We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

2

Alzheimer's Disease Genomics and Clinical Applications

Tih-Shih Lee[1] and Mei Sian Chong[2]
[1]*Duke University Medical School*
[2]*Tan Tock Seng Hospital*
[1]*USA*
[2]*Singapore*

1. Introduction

The prevalence of dementia is expected to increase exponentially worldwide. Global estimates of Alzheimer's disease (AD) - generally considered to be the most common subtype of dementia - are expected to increase from the current estimated 25 million to 63 million in 2030, and by 2050, a staggering 114 million (Wimo et al., 2003).

Traditional approaches in AD diagnosis (Diagnostic and Statistical Manual- IV (DSM-IV) – Text Revision (American Psychiatric Association [APA], 2000) and National Institute of Neurological Disorders and Stroke- Alzheimer Disease and Related Disorders (NINCDS-ADRDA) (McKhann et al., 1984) criteria have varying diagnostic accuracy of 65-96% and specificity of 23-88% compared to the neuropathologic gold standard (Kazee et al., 1993; Lim et al., 1999; Petrovich et al., 2001; Varma et al., 1999). Studies have shown that the hallmark histopathological changes of AD (β-amyloid plaques and neurofibrillary tangles) precede the clinical onset of disease by as long as 20-30 years (Price & Morris, 1999). This translates clinically to functional and structural brain damage where these pathologic changes may occur prior to apparent clinical manifestations of cognitive decline by way of standard clinical assessments. This has fuelled an increasing shift of diagnostic focus to the pre-dementia transitional state between normal aging and early AD, which represents a window of opportunity for identifying subjects at a phase when pathogenesis has already begun but clinical diagnosis of established dementia is still not achievable. This would logically be the stage most amenable to disease-modifying interventions (such as β- and gamma-secretase inhibitors, anti-amyloid and anti-neurofibrillary tangle therapies). Diagnostic focus thus has shifted towards prodromal stages of Alzheimer's Disease (AD), such as mild cognitive impairment (MCI) (Morris et al., 2001; Peterson, 2004). Clinical criteria alone, which by their very nature subjective and entail judgment, are thus inadequate to identify the pre-clinical stages of AD and may have contributed to the disappointing results of therapeutic trials in MCI (a heterogeneous entity) to date. This has prompted revisions in the upcoming DSM-V criteria due in 2013 (Kupfer & Regier, 2010) which include major and minor neurocognitive disorder classification, as well as the proposed revision of NINCDS-ADRDA criteria for AD to include prodromal AD and preclinical AD, which characterises earliest stage of AD that predate crossing of the dementia threshold of functional disability. In the proposed criterion by Dubois et al (Dubois et al., 2007), other than clinical criterion of episodic memory deficit,

they have also included in criterion E, dominant genetic mutation within the immediate family of amyloid precursor protein (Chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1). In consideration of important genetic factors, the presence of a proven autosomal dominant mutation has been taken as evidence to support AD diagnosis even when clinical features fall outside typical AD criteria. In the working draft for the revised NINCDS-ADRDA research criteria for MCI-AD and preclinical AD, there are also considerations given to genetics and its influence on disease progression in these pre-dementia states.

The rate and presence of clinical manifestation of AD is postulated to be influenced by the complex relationship of age, genetic factors, cognitive reserve, cerebrovascular disease, which might affect the neuropathogenic progress of amyloid toxicity and subsequent clinical presentation of AD (Jack et al., 2010). Hence in recent years, there has been increasing interest in the role of genomics in understanding AD and disease progression.

In this chapter, we will review the application of genomic, transcriptomic and other 'omic' platforms and their role in the development of novel diagnostic strategies for AD diagnosis, prediction of disease progression and therapeutic drug responses. We will discuss the potential clinical applications, the current limitations, ethical dilemmas and the future direction of genomics in AD.

2. Genetics of AD

The genetic underpinning of AD is heterogeneous and complex, without a straightforward mode of inheritance for the vast majority of cases. The heritability of AD in general is estimated to be around 60% (Bergem et al., 1997a, 1997b).

In general, AD can be divided into 2 forms: early onset AD (EOAD) usually those below 65 years of age, and patients with the late onset AD (LOAD), above 65 years. EOAD largely follows a Mendelian autosomal dominant inheritance but they account for less than 5% of all AD. Linkage studies have identified three genes thus far for which multiple mutations can lead to the pathology. These genes are the amyloid precursor protein (APP) gene on chromosome 21q, the presenilin 1 (PSEN1) gene on 14q, and presenilin 2 (PSEN2) gene on 1q. These mutations all affect Amyloid Precursor Protein (APP) processing and lead to the increased synthesis of Aβ40 and Aβ42 (See Figure 1). These peptides aggregate to form amyloid plaques. Given their rarity, these three gene mutations contribute minimally to the estimated 60% heritability of AD. The importance of these rare mutations lies in the identification of pathogenic pathways, specifically those involving the catabolism of APP. Hence accumulation of Aβ40 and Aβ42 is attributed to increased activity of the β and γ secretases in familial cases of AD with APP, PSEN1 and PSEN2 gene mutations. However environmental or other non-genetic or epigenetic factors may also affect the activities of the secretases. This may account for why some cases of PSEN1 and PSEN2 mutations show incomplete penetrance and variable onset of illness (Tanzi et al., 1996, 1999).

Normal individuals with first-degree relatives affected by AD, especially one parent, are at 4 to10-fold higher risk of developing LOAD compared to those with no family history. However no clear Mendelian pattern of transmission has been identified as yet for LOAD. Those subjects with a maternal history of dementia showed reduced cerebral metabolic rate of glucose in the same regions as clinically affected AD subjects (posterior cingulate cortex, precuneus, parietotemporal and frontal cortices, medial temporal lobes) and these effects remained after age, gender and education adjustments were made. This may be suggestive

of either chromosome X transmission or inheritance of mitochondrial DNA (mtDNA). This is especially pertinent as mtDNA deficits are proposed to be involved in AD (Lin & Beal, 2006; Mosconi et al.,2007) with further recent evidence for sub-haplotype H5 of mtDNA, especially in females, to be a risk factor for late onset AD, independent of APOE status (Santoro et al., 2010).

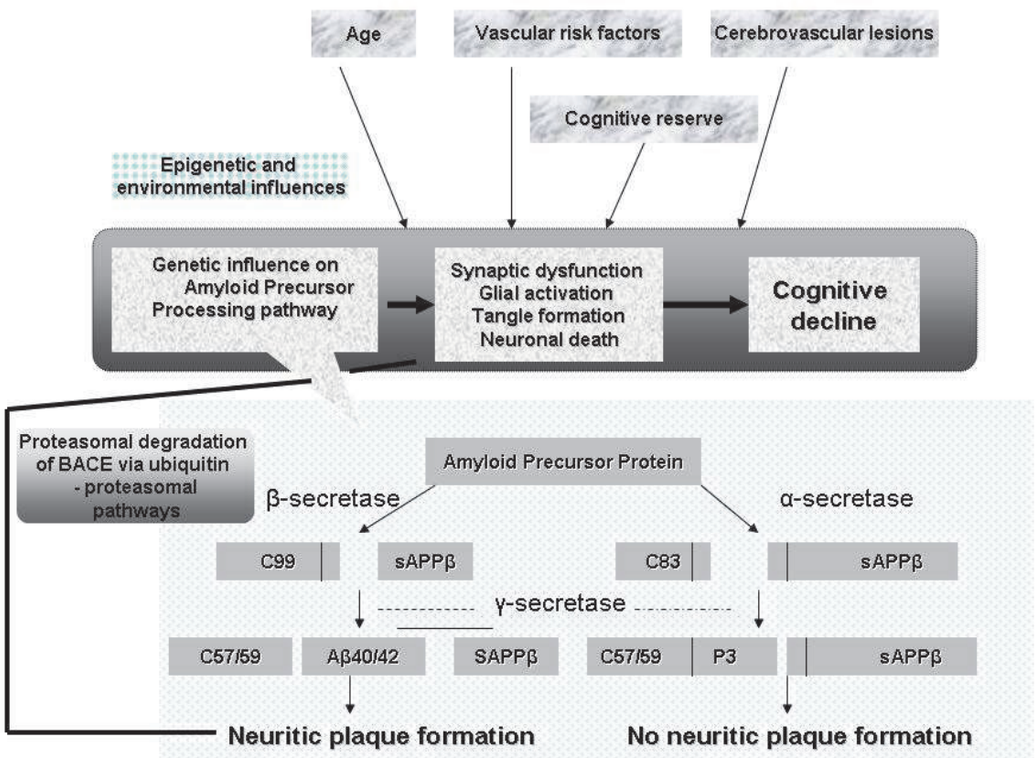


Fig. 1. Hypothetical pathophysiological cascade of AD and genetic influences on amyloid precursor pathways

