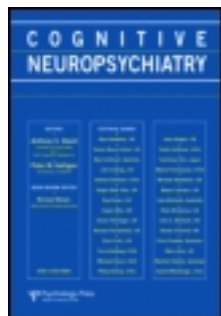


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Epigenetics, genomic mutations and cognitive function

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Epigenetics, genomic mutations and cognitive function

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Introduction. There is growing interest in the role of single genes in cognitive functions. Association studies are the most commonly applied method in this field. This method assumes that the genetic information affecting cognitive processes is “static” and unchanging. However, there is accumulating evidence that dynamic genomic and epigenetic alterations can modulate complex cognitive processes, and influence susceptibility to disorders associated with impaired cognitive functioning.

Methods. We present an overview of genomic and epigenetic mechanisms, and discuss the cognitive and psychiatric consequences of genomic and genetic abnormalities.

Results. Genomic and epigenetic changes can affect complex cognitive functions, including learning and memory and are causative in several developmental and psychiatric disorders effecting language, social functioning and IQ.

Conclusions. Genomic and epigenetic disorders are “experiments of nature” that offer unique and valuable insight in to the physiology of general and specific cognitive functions.

Keywords: Cognition; Epigenetics; Genomics; Mutations; CNV.

INTRODUCTION

The most commonly applied method to evaluate the potential role of individual genes in cognitive processes is using association studies, in which the strength of the relationship between the variants of a specific candidate gene and phenotype (cognition) is tested (Goldberg & Weinberger, 2004). This method assumes that the genetic information affecting cognitive processes is “static” and unchanging.

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However, numerous epidemiological, clinical, and molecular features associated with complex cognitive processes are difficult to explain using this traditional gene-based model. These include the incomplete concordance between MZ twins in cognitive performance, gender differences in cognitive abilities, a fluctuating course of cognitive disorders with periods of remission and relapse, peaks of susceptibility to disease coinciding with hormonal changes, and parent-of-origin effects (Mill & Petronis, 2007; Mill et al., 2008). These observations have led to speculation about the importance of dynamic genomic and epigenetic factors in modulating complex cognitive processes such as learning and the formation of memories, and in influencing susceptibility to disorders associated with impaired cognitive functioning.

The following review presents a brief background to the dynamic genomic and epigenetic modifications occurring in the human genome, and the causes and consequences of several disorders of genomic and epigenetic origin that result in a disruption in human cognitive abilities. Although our understanding of these processes is incomplete and is still under extensive investigation, we discuss implications for research on cognition and psychiatric disorders.

GENOMIC MODIFICATION

Several recent studies have highlighted the high number of copy number variations (CNVs), comprising deletions, insertions, duplications, repeats and other complex multi-site variants, that occur in the genome (Redon et al., 2006) (see Figure 1). CNVs are defined as DNA segments of 1 kb or larger which are present in variable copy numbers in comparison with a reference genome (Feuk, Carson, & Scherer, 2006; Feuk, Marshall, Wintle, & Scherer, 2006). CNV polymorphisms are more dynamic than point mutations to the DNA sequence, and often occur *de novo*. Whilst it has been known for some time that gene copy number is often elevated in various types of cancer

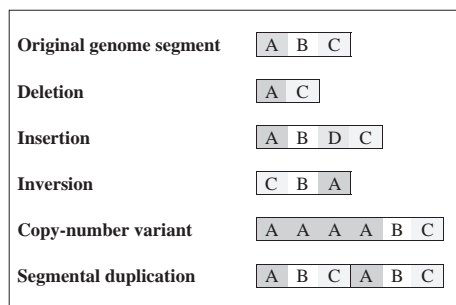


Figure 1. Structural variations in the human genome.

and that chromosomal rearrangements predispose to mental retardation (Knight et al., 1999), copy number variation has also been recently associated with various complex neuropsychiatric cognitive disorders such as autism and schizophrenia (Cook & Scherer, 2008; Sebat et al., 2007) (see later).

One type of CNVs, trinucleotide repeats, have been linked to a number of genetic disorders that do not appear to follow classical Mendelian inheritance patterns such as Fragile X syndrome (see below). These trinucleotide repeat disorders are caused by problems in recombination and replication during meiosis. In most trinucleotide repeat disorders, the larger the expansion the more pathogenic the effects of the repeat; the severity of disease generally increases with length. For most trinucleotide repeat disorders, there is a “threshold” repeat length, above which the phenotypic effects of the expansion become more severe.

