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Review Article

Copy Number Variations and Psychiatric Disorders

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Abstract

Copy number variations (CNVs) are gains and losses of DNA segments in the human genome, and form genetic variations. Recent studies have shown that CNVs contribute to the phenotypic variation in humans and are associated with complex diseases, including psychiatric disorders. Emerging evidence indicates that CNVs play a role in the genetic etiology of mental retardation, autism, schizophrenia, and bipolar disorders. This review summarizes the latest findings of recent research on the role of CNVs in the pathogenesis of these four psychiatric disorders. The positive association of CNVs with psychiatric disorders has several implications: (1) at least in some patients, the genetic defects in each patient are individualized with high penetrance, which is different from the prevailing common variant hypothesis of complex psychiatric disorders; (2) the identification of pathogenic CNVs in psychiatric disorders would bring new insight into the pathogenesis of mental disorders; (3) array-based comparative genomic hybridization technology has the potential to become a useful laboratory tool in clinical practice to help in diagnosing psychiatric disorders. (*Tzu Chi Med J* 2009;21(3):197–203)

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1. Current status of genetic etiology studies of major psychiatric disorders

Schizophrenia, bipolar affective disorder, mental retardation (MR), and autism are serious debilitating mental disorders that together affect at least 1% of the general population. These disorders are chronic and result in impaired cognitive and social functioning in affected patients, and present a serious burden to their families and communities. Currently, pharmacotherapy is the treatment of choice for these disorders. However, medication can only control the symptoms; there is no known cure. Hence, there is an urgent need to understand the etiology and the pathogenesis of these disorders to develop new treatment for the affected patients.

The search for the etiology of psychiatric disorders is a challenging task. Family, twin, and adoption studies have demonstrated a high influence of genetic factors in the etiology of psychiatric disorders. However, except for a few cases, the genetic etiology of most patients remains elusive. The reasons for the difficulty in identifying the genetic defects related to psychiatric disorders can be attributed to the clinical heterogeneity and the etiological heterogeneity in patients with psychiatric disorders.

Currently, two hypotheses guide the strategy of the genetic study of psychiatric disorders: the multiple common variants hypothesis and the individualized rare mutation hypothesis [1–3]. The multiple common variants hypothesis is the prevailing one, and proposes that mental disorders are the joint results of common variants of multiple genes that surpass a certain threshold, with each common variant contributing a small-to-modest risk. Based on this theory, numerous case-control association studies of candidate genes have been conducted [4,5]. Recently, with the availability of high throughput whole-genome single nucleotide polymorphism (SNP) genotyping technology, the genome-wide association study has become the state-of-the-art approach in searching for susceptible genes of common complex diseases [6–9].

In contrast to the common variants hypothesis, the individualized rare mutation hypothesis of psychiatric disorders postulates that psychiatric disorders are associated with rare mutations in certain important genes that have a high penetrance. These rare genetic mutations are highly individualized in affected patients; each patient has his own specific disease-associated mutation. Chromosomal abnormalities associated with psychiatric disorders provide a good example of the rare mutation hypothesis of complex psychiatric disorders. Numerous anecdotal case reports of chromosomal abnormalities associated with psychiatric disorders can be found in the literature [10–12]. Most chromosomal abnormalities found in psychiatric patients are individualized rare mutations, with only a few being recurrent.

The association of chromosomal aberrations with psychiatric disorders indicates that genomic rearrangement is one underlying genetic mechanism of psychiatric disorders, and that psychiatric disorders can also be considered as part of the genomic disorders. However, the yield of karyotyping analysis in psychiatric patients is low; less than 1% of patients with schizophrenia, and less than 5% of patients with autism were found to have disease-associated chromosomal abnormalities. The low frequency of chromosomal abnormalities in psychiatric patients can be partly attributed to the limited resolution of conventional karyotyping analysis in detecting chromosomal deletion and duplication, collectively known as copy number variations (CNVs). Recently, the development of whole genome array-based comparative genomic hybridization (array CGH) technology has greatly facilitated the detection of submicroscopic CNVs, due to its improved resolution; this is also known as the molecular karyotyping method [13,14].