Multiple association studies have showed apolipoprotein e4 (APOE e4) to be a genetic susceptibility factor, and another allele e2 to be likely protective. Apolipoprotein has three alleles e2, e3, e4 located on chromosome 19. They encode cholesterol transport protein APOE which is the primary cholesterol transporter in the brain. APOE proteins play a central role in the regulation of cholesterol and triglyceride metabolism. They are also present in amyloid plaques. In 25% of LOAD patients, there is at least one affected relative in the family (Ritchie & Lovestone., 2002). In Caucasian populations, 3-fold increased risk of developing AD has been reported for heterozygous APOE e4 and 8-fold risk in homozygous APOE e4 (Roses, 1996). Regional, racial and ethnic differences have been observed in APOE e4 genotype frequency, with lower carrier status estimates in Asian, southern European/Mediterranean communities compared to North American or North European counterparts (Crean et al., 2011). The influence of APOE e4 on AD risk, while applicable between ages 40 and 90 years, diminishes after the age of 70, and varies across ethnic groups (Farrer et al., 1997).

The mechanism for the effects of APOE isoforms on brain damage is unclear although a recent study demonstrated APOEe4 to cause mitochondrial respiratory dysfunction in neuronal cells

through APOEe4 domain interaction. APOEe4, not APOEe3, causes reduced expression of mitochondrial respiratory complexes and perturbed mitochondrial respiratory function in neuronal cells; thus suggesting that the structure of APOEe4 could be a potential therapeutic target for APOEe4-related neurodegeneration (Chen et al., 2010). Other studies have suggested that APOEe4 is a disease modifier exerting its effect on disease risk by influencing age of onset rather than disease risk per se (Serretti et al., 2007). In this hypothesis, APOEe4 genotype modulates disease risk likely by its effect on earlier amyloid β accumulation.

While APOEe4 status exerts a modulatory effect on disease trajectory and clinical expression of disease, it has not been consistently shown to predict MCI-converters (Jack et al., 1999; Killiany et al.,2002; Korf et al.,2004 ; Martins et al, 2006; Okonkwo et al., 2010; Petersen et al., 2005; Wang et al., 2011). A recent study showed APOE subjects to have 6 times increased risk of MCI conversion to AD (Barabash et al., 2009). The role of APOEe4 genotype in cholesterol metabolism and Aβ clearance and interactions in vascular risk factors is becoming increasingly recognized (Martins et al., 2006). Midlife high systolic blood pressure has a stronger adverse effect on cognitive function in the presence of APOEe4 genotype (Peila et al., 2001). Histopathologic data suggest an association between APOEe4 and small vessel arteriolosclerosis and microinfarcts of the deep nuclei (Yip et al., 2005).

In cognitively normal individuals, APOEe2 carriers have slower rate of hippocampal atrophy over 2 years than individuals with e3/3. The e2 carriers also have higher CSF β-amyloid (Chiang et al., 2010; Morris et al., 2010) and lower phosphorylated-tau (p-tau) (Chiang et al., 2010) suggesting less AD pathology. Morris also showed a gene dose effect for the APOE genotype, with greater mean cortical binding potential for Pittsburgh Compound-B binding increases and greater reductions in CSF $A\beta_{42}$ with increased numbers of APOE alleles; with no effect on CSF tau or p-tau_{181} (Morris et al., 2010). These findings are also supported by the Alzheimer Disease Neuroimaging Initiative study (Vemuri et al., 2010). Mosconi et al has also shown that normal APOEe4 carriers with subjective memory complaints have decreased cerebral metabolic rates for glucose (CMRglc) on 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) (Mosconi L et al., 2008).

Apart from its effects on clinical progression in at-risk individuals, there have also been studies on APOE polymorphism in Alzheimer's disease patients and neuropsychiatric symptoms. APOEe4 AD subjects have been found to be associated with more depressive symptoms and apathy (D'Onofrio et al., 2010; Fritze et al., 2010). However this association has been inconsistent (Slifer et al., 2009).

The relationship of APOE genotype with brain function is complex. The APOEe4 carrier state is likely to increase the brain's vulnerability to late-life pathology or cognitive decline (Filippinin et al., 2009). APOE also has been postulated to interact with other factors, such as homocysteine (Minagawa et al., 2010), smoking (Rusanen et al., 2010), testosterone (Panizzon et al., 2010), and other genetic factors like GAB2 haplotype (Liang et al., 2011) which is possibly protective, These allude to potential gene-gene interactions between APOE and other factors for clinical AD manifestations. APOE as a genetic risk factor is not fully penetrant, and neither necessary nor sufficient for AD development (Ertekin-Taner et al., 2010).

Genetic risk factors are traditionally studied using linkage analysis followed by positional cloning, and association studies. A major drawback is that these hypothesis-driven studies depend on pre-existing knowledge limiting their potential to uncover novel genes and pathways. Over the past decade, a high-throughput hypothesis-free approach - genome-wide association study (GWAS) has taken off. This approach examines genetic variation across an entire genome and is designed to identify whether certain genes or their variants

are skewed to a particular population of individuals affected with disease when compared with a control population. This follows recent advancements in developing microarray platforms that allow researchers to survey the human genome for single base pair differences - single-nucleotide polymorphisms (SNPs) - across many disease cases and unaffected controls. For example, Illumina's Infinium HD Beadchip Human Omni1-Quad® and Human 1MDuo® now have excess of one million markers (www.illumina.com). Affymetrix Genome-Wide Human SNP Array 6.0® is a single array that features more than 1.8 million markers for genetic variation, including more than 900,000 single nucleotide polymorphisms (SNPs) (www.affymetrix.com).

By different gene discovery methods, hundreds of genes have been associated with LOAD but most have not been consistently replicated except for APOEe4 (Betram et al., 2008). Some of the other susceptibility genes reported include ubiquilin 1 (UBQLN1), a presenilin interactor that promotes the accumulation of presenilin 1 protein and regulates its endoproteolysis (Betram et al., 2005); insulin degrading enzyme (IDE), which regulates Aβ42 levels in brain neurons and microglial cells (Farris et al., 2003; Prince et al., 2003); sortilin-related sorting receptor (SORL1), which appears to play a key role in the differential sorting of APP. Under-expression of SORL1 leads to APP release into late endosomal pathways and processed by beta-secretase cleavage and yielding Aβ (Andersen et al., 2007; Rogaeva et al., 2007). A recent study has also shown MTHFD1L association with AD, which might influence homocysteine-related pathways, thus supporting biological evidence of folate-pathway abnormalities as homocysteine has been implicated in AD (Naj et al., 2010). There is also some recent evidence supporting the role of intermediate genotypes in influencing age-related cognitive decline and neuropathologically-proven AD pathology, suggesting divergent pathways to AD (Shulman et al., 2010).

The association studies results can be accessed openly on the AlzGene database - (http://www.alzforum.org/res/com/gen/alzgene) for the most up-to-date information. This is a huge and rapidly growing database of genes and proteins that researchers have found and made available in an open access platform which summarizes results of case-control AD studies across different racial populations. In the recent 2 years, results from large population GWAS studies showed association with the established APOE locus (most significant SNP,rs2075650, P = 1.8 x 10(-157)) as well as observed genome-wide significant association with SNPs at two loci not previously associated with the disease: at the CLU (also known as APOJ) gene on chromosome 8(rs11136000, P = 1.4 x 10(-9)) and 5' to the PICALM gene (rs3851179, P = 1.9 x 10(-8)) (Harold D et al., 2009; Seshadri et al., 2010); rs744373 near BIN1 (odds ratio [OR],1.13; 95% confidence interval [CI],1.06-1.21 per copy of the minor allele; P = 1.59x10(-11)) and rs597668 near EXOC3L2/BLOC1S3/MARK4 (OR, 1.18; 95% CI, 1.07-1.29; P = 6.45x10(-9)) in a separate Spanish sample (Seshadri et al., 2010). Similar results were replicated in a large European study, which showed CLU, (OR = 0.86, 95% CI 0.81-0.90, P = 7.5 x 10(-9) for combined data) and the other within CR1, encoding the complement component (3b/4b) receptor 1, on chromosome 1 (rs6656401, OR = 1.21, 95% CI 1.14-1.29, P = 3.7 x 10(-9) for combined data). Previous biological studies have supported CLU and CR1's role in Abeta peptide clearance (Lambert et al., 2009) and their interactions with APOE genotype (Gyungah et al., 2010). Another gene locus of interest is TOMM40, gene in LD with APOE, which may contribute to APOE correlations with AD risk and age of onset (Roses et al., 2009) (See Table 1). Although genetic associations have been demonstrated, such as CLU and PICALM, in a study by Seshadri, these loci did not improve AD risk prediction (Seshadri et al., 2010).

