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# Genetics of Cognition- What can Developmental Disorders Teach Us?

Berit Kerner, M.D.  
*University of California, Los Angeles  
United States of America*

## 1. Introduction

Unprecedented progress in the field of genetics and genomics has offered the opportunity to explore the human brain to a larger extent than ever before. Especially the acquisition, coding, storage, recall, and decoding of information that form the response to an ever-changing environment are very active areas of research. The sequencing of the entire human genome and the description of inter-individual genomic variations ranging from single base pair changes to large-scale structural variations allow to link individual differences in cognitive ability to genomic changes, therefore advancing our understanding of information processing, storage, learning and memory (Subramanian et al., 2001).

In recent years, a major advancement in cognitive neuroscience in recent years has been the discovery of germline mutations in genes of the ras-induced mitogen-activated protein kinase (RAS/MAPK) signalling cascade, a unique signalling pathway transmitting signals from cell surface receptors to the nucleus with subsequent changes in gene transcription. A group of individuals affected with developmental disorders and variable degrees of cognitive impairment, who shared additional abnormalities in other body systems, have been instrumental to this process (Tidyman & Rauen, 2008; Tidyman & Rauen, 2009). Individuals with Noonan syndrome, LEOPARD syndrome, Costello syndrome, Cardio-Facio-Cutaneous syndrome, and Neurofibromatosis (NF1) have clinical symptoms in a number of body systems, including variable abnormalities in learning and memory. Cardiac malformations, skeletal abnormalities, skin manifestations, an increased risk for cancer, and characteristic facial features are often found in individuals affected with these rare genetic syndromes. Even though each syndrome represents a unique clinical entity that can be differentiated based on the combination of clinical symptoms and disease course, they also share a number of overlapping symptoms suggesting that these syndromes could be causally related disorders. The majority of individuals affected with these syndromes were found to have rare mutations in a variety of genes that could be linked to the RAS/MAPK signalling pathway. The identification of unique mutations in each disorder ultimately shed some light on the pathophysiology of the neuro-cardio-facial-cutaneous syndrome family. These rare Mendelian developmental disorders are instructive example for the successful application of classical genetic linkage studies, positional focused sequencing approaches, and candidate gene approaches in combination with detailed phenotyping that eventually

Source: Cognitive Maps, Book edited by: Karl Perusich,  
ISBN 978-953-307-044-5, pp. 140, January 2010, INTECH, Croatia, downloaded from SCIYO.COM

led to the discovery of a neurophysiological system that might play a key role in cognitive and developmental processes.

Developmental disorders with cognitive disabilities in general are common, affecting about 1-2% of the population; however, the identification of the underlying genetic cause is hindered by the heterogeneity of the disorders. Many different genetic and environmental causes could potentially lead to the rather non-specific symptom of cognitive impairment. Genetic mutations that have been identified in some affected individuals are usually rare and may constitute new changes that have not been inherited from the parents. This makes the identification of underlying genetic factors difficult. Large-scale genetic mapping techniques, such as genome-wide association studies or linkage analysis in a large number of families are impractical under these scenarios. In the neuro-cardio-facio-cutaneous syndromes, it took the careful delineation of the clinical phenotype of the patients, prior knowledge of signalling pathways, and knowledge of genomic variance to link the phenotype to specific genomic variants. Researchers focussing on x-linked mental retardation took a different approach (Tarpey et al., 2009). Direct sequencing of all coding regions on the X chromosome in a heterogeneous group of families, in which mental retardation was inherited in an X-linked mode, led to the discovery of new genes involved in mental retardation. Nevertheless, much more inter-individual genomic variability was discovered than ever expected and a large proportion of this variability was found not to be related to mental retardation.

The progress in the field of mental retardation research can be helpful in understanding what to expect and how to approach other common mental disorders such as schizophrenia and mood disorders. In these conditions progress has been less impressive. Developmental syndromes, non-syndromic mental retardation, and psychiatric disorders share many common features, sometimes even overlapping symptoms. In this article, we will try to explore and compare approaches to brain function in different but intimately related disciplines of research and to open up ways for new approaches to the complexity of the brain. Great progress has been made in understanding the function of the brain and much more will be learned now that direct sequencing of single individuals is within reach as a cost-effective approach to the study of inter-individual genomic variation. However, it also has become clear that an overly simplistic understanding of the relationship between genomic variation and physiological consequences is questionable (Raymond et al., 2009).

