collagen, type XX, alpha 1	-	-	-	-	2.49	-	-	-	-	-	-	-
1427883_a_at	Col3a1	procollagen, type III, alpha 1	-	-	-	-	1.61	1.98	-1	-	-	-	-	-
1425476_at	Col4a5	procollagen, type IV, alpha 5	-	-	-	-	1.43	-	-	-	-	-	-	-
1421--7_at	Col4a6	procollagen, type IV, alpha 6	-	-	-	-	1.36	-	-	-	-	-	-	-
1422437_at	Col5a2	procollagen, type V, alpha 2	-	-	-	-	1.06	-	-	-	-	-	-	-
144859-_at	Col6a1	procollagen, type VI, alpha 1	-	-	-	-1.3	1.29	-	1.16	-	2.31	-	2.25	-
145225-_a_at	Col6a2	procollagen, type VI, alpha 2	-	-	-	-1.1	1.2	-	-	-	1.37	-	-	-
1424131_at	Col6a3	procollagen, type VI, alpha 3	-	-	-	-	-1	-	-	-	-1.1	-	-	-
141844-_at	Col8a1	procollagen, type VIII, alpha 1	-	-	-	-	-1.3	-1	-	-1.1	-1.9	-	-	-
146-693_a_at	Col9a3	procollagen, type IX, alpha 3	-1.1	-	-	-	-	-	-	-	-1.9	-	-	-
1449183_at	Comt	catechol-O-methyltransferase	-	-	-	-	1.00	-	-	-	-	-	-	-
1427822_a_at	Copg2as2	coatomer protein complex, subunit gamma 2, antisense 2	-	-	-	-1	-	-	-	-	-	-	-	-
144982-_at	Cort	cortistatin	-	-	-	-	-1.13	-	-	-	-	-	-	-
1416--2_x_at	Cotl1	coactosin-like 1 (Dictyostelium)	-	-	-	-	-	1.2	-	-	-	-	-	-
1435275_at	Cox6b2	cytochrome c oxidase subunit VIb polypeptide 2	-	-	-	-	-	-	-	-	-1.6	-	-	-

1449218_at	Cox8b	cytochrome c oxidase, subunit VIIIb	-	-	-	-	-1.9	-1.5	-	-1.5-4	-3.2	-	-	-
1417496_at	Cp	ceruloplasmin	-	1.4	-	1.9	-1	-	-	-	-	-	-	-
1418-18_at	Cpd	carboxypeptidase D	-	-	-	1.93	1.2	-	-	-	-	-	-	-
1456-48_at	Cpeb3	cytoplasmic polyadenylation element binding protein 3	-	-	-	-	-1.08	-	-	-	-	-	-	-
1449921_s_at	Cpne6	copine VI	-	-	-	-	-1.11	-	-	-	-	-	-	-
1419295_at	Creb3l1	cAMP responsive element binding protein 3-like 1	-	-	-	-	-	-	-	-	-1	-	-	-
1415947_at	Creg1	cellular repressor of E1A-stimulated genes 1	-	-	-	-	1.35	-	-	-	-	-	-	-
1449-37_at	Crem	cAMP responsive element modulator	1.83	1.74	-	1.58	1.58	-	-	-	-	-	-	-
1423353_at	Crispld1	cysteine-rich secretory protein LCCL domain containing 1	-	-	-	-	-1.50	-1	-	-	-	-	-	-
14162-1_at	Crk	v-crk sarcoma virus CT1- oncogene homolog (avian)	-	-	-	1.15	-	-	-	-	-	-	-	-
1425556_at	Crkrs	Cdc2-related kinase, arginine/serine-rich	-	-	-	1.31	-	-	-	-	-	-	-	-
1418476_at	Crlf1	cytokine receptor-like factor 1	-	-	-	-	-1.79	-	-	-	-	-	-	-
142-686_at	Cryba4	crystallin, beta A4	-	-	-	-	2.23	1.19	-	-	-	-	-	-
14183-6_at	Crybb1	crystallin, beta B1	-	-	-	-	1.56	-	-	-	-	-	-	-
1416776_at	Crym	crystallin, mu	-	-	-	-	-1.01	-	-	-	-	-	-	-
1425155_x_at	Csf1	colony stimulating factor 1 (macrophage)	-	-	-	-	1.33	-	-	-	-	-	-	-
1423593_a_at	Csf1r	colony stimulating factor 1 receptor	-	-	-	-	2.36	1.5	1.25	-	-	-	-	-
142-7-3_at	Csf2ra	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	-	-	-	-	1.02	-	-	-	-	-	-	-
1421326_at	Csf2rb	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	-	-	-	-	2.97	1.4	-	-	1.12	-	-	-
144936-_at	Csf2rb2	colony stimulating factor 2 receptor, beta 2, low-affinity (granulocyte-macrophage)	-	-	-	-	2.12	-1	-	-	-	-	-	-
14188-6_at	Csf3r	colony stimulating factor 3 receptor (granulocyte)	-	-	-	-	2.05	1.38	-	-	-	-	-	-
1419-38_a_at	Csnk2a1	casein kinase 2, alpha 1 polypeptide	-	-	-	1.62	-	-	-	-	-	-	-	-
1435792_at	Csprs	component of Sp1---rs	-	-	-	-	1.27	-	-	-	-	-	-	-
14192-2_at	Cst7	cystatin F (leukocystatin)	-	-	-	-	7.67	6.64	4.29	3.66	2.47	-	-	-
1449-42_at	Ctcf	CCCTC-binding factor	-	-	-	1.77	-	-	-	-	-	-	-	-
1416953_at	Ctgf	connective tissue growth factor	-	-	-	-	2.16	-	-	-	1.76	-	-	-
1416811_s_at	Ctla2a	cytotoxic T lymphocyte-associated protein 2 alpha	3.06	2.57	-	-	2.07	1.36	1.21	1.69	1.38	-	-	-
1452352_at	Ctla2b	cytotoxic T lymphocyte-associated protein 2 beta	-	2.15	-	-	3.5	2.53	1.94	1.69	-	-	-	-
143-533_a_at	Ctnnb1	catenin (cadherin associated protein), beta 1	-	-	-	-	1.02	-	-	1.2	-	-	-	-
142268-_at	Ctr9	Ctr9, Paf1/RNA polymerase II complex component, homolog (S. cerevisiae)	-	-	-	1.01	-	-	-	-	-	-	-	-
1448128_at	Ctsa	cathepsin A	-	-	-	-	1.52	1.04	-	-	-	-	-	-
1448732_at	Ctsb	cathepsin B	-	-	-	-	1.51	-	-	1.13	-	-	-	-

1416382_at	Ctsc	cathepsin C	-	-	-	-	1.68	1.5	-	-	-	-	-	-
1448118_a_at	Ctsd	cathepsin D	-	-	-	-	1.63	1.35	-	-	-	-	-	-
1418989_at	Ctse	cathepsin E	-	-	1.13	-	1.13	-	-	-	-	-	-	-
1418365_at	Ctsh	cathepsin H	-	-	-	-	2.71	1.96	1.56	-	-	-	-	-
145131-_a_at	Ctsl	cathepsin L	-	-	-	-	1.19	-	-	-	-	-	-	-
1448591_at	Ctss	cathepsin S	-	-	-	-	1.54	1.43	-	-	-	-	-	-
1417869_s_at	Ctsz	cathepsin Z	-	-	-	-	2.78	2.27	1.38	1.17	-	-	-	-
14493--_at	Cttnbp2nl	CTTNBP2 N-terminal like	-	-	-	-	1.29	-	-	-	-	-	-	-
1422794_at	Cul3	cullin 3	-	-	-	-	1.11	-	-	-	-	-	-	-
1417453_at	Cul4b	cullin 4B	-	-	-	-	-	-	-	-	-1.7	-	-	-
145--19_at	Cx3cr1	chemokine (C-X3-C) receptor 1	-	1.46	-	-	2.49	1.46	1.0-1	1.28	-	-	-	-
14192-9_at	Cxcl1	chemokine (C-X-C motif) ligand 1	3.25	-	-	-	-	-	1.01	1.28	-	-	-	-
141893-_at	Cxcl1-	chemokine (C-X-C motif) ligand 1-	-	-	-	-	5.11	3.09	1.98	1.45	1.93	-	-	-
1417574_at	Cxcl12	chemokine (C-X-C motif) ligand 12	-	-1.2	-	-	-	-	-	-	-	-	-	-
1417851_at	Cxcl13	chemokine (C-X-C motif) ligand 13	-	-	-	-	4.44	2.05	1.3	-	3.84	-	-	-
1449195_s_at	Cxcl16	chemokine (C-X-C motif) ligand 16	-	-	-	-	3.21	1.9	1.48	-	-	-	-	-
1449984_at	Cxcl2	chemokine (C-X-C motif) ligand 2	2.36	1.58	-	-	-	-	-	-	-	-	-	-
1419728_at	Cxcl5	chemokine (C-X-C motif) ligand 5	-	-	-1.3	-	-	1.57	-	-	-	-	-	-
1418652_at	Cxcl9	chemokine (C-X-C motif) ligand 9	-	-	-	-	3.40	1.55	-	-	-	-	-	-
144871-_at	Cxcr4	chemokine (C-X-C motif) receptor 4	-	1.44	-	-	-	1.62	-	-	-	-	-	-
1425832_a_at	Cxcr6	chemokine (C-X-C motif) receptor 6	-	-	-	-	1.83	-	-	-	-	-	-	-
1422185_a_at	Cyb5r3	cytochrome b5 reductase 3	-	-	-	-	1.02	-	-	-	-	-	-	-
1454268_a_at	Cyba	cytochrome b-245, alpha polypeptide	-	-	-	-	2.78	2.16	1.47	1.07	-	-	-	-
1422978_at	Cybb	cytochrome b-245, beta polypeptide	-	-	-	-	1.61	-	-	-	-	-	-	-
142363-_at	Cygb	cytoglobin	-	-	-	-	-1.89	-	-	-	-	-	-	-
1416613_at	Cyp1b1	cytochrome P45-, family 1, subfamily b, polypeptide 1	1.89	1.38	-	-	1.59	-	-	-	1.21	-	-	-
1449316_at	Cyp4f15	cytochrome P45-, family 4, subfamily f, polypeptide 15	-	-	-	-	-1.80	-	-	-	-	-	-	-
1417-7-_at	Cyp4v3	cytochrome P45-, family 4, subfamily v, polypeptide 3	-	-	-	-	1.68	-	-	-	-	-	-	-
1416-39_x_at	Cyr61	cysteine rich protein 61	1.51	-	-	-	2.59	-	-	-	-	-	-	-
1419-7-_at	Cys1	cystin 1	-	-	-	-	-1.85	-	-	-	-	-	-	-
1418944_at	Cysltr1	cysteinyl leukotriene receptor 1	-	-	-	-	1.09	-	-	-	-	-	-	-
1449823_at	Dach2	dachshund 2 (Drosophila)	-	-	-1	-	-	-	-	-	-	-	-	-
142379-_at	Dap	death-associated protein	-	-	-	-	1.31	-	-	-	-	-	-	-
1419542_at	Dazl	deleted in azoospermia-like	-	-	-	-	-1.24	-	-	-	-	-	-	-

145-67-_at	Dbh	dopamine beta hydroxylase	-	-	-	-	1.23	-	-	-	-	-	-	-
1451734_a_at	Dbn1	drebrin 1	-	-	1.19	-	-	-	-	-	-	-	-	-
14493-7_at	Dbndd1	dysbindin (dystrobrevin binding protein 1) domain containing 1	-	-	-	-	-1.44	-	-	-	-	-	-	-
1438211_s_at	Dbp	D site albumin promoter binding protein	-	-1.4	-	-	-	-	-	-	-	-	-	-
1451917_a_at	Dclk1	doublecortin-like kinase 1	1.5	-	-	1.68	1.57	-	-	1	-	-	-	-
1452-79_s_at	Dcun1d1	DCUN1D1 DCN1, defective in cullin neddylation 1, domain containing 1 (S. cerevisiae)	-	-	-	1.18	-	-	-	-	-	-	-	-
1418139_at	Dcx	doublecortin	-	-	-	-	-1.49	-	-	-	-	-	-	-
1415798_at	Ddr1	discoidin domain receptor family, member 1	-	-	-	-	1.49	-	-	-	-	-	-	-
1448271_a_at	Ddx21	DEAD (Asp-Glu-Ala-Asp) box polypeptide 21	-	-	-	-	1.04	-	-	-	-	-	-	-
1426832_at	Ddx26b	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 26B	-	-	-	-	1.04	-	-	-	-	-	-	-
1424598_at	Ddx6	DEAD (Asp-Glu-Ala-Asp) box polypeptide 6	-	-	-	1.43	-	-	-	-	-	-	-	-
1419367_at	Decr1	2,4-dienoyl CoA reductase 1, mitochondrial	-	-	-	-	1.07	-	-	-	-	-	-	-
1452546_x_at	Defb11	defensin beta 11	-1.5	-	-	-	-2	-	-	-	-	-1	-	-
14276-2_at	Dep1	diabetic embryopathy 1	-	-	-	-	-	-	-	1.18	-	-	-	-
14243-3_at	Depdc7	DEP domain containing 7	-	-	-	-	-1.01	-	-	-	-	-	-	-
1424-47_at	Dera	2-deoxyribose-5-phosphate aldolase homolog (C. elegans)	-	-	-	-	-0.99	-	-	-	-	-	-	-
1415677_at	Dhrs1	dehydrogenase/reductase (SDR family) member 1	-	-	-	-	2.21	1.0-3	1.0-3	-	-3	-	-	-
1424398_at	Dhx36	DEAH (Asp-Glu-Ala-His) box polypeptide 36	-	-	-	1.33	-	-	-	-	-	-	-	-
1451426_at	Dhx58	DEXH (Asp-Glu-X-His) box polypeptide 58	-	-	-	-	2.25	1.03	-	-	-	-	-	-
1422944_a_at	Diap3	diaphanous homolog 3 (Drosophila)	-	-	-	1.47	-	-	-	-	-	-	-	-
1418938_at	Dio2	deiodinase, iodothyronine, type II	1.89	-	-	1.17	-	-	-	-	-	-	-	-
142-512_at	Dkk2	dickkopf homolog 2 (Xenopus laevis)	-	-	-	-	1.37	-	-	-	-	-	-	-
1419581_at	Dlg4	discs, large homolog 4 (Drosophila)	-	-	1.14	-	-	-	-	-	-	-	-	-
14192-4_at	Dll1	delta-like 1 (Drosophila)	-	-	-	-	-1.00	-	-	-	-	-	-	-
144947-_at	Dlx1	distal-less homeobox 1	-	-	-1.1	-	-2.2	-	-	-	-1.7	-	-	-
1419845_at	Dlx1as	distal-less homeobox 1, antisense	-	-	-	-	-1.40	-	-	-	-	-	-	-
1448877_at	Dlx2	distal-less homeobox 2	-	-	-	-	-1.44	-	-	-	-	-	-	-
1449863_a_at	Dlx5	distal-less homeobox 5	-	-	-1.1	-	-2.2	-	-	-	-1.6	-	-	-
1418592_at	Dnaja4	DnaJ (Hsp4-) homolog, subfamily A, member 4	1.04	-	1.05	-	-	-	-	-	-	-	-	-
1416756_at	Dnajb1	DnaJ (Hsp4-) homolog, subfamily B, member 1	1.33	-	1.26	-	-	-	-	-	-	-	-	-
1421961_a_at	Dnajb5	DnaJ (Hsp4-) homolog, subfamily B, member 5	1.2-6	-	1.26	-	-	-	-	-	-	-	-	-
1429777_at	Dnajb6	DnaJ (Hsp4-) homolog, subfamily B, member 6	1.05	-	-	-	-	-	-	-	-	-	-	-
1448794_s_at	Dnajc2	DnaJ (Hsp4-) homolog, subfamily C, member 2	-	-	-	-1	-	-	-	-	-	-	-	-

1449372_at	Dnajc3a	DnaJ (Hsp4-) homolog, subfamily C, member 3A	-	-	-	1.16	-	-	-	-	-	-	-	-
1452638_s_at	Dnm1l	dynamin 1-like	-	-	-	-	-	-	-	1.06	-	-	-	-
1423-65_at	Dnmt3a	DNA methyltransferase 3A	-	-	-	1.29	-	-	-	-	-	-	-	-
1449757_x_at	Dntt	deoxynucleotidyltransferase, terminal	1.25	-	-	-	-	-	-	-	-	-	-	-
1427882_at	Dnttip2	deoxynucleotidyltransferase, terminal, interacting protein 2	-	-	-	1.07	-	-	-	-	-	-	-	-
1436862_at	Doc2a	double C2, alpha	-	-	-	-	-1.29	-	-	-	-	-	-	-
142-667_at	Doc2b	double C2, beta	-	-	-	-	-1.84	-	-	-	-	-	-	-
14228-8_s_at	Dock2	dedicator of cyto-kinesis 2	-	-	-	-	2.26	1.38	-	-	-	-	-	-
1449419_at	Dock8	dedicator of cytokinesis 8	-	-	-	-	1.91	1.24	-	-	-	-	-	-
1439476_at	Dsg2	desmoglein 2	-	-	-	-	-1.09	-	-	-	-	-	-	-
1435494_s_at	Dsp	desmoplakin	-	-	-	-	-1.30	-1.3	-	-	-	-	-	-
1419223_a_at	Dtna	dystrobrevin alpha	-	-	-	1.07	1.13	-	-	-	-	-	-	-
144883-_at	Dusp1	dual specificity phosphatase 1	1.07	-	-	-	-	-	-	-	-	-	-	-
1452594_at	Dusp11	dual specificity phosphatase 11 (RNA/RNP complex 1-interacting)	-	-	-	-	1.27	-	-	-	-	-	-	-
145-698_at	Dusp2	dual specificity phosphatase 2	-	-	-	-	1.70	-	-	-	-	-	-	-
1419269_at	Dut	deoxyuridine triphosphatase	-	-	-	-	-1.34	-	-	-	-	-	-	-
1449928_at	Dynlt3	dynein light chain Tctex-type 3	-	-	-	1.04	-	-	-	-	-	-	-	-
1426226_at	Dyrk1a	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a	-	-	-	1.07	-	-	-	1.22	-	-	-	-
1452792_at	Dzip1	DAZ interacting protein 1	-	-	-	-	-1.81	-	-	-	-	-	-	-
1449222_at	Ebi3	Epstein-Barr virus induced gene 3	-	-	-	-	2.22	1.05	-	-	-	-	-	-
1434177_at	Ece1	endothelin converting enzyme 1	-	-	-1.7	-	-1.8	-	-	-	-	-	-	-
1422586_at	Ecel1	endothelin converting enzyme-like 1	-	-	-	-	-1.8	-	-1.4	-	1.18	-	-	-
1448613_at	Ecm1	extracellular matrix protein 1	-	-	-	-	1.51	-	-	-	-	-	-	-
1424-65_at	Edem1	ER degradation enhancer, mannosidase alpha-like 1	-	-	-	-	3.21	2.38	1.68	1.36	-	-	-	-
1423695_at	Edem2	ER degradation enhancer, mannosidase alpha-like 2	-	-	-	-	1.16	-	-	-	-	-	-	-
146-661_at	Edg3	endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	-	-	-	-	1.17	-	-	-	-	-	-	-
1417-18_at	Efemp2	epidermal growth factor-containing fibulin-like extracellular matrix protein 2	-	-	-	-	1.00	-	-	-	-	-	-	-
1419639_at	Efnb2	ephrin B2	-	-	-	-	-1.36	-	-	-	-	-	-	-
1419332_at	Egfl6	EGF-like-domain, multiple 6	-	-	-	-	-1.4	-	-1.3-9	-	-1.3	-	-	-
145111-_at	Egln1	EGL nine homolog 1 (C. elegans)	-	-	-	1.04	-	-	-	-	-	-	-	-
1418649_at	Egln3	EGL nine homolog 3 (C. elegans)	-	-	-	-	1.82	-	-	-	-	-	-	-
1427683_at	Egr2	early growth response 2	-	-	-	-	-	-	-	-1.1	-	-1.6	-	-
1449852_a_at	Ehd4	EH-domain containing 4	-	-	-	-	1.53	1.04	-	-	-	-	-	-
1422--5_at	Eif2ak2	eukaryotic translation initiation factor 2-alpha kinase 2	-	-	-	-	1.20	-	-	-	-	-	-	-