Accumulating evidence, using array CGH, suggests that CNVs play an important role in the pathogenesis of psychiatric disorders. This review aims to summarize the latest findings of recent research on the role of CNVs in the genetic etiology of major psychiatric disorders, including MR, schizophrenia, bipolar disorders, and autism.

2. Population genetics of CNVs

CNVs are defined as gains and losses of DNA segments in the human genome, and cause human genome variations. The human genome has a high content of repetitive sequences that function as mediators to facilitate the formation of CNVs via unequal crossover [15–17]. Theoretically, the size of CNV can range from several base pairs to megabase pairs; however, in the current literature, the size of CNV is usually defined as larger than 1 kb. Three major platforms of array CGH that differ in the design of the probes are currently used to detect CNVs, including oligonucleotide-based array [18], SNP array [19–21], and bacterial artificial chromosome-based array [22–24].

One recent study systematically investigated the occurrence of CNVs across the human genome in 270 multiethnic subjects from the HapMap project, which provides an update overview of the population genetics of CNVs. This study identified 3.048 CNVs from 270 subjects, and 76% of these CNVs were larger than 10 kb, while 64% of the CNVs were from 5 to 10 kb. CNVs larger than 50 kb were rare in this sample. Approximately half of the CNVs (1320 of 3048) were observed in multiple unrelated individuals, with the population frequency larger than 1%; these are referred to as copy number polymorphisms. As to the rare CNVs that accounted for the other half of the CNVs found in this study, the researchers found that the majority of rare CNVs (50 out of 60) were inherited from their parents [25]. Another study examined the CNVs in 300 Han Chinese from Taiwan and found some characteristic CNVs for this sample, suggesting that different populations have their own characteristic CNVs; this should be taken into consideration when conducting CNV studies in different populations [26].

CNVs contribute to genomic diversity and may influence the expression of genes located in and near the CNV regions. Hence, CNVs have a broad influence on the phenotypic spectrum of human traits, including human diseases. CNVs associated with human diseases are referred to as pathogenic CNVs, and the related diseases are known as genomic disorders.

Genomic disorders are not new; several rare genetic diseases have been known to be associated with CNVs, such as Charcot-Marie-Tooth disease type 1A, hereditary neuropathy with liability to pressure palsies (27), Bardet-Bidle syndrome (28), Smith-Magenis syndrome (29), velocardiofacial syndrome, and Williams-Beuren syndrome (30). With the employment of array CGH technology, recent studies have discovered that submicroscopic CNVs play a role in the genetic mechanism of common complex diseases, especially in sporadic cases (31). For example, CNVs were reported to be associated with autoimmune diseases, such as systemic lupus erythematosus, psoriasis, Crohn's disease, rheumatoid arthritis, and diabetes mellitus type 1 (32). Notably, accumulating data suggest that CNVs also play an essential role in neurodevelopmental disorders (33). The association of CNVs with psychiatric disorders will be elaborated on in the following sections.

3. CNV and MR

MR is a childhood-onset neurodevelopmental disorder characterized by reduced intellectual function that results in learning disability and impaired social adaptation. It is a highly heterogeneous disorder with a prevalence of 1–3% in the general population, and males are more often affected than females (34). Approximately 10% of MR is due to gross chromosomal abnormalities, including chromosomal number aberrations, reciprocal translocation, insertions, and deletions (35–37). The advent of array CGH has increased the detection of cryptic chromosomal imbalances in MR that was not possible using routine karyotype analysis (38,39).

Two studies discovered gains and losses of DNA in 13–21% of patients with apparently balanced translocation and an abnormal phenotype (40,41). One study reported that in 117 karyotypically-normal patients diagnosed with unexplained MR (mild to severe) and/or congenital malformations, 18 pathogenic CNVs and nine potentially pathogenic CNVs were identified (42). In a multicenter study, McMullan et al reported that 15% of 120 unexplained MR patients were found to have *de novo* CNVs (43). Taken together, these studies support the utility of array CGH in detecting the chromosomal imbalances associated with MR and congenital anomalies, and the diagnostic yield has been increased by an additional 8–17% (44).