## **2. The RAS/MAPK signalling cascade**

The identification of mutations in proteins linked to the RAS/MAPK cascade in individuals with severe impairment of cognitive functions has led to the discovery of a signal pathway that appears to play a central role in cognitive development (Figure 1) (Aoki et al., 2008). Through cascading protein phosphorylations, information is transmitted from the cell surface to the cell nucleus leading to long lasting changes in cell metabolism and cell growth (Hancock, 2003). A key component of the RAS/MAPK signalling pathway is a family of small G-protein coupled molecules known as the RAS kinase family. These molecules, which have been implemented in cancer (Gibbs et al., 1984), transition between two functional states, an inactive form, which is bound to guanine-dinucleotide-phosphate (GDP) and an active form, which is bound to guanine-trinucleotide-phosphate (GTP). The transition between the inactive and the active state is facilitated by guanine-nucleotide-

exchange factors (GEFs), whereas the transition from the active state back to the inactive state is catalyzed through GTPase-stimulating proteins (GAPs). The RAS GTPase activity can be stimulated among others by tyrosine kinase-coupled growth factor receptors. The tyrosine kinase recruits a docking protein, for example growth factor receptor-bound protein 2 (GRB2) or Src-homology-2-containing tyrosine phosphatase (SHP-2), which is the protein product of the gene tyrosine-protein phosphatase non-receptor type 11 (*PTPN11*). The tyrosine kinase/SHP-2 complex subsequently activates the GEF proteins, which then transform RAS from its inactive to its active state. Activation of RAS proteins leads to the recruiting of Raf kinases, for example CRAF, encoded by the gene v-raf-1 murine leukemia viral oncogene homologue 1 (*RAF1*) and v-raf murine sarcoma viral oncogene homologue B1 (*BRAF*) to the membrane. This event leads to the subsequent phosphorylation of the first member of the RAS/MAPK cascade, which starts a phosphorylation cascade of kinases, including the dual specificity mitogen-activated protein kinase kinase 1/2 (MEK1/MEK2), the MAP kinase kinase (MAP2Ks), and the extracellular signal-regulated kinase 1/2 (ERK1/ERK2), also known as MAP kinases (MAPKs). Activated ERK1 and ERK2 phosphorylate both nuclear and cytosolic substrates, connecting the cell surface receptors to nuclear transcription factor complexes and signalling molecules in the cytoplasm (Yoon & Seger, 2006). The ribosomal S6-kinase 2 (RSK2) is one of those proteins that connect the RAS/MAPK cascade to the cAMP response-element (CRE) binding (CREB) protein, a transcriptional regulator. Subsequent changes in gene expression lead to long lasting alterations in cell metabolism, cell growth and mobility. In the brain, alterations in synaptic strength, changes in the electric properties of the cell membrane, increase in the responsiveness to neurotransmitters, and even changes in the number and size of synapses have been observed (Weeber et al., 2002). In addition to tyrosine-kinase bound growth factor receptors, this cascade can also be activated through other mechanisms. Phospholipase C (PLC) and phosphoinositide 3-kinase (PI3K) can activate RAS and provide links to neurotransmitter pathways of metabotropic glutamate receptors, acetylcholine (ACH), and serotonin receptors.

### 3. The neuro-cardio-facio-cutaneous syndrome family

Several excellent recent reviews of the neuro-cardio-facio-cutaneous syndromes and their underlying genetic risk factors have recently been published (Tidyman & Rauen, 2008; Tidyman & Rauen, 2009). Therefore, only a brief overview summarizing the clinical features and mutations found in these syndromes will be given in this text.

#### 3.1 Noonan syndrome

Noonan syndrome (MIM 163950) is an autosomal dominant disorder with characteristic craniofacial features, congenital heart defects, and short stature. Ophthalmological abnormalities, musculoskeletal and cutaneous anomalies are common in these patients as well (Noonan, 1968; Shaw et al, 2007). Impairment in cognitive functions, such as learning and memory, is a variable symptom and occurs only in about 25-30% of individuals with this syndrome (Lee et al., 2005). Genetic linkage studies have mapped this disorder to a region on chromosome 12. Subsequently, mutations in the coding region of the gene *PTPN11*, located on chromosome 12q24.13, were found in patients with Noonan syndrome by positional sequencing of candidate genes in the region (Tartaglia et al., 2001). *PTPN11*