Year published	Authorship	Source	Initial Number of cases/ controls	Reported Genes
2011	Lee (Lee et al., 2011)	US	549/544	CUGBP2 (APOE4 homozygous), HPCAL1, PCDH21, LRITI, RGR, CLU, PICALM, BIN1
2010	Carrasquillo (Carrasquillo et al., 2010)	US	1829/2576	CLU, CRI, PICALM
2010	Seshadri (Seshadri et al., 2010)	US	10968/14642	APOE
2010	Naj (Naj et al., 2010)	US	931/1104	APOE,TOMM40, MTHFD1L, PVRL2
2009	Heinzen (Heinzen et al., 2010)	US	331/368	TOMM40, APOE, RFC3, TTLL7, PAX2, SASHI
2009	Harold (Harold et al., 2009)	US/ Europe	3941/7848	APOE, TOMM40, CLU, PICALM
2009	Lambert (Lambert et al., 2009)	Europe	2032/528	APOE, CR1, CLU
2009	Carrasquillo (Carrasquillo et al., 2009)	US	844/1255	PCDH11X
2009	Poduslo (Poduslo et al., 2009)*	US	140(family) & 199 (unrelated)/85 (unrelated controls)	TRPC4AP
2009	Feulner (Feulner et al., 2009)	Germany	491/479	TOMM40, APOE
2009	Beecham (Beecham et al., 2009)	US	492/496	FAM113B, ZNF224
2008	Bertram (Bertram et al., 2005) #	US	941/404	CD33
2008	Abraham (Abraham et al., 2008)	UK	1082/1239	PVRL2, TOMM40, APOE

Year published	Authorship	Source	Initial Number of cases/ controls	Reported Genes
2008	Li (Li et al., 2008)	Canada/ UK	753/736	APOE, APOC1
2008	Webster (Webster et al., 2008)	US	664/422	APOE
2007	Reiman (Reiman et al., 2007)	US/ Netherlands	415/260	GAB2
2007	Coon (Coon et al., 2007)	US/Netherlands	664/422	APOE
2007	Grupe (Grupe et al., 2007)	UK/US	1428/1666	GALP, THNK1, chr14q32.13, PCK1, LMNA, PGBD1, LOC651924, chr7p152, THEMS, MYH13, CTSS, UBD, BCR, AGC1, TRAK2, EBF3

All case control studies except # (family-based) and * (family-based and case control)

Table 1. Selected recent GWAS studies and genes reported Adapted from the Alzheimer Disease database of the National Human Genome Research Institute, NIH. (www.genome.gov)

Recent findings in an adequately powered study failed to detect evidence for association between common variants in BIN1, CLU, CR1 and PICALM with CSF Aβ42 and ptau-42; This original hypothesis that gene variants might affect risk via an additive effect has yet to be substantiated. The authors concluded that the negative findings might suggest that the rare, rather than common, variations influence the CSF biomarkers and that other complex, non-additive genetic mechanisms, such as gene-gene and gene-environment interactions play major roles (Kauwe et al., 2011).
Copy number variations (CNV) which include segments of DNA ranging from 1kb – several Mb have been postulated to show differences in regional copy number when comparing 2 or more genomes although a recent study did not show any new SNPs of genome-wide significance (Heinzen et al., 2010).

3. From genomes to transcriptomes

Beyond DNA, other sources of variability are related to transcriptional, translational and post-translational modifications all the way to environmental factors. Hence from the study of the collective genotypes of an individual, one logically moves to the study of the genome-wide gene expression products, also called 'transcriptomics'. Here we are not looking only at which genes are present in an individual but which genes are actually transcribed into

messenger RNA (mRNA). While the genome is fixed for an individual, the transcriptome, i.e. the set of mRNAs produced in an individual corresponding to its genome, varies between different tissue types, across the life cycle of the cells, the life cycle of the organism, changes in the internal or external milieu, epigenetic and other factors. Hence the transcriptome reflects the genes that are being actively expressed in the tissue or cell type under study at one point in time. Transcriptomics usually employs high-throughput techniques based on oligonucleotide microarray technology platforms. For example Illumina's Whole-genome expression HT-12 v4.0 beadchip® targets more than 28,000 coding transcripts with well-established annotations derived from the RefSeq and the UniGene databases (www.illumina.com). Another one commonly used is the Affymetrix GeneChip Human Genome U133 Plus 2.0 Array® (www.affymetrix.com).

An example of a transcriptomic study would be comparing the mRNA levels between samples obtained from AD patients versus healthy controls. Significant differences in mRNA levels would imply that the genes are expressed to different degrees and this may lead downstream to different levels of protein translation and several steps further into disease phenotypes.

The first area of interest is whether the findings from transcriptomics correspond to those obtained from classical genetics or GWAS, for example, with reference to APOEe4, APP, PSEN1, PSEN2. A seminal study by Liang and coworkers demonstrated how different regions of the brain have different expression profiles by analyzing six anatomically discrete postmortem brain regions – entorhinal cortex, hippocampus, middle temporal, posterior cingulate, superior frontal gyri and primary visual cortex, comparing AD patients with normal controls (Liang et al., 2008). They showed a correlation between their findings with those obtained by other investigators using genotyping and GWAS. They found altered expression of factors previously implicated in AD pathogenesis, including APP, PSEN1, SORL1, and BACE1. APP gene expression was markedly increased in the hippocampus, medial temporal, posterior cingulated gyri and visual cortex in AD subjects whereas BACE1 displayed decreased expression in entorhinal cortex, medial temporal gyrus and hippocampus. They also found decreased expression for microtubule associated protein tau (MAPT) and decreased expression for alpha and beta tubulin proteins (which form the building blocks of microtubules) in entorhinal cortex, hippocampus, medial temporal and posterior cingulated gyri. These observations may help in explaining the relationship between NFTs and amyloid plaques.

Other investigators have focused on specific regions of the brain. Studying specifically the neocortex, Tan and co-workers found evidence of synaptic dysfunction, disturbed neurotransmission and activation of neuroinflammation in AD subjects when compared to normal controls (Tan et al., 2010). In a case control study of 22 AD subjects and 9 normal controls, Blalock examined gene expression patterns in the hippocampus and found up-regulation of many transcription factor/signaling genes regulating proliferation and differentiation, including tumor suppressors, oligodendrocyte growth factors and protein kinase A modulators. In addition, there was up-regulation of adhesion, apopotosis, lipid metabolism and initial inflammation processes. Protein folding/metabolism and signaling pathways were conversely down-regulated (Blalock et al., 2004).

To overcome the limitations of gene expression profiling due to the substantial intra-individual regional brain differences and inter-individual heterogeneity, Dunckley compared the gene expression profiles of three groups: (1) neurofibrillary tangle-bearing entorhinal cortex neurons from 19 AD patients with (2) adjacent non-tangle bearing neurons from the same patients and (3) histologically normal non-AD controls. 225 genes showed

progressively increased and decreased expression in the 3 groups. Not unexpectedly many of the genes coded for proteins implicated in NFT formation, especially in the early stages of formation (Dunckley et al., 2006).

Another approach employed was to correlate gene expression profiles according to histological staging of AD. Bossers and co-workers correlated changes in gene expression to the progression of AD in prefrontal cortex brain samples from 49 patients using the standard Braak histopathological system of staging post mortem brain tissue samples for neurofibrillary changes as an objective indicator of AD progression et al (Bossers et al., 2010). The Braak stages range from I to VI, with an additional Stage 0 referring to the absence of neurofibrillary change. They found 2 distinct patterns of tightly co-regulated groups of genes. Firstly, there was an increase in the expression of genes involved in synaptic activity and changes in the plasticity during the early Braak stages. However, the expression of this same group of genes was reduced in the later Braak stages. There was also an increase in intracellular amyloid beta staining from Braak Stages I to II but a decrease in Braak stages IV to VI. For the genes up-regulated in the early Braak stages, there were several genes involved in amyloid precursor protein processing and beta amyloid clearance. The authors thus suggested that the temporally correlated upregulation of synaptic genes activity represents a compensatory mechanism against increased soluble amyloid beta (Aβ) levels, and that this could possibly be a good place to identify new targets of anti-dementia drug development.