1416661_at	Eif3s1-	eukaryotic translation initiation factor 3, subunit 1- (theta)	-	-	-	1.99	-	-	-	-	-	-	-	-
143-98-_a_at	Eif4a1	eukaryotic translation initiation factor 4A1	-	-	-	1.14	-	-	-	-	-	-	-	-
1421985_a_at	Eif4e2	eukaryotic translation initiation factor 4E member 2	-	-	-	-	1.25	-	-	-	-	-	-	-
1417562_at	Eif4ebp1	eukaryotic translation initiation factor 4E binding protein 1	-	-	-	-	1.33	-	-	-	-	-	-	-
1427-37_at	Eif4g1	eukaryotic translation initiation factor 4, gamma 1	-	-	-	1.04	-	-	-	-	-	-	-	-
14346-5_at	Eif5b	eukaryotic translation initiation factor 5B	-	-	-	1.11	-	-	-	-	-	-	-	-
1423693_at	Ela1	elastase 1, pancreatic	-	-	-	-	2.14	1.15	1.01	-	1.41	-	-	-
1421883_at	Elavl2	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2 (Hu antigen B)	-	-	-	-	-1.60	-	-	-	-	-	-	-
1452894_at	Elavl4	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 4 (Hu antigen D)	-	-	-	-	-2.08	-	-	-	-	-	-	-
141754-_at	Elf1	E74-like factor 1	-	-	-	1.13	1.23	-	-	-	-	-	-	-
1448797_at	Elk3	ELK3, member of ETS oncogene family	-	-	1.12	-	1.92	1.34	-	-	1.3	-	-	-
1424-97_at	Elovl7	ELOVL family member 7, elongation of long chain fatty acids (yeast)	-	-	-	1.55	-	-	-	-	-	-	-	-
1415857_at	Emb	embigin	-	-	-	-	-1.2	-	-	-	-1.4	-	-	-
1449581_at	Emid1	EMI domain containing 1	-	-	-	-	2.48	1.22	-	-	-	-	-	-
1416529_at	Emp1	epithelial membrane protein 1	-	1.05	-	-	2.16	1.21	-	-	1.42	-	-	-
14171-4_at	Emp3	epithelial membrane protein 3	-	-	-	-	1.50	-	-	-	-	-	-	-
1451161_a_at	Emr1	EGF-like module containing, mucin-like, hormone receptor-like sequence 1	-	-	-	-	2.67	1.75	1.36	-	-	-	-	-
1426541_a_at	Endod1	endonuclease domain containing 1	-	-	-	1.48	-	-	-	-	-	-	-	-
1419276_at	Enpp1	ectonucleotide pyrophosphatase/phosphodiesterase 1	-	-	-	-	1.86	-1	-	-	-	-	-	-
1415894_at	Enpp2	ectonucleotide pyrophosphatase/phosphodiesterase 2	-	-	-	-	-1	-	-1	-	-1.2	-	-	-
1423326_at	Entpd1	ectonucleoside triphosphate diphosphohydrolase 1	-	-	-	-	2.17	1.45	-	-	-	-	-	-
1433491_at	Epb4.1l2	erythrocyte protein band 4.1-like 2	-	-	-	-	1.60	-	-	1.16	-	-	-	-
1455628_at	Epb4.1l4b	erythrocyte protein band 4.1-like 4b	-	-	-	-	-1.33	-	-	-	-	-	-	-
1425575_at	Epha3	Eph receptor A3	-	-	-	-	-1.68	-	-	-	-	-	-	-
1421929_at	Epha4	Eph receptor A4	-	-	-	1.94	-	-	-	-	-	-	-	-
1421527_at	Epha6	Eph receptor A6	-	-	-	-	-1.08	-	-	-	-	-	-	-
145155-_at	Ephb3	Eph receptor B3	-	-	-	-	-0.99	-	-	-	-	-	-	-
1417843_s_at	Eps8l2	EPS8-like 2	-	-	1.29	-	-	-	-	-	-	-	-	-
1452-87_at	Epsti1	epithelial stromal interaction 1 (breast)	-	-	-	-	3.32	1.93	1.54	1.38	-	-	-	-
1421114_a_at	Epyc	epiphycan	-	-	-	-	-1.18	-	-	-	-	-	-	-
14392--_x_at	Erdr1	erythroid differentiation regulator 1	-	-	-	-	3.02	2.55	-	3.11	-	-	-	-
1423333_at	Ergic1	endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1	-	-	-	-	1.05	-	-	-	-	-	-	-
1453796_a_at	Ergic2	ERGIC and golgi 2	-	-	-	1.15	-	-	-	-	-	-	-	-
1419816_s_at	Errfi1	ERBB receptor feedback inhibitor 1	1.51	-	1.32	1.42	-	-	-	-	-	-	-	-

1424325_at	Esco1	establishment of cohesion 1 homolog 1 (S. cerevisiae)	-	-	-	1.75	-	-	-	-	-	-	-	-
142688-_at	Etl4	enhancer trap locus 4	-	-	-	-	-1.84	-	-	-	-	-	-	-
1433515_s_at	Etnk1	ethanolamine kinase 1	-	-	-	-	-	-	-	1.04	-	-	-	-
1418635_at	Etv3	ets variant gene 3	-	-	-	-	1.55	-	-	-	-	-	-	-
145--82_s_at	Etv5	ets variant gene 5	-	-	-	-	-0.99	-	-	-	-	-	-	-
14265-5_at	Evi2b	ecotropic viral integration site 2b	-	-	-	-	2.69	1.46	-	-	-	-	-	-
141716-_s_at	Expi	extracellular proteinase inhibitor	-	-	-	-	2.83	-	-	-	-	-	-	-
1424595_at	F11r	F11 receptor	-	-	-	-	1.28	-	-	-	-	-	-	-
1448929_at	F13a1	coagulation factor XIII, A1 subunit	-	1.16	-	-	-	-	-	-	-	-	-	-
14189-7_at	F5	coagulation factor V	-1.2	-	-	-	-2.6	-1.6	-	-2	-3.7	-	-	-
1427393_at	F9	coagulation factor IX	-	-	-	-	2.66	1.72	-	-	-	-	-	-
145-779_at	Fabp7	fatty acid binding protein 7, brain	-	-	-	-	1.49	-	-	-	-	-	-	-
1417552_at	Fap	fibroblast activation protein	-	-	-	-	-1.8	-	-	-	-2.7	-	-	-
146-251_at	Fas	Fas (TNF receptor superfamily member)	-	-	-	-	1.08	-	-	-	-	-	-	-
1418569_at	Fblim1	filamin binding LIM protein 1	-	-	-	-	1.53	1.26	-	-	-	-	-	-
14234-7_a_at	Fbln2	fibulin 2	-	-	-	-	-	-	-	-	1.41	-	-	-
1416164_at	Fbln5	fibulin 5	-	-	-	-	2.4	-	-	-	1.63	-	-	-
141834-_at	Fcer1g	Fc receptor, IgE, high affinity I, gamma polypeptide	-	-	-	-	2.91	2.27	1.6	1.44	-	-	-	-
1417876_at	Fcgr1	Fc receptor, IgG, high affinity I	-	-	-	-	3.95	2.69	2.17	1.44	1.31	-	-	-
1435477_s_at	Fcgr2b	Fc receptor, IgG, low affinity IIb	-	-	-	-	3.43	2.1	2.24	1.53	2.49	-	-	-
144862-_at	Fcgr3	Fc receptor, IgG, low affinity III	-	-	-	-	2.91	2.13	1.84	1.23	-	-	-	-
1425225_at	Fcgr4	Fc receptor, IgG, low affinity IV	-	-	-	-	4.03	2.61	2.15	1.38	2.32	-	-	-
1427368_x_at	Fes	feline sarcoma oncogene	-	-	-	-	1.67	1.2	-	-	-	-	-	-
1419515_at	Fgd2	FYVE, RhoGEF and PH domain containing 2	-	-	-	-	1.80	-	1.11	-	-	-	-	-
1439959_at	Fgf11	fibroblast growth factor 11	-	-	-	-	-1.19	-	-	-	-	-	-	-
1435747_at	Fgf14	fibroblast growth factor 14	-	-	-	-	-1.66	-	-	-	-	-	-	-
1451912_a_at	Fgfrl1	fibroblast growth factor receptor-like 1	-	-	-	-	1.41	-	-	-	-	-	-	-
1421854_at	Fgl2	fibrinogen-like protein 2	-	-	-	-	2.41	-	-	-	1.96	-	-	-
1435551_at	Fhod3	formin homology 2 domain containing 3	-	-	-1.2	-	1.19	-	-	-	-	-	-	-
1449528_at	Figf	c-fos induced growth factor	-	-	-	-1.7	-	-	-	-	-	-	-	-
1422733_at	Fjx1	four jointed box 1 (Drosophila)	-	-	-	-	-	-	-	1.11	-	-	-	-
1433512_at	Fli1	Friend leukemia integration 1	-	-	-	-	2.21	1.4	-	-	-	-	-	-
1449-73_at	Flnc	filamin C, gamma (actin binding protein 28-)	-	-	-	-	1.20	-	-	-	-	-	-	-
1426825_at	Fmnl3	formin-like 3	-	-	-	-	1.21	-	-	-	-	-	-	-

1456-84_x_at	Fmod	fibromodulin	-	-	-	-	1.38	-	-	-	-	-	-	-
1426-86_a_at	Fmr1	fragile X mental retardation syndrome 1 homolog	-	-	-	1.08	-	-	-	-	-	-	-	-
1434739_at	Fmr1nb	fragile X mental retardation 1 neighbor	-	-	-	-	-	1.15	-	-	-	-	-	-
1426642_at	Fn1	fibronectin 1	-	-	-	-	1.03	-	-	-	1.79	-	-	-
145-995_at	Folr1	folate receptor 1 (adult)	-	-	-	-	-2.2-9	-1.6	-	-1.8	-3.7	-	-	-
1451648_a_at	Folr2	folate receptor 2 (fetal)	-	-	-	-	-0.98	-	-	-	-	-	-	-
14231--_at	Fos	FBJ osteosarcoma oncogene	1.63	-	-	-	-	-	-	-	-	-	-	-
1422134_at	Fosb	FBJ osteosarcoma oncogene B	2.81	2.51	1.85	-	-	-	-	-	-	-	-	-
1417487_at	Fosl1	fos-like antigen 1	2.15	2.02	-	-	-	-	-	-	-	-	-	-
1435221_at	Foxp1	forkhead box P1	-	-	-	-	-1.65	-	-	-	-	-	-	-
145522-_at	Frat2	frequently rearranged in advanced T-cell lymphomas 2	-	-	-	-	-1.13	-	-	-	-	-	-	-
1423465_at	Frrs1	ferric-chelate reductase 1	-	-	-	-	1.19	1.07	-	-	-	-	-	-
1416658_at	Frzb	frizzled-related protein	-	-	-	-	-	-1.1	-	-1.2	-	-	-	-
1418364_a_at	Ftl1	ferritin light chain 1	-	-	-	-	1.15	-	-	-	-	-	-	-
1437544_at	Fubp1	far upstream element (FUSE) binding protein 1	-	-	-	1.25	-	-	-	-	-	-	-	-
1418527_a_at	Fusip1	FUS interacting protein (serine-arginine rich) 1	-	-	-	1.34	-	-	-	-	-	-	-	-
1418296_at	Fxyd5	FXYD domain-containing ion transport regulator 5	-	-	-	-	1.30	-	-	-	-	-	-	-
1452117_a_at	Fyb	FYN binding protein	-	-	-	-	3.22	2.03	1.77	1.3	-	-	-	-
1424342_at	Fyttd1	forty-two-three domain containing 1	-	-	-	1.38	-	-	-	-	-	-	-	-
1422327_s_at	G6pd2	glucose-6-phosphate dehydrogenase 2	-	-	-	-	1.29	-	-	-	-	-	-	-
1419761_a_at	Gabpb1	GA repeat binding protein, beta 1	1.11	-	-	1.09	-	-	-	-	-	-	-	-
142128-_at	Gabra1	gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 1	-	-	-	1.27	-1	-	-	1.1-5	-	-	-	-
1417121_at	Gabra6	gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 6	-	-	-	-	-	-	-	-	1.74	-	1.85	1.02
142119-_at	Gabrb3	gamma-aminobutyric acid (GABA-A) receptor, subunit beta 3	-	-	-	1.58	-	-	-	-	-	-	-	-
146-4-8_at	Gabrg1	gamma-aminobutyric acid (GABA-A) receptor, subunit gamma 1	-	-	-	-	-1.02	-	-	-	-	-	-	-
1418177_at	Gabrg2	gamma-aminobutyric acid (GABA-A) receptor, subunit gamma 2	-	-	-	-	1.18	-	-	-	-	-	-	-
1421978_at	Gad2	glutamic acid decarboxylase 2	-	-	-	2.47	-	-	-1.2	-	-	-	-	-
145-971_at	Gadd45b	growth arrest and DNA-damage-inducible 45 beta	1.98	1.1	1.21	-	1.25	-	-	-	-	-	-	-
1453851_a_at	Gadd45g	growth arrest and DNA-damage-inducible 45 gamma	2.28	1.33	-	-	1.25	-	-	-	-	-	-	-
146-668_at	Gal	galanin	-	-	-	-	1.73	-	-	-	1.43	-	-	-
1423237_at	Galnt1	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1	-	-	-	-	1.05	-	-	-	-	-	-	-
1455915_at	Galnt4	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 4	-	-	-	-	1.26	-	-	-	-	-	-	-

1425581_s_at	Galnt7	UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 7	-	-	-	1.21	-	-	-	-	-	-	-	-
1421448_at	Garnl1	GTPase activating RANGAP domain-like 1	-1	-	-	1.35	-	-	-	1.08	-	-	-	-
145--99_a_at	Gba	glucosidase, beta, acid	-	-	-	-	1.26	-	-	-	-	-	-	-
141824-_at	Gbp2	guanylate nucleotide binding protein 2	1.52	-	-	-	3.05	2.12	1.61	1.01	2.36	-	-	-
1418392_a_at	Gbp3	guanylate nucleotide binding protein 3	-	-	-	-	3.09	1.75	1.42	-	1.97	-	-	-
143438-_at	Gbp6	guanylate binding protein 6	-	-	-	-	2.15	1.22	-	-	1.69	-	-	-
14518--_at	Gcc2	GRIP and coiled-coil domain containing 2	-	-	-	2.12	-	-	-	-	-	-	-	-
142-499_at	Gch1	GTP cyclohydrolase 1	-	-	-	-	1.33	-	-	-	-	-	-	-
143-826_s_at	Gcnt2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme	1.68	-	-	-	1.12	-	-	-	-	-	-	-
143-826_s_at	Gcnt2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme	-	-	-	-	1.12	-	-	-	-	-	-	-
1424--7_at	Gdf1-	growth differentiation factor 1-	-	-	-	-	-1.94	-	-	-	-	-	-	-
1431645_a_at	Gdi2	guanosine diphosphate (GDP) dissociation inhibitor 2	-	-	-	-	1.01	-	-	-	-	-	-	-
1419-8-_at	Gdnf	glial cell line derived neurotrophic factor	-	-	-	-	3.45	-	-	-	1.41	-	-	-
1429-76_a_at	Gdpd2	glycerophosphodiester phosphodiesterase domain containing 2	-	-	-	-	1.23	-	-	-	-	-	-	-
142415-_at	Gdpd5	glycerophosphodiester phosphodiesterase domain containing 5	-	-	-	-	1.14	-	-	-	-	-	-	-
1426-63_a_at	Gem	GTP binding protein (gene overexpressed in skeletal muscle)	1.79	-	-	1.62	2.21	-	-	-	-	-	-	-
14265-8_at	Gfap	glial fibrillary acidic protein	-	-	-	-	2.12	1.8-3	1.56	1.25	1.32	-	-	-
1418753_at	Gfpt2	glutamine fructose-6-phosphate transaminase 2	-	-	-	-	2.14	1	-	-	-	-	-	-
145-44-_at	Gfra1	glial cell line derived neurotrophic factor family receptor alpha 1	1.06	-	-	-	2.71	-	-	-	1.87	-	-	-
1418483_a_at	Ggta1	glycoprotein galactosyltransferase alpha 1, 3	-	-	-	-	2.72	1.57	1.3	-	1.91	-	-	-
1424375_s_at	Gimap4	GTPase, IMAP family member 4	-	-	-	-	2.39	1.17	1.06	-	-	-	-	-
1427891_at	Gimap6	GTPase, IMAP family member 6	-	-	-	-	-	-	-	-	1.23	-	-	-
1454759_at	Git1	G protein-coupled receptor kinase-interactor 1	-	-	-	-	-1.07	-	-	-	-	-	-	-
14158-1_at	Gja1	gap junction membrane channel protein alpha 1	-	-	-	1.48	1.21	-	-	2.1-7	-	-	-	-
1422-42_at	Gje1	gap junction membrane channel protein epsilon 1	-	-	-	1.68	-	-	-	-	-	-	-	-
1418248_at	Gla	galactosidase, alpha	-	-	-	-	1.05	-	-	-	-	-	-	-
14162-5_at	Glb1	galactosidase, beta 1	-	-	-	-	1.15	-	-	-	-	-	-	-
1424927_at	Glipr1	GLI pathogenesis-related 1 (glioma)	-	-	-	-	2.11	1	-	-	-	-	-	-
1428492_at	Glipr2	GLI pathogenesis-related 2	1.42	1.05	-	-	1.84	-	-	-	-	-	-	-
1421732_at	Glrp1	glutamine repeat protein 1	-	-	-	-	1.24	-	-	-	-	-	-	-
14524-9_at	Gltscr2	glioma tumor suppressor candidate region gene 2	1.28	-	-	-	-	-	-	-	-	-	-	-
1424825_a_at	Glycam1	glycosylation dependent cell adhesion molecule 1	-	-	-	-	3.53	2.28	1.37	-	-	-	-	-
1435998_at	Gm288	gene model 288, (NCBI)	-	-	-	-	-	-	-	-	1.72	1.56	1.51	1.06

1416188_at	Gm2a	GM2 ganglioside activator protein	-	-	-	-	1.44	-	-	1.25	-	-	-	-
1417-69_a_at	Gmfb	glia maturation factor, beta	-	-	-	2.4	-	-	-	-	-	-	-1	-
1419194_s_at	Gmfg	glia maturation factor, gamma	-	-	-	-	2.38	1.81	1.42	-	-	-	-	-
1428784_at	Gmip	Gem-interacting protein	-	-	-	-	1.33	-	-	-	-	-	-	-
1421-26_at	Gna12	guanine nucleotide binding protein, alpha 12	-	-	-	-	-	-	-	1.13	-	-	-	-
1422556_at	Gna13	guanine nucleotide binding protein, alpha 13	-	-	-	1.43	1.11	-	-	-	-	-	-	-
1449848_at	Gna14	guanine nucleotide binding protein, alpha 14	-	-	-	-	1.57	-	-	-	1.36	-	-	-
14213-2_a_at	Gna15	guanine nucleotide binding protein, alpha 15	-	-	-	-	-	-	-	1.67	-	-	-	-
142751-_at	Gnai1	guanine nucleotide binding protein, alpha inhibiting 1	-	-	-	1.35	-1.1	-	-	-	-	-	-	-
1421947_at	Gng12	guanine nucleotide binding protein (G protein), gamma 12	-	-	-	-	1.13	-	-	-	-	-	-	-
1421845_at	Golph3	golgi phosphoprotein 3	-	-	-	1.26	-	-	-	-	-	-	-	-
146-46-_a_at	Gorasp2	golgi reassembly stacking protein 2	-	-	-	-	-	-	-	-1	-	-	-	-
1419499_at	Gpam	glycerol-3-phosphate acyltransferase, mitochondrial	-	-	-	-	1.20	-	-	-	-	-	-	-
1421-88_at	Gpc4	glypican 4	-	-	-	-	1.07	-	-	-	-	-	-	-
1418-5-_at	Gpld1	glycosylphosphatidylinositol specific phospholipase D1	-	-	-	-	1.00	-	-	-	-	-	-	-
14483-3_at	Gpnmb	glycoprotein (transmembrane) nmb	-	-	-	-	3.71	2.78	1.97	1.77	2.32	-	-	-
1419721_at	Gpr1-9a	G protein-coupled receptor 1-9A	-	-	-	-	3.06	2.1-4	1.18	1.09	1.44	-	-	-
1449472_at	Gpr12	G-protein coupled receptor 12	-	-	-	-	-1.55	-	-	-	-	-	-	-
1429775_a_at	Gpr137b-ps	G protein-coupled receptor 137B, pseudogene	-	-	-	-	1.17	-	-	-	-	-	-	-
146-275_at	Gpr3	G-protein coupled receptor 3	-	1.03	-	-	-	-	-	-	-	-	-	-
1422542_at	Gpr34	G protein-coupled receptor 34	-2.1	-2.3	-1.9	-	2.42	1.12	-	-	-	-	-	-
1449175_at	Gpr65	G-protein coupled receptor 65	1.2	-	-	-	3.32	2.04	-	1.03	-	-	-	-
142-591_at	Gpr84	G protein-coupled receptor 84	2.41	2.01	-	-	3.77	2.96	2.03	1.55	1.36	-	-	-
1424897_at	Gpr85	G protein-coupled receptor 85	-	-	-	-	-1.85	-	-	-	-	-	-	-
1418396_at	Gpsm3	G-protein signalling modulator 3 (AGS3-like, C. elegans)	-	-	-	-	1.67	1.25	-	-	-	-	-	-
14491-6_at	Gpx3	glutathione peroxidase 3	-	-	1.29	-	-	-	-	-	-	-	-	-
1419593_at	Greb1	gene regulated by estrogen in breast cancer protein	-	-	-	-	1.14	-	-	-	-	-	-	-
1418492_at	Grem2	gremlin 2 homolog, cysteine knot superfamily (Xenopus laevis)	-	-	-	-	1.63	-	-	-	1.83	-	-	-
1435239_at	Gria1	glutamate receptor, ionotropic, AMPA1 (alpha 1)	-	-	-	-	-1.31	-	-	-	-	-	-	-
142-563_at	Gria3	glutamate receptor, ionotropic, AMPA3 (alpha 3)	-	-	-	1.29	-	-	-	-	-	-	-	-
1427676_a_at	Grik1	glutamate receptor, ionotropic, kainate 1	-	-	-	-	-1.28	-	-	-	-	-	-	-
14257--_at	Grm1	glutamate receptor, metabotropic 1	-	-	-	-	-1.07	-	-	-	-	-	-	-
1448148_at	Grn	granulin	-	-	-	-	####	1.78	1.5	1.08	-	-	-	-
1424525_at	Grp	gastrin releasing peptide	-	-	-	-1.1	-1.7	-	-	-	-	-	-	-