Three studies reported that recurrent microdeletions at 16p11.2 account for around 1% of autism. Interestingly, in a screening of 4284 patients with MR or multiple congenital anomalies, 22 individuals were found to have a 16p11.2 deletion. These individuals were not found to have autism, suggesting that subjects with a 16p11.2 microdeletion may have varied clinical presentations ranging from MR, autism, learning and speech problems, to a normal phenotype (45).

Although array CGH is a useful tool to detect CNVs, it is sometimes difficult to distinguish the pathogenic from the benign. Webber's group used a novel, statistically robust approach that forges links between 148 MR-associated CNVs and phenotypes from around 5000 mouse gene knockout experiments. Using this approach, they were able to identify 78 candidate genes that may contribute to MR and related phenotypes (46).

4. CNV and autism

Autism was first described by Leo Kanner in 1943 as a childhood neurodevelopmental disorder (47). The term is one of the diagnoses within the category of pervasive developmental disorders, which also includes Rett syndrome, pervasive developmental disorders not otherwise specified, and Asperger's syndrome. These diseases are also known as autism spectrum disorders (ASDs). The prevalence is 0.1–0.2% for autism and 0.6% for ASDs (48). Family, twin and adoption studies have shown that the genetic factor plays an important role in the etiology of ASDs; the estimated heritability of ASDs is approximately 90% (49,50).

The genetic underpinnings of ASDs are complex and remain largely unknown. Cytogenetic studies have shown that chromosomal structural aberrations such as translocation, inversion, deletion, and duplication account for approximately 3–5% of autism cases (19,51). The employment of array CGH in the genetic study of ASDs revealed several novel submicroscopic CNVs associated with ASDs.

Three recent studies reported that a recurrent microdeletion at chromosome 16p11.2 is an important CNV associated with autism. Weiss et al found that around 1% of idiopathic and non-syndromic autism cases carried a ~593kb microdeletion and a reciprocal duplication among a sample of multiplex families in the Autism Genetic Resource Exchange (21). Kumar et al also discovered this recurrent microdeletion at 16p11.2 in around 0.6% of autism cases (absent in all controls) (22). Marshall et al reported the same 16p11.2 microdeletion in around 1% of their sample that contained 427 unrelated ASD cases (20).

Duplication of chromosome 15q11-q13 accounts for another 1–3% of ASDs, and is the most frequently found duplication in ASDs. The parental origin of the duplication can influence the phenotype of the affected patients (52). Maternally derived duplications of chromosome 15q11–q13 confer a high risk of ASD (>85%), in contrast to paternally derived duplications whose effects can range from none to mild developmental and cognitive impairment (51,53).

Many rare genomic disorders, such as William syndrome (deletion at 7q11.23), Potocki-Lupski syndrome (duplication at 17p11.2), velocardiofacial syndrome/DiGeorge syndrome (deletion at 22q11.2), Prader-Willi syndrome (paternal deletion at 15q11.2-13) and Angelman syndrome (maternal deletion at 15q11.2-13) also present with ASD-like phenotypes. For example, more than 90% cases of Potocki-Lupski syndrome show features of ASD (53), and approximately 25% of patients with velocardiofacial syndrome/DiGeorge syndrome have psychiatric manifestations that include schizophrenia, attention-deficit hyperactivity disorder, and ASDs (54). Taken together, these data indicate that some CNVs are disease-specific, while others have pleiotropic effects that affect many organs and tissues in affected patients, and lead to various clinical symptoms.