The most important factor in transcriptomics and also the downstream 'omic's is the tissue of study. Human brain tissue for analysis can only be obtained post-mortem and sampled only once. This tissue usually reflects a late-stage disease unless an AD subject had died of another cause early in the disease. Moreover RNA quality and quantity are highly dependent on the pre and post-mortem conditions and around tissue harvesting. The other major concern is the region of sampling as the brain is anatomically and histologically extremely heterogeneous. The choice of which anatomical brain region to study, gray versus white matter, neocortex versus archicortex greatly influences the results. Therefore much transcriptomic research endeavor has been directed towards blood. Blood is readily available and can be re-sampled repeatedly, allowing for longitudinal assessment of gene dysregulation at different disease stages. This could assist in making diagnoses, tracking the disease course and evaluation of disease altering interventions. Blood derived nuclear material is by no means a direct proxy for neuronal tissue, but it may reflect certain aspects of the CNS milieu, or systemic manifestations of the underlying disease. More importantly they can serve as peripheral biomarkers of disease. Gene expression profiling of peripheral blood has been shown to provide distinctive profiles for a few neurological conditions (Tang Y et al., 2001, 2003). Similarly psychiatric disorders were also found to have unique gene expression signatures (Tsuang et al. , 2005). Nevertheless extrapolating blood-derived data to the brain tissue still poses major challenges. In transcriptomic studies, due to the large numbers of genes in the genome that are differentially expressed, the up or down-regulated genes may be implicated as potentially casually related to AD pathology, downstream consequences of the disorder, reflect compensatory mechanisms, or found simply by chance alone. This type-one error is likely by virtue of the large number of genes sampled.

Probably the first major publication on the blood-derived gene expression for AD was by Maes and his co-workers who studied the expression profiling of blood mononuclear cells of AD subjects versus normal controls (Maes et al., 2008). They reported that 28% of the upregulated genes and 16% of the downregulated genes have been previously reported to

exhibit similar expression patterns in AD brain, whereas only 4% of affected genes were divergent in terms of expression between blood and brain. This comparison is important as it suggested the systemic nature of altered gene expression in AD and demonstrated the usefulness of blood as putative probes of CNS dysfunction. After comparing over 6000 genes, they found a significant decline in gene expression in the pathways of cytoskeletal maintenance, cellular trafficking, cellular stress response, redox homeostasis, transcription and DNA repair (Maes et al., 2007). Moreover they reported that the majority of upregulated transcripts function in apoptotic and inflammatory pathways, including those involved in TNF alpha signaling and caspase pathways. Using whole blood samples of AD patients versus normal controls, Grunblatt et al found that five out of 33 genes were differentially expressed and showed significant correlation to the severity of AD (Grunblatt et al., 2009).

More recently, Booij et al developed a 96-gene microarray using blood samples from a large clinical cohort of 203 probable AD patients and 209 cognitively healthy age-matched controls and has patented it for commercial use, specifically for detection of early AD - ADtect® by DiaGenic ASA based in Oslo, Norway (www.diagenic.com). A disease classification algorithm was developed on samples from 208 individuals (AD = 103; controls = 105) and was validated in two steps using an independent initial test set (n = 74; AD= 32; controls = 42) and another second test set (n = 130; AD= 68; controls = 62). In the initial analysis, diagnostic accuracy was 71.6±10.3%, with sensitivity 71.9±15.6% and specificity 71.4±13.7%. (Booij et al., 2010; Rye et al., 2010).

In summary, the transcriptomic studies regardless of tissue of origin, has yielded a large number of genes and putative mechanisms and pathways, including the 'usual suspects' as outlined previously. However no simple conclusions can be arrived at from this approach at this time. The fragmented and sometime incongruous lists of pathways and mechanisms attest to the heterogeneous nature of AD and await further replication and confirmation. Furthermore, most of the transcriptomic studies have focused on neuroanatomical and histological stages of AD. The current lack of longitudinal data and translation of genetic correlations to neuroimaging changes limits its role to a primarily investigative exploration of AD pathogenesis.

4. The other 'Omics'

Looking further downstream, although microarray studies can reveal the relative amounts of different mRNAs in the cell, levels of mRNA per se are not directly proportional to the level of the proteins they code for nor the eventual protein configuration. Each protein first arises as an unfolded polypeptide when translated from mRNA to a linear chain of amino acids. The amino acids interact with each other to produce complex three dimensional structures, and their folding configuration is essential to protein function. The complete protein complement of a cell, including protein structures is now referred to as the proteome. Proteomics refer to the study of the plethora of proteins across the whole organism and is one step closer to the phenotype (Simonsen et al., 2007).

Like transcriptomics, proteomics is usually applied to compare the differences in abundances of proteins between diseased and normal subjects. The technologies involved in proteomics are very complex and beyond the scope of this review. Proteomic discoveries are limited thus far but more would be expected in the next few years. The proteomic techniques have been applied to discover biomarkers for AD in CSF but the results thus far are inconclusive. Simonsen et al found a 17-protein biomarker using cerebrospinal fluid

samples to predict the progression from mild cognitive impairment to AD in a sample of 113 patients (Papassotiropoulos et al., 2006). German et al. reported finding three discriminating peaks in common but these peaks still await identification of the proteins and peptides (German et al. , 2007). Portelius proposed that targeted proteomics on Aβ may provide novel assays for biomarkers for AD (Portelius et al., 2008). Investigating the proteome of the hippocampus, Sultana and her co-workers employed 2-dimensional gel electrophoresis and mass spectrometry to determine the changes in protein levels in AD and controls (Sultana et al. , 2007). They identified 18 proteins with altered protein levels and which were involved in regulating different cellular functions. This study gives preliminary data on the levels of key proteins in the AD brain. A comprehensive review of the state of the art of proteomics in AD has been published by Zellner (Zellner et al., 2009).

As a corollary to proteomics, metabolomics is the global approach to understanding regulation of metabolic pathways and metabolic networks (Kaddurah-Daouk et al., 2009). This involves the study of the complete set of small-molecule metabolite, such as metabolic intermediates, hormones, other signaling molecules, and secondary metabolites. The metabolome is dynamic, changing from minute to minute and provides a snapshot of the physiology of the cell. It is not currently possible to analyze the entire range of metabolites by a single analytical method. Kaddurah-Daouk compared samples from post-mortem ventricular cerebrospinal fluid of 15 AD with 15 non-demented subjects and identified alterations in tyrosine, tryptophan, purine and tocopherol pathways in patients in AD (Kaddurah-Daouk et al., 2010). She also noted a reduction in norepinephrine and its related metabolites. Barba and co-authors published a useful review of the rationale and methodology of metabolomics in AD (Barba et al., 2008). The applications for metabolomic analysis in AD is still in infancy but will emerge as a powerful tool in CNS research, as it complements data derived from the other 'omics' to assist in providing a systems approach to the study of human health and disease.

Epigenetics refer to molecular and cellular effects on gene expression without a change in the DNA sequence. These effects include DNA methylation, histone modification and RNA mediated gene silencing. Epigenomics is the genomic-wide study of epigenetic effects. While all nucleated cells in an individual contain the same genome, they contain very different epigenomes depending on tissue type, developmental stage, environmental influences and other parameters (Murrell et al., 2005; Stamatoyannopoulos et al., 2008). These affect the individual presently and can be transmitted into the next generation without a change in the underlying DNA code. Epigenetic contribution is vital to achieve either stable expression or repression of genes at various stages of development (Chouliaras et al., 2010; Wu et al., 2008).

DNA methylation is currently one of the most studied modification and is accomplished through DNA methyltransferases, which transfer a methyl group to the cystosine of CpG dinucleotides. The cystosine DNA-methyltransferase genes play a critical role in the establishment of transcriptionally repressive complexes. It plays an important role in gene silencing and regulating gene expression. Epigenetic mechanisms are dynamic and changeable even in fully differentiated brain cells. Among the various epigenetic mechanisms, histone acetylation and phosphorylation can open up the chromatin structure and may favor gene transcription. DNA methylation is more often associated with increased condensation of chromatin and gene silencing. However the effects of such epigenetic mechanisms may be gene dependent (Gräff et al., 2009).