145-886_at	Gsg2	germ cell-specific gene 2	-	-	-	-	1.06	-	-	-	-	-	-	-
1415812_at	Gsn	gelsolin	-	-	-	-	1.14	1.04	-	-	-	-	-	-
1421-4-_a_at	Gsta2	glutathione S-transferase, alpha 2 (Yc2)	-	-	-	-1.4	-	-	-	-	-	-	-	-
1416531_at	Gsto1	glutathione S-transferase omega 1	-	-	-	-	1.17	-	-	-	-	-	-	-
1448124_at	Gusb	glucuronidase, beta	-	-	-	-	2.99	1.96	-	1.1	-	-	-	-
1419-6-_at	Gzmb	granzyme B	-	-	-	-	-0.99	-	-	-	-	-	-	-
1451683_x_at	H2-D1	histocompatibility 2, D region locus 1	-	-	-	-	3.31	2.04	1.43	1.16	-	-	-	-
1422527_at	H2-DMa	histocompatibility 2, class II, locus DMa	-	-	-	-	1.12	-	-	-	-	-	-	-
1418638_at	H2-DMb1	histocompatibility 2, class II, locus Mb1	-	-	-	-	####	1.19	-	-	-	-	-	-
144958-_s_at	H2-DMb2	histocompatibility 2, class II, locus Mb2	-	-	-	-	1.44	-	-	-	-	-	-	-
1424948_x_at	H2-K1	histocompatibility 2, K1, K region	-	-	-	-	2.61	1.76	1.5	1.16	-	-	-	-
1451931_x_at	H2-L	histocompatibility 2, D region	-	-	-	-	2.78	1.88	1.55	-	-	-	-	-
1421358_at	H2-M3	histocompatibility 2, M region locus 3	-	-	-	-	2.26	1.09	-	-	-	-	-	-
1419297_at	H2-Oa	histocompatibility 2, O region alpha locus	-	-	-	-	1.96	1.75	-	-	-	-	-	-
1451644_a_at	H2-Q1	histocompatibility 2, Q region locus 1	-	-	-	-	1.97	-	-	-	-	-	-	-
1418536_at	H2-Q8	histocompatibility 2, Q region locus 8	-	-	-	-	3.29	1.91	-	-	-	-	-	-
1449875_s_at	H2-T1-	histocompatibility 2, T region locus 1-	-	-	-	-	1.32	-	-	-	-	-	-	-
1449556_at	H2-T23	histocompatibility 2, T region locus 23	-	-	-	-	2.24	1.2-5	1.25	-	1.22	-	-	-
142216-_at	H2-T24	histocompatibility 2, T region locus 24	-	-	-	-	1.30	-	-	-	-	-	-	-
142-589_at	Has3	hyaluronan synthase 3	-	-	-	-	-1.31	-1.1	-	-	-	-	-	-
1451584_at	Havcr2	hepatitis A virus cellular receptor 2	-	-	-	-	3.02	1.81	1.55	1.06	-	-	-	-
141835-_at	Hbegf	heparin-binding EGF-like growth factor	1.4	1.27	-	-	2.47	-	-	-	1.64	-	-	-
1449455_at	Hck	hemopoietic cell kinase	-	-	-	-	2.71	1.73	1.35	-	1.07	-	-	-
1418842_at	Hcls1	hematopoietic cell specific Lyn substrate 1	-	-	-	-	2.57	1.73	-	1.03	-	-	-	-
1435977_at	Hdgfrp3	hepatoma-derived growth factor, related protein 3	-	-	-	-	-1.05	-	-	-	-	-	-	-
1449615_s_at	Hdlbp	high density lipoprotein (HDL) binding protein	-	-	-	1.41	-	-	-	-	-	-	-	-
14247-3_at	Hemk1	HemK methyltransferase family member 1	-	-	-	-	-	-	-	-	-1.7	-	-	-
1456-1-_x_at	Hes5	hairy and enhancer of split 5 (Drosophila)	-1.4	-	-	-1.3	-1.5	-	-	-	-	-	-	-
1449-24_a_at	Hexa	hexosaminidase A	-	-	-	-	1.41	1.04	-	-	-	-	-	-
146-18-_at	Hexb	hexosaminidase B	-	-	-	-	1.75	1.48	-	-	-	-	-	-
1423319_at	Hhex	hematopoietically expressed homeobox	-	-	-	-	1.80	1.21	-	-	-	-	-	-
1448183_a_at	Hif1a	hypoxia inducible factor 1, alpha subunit	-	-	-	-	1.01	-	-	-	-	-	-	-
1424755_at	Hip1	huntingtin interacting protein 1	-	-	-	1.25	-1.3	-	-	-	-	-	-	-
1438--9_at	Hist1h2ae	histone cluster 1, H2ae	-	-	-	-	1.52	-	-	-	-	-	-	-

1422947_at	Hist1h3a	histone cluster 1, H3a	2.25	-	-	-	1.11	-	-	-	-	-	-	-
1428-14_at	Hist1h4h	histone cluster 1, H4h	-	-	-	-	1.71	-	-	-	-	-	-	-
146-314_s_at	Hist2h3c1	histone cluster 2, H3c1	1.32	-	1.01	-	1.36	-	-	-	-	-	-	-
1422612_at	Hk2	hexokinase 2	-	-	-	-	2.31	1.39	1.39	-	-	-	-	-
1434735_at	Hlf	hepatic leukemia factor	-	-	-	-	-1.80	-	-	-	-	-	-	-
1452534_a_at	Hmgb2	high mobility group box 2	1.65	-	-	1.3	1.16	-	-	-	-	-	-	-
1427229_at	Hmgcr	3-hydroxy-3-methylglutaryl-Coenzyme A reductase	-	-	-	-	1.58	-	-	-	-	-	-	-
1428242_at	Hmha1	histocompatibility (minor) HA-1	-	-	-	-	1.56	1.11	-	-	-	-	-	-
1448239_at	Hmox1	heme oxygenase (decycling) 1	2.72	1.52	-	-	1.67	-	-	-	-	-	-	-
14177-2_a_at	Hnmt	histamine N-methyltransferase	-	-	-	-	-1.07	-	-	-	-	-	-	-
1421768_a_at	Homer1	homer homolog 1 (Drosophila)	1.91	1.67	1.33	1.79	2.05	-	-	-	1.25	-	-	-
1424367_a_at	Homer2	homer homolog 2 (Drosophila)	-	-	-	-	-2.17	-	-	-	-	-	-	-
1425833_a_at	Hpca	hippocalcin	-	-	-	-	-1.68	-	-	-	-	-	-	-
14199-5_s_at	Hpgd	hydroxyprostaglandin dehydrogenase 15 (NAD)	-	-	-	-	2.38	1.27	-	-	1.75	-	-	-
143595-_at	Hr	hairless	-	-	-	-	1.27	-	-	-	-	-	-	-
145--1-_at	Hsd17b12	hydroxysteroid (17-beta) dehydrogenase 12	-	-	-	1.79	1.26	-	-	-	-	-	-	-
14493-6_at	Hsf2	heat shock factor 2	-	-	-	-1.2	-	-	-	-	-	-	-	-
1423566_a_at	Hsp11-	heat shock protein 11-	1.56	-	1.23	-	-	-	-	-	-	-	-	-
1416365_at	Hsp9-ab1	heat shock protein 9-kDa alpha (cytosolic), class B member 1	-	-	-	1.12	-	-	-	-	-	-	-	-
1438-4-_a_at	Hsp9-b1	heat shock protein 9-kDa beta (Grp94), member 1	-	-	-	1.89	-	-	-	-	-	-	-	-
1452388_at	Hspa1a	heat shock protein 1A	3.48	2.29	2.37	-	-1.3	-	-	-	-	-	-	-
1427126_at	Hspa1b	heat shock protein 1B	3.98	2.61	2.94	-	-1.6	-	-	-	-	-	-	-
1416147_at	Hspa4	heat shock protein 4	-	-	1.01	-	-	-	-	-	-	-	-	-
1422943_a_at	Hspb1	heat shock protein 1	2.98	2.16	2.28	1.4	2.18	-	-	-	-	-	-	-
1449872_at	Hspb3	heat shock protein 3	-	-	-	-	3.15	1.19	-	-	1.58	-	-	-
1417-14_at	Hspb8	heat shock protein 8	-	-	1.48	-	1.19	-1	-	-	-	-	-	-
143871-_at	Htr1a	5-hydroxytryptamine (serotonin) receptor 1A	-	-	-	-	-2.41	-	-	-	-	-	-	-
145-548_at	Htr1f	5-hydroxytryptamine (serotonin) receptor 1F	-	-	-	-	-1.8	-	-	-	-1.5	-	-	-
1424-32_at	Hvcn1	hydrogen voltage-gated channel 1	-	-	-	-	2.39	1.78	-	-	-	-	-	-
1424-67_at	Icam1	intercellular adhesion molecule	-	-	-	-	2.8	1.52	1.36	-	1.39	-	-	-
142293-_at	Icam4	intercellular adhesion molecule 4, Landsteiner-Wiener blood group	-	-	-	-	-1.78	-	-	-	-	-	-	-
1418619_at	Icam5	intercellular adhesion molecule 5, telencephalin	-	-	-	-	-1.05	-	-	-	-	-	-	-
1425895_a_at	Id1	inhibitor of DNA binding 1	1.11	-	1.06	-	-	-	-	-	-	-	-	-
1453596_at	Id2	inhibitor of DNA binding 2	1.39	-	-	-	-	-	-	-	-	-	-	-

141663-_at	Id3	inhibitor of DNA binding 3	-	-	-	-	1.43	-	-	-	-	-	-	-
1417612_at	Ier5	immediate early response 5	1.09	-	1.22	-	1.33	-	-	-	-	-	-	-
14196-3_at	Ifi2-4	interferon activated gene 2-4	-	-	-	-	3.36	2.02	-	-	-	-	-	-
1452349_x_at	Ifi2-5	interferon activated gene 2-5	-	1.61	-	-	3.7	1.89	-	-	-1.6	-	-	-1.9
1426278_at	Ifi27	interferon, alpha-inducible protein 27	-	-	-	-	4.46	3.22	2.32	-	-	-	-	-
1422476_at	Ifi3-	interferon gamma inducible protein 3-	-	-	-	-	2.53	1.58	1.28	-	-	-	-	-
1424617_at	Ifi35	interferon-induced protein 35	-	-	-	-	2.09	1.17	-	-	-	-	-	-
1423555_a_at	Ifi44	interferon-induced protein 44	-	-	-	-	4.63	2.93	2.19	1.56	1.15	-	-	-
1417292_at	Ifi47	interferon gamma inducible protein 47	-	-	-	-	2.24	-	-	-	-	-	-	-
1426276_at	Ifih1	interferon induced with helicase C domain 1	-	-	-	-	2.02	1.11	-	-	-	-	-	-
145-783_at	Ifit1	interferon-induced protein with tetratricopeptide repeats 1	-	-	-	-	3.93	2.72	1.7-6	-	1.49	1.13	-	-
1418293_at	Ifit2	interferon-induced protein with tetratricopeptide repeats 2	-	-	-	-	2.48	1.21	-	-	-	-	-	-
1449-25_at	Ifit3	interferon-induced protein with tetratricopeptide repeats 3	-	-	-	-	3.38	2.11	1.7	-	-	-	-	-
1423754_at	Ifitm3	interferon induced transmembrane protein 3	-	-	-	-	2.26	1.64	1.27	-	-	-	-	-
144-865_at	Ifitm6	interferon induced transmembrane protein 6	-	-	-	-	1.22	-	-	-	-	-	-	-
1451462_a_at	Ifnar2	interferon (alpha and beta) receptor 2	-	-	-	-	-0.98	-	-	-	-	-	-	-
1448167_at	Ifngr1	interferon gamma receptor 1	-	-	-	-	1.31	-	-	-	-	-	-	-
1452-14_a_at	Igf1	insulin-like growth factor 1	-	-	-	-	2.62	1.67	1.7	-	-	-	-	-
1417933_at	Igfbp6	insulin-like growth factor binding protein 6	-	-	-	-	-1.38	-	-	-	-	-	-	-
1423584_at	Igfbp7	insulin-like growth factor binding protein 7	-	-	-	-	1.06	-	-	-	-	-	-	-
1425763_x_at	Igh	immunoglobulin heavy chain complex	-	-	-	-	-	1.36	-	-	-	-	-	-
1427329_a_at	Igh-6	immunoglobulin heavy chain 6 (heavy chain of IgM)	-	-	-	-	-	-	-	-	1.47	-	-	-
1421653_a_at	Igh-VJ558	immunoglobulin heavy chain (J558 family)	-	-	-	-	-	1.18	-	-	-	-	-	-
1452417_x_at	Igk-C	immunoglobulin kappa chain, constant region	-2.6	-	-	-	-	-	-	-	-	-	-	-
1427455_x_at	Igk-V1	immunoglobulin kappa chain variable 1 (V1)	-2.4	-	1.22	-	-	-	-	-	-	-	-	-
14514-7_at	Igsf5	immunoglobulin superfamily, member 5	-	-	-	-	-	-	-	-	-1.1	-	-	-
14214-8_at	Igsf6	immunoglobulin superfamily, member 6	-	-	-	-	2.42	1.36	1.56	-	-	-	-	-
1417141_at	Igtp	interferon gamma induced GTPase	-	-	-	-	2.36	1.41	-1	-	2.07	-	-	-
1419-42_at	Iigp1	interferon inducible GTPase 1	-	-	-	-	3.5	2.17	1.3-7	-	2.49	-	-	-
1417793_at	Iigp2	interferon inducible GTPase 2	-	-	-	-	2.1	1.39	-	-	1.81	-	-	-
1448731_at	Il1-ra	interleukin 1- receptor, alpha	-	-	-	-	2.02	-	-	-	-	-	-	-
1419455_at	Il1-rb	interleukin 1- receptor, beta	-	-	-	-	1.05	-	-	-	-	-	-	-
1449982_at	Il11	interleukin 11	1.13	-	-	-	-	-	-	-	-	-	-	-
1427164_at	Il13ra1	interleukin 13 receptor, alpha 1	-	-	-	-	1.86	1.11	-	-	-	-	-	-

145-424_a_at	Il18bp	interleukin 18 binding protein	-	-	-	-	1.12	-	-	-	-	-	-	-
142-462_at	Il1rapl2	interleukin 1 receptor accessory protein-like 2	-	-	-	-	-1.43	-	-	-	-	-	-	-
1451798_at	Il1rn	interleukin 1 receptor antagonist	1.52	-	-	-	-	-	-	-	-	-	-	-
1416295_a_at	Il2rg	interleukin 2 receptor, gamma chain	-	-	-	-	4.12	2.56	1.65	1.15	1.59	-	-	-
1421-34_a_at	Il4ra	interleukin 4 receptor, alpha	-	-	-	-	-0.98	-	-	-	-	-	-	-
145-297_at	Il6	interleukin 6	2.09	-	-	-	-	-	-	-	-	-	-	-
1452416_at	Il6ra	interleukin 6 receptor, alpha	-	-	-	-	1.05	-	-	-	-	-	-	-
1422546_at	Ilf3	interleukin enhancer binding factor 3	-	-	-	1.09	-	-	-	-	-	-	-	-
1422728_at	Inha	inhibin alpha	-	-	-	-1.1	-	-	-	-	-	-	-	-
1422-53_at	Inhba	inhibin beta-A	2.93	3.35	1.79	2.72	2.78	1.79	-	1.09	1.06	-	-	-
1448965_at	Inoc1	INO8- complex homolog 1 (S. cerevisiae)	-	-	-	1.38	-	-	-	-	-	-	-	-
141811-_a_at	Inpp5d	inositol polyphosphate-5-phosphatase D	-	-	-	-	2.57	1.71	1.45	-	-	-	-	-
1421399_at	Insm1	insulinoma-associated 1	-	-	-	-	-1.70	-	-	-	-	-	-	-
1459894_at	Iqgap2	IQ motif containing GTPase activating protein 2	-	-	-	-	-1.97	-	-	-	-	-	-	-
143485-_at	Iqgap3	IQ motif containing GTPase activating protein 3	-	-	-	-	1.24	-	-	-	-	-	-	-
145175-_at	Irak4	interleukin-1 receptor-associated kinase 4	-	-	-	-	1.27	-	-	-	-	-	-	-
146-231_at	Irf5	interferon regulatory factor 5	-	-	-	-	1.40	-	-	-	-	-	-	-
1417244_a_at	Irf7	interferon regulatory factor 7	-	-	-	-	3.37	2.12	1.54	-	-	-	-	-
1416714_at	Irf8	interferon regulatory factor 8	-	-	-	-	3.34	2.28	1.85	1.2-3	-1	-	-	-
1418825_at	Irgm	immunity-related GTPase family, M	-	-	-	-	2.5	1.39	-	-	1.5	-	-	-
1419569_a_at	Isg2-	interferon-stimulated protein	-	-	-	-	2.28	1.2	1.1	-	-	-	-	-
1421322_a_at	Isgf3g	interferon dependent positive acting transcription factor 3 gamma	-	-	-	-	1.78	-	-	-	-	-	-	-
145-723_at	Isl1	ISL1 transcription factor, LIM/homeodomain	-	-	-2.9	-	-2.7	-2.2	-2.1	-	-3.4	-	-	-
1425-5-_at	Isoc1	isochorismatase domain containing 1	-	-	-	1.59	-	-	-	-	-	-	-	-
1423267_s_at	Itga5	integrin alpha 5 (fibronectin receptor alpha)	-	1.17	-	-	-	-	-	-	-	-	-	-
1422444_at	Itga6	integrin alpha 6	-	-	-	-	2.12	1.38	-	-	-	-	-	-
1422-46_at	Itgam	integrin alpha M	-	-	-	-	2.63	1.46	1.16	1.29	-	-	-	-
1421198_at	Itgav	integrin alpha V	-	-	-	-	1.27	-	-	-	-	-	-	-
1419128_at	Itgax	integrin alpha X	-	-	-	-	2.22	1.46	1.43	-	-	-	-	-
1426918_at	Itgb1	integrin beta 1 (fibronectin receptor beta)	-	-	-	-	1.15	-	-	-	-	-	-	-
145-678_at	Itgb2	integrin beta 2	-	-	-	-	3.27	2.25	-	1.11	-	-	-	-
1417534_at	Itgb5	integrin beta 5	-	-	-	-	1.86	1.55	1	-	-	-	-	-
14236-8_at	Itm2a	integral membrane protein 2A	-1.1	-	-1	-	-	-	-	-	-	-	-	-
1424-37_at	Itpka	inositol 1,4,5-trisphosphate 3-kinase A	-	-	-	-	-1.40	-	-	-	-	-	-	-

146-2-3_at	Itpr1	inositol 1,4,5-triphosphate receptor 1	-	-	-	-	-1.76	-	-	-	-	-	-	-
1427287_s_at	Itpr2	inositol 1,4,5-triphosphate receptor 2	-	-	-	-	1.78	1.09	-	-	-	-	-	-
1423184_at	Itsn2	intersectin 2	-	-	-	1.48	-	-	-	-	-	-	-	-
1451547_at	Iyd	iodotyrosine deiodinase	-	-	-	-	-2.5	-	-	-	-1.7	-	-	-
14338-4_at	Jak1	Janus kinase 1	-	-	-	2.13	-	-	-	-	-	-	-	-
142575-_a_at	Jak3	Janus kinase 3	-	-	-	-	1.19	-	-	-	-	-	-	-
1431416_a_at	Jam2	junction adhesion molecule 2	-	-	-	-	1.92	-	-	-	-	-	-	-
145236-_a_at	Jarid1a	jumonji, AT rich interactive domain 1A (Rbp2 like)	1.01	-	-	1.75	-	-	-	-	-	-	-	-
1427359_at	Jhdm1d	jumonji C domain-containing histone demethylase 1 homolog D (S. cerevisiae)	1.32	-	-	1.48	-	-	-	-	-	-	-	-
14174-9_at	Jun	Jun oncogene	1.27	-	-	-	-	-	-	-	-	-	-	-
1415899_at	Junb	Jun-B oncogene	1.59	-	-	-	-	-	-	-	-	-	-	-
1416956_at	Kcnab2	potassium voltage-gated channel, shaker-related subfamily, beta member 2	-	-	-	-	-1.10	-	-	-	-	-	-	-
1422834_at	Kcnd2	potassium voltage-gated channel, Shal-related family, member 2	-	-	-	1.19	-	-	-	-	-	-	-	-
141664-_at	Kcne1l	potassium voltage-gated channel, Isk-related family, member 1-like	-	-	-	-	4.67	2.51	1.86	1.44	1.97	-	-	-
1449421_a_at	Kcne2	potassium voltage-gated channel, Isk-related subfamily, gene 2	-	-	-	-	-3.1	-1.8	-	-2.2	-4.7	-	-	-
1449544_a_at	Kcnh2	potassium voltage-gated channel, subfamily H (eag-related), member 2	-	-	-	-	-1.7	-	-	-	-1.2	-	-	-
1448459_at	Kcnip1	Kv channel-interacting protein 1	-	-	-	-	-1.48	-	-	-	-	-	-	-
1449129_a_at	Kcnip3	Kv channel interacting protein 3, calsenilin	-	-	-	-	-0.99	-	-	-	-	-	-	-
1455896_a_at	Kcnk1	potassium channel, subfamily K, member 1	-	-	-1	1.05	1	-	-	-	-	-	-	-
1421419_at	Kcnk4	potassium channel, subfamily K, member 4	-	-	-	-	-1.68	-	-	-	-	-	-	-
1431844_at	Kcnmb2	potassium large conductance calcium-activated channel, subfamily M, beta member 2	-	-	-	-	-1.58	-	-	-	-	-	-	-
1451595_a_at	Kcnq2	potassium voltage-gated channel, subfamily Q, member 2	-	-	-	-	-1.38	-	-	-	-	-	-	-
1427426_at	Kcnq5	potassium voltage-gated channel, subfamily Q, member 5	-	-	-	-	-3.1	-1.1	-1.1	-	-1.2	-	-	-
142-537_at	Kctd4	potassium channel tetramerisation domain containing 4	-	-	-	-	-1.48	-	-	-	-	-	-	-
1453317_a_at	Khdrbs3	KH domain containing, RNA binding, signal transduction associated 3	-	-	-	-	-1.84	-	-	-	-	-	-	-
14241-7_at	Kif18a	kinesin family member 18A	-	-	-	-	3.08	-	-	-	1.28	-	-	-
1423995_at	Kif1b	kinesin family member 1B	-	-	-	1.09	-	-	-	-	-	-	-	-
1426325_at	Kif1c	kinesin family member 1C	-	-	1.15	-	-	-	-	-	-	-	-	-
1418431_at	Kif5b	kinesin family member 5B	-	-	-	1.54	-	-	-	-	-	-	-	-
1422945_a_at	Kif5c	kinesin family member 5C	-	-	-	1.68	-	-	-	-	-	-	-	-
1426493_a_at	Kifc2	kinesin family member C2	-	-	-	-	-1.23	-	-	-	-	-	-	-
1452514_a_at	Kit	kit oncogene	-	-	-	-	-1.04	-	-	-	-	-	-	-