EPIGENETIC MODIFICATION

Epigenetics refers to the reversible regulation of various genomic functions, occurring independently of DNA sequence, mediated principally through changes in DNA methylation and chromatin structure (Jaenisch & Bird, 2003). Epigenetic processes are essential for normal cellular development and differentiation, and allow the long-term regulation of gene function through non-mutagenic mechanisms (Henikoff & Matzke, 1997).

Like the DNA sequence, the epigenetic profile of somatic cells is inherited during mitosis. Unlike the DNA sequence, which is stable and strongly conserved, epigenetic processes can be highly dynamic: they are tissue-specific, developmentally regulated, and often induced by exposure to a range of external environmental factors (Dolinoy, Weidman, & Jirtle, 2007).

Cytosine methylation is the best understood and most stable epigenetic modification modulating the transcriptional plasticity of mammalian genomes (Figure 2). It is intrinsically linked to the regulation of gene expression, with many genes demonstrating an inverse correlation between the degree of promoter DNA methylation and the level of expression (Jaenisch & Bird, 2003). The methylation of CpG sites in the promoter regulatory regions of many genes disrupts the binding of transcription factors and attracts methyl-binding proteins that initiate chromatin compaction and gene silencing.

The post-translational modification of histones, the basic proteins around which DNA is wrapped to form nucleosomes, comprises the other major type of epigenetic mechanism related to gene expression (Figure 2). A number of covalent histone modifications, occurring at specific residues, have been described (e.g., acetylation, methylation, phosphorylation, SUMOylation, and ubiquitylation), which together constitute a complex “histone code”

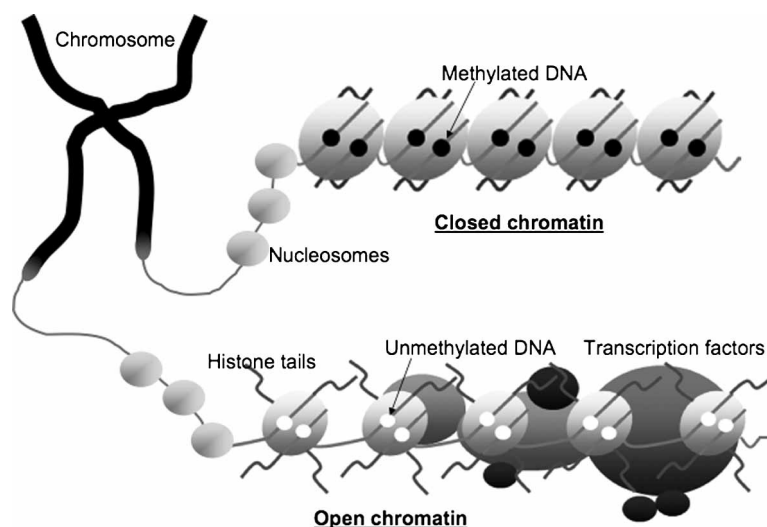


Figure 2. The main components of the epigenetic code. The two main components of the epigenetic code are DNA methylation and Histone modification. DNA Methyl marks added to certain DNA bases repress gene activity. A combination of different molecules can attach to the “tails” of proteins called histones. These alter the activity of the DNA wrapped around them.

modulating gene expression via alterations in chromatin structure (Berger, 2007).

While often investigated independently, epigenetic modifications to DNA and histones are not mutually exclusive, and clearly interact in a number of ways; it is becoming apparent that the classification of epigenetic mechanisms in terms of either gene activation or suppression might be too simplistic (Berger, 2007).

Recently, a third epigenetic system involving small interfering RNA (siRNA) has been described (Hamilton, Voinnet, Chappell, & Baulcombe, 2002). It has been shown that siRNA can suppress the activity of specific genes via targeted RNA interference (RNAi), a mechanism important in the developmental regulation of gene expression. RNAi is known to cause epigenetic changes in gene transcription, mediated by both DNA methylation and histone modifications.

COGNITIVE PHENOTYPE OF GENOMIC AND EPIGENETIC DISORDERS

Several developmental conditions, including common forms of mental retardation, can be attributed, at least in part, to dynamic disruption in the brain’s genomic and epigenetic function.

COGNITIVE PHENOTYPE IN GENOMIC DISORDERS

The term “genomic disorder” is typically used to describe a gain (duplication) or loss (deletion) of a specific chromosomal region, associated with a clinical genetic syndrome that may present with congenital anomalies, or with impairment in neurological and cognitive function. In general, the clinical features are believed to reflect changes in normal copy number or dosage of the genes contained within a given genomic interval, one or more of which contribute to the resulting phenotype (Emanuel, 2008).