encodes the protein tyrosine phosphatase SHP-2, which is an initiator of the RAS/MAPK signalling cascade (Figure 1). Mutations in *PTPN11* led to structural and functional changes in SHP-2, and therefore, an involvement of the gene in the pathophysiology of Noonan syndrome appeared likely. Soon, however, it became clear that missense mutations in this gene could explain only a portion of the cases clinically diagnosed with Noon syndrome indicating genetic heterogeneity (Tartaglia et al., 2001). Subsequently, mutations in the coding regions of other genes involved in the RAS/MAPK pathway were found. Sequencing of candidate genes identified mutations in the genes son of sevenless homolog 1 (*SOS1*) (Roberts et al., 2007; Tartaglia et al., 2007), v-raf-1 murine leukaemia viral oncogene homolog 1 (*Raf1*) (Pandit et al., 2007; Razzaque et al., 2007), and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) (Schubbert et al., 2006; Zenker et al., 2007). Even though the most frequent genetic cause of Noonan syndrome is a mutation in the gene *PTPN11*, individual mutations are rare and scattered throughout several coding regions of the gene prohibiting a simple predictive genetic test. All known mutations affect the stability of the inactive form of the protein leading to a gain of function and increased signalling activity through the RAS/MAPK phosphorylation cascade. A simple genotype/phenotype correlation has not been feasible. Especially cognitive impairment is variable in this syndrome and not linked to a specific mutation. A recent comparison of patients with mutations in the genes *PTPN11* and *SOS1*, however, indicated that learning disabilities were absent in patients with mutations in *SOS1* (Pierpont et al., 2009), whereas cognitive impairments were common among individuals with *PTPN11* mutations and those with unknown mutation status. In addition to the effect of specific mutations, individual specific genetic background, gene-gene interactions, and compensatory mechanisms might account for the variability in the phenotype (Tartaglia et al., 2002).

### 3.2 LEOPARD syndrome

LEOPARD syndrome (MIM 151100) is an allelic disorder to Noonan syndrome, because it is caused by mutations in the same genes, *PTPN11* and *RAF1* (Digilio et al., 2002; Legius et al., 2002; Pandit et al., 2007). In LEOPARD syndrome the functional consequence of mutations in *PTPN11* is a loss of function instead of the gain of function usually found in Noonan syndrome. LEOPARD syndrome is characterized by cutaneous changes (Lentiginos), EKG abnormalities, ocular abnormalities, pulmonary valve stenosis, abnormal genitalia, retardation of growth, and deafness. The clinical phenotype of the affected individuals is quite similar to Noonan syndrome despite opposite effects of the mutations on the function of the protein.

### 3.3 Costello syndrome

In 1971, Costello described a new genetic syndrome with characteristic facial features, ectodermal anomalies, especially nasal papillomas, and developmental delay (Costello, 1971; Costello, 1977). Subsequently, extensive reviews have summarized findings in similarly affected individuals and have delineated the clinical phenotype now known as Costello syndrome (MIM 218040). Even though this genetic syndrome is clearly distinct from Noonan syndrome, both syndromes share some overlapping features (Hennekam, 2003). Individuals affected with Costello syndrome have more severe cognitive impairment

than individuals affected with Noonan syndrome (Axelrad et al., 2007; Delrue et al., 2003). Search for mutations in genes of the RAS/MAPK signalling pathway led to the identification of a variety of mutations in the gene v-Ha-ras Harvey rat sarcoma viral oncogene homologue (*HRAS*) (Aoki et al., 2005; van Steensel et al., 2006; Zampino et al., 2007). The functional consequences of these mutations are increased *HRAS* activity and an increase in signalling through the RAS/MAPK pathway. The phenotype in patients with Costello syndrome is variable even with identical mutations in *HRAS* (Gripp et al., 2006; Kerr et al., 2006).

### 3.4 Cardio-facio-cutaneous syndrome

Cardio-facio-cutaneous (CFC) syndrome (MIM 214080) is characterized by distinct facial features resembling Noonan syndrome; ectodermal abnormalities, musculo-skeletal findings, and cardiac malformations. Ocular symptoms are frequently present as well (Reynolds et al., 1986, Borradori & Blanchet-Bardon, 1993; Wieczorek et al., 1997; Young et al., 1993; Grebe & Clericuzio, 2000; Sabatino et al., 1997; Herman & McAlister, 2005; Chan et al., 2002). Many features of this syndrome are overlapping with Noonan syndrome causing diagnostic uncertainty especially in young infants. However, in contrast to Noonan syndrome, cognitive impairment is universally present in patients with CFC syndrome (Yoon et al., 2007). Ultimately, the identification of a wide variety of mutations in the gene *BRAF* helped to clarify the diagnostic uncertainties (Rauen, 2006; Schulz et al., 2008; Narumi et al., 2007; Nava et al., 2007; Gripp et al., 2007). Mutations in three other related genes, *MAP2K1*, *MAP2K2* (Rodriguez-Viciano et al., 2006) and Ki-ras2 Kisten rat sarcoma viral oncogene homologue (*KRAS*) (Schubbert et al. 2006; Niihori et al., 2006) have also been identified in patients with CFC syndrome.