14234--_at	Kl	klotho	-	-	-	-	-	-	-	-	-3.2	-	-	-
1448541_at	Klc1	kinesin light chain 1	-	-	-	-	1.03	-	-	-	-	-	-	-
141635-_at	Klf16	Kruppel-like factor 16	-	-	-	-	-1.16	-	-	-	-	-	-	-
1417394_at	Klf4	Kruppel-like factor 4 (gut)	1.39	-	-	-	-	-	-	-	-	-	-	-
1427742_a_at	Klf6	Kruppel-like factor 6	1.41	-	-	-	-	-	-	-	-	-	-	-
1436952_at	Klf9	Kruppel-like factor 9	1.29	-	-	-	-	-	-	-	-	-	-	-
1451793_at	Klhl24	kelch-like 24 (Drosophila)	-	-	-	1.74	-	-	-	-	-	-	-	-
1449313_at	Klk1b5	kallikrein 1-related peptidase b5	-	1.03	-	-	-	-	-	-	-	-	-	-
1448982_at	Klk6	kallikrein related-peptidase 6	-	-	-	-	3.32	2.56	-	-	2.52	-	-	-
146-245_at	Klrd1	killer cell lectin-like receptor, subfamily D, member 1	-	-	-	-	1.28	-	-	-	-	-	-	-
14495-4_at	Kpna1	karyopherin (importin) alpha 1	-	-	-	1.24	-	-	-	-	-	-	-	-
1434357_a_at	Kpnb1	karyopherin (importin) beta 1	-	-	-1	-	-	-	-	-	-	-	-	-
1448169_at	Krt18	keratin 18	-	-	-	-	-2	-1	-	-1.6	-3.2	-	-	-
1427154_at	Krt2	keratin 2	-	-	-	-	-1.56	-	-	-	-	-	-	-
1433923_at	Krt77	keratin 77	-	-	-	-	-1.51	-	-	-	-	-	-	-
1435989_x_at	Krt8	keratin 8	-	-	-	-	-1.3	-	-	-1.1-5	-2.4	-	-	-
145-435_at	L1cam	L1 cell adhesion molecule	-	-	-	-	-1.70	-	-	-	-	-	-	-
1449911_at	Lag3	lymphocyte-activation gene 3	-	-	-	-	3.62	2.35	2.05	1.49	-	-	-	-
143-447_a_at	Lair1	leukocyte-associated Ig-like receptor 1	-	-	-	-	2.79	1.53	-	-	-	-	-	-
1428-94_at	Lamp2	lysosomal-associated membrane protein 2	-	-	-	-1	1.07	-	-	-	-	-	-	-
1427-12_at	Lancl1	LanC (bacterial lantibiotic synthetase component C)-like 1	-	-	-	-	-1	-	-	-	1.52	-	-	-
1426-25_s_at	Laptm5	lysosomal-associated protein transmembrane 5	-	-	-	-	2.50	2.18	-	1.44	-	-	-	-
1426169_a_at	Lat2	linker for activation of T cells family, member 2	-	-	-	-	2.66	1.29	1.02	1.08	-	-	-	-
1451629_at	Lbh	limb-bud and heart	-	1.56	-	-	1.53	-	-	-	-	-	-	-
144855-_at	Lbp	lipopolysaccharide binding protein	-	-	-	-	-	-	-	-	-1.7	-	-	-
142-55-_at	Lce1f	late cornified envelope 1F	-	-	-	-	2.73	-	-	-	-	-	-	-
1421316_at	Lce1g	late cornified envelope 1G	-	-	-	-	1.38	-	-	-	-	-	-	-
1427747_a_at	Lcn2	lipocalin 2	-	4.65	-	-	6.03	3.66	2.85	1.78	2.84	-	-	-
1415983_at	Lcp1	lymphocyte cytosolic protein 1	-	-	-	-	2.88	1.78	1.48	1.16	1.05	-	-	-
1418641_at	Lcp2	lymphocyte cytosolic protein 2	-	-	-	-	2.61	1.24	1.33	-	-	-	-	-
1439479_at	Lct	lactase	-	-	-	-	-2.47	-	-	-1	-	-	-	-
14211-1_a_at	Ldb2	LIM domain binding 2	-	-	-	-	-1.95	-	-	-	-	-	-	-
1424378_at	Ldlrap1	low density lipoprotein receptor adaptor protein 1	-	-	-	-	1.39	1.16	-	-	-	-	-	-
146-258_at	Lect1	leukocyte cell derived chemotaxin 1	-	-	-	-	1.28	1.31	-	-	-	-	-	-

1417638_at	Lefty1	left right determination factor 1	-	-	-	-	-1.5	-	-	-	-1.1	-	-	-
14268-8_at	Lgals3	lectin, galactose binding, soluble 3	1.32	1.04	-	-	1.73	1.87	-	-	-	-	-	-
144838-_at	Lgals3bp	lectin, galactoside-binding, soluble, 3 binding protein	-	-	-	-	3.51	2.51	1.76	-	-	-	-	-
1421217_a_at	Lgals9	lectin, galactose binding, soluble 9	-	-	-	-	3.14	1.74	1.61	1.31	-	-	-	-
1448883_at	Lgmn	legumain	-	-	-	-	1.81	1	-	-	-	-	-	-
1425-94_a_at	Lhx6	LIM homeobox protein 6	-	-	-	-	-1.72	-	-	-	-	-	-	-
14273--_at	Lhx8	LIM homeobox protein 8	-	-	-1.8	-	-1.9	-	-2.2	-	-	-	-	-
1419324_at	Lhx9	LIM homeobox protein 9	-	-1.1	-	-	-2.2	-	-1.7	-1.3	-	-	-	-
14212-7_at	Lif	leukemia inhibitory factor	1.43	1.56	-	-	-	-	-	-	-	-	-	-
142-394_s_at	Lilrb4	leukocyte immunoglobulin-like receptor, subfamily B, member 4	3.14	1.98	-	-	4.41	2.66	2.16	-	1.42	-	-	-
141823-_a_at	Lims1	LIM and senescent cell antigen-like domains 1	-	-	-	1.3	1.33	-	-	-	-	-	-	-
1449262_s_at	Lin7c	lin-7 homolog C (C. elegans)	-	-	-	1.37	-	-	-	1.05	-	-	-	-
1428118_at	Lingo1	leucine rich repeat and Ig domain containing 1	-	-	-	-	1.02	-	-	-	-	-	-	-
1423141_at	Lipa	lysosomal acid lipase A	-	-	-	-	1.08	-	-	-	-	-	-	-
1421262_at	Lipg	lipase, endothelial	-	-	1.1	-	-	-	-	-	-	-	-	-
14163-4_at	Litaf	LPS-induced TN factor	-	-	-	-	1.01	-	-	-	-	-	-	-
1418478_at	Lmo1	LIM domain only 1	-	-	-	-	-2.88	-1.2	-	-	-	-	-	-
1454-86_a_at	Lmo2	LIM domain only 2	-	-	-	-	1.06	-	-	-	-	-	-	-
1431213_a_at	LOC67527	murine leukemia retrovirus	1.95	-	1.82	-	1.83	-	-	1.17	1.86	-	-	-
1431591_s_at	LOC677168	similar to ISG15 ubiquitin-like modifier	-	-	-	-	3.44	1.96	1.53	-	-	-	-	-
1426221_at	Loh11cr2a	loss of heterozygosity, 11, chromosomal region 2, gene A homolog (human)	-	-	-	-	1.19	-	-	-	-	-	-	-
1416121_at	Lox	lysyl oxidase	-	-	-	-	1.77	1.07	-	-	-	-	-	-
1418269_at	Loxl3	lysyl oxidase-like 3	-	-	-	-	1.57	-	-	-	-	-	-	-
142435-_s_at	Lpgat1	lysophosphatidylglycerol acyltransferase 1	-	-	-	1.18	-	-	-	-	-	-	-	-
1448998_at	Lpo	lactoperoxidase	-	-	-	-	2.01	-	-	-	1.08	-	-	-
1424965_at	Lpxn	leupaxin	-	-	-	-	2.13	1.48	1.13	-	-	-	-	-
141729-_at	Lrg1	leucine-rich alpha-2-glycoprotein 1	-	1.52	-	-	-	-	-	-	-	-	-	-
1449893_a_at	Lrig1	leucine-rich repeats and immunoglobulin-like domains 1	-	-	-	-	1.95	-	-	-	-	-	-	-
14484-9_at	Lrmp	lymphoid-restricted membrane protein	-	-	-	-	2.30	1.79	-	-	-	-	-	-
1451174_at	Lrrc33	leucine rich repeat containing 33	-	-	-	-	1.28	-	-	-	-	-	-	-
1433842_at	Lrrfip1	leucine rich repeat (in FLII) interacting protein 1	-	-	-	-	1.76	-	-	-	-	-	-	-
1451986_s_at	Lrrk1	leucine-rich repeat kinase 1	-	-	-	-	1.81	-1	-	-	1.18	-	-	-
1431394_a_at	Lrrk2	leucine-rich repeat kinase 2	-	-	-	-	1.15	-	-	-	-	-	-	-
1437746_at	Lrrtm1	leucine rich repeat transmembrane neuronal 1	-	-	-	-	-1.40	-	-	-	-	-	-	-

1417756_a_at	Lsp1	lymphocyte specific 1	-	-	-	-	1.44	-	-	-	-	-	-	-
1425548_a_at	Lst1	leukocyte specific transcript 1	-	-	-	-	1.20	-	-	-	-	-	-	-
144887-_at	Ltbp1	latent transforming growth factor beta binding protein 1	-	-	-	-	1.55	-	-	-	-	-	-	-
1416435_at	Ltbr	lymphotoxin B receptor	-	-	-	-	1.11	-	-	-	-	-	-	-
1419692_a_at	Ltc4s	leukotriene C4 synthase	-	-	-	-	1.16	1.14	-	-	-1.6	-	-	-
14527-8_a_at	Luc7l	Luc7 homolog (S. cerevisiae)-like	-	-	-	1.49	-	-	-	-	-	-	-	-
14229-3_at	Ly86	lymphocyte antigen 86	-	-	-	-	2.34	2.06	1.36	-	-	-	-	-
1449156_at	Ly9	lymphocyte antigen 9	-	-	-	-	2.92	1.78	-	-	-	-	-	-
1449874_at	Ly96	lymphocyte antigen 96	-	-	-	-	1.14	-	-	-	-	-	-	-
141912-_at	Lyl1	lymphoblastomic leukemia	-	-	-	-	1.86	1.32	1.06	-	-	-	-	-
1425598_a_at	Lyn	Yamaguchi sarcoma viral (v-yes-1) oncogene homolog	-	-	-	-	2.54	1.47	1.2	1.25	-	-	-	-
1431569_a_at	Lypd1	Ly6/Plaur domain containing 1	-	-	-	-	-1.97	-	-	-	-	-	-	-
1422341_s_at	Lypla3	lysophospholipase 3	-	-	-	-	1.53	-	-	-	-	-	-	-
1429379_at	Lyve1	lymphatic vessel endothelial hyaluronan receptor 1	-	1.97	-	-	-	-	-	-	-	-	-	-
1423547_at	Lyzs	lysozyme	-	-	-	-	3.56	2.61	1.86	1.35	-	-	-	-
1418936_at	Maff	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein F (avian)	2.78	2.57	-	-	1.27	1.39	1.52	1.22	-	-	-	-
1417217_at	Magel2	melanoma antigen, family L, 2	-	-	-1.2	-	-1.9	-	-1.3	-	-	-	-	-
1432558_a_at	Mal	myelin and lymphocyte protein, T-cell differentiation protein	-	-	-	1.19	-	-	-	-	-	-	-	-
1427-42_at	Mal2	mal, T-cell differentiation protein 2	-	-	-	-	-1.51	-	-	-	-	-	-	-
1452378_at	Malat1	metastasis associated lung adenocarcinoma transcript 1 (non-coding RNA)	1.45	-	-	1.89	-	-	-	1.29	-	-	-	-
141711-_at	Man1a	mannosidase 1, alpha	-	-	-	1.49	-	-	-	-	-	-	-	-
141634-_a_at	Man2b1	mannosidase 2, alpha B1	-	-	-	-	1.37	-	-	-	-	-	-	-
1416584_at	Man2b2	mannosidase 2, alpha B2	-	-	-	-	-0.98	-	-	-	-	-	-	-
1426233_at	Map2k4	mitogen activated protein kinase kinase 4	-	-	-	1.09	-	-	-	-	-	-	-	-
1449283_a_at	Mapk12	mitogen-activated protein kinase 12	-	-	-	-	1.67	-	-	-	1.27	-	-	-
1426648_at	Mapkapk2	MAP kinase-activated protein kinase 2	-	-	1.03	-	1.16	-	-	-	-	-	-	-
1422765_at	Mapre1	microtubule-associated protein, RP/EB family, member 1	-	-	-	1.12	-	-	-	-	-	-	-	-
1415972_at	Marcks	myristoylated alanine rich protein kinase C substrate	-	-	-	-	1.06	-	-	-	-	-	-	-
1419442_at	Matn2	matrilin 2	-	-	-	-	-1.76	-	-	-	-	-	-	-
1418464_at	Matn4	matrilin 4	-	-	-	-	1.79	-	-	-	-	-	-	-
14258-3_a_at	Mbd2	methyl-CpG binding domain protein 2	-1	-	-	-	-	-	-	-	-	-	-	-
1425263_a_at	Mbp	myelin basic protein	-	-	-	1.53	-	-	-	1.47	-	-	-	-
1428-31_at	Mchr1	melanin-concentrating hormone receptor 1	-	-	1.01	-	-	-	-	-	-	-	-	-
1416881_at	Mcl1	myeloid cell leukemia sequence 1	1.63	-1	-	-	1.88	-	-	-	-	-	-	-

142--28_s_at	Mcm3	minichromosome maintenance deficient 3 (S. cerevisiae)	-	-	-	-	1.75	1.31	-	-	-	-	-	-
1416251_at	Mcm6	minichromosome maintenance deficient 6 (MIS5 homolog, S. pombe) (S. cerevisiae)	-	-	-	-	-	1.53	-	-	-	-	-	-
1427-4-_at	Mdfic	MyoD family inhibitor domain containing	-	-	-	-	-	-	-	-	-1.2	-	-	-
1427718_a_at	Mdm2	transformed mouse 3T3 cell double minute 2	-	-	-	1.1	-	-	-	-	-	-	-	-
1421-27_a_at	Mef2c	myocyte enhancer factor 2C	-	-	-	-	1.16	1.01	-	-	1.11	-	-	-
1416558_at	Melk	maternal embryonic leucine zipper kinase	-	-	-	-	1.28	-	-	-	-	-	-	-
1424-1-_at	Mfap4	microfibrillar-associated protein 4	-	-	-	-	1.35	-	-	-	-	-	-	-
1416992_at	Mfng	MFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	-	-	-	-	1.35	-	-	-	-	-	-	-
1422646_at	Mga	MAX gene associated	-	-	-	1.23	-	-	-	-	-	-	-	-
1421178_at	Mgat4c	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	-	-	-	-	-1.23	-	-	-	-	-	-	-
1426817_at	Mki67	antigen identified by monoclonal antibody Ki 67	-	-	-	-	2.97	2.26	1.72	1.17	-	-	-	-
142637-_at	Mlstd2	male sterility domain containing 2	-	-	-	1.13	-	-	-	-	-	-	-	-
1419185_a_at	Mlxipl	MLX interacting protein-like	-	-	-	-	1.56	1.29	-	-	-	-	-	-
1422626_at	Mmp16	matrix metallopeptidase 16	-	-	-	1.13	-	-	-	-	-	-	-	-
1421977_at	Mmp19	matrix metallopeptidase 19	-	-	-	-	1.79	-	-	-	-	-	-	-
1424483_at	Mobkl1b	MOB1, Mps One Binder kinase activator-like 1B (yeast)	-	-	-	-	1.18	-	-	1.07	-	-	-	-
145--88_a_at	Mobp	myelin-associated oligodendrocytic basic protein	1.05	-	-	1.87	-	-	-	-	-	-	-	-
145392-_a_at	Mospd2	motile sperm domain containing 2	-	-	-	-	1.07	-	-	-	-	-	-	-
1438676_at	Mpa2l	macrophage activation 2 like	-	-	-	-	3.1	1.52	-	-	2.07	-	-	-
1427-76_at	Mpeg1	macrophage expressed gene 1	-	-	-	-	3.21	2.78	1.74	1.57	-	-	-	-
1421-64_at	Mpp5	membrane protein, palmitoylated 5 (MAGUK p55 subfamily member 5)	-	-	-	1.26	-	-	-	-	-	-	-	-
1455179_at	Mpp7	membrane protein, palmitoylated 7 (MAGUK p55 subfamily member 7)	-	-	1.01	-1	-	-	-	-	-	-	-	-
1421-45_at	Mrc2	mannose receptor, C type 2	-	-	-	-	1.15	-	-	-	-	-	-	-
1423467_at	Ms4a4b	membrane-spanning 4-domains, subfamily A, member 4B	-	-	-	-	2.85	1.33	-	-	-	-	-	-
145-291_s_at	Ms4a4c	membrane-spanning 4-domains, subfamily A, member 4C	-	-	-	-	2.92	1.15	-	-	-	-	-	-
1418826_at	Ms4a6b	membrane-spanning 4-domains, subfamily A, member 6B	-	-	-	-	2.61	1.45	-	-	-	-	-	-
145-234_at	Ms4a6c	membrane-spanning 4-domains, subfamily A, member 6C	-	-	-	-	2.66	1.72	-	-	-	-	-	-
1419598_at	Ms4a6d	membrane-spanning 4-domains, subfamily A, member 6D	-	-	-	-	2.72	1.45	1.35	-	1.19	-	-	-
1424754_at	Ms4a7	membrane-spanning 4-domains, subfamily A, member 7	-	-	-	-	2.88	1.7	-	-	-	-	-	-
145-379_at	Msn	moesin	1.45	-	1.04	-	2.86	1.68	1.42	2.0	1.07	-	-	-
1448-61_at	Msr1	macrophage scavenger receptor 1	1.88	-	-	-	1.04	-	-	-	-	-	-	-
1448891_at	Msr2	macrophage scavenger receptor 2	-	-	-	-	3.26	2.39	1.86	1.49	-	-	-	-

14486-1_s_at	Msx1	homeo box, msh-like 1	-	-	-	-	-1	-	-	-	-1.1	-	-	-
1439-45_x_at	Mtac2d1	membrane targeting (tandem) C2 domain containing 1	-	-	1.19	1.18	-	-	-	-	-	-	-	-
145-397_at	Mtap1b	microtubule-associated protein 1 B	-	-	-	1.22	-	-	-	-	-	-	-	-
1437855_at	Mtap4	microtubule-associated protein 4	-	-	-	-	-1.15	-	-	-	-	-	-	-
142-472_at	Mtpn	myotrophin	-	-	-	1.65	-	-	-	1.36	-	-	-	-
14519-5_a_at	Mx1	myxovirus (influenza virus) resistance 1	-	-	-	-	2.66	1.61	-	-	-	-	-	-
1425732_a_at	Mxi1	Max interacting protein 1	-	-	-	-	-	-	-	-1	-	-	-	-
14526-8_at	Mycbp	c-myc binding protein	-	-	-	-	-	-	-	-	-1.3	-	-	-
1434777_at	Mycl1	v-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	-	-	-	-	-1.03	-	-	-	-	-	-	-
1428835_at	Myh14	myosin, heavy polypeptide 14	-	-	-	-	-1.19	-	-	-	-	-	-	-
1448553_at	Myh7	myosin, heavy polypeptide 7, cardiac muscle, beta	-	-	-	-	-1.7	-	-	-	-1.4	-	-	-
145-651_at	Myo1-	myosin X	-	-	-	1.29	-	-	-	-	-	-	-	-
142-159_at	Myo1e	myosin IE	-	-	-	-	1.62	-	-	-	-	-	-	-
1421618_at	Myo1f	myosin IF	-	-	-	-	1.34	-	-	-	-	-	-	-
1427892_at	Myo1g	myosin IG	-	-	-	-	1.47	-	-	-	-	-	-	-
1452298_a_at	Myo5b	myosin Vb	-	-	-	-	-2.15	-	-	-	-	-	-	-
14177-6_at	Naglu	alpha-N-acetylglucosaminidase (Sanfilippo disease IIIB)	-	-	-	-	1.70	1.58	-	-	-	-	-	-
146-273_a_at	Naip2	NLR family, apoptosis inhibitory protein 2	-	-	-	-	3.05	1.95	1.08	-	-	-	-	-
1421525_a_at	Naip5	NLR family, apoptosis inhibitory protein 5	-	-	-	-	3.30	2.05	1.61	1.16	-	-	-	-
1418-46_at	Nap1l2	nucleosome assembly protein 1-like 2	-	-	-	-	-1.13	-	-	-	-	-	-	-
1418-23_at	Narg1	NMDA receptor-regulated gene 1	-	-	-	1.33	-	-	-	-	-	-	-	-
14253-1_at	Ncam2	neural cell adhesion molecule 2	-	-	-	-	1.89	-	-	-	1.29	-	-	-
1451767_at	Ncf1	neutrophil cytosolic factor 1	-	-	-	-	2.42	1.13	-	1.31	-	-	-	-
1448561_at	Ncf2	neutrophil cytosolic factor 2	-	-	-	-	2.49	1.55	-	-	-	-	-	-
1418465_at	Ncf4	neutrophil cytosolic factor 4	-	-	-	-	2.24	1.53	-	-	-	-	-	-
1428787_at	Nckap1l	NCK associated protein 1 like	-	-	-	-	2.54	1.63	1.29	-	-	-	-	-
1423413_at	Ndrg1	N-myc downstream regulated gene 1	-	-	-	1.1	-	-	-	1.03	-	-	-	-
142816-_at	Ndufab1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1	-	-	-	-	-1.07	-	-	-	-	-	-	-
1418961_at	Necap2	NECAP endocytosis associated 2	-	-	-	-	1.37	-	-	-	-	-	-	-
145-767_at	Nedd9	neural precursor cell expressed, developmentally down-regulated gene 9	1.09	1.49	-	-	1.22	-	-	-	-	-	-	-
1424847_at	Nefh	neurofilament, heavy polypeptide	-	-	-	-	-1.47	-	-	-	-	-	-	-
142585-_a_at	Nek6	NIMA (never in mitosis gene a)-related expressed kinase 6	-	-	-	-	1.79	-	-	-	-	-	-	-
1421321_a_at	Net1	neuroepithelial cell transforming gene 1	-	-	-	-	1.34	-	-	-	-	-	-	-