Williams syndrome

Williams syndrome occurs in 1 of every 20,000 live births (Stromme, Bjornstad, & Ramstad, 2002), and arises from deletions in chromosome 7 (7q11.23) that typically include multiple genes (approximately 28 genes).

Williams syndrome patients exhibit an interesting idiosyncratic social behavioral syndrome – high sociability and empathy for others. Typically, Williams syndrome patients are socially fearless, engaging eagerly in social interaction even with strangers. Intriguingly, this remarkable hypersociability is coupled with a strong undercurrent of anxiety that relates to non-social objects (Meyer-Lindenberg, Mervis, & Berman, 2006).

Williams syndrome is associated with mild to moderate mental retardation. In particular, a severe visuospatial construction deficit is a fundamental stable phenotype in Williams syndrome, contrasting with a relative strength in verbal short-term memory and language. Attention deficit hyperactivity disorder (ADHD) is also common (Meyer-Lindenberg, Mervis, & Berman, 2006).

Because of the large number of genes effected by the full deletion of the chromosome, patients can be found with only “partial” deletions and this can be used for clarifying more specific genotype/phenotype relationships (e.g., Meyer-Lindenberg, Mervis, & Berman, 2006). Williams syndrome thus provides an interesting example of genetic contributions to complex social behaviors (Deutsch, Rosse, & Schwartz, 2007).

22q11 Deletion syndrome (Velocardiofacial/DiGeorge syndrome)

A deletion at chromosome 22q11 is the most frequently known deletion found in humans, occurring in approximately one of every 4000 live births. Its occurrence is associated with a characteristic facial dysmorphism, a range of congenital abnormalities, and cognitive psychiatric problems,

especially psychosis (Williams & Owen, 2004). The 22q11 deletion syndrome is associated with a high frequency of learning disabilities. Patients have relatively preserved verbal IQ in comparison to performance IQ. The relative strength in verbal abilities is evident despite speech and language impairments which are common in the disorder (Wang et al., 1998). More specific cognitive impairments have been characterized, especially deficits in visual-spatial memory (Bearden et al., 2001).

22q13 Deletion syndrome

22q13.3 deletions result from the loss of genetic material from the terminus of the long arm of one copy of chromosome 22. Monosomy 22q13.3 can accompany a simple deletion, an unbalanced translocation, or a ring chromosome. About 75% of all cases are simple deletions, with the remaining 25% of cases resulting from structural rearrangements of the affected segment. Deletion 22q13.3 is usually a *de novo* finding; however, approximately 20% of cases are familial, in which a child receives an unbalanced chromosome complement from a parent who carries a balanced reciprocal translocation (Cusmano-Ozog, Manning, & Hoyme, 2007). Bonaglia et al. (2001) suggested that proline rich synapse associated protein 2 (SHANK3) was a good candidate gene for the 22q13.3 deletion syndrome, as it is preferentially expressed in the cerebral cortex and cerebellum, and encodes a scaffolding protein involved in the postsynaptic density of excitatory synapses.

Mental retardation is frequently observed, with the majority of individuals in the moderate to severe range. Speech delay or severe language impairment with little to no speech is common. In addition to mental retardation and speech delay, most patients meet diagnostic criteria for autism and demonstrate behavioral deficits including: poor eye contact, stereotypical behaviors, self-stimulation, repetitive chewing behaviors, bruxism, biting, hitting and abnormal sleep patterns translocation (Cusmano-Ozog, Manning, & Hoyme, 2007).

Deletion on chromosome 1q21.1

De novo and inherited deletions on chromosome 1q21.1 have recently been associated with a broad range of developmental and psychiatric disorders, including mental retardation, autism (Mefford et al., 2008) and schizophrenia (International Schizophrenia Consortium, 2008; Stefansson et al., 2008). It has been suggested that deletions on chromosome 1q21.1 are evident in 0.5% of persons with developmental abnormalities, and 0.26% of patients with schizophrenia. Importantly, this deletion is characterized by a high degree of phenotypic variability and lack of distinct syndromic features

demonstrating some of the challenges in understanding the role of structural variants in human disease and cognition (Mefford et al., 2008). Investigation of genetic and environmental modifiers is therefore necessary to fully understand etiological processes of genomic disorders.

COGNITIVE PHENOTYPE IN EPIGENETIC DISORDERS

Mutations in genes that affect global epigenetic profiles can give rise to human diseases, which can be inherited or somatically acquired (Egger, Liang, Aparicio, & Jones, 2004). Many of these epigenetic abnormalities result in cognitive disabilities. Interestingly, many of these “epigenetic” disorders also involve structural changes to the genome, for example the expanded triplet repeats of Fragile X and the deletion on chromosome 15q in Angelman syndrome. This suggests a common mechanism by which the gross physical changes causing genomic disorders may exert their effects.