### 3.5 Neurofibromatosis

Neurofibromatosis (NF1) is clinically quite distinct from the neuro-cardio-facio-cutaneous syndrome family. NF1 occurs in about 1 in 4,000 birth and is characterized by the development of benign neurofibromas of the peripheral nervous system and skin discolorations (Riccardi, 1981). Gliomas of the peripheral nerves and skeletal dysplasias can occasionally occur. Mild cognitive impairment manifested as learning disability is present in about 40% to 60% of patients. Neurofibromatosis is characterized by incomplete penetrance, which means that even if an individual carries a disease-causing mutation the expression of the disease phenotype is highly variable. The identification of mutations in the gene neurofibromin shed light on possible underlying pathomechanisms in this disorder (Viskochil et al., 1990; O'Connell et al., 1992). Neurofibromin is a GAP protein, which transforms activated RAS protein back to the inactive state. The neurofibromin gene is highly expressed in the developing brain of the embryo. In the adult brain, expression can be found in the Purkinje cells, pyramidal cells, Schwann cells and oligodendrocytes. The RAS/MAPK signalling pathway plays a critical role in memory formation and learning through long lasting alterations of gene expression in neuronal cells. Therefore, learning deficits could be explained by alterations in this important signalling pathway, however, learning disabilities in patients with Neurofibromatosis are variable (Costa et al., 2001; Costa et al., 2002). Neurofibromin knock-out mice have confirmed learning deficits in mice due to RAS hyperactivity. Treatment with a farnesyl-transferase inhibitor could reverse some of the effects of the mutation in mice (Costa et al., 2002).