1418-47_at	Neurod6	neurogenic differentiation 6	-1.3	-	-	-	-2.9	-	-	-	-1.3	-	-	-
1417621_at	Nfatc1	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1	-	-	-	-	1.14	-	-	-	-	-	-	-
1426-32_at	Nfatc2	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2	-	-	-	-	-1.18	-	-	-	-	-	-	-
1416543_at	Nfe2l2	nuclear factor, erythroid derived 2, like 2	-	-	-	-	1.21	-	-	-	-	-	-	-
1418932_at	Nfil3	nuclear factor, interleukin 3, regulated	2.09	1.51	1.31	-	1.69	-	-	-	-	-	-	-
14483-6_at	Nfkbia	nuclear factor of kappa light chain gene enhancer in B-cells inhibitor, alpha	-	-	-	-	1.00	-	-	-	-	-	-	-
1448728_a_at	Nfkbiz	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	1.22	-	-	-	-	-	-	-	-	-	-	-
1417996_at	Ngb	neuroglobin	-	-	-1.4	-	-1.9	-	-1.3	-	-	-	-	-
1423516_a_at	Nid2	nidogen 2	-	-	-	-	-	-	-	-	-1.3	-	-	-
145-753_at	Nkg7	natural killer cell group 7 sequence	-	-	-	-	1.26	-	-	-	-	-	-	-
1423249_at	Nktr	natural killer tumor recognition sequence	-	-	-	1.32	-	-	-	-	-	-	-	-
1424981_at	Nln	neurolysin (metallopeptidase M3 family)	-	-	-	-	1.12	-	-	-	-	-	-	-
1422342_at	Nmbr	neuromedin B receptor	-	-	-	-	-	-	-	-	2.61	-	-	-
1425719_a_at	Nmi	N-myc (and STAT) interactor	-	-	-	-	1.16	-	-	-	-	-	-	-
1438483_at	Nos1	nitric oxide synthase 1, neuronal	-	-	-	-	-2.39	-	-	-	-	-	-	-
1455556_at	Notch2	Notch gene homolog 2 (Drosophila)	-	-	-	-1.1	-	-	-	-	-	-	-	-
1421965_s_at	Notch3	Notch gene homolog 3 (Drosophila)	-	-	-	-	1.03	-	-	-	-	-	-	-
1449146_at	Notch4	Notch gene homolog 4 (Drosophila)	-	-	-	-	1.12	-	-	-	-	-	-	-
1426851_a_at	Nov	nephroblastoma overexpressed gene	-	-	-	-	-2.90	-	-	-	-	-	-	-
14169-1_at	Npc2	Niemann Pick type C2	-	-	-	-	1.53	1.26	-	-	-	-	-	-
1424265_at	Npl	N-acetylneuraminate pyruvate lyase	-	-	-	-	1.92	1.01	-	-	1.17	-	-	-
1435184_at	Npr3	natriuretic peptide receptor 3	-	-	-	-	-2.5	-	-	-	-1.6	-	-	-
144996-_at	Nptx2	neuronal pentraxin 2	-	2.53	1.64	1.62	2.49	1.52	-	-	1.89	-	-	-
1419127_at	Npy	neuropeptide Y	-	-	-	-	1.57	-	-	-	1.09	-	-	-
1417489_at	Npy2r	neuropeptide Y receptor Y2	-	-	-	-	-3.50	-1.1	-	-	-	-	-	-
1416959_at	Nr1d2	nuclear receptor subfamily 1, group D, member 2	-	-	-	1.06	-	-	-	1.05	-	-	-	-
1425-14_at	Nr2c2	nuclear receptor subfamily 2, group C, member 2	-	-	-	1.2	-	-	-	-	-	-	-	-
145-75-_a_at	Nr4a2	nuclear receptor subfamily 4, group A, member 2	1.69	-	-	-	-	-	-	-	-	-	-	-
1418469_at	Nrip1	nuclear receptor interacting protein 1	-	-	-	1.04	-	-	-	-	-	-	-	-
1431597_a_at	Nrip3	nuclear receptor interacting protein 3	-	-	-	-	1.89	-	-	-	-	-	-	-
145-946_at	Nrl	neural retina leucine zipper gene	-	-	-	-	-1.03	-	-	-	-	-	-	-
1417971_at	Nrm	nurim (nuclear envelope membrane protein)	-	-	-	-	1.14	-	-	-	-	-	-	-
1418588_at	Nrsn1	neurensin 1	-	-	-	-	-1.27	-	-	-	-	-	-	-

142-837_at	Ntrk2	neurotrophic tyrosine kinase, receptor, type 2	-	-	-	1.59	-	-	-	-	-	-	-	-
142286-_at	Nts	neurotensin	-1	1.34	-	-	-3.4	-	-1.2	-	-	-	-	-
142-799_at	Ntsr1	neurotensin receptor 1	-	-	-	-	-1.21	-	-	-	-	-	-	-
1416491_at	Numbl	numb-like	-	-	1.21	-	-	-	-	-	-	-	-	-
1419665_a_at	Nupr1	nuclear protein 1	-	-	-	-	2.63	-	1.25	-	1.97	-	-	-
14163-9_at	Nusap1	nucleolar and spindle associated protein 1	-	-	-	-	1.89	-	-	-	-	-	-	-
1459921_at	Nxph1	neurexophilin 1	-	-	-	-	-1.77	-	-	-	-	-	-	-
1424775_at	Oas1g	2'-5' oligoadenylate synthetase 1G	-	-	-	-	3.55	2.41	1.79	1.17	-	-	-	-
1425-65_at	Oas2	2'-5' oligoadenylate synthetase 2	-	-	-	-	1.64	-	-	-	-	-	-	-
1424339_at	Oasl1	2'-5' oligoadenylate synthetase-like 1	-	-	-	-	2.14	1.19	-	-	2.11	-	-	-
1453196_a_at	Oasl2	2'-5' oligoadenylate synthetase-like 2	-	-	-	-	4.31	2.8	2.32	1.14	-	-	-	-
1453644_at	Obp1a	odorant binding protein Ia	-1.7	-	-	-	-	-	-	-	-	-	-	-
1427364_a_at	Odc1	ornithine decarboxylase, structural 1	1.29	-	-	-	-	-	-	-	-	-	-	-
1422512_a_at	Ogfr	opioid growth factor receptor	-	-	-	-	1.04	-	-	-	-	-	-	-
1424413_at	Ogfrl1	opioid growth factor receptor-like 1	-	-	-	-	-1.03	-	-	-	-	-	-	-
1419663_at	Ogn	osteoglycin	-1.6	-	-	-	-1.7	-	-	-2.1	-	-	-	-
1455796_x_at	Olfm1	olfactomedin 1	-	-	-	-	-1.16	-	-	-	-	-	-	-
1448475_at	Olfml3	olfactomedin-like 3	-	-	-	-	2.88	1.91	1.48	1.11	-	-	-	-
14262-4_a_at	Oprl1	opioid receptor-like 1	-	-	-	-	-1.67	-	-	-	-	-	-	-
1418674_at	Osmr	oncostatin M receptor	2.89	2.32	-	-	3.64	2.28	1.88	1.34	2.55	-	-	-
1425926_a_at	Otx2	orthodenticle homolog 2 (Drosophila)	-	-	-	1.17	-2.3	-1.7	-1.8	-	-3.1	-	-	-
14492-5_at	Ovol2	ovo-like 2 (Drosophila)	-	-	-	-	-	-	1.08	-	1.06	-	-	-
1452527_a_at	P2rx4	purinergic receptor P2X, ligand-gated ion channel 4	-	-	-	-	1.35	-	-	-	-	-	-	-
1449433_at	P2rx5	purinergic receptor P2X, ligand-gated ion channel, 5	-	-	-	-	-1	-	-	-	1.03	-	-	-
1431724_a_at	P2ry12	purinergic receptor P2Y, G-protein coupled 12	-	-2.5	-	-	1.15	-	-	-	-	-	-	-
1425214_at	P2ry6	pyrimidinergic receptor P2Y, G-protein coupled, 6	-	-	-	-	3.11	2.05	1.72	1.29	-	-	-	-
1426519_at	P4ha1	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha 1 polypeptide	-	-	1.05	1.56	1.29	-	-	1.52	-	-	-	-
1426519_at	P4ha1	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha 1 polypeptide	-	-	-	-	1.24	-	-	1.5	-	-	-	-
1423-6-_at	Pa2g4	proliferation-associated 2G4	-	-	-	1.21	-	-	-	-	-	-	-	-
1427228_at	Palld	palladin, cytoskeletal associated protein	-	-	-	-	1.48	-	-	-	-	-	-	-
14189-8_at	Pam	peptidylglycine alpha-amidating monooxygenase	-	-	-	-1.8	-	-	-	-	-	-	-	-
1455836_at	Papola	poly (A) polymerase alpha	-	-	-	1.34	-	-	-	-	-	-	-	-

1427633_a_at	Pappa	pregnancy-associated plasma protein A	-	-	-	-	2.19	-	-	-	1.47	-	-	-
1421989_s_at	Papss2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	-	-	-	-	1.86	-	-	-	1.12	-	-	-
1426774_at	Parp12	poly (ADP-ribose) polymerase family, member 12	-	-	-	-	1.46	-	-	-	-	-	-	-
1451564_at	Parp14	poly (ADP-ribose) polymerase family, member 14	-	-	-	-	2.96	1.68	-	-	-	-	-	-
1451969_s_at	Parp3	poly (ADP-ribose) polymerase family, member 3	-	-	-	-	1.91	1.93	1.32	-	2.17	-	-	-
1416897_at	Parp9	poly (ADP-ribose) polymerase family, member 9	-	-	-	-	2.48	1.52	1.01	-	-	-	-	-
1416875_at	Parvg	parvin, gamma	-	-	-	-	1.19	-1	-	-	-	-	-	-
142691-_at	Pawr	PRKC, apoptosis, WT1, regulator	-	-	-	-	1.07	-	-	-	-	-	-	-
1448627_s_at	Pbk	PDZ binding kinase	-	-	-	-	2.44	1.98	-	-	-	-	-	-
1425383_a_at	Pbx1	pre B-cell leukemia transcription factor 1	-	-	-	1.67	-	-	-	-	-	-	-	-
1451132_at	Pbxip1	pre-B-cell leukemia transcription factor interacting protein 1	-	-	-	-	1.15	1.07	-	-	-	-	-	-
14183-4_at	Pcdh21	protocadherin 21	-	-1	-1.1	-	-1.7	-1	-1.1	-1.38	-	-	-	-
1422877_at	Pcdhb12	protocadherin beta 12	-	-	-	-	-	-1	-1	-	-	-	-	-
1435635_at	Pcmtd1	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 1	-	-	-	1.2	-	-	-	-	-	-	-	-
1437165_a_at	Pcolce	procollagen C-endopeptidase enhancer protein	-1.3	-	-	-	-	-	-	-	-1.3	-	-	-
1451527_at	Pcolce2	procollagen C-endopeptidase enhancer 2	-	-	-	-	-	-	-	-	-1.1	-	-	-
1421396_at	Pcsk1	proprotein convertase subtilisin/kexin type 1	1.53	1.75	-	-	1	-	-	-	-	-	-	-
1435143_at	Pctk2	PCTAIRE-motif protein kinase 2	-	-	-	-	1.60	1.11	-	-	-	-	-	-
142-984_at	Pctp	phosphatidylcholine transfer protein	-	-	-	-	1.31	-	-	-	-	-	-	-
1449835_at	Pdcd1	programmed cell death 1	-	-	-	-	1.14	-	-	-	-	-	-	-
141939-_at	Pde1-a	phosphodiesterase 1-A	-	-	-	-1	-	-	-	-	-	-	-	-
1449298_a_at	Pde1a	phosphodiesterase 1A, calmodulin-dependent	-	-	-	-	-2.33	-	-	-	-	-	-	-
14522-2_at	Pde2a	phosphodiesterase 2A, cGMP-stimulated	-	-	-	-	-2.02	-	-	-	-	-	-	-
146-426_at	Pde4dip	phosphodiesterase 4D interacting protein (myomegalin)	-	-	-	1.59	-	-	-	-	-	-	-	-
1426319_at	Pdgfd	platelet-derived growth factor, D polypeptide	-	-	-	-	1.07	-	-	-	-	-	-	-
1421916_at	Pdgfra	platelet derived growth factor receptor, alpha polypeptide	-	-	-1	-	-	-	-	-	-	-	-	-
1449178_at	Pdlim3	PDZ and LIM domain 3	-	-	-	-	1.50	-	-	-	-	-	-	-
1417928_at	Pdlim4	PDZ and LIM domain 4	-	1.05	-	-	1.43	1.03	-	-	-	-	-	-
145-786_x_at	Pdlim5	PDZ and LIM domain 5	-	-	-	2.15	1.21	1.19	-	-	-	-	-	-
14193-9_at	Pdpn	podoplanin	-	-	-	-	1.11	-	-	-	-	-	-	-
141789-_at	Pdxp	pyridoxal (pyridoxine, vitamin B6) phosphatase	-	-	-	-	-1.06	-	-	-	-	-	-	-
1416266_at	Pdyn	prodynorphin	-	-	-	-	2.49	-	-	-	2.06	-	-	-
1421287_a_at	Pecam1	platelet/endothelial cell adhesion molecule 1	1.21	-	1.22	-	-	-	-	-	-	-	-	-

1427-38_at	Penk1	preproenkephalin 1	-	-	-	-	2.78	2.05	-	-	1.61	1.15	-	-
1416271_at	Perp	PERP, TP53 apoptosis effector	-	-	-	-	-	-	-	-	-1.3	-	-	-
1416432_at	Pfkfb3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	-	-	-	-	1.51	-	-	-	-	-	-	-
143-634_a_at	Pfkp	phosphofructokinase, platelet	-	-	-	-	-	-	-	1.29	-	-	-	-
1419249_at	Pftk1	PFTAIRE protein kinase 1	-	-	-	1.24	-1.8	-	-	-	-	-	-	-
1418329_at	Pgpep1	pyroglutamyl-peptidase I	-	-	-	-	1.91	-	-	-	-	-	-	-
14566-6_a_at	Phactr1	phosphatase and actin regulator 1	-	-	-	-	-1.32	-	-	-	-	-	-	-
1454714_x_at	Phgdh	3-phosphoglycerate dehydrogenase	-	-	-	-	-	-	-	-	-3.2	-	-3.3	-3.2
1428394_at	Phyhd1	phytanoyl-CoA dioxygenase domain containing 1	-	-	-	-	1.44	-	-	-	-	-	-	-
14227-8_at	Pik3cg	phosphoinositide-3-kinase, catalytic, gamma polypeptide	-	-	-	-	2.29	1.47	-	-	-	-	-	-
1427327_at	Pilra	paired immunoglobin-like type 2 receptor alpha	-	-	-	-	1.40	-	-	-	-	-	-	-
1435872_at	Pim1	proviral integration site 1	1.68	1.49	-	-	-	-	-	-	-	-	-	-
145-389_s_at	Pip5k1b	phosphatidylinositol-4-phosphate 5-kinase, type 1 beta	-	-	-	-	-1.31	-	-	-	-	-	-	-
141928-_at	Pip5k2a	phosphatidylinositol-4-phosphate 5-kinase, type II, alpha	-	-	-	1.4	-	-	-	1.22	-	-	-	-
1421137_a_at	Pkib	protein kinase inhibitor beta, cAMP dependent, testis specific	-	-	-1.1	-	-	-	-	-	-	-	-	-
1449799_s_at	Pkp2	plakophilin 2	-	-	-	-	-2.43	-	-	-	-	-	-	-
1417814_at	Pla2g5	phospholipase A2, group V	-1.6	-	-	-	-	-	-	-	-1.7	-	-	-
1451335_at	Plac8	placenta-specific 8	-	-	-	-	1.48	1.06	-	-	-	-	-	-
145259-_a_at	Plac9	placenta specific 9	-	-	-	-	1.77	-	-	-	-	-	-	-
14256--_a_at	Plcb1	phospholipase C, beta 1	-	-	-	1.55	-	-	-	-	-	-	-	-
1425339_at	Plcb4	phospholipase C, beta 4	-	-	-	1.41	-	-	-	-	-	-	-	-
1452398_at	Plce1	phospholipase C, epsilon 1	-	-	-	-	2.04	1.28	-	-	1.19	-	-	-
1426926_at	Plcg2	phospholipase C, gamma 2	-	-	-	-	1.79	1.16	-	-	-	-	-	-
1433678_at	Pld4	phospholipase D family, member 4	-	-	-	-	2.66	2.14	1.4	1.07	-	-	-	-
1452178_at	Plec1	plectin 1	-	-	-	-	1.64	-1	-	-	-	-	-	-
1448749_at	Plek	pleckstrin	1.53	-	-	-	3.69	2.24	1.91	1.81	-	-	-	-
1417289_at	Plekha2	pleckstrin homology domain-containing, family A (phosphoinositide binding specific) member 2	-	-	-	-	1.31	1.2-6	-	-	1.46	-	-	-
1426-13_s_at	Plekha4	pleckstrin homology domain containing, family A (phosphoinositide binding specific) member 4	-	-	-	-	1.81	-	-	-	-	-	-	-
1423862_at	Plekhf2	pleckstrin homology domain containing, family F (with FYVE domain) member 2	-	-	-	-	1.23	-	-	-	-	-	-	-
14182-1_at	Plekhg2	pleckstrin homology domain containing, family G (with RhoGef domain) member 2	-	-	-	-	1.48	-	-	-	-	-	-	-
1417128_at	Plekho1	pleckstrin homology domain containing, family O member 1	-	-	-	-	1.42	-	-	-	-	-	-	-

1416289_at	Plod1	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1	-	-	-	-	1.70	1.29	-	-	-	-	-	-
1416687_at	Plod2	procollagen lysine, 2-oxoglutarate 5-dioxygenase 2	-	-	-	-	1.37	-	-	-	-	-	-	-
1425467_a_at	Plp1	proteolipid protein (myelin) 1	-	-	-	1.17	-	-	-	-	-	-	-	-
1448961_at	Plscr2	phospholipid scramblase 2	-	-	-	-	2.81	1.6	-	-	-	-	-	-
1418912_at	Plxdc2	plexin domain containing 2	-	-	-	-	2.20	1.57	-	-	-	-	-	-
145-9-6_at	Plxnc1	plexin C1	-	-	-	1.08	-	-	-	-	-	-	-	-
14182-3_at	Pmaip1	phorbol-12-myristate-13-acetate-induced protein 1	-	-	-	-	1.37	-	-	-	-	-	-	-
1417133_at	Pmp22	peripheral myelin protein	-	-	-	-	1.19	-	-	-	-	-	-	-
1427893_a_at	Pmvk	phosphomevalonate kinase	1.02	-	-	-	-	-	-	-	-	-	-	-
1422711_a_at	Pnck	pregnancy upregulated non-ubiquitously expressed CaM kinase	-	-	-	-	-1.48	-	-	-	-	-	-	-
1427885_at	Pold4	polymerase (DNA-directed), delta 4	-	-	-	-	1.24	-	-	-	-	-	-	-
141819-_at	Pon1	paraoxonase 1	-	-	-	-	-1.4	-	-	-	-2.3	-	-	-
1419298_at	Pon3	paraoxonase 3	-	-	-	-	1.62	1.26	-	-	-	-	-	-
146--38_at	Pou3f1	POU domain, class 3, transcription factor 1	-	-	-	-	-2.65	-	-	-	-	-	-	-
1449937_at	Pp11r	placental protein 11 related	-	1.24	-	-	2.07	1.21	1.29	-	1.17	-	-	-
146-336_at	Ppargc1a	peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	-	-	-	1.16	-	-	-	-	-	-	-	-
141848-_at	Ppbp	pro-platelet basic protein	-	-	-	-	-	-	-	-	1.03	-	-	-
1424335_at	Ppcdc	phosphopantothenoylcysteine decarboxylase	-	-	-	-	1.11	-	-	-	-	-	-	-
1452846_at	Ppfia4	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 4	-	-	-	-	1.48	-	-	-	-	-	-	-
1416498_at	Ppic	peptidylprolyl isomerase C	-	-	-	-	1.07	-	-	-	-	-	-	-
142533-_a_at	Ppm1b	protein phosphatase 1B, magnesium dependent, beta isoform	-	-	-	1.09	-	-	-	-	-	-	-	-
1418-86_at	Ppp1r14a	protein phosphatase 1, regulatory (inhibitor) subunit 14A	-	-1.5	-	-	-	-	-	-	-	-	-	-
1425631_at	Ppp1r3c	protein phosphatase 1, regulatory (inhibitor) subunit 3C	1.27	-	1.21	-	1.39	-	-	-	-	-	-	-
145-368_a_at	Ppp3r1	protein phosphatase 3, regulatory subunit B, alpha isoform (calcineurin B, type I)	-	-	-	1.25	-	-	-	-	-	-	-	-
1452191_at	Prcp	prolylcarboxypeptidase (angiotensinase C)	-	-	-	-	1.28	-	-	-	-	-	-	-
142-425_at	Prdm1	PR domain containing 1, with ZNF domain	-	-	-	-	1.23	-	-	-	-	-	-	-
1423223_a_at	Prdx6	peroxiredoxin 6	-	-	-	-	1.12	-	-	-	-	-	-	-
1449824_at	Prg4	proteoglycan 4 (megakaryocyte stimulating factor, articular superficial zone protein)	-	-	-	-	-1.2	-	-	-1.8	1.34	-	-	-
1427414_at	Prkar2a	protein kinase, cAMP dependent regulatory, type II alpha	1.24	-	-	-	-	-	-	-	-	-	-	-
1455758_at	Prkcc	protein kinase C, gamma	-	-	-	-	-1.94	-	-	-	-	-	-	-
1422847_a_at	Prkcd	protein kinase C, delta	-	-	-	-	-	-	-	-	-2	-	-	-
1448556_at	Prlr	prolactin receptor	-	-	-	-	-1.3	-	-	-	-1.4	-	-	-