Fragile X syndrome

The fragile X syndrome is caused by an expanded triplet repeat (CGG) on the X chromosome (Xq27.3). The disorder is called fragile X because the many repeats cause the chromosome to be fragile at that point and to break during laboratory preparation of chromosomes. The frequency of fragile X is estimated as 1 in 5000 males and 1 in 10,000 females (Crawford, Acuna, & Sherman, 2001).

The triplet repeat is in an untranslated region at the beginning of a gene (Fragile X Mental Retardation-1, FMR1) that, when expanded to a full mutation, prevents that gene from being transcribed. The full mutation for fragile X, with its hundreds of CGG repeats, causes hypermethylation and thus shuts down transcription of the FMR1 gene (Plomin, DeFries, McClearn, & McGuffin, 2008). This leads to the absence of Fragile X Mental Retardation Protein (FMRP), a molecule that is widely expressed in brain and has been shown to regulate translation of mRNAs important for synaptic plasticity and neuronal maturation (Penagarikano, Mulle, & Warren, 2007).

Most cases of fragile X males are moderately disabled, but many are only mildly disabled and some have normal intelligence. Only about one-half of girls with fragile X are affected, because one of the two X chromosomes for girls could be normal. In addition to mental retardation, learning disabilities, hyperactivity, aggressiveness, and autism-like symptoms are also common (Spreen, Risser, & Edgell, 1995). For fragile X males, IQ declines during adolescence have been reported (Spreen, Risser, & Edgell, 1995).

The study of the molecular basis of Fragile X syndrome has translated to some promising therapeutic strategies to reactivate the silenced FMR-1 gene, or to compensate for the absence of FMRP. The latter approach has proved effective in reducing deficits in several animal models of Fragile X, and clinical trials are planned in humans (Penagarikano et al., 2007).

Rett syndrome

Rett syndrome is the most common single-gene cause of general cognitive disability in females (1 in 10,000). The disorder shows few effects in infancy, although the head, hands, and feet are slow to grow. Cognitive development is normal during infancy but, by school age, girls with Rett syndrome are generally unable to talk and about half are unable to walk (Weaving, Ellaway, Gecz, & Christodoulou, 2005).

The disorder was mapped to the long arm of the X chromosome (Xq28), and then to a specific gene (MECP2, which encodes methyl-CpG-binding protein-2) (Amir et al., 1999). MECP2 is a gene involved in the methylation process that silences other genes during development and thus has diffuse effects throughout the brain (Bienvenu & Chelly, 2006). Males with MECP2 mutations usually die before or shortly after birth (Plomin, DeFries, McClearn, & McGuffin, 2008).

The disorder is characterized by severe to profound mental retardation, stereotyped movements and diminished social interests, as well as impairments in expressive and receptive language (American Psychiatric Association, 1994).

Angelman syndrome

Angelman syndrome is a severe form of mental retardation that occurs in 1 of every 15,000–20,000 births. It results from deregulation of one or more imprinted genes at 15q11–13 (Weeber, Levenson, & Sweatt, 2002).

It is often accompanied by a happy disposition with bouts of inappropriate laughter, hyperactivity, and sleep disorders (Laan, v Haeringen, & Brouwer, 1999). All patients have severe mental retardation and delayed motor milestones. Language does not develop, with most patients having a vocabulary of only one or two words despite having reasonable comprehension of simple commands and sentences (Laan, v Haeringen, & Brouwer, 1999).

Prader-Willi syndrome

The incidence of Prader-Willi syndrome is estimated to be between 1:10,000 and 1:25,000 births. It is caused by a faulty genomic imprinting on

chromosome 15q11– defined as parent-specific, monoallelic expression of a gene (Egger, Liang, Aparicio, & Jones, 2004). In such conditions, an abnormal phenotype is established as a result of the absence of the paternal or maternal copy of an imprinted gene or because of deregulation of an imprinted gene. The majority of cases (about 70%) are caused by a *de novo* deletion on chromosome 15 inherited from the father, whilst about 25–30% are caused by inheriting two chromosome 15 s from the mother, instead of one from the mother and one from the father (maternal disomy).

Most people with Prader-Willi syndrome have borderline or moderate learning difficulties. The average IQ is around 70, but some have normal IQ. Language impairments are evident, as well as impairments in memory, attention and reasoning. Visual organization and perception are good (Holm et al., 1993).