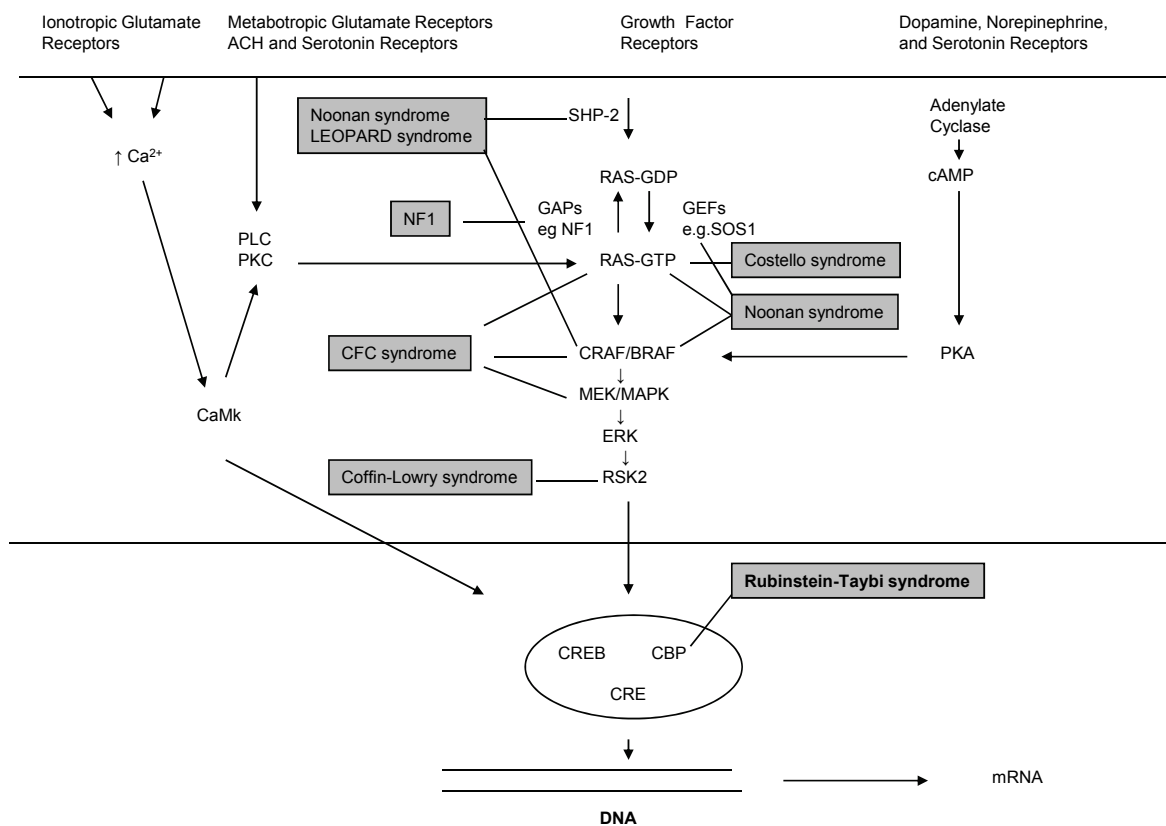


Fig. 1. The Neuro-Cardio-Facio-Cutaneous syndrome family and its relationship to mutations in proteins of the RAS/MAPK signalling cascade. Solid lines indicate associations to mutations in the proteins involved in the signalling cascade. Arrows indicate activating and inactivating events. Abbreviations:  $\text{Ca}^{2+}$ , ionic calcium; ACH, Acetylcholine; CaMk, Calcium-calmodulin kinase; PLC, Phospholipase C; PKC, Phosphokinase C; SHP-2, Src homology 2 domain-containing-transforming protein; NF1, neurofibromatosis type 1; GDP, guanine dinucleotide phosphate; GEF, guanine-nucleotide-exchange factor; SOS1, son of sevenless homologue 1; GTP, guanine trinucleotide phosphate; GAP, GTPase-stimulating proteins; cAMP, cyclic adenosine monophosphate; PKA, Protein kinase A; CRAF, RAF1 *v-raf-1* murine leukemia viral oncogene homolog 1; BRAF, *v-raf* murine sarcome viral oncogene homolog B1; MEK, mitogen-activated protein kinase kinase; MAPK, mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; RSK2, ribosomal S6-kinase 2; CREB, CRE binding protein; CBP, CREB binding protein; CRE, cAMP response-element; CFC, cardio-facio-cutaneous.

### 3.7 Coffin-Lowry syndrome

Coffin-Lowry syndrome (MIM 303600) is a severe mental retardation syndrome with mutations in the ERK/CREB pathway, which is activated by the RAS/MAPK signalling cascade (Figure 1). This rare mental retardation disorder is characterized by an abnormal gait, facial abnormalities including protruding forehead, wide nose, and irregular teeth. Individuals affected with this syndrome are often short with poor bone mineralization and underdevelopment of the musculature (Coffin et al., 1966; Lowry et al., 1971). Coffin-Lowry

syndrome is caused by a wide variety of mutations in the gene 90 kDa ribosomal S6 serine-threonine kinase 2 (*RSK2*) located on chromosome Xp22.2 (Trivier et al., 1996). The spectrum of mutations includes splice site alterations, missense mutations, frame-shift alterations, and nonsense mutations. In the hippocampus, *RSK2* phosphorylates and activates a number of nuclear proteins including CREB when activated by the ERK pathway (Jacquot et al., 1998; Xing et al., 1996). The *RSK2* mutant mouse model resembles the Coffin-Lowry syndrome patients in that it shows marked deficits in motor development, coordination and spatial learning (Dufresne et al., 2001).

Syndrome	Gene	Chromosome	References
Noonan syndrome	<i>PTPN11</i>	12q24.13	Tartaglia et al., 2001
	<i>SOS1</i>	2p22-p21	Roberts et al., 2007 Tartaglia et al., 2007
	<i>RAF1</i>	3p25	Pandit et al., 2007; Razzaque et al., 2007
	<i>KRAS</i>	12p12.1	Schubbert et al., 2006; Zenker et al., 2007
LEOPARD syndrome	<i>PTPN11</i>	12q24.13	Digilio et al., 2002; Legius et al., 2002
	<i>RAF1</i>	3p25	Pandit et al., 2007
Costello syndrome	<i>HRAS</i>	11p15.5	Aoki et al., 2005
Cardio-facio-cutaneous syndrome	<i>BRAF</i>	7q34	Rauen, 2006; Schulz et al., 2008; Narumi et al., 2007; Nava et al., 2007; Gripp et al., 2007
	<i>MAP2K1</i>	15q22.31	Rodriguez-Viciano et al., 2006
	<i>MAP2K2</i>	19p13.3	Rodriguez-Viciano et al., 2006
	<i>KRAS</i>	12p12.1	Schubbert et al., 2006; Niihori et al., 2006
Neurofibromatosis	<i>NF1</i>	17q11.2	Viskochil et al., 1990
Coffin-Lowry syndrome	<i>RSK2</i>	Xp22.2	Trivier et al., 1996
Rubinstein-Taybi syndrome	<i>CBP</i>	16p13.3	Petrij et al., 1995