142-664_s_at	Procr	protein C receptor, endothelial	1.25	-	-	-	1.01	-	-	-	-	-	-	-
1426246_at	Pros1	protein S (alpha)	1.19	-	-	-	2.14	1.16	-	-	1.24	-	-	-
1421336_at	Prox1	prospero-related homeobox 1	-	-	-	-	1.97	-	-	-	-	-	-	-
142-917_at	Prpf4-a	PRP4- pre-mRNA processing factor 4- homolog A (yeast)	-	-	-	1.91	-	-	-	-	-	-	-	-
1425528_at	Prrx1	paired related homeobox 1	-	-	-1.1	-	-	-	-	-	-	-	-	-
142-388_at	Prss12	protease, serine, 12 neurotrypsin (motopsin)	-	-	-	-	-1.7	-	-	-	1.48	-	-	-
1431-57_a_at	Prss23	protease, serine, 23	-	-	-	-	1.91	-	-	-	-	-	-	-
14512-6_s_at	Pscdbp	pleckstrin homology, Sec7 and coiled-coil domains, binding protein	-	-	-	-	1.44	1.14	-	-	-	-	-	-
1418749_at	Psd3	pleckstrin and Sec7 domain containing 3	-	-	-	-	-1.08	-	-	-	-	-	-	-
1422962_a_at	Psmb8	proteasome (prosome, macropain) subunit, beta type 8 (large multifunctional peptidase 7)	-	-	-	-	2.71	1.81	1.39	-	1.7	-	-	-
145-696_at	Psmb9	proteasome (prosome, macropain) subunit, beta type 9 (large multifunctional peptidase 2)	-	-	-	-	2.46	-	1.03	-	1.28	-	-	-
142456-_at	Pstpip1	proline-serine-threonine phosphatase-interacting protein 1	-	-	-	-	2.08	1.19	-	-	-	-	-	-
1421492_at	Ptgds2	prostaglandin D2 synthase 2, hematopoietic	-	-	-	-	2.46	1.15	1.11	1.06	-	-	-	-
1421-73_a_at	Ptger4	prostaglandin E receptor 4 (subtype EP4)	-	-	-	-	2.98	-1	-	-	1.09	-	-	-
1436448_a_at	Ptgs1	prostaglandin-endoperoxide synthase 1	-	-	-	-	2.21	1.42	-	1.09	-	-	-	-
1417262_at	Ptgs2	prostaglandin-endoperoxide synthase 2	2.15	-	-	-	-	-	-	-	-	-	-	-
1422324_a_at	Pthlh	parathyroid hormone-like peptide	-	-	-	-	2.35	-	-	-	-	-	-	-
1434653_at	Ptk2b	PTK2 protein tyrosine kinase 2 beta	-	-	-	-	-1.19	-	-	-	-	-	-	-
1452427_s_at	Ptplad1	protein tyrosine phosphatase-like A domain containing 1	-	-	-	1.16	-	-	-	1.2-4	-	-	-	-
145-967_at	Ptplad2	protein tyrosine phosphatase-like A domain containing 2	-	-	-	-	2.78	1.64	1.18	-	-	-	-	-
1419125_at	Ptpn18	protein tyrosine phosphatase, non-receptor type 18	-	-	-	-	2.33	1.7	-	-	-	-	-	-
142513-_a_at	Ptpn5	protein tyrosine phosphatase, non-receptor type 5	-	-	-	-	-	-	-	-	1.05	-	-	-
146-188_at	Ptpn6	protein tyrosine phosphatase, non-receptor type 6	-	-	-	-	3.35	2.18	1.66	-	-	-	-	-
1422124_a_at	Ptprc	protein tyrosine phosphatase, receptor type, C	-	-	-	-	3.28	2.29	1.63	-	1.12	-	-	-
1427629_at	Ptprj	protein tyrosine phosphatase, receptor type, J	-	-	-	-	1.03	-	-	-	-	-	-	-
143168-_a_at	Ptprk	protein tyrosine phosphatase, receptor type, K	-	-	-	-	1.04	-	-	-	-	-	-	-
1417676_a_at	Ptpro	protein tyrosine phosphatase, receptor type, O	-	-	-	-	2.13	-	-	-	1.71	-	-	-
145-174_at	Ptprt	protein tyrosine phosphatase, receptor type, T	-	-	-	1.59	-1.1	-	-	-	-	-	-	-
1416674_at	Ptpru	protein tyrosine phosphatase, receptor type, U	-	-	-	-	-1.14	-	-	-	-	-	-	-
1418666_at	Ptx3	pentraxin related gene	3.08	2.77	-	1.66	2.01	1.53	1.04	-	2.24	-	-	-
1417653_at	Pvalb	parvalbumin	-	-	-	-	-2.46	-	-	-	-	-	-	-
14239-5_at	Pvr	poliovirus receptor	1.06	-	-	-	-	-	-	-	-1.1	-	-	-

1448673_at	Pvrl3	poliovirus receptor-related 3	-	-	-	1.21	-1	-	-	-	-	-	-	-
1417346_at	Pycard	PYD and CARD domain containing	-	-	-	-	3.21	2.21	1.69	1.26	1.1	-	-	-
143533-_at	Pyhin1	pyrin and HIN domain family, member 1	-	-	-	-	4.88	3.11	2.38	1.52	-	-	-	-
142-899_at	Rab18	RAB18, member RAS oncogene family	-	-	-	1.17	-	-	-	1.06	-	-	-	-
1419946_s_at	Rab2	RAB2, member RAS oncogene family	-	-	-	-	-1.23	-	-	-	-	-	-	-
1438-97_at	Rab2-	RAB2-, member RAS oncogene family	-	-	-	-	-	-	-	-	-1.3	-	-	-
14245-4_at	Rab22a	RAB22A, member RAS oncogene family	-	-	-	1.15	-	-	-	-	-	-	-	-
1417214_at	Rab27b	RAB27b, member RAS oncogene family	-	-	-	-	-1.35	-	-	-	-	-	-	-
1431691_a_at	Rab31	RAB31, member RAS oncogene family	1.06	-	-	-	1.28	-	-	-	-	-	-	-
1416527_at	Rab32	RAB32, member RAS oncogene family	-	-	-	-	2.37	-	-	-	-	-	-	-
14177--_at	Rab38	Rab38, member of RAS oncogene family	-	-	-	-	-1.20	-	-	-	-	-	-	-
1422583_at	Rab3b	RAB3B, member RAS oncogene family	-	-	-	-	-1.43	-	-	-	-	-	-	-
1432432_a_at	Rab3c	RAB3C, member RAS oncogene family	-	-	-	1.08	-	-	-	-	-	-	-	-
1456442_at	Rab3il1	RAB3A interacting protein (rabin3)-like 1	-	-	-	-	1.62	-	-	-	-	-	-	-
1451362_at	Rab7l1	RAB7, member RAS oncogene family-like 1	-	-	-	-	2.37	-	-	-	-	-	-	-
141762-_at	Rac2	RAS-related C3 botulinum substrate 2	-	-	-	-	2.51	1.45	-	-	-	-	-	-
1418188_a_at	Ramp2	receptor (calcitonin) activity modifying protein 2	-	-	-	2.24	-	-	-	-	-	-	-	-
1435518_at	Rap1b	RAS related protein 1b	-	-	-	-	1.00	-	-	-	-	-	-	-
1448885_at	Rap2b	RAP2B, member of RAS oncogene family	-	-	-	1.15	-	-	-	-	-	-	-	-
1417333_at	Rasa4	RAS p21 protein activator 4	-	-	-	-	1.62	1.04	-	-	-	-	-	-
1417858_at	Rasal1	RAS protein activator like 1 (GAP1 like)	-	-	-	-	-1.30	-	-	-	-	-	-	-
1427344_s_at	Rasd2	RASD family, member 2	-	-	-	-	-2.07	-	-	-	-	-	-	-
1424734_at	Rasgrf1	RAS protein-specific guanine nucleotide-releasing factor 1	-	-	-	-	-1.01	-	-	-	-	-	-	-
145-143_at	Rasgrp1	RAS guanyl releasing protein 1	-	-	-	-	1.21	-	-	-	-	-	-	-
1427975_at	Rasl1-a	RAS-like, family 1-, member A	-	-	-	-	-1.59	-	-	-	-	-	-	-
1449292_at	Rb1cc1	RB1-inducible coiled-coil 1	-	-	-	1.56	-	-	-	-	-	-	-	-
1454875_a_at	Rbbp4	retinoblastoma binding protein 4	-	-	-	1.02	-	-	-	1.21	-	-	-	-
1425115_at	Rbbp6	retinoblastoma binding protein 6	-	-	-	-	-1.29	-	-	-	-	-	-	-
1424156_at	Rbl1	retinoblastoma-like 1 (p1-7)	-	-	-	-	1.45	-	-	-	-	-	-	-
142-6-7_at	Rbm18	RNA binding motif protein 18	-	-	-	1.17	-	-	-	1.08	-	-	-	-
1425522_at	Rbm25	RNA binding motif protein 25	-	-	-	1.47	-	-	-	-	-	-	-	-
1426225_at	Rbp4	retinol binding protein 4, plasma	-	-	-	-	-1.32	-	-	-	-	-	-	-
1418114_at	Rbpj	recombination signal binding protein for immunoglobulin kappa J region	-	-	-	-	1.06	-	-	-	-	-	-	-
14166-1_a_at	Rcan1	regulator of calcineurin 1	1.61	-	1.22	-	-	-	-	-	-	-	-	-

1416389_a_at	Rcbtb2	regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 2	-	-	-	-	1.05	-	-	-	-	-	-	-
1424194_at	Rcsd1	RCSD domain containing 1	-	-	-	-	1.39	-	-	-	-	-	-	-
14188-8_at	Rdh5	retinol dehydrogenase 5	-	-	-	-	-1.2	-	-	-1.1	-2.6	-	-	-
141618-_a_at	Rdx	radixin	-	-	-	1.54	-	-	-	-	-	-	-	-
1424778_at	Reep3	receptor accessory protein 3	-	-	-	1.33	1.3	-	-	-	-	-	-	-
1417856_at	Relb	avian reticuloendotheliosis viral (v-rel) oncogene related B	-	-	-	-	1.03	-	-	-	-	-	-	-
144886-_at	Rem2	rad and gem related GTP binding protein 2	-	-	-	-	-1.36	-	-	-	-	-	-	-
145-1-7_a_at	Renbp	renin binding protein	-	-	-	-	1.23	-	-	-	-	-	-	-
1451236_at	Rerg	RAS-like, estrogen-regulated, growth-inhibitor	-	-	-	-	-2.4	-1.2	-	-	-1.8	-	-	-
145192-_a_at	Rfc1	replication factor C (activator 1) 1	-	-	-	1.09	-	-	-	-	-	-	-	-
1416882_at	Rgs1-	regulator of G-protein signalling 1-	-	-	-	-	1.43	1.28	-	-	-	-	-	-
1419221_a_at	Rgs14	regulator of G-protein signaling 14	-	-	-	-	-1.55	-	-	-	-	-	-	-
145-693_at	Rgs17	regulator of G-protein signaling 17	-	-	-	-	-1.37	-	-	-	-	-	-	-
1419247_at	Rgs2	regulator of G-protein signaling 2	-	-	-	-	1.22	-	-	-	-	-	-	-
1448285_at	Rgs4	regulator of G-protein signaling 4	-	-	-	-	1.03	-	-	-	-	-	-	-
142-941_at	Rgs5	regulator of G-protein signaling 5	-	-	-	1.18	1.01	-	-	-	-	-	-	-
1453-6-_at	Rgs8	regulator of G-protein signaling 8	-	-	-	-	-1.18	-	-	-	-	-	-	-
1424138_at	Rhbdf1	rhomboid family 1 (Drosophila)	-	-	-	-	2.22	-	-	-	1.3	-	-	-
14486-5_at	Rhoc	ras homolog gene family, member C	-	-	-	-	1.36	-	-	-	-	-	-	-
1418892_at	Rhoj	ras homolog gene family, member J	2.44	2.32	-	-	2.11	1.31	1.02	-	1.86	-	-	-
1426368_at	Rin2	Ras and Rab interactor 2	-	-	-	-	1.54	-	-	-	-	-	-	-
14226-3_at	Rnase4	ribonuclease, RNase A family 4	-	-	-	-	1.49	1.21	-	1.17	-	-	-	-
1452734_at	Rnaset2b	ribonuclease T2B	-	-	-	-	-0.98	-	-	-	-	-	-	-
142-62-_a_at	Rnf13	ring finger protein 13	-	-	-	1.01	-	-	-	-	-	-	-	-
1431-3-_a_at	Rnf14	ring finger protein 14	-	-	-	1.29	-	-	-	1.68	-	-	-	-
1452361_at	Rnf2-	ring finger protein 2-	-	-	-	1.33	-	-	-	-	-	-	-	-
1436277_at	Rnf2-7	ring finger protein 2-7	-	-	-	-1.1	-1.8	-1.2-3	-	-	-	-	-	-
1427231_at	Robo1	roundabout homolog 1 (Drosophila)	-	-	-	-	-1.69	-	-	-	-	-	-	-
146-729_at	Rock1	Rho-associated coiled-coil containing protein kinase 1	-	-	-	2.11	-	-	-	-	-	-	-	-
1425162_at	Rorb	RAR-related orphan receptor beta	1.08	-	-	1.05	-	-	-	-	-	-	-	-
1419585_at	Rp2h	retinitis pigmentosa 2 homolog (human)	-	-	-	-	1.08	-	-	-	-	-	-	-
1421144_at	Rpgrip1	retinitis pigmentosa GTPase regulator interacting protein 1	-	-	-	-	-	-	-	-	-	-	-	-1.4

1449961_at	Rph3a	rabphilin 3A	-	-	-	1.04	-	-	-	-	-	-	-	-
1455871_s_at	Rpl13	ribosomal protein L13	-	-	-	-	1.05	-	-	-	-	-	-	-
1423856_at	Rpl17	ribosomal protein L17	-	-	-	-	-1.45	-	-	-	-	-	-	-
1448845_at	Rpp25	ribonuclease P 25 subunit (human)	-	-	-	-	-1.59	-	-	-	-	-	-	-
1416896_at	Rps6ka1	ribosomal protein S6 kinase polypeptide 1	-	-	-	-	1.37	-	-	-	-	-	-	-
1422562_at	Rrad	Ras-related associated with diabetes	-	1.43	-	-	1.03	-	-	-	-	-	-	-
1418448_at	Rras	Harvey rat sarcoma oncogene, subgroup R	-	-	-	-	1.10	-	-	-	-	-	-	-
1452767_at	Rrbp1	ribosome binding protein 1	-	-	-	-	1.25	1.1	-	-	-	-	-	-
145-28-_a_at	Rrh	retinal pigment epithelium derived rhodopsin homolog	-	-	-	-	-1.3	-	-	-	-1.8	-	-	-
1434437_x_at	Rrm2	ribonucleotide reductase M2	-	-	-	-	2.01	-	-	-	-	-	-	-
1421--9_at	Rsad2	radical S-adenosyl methionine domain containing 2	-	-	-	-	3.62	2.21	1.16	1.21	-	-	-	-
1449319_at	Rspo1	R-spondin homolog (Xenopus laevis)	-	-	-	-	1.02	-	-	-	-	-	-	-
1455893_at	Rspo2	R-spondin 2 homolog (Xenopus laevis)	-	-	-	-	-1.92	-	-	-	-	-	-	-
141858-_at	Rtp4	receptor transporter protein 4	-	-	-	-	3.09	2.05	1.47	-	-	-	-	-
1452631_at	Rufy2	RUN and FYVE domain-containing 2	-	-	-	1.04	-	-	-	-	-	-	-	-
14244-2_at	Rufy3	RUN and FYVE domain containing 3	-	-	-	1.09	-	-	-	-	-	-	-	-
1422864_at	Runx1	runt related transcription factor 1	-	-	-	-	2.55	1.3	-	1.51	1.42	-	-	-
1448785_at	Runx1t1	runt-related transcription factor 1; translocated to, 1 (cyclin D-related)	-	-	-	-	-2.76	-	-	-	-	-	-	-
1424244_at	Rwdd4a	RWD domain containing 4A	-	-	-	1.18	-	-	-	-	-	-	-	-
145-123_at	Ryr2	ryanodine receptor 2, cardiac	-	-	-	-	-1.27	-	-	-	-	-	-	-
1416762_at	S1--a1-	S1-- calcium binding protein A1- (calpactin)	1.1	-	-	-	1.3	-	-	-	-	-	-	-
146-351_at	S1--a11	S1-- calcium binding protein A11 (calgizzarin)	-	-	-	-	1.89	1.09	1.03	-	-	-	-	-
1424542_at	S1--a4	S1-- calcium binding protein A4	-	-	-	-	3.36	1.96	1.9-4	-1	1.31	-	-	-
1421375_a_at	S1--a6	S1-- calcium binding protein A6 (calcyclin)	-	-	-	-	2.41	1.8	1.36	-	1.05	-	-	-
145-788_at	Saa1	serum amyloid A 1	1.19	-	-	-	-	-	-	-	-	-	-	-
1419-75_s_at	Saa2	serum amyloid A 2	1.16	-	-	-	-	-	-	-	-	-	-	-
145-826_a_at	Saa3	serum amyloid A 3	1.53	-	-	-	-	-	-	-	-	-	-	-
1423-1-_at	Sacs	sacsin	-	-	-	1.08	-	-	-	-	-	-	-	-
1436172_at	Samd9l	sterile alpha motif domain containing 9-like	-	-	-	-	1.87	1.11	-	-	-	-	-	-
1418131_at	Samhd1	SAM domain and HD domain, 1	-	-	-	-	1.30	-	-	-	-	-	-	-
1421457_a_at	Samsn1	SAM domain, SH3 domain and nuclear localization signals, 1	-	-	-	-	3.27	1.93	1.77	-	-	-	-	-
1427-17_at	Satb2	special AT-rich sequence binding protein 2	-	-	-	-	-3.34	-	-	-	-	-	-	-
14484-4_at	Scamp2	secretory carrier membrane protein 2	-	-	-	-	1.46	-	-	-	-	-	-	-
14512-4_at	Scara5	scavenger receptor class A, member 5 (putative)	-	-	-	1.04	-	-	-	-	-2	-	-	-

146-235_at	Scarb2	scavenger receptor class B, member 2	-	-	-	-	1.45	-	-	1.03	-	-	-	-
1415824_at	Scd1	stearoyl-Coenzyme A desaturase 1	-	-	-	-	-1.42	-	-	-1.2	-	-	-	-
145-7-8_at	Scg2	secretogranin II	-	-1	-	-	1.6	-	-	-	1.33	-	-	-
1419699_at	Scgb3a1	secretoglobin, family 3A, member 1	-	-	-	-	1.90	-	-	-	-	-	-	-
145-12-_at	Scn1a	sodium channel, voltage-gated, type I, alpha	-	-	-	1.22	-1.1	-	-	-	-	-	-	-
1435767_at	Scn3b	sodium channel, voltage-gated, type III, beta	-	-	-	-	-2.34	-	-	-	-	-	-	-
143-999_a_at	Scoc	short coiled-coil protein	-	-	-	-1	-	-	-	-	-	-	-	-
1423986_a_at	Scotin	scotin gene	-	-	-	-	1.11	-	-	-	-	-	-	-
1426555_at	Scpep1	serine carboxypeptidase 1	-	-	-	-	1.32	-	-	-	-	-	-	-
142-764_at	Scrg1	scrapie responsive gene 1	-	-	-	-	1.66	-	-	-	-	-	-	-
1437279_x_at	Sdc1	syndecan 1	-	-	-	-	-	1.72	-	-	-	-	-	-
1417-12_at	Sdc2	syndecan 2	-	-	-	1.15	1.03	-	-	-	-	-	-	-
145--27_at	Sdc3	syndecan 3	-	-	-	1.65	1.06	-	-	-	-	-	-	-
1448793_a_at	Sdc4	syndecan 4	1.24	-	1.15	-	1.35	1.12	-	1.04	-1	-	-	-
1424-9-_at	Sdcbp2	syndecan binding protein (syntenin) 2	1.29	-	-	-	-	-	-	-	-	-	-	-
14182-6_at	Sdf2l1	stromal cell-derived factor 2-like 1	-	-	-	-	1.20	-	-	-	-	-	-	-
145-823_at	Sebox	SEBOX homeobox	-	-	-	-	-1.36	-	-	-	-	-	-	-
1424926_at	Sec63	SEC63-like (S. cerevisiae)	-	-	-	1.26	-	-	-	-	-	-	-	-
14242-2_at	Seh1l	SEH1-like (S. cerevisiae	-	-	-	-	1.12	-	-	-	-	-	-	-
1449127_at	Selplg	selectin, platelet (p-selectin) ligand	-	-	-	-	1.80	1.33	-	-	-	-	-	-
142-416_at	Sema3a	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	-	-	-	-	2.24	-	-	-	1.98	-	-	-
14259-6_a_at	Sema3e	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E	-	-	-	1.58	-1.1	-	-	-	-	-	-	-
142-824_at	Sema4d	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	-	-	-	-	1.71	-	-	-	-	-	-	-
142-877_at	Sep6	septin 6	-	-	-	-	-1.94	-	-	-	-	-	-	-
1437513_a_at	Serinc1	serine incorporator 1	-	-	-	1.19	-	-	-	1.14	-	-	-	-
1456-8-_a_at	Serinc3	serine incorporator 3	-	-	-	-	-	-	-	1.36	-	-	-	-
1424923_at	Serpina3g	serine (or cysteine) peptidase inhibitor, clade A, member 3G	-	-	-	-	-	-	-	-	-	1.31	-	-
14191--_at	Serpina3n	serine (or cysteine) peptidase inhibitor, clade A, member 3N	1.86	1.62	-	-	3.77	2.76	2.11	1.87	2.81	-	-	-
1426318_at	Serpinb1b	serine (or cysteine) peptidase inhibitor, clade B, member 1b	-1.8	-	-	-	-	-	-	-	-2.3	-	-	-
141868-_at	Serpind1	serine (or cysteine) peptidase inhibitor, clade D, member 1	-	-	-1	-	-	-	-	-	-	-	-	-
1419149_at	Serpine1	serine (or cysteine) peptidase inhibitor, clade E, member 1	2.61	2.04	-	-	2.24	1.16	-	-	1.98	-	-	-
1453724_a_at	Serpinf1	serine (or cysteine) peptidase inhibitor, clade F, member 1	-	-	-	-	3.5	1.56	1.32	-	1.77	-	-	-