In investigating LOAD, Wang and his co-workers proposed that epigenetic contribution in the development of the disease could be inferred from several observations (Wang et al., 2008). These include the fact that sporadic cases of AD dominate over familial ones; a concordance rate of monozygotic twins well below 100%; differential susceptibility and course of illness in males and females; parent-of-origin effect; and relatively late age of disease onset. In AD brain they found aberrant histone modifications and abnormal folate (Coppede et al., 2010) and homocysteine levels, which were indicative of abnormal methylation homeostasis and epigenetic dysregulation. Even for EOAD, the difference in penetrance and expressivity can be attributed in part to epigenetic phenomenon. They argued that the epigenome is particularly susceptible to dysregulation during embryonic and neonatal development, puberty and old age. When studying DNA methylation patterns on a series of candidate genes in postmortem brains and lymphocytes from LOAD patients versus healthy controls, they further found that the largest inter-individual variance in DNA was observed in PSEN1 and APOE promoters and postulated that hypomethylation of PSEN1 promoter could induce an overexpression of PSEN1. They also found that there were substantial differences in the epigenetic profiles between old monozygotic twins that can be attributed to one's environmental exposure, lifestyle, diet, or merely stochastic fluctuations. They reported that the strongest age-effects were detected in NCSTN gene that codes for nicastrin, which participates in the regulation of gamma-secretase cleavage of the APP. Hence they hypothesized that neuronal tissue in the AD brain may be prone to collecting epimutations with time due to their post-mitotic state, as opposed to cells which are constantly being renewed.

Mastroeni and co-workers studied the immunoreactivity for two markers of DNA methylation and eight methylation maintenance factors in the entorhinal cortex layer II, a region that has been implicated in the histopathology of AD (Mastroeni et al., 2010). They demonstrated neuronal immunoreactivity for all 10 of the epigenetic markers and factors, with significant decrements in AD cases. These decrements were particularly marked in certain neurofibrillary tangle-bearing neurons. In addition, two of the DNA methylation maintenance factors were decreased in AD subjects. Hence they concluded that epigenetic dysfunction occurred in AD-vulnerable neurons.

5. Clinical applications of the 'Omics'

The involvement of genetic approaches in the diagnosis, risk prediction of AD in the established and at-risk (pre-dementia) states includes its use in combination with clinical parameters and biomarker supplementation (Crunchaga et al., 2010). Another potential application is based on quantitative endophenotype data to provide greater statistical power for subject inclusion in clinical therapeutic trials via genetics-imaging approaches. This later approach has been adopted by the US NIH Alzheimer's Disease Neuroimaging Initiative (ADNI) and European Union FP6-funded AddNeuroMed study (Mueller SG, 2005) (Lovestone et al., 2007; Shen et al., 2010). Specific loci such as PICALM has been shown to be the most significant gene associated with entorhinal cortical thickness (Biffi et al., 2010). Over-representation of rs10845840, located in the GRIN2B gene, which encodes the N-methyl-d-aspartate (NMDA) glutamate receptor NR2B subunit has been found to be associated with lower temporal lobe volume (Stein et al., 2010). Distinct variants of SORL1 has been demonstrated to be associated with cerebrovascular and neurodegenerative

changes related to AD (Cuenco et al., 2008); and APOE and TOMM40 with multiple brain regions (Shen et al., 2010).

APOE genotype has also been shown to be associated with increased blood oxygen level-dependent (BOLD) signal on functional magnetic resonance imaging (fMRI) in the occipital and perisylvian cortices bilaterally. More work needs to be done looking at the paradigm, family history and age to further interpret the BOLD differences between e4 carriers and non-carrier states, which might provide information on default modal networks involved in AD (Ringman et al., 1993; Trachtenberg et al., 2010).

The effects of genetics on therapeutic response to AD are potentially via the use of genomic information for the selection of at-risk groups as well as genetic influences on treatment efficacy and complications in the burgeoning field of pharmacogenomics. In particular, it has been shown that those with APOEe4 genotype do better on donepezil during the initial 1-year period (Petersen et al., 2005); but fair less well during the phase II trial of rosiglitazone (Risner et al., 2006) (peroxisome proliferator-activated receptor γ agonist), and the higher incidence of reversible vasogenic edema when treated with bapineuzumab (Kaufer et al., 2009). There is also some epidemiological rationale for the use of curcuminoids in AD which may be explained by the enhanced phagocytosis of Aβ via upregulation of transcription of specific genes (MGAT3) and translation of TLR2-4 (Fiala et al., 2007).

The main utility of GWAS currently lies in its potential in their hypothesis-generating nature to understand the pathophysiological pathways and ability to correct for population stratifications using principal component adjustments in homogenous populations, especially when low levels of increased risks are involved. Although there are current studies proposing the use of a 96-gene expression array (using blood RNA) for early AD diagnosis (Booij et al., 2010; Rye et al., 2010), the clinical accuracy is modest, estimated at 80%, and comparable to current clinical assessment methods.

While the idea of a diagnostic gene test kit to diagnose early AD is appealing, we have to be mindful of the diagnosis in asymptomatic at-risk individuals, given the current lack of concrete benefit of disease-modifying treatments and the modest benefits conferred by cognitive enhancers (Caselli et al., 2010). There are also concerns about the amount of age-related AD-like pathology one would accept as normal before offering potentially useful but yet unproven treatment strategies, which might promote 'cognitive hypochondriasis'. An example would be the controversial "Alzheimer's Mirror" genetic test developed by Smart Genetics, a Philadelphia company, which developed test kit for APOE variants and ceased operations 8 months after initial launch (Erika et al., 2008).

6. Limitations of methods and works in progress

Foremost is the absence of a time axis as most studies are based on a snapshot. While this is not vital in DNA studies, it is very relevant for transcriptomic, proteomic, metabolomics, epigenomic and most imaging studies. As mentioned previously, human tissue derived from postmortem specimens largely reflects advanced or terminal stage of disease and the quality of the tissue is dependent on the agonal and postmortem conditions. CSF and blood can only be a proxy of the intracerebral condition. However sampling CSF and blood allows longitudinal study and repeated sampling. Another major issue is 'spatial'. The brain is not a homogenous tissue and regional differences are significant. Hence whole brain sampling will not reflect regional variation and significant differences may be 'lost in translation'. This

has been somewhat mitigated by microdissection and single-cell sampling. However looking at individual cells or cell types ignores the complex and interconnected nature of brain tissue and function. Other researchers have focused on studying transgenic mice or cell lines as informative proxies. Therefore there is no single best approach, and a combination of approaches, analyzed collectively and stratified according to ethnic variability will likely yield the most meaningful results.

There is currently strong interests in genomics and the various groups, for example the Dominantly Inherited Alzheimer Network (DIAN) (http://www.dian-info.org), which is presently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer's disease. Others include the ADNI Genetics Core and OPAL (Opportunity for Prevention of Alzheimer's) (http://www.opalstudy.org) which are recruiting normal subjects, defined by neuropsychological testing, between 60 and 87 years and genotyped for APOE status and TOMM40 '523 polymorphisms. Then, based on their age and TOMM40 status, they will either fall into the high-risk or low-risk category for developing Alzheimer's in the next five years with potential therapeutic drug administered.

7. Conclusions

In recent years, there has been much progress made in the recent high throughput technologies that has led to a better understanding of AD. Mutations in the genes APP, PSEN1 and PSEN2 in autosomal dominant inheritance patterns in EOAD are fairly well established. For LOAD, with an estimated heritability of around 60%, the principal susceptibility gene remains APOEe4 with several others, which play much lesser roles. There is evidence for APOE gene profiling for prospective epidemiological study research and pharmacogenetics in identifying high-risk individuals as well as the potential response to current therapeutic agent with calls for APOEe4 genotype to be a covariate for AD clinical trials in view of its modulatory effect on disease progression (Farlow et al., 2010). Broader genetic profiling via GWAS approach very recently has identified susceptibility at-risk genes. However, the individual effects of these identified gene loci are individually small but may identify genes for further functional investigation.

The endeavors in gene expression, proteomics and metabolomics, all downstream from genomics, are relatively early in their development and the results are very preliminary. This is in part due to the limitations of the technology and the tremendous challenges posed by analyzing huge datasets with current bioinformatic and computational biology capabilities. Epigenomics is another burgeoning area of tremendous promise. It runs parallel to genomics for it affects gene transcription and translation in ways beyond the actual DNA code. Extraneous and environmental factors can affect the epigenetic modifications. While DNA methylation and histone modifications are better understood, a far larger scope of epigenomics lies in the near horizon. Integrative approaches to complex multi-gene interaction and epigenetic effects using sophisticated algorithms have begun and would likely yield more robust results. However, the current state of genomics in diagnostics, risk prediction and potential inclusion in therapeutic trials still favor the established APOE given the demonstration of modulatory effect even in the preclinical stages of disease. The unfulfilled potential of these other high throughput platforms lie mainly in the lack of longitudinal data reflecting change as well as correlations with a more 'measurable' structural and functional brain measure, limiting its current role to a purely investigative one.