Table 1. Genetic syndromes linked to genes in the RAS/MAPK pathway

### 3.8 Rubinstein-Taybi syndrome

A patho-mechanistically related disorder is the Rubinstein-Taybi syndrome (MIM 180849), a rare mental retardation syndrome occurring with a frequency of 1 in 125,000 live births. This autosomal dominant syndrome is characterized by distinct facial features, broad digits, angulated thumb, and blunted growth (Rubinstein & Taybi, 1963; Rubinstein, 1990). A variety of mutations in the gene transcriptional co-activator CREB-binding protein (*CREB*) have been identified in about 50% of patients (Petrij et al., 1995; Blough et al., 2000). *CREB* is located on chromosome 16p13.3. Mutations in this gene lead to protein changes that interfere with the binding of the transcription factor CRE through alterations in the chromatin structure within the promoter regions of the CRE regulated genes (Ogryzko et al.,



1996). A mouse model carrying a dominant negative mutation in *CREB* displayed nearly all the features of Rubinstein-Taybi syndrome including deficits in long-term memory (Oike et al., 1999). The short-term memory was unimpaired.

From this short overview of the neuro-cardio-facio-cutaneous syndromes it becomes clear that despite the common effect of increased signal transmission through the RAS/MAPK pathway, known mutations in component of this pathway lead to highly variable but distinct effects on the phenotype (Cesarini et al., 2009; Niihori et al., 2006; Rodriguez-Viciana et al., 2006; Garnett et al., 2005). The degree of cognitive impairment varies among syndromes, ranging from normal cognition in some cases of NF1 and Noonan syndrome to severe impairment in some cases of CFC-syndrome (Denayer et al., 2008). Overall, it can be said that mutations upstream of RAS seem to have less severe and more variable effects on cognitive impairment, whereas mutations in genes closer to the nucleus appear to have more detrimental effects. The success in identifying the underlying genetic mutations in these rare developmental Mendelian disorders was based on the presence of overlapping clinical phenotypes that pointed to possible candidate pathways. Common symptoms in many body systems allowed for the identification of groups of patients that were similar in their underlying pathophysiology and their genetic risk factors. Nevertheless, even in these homogeneous patient populations the genetic causes of the disorders were highly variable often involving several genes in the same pathway. Despite the success described above, the known mutations still explain only a portion of all the cases diagnosed with a particular syndrome on clinical grounds.

X-linked mental retardation is another example of a condition that is characterized by extensive heterogeneity. Only a percentage of cases can be explained by known genetic mutations. The absence of additional clinical features prohibits the sub-classification of patients into more homogeneous groups based on clinical presentation. The underlying heterogeneity of the genetic causes hinders the utilization of family-based linkage analyses and population-based association studies. Therefore, this disease category required a substantially different approach to the identification of the underlying genetic causes.

#### **4. X-linked mental retardation**

The frequency of mild to moderate mental disability defined as an IQ between 50 and 70 is about 2-3% in the general population; more severe intellectual impairment is found in 0.5 to 1% of the population (Raymond, 2006). A significant portion of these disorders is inherited in an X-linked mode. About 80 genes located on the X-chromosome are known to be involved in mental retardation to date and many more are likely to be discovered. Many families have rare or even private disease-causing mutations that are not shared with other families and in a large percentage of these families mental retardation is the only symptom present. Direct re-sequencing approaches appear to be the only way to identify the underlying mutations in these families.

A recent study involving patients affected with X-linked mental retardation used a large-scale systematic re-sequencing approach to explore genomic variants present in the patients compared to their unaffected relatives. The study involved 208 families and focussed on the coding exons of all the genes located on the X-chromosome in a systematic approach (Tarpey et al., 2009). First, protein truncating changes in the coding regions of genes were analyzed since these changes could be expected to have the most severe consequences for the function of the protein. Using this approach mutations in four new genes were detected that were not previously known to be involved in mental retardation. A large number of

truncating mutations were identified. Overall, the majority of truncating mutations were not associated with disease status at all and even loss of about 1% of genomic material on the x-chromosome was compatible with a normal phenotype. Truncating mutations associated with the phenotype were found in 10% of the genes located on the X-chromosome. However, each particular genomic change explained only a very small portion of mental retardation in the sample and in the majority of families the underlying genetic mutation could not be identified.

In addition to truncating mutations, a large number of single nucleotide polymorphisms were found. Almost 2,000 single-nucleotide genomic variants were detected in the coding sequences of the genes alone. Almost half of these mutations were missense mutations leading to amino acid substitutions in the encoded proteins. Rare small insertions and deletions were also present. Nearly half of the mutations were found only once in the sample. Slightly more than half of the recurrent variants could be found in public databases for common genomic polymorphisms. On average, the genomic sequence of any two individuals differed by about 100 variants in the coding regions alone. These results demonstrate the large amount of genomic variability that is present between any two individual genomes. Evaluation of the functional consequences of those genomic variants would be a daunting task. In addition it is likely that many variants with physiological consequences have been missed since introns of genes, the promoter regions or other non-coding regions have not even been sequenced in this study. These genomic regions are known to have important regulatory functions for gene expression and are even more variable than the coding regions themselves.