EPIGENETICS IN LEARNING AND MEMORY PROCESSES

The formation of long-term memories is thought to involve rapid changes in gene expression, and there is growing evidence that histone modifications and DNA methylation may be involved (Tsankova, Renthal, Kumar, & Nestler, 2007). Animal studies have documented a role for histone modifications processes in hippocampus-dependent memory formation, including spatial mazes, contextual fear conditioning and novel object recognition (Levenson & Sweatt, 2005). Synaptic plasticity is believed to contribute to the formation of long-term memories and also seems to have an epigenetic component (Guan et al., 2002).

Recent findings have also implicated changes in DNA methylation in learning and memory. In contrast to the more traditional view that DNA methylation is a highly stable modification, they suggest that DNA methylation may be subject to rapid and dynamic regulation in the nervous system (Tsankova, Renthal, Kumar, & Nestler, 2007). Contextual fear conditioning induced DNA methyltransferase expression has been documented in the hippocampus. Fear conditioning also induced demethylation of the *reelin* promoter, indicating that both DNA methylation and demethylation are highly regulated (for review see Tsankova, Renthal, Kumar, & Nestler, 2007).

GENOMIC AND EPIGENETIC CHANGES IN COMPLEX POLYGENETIC COGNITIVE-BEHAVIORAL DISORDERS

Psychiatric disorders have a complex phenotype of cognitive and behavioral impairments, resulting from a multifactorial polygenetic and environmental etiology. Schizophrenia, in particular, is characterized by severe cognitive

and social impairment (Reichenberg & Harvey, 2007; Reichenberg et al., 2002; MacCabe et al., 2008). Genomic and epigenetic research in psychiatry is still in its infancy, and relatively few studies have empirically investigated the role of such factors in schizophrenia.

Four very recent studies, all using different designs, have provided evidence that schizophrenia is associated with *de novo* copy number variations (International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Walsh et al., 2008; Xu et al., 2008). For example, Walsh et al. (2008) performed genome-wide scans in 418 individuals with schizophrenia and 268 healthy controls, for CNVs of >100 kb. They identified 53 such CNVs that had not been previously reported, and these were three times more common in cases of schizophrenia than controls. Furthermore, the novel CNVs detected in the cases, but not those in controls, were overrepresented in pathways important in neurodevelopment. These data imply that rare *de novo* mutations are responsible for a higher proportion of the genetic risk for schizophrenia than previously assumed, and this may help to explain why schizophrenia persists in the population despite severely impairing fertility (MacCabe et al., 2009).

The possible role of such mutations in cognition and social development is still to be studied in detail, but examples for this approach already exists: The 22q11 deletion syndrome is characterized by adult-onset psychosis in around 30% of cases (Murphy, Jones, & Owen, 1999), coupled with intellectual deterioration (Gothelf et al., 2005). Of particular interest, the catechol-O-methyltransferase (COMT) gene is located in the deleted region. COMT is responsible for metabolising catecholamines, including dopamine, and been studied extensively as a candidate gene for schizophrenia (Williams, Owen, & O'Donovan, 2007), and for executive control functions (Egan et al., 2001).

A recent study of post-mortem brain tissue from patients with bipolar disorder and schizophrenia uncovered evidence for DNA methylation differences in numerous loci, including several genes that have been functionally linked to disease etiology (Mill et al., 2008). Consistent with increasing evidence for altered glutamatergic and GABAergic neurotransmission in the pathogenesis of major psychosis, epigenetic changes were identified in loci associated with both these neurotransmitter pathways. Glutamate and GABA have important roles in higher-order cognitive and social functioning (Gray & Roth, 2007; Tan et al., 2007).

SUMMARY AND CONCLUSIONS

Genomic and epigenetic research in psychiatry and cognitive psychology is still in its infancy. Genetic and epigenetic disorders are “experiments

of nature” that offer unique and valuable insight in to the physiology of general and specific cognitive functions. The various genetic and epigenetic syndromes present a unique opportunity to study neuropsychology, cognitive development and neurobiology. In particular, general intellectual ability, language and social cognition.

Major advances in the understanding of cognitive development could come from delineating the combined contribution of the different genes affected in genomic and epigenetic disorders. Several complementary strategies can be followed. The detection and study of individuals with atypical deletions (e.g., partial deletions in Williams syndrome) – which, although rare, sometimes occur as a result of the complexity of genetic structures – may allow making inferences about contributions of groups of genes. Mouse knockout models can be developed to allow the investigation of single gene, and gene interaction effects in animals. With the development of novel microarray-based “epigenomic” techniques, it is now feasible to investigate epigenetic and genomic modifications on a global scale across the genome, including epigenetic and genomic cognitive functions association studies.

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