1417498_at	Serpinf2	serine (or cysteine) peptidase inhibitor, clade F, member 2	-	-	-	-	2.84	1.45	-	-	1.89	-	-	-
1416625_at	Serping1	serine (or cysteine) peptidase inhibitor, clade G, member 1	-	-	-	-	2.15	1.18	-	-	-	-	-	-
145-843_a_at	Serpinh1	serine (or cysteine) peptidase inhibitor, clade H, member 1	-	-	1.06	-	1.16	1.04	-	-	-	-	-	-
1448443_at	Serpini1	serine (or cysteine) peptidase inhibitor, clade I, member 1	-	-	-	-	-1.51	-	-	-	-	-	-	-
1422894_at	Sfmbt1	Scm-like with four mbt domains 1	-	-	-	1.61	-	-	-	-	-	-	-	-
1418747_at	Sfpi1	SFFV proviral integration 1	-	-	-	-	2.21	1.3	-	-	-	-	-	-
1418639_at	Sftpc	surfactant associated protein C	-	-	-	-	-1.00	-	-	-	-	-	-	-
142-918_at	Sgk3	serum/glucocorticoid regulated kinase 3	1.38	-	1.3	1.22	-	-	-	-	-	-	-	-
1415893_at	Sgpl1	sphingosine phosphate lyase 1	-	-	-	-	1.34	-	-	-	-	-	-	-
1422644_at	Sh3bgr	SH3-binding domain glutamic acid-rich protein	-	-	-	-	1.00	-	-	-	-	-	-	-
1448328_at	Sh3bp2	SH3-domain binding protein 2	-	-	-	-	2.57	1.52	1.05	-	-	-	-	-
1449-84_s_at	Sh3d19	SH3 domain protein D19	-	-	-	-	-	-	-	-	-	-	1.04	-
1449228_at	Sh3gl2	SH3-domain GRB2-like 2	-	-	-	-	-	-	-	1.05	-	-	-	-
1418-1-_a_at	Sh3glb1	SH3-domain GRB2-like B1 (endophilin)	-	-	-	-	1.26	-	-	-	-	-	-	-
1436167_at	Shf	Src homology 2 domain containing F	-	-	-	-	-1.13	-	-	-	-	-	-	-
1424975_at	Siglec5	sialic acid binding Ig-like lectin 5	-	-	-	-	2.50	1.57	-	-	-	-	-	-
14162-6_at	Sipa1	signal-induced proliferation associated gene 1	-	-	-	-	1.14	-	-	-	-	-	-	-
1416986_a_at	Sirpa	signal-regulatory protein alpha	-	-	-	-	1.05	-	-	-	-	-	-	-
142-819_at	Sla	src-like adaptor	-	-	-	-	2.09	-	-	-	-	-	-	-
1425-86_a_at	Slamf6	SLAM family member 6	-	-	-	-	1.87	-	-	-	-	-	-	-
1425294_at	Slamf8	SLAM family member 8	-	-	-	-	1.72	-	-	1.27	-	-	-	-
1419315_at	Slamf9	SLAM family member 9	-	-	-	-	2.62	1.92	1.39	-	-	-	-	-
1428776_at	Slc1-a6	solute carrier family 1- (sodium/bile acid cotransporter family), member 6	2.24	1.75	-	-	-	-	-	-	-	-	-	-
142-361_at	Slc11a1	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1	-	-	-	-	2.52	1.61	1.43	1.15	-	-	-	-
1417623_at	Slc12a2	solute carrier family 12, member 2	-	-	-	2.42	-	-	-	-	-	-	-	-
1428114_at	Slc14a1	solute carrier family 14 (urea transporter), member 1	-	-	-	-	2.63	1.42	1.18	-	1.71	-	-	-
142-697_at	Slc15a3	solute carrier family 15, member 3	1.73	1.32	-	-	3.57	3	-	1.6	-	-	-	-
142-445_at	Slc16a8	solute carrier family 16 (monocarboxylic acid transporters), member 8	-	-	-	-	-1.2	-	-	-	-1.5	-	-	-
141861-_at	Slc17a6	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6	-	-	-	1.08	-2	-	-	-	-	-	-	-
1426341_at	Slc1a3	solute carrier family 1 (glial high affinity glutamate transporter), member 3	-	-	-	-	1.10	-	-	-	-	-	-	-
1416629_at	Slc1a5	solute carrier family 1 (neutral amino acid transporter), member 5	-	-	-	-	1.74	-	-	-	-	-	-	-
1418933_at	Slc1a6	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	-	-	-	-	-1.09	-	-	-	-	-	-	-

1438824_at	Slc2-a1	solute carrier family 2-, member 1	1.23	-	-	-	-	-	-	-	-	-	-	-
1417639_at	Slc22a4	solute carrier family 22 (organic cation transporter), member 4	-	-	-	-	1.47	-	-	-	-	-	-	-
1426883_at	Slc25a45	solute carrier family 25, member 45	-	-	-	-	1.18	-	-	-	-	-	-	-
1419725_at	Slc26a4	solute carrier family 26, member 4	-	-	-	-	-1.08	-	-	-	-	-	-	-
1416316_at	Slc27a2	solute carrier family 27 (fatty acid transporter), member 2	-	-	-	-	-2.57	-	-	-	-	-	-	-
1455731_at	Slc29a3	solute carrier family 29 (nucleoside transporters), member 3	-	-	-	-	1.57	-	-	-	-	-	-	-
143375-_at	Slc31a1	solute carrier family 31, member 1	-	-	-	-	-	-	-	-	-1.7	-	-	-
1422756_at	Slc32a1	solute carrier family 32 (GABA vesicular transporter), member 1	-	-	-	-	-2.36	-	-	-	-	-	-	-
1452492_a_at	Slc37a2	solute carrier family 37 (glycerol-3-phosphate transporter), member 2	-	-	-	-	-0.99	1.22	-	-	-	-	-	-
14187-6_at	Slc38a3	solute carrier family 38, member 3	-	-	-	-	-0.98	-	-	-	-	-	-	-
1454622_at	Slc38a5	solute carrier family 38, member 5	-	-	-	-	1.27	-	-	-	-	-	-	-
1424675_at	Slc39a6	solute carrier family 39 (metal ion transporter), member 6	-	-	-	1.19	-	-	-	-	-	-	-	-
1417-61_at	Slc4-a1	solute carrier family 4- (iron-regulated transporter), member 1	-	-1.4	-1	-	-	-	-	-	-	-	-	-
1422788_at	Slc43a3	solute carrier family 43, member 3	-	-	-	-	4	2.27	-	1.13	1.83	-	-	-
1428-65_at	Slc44a2	solute carrier family 44, member 2	-	-	-	-	1.00	-	-	-	-	-	-	-
14251-9_at	Slc44a3	solute carrier family 44, member 3	1.54	1.15	-	-	1.02	-	-	-	-	-	-	-
1418395_at	Slc47a1	solute carrier family 47, member 1	-1.4	-	-1.1	-1.6	-	-	-	-	1.09	-	-	-
1448596_at	Slc6a8	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	1.02	-	-	-	-	-	-	-	-	-	-	-
1426--8_a_at	Slc7a2	solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	-	-	-	-	1.54	-	-	-	-	-	-	-
1417392_a_at	Slc7a7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	-	-	-	-	2.36	1.41	1.2	-	-	-	-	-
144-2-1_at	Slc8a1	solute carrier family 8 (sodium/calcium exchanger), member 1	-	-	-	-	-2.22	-	-	-	-	-	-	-
14492-3_at	Slco1a5	solute carrier organic anion transporter family, member 1a5	-	-	-	-	1.37	-	-	-	-	-	-	-
145-165_at	Slfn2	schlafen 2	-	-	-	-	1.61	-	-	-	-	-	-	-
1451655_at	Slfn8	schlafen 8	-	-	-	-	3.51	2.24	1.6	1.33	-	-	-	-
1425277_at	Slit1	slit homolog 1 (Drosophila)	-	-	-	-	-1.40	-	-	-	-	-	-	-
1427-86_at	Slit3	slit homolog 3 (Drosophila)	-	-	-	-	-1.15	-	-	-	-	-	-	-
1425487_at	Slu7	SLU7 splicing factor homolog (S. cerevisiae)	-	-	-	1.12	-	-	-	-	-	-	-	-
143-526_a_at	Smarca2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	-	-	-	-	-1.09	-	-	-	-	-	-	-
14242-7_at	Smarca5	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5	-	-	-	1.8	-	-	-	-	-	-	-	-
1423417_at	Smarcc1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1	-	-	-	1.01	-	-	-	-	-	-	-	-
1417831_at	Smc1a	structural maintenance of chromosomes 1A	-	-	-	1.62	-	-	-	-	-	-	-	-

142291-_s_at	Smc6	structural maintenance of chromosomes 6	-	-	-	1.63	-	-	-	-	-	-	-	-
143419-_at	Sms	spermine synthase	-	-	-	-	-1.10	-	-	-	-	-	-	-
1419766_at	Snf1lk	SNF1-like kinase	-	1.03	-	-	-	-	-	-	-	-	-	-
1433675_at	Snord22	small nucleolar RNA, C/D box 22	1.17	-	-	-	-	-	-	-	-	-	-	-
1429--3_at	Snw1	SNW domain containing 1	-	-	-	1.42	-	-	-	-	-	-	-	-
1417697_at	Soat1	sterol O-acyltransferase 1	-	-	-	1.81	1.58	1.26	-	-	-	-	-	-
14185-7_s_at	Socs2	suppressor of cytokine signaling 2	-	-	-	-	-1.21	-	-	-	-	-	-	-
1416576_at	Socs3	suppressor of cytokine signaling 3	4.07	2.88	1.81	-	2.56	-	-	-	2.3	-	-	-
142-951_a_at	Son	Son cell proliferation protein	-	-	-	1.01	-	-	-	-	-	-	-	-
1425826_a_at	Sorbs1	sorbin and SH3 domain containing 1	1.01	-	-	-	-	-	-	-	-	-	-	-
1419358_at	Sorcs2	sortilin-related VPS1- domain containing receptor 2	-	-	-	-	1.13	-	-	-	1.12	-	-	-
1425111_at	Sorcs3	sortilin-related VPS1- domain containing receptor 3	-	-	-	-	1.49	-	-	-	-	-	-	-
144934-_at	Sostdc1	sclerostin domain containing 1	-1.6	-	-	-	-2.2	-1.3	-	-1.6	-3.2	-	-	-
143679-_a_at	Sox11	SRY-box containing gene 11	1.89	-	-	-	-	-	-	-	-	-	-	-
1451821_a_at	Sp1--	nuclear antigen Sp1--	-	-	-	-	1.91	-	-	-	-	-	-	-
14215-4_at	Sp4	trans-acting transcription factor 4	-	-	-	1.75	-	-	-	-	-	-	-	-
1416589_at	Sparc	secreted acidic cysteine rich glycoprotein	-	-	-	-	1.84	-	-	-	-1	-	-	-
1424118_a_at	Spc25	SPC25, NDC8- kinetochore complex component, homolog (S. cerevisiae)	-	-	-	-	2.12	-	-	-	-	-	-	-
1424875_at	Spg2-	spastic paraplegia 2-, spartin (Troyer syndrome) homolog (human)	-	-	-	-	-0.98	-	-	-	-	-	-	-
1451596_a_at	Sphk1	sphingosine kinase 1	1.67	1.03	-	-	-	-	-	-	-	-	-	-
1438968_x_at	Spint2	serine protease inhibitor, Kunitz type 2	-	-	-	-	1.52	1.39	-	-	-1.5	-	-	-
1419256_at	Spnb2	spectrin beta 2	-	-	-	1.4	-	-	-	-	-	-	-	-
1452269_at	Spnb3	spectrin beta 3	-	-	-	-	-1.01	-	-	-	-	-	-	-
1449979_a_at	Spock3	sparc/osteonectin, cwcv and kazal-like domains proteoglycan 3	-	-	-	-	1.46	-	-	-	1.01	-	-	-
1424415_s_at	Spon1	spondin 1, (f-spondin) extracellular matrix protein	-	-	-	-	-1.20	-	-	-	-	-	-	-
1449254_at	Spp1	secreted phosphoprotein 1	-	1.1	-	-	1.8	1.38	1.63	-	-	-	-	-
1423162_s_at	Spred1	sprouty protein with EVH-1 domain 1, related sequence	-	-	-	1.66	-	-	-	-	-	-	-	-
1428472_at	Spsb1	splA/ryanodine receptor domain and SOCS box containing 1	1.36	-	-	-	-	-1	-	-	-	-	-	-
1448168_a_at	Spt1	salivary protein 1	-1	-	-	-	-	-	-	-	-	-	-	-
1424588_at	Srgap3	SLIT-ROBO Rho GTPase activating protein 3	-	-	-	-	-1.20	-	-	-	-	-	-	-
1417426_at	Srgn	serglycin	-	-	-	-	1.48	-	-	-	-	-	-	-
145168-_at	Srxn1	sulfiredoxin 1 homolog (S. cerevisiae)	1.94	1.29	1.27	-	-	-	-	-	-	-	-	-
1419361_at	Ss18	synovial sarcoma translocation, Chromosome 18	-	-	-	-	1.25	-	-	1.26	-	-	-	-
1417954_at	Sst	somatostatin	-	-	-	-	-2.37	-	-	-	-	-	-	-

1418-76_at	St14	suppression of tumorigenicity 14 (colon carcinoma)	-	-	-	-	1.76	1.31	-1	-	-	-	-	-
1449-78_at	St3gal6	ST3 beta-galactoside alpha-2,3-sialyltransferase 6	-	-	-	-	1.00	-	-	-	-	-	-	-
141942-_at	St6galnac5	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 5	-	-	-	-	-1.83	-	-	-	-	-	-	-
145-199_a_at	Stab1	stabilin 1	-	-	-	-	1.40	1.18	-	-	-	-	-	-
1424581_at	Stac2	SH3 and cysteine rich domain 2	-	-	-	-	-1.41	-	-	1.29	-	-	-	-
1427-72_at	Stard8	START domain containing 8	-	-	-	-	1.01	-	-	-	-	-	-	-
145--33_a_at	Stat1	signal transducer and activator of transcription 1	-	-	-	-	2.57	1.26	-1	-1	1.4	-	-	-
1426587_a_at	Stat3	signal transducer and activator of transcription 3	1.27	1.13	-	-	1.34	-	-	-	1.32	-	-	-
1426353_at	Stat6	signal transducer and activator of transcription 6	-	-	-	-	1.15	-	-	-	-	-	-	-
1425534_at	Stau2	staufen (RNA binding protein) homolog 2 (Drosophila)	-	-	-	-	-1.45	-	-	-	-	-	-	-
1451532_s_at	Steap1	six transmembrane epithelial antigen of the prostate 1	-	-	1.13	1.19	-2.3	-1.6	-	-1.6-7	-4.4	-	-	-
146-197_a_at	Steap4	STEAP family member 4	-	1.18	-	-	-	1.01	1	-	-	-	-	-
1431434_at	Stk39	serine/threonine kinase 39, STE2-/SPS1 homolog (yeast)	-	-	-	1.6	-	-	-	-	-	-	-	-
142965-_at	Stk4-	serine/threonine kinase 4-	-	1.01	-	-	-	-	-	-	-	-	-	-
142328-_at	Stmn2	stathmin-like 2	-	-	-	-	-1.59	-	-	-	-	-	-	-
14188-4_at	Sucnr1	succinate receptor 1	-	-	-	-	3.01	-	1.03	-	1.25	-	-	-
143-388_a_at	Sulf2	sulfatase 2	-	-	-	-	1.02	-	-	-	-	-	-	-
142-47-_at	Sult1c1	sulfotransferase family, cytosolic, 1C, member 1	-	-	-	-	-1.9	-1.6	-1.5	-2	-2.6	-	-	-
14494-9_at	Sult1c2	sulfotransferase family, cytosolic, 1C, member 2	-	-	-	-	-1.7	-	-	-	-2.3	-	-	-
1417335_at	Sult2b1	sulfotransferase family, cytosolic, 2B, member 1	-	-1	-	-	-	-	-	-	-	-	-	-
146-694_s_at	Svil	supervillin	-	-	-	-	1.17	-	-	-	-	-	-	-
1418261_at	Syk	spleen tyrosine kinase	-	-	-	-	1.40	-	-	-	-	-	-	-
145-743_s_at	Syncrip	synaptotagmin binding, cytoplasmic RNA interacting protein	-	-	-	-	-	-	-	1.06	-	-	-	-
1419289_a_at	Syngr1	synaptogyrin 1	-	-	-	-	2.79	1.72	1.47	1.2	-	-	-	-
1417-81_a_at	Syngr2	synaptogyrin 2	-	-	-	-	1.62	1.24	-	-	-	-	-	-
1434-89_at	Synpo	synaptopodin	-	1.13	-	-	2.53	1.39	-	-	1.43	-	-	-
1422882_at	Sypl	synaptophysin-like protein	-	-	-	1.18	-	-	-	-	-	-	-	-
1431191_a_at	Syt1	synaptotagmin I	-	-	-	1.46	-1.3	-	-	-	-	-	-	-
1422955_at	Syt17	synaptotagmin XVII	-	-	-	-1	-	-	-	-	-	-	-	-
144-323_at	Syt2	synaptotagmin II	-	-	-	-	-1.92	-	-	-	-	-	-	-
1416783_at	Tac1	tachykinin 1	-	-	-	-	-2.18	-	-	-	-	-	-	-
1437-29_at	Tacr3	tachykinin receptor 3	-	-	-1	-	-1.1	-	-	-	-	-	-	-
1416579_a_at	Tacstd1	tumor-associated calcium signal transducer 1	-	-	-	-	1.09	-	-	-	-	-	-	-