Moving forward, large scale collaborative efforts across high throughput technologies are required to understand the role of amyloid, lipid homeostasis and chronic inflammation in AD pathogenesis as well as therapeutic interventions directed at these various proposed pathways.

There is a need for diagnostic-therapeutic co-development approach especially in complex disorders such as AD to create diagnostic and prognostic algorithms via a multi-modal approach together with clinical and biomarker supplementation. This will lead to eventually fulfill the role of genomics in predictive, preventive and personalized medicine. In anticipation of this, a recent GRIPS (Genetic Risk Prediction Studies) Statement recommendation has also been published to enhance transparency of study reporting, and thereby improve the synthesis and application of multiple studies which may differ in terms of study design, protocol and analytical methods (Janssens et al., 2011).

8. References

Abraham R, Moskvina V, Sims R, et al. (2008) A genome-wide association study for late-onset Alzheimer's disease using DNA pooling. *BMC Med Genomics*; 1:44.

American Psychiatric Association. (2000) Diagnostic and statistical manual of mental disorders (IV-TR) 4th edn – text revision. Washington, DC.

Andersen OM, Willnow TE, Graff-Radford N, et al. (2007) The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat Genet*. Feb; 39 (2): 168-77.

Barabash A et al. Neurobiology Aging (2009); 30:1254-64. APOE, ACT and CHRNA7 genes in the conversion from amnestic MCI to AD. *Neurobiology Aging*; 30:1254-64.

Barba I, Fernandez-Montesinos R, Garcia-Dorado D, et al. (2008) Alzheimer's Disease beyond the genomic era:nuclear magnetic resonance (NMR) spectroscopy-based metabolomics. *J cell Mol Med* 12(5A): 1477-85.

Beach T, Leung D, Bryden L, et al. (2008) Sorl1 as an Alzheimer's disease predisposition gene? *Neurodegener Dis.,* 5(2):60-4.

Beecham GW, Martin ER, Li YJ, et al. (2009) Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Genet*, 84:35-43.

Bergem AL, Engedal K, Kringlen E. (1997) The role of heredity in late-onset Alzheimer disease and vascular dementia. A twin study. *Arch Gen Psychiatry*, 54: 264-70.

Bergem AL, Lannfelt L. (1997) Apolipoprotein E type epsilon4 allele, heritability and age at onset in twins with Alzheimer disease and vascular dementia. *Clin Genet*, Nov; 52(5): 408-13.

Bertram L, Hilunen M, Parkinson M, et al. (2005) Family-based association between Alzheimer's disease and variants in UBQLN1. *N Engl J Med* 352: 884-894.

Betram L, Lange C, Mullin K, et al. (2008) Genome-wide association analysis revelas putative Alzheimer's disease susceptibility loci in addition to APOE. *Am J Hum Genet*, 83:623-32.

Biffi A, Anderson CD, Desikan RS et al. (2010) Genetic variation and Neuroimaging Measures in Alzheimer Disease. *Arch Neurol*, 67(6):677-85.

Blalock EM, Geddes JW, Chen KC, et al. (2004) Incipient Alzheimer's disease: Microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *PNAS*, 101(7):2173-2178.

Booij BB, Lindahl T, Wetterberg P, et al. (2011) A gene expression pattern in blood for the early detection of Alzheimer's Disease 23:1-11. *J Alzheimers Dis.* Jan 1;23(1):109-19.

Bossers K, Wirz KTS, Meerhoff GF, et al. (2010) Concerted Changes in Transcripts in the Prefrontal Cortex Precede Neuropathology in Alzheimer's Disease. *Brain* 133: 3699-3723.

Carrasquillo MM, Belbin O, Hunter TA, et al. (2010) Replication of CLU, CR1, and PICALM associations with alzheimer disease. *Arch Neurol.* Aug; 67(8):961-4. Epub Jun 14.

Carrasquillo MM, Zou F, Pankratz VS, et al. (2009) Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer disease. *Nat Gent,* 41:192-8.

Caselli RC, Dueck AC. (2010) APOE ε 2 and presymptomatic stage Alzheimer disease. *Neurology*, 75:1952-3.

Chen HK, Ji ZS, Dodson SE, et al (2011) Apolipoprotein E4 Domain Interaction mediates detrimental effects on Mitochondria and is a potential Therapeutic target for Alzheimer's disease. *J Biol Chem*. Feb 18; 286(7):5215-21.

Chiang GC, Insel PS, Tosun D, et al. (2010) Hippocampal atrophy rates and CSF biomarkers in elderly APOE2 normal subjcts. *Neurology*; 75:1976-81.

Chouliaras L, Sierksma ASR, Kenis G et al. (2010) Gene-Environment Interaction Research and Transgenic Mouse Modles of Alzheimer's disease. *Int J Alz Dis.* Oct 5.

Coon KD, Myers AJ, Craig DW, Webster JA et al. (2007) A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. *J Clin Psychiatry*; 68:613-18.

Coppede F. (2010) One-Carbon Metabolism and Alzheimer's disease: Focus on Epigenetics. *Curr Genomics*; 11:246-60.

Crean S, Ward A, Mercaldi CJ, et al. (2011) Apolipoprotein E ε4 prevalence in Alzheimer's disease patients varies across global populations: A Systematic Literative Review and Meta-Analysis. *Dement Geriatr Cogn Disord*; 31;20-30.

Crunchaga C, Kauwe JSK, Mayo, et al. (2010) SNPs associated with cerebrospinal fluid phospho-tau levels influence rate of decline in Alzheimer's disease. *PLOS*; 6(9): e1001101.

Cuenco KT, Lunetta KL, Clinton T, et al. (2008) Association of distinct variants in SORL1 with cerebrovascular and neurodegenerative changes related to Alzheimer disease. Arch Neurol; 65:1640-8.

D'Onofrio G, Panza F, Seripa D, et al. (2010) The APOE polymorphism in Alzheimer's disease patients with neuropsychiatric symptoms and syndromes. *Int J Geriatr Psychiatry.* Oct 29.

Dubois B, Feldman HH, Jacova C, et al. (2007) Research criteria for diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*; 6:734-46.

Dunckley T, Beach TG, Ramsey KE, et al. (2006) Gene expression correlates of neurofibrillary tangles in AD. *Neurobiol Aging*. 27(10):1359-1371.

Ertekin-Taner N. (2010) Genetics of Alzheimer's disease in the pre- and post-GWAS era. *Alz Res Therapy*, 2:3.

Farlow MR. (2010) Should the ApoE genotype be a covariate for clinical trials in Alzheimer disease? *Alz Res Ther*; 2:15.

Farrer LA, Cupples LA, Haines JL, et al. (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *JAMA*; 278: 1349-1356.

Farris W, Mansourian S, Chang Y, et al. (2003) Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci USA* 100: 4162-67.

Feulner TM, Laws SM, Friedrich P, et al. (2009) Examination of the current top candidate genes for AD in a genome-wide association study. *Mol Psychiatry*, Jan 6.

Fiala M, Liu PT, Espinosa-Jeffrey A, et al. (2007) Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. *Proc Natl Acad Sci U S A*. Jul 31;104(31):12849-54.

Filippinin N, Ebmeir KP, Macintosh BJ, et al. (2011) Differential effects of the APOE genotype on brain function across lifespan. *Neuroimage*; 54:602-610.

Fritze F, Ehrt U, Sonnesyn H, et al. (2010) Depression in mild dementia: associations with diagnosis, APOE genotype and clinical features. *Int J Geriatr Psychiatry.* Oct 28.

German DC, Gurnani P, Nandi A, et al. (2007) Serum biomarkers for Alzheimer's disease: proteomic discovery. *Biomed Pharmacother*. Aug; 61(7): 383-9.

Gräff J, Mansuy IM. (2009) Epigenetic dysregulation in cognitive disorders. *European Journal of Neuroscience* pp. 1-8.

Grunblatt E, Bartl J, Zehetmayer, et al. (2009) Gene expression as peripheral biomarkers for sporadic Alzheimer's Disease. *J Alzheimer's Disease*, 16:627-634.