CNVs associated with autism can help identify susceptibility genes to autism; genes located at or near the CNV regions can be considered as candidate genes of autism. For example, ubiquitin protein ligase E3A (UBE3A) and gamma-aminobutyric acid A receptor beta 3 within the 15q11-q13 were reported as autism susceptibility genes (52,55). The SHANK3 gene, located within a recurrent deletion at 22q13 associated with autism, was also reported to be a susceptibility gene of autism (18,56,57). In an analysis of genome-wide CNVs detected from a cohort of 1336 ASD cases and 1110 controls of European ancestry, the NRGN1 and ASTN2 genes that encode neuronal cell-adhesion molecules, and the UBE3A, PARK2, and FBXO40 genes (58), the post-synaptic density genes, SHANK3, NLGN4, and NRXN1-PSD, and the synapse complex genes, DPP6, DPP10 and PCDH9, were found to be implicated in conferring susceptibility to autism in the CNV study by Marshall et al (20). Neurexin 1 (NRXN1) at chromosome 11p12-13 was also considered as a candidate gene of autism in a family-based genome-wide linkage and CNV analysis by the Autism Genome Project Consortium (19).

5. CNV and schizophrenia and bipolar disorders

Schizophrenia is a devastating lifetime brain disorder, characterized by hallucinations, delusions and cognitive deficits, beginning in late adolescence. Schizophrenia is also a complex genetic disorder with an estimated heritability up to 80% (59). In spite of the high heritability, studies searching for genes linked to schizophrenia have been unsuccessful. The results from previous genome-wide linkage and case-control association studies have not been as compelling and consistent as those for other complex diseases, such as type 1 and type 2 diabetes mellitus. Even the most powerful method, the genome-wide association study, could not find a consistent susceptibility gene for schizophrenia. Recently, several reports supporting the association between CNVs and schizophrenia have been published. In this section, we will discuss the evidence, possible mechanisms, and implications of CNVs on the genetics of schizophrenia.

Several research groups from North America, South Africa and Europe found strong evidence that patients with schizophrenia carried an increased burden of rare (frequency $<1\%$) and large (>100 kb) CNVs. One study reported that 15% of cases and 20% of young-onset (<18 years old) cases were found to have novel CNVs, versus 5% of controls in the first phase of the study. The proportion of these structural variants was 23% in childhood-onset cases versus 13% in their parents as controls in the second phase of the study, using independently replicated groups of subjects (60). The other group found that the frequency of *de novo* CNVs in sporadic schizophrenia was 10% versus 1.3% in controls (61). The authors suggested that a rare *de novo* germ line mutation of CNV events contributes to the vulnerability to schizophrenia. In addition to the *de novo* CNVs, several recurrent CNVs at 1q21.1, 15q11.2, 15q13.3 and 22q11.2 were found in several studies with a large sample size. The frequency of recurrent CNVs at these "hot" loci was found in around 0.2–0.6% of schizophrenia patients, with an estimated odds ratio from 3 to 25 (62–64). Nevertheless, one study showed a negative association between CNVs and schizophrenia in a Han Chinese population (65). The discrepant results may be due to the sample size of this study (155 patients *vs.* 187 controls), or to the heterogeneity of the genetic etiology of schizophrenia in different populations.

In contrast to the often contradictory findings of traditional linkage and association studies, most studies on CNVs in schizophrenia are consistent with each other. The identification of CNVs associated with schizophrenia may also shed some light on the pathogenesis of schizophrenia, which can be revealed through the change in gene dosage by deletion, duplication, truncation, or the formation of a chimera gene in the CNV regions. For example, the gene dosage of CNTNAP2 encodes a transmembrane protein of the neurexin superfamily that mediates cell-cell interactions in the nervous system, and was associated with schizophrenia and epilepsy (66). Recently, multiple deletions affecting NRXN1 exons that confer a risk of schizophrenia were reported by Rujescu et al (67). Besides NRXN1, three additional candidate genes (MYT1L, CTNND2 and ASTN2) disrupted by rare CNVs in schizophrenic patients were reported by Vrijenhoek et al (68). Using pathway analysis, Walsh et al (60) found that rare schizophrenia-associated CNVs disproportionately occurred at

signaling networks controlling neurodevelopment, including neuregulin and glutamate pathways. However, this result was not supported by another group [69]. The pathogenesis of CNVs associated with schizophrenia may not be as straightforward as the disruption, or the gene dosage changes of candidate genes. Other mechanisms, such as altered gene expression, epigenetic modulation, pleiotropic effects and second hit mutations, may also be involved.