14235-5_at	Tagln	transgelin	-	-	-	-	1.86	-	-	-	-	-	-	-
14394-7_x_at	Tagln2	transgelin 2	-	-	-	-	1.34	-1	-	-	-	-	-	-
1449389_at	Tal1	T-cell acute lymphocytic leukemia 1	-	-	-	-	1.00	-	-	-	-	-	-	-
1416-16_at	Tap1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	-	-	-	-	1.49	-	-	-	-	-	-	-
1453913_a_at	Tap2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	-	-	-	-	1.16	-	-	-	-	-	-	-
1421812_at	Tapbp	TAP binding protein	-	-	-	-	1.18	-	-	-	-	-	-	-
1416-62_at	Tbc1d15	TBC1 domain family, member 15	-	-	-	1.1	-	-	-	-	-	-	-	-
1416827_at	Tbxas1	thromboxane A synthase 1, platelet	-	-	-	-	1.78	1.23	-	-	-	-	-	-
1418-91_at	Tcfcp2l1	transcription factor CP2-like 1	-	-	-	-	1.25	-	-	-	-	-	-	-
1456515_s_at	Tcfl5	transcription factor-like 5 (basic helix-loop-helix)	-	-	-	-	-	-	-	-	-1.7	-	-	-
142-635_a_at	Tcirg1	T-cell, immune regulator 1, ATPase, H+ transporting, lysosomal V- protein A3	-	-	-	-	1.79	1.32	-	-	-	-	-	-
14482--_at	Tcn2	transcobalamin 2	-	-	-	-	-	1	-	-	-	-	-	-
145-989_at	Tdgf1	teratocarcinoma-derived growth factor	-	-	-	-	2.02	-	-	-	-	-	-	-
1419-93_at	Tdo2	tryptophan 2,3-dioxygenase	1.18	-	-	-	-2.3	-	-1.5	-1.4	-	-	-	-
1452432_at	Tfpi	tissue factor pathway inhibitor	-	-	-	-	1.03	-	-	-	-	-	-	-
142-653_at	Tgfb1	transforming growth factor, beta 1	-	-	-	-	2.40	1.98	1.37	1.1	-	-	-	-
1418136_at	Tgfb1i1	transforming growth factor beta 1 induced transcript 1	-	-	-	-	-0.98	-	-	-	-	-	-	-
142-895_at	Tgfbr1	transforming growth factor, beta receptor I	-	-	-	-	1.40	-	-	-	-	-	-	-
1426397_at	Tgfbr2	transforming growth factor, beta receptor II	-	-	-	-	2.01	1.54	-	-	-	-	-	-
1422286_a_at	Tgif1	TG interacting factor 1	-	-	-	-	2.1	1.09	-	-	1.15	-	-	-
1451416_a_at	Tgm1	transglutaminase 1, K polypeptide	1.76	1.74	-	-	4.43	2.87	1.87	1.35	2.16	-	-	-
14219-5_at	Tgs1	trimethylguanosine synthase homolog (S. cerevisiae)	-	-	-	1.59	-	-	-	-	-	-	-	-
1421811_at	Thbs1	thrombospondin 1	1.52	-	-	1.05	2.03	-	-	-	2.19	-	-	-
1422571_at	Thbs2	thrombospondin 2	-	-	-	-	1.01	-	-	-	-	-	-	-
1449388_at	Thbs4	thrombospondin 4	-	-	-	-	1.19	-	-	-	-	-	-	-
146-227_at	Timp1	tissue inhibitor of metalloproteinase 1	2.53	1.96	1.62	-	4.39	2.39	2.64	1.44	2.61	-	-	-
146-287_at	Timp2	tissue inhibitor of metalloproteinase 2	-	-	-	-	2.04	1.55	1.03	1.22	-	-	-	-
145-974_at	Timp4	tissue inhibitor of metalloproteinase 4	-	-	-	-	1.32	-	-	-	-	-	-	-
1452161_at	Tiparp	TCDD-inducible poly(ADP-ribose) polymerase	1.41	-	-	1.55	-	-	-	-	-	-	-	-
1417896_at	Tjp3	tight junction protein 3	-	-	-	-	-	-	-	-	-1.8	-	-	-
1416258_at	Tk1	thymidine kinase 1	-	-	-	-	1.54	-	-	-	-	-	-	-
142-753_at	Tll1	tolloid-like	-	-	-	-	4.06	1.1	-	-	2.28	-	-	-
14484-2_at	Tln1	talin 1	-	-	-	-	1.22	-	-	-	-	-	-	-

1449-49_at	Tlr1	toll-like receptor 1	-	-	-	-	2.87	1.79	-	-	-	-	-	-
1419132_at	Tlr2	toll-like receptor 2	-	-	-	-	3.56	2.56	-	-	-	-	-	-
1418162_at	Tlr4	toll-like receptor 4	-	-	-	-	1.84	-	-	-	-	-	-	-
1422-1-_at	Tlr7	toll-like receptor 7	-	-	-	-	2.96	1.82	1.41	-	-	-	-	-
1448-69_at	Tm4sf1	transmembrane 4 superfamily member 1	-	-	-	-	1.26	-	-	-	-	-	-	-
142377-_at	Tmc6	transmembrane channel-like gene family 6	-	-	-	-	-	-	-	-	-	1.1	-	-
14281-8_x_at	Tmcc2	transmembrane and coiled-coil domains 2	-	-	-	-	-1.13	-	-	-	-	-	-	-
1451794_at	Tmcc3	transmembrane and coiled coil domains 3	-	-	1.16	-	-1	-	-	-	-	-	-	-
142-867_at	Tmed2	transmembrane emp24 domain trafficking protein 2	-	-	-	1.43	-	-	-	1.31	-	-	-	-
1449533_at	Tmem1--	transmembrane protein 1--	-	-	-	-	2.11	-	-	-	-	-	-	-
1425-25_at	Tmem1-6a	transmembrane protein 1-6A	-	-	-	-	2.25	1.28	-	-	-	-	-	-
1451344_at	Tmem119	transmembrane protein 119	-	-	-	-	2.19	1.65	1.09	-	-	-	-	-
1424354_at	Tmem14-	transmembrane protein 14-	-	-	-	-	1.46	-	-	-	-	-	-	-
1428-74_at	Tmem158	transmembrane protein 158	-	-	-	-	-1.21	-	-	-	-	-	-	-
1427911_at	Tmem173	transmembrane protein 173	-	-	-	-	1.87	1.07	1	-	-	-	-	-
14239-9_at	Tmem176a	transmembrane protein 176A	-	-	-	-	1.57	-	-	-	-	-	-	-
1418--4_a_at	Tmem176b	transmembrane protein 176B	-	-	-	-	1.02	-	-	-	-	-	-	-
1451458_at	Tmem2	transmembrane protein 2	1.31	-	-	-	-	-	-	-	-	-	-	-
1435-64_a_at	Tmem27	transmembrane protein 27	-	-	-	-	-1.3	-	-	-1.1	-2.7	-	-	-
14311-5_a_at	Tmem33	transmembrane protein 33	-	-	-	1.01	-	-	-	-	-	-	-	-
1423852_at	Tmem46	transmembrane protein 46	-	-	-	-	-1.48	-	-	-	-	-	-	-
1449885_at	Tmem47	transmembrane protein 47	-	-	-	-	1.11	-	-	-	-	-	-	-
1421491_a_at	Tmem49	transmembrane protein 49	-	-	-	1.09	-	-	-	-	-	-	-	-
1436212_at	Tmem71	transmembrane protein 71	-	-	-	-	1.13	-	-	-	-	-	-	-
1424454_at	Tmem87a	transmembrane protein 87A	-	-	-	-1.2	-	-	-	-	-	-	-	-
14227-5_at	Tmepai	transmembrane, prostate androgen induced RNA	-	1.2	-	-	2.42	1.64	1.36	1.27	1.52	-	-	-
1423-88_at	Tmod3	tropomodulin 3	-	-	-	-	1.06	-	-	-	-	-	-	-
1416342_at	Tnc	tenascin C	-	-	-	-	2.55	1.63	1.25	-	1.39	-	-	-
1438855_x_at	Tnfaip2	tumor necrosis factor, alpha-induced protein 2	-	-	-	-	1.69	1.09	1.18	-	-	-	-	-
1418571_at	Tnfrsf12a	tumor necrosis factor receptor superfamily, member 12a	1.73	1.46	-	-	2.12	-	-	-	-	-	-	-
1423182_at	Tnfrsf13b	tumor necrosis factor receptor superfamily, member 13b	-	-	-	-	1.87	-	-	-	-	-	-	-
1417291_at	Tnfrsf1a	tumor necrosis factor receptor superfamily, member 1a	-	-	-	-	1.39	1.03	-	-	-	-	-	-
1418-99_at	Tnfrsf1b	tumor necrosis factor receptor superfamily, member 1b	-	-	-	-	1.88	1.02	-	-	-	-	-	-
1419-83_at	Tnfsf11	tumor necrosis factor (ligand) superfamily, member 11	-	-	-	-	2.06	-	-	-	1.52	-	-	-

1448298_at	Tnk2	tyrosine kinase, non-receptor, 2	-	-	-	-	-1.00	-	-	-	-	-	-	-
1416889_at	Tnni2	troponin I, skeletal, fast 2	-	-	-	-	1.64	1	-	-	-	-	-	-
1418726_a_at	Tnnt2	troponin T2, cardiac	-	-	-	-	-	-	1.3	-	2.66	-	-	-
1454694_a_at	Top2a	topoisomerase (DNA) II alpha	-	-	-	-	2.29	1.46	-	-	-	-	-	-
1417754_at	Topors	topoisomerase I binding, arginine/serine-rich	-	-	-	1.33	-	-	-	-	-	-	-	-
1426-84_a_at	Tor1aip1	torsin A interacting protein 1	-	-	-	-	1.02	-	-	-	-	-	-	-
1421998_at	Tor3a	torsin family 3, member A	-	-	-	-	2.19	1.27	-	-	-	-	-	-
1423312_at	Tpbg	trophoblast glycoprotein	-	1.12	-	-	1.08	-	-	-	-	-	-	-
14243-4_at	Tpcn2	two pore segment channel 2	-	-	-	-	1.11	-	-	-	-	-	-	-
1449996_a_at	Tpm3	tropomyosin 3, gamma	-	-	-	-	1.25	-	-	-	-	-	-	-
1451268_at	Tram1l1	translocation associated membrane protein 1-like 1	-	-	-	-	-0.99	-	-	-	-	-	-	-
1421792_s_at	Trem2	triggering receptor expressed on myeloid cells 2	-	-	-	-	3.58	2.7	2.01	1.71	-	-	-	-
145-672_a_at	Trex1	three prime repair exonuclease 1	-	-	-	-	1.35	-	-	-	-	-	-	-
1459994_x_at	Trfr2	transferrin receptor 2	-	-	-	-1.1	-1.3	-	-	-	-	-	-	-
1418756_at	Trh	thyrotropin releasing hormone	-	-	-	-	4.9	1.67	-	-	6.42	-	-	-
1449571_at	Trhr	thyrotropin releasing hormone receptor	-	-	-	-1.7	-1.1	-	-	-	-	-	-	-
142488-_at	Trib1	tribbles homolog 1 (Drosophila)	1.35	1.09	-	-	-	-	-	1.33	-	-	-	-
1437432_a_at	Trim12	tripartite motif protein 12	-	-	-	-	1.91	1.19	-	-	-	-	-	-
144894-_at	Trim21	tripartite motif protein 21	-	-	-	-	1.39	-	-	-	-	-	-	-
1425974_a_at	Trim25	tripartite motif protein 25	-	-	-	-	1.79	1.25	-	-	-	-	-	-
1417961_a_at	Trim3-	tripartite motif protein 3-	-	-	-	-	3.82	2.63	1.62	1.08	1.34	-	-	-
1424857_a_at	Trim34	tripartite motif protein 34	-	-	-	-	2.14	1.31	-	-	-	-	-	-
1426784_at	Trim47	tripartite motif protein 47	-	-	-	-	1.23	-	-	-	-	-	-	-
145265-_at	Trim62	tripartite motif-containing 62	-	-	-	-1.1	-1.1	-	-	-	-	-	-	-
1422-48_at	Trpc5	transient receptor potential cation channel, subfamily C, member 5	-	-	-	1.11	-1.1	-	-	-	-	-	-	-
14168-1_at	Trpm7	transient receptor potential cation channel, subfamily M, member 7	-	-	-	1.96	-	-	-	-	-	-	-	-
1456-14_s_at	Trpt1	tRNA phosphotransferase 1	-	-	-	-	2.71	1.88	-	-	-	-	-	-
1417545_at	Trpv4	transient receptor potential cation channel, subfamily V, member 4	-1	-	-	-	-	-	-	-	-1.7	-	-	-
145---4_at	Tslp	thymic stromal lymphopoietin	1.35	-	-	-	-	-	-	-	-	-	-	-
1432417_a_at	Tspan2	tetraspanin 2	-	-	-	1.31	-	-	-	1.14	-	-	-	-
1418398_a_at	Tspan32	tetraspanin 32	-	-	-	-	1.17	-	-	-	-	-	-	-
14516-8_a_at	Tspan33	tetraspanin 33	-	-	-	-	-	-	-	-	-1.2	-	-	-
1448276_at	Tspan4	tetraspanin 4	-	-	-	-	1.06	-	-	-	-	-	-	-
143153-_a_at	Tspan5	tetraspanin 5	-	-	-	1.28	-	-	-	-	-	-	-	-

1438948_x_at	Tspo	translocator protein	-	-	-	-	1.60	1.12	-	-	-	-	-	-
146-717_at	Tspyl1	testis-specific protein, Y-encoded-like 1	-	-	-	1.05	-	-	-	-	-	-	-	-
14486-9_at	Tst	thiosulfate sulfurtransferase, mitochondrial	-	-	-	-	1.21	-	-	-	-	-	-	-
143213-_a_at	Ttc14	tetratricopeptide repeat domain 14	-	-	-	1.06	-	-	-	-	-	-	-	-
1416482_at	Ttc3	tetratricopeptide repeat domain 3	-	-	-	1.24	-1.3	1.09	-	-	-	-	-	-
145158-_a_at	Ttr	transthyretin	-	-	-	-	-2	-1.4	-	-1.3	-1.9	-	-	-
142-925_at	Tub	tubby candidate gene	-	-	-	-	-1.20	-	-	-	-	-	-	-
1416431_at	Tubb6	tubulin, beta 6	2.25	2.16	1.32	-	2.12	1.46	1.24	-	1.56	-	-	-
1416689_at	Tuft1	tuftelin 1	-	-	-	-	-	-	-	-	-1.2	-	-	-
142-873_at	Twf1	twinfilin, actin-binding protein, homolog 1 (Drosophila)	-	-	-	1.39	1.26	-	-	1.29	-	-	-	-
1448925_at	Twist2	twist homolog 2 (Drosophila)	-	-	-	-	-1.44	-	-	-	-	-	-	-
1415997_at	Txnip	thioredoxin interacting protein	-	-	1.39	-	-	-	-	-	-	-	-	-
145-792_at	Tyrobp	TYRO protein tyrosine kinase binding protein	-	-	-	-	2.62	2.25	1.46	1.36	-	-	-	-
1426971_at	Ube1l	ubiquitin-activating enzyme E1-like	-	-	-	-	2.03	1.34	-	-	-	-	-	-
1452954_at	Ube2c	ubiquitin-conjugating enzyme E2C	-	-	-	-	2.06	-	-	-	-	-	-	-
145548-_s_at	Ube2d3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)	-	-	-	1	-	-	-	-	-	-	-	-
1424358_at	Ube2e2	ubiquitin-conjugating enzyme E2E 2 (UBC4/5 homolog, yeast)	-	-	-	-	-1.10	-	-	-	-	-	-	-
1416681_at	Ube3a	ubiquitin protein ligase E3A	-	-	-	1.42	-	-	-	-	-	-	-	-
1426485_at	Ubxd2	UBX domain containing 2	-	-	-	1.54	-	-	-	-	-	-	-	-
1448188_at	Ucp2	uncoupling protein 2 (mitochondrial, proton carrier)	-	-	-	-	1.12	1.06	-	-	-	-	-	-
1421269_at	Ugcg	UDP-glucose ceramide glucosyltransferase	-	-	-	1.06	-	-	-	-	-	-	-	-
1426261_s_at	Ugt1a6a	UDP glucuronosyltransferase 1 family, polypeptide A6A	-	-	-	-	1.95	1.09	-	-	-	-	-	-
1424783_a_at	Ugt1a9	UDP glucuronosyltransferase 1 family, polypeptide A9	-	-	-	-	1.47	-1	-	-	-	-	-	-
1419-64_a_at	Ugt8a	UDP galactosyltransferase 8A	-	-	-	1.17	-	-	-	1.06	-	-	-	-
141581-_at	Uhrf1	ubiquitin-like, containing PHD and RING finger domains, 1	-	-	-	-	1.46	-1	-	-	-	-	-	-
1449522_at	Unc5c	unc-5 homolog C (C. elegans)	-	-	-	-	-1.05	-	-	-	-	-	-	-
1423768_at	Unc93b1	unc-93 homolog B1 (C. elegans)	-	-	-	-	2.02	1.27	1.08	-	-	-	-	-
1418191_at	Usp18	ubiquitin specific peptidase 18	-	-	-	-	4.25	2.54	1.86	1.03	1.62	-	-	-
1456-43_at	Usp22	ubiquitin specific peptidase 22	-	-	-	-	-	-	-	1.42	-	-	-	-
1419277_at	Usp48	ubiquitin specific peptidase 48	-	-	-	1.21	-	-	-	-	-	-	-	-
1421863_at	Vamp1	vesicle-associated membrane protein 1	-	-	-	-	-1.29	-	-	-	-	-	-	-
14211-2_a_at	Vamp3	vesicle-associated membrane protein 3	-	-	-	-	1.23	-	-	-	-	-	-	-
1422932_a_at	Vav1	vav 1 oncogene	-	-	-	-	1.91	1.37	-	-	-	-	-	-
1415989_at	Vcam1	vascular cell adhesion molecule 1	-	-	-	1.02	1.46	-	-	1.04	-	-	-	-

145-641_at	Vim	vimentin	1.49	1.01	-	-	2.78	2.45	1.67	1.49	1.84	-	-	-
1449869_at	Vpreb1	pre-B lymphocyte gene 1	-	-	-	-	-	-	-	-	-1.7	-	-	-
1415784_at	Vps35	vacuolar protein sorting 35	-	-	-	1.29	-	-	-	1.11	-	-	-	-
1426399_at	Vwa1	von Willebrand factor A domain containing 1	-	-	-	-	1.88	-	-	-	-	-	-	-
1419631_at	Was	Wiskott-Aldrich syndrome homolog (human)	-	-	-	-	2.02	1.28	-	-	-	-	-	-
1418545_at	Wasf1	WASP family 1	-	-	-	-	-1.16	-	-	-	-	-	-	-
1454673_at	Wasf2	WAS protein family, member 2	-	-	-	-	-0.98	-	-	-	-	-	-	-
1423-54_at	Wdr1	WD repeat domain 1	-	-	1.04	-	-	-	-	1.13	-1.2	-	-	-
1423961_at	Wdr26	WD repeat domain 26	-	-	-	-	-0.99	-	-	-	-	-	-	-
1416773_at	Wee1	wee 1 homolog (S. pombe)	-	-	-	-	-1.19	-	-	-	-	-	-	-
1424351_at	Wfdc2	WAP four-disulfide core domain 2	-	-	-	-	-1.8	-1	-	-1.4	-3.2	-	-	-
1436954_at	Wipf1	WAS/WASL interacting protein family, member 1	-	-	-	-	1.23	-	-	-	-	-	-	-
1419-15_at	Wisp2	WNT1 inducible signaling pathway protein 2	-	-	-	-	3.47	-	-	-	2.07	-	-	-
1436746_at	Wnk1	WNK lysine deficient protein kinase 1	-	-	-	1.17	-	-	-	-	-	-	-	-
146-657_at	Wnt1-a	wingless related MMTV integration site 1-a	-	-	-	-	1.2	-	-	-	1.38	-	-	-
1449425_at	Wnt2	wingless-related MMTV integration site 2	-	-	-	-	-2.5	-	-	-	-1.2	-	-	-
145-782_at	Wnt4	wingless-related MMTV integration site 4	-	-	-	-	-1.23	-	-	-	-	-	-	-
1417817_a_at	Wwtr1	WW domain containing transcription regulator 1	-	-	-	-	1.5	-	-	-	1.17	-	-	-
1451--6_at	Xdh	xanthine dehydrogenase	-	-	-	-	1.91	-	-	-	1.26	-	-	-
1422-11_s_at	Xlr	X-linked lymphocyte-regulated complex	-	-	-	-	2.35	1.42	-	-	-	-	-	-
1449347_a_at	Xlr4b	X-linked lymphocyte-regulated 4B	-	-	-	-	2.68	2.32	1.96	-	-	-	4.01	-
1422842_at	Xrn2	5'-3' exoribonuclease 2	-	-	-	1.15	-	-	-	-	-	-	-	-
1427221_at	Xtrp3s1	X transporter protein 3 similar 1 gene	-	-	-	-	-	-	-	-1.3	-	-	-	-
1421-48_a_at	Ypel1	yippee-like 1 (Drosophila)	-	-	-	-	-1.49	-	-	-	-	-	-	-
142-816_at	Ywhag	3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	-	-	-	-	-	-	-	1.32	-	-	-	-
1429947_a_at	Zbp1	Z-DNA binding protein 1	-	-	-	-	2.00	1.01	-	-	-	-	-	-
1427638_at	Zbtb16	zinc finger and BTB domain containing 16	-	-	-	1.12	-	-	-	-	-	-	-	-
145--93_s_at	Zbtb7a	zinc finger and BTB domain containing 7a	-	-	-	1.62	-	-	-	-	-	-	-	-
142636-_at	Zc3h11a	zinc finger CCCH type containing 11A	-	-	-	2.06	-	-	-	-	-	-	-	-
141817-_a_at	Zcchc14	zinc finger, CCHC domain containing 14	-	-	-	1.61	-	-	-	-	-	-	-	-
1452655_at	Zdhhc2	zinc finger, DHHC domain containing 2	-	-	-	1.22	-	-	-	-	-	-	-	-
142-65-_at	Zfhx3	zinc finger homeobox 3	-	-	-	-	-	1.31	-	-	-	-	-	-
1417792_at	Zfml	zinc finger, matrin-like	-	-	-	1.44	-	-	-	-	-	-	-	-

14561-8_x_at	Zfp179	zinc finger protein 179	-	-	-	-	-1.29	-	-	-	-	-	-	-
142-944_at	Zfp185	zinc finger protein 185	-	-	-	-	-1.2	-	-	-	-1.4	-	-	-
1425287_at	Zfp189	zinc finger protein 189	-	-	-	-	-1.36	-	-	-	-	-	-	-
142281-_at	Zfp191	zinc finger protein 191	-	-	-	1.34	-	-	-	-	-	-	-	-
1452519_a_at	Zfp36	zinc finger protein 36	1.83	1.47	-	-	1.08	-	-	-	-	-	-	-
1451816_at	Zfp451	zinc finger protein 451	-	-	-	1.06	-	-	-	-	-	-	-	-
1451332_at	Zfp521	zinc finger protein 521	-	-	-1.1	-	-	-	-	-	-	-	-	-
1436-26_at	Zfp7-3	zinc finger protein 7-3	-	-	-	-	1.40	-	-	-	-	-	-	-
1426326_at	Zfp91	zinc finger protein 91	-	-	-	1.2	2.75	1.88	1.27	-	-	-	-	-
1451-46_at	Zfpm1	zinc finger protein, multitype 1	-	-	-	-	-1.16	-	-	-	-	-	-	-
1428-46_a_at	Zfx	zinc finger protein X-linked	1	-	-	2.44	-	-	-	-	-	-	-	-
1427539_a_at	Zwint	ZW1- interactor	1.44	-	-	-	-	-	-	-	-	-	-	-