In summary, it could be said that substantial genetic heterogeneity was found underlying X-linked mental retardation. At least 10% of the genes located on the X-chromosome were involved, individual mutations were generally rare and each identified gene accounted only for a small portion of the cases. In addition to disease-causing mutations, a large number of rare non-synonymous mutations were identified that had no apparent effect on the phenotype. A surprising result of this study was that a large number of mutations interrupting the function of the gene were not causally related to mental retardation at all. In fact, loss of about 1% of genetic material on the X-chromosome was compatible with a normal phenotype. In this context it is important to stress that the identification of a rare truncating mutation in studies with large sample size will still require careful follow-up evaluation of the functional consequences and should not be considered as evidence for disease causation *per se* (Raymond et al., 2009). Despite its success, this study paints a daunting picture of the task ahead in the search for genomic variants underlying common complex disorders. Nevertheless, even the identification of rare mutations in a small number of cases might shed some light on underlying pathomechanisms of the disease.

Schizophrenia is another disorder that is heavily researched, because improvement in the understanding of the underlying pathophysiology of this disorder promises to provide new treatment options. Schizophrenia shares many features with developmental disorders, as well as mental retardation syndromes including strong evidence for a genetic cause of the disease. Until now much uncertainty still exists regarding specific genetic variants that might contribute to the phenotype.

## 5. Schizophrenia

Schizophrenia is a common psychiatric disorder affecting about 0.5%-1% of the population. The clinical phenotype is characterized by dissociation of thoughts and emotions, distorted

perception of reality manifested as hallucinations and delusions, as well as emotional flattening over the disease course. The age of onset is usually in adolescence. Schizophrenia is often conceptualized as a complex disorder caused by multiple common genomic variants with small effect size in combination with environmental risk factors (Williams et al., 2009). Significant familiarity and heritability have been demonstrated for this disorder (Cardno & Gottesman, 2000). Despite the fact that genetic risk factors play an important role in the manifestation of the disease, it has been difficult to replicate genome-wide significant linkage signals consistently (Williams et al., 2009). Even genome-wide association studies in thousands of individuals still left some doubt about underlying genetic risk factors (Allen et al., 2008; Need et al., 2009). The increase in power that was hoped for by collecting ever larger sample sizes might have been counteracted by increased heterogeneity of the disease (Craddock et al., 2008). If the same degree of heterogeneity is present in schizophrenia as it was found in developmental disorders or X-linked mental retardation, these results would not be surprising.

Schizophrenia is often conceptualized as a developmental disorder. Candidate gene studies based on various hypotheses of disease pathology have been numerous with inconsistent results (Allen et al., 2008). In particular, these studies have been hindered by the fact that the symptoms of schizophrenia are rather non-specific and manifestations in other body systems are often lacking. Due to possible heterogeneity, replication of candidate gene association studies has been difficult and results have often not been convincing. Positional candidate gene studies that follow-up on significant family-based linkage studies have been more successful revealing several potential risk genes including neuregulin 1 (*NRG1*), dystrobrevin-binding protein 1 (*DTNBP1*), and D-amino acid oxidase inhibitor (*DAOA*), among others (Williams et al. 2009). However, overall mutations in these genes could explain only a very small percentage of cases.

Recently, the focus of research has shifted from common single nucleotide polymorphisms to rare structural variants. This shift might have been inspired by the finding that about 10% of neuro-developmental disorders including autism and mental retardation are caused by non-inherited deletions and insertions of genetic material (Sebat et al, 2007; Autism Genome Project Consortium, 2007). Recent genome-wide studies in schizophrenia reported large multigenic deletions located on chromosomes 1q21.1 and 15q13.3, which were present in a very small number of individuals diagnosed with schizophrenia (International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Need et al., 2009; Kirov G, 2009). In addition, exon-disrupting copy number variations have been identified in the gene *NRXN1* (Rujescu et al., 2009). Several of the deletions associated with schizophrenia had previously been associated with mental retardation, autism, ADHD, and other neuro-developmental disorders, including seizures (Mefford et al., 2008; Wassink et al., 2001; Sharp et al., 2008). Subsequent studies have confirmed these associations in a number of individuals (van Bon et al, 2009; Helbig et al., 2009; Miller et al., 2009; Ben-Shachar et al., 2009). It is long known that autism and other mental disorders share common symptoms with schizophrenia. The presence of a small number of individuals affected with these mental disorders in a large sample of thousands of cases affected with schizophrenia could lead to statistically significant results. Especially in large samples diagnostic uncertainty cannot always be completely excluded, and therefore, careful follow-up with functional studies on the results in schizophrenia would be prudent. Overall, research in schizophrenia points to the possibility of heterogeneity similar to results in rare Mendelian developmental disorders and complex X-linked mental retardation.