Grupe A, Abraham , Li Y, et al. (2007) Evidence for novel susceptibility genes for late-onset Alzheimer's disease from a genome-wide association study of putative functional variants. *Hum Mol Genet.* Apr 15;16(8):865-73.

Gyungah J et al. (2010) Meta-analysis confirms CR1, CLU and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotype. *Arch Neurol.* Dec;67(12):1473-84.

Harold D et al. (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. Oct; 41(10): 1088-93.

Hayden EC. (2008) Alzheimer's tests under fire. *Nature*; 455:1155.

Heinzen EL Need AC, Hayden KM, et al. (2010) Genome-wide scan of copy number variation in late-onset Alzheimer's disease. *J Alzheimers Dis*. 19(1):69-77.

Lee JH, Cheng R, Barral S (2011) Identification of Novel Loci for Alzheimer Disease and Replication of CLU, PICALM, and BIN1 in Caribbean Hispanic Individuals. *Arch Neurol*. Mar;68(3):320-8.

Jack CR, Knowpman DS, Jagust WJ, et al. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 9:119-28.

Jack CR, Peterson RC, Xu XC, et al. (1999) Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*; 52:1397-1403.

Janssens ACJW, Ioannidis JPA, van Duijin CM, et al. (2011) Strengthening the Reporting of Genetic Risk Prediction Studies: The GRIPS Statement. *Ann Intern Med;* 154:421-5.

Kaddurah-Daouk R, Krishnan KR. (2009) Metabolomics: a global biochemical approach to the study of central nervous system diseases. *Neuropsychopharmacology*. Jan; 34(1):173-86.

Kaddurah-Daouk R, Rozen S, Matson W, et al. (2010) Metabolomic Changes in autopsyconfirmed Alzheimer's Disease. *Alzheimers Dement*. Nov 12.

Kaufer D, Gandy S.(2009) APOE e4 and bapineuzumab: infusing pharmacogenomics into Alzheimer disease therapeutics. *Neurology*; 73:2052-3.

Kauwe JSK, Cruchaga C, Karch CM, et al. (2011) Fine Mapping of Genetic Variations in BIN1, CLU, CR1 and PICALM for Association with Cerebrospinal fluid biomarkers for Alzheimer's disease. *PLoS One*. Feb 9;6(2):e15918.

Kazee AM, Eskin TA, Laphan LW, et al. (1993) Clinicopathological correlates in Alzheimer disease: assessment of clinical and pathologic diagnostic criteria. *Alzheimer Dis Assoc Disord*, 7:152-64.

Killiany RJ, Gomez-Isla T, Moss M, et al. (2000) Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Ann Neurol*; 47: 430-439.

Killiany RJ, Hyman BT, Gomez-Isla T, et al. (2002) MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology*; 58:1188-96.

Korf ESC, Wahlund L-O, Visser PJ, et al. (2004) Medial Temporal Lobe Atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology*, 63:94-100.

Kupfer DJ, Regier DA. (2010) Why All of Medicine Should Care about DSM-5. *JAMA*; 303(19):1974-5.

Lambert JC, Heath S, Even G. (2009) Genome-wide association study identifies variants at CLU and CR1associated with Alzheimer's disease. *Nat Genet*. Oct; 41(10):1094-9. Epub 2009 Sep 6.

Lee JH, Cheng R, Barral S et al. (2010) Identification of Novel Loci for Alzheimer Disease and Replication of CLU, PICALM, and BIN1 in Caribbean Hispanic Individuals. *Arch Neurol*. 2011 Mar; 68(3):320-8. Epub Nov 8.

Li H, Wetten S, Li L, et al. (2008) Candidate single-nucleotide polymorphisms from a genome wide association study of Alzheimer disease. *Arch neurol*; 65:45-53.

Liang WS, Chen K, Lee W, et al. (2011) Association between GAB2 haplotype and higher glucose metabolism in Alzheimer's disease-affected brain regions in cognitively normal APOEe4 carriers. *Neuroimage*. Feb 1;54(3):1896-902. Epub (2010) Oct 1

Liang WS, Dunckley T, Beach TG, et al. (2008) Altered neuronal gene expression in brain regions differentially affected by Alzheimer's diseases: a reference data set. *Physiol Genomics* 33 240-256.

Lim A, Tsuang D, Kukull W et al. (1999) Clinico-pathological correlation of Alzheimer's disease in a community-based case series. *J Am Geriatr Soc*; 47:564-69.

Lovestone S, Francis P, Strandgaard K. (2007) Biomarkers for disease modification trials - the innovative medicines initiative and Add *NeuroMed.* J Nutr Health Aging; 11; 359-61.

Maes OC, Xu S, Yu B, et al. (2007) Transcriptional profiling of Alzheimer blood mononuclear cells by microarray. *Neurobiol Aging*, 28:1795-1809.

Maes OC, Xu S, Yu B, et al. (2008) Transcriptional profiling of Alzheimer blood mononuclear cells by microarray. *Neurobiology of Aging,* 28 1795-1809.

Martins IJ, Hone E, Foster JK, et al. (2006) Apolipoprotein E, cholesterol metabolism, diabetes and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. *Molecular Psy*; 11:721-36.

Mastroeni D, Grover A, Delvaux E, et al. (2010) Epigenetic Changes in Alzheimer's disease: Decrements in DNA Methylation *Neurobiol Aging* 31(12): 2025-2037.

McKhann G, Drachmann DA, Folstein M, e al. (1984) Clinical diagnosis of Alzheimer's disease – report o the NINCDS-ADRDA workgroup under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*; 34:939-44.

Minagawa H, Watanabe AM, Akatsu H, et al. (2010) Homocysteine, Another Risk Factor for Alzheimer Disease, Impairs Apolipoprotein E3 function. *J Biol Chem*; 285(49):38382-88.

Morris JC, Roe CM, Xiong C, et al. (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol*; 67:122-131.

Morris JC, Storandt M, Miller JP, et al. (2001) Mild cognitive impairment represents early stage Alzheimer's disease. *Arch Neurol*; 58:397-405.

Mosconi L, Brys M, Switalski R, et al. (2007) Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. *Proc Natl Acad Sci U S A*. 2007 Nov 27;104(48):19067-72. Epub, Nov 14.19.

Lin MT, Beal MF. (2006) Alzheimer's APP mangles mitochondria. *Nat Med*. Nov;12(11):1241-3.

Mosconi L, De Santi S, Brys M, et al. (2008) Hypometabolism and altered cerebrospinal fluid markers in normal Apolipoprotein E e4 carriers with subjective memory complaints. *Biol Psy*; 63(3): 609-18.

Mueller SG, Weiner MW, Thal LJ, et al. (2005) Ways towards an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzherimers Dement*; 1:55-66.

Murrell A, Rakyan VK, Beck S. (2005) From genome to epigenome. *Hum Mol Genet*. Apr 15;14 Spec No 1:R3-R10. Review.

Naj AC, Beecham GW, Martin ER, et al. (2010) Dementia Revealed: Novel Chromosome 6 Locus for Late-Onset Alzheimer Disease Provides Genetic Evidence for Folate-Pathway Abnormalities. *PLoS Genet*. Sep 23;6(9). 58.

Shulman JM, Chibnik LB, Aubin C, et al. (2010) Intermediate phenotypes identify Divergent Pathways to Alzheimer's disease. *PLoS One*. Jun 21;5(6):e11244.

Okonkwo OC, Alosco ML, Jerskey BA, et al. (2010) Cerebral atrophy, apolipoprotein E e4, and rate of decline in everyday function among patients with amnestic mild cognitive impairment. *Alz Dement*; 6:404-411.

Panizzon M, Hauger R, Dale Am, et al. (2010) Testosterone modifies the effect of APOE genotype on hippocampal volume in middle-aged men. *Neurology*; 75:874-880.

Pankratz VS, Dickson DW et al. (2010) Replication of CLU, CR1, and PICALM associations with alzheimer disease. *Arch Neurol*. Aug;67(8):961-4.

Papassotiropoulos A, Fountoulakis M, Dunckley T, et al. (2006) Genetics, transcriptomics and proteomics of Alzheimer's disease. *J Clin Psychiatry* 67(4): 652-670.

Peila R, White LR, Petrovich H, et al. (2001) Joint effect of the APOE gene and midlife systolic hypertension on late-life cognitive impairment: The Honolulu-Asia Aging Study. *Stroke*, 32:2882-2889.

Petersen RC, Thomas RG, Grundman et al. (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*, 352:2379-88.

Petersen RC, Thomas RG, Grundman M, et al. (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*, 352: 2379-88.