The association between CNVs and bipolar disorder has been relatively less reported. Lachman et al reported a nominally significant association of the CNV containing GSK3β with bipolar disorder (p=0.002) [70]. One genome-wide CNV survey showed increased singleton deletions (deletions that appear only once in the dataset) in bipolar disorder (cases, 16.2% *vs.* controls, 12.3%; p=0.007 with permutation). Moreover, a marginally greater overall burden of CNVs in patients with an earlier age (<18 years old) at onset of mania was observed in the study (younger onset, 18.9% *vs.* older onset, 14.7%; p=0.05) [71]. Based on this initial evidence, rare CNVs may also play a role in genetic vulnerability to bipolar disorder. Further studies with a large sample size are needed to address this issue.

6. Implications and perspectives of CNV in psychiatric disorders

What are the implications of the positive association of CNVs with psychiatric disorders? First, rare CNVs with high penetrance in the studies mentioned above support the "common disease, rare variants" hypothesis, which may indicate a growing paradigm shift from the "common disease, common variants" hypothesis in the genetic model of complex psychiatric disorders. The "common disease, common variants" hypothesis can explain the observed decline in the risk of recurrence of psychiatric disorders with the increased genetic distance from affected individuals. However, several features of psychiatric disorders support the "multiple rare alleles" model: (a) occasionally, families have been severely affected, but no closely affected relatives were found; (b) increased paternal age is associated with an increased risk of psychiatric disorders, which is compatible with the increased rate of *de novo* germ line mutations with advancing paternal age; (c) decreased fecundity of psychiatric patients that would lead to a diminishment of disease-associated alleles does not reduce the incidence and the prevalence of psychiatric disorders, which can be explained by the ongoing *de novo* mutations in affected patients [72]. The association of CNVs with psychiatric disorders lends support to the multiple rare variants hypothesis of psychiatric disorders. It is noteworthy that the two models are not mutually exclusive; they may be present in different subgroups of patients under the same psychiatric diagnosis.

Second, some patients with different psychiatric diagnoses shared a common CNV region associated with their disease, suggesting that there might be some common pathogenetic pathways underlying different psychiatric symptoms. For example, a common CNV at 16p11.2 was found in both schizophrenia and autism, with deletion in autism and duplications in schizophrenia. It is thus proposed that schizophrenia and autism are disorders of the "social brain", but at opposite ends of the same spectrum. As schizophrenia and other psychotic disorders result from "overdevelopment" of the social brain, ASD reflects underdevelopment [73].

Third, the mysteries of the origin and nature of CNVs are still unsolved. What is known is that certain human genomic regions are prone to recurrent CNV formation. Notably, genes involved in brain development and synaptic plasticity are overrepresented at sites of CNVs [74]. From the viewpoint of evolution, the observation that this instability in humans is recent in origin and tolerated at neural gene-rich sites may account for the development of intelligence in hominids. In other words, a relaxed control from brain function-associated regions of the human genome may result in our unique creativity and language ability. But mental disorders like schizophrenia, MR, bipolar disorder, and autism may be a heavy price to pay for a smarter brain. It has been noted that environment stressors such as famine and/or severe psychological stress may increase CNV mutation rates either globally or at targeted genomic regions [75–77].

Finally, only CNVs greater than 50–100 kb have been assayed to date, and there are still many more loci and biological functions to be assessed. So far, the CNVs account for perhaps only 2–4% of schizophrenia [78], and this varies with different populations. CNV studies provide a complementary approach to traditional SNP-based analyses, and may help us to uncover a part of the puzzling "missing heritability" in psychiatric genetics [79].

7. Summary

CNVs of genomic DNA are not new; they are already present in our genome. With the development of the new technology of array CGH, we are able to detect submicroscopic CNVs and start to understand their association with complex disorders, including mental disorders. If CNVs can account for 5–10% of the genetic etiology of psychiatric patients, the array CGH would have a potential to be used as a laboratory test to help in the clinical diagnosis of psychiatric patients in clinical practice. In addition, studying the

impact of CNVs on the gene expression profile of affected patients would bring new insight into the pathogenesis of psychiatric disorders. This would contribute to the development of new treatments for psychiatric disorders in the future.

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