## 6. Discussion

Finding genetic risk factors in common complex mental disorders is an area of intense research. Linkage studies, positional candidate gene sequencing approaches, as well as the search for truncating mutations that severely disrupt the function of a protein are traditional tools that have been applied successfully to rare Mendelian genetic syndromes leading to the identification of rare Mendelian variants. In common complex mental disorders, on the other hand, it has been the accepted hypothesis that different genetic risk factors might play a role. Common complex disorders are thought to involve common genomic variants present in at least one percent of the population. Genome-wide association studies have been designed to find few common risk variants that would explain the pathophysiology of common complex disorders. Even though these studies have been successful in identifying common variants with low associated risk in some disorders, it has to be admitted that the majority of cases still remains unexplained. This scenario leaves several open questions. Could it be that common complex disorders after all are not so different from rare Mendelian disorders? Could it be that the effect of the mutations involved is only less pronounced and easier to compensate? Could it be that common complex disorders are as heterogeneous as Mendelian disorders, as demonstrated in X-linked mental retardation? In this disorder close to hundred different genetic causes have been identified, each of which is individually rare. Nevertheless, the majority of cases still remains unexplained. Could psychiatric disorders such as bipolar disorder and schizophrenia be more heterogeneous with regard to their underlying pathophysiology and genetic risk factors than we ever would have imagined? Could it be that these disorders are caused by many rare genetic mutations, some of which would be present in only a small number of families? The answer to these questions can only come from further research. However, even considering these scenarios would require different strategic approaches. It might be useful to reconsider proven technologies, such as positional candidate gene sequencing and family based studies in addition to large-scale genome-wide approaches. It could be useful to consider the possibility that collecting an ever-larger number of samples might only increase the heterogeneity of the cases. In the end it might be useful to refocus on the evaluation of functional consequences of mutations instead of being mesmerized by bio-statistical p-values. The answer to these questions must remain unknown. The comparison of different research strategies in related fields might be instructive and inspiring. After all, mental retardation is about as frequent as psychotic disorders in the general population and developmental syndromes might actually be among samples of schizophrenia patients, since they often share symptoms of hallucinations and delusions. In the end, considering all possible approaches might be the way that will enhance our understanding of mental disorders.

## 7. Conclusion

As the focus in common complex mental disorders has shifted from hypothesis-based candidate gene approaches to genome-wide explorations, the focus might shift from common genomic variants to the detection of rare variants. Research strategies might adjust as well moving from genome-wide association studies of common variants to re-sequencing approaches of entire genomes. While this shift takes place it could be instructive to study some of the lessons learned from hypothesis driven re-sequencing approaches in

developmental disorders and chromosome-wide re-sequencing studies in X-linked mental retardation. Re-sequencing approaches have been successful in identifying new genes of unknown function, for which prior hypothesis did not exist before. On the other hand, follow-up and evaluation of the large amount of common and rare variants identified by this approach could be challenging. As genome-wide re-sequencing studies will most likely reveal a tremendous amount of genomic variants, hypothesis driven approaches might be very useful in follow-up of genome-wide sequencing approaches, particularly in a world of limited resources of time and money. Family-based re-sequencing approaches as compared to population-based approaches will allow detecting the segregation of the phenotype with the genotype. This might be a useful prerequisite for separating random noise of genomic variability from disease causing variants. Functional tests will in the end be required to ultimately inform about disease patho-physiology. Last but not least, rare and private mutations might be more commonly involved in disease pathology than we would have ever imagined.

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## **Cognitive Maps**

Edited by Karl Perusich

ISBN 978-953-307-044-5

Hard cover, 140 pages

**Publisher** InTech

**Published online** 01, January, 2010

**Published in print edition** January, 2010

### **How to reference**

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

Berit Kerner (2010). Genetics of Cognition-What can Developmental Disorders Teach Us?, Cognitive Maps, Karl Perusich (Ed.), ISBN: 978-953-307-044-5, InTech, Available from:

<http://www.intechopen.com/books/cognitive-maps/genetics-of-cognition-what-can-developmental-disorders-teach-us->

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Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
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### **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

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