Peterson RC. (2004) Mild cognitive impairment as a diagnostic entity. *J Int Med*, 256:183–94.

Petrovich H, White LR, Ross GW, et al. (2001) Accuracy of clinical criteria for AD in the Honolulu-Asia Aging Study: a population-based study. *Neurology*, 57:226-34.

Poduslo SE, Huang R, Huang J et al. (2009) Genome screen of late-onset Alzheimer's extended pedigrees identified TRPC4AP by haplotype analysis. *Am J Med Genet B Neuropsychiatr Genet*, 150B:50-5.

Portelius E, Zetterberg H, Gobom J, et al. (2008) Targeted proteomics in Alzheimer's disease: Focus on amyloid-beta. *Expert Rev Proteomics* 5(2): 225-37.

Price JL, Morris JC. (1999) Tangles and plaques in nondemented aging and preclinical Alzheimer disease. *Ann Neurol*, 45:358-68.

Prince JA, Feuk L, Gu HF, et al. (2003) Genetic variation in a haplotype block spanning IDE influence Alzheimer's disease. *Hum Mutat*, 22: 363-71.

Reiman EM, Webster JA, Myers AJ, et al. (2007) GAB2 alleles modify Alzheimer's risk in APOE episilon4 carriers. *Neuron*, 54:713-20.

Ringman JM, Medina LD, Braskie M, et al. (2011) Effects of Risk Genes on BOLD activation in presymptomatic carriers of familial Alzheimer's disease mutations during a novelty encoding task. *Cerebral Cortex*. Apr;21(4):877-83.

Risner ME, Saunders AM, Altman JF, et al. (2006) Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J*, 6 :246-54.

Ritchie K, Lovestone S. (2002) The dementias. *Lancet*. Nov 30; 360 (9347):1759-66.

Rogaeva E, Meng Y, Lee JH, et al. (2007) The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer's disease. *Nat Genet.* Feb; 39(2): 168-77.

Roses AD, Lutz MW, Amrine-Madsen H, et al. (2009) A TOMM40 variable-length polymorphism predicts age of late-onset Alzheimer's disease. *Pharmacogenomics,* 69:1-10.

Roses AD. (1996) Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annu Rev Med*. 47:387-400. Review.

Rusanen M, Rovio S, Gan Du T, et al. (2010) Midlife smoking, apolipoprotein E and risk of dementia and Alzhiemer's disease: A population-based cardiovascular risk factors, aging and dementia study. *Dement Geriatr Disord*, 30:277-284.

Rye PD, Booij BB, Grave G, et al. (2010) A novel blood test for the early detection of Alzheimer's Disease. *J Alzheimer's Disease*, 23:1-9.

Santoro A, Balbi V, Balducci E, et al. (2010) Evidence for Sub-haplogroup h5 of Mitochondrial DNA as a Risk Factor for Late Onset Alzheimer's Disease. *PLoS One,* Aug 6;5(8):e12037.

Serretti A, Olgiati P, Ronchi DD. (2007) Genetics of Alzheimer's disease: A rapidly evolving field. *Journal of Alzheimer's disease*, 73-92.

Seshadri S et al. (2010) Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA*, May 12; 303(18):1832-40.

Shen L, Kim S, Risacher SL, et al. (2010) Alzheimer's Disease Neuroimaging Initiative. Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: A study of the ADNI cohort. *Neuroimage*, 53(3):1051-63.

Simonsen AH, McGuire J, Hansson O, et al. (2007) Novel Panel of Cerebrospinal Fluid Biomarkers for the Prediction of Progression to Alzheimer Dementia in Patients With Mild Cognitive Impairment. *Arch Neurol*, 64(3):366-370.

Slifer MA, Martin ER, Gilbert JR, et al. (2009) Resolving the relationship between Apolipoprotein E and depression. *Neurosci Lett*, 455(2): 116-119.

Stamatoyannopoulos JA, Dunham I. (2008) Epigenomics at the tipping point. *Pharmacogenomics*, 9:12, 1781-83.

Stein JL, Hua X, Morra JH et al. (2010) Genome-wide Analysis reveals novel genes influencing temporal lobe structure with relevance to neurodegeneration in Alzheimer's disease. *Neuroimage*, 51(2): 542-44.

Sultana R, Boyd-Kimball D, Cai J, et al. (2007) Proteomics Analysis of the Alzheimer's Disease Hippocampal Proteome. *JAD*, 11(2): 153-164.

Tan MG, Chua WT, Esiri MM, et al. (2010) Genome wide profiling of altered gene expression in the neocortex of AD. *J Neuroscience Research*, 88:1157-1169.

Tang Y, Lu A, Arnow BJ, et al. (2001)Blood genomic responses differ after stroke, seizures, hypoglycemia and hypoxia: blood genomic fingerprints of disease. *Ann. Neurol*., 50: 699 – 707.

Tang Y, Nee AC, Lu A, et al. (2003) Blood genomic expression profile for neuronal injury. *J. Cereb. Blood Flow Metab*. 23: 310 – 319.

Tanzi RE, Dovacs DM, Kim TW, et al. (1996) The gene defects responsible for familial Alzheimer's disease. *Neurobiol Dis* 3:159-168.

Tanzi RE. (1999) A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorder. *J Clin Invest*, 104:1175-1179.

Trachtenberg AJ, Filippini N, Mackay CE. (2010) The effects of APOE-epsilon4 on the BOLD response. *Neurobiol Aging*. Apr 19.

Tsuang MT, Nossova N, Yager T, et al. (2005) Assessing the validity of blood-based gene expression profiles for the classification of schizophrenia and bipolar disorder: a preliminary report. *Am. J. Med. Genetics* Part B; 133B: 1 - 5.

Varma AR, Snowden JS, Lloyd JJ, et al. (1999) Evaluation of the NINCDS-ADRD criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. *J Neurol Neurosurg Psychiatry*; 66:184-88.

Vemuri P, Wiste HJ, Weigand SD, et al. (2010) Effect of Apolipoprotein E on biomarkers of Amyloid Load and Neuronal Pathology in Alzheimer disease. *Ann Neurol*, 67:308-16.

Wang P, Hong C, Lin K et al. (2011) APOEe4 increases risk of progression from amnestic mild cognitive impairment to Alzheimer's disease among ethnic Chinese in Taiwan. *J Neurol Neurosurg Psychiatri*, 82:165-9.

Wang S, Oelze B, Schumacher A. (2008) Age-specific epigenetic drift in late-onset Alzheimer's disease. *PLoS ONE*, Jul 16:3(7): e2698.

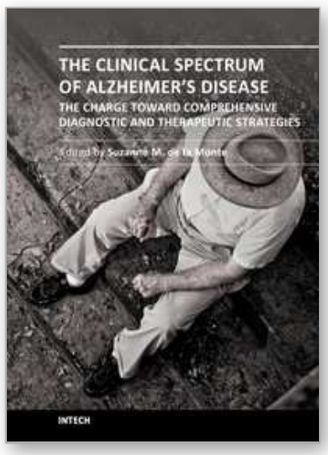
Webster JA, Myers AJ, Pearson JV, et al. (2008) Sorl1 as an Alzheimer's disease predisposition gene? *Neurodegener Dis*; 5(2):60-4.

Wimo A, Winbald B, Aguero Torres H, et al. (2003) The magnitude of dementia occurrencein the world. *Alz Dis Assoc Disord*, 17: 63-67.

Wu J, Basha MR, Zawia NH. (2008) The environment, epigenetics and amyloidogenesis. *J Mol Neurosci*, 34(1): 1-7.

Yip AG, McKee A, Green RC, et al. (2005) APOE, vascular pathology and the AD brain. *Neurology*, 65:259-265.

Zellner M, Veitinger M, Umlauf E. (2009) The Role of Proteomics in Dementia and Alzheimer's Disease. *Acta Neuropathol*, 118: 181-195.



The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

Edited by Dr. Suzanne De La Monte

ISBN 978-953-307-993-6
Hard cover, 362 pages
Publisher InTech
Published online 06, September, 2011
Published in print edition September, 2011

The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Tih-Shih Lee and Mei Sian Chong (2011). Alzheimer’s Disease Genomics and Clinical Applications, The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies, Dr. Suzanne De La Monte (Ed.), ISBN: 978-953-307-993-6, InTech, Available from: http://www.intechopen.com/books/the-clinical-spectrum-of-alzheimer-s-disease-the-charge-toward-comprehensive-diagnostic-and-therapeutic-strategies/alzheimer-s-disease-genomics-and-clinical-applications

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen