Genomic copy number variations: A breakthrough in our knowledge on schizophrenia etiology?

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Submitted: 2012-01-22 Accepted: 2012-03-07 Published online: 2012-04-25

Key words: **schizophrenia; genetics; DNA copy number variations; gene expression; population characteristics**

Neuroendocrinol Lett 2012; **33**(2):183–190 **PMID:** 22592199 NEL330212A08

Abstract

OBJECTIVES: The term "copy number variation/variant" (CNV) denotes a DNA sequence with a magnitude of 1 kb at least which is differently represented among individuals based on its deletion or duplication. Since 2008, multiple studies have reported copy number variations in schizophrenia, and they seem to fill in a gap in our knowledge on the genetic background of schizophrenia. The aim of this review is to sum up the current findings related to CNVs in schizophrenia in order to facilitate further research.

METHODS: We searched the PubMed computer database using the key words "schizophrenia AND CNVs" on 26th October 2011. Out of 91 obtained results, we selected the references based on their relevance.

RESULTS: The CNVs at genome loci 1q21.1, 2p16.3, 3q29, 15q11.2, 15q13.3, 16p13.1 and 22q11.2 were associated with schizophrenia most frequently. The data provide evidence for low prevalent, but highly penetrant CNVs associated with schizophrenia. CNV deletions show higher penetrance than duplications. Larger CNVs often have higher penetrance than smaller CNVs. Although the vast majority of CNVs are inherited, CNVs that have newly occurred as de novo mutations have more readily been implicated in schizophrenia. De novo CNVs may be responsible for the presence of schizophrenia in only one of the two monozygotic twins, who otherwise have identical genomes.

CONCLUSION: Identifying CNVs in schizophrenia can lead to changes in the treatment and genetic counselling. Our knowledge on the genetic background of neurodevelopmental disorders may also reduce stigma in schizophrenia.

ORIGINAL ARTICLE

Abbreviations:

APBA2 - Amyloid beta (A4) precursor protein-binding, family A, member 2
ASD - Autistic spectrum disorder
ASTN2 - Astrotactin 2
A2BP1 - Ataxin 2-binding protein 1
BDH1 - 3-hydroxybutyrate dehydrogenase, type 1
CACNA1B - Calcium channel, voltage-dependent, N type, alpha 1B subunit
CEBPD - CCAAT/enhancer binding protein, delta
CHRNA7 - Neuronal acetylcholine receptor subunit alpha-7
CI - Confidence interval
CNV - Copy number variation/variant
COMT - Catechol-O-methyltransferase
CTNND2 - Catenin delta 2 neural plakophilin-related arm-repeat protein
CYFIP1 - Cytoplasmic FMRP interacting protein 1
DLG1 - Discs large homolog 1
DNA - Deoxyribonucleic acid
DOC2A - Double C2-like domains, alpha
GST - Glutathione S-transferase
GSTM1 - Glutathione S-transferase mu 1
GSTT2 - Glutathione S-transferase theta 2
GWAS - Genome-wide association study
IL1RAPL1 - Interleukin 1 receptor accessory protein-like 1
LHX5 - LIM homeobox protein 5
MGS - Molecular Genetics of Schizophrenia study
mRNA - Messenger ribonucleic acid
MYT1L - Myelin transcription factor 1-like
NDE1 - NudE nuclear distribution gene E homolog 1
NRXN1 - Neurexin-1-alpha
NTAN1 - N-terminal asparagine amidase
OR - Odds ratio
PAK2 - p21 protein (Cdc42/Rac)-activated kinase 2
PRKAB2 - 5'-AMP-activated protein kinase subunit beta-2
PRODH - Proline dehydrogenase 1
RET - Ret proto-oncogene
RIT2 - Ras-like without CAAX 2
RXRA - Retinoid x receptor, alpha
SELENBP1 - Selenium binding-protein1
SNP - Single nucleotide polymorphism
SSTR5 - Somatostatin receptor 5
STK11 - Serine/threonine kinase 11
TFRC - Transferrin receptor
VCFS - Velo-Cardio-Facial Syndrome
VIPR2 - Vasoactive intestinal peptide receptor 2
ZNF804A - Zinc finger protein 804A;

INTRODUCTION

Recent genomic microarray technology has allowed genomewide discovery of small deletions or duplications, known as copy number variations/variants (CNVs). The term "copy number variant" denotes a DNA (Deoxyribonucleic acid) sequence with a magnitude of 1 kb at least (by current convention) which is differently represented among individuals based on its deletion or duplication (Hywel *et al.* 2009). CNVs are too small to be identified by standard karyotype. Most of the CNVs can be detected by the same technology which is used in genome-wide association studies (GWASs) (Hywel *et al.* 2009).

CNVs are generated by diverse mutational mechanisms including meiotic recombination, homology-directed and non-homologous repair of double-strand breaks, and errors in replications (Conrad *et al.* 2010).

Copy number variations account for roughly 12% of human genomic DNA and each variation may range from one kilobase to several megabases in size (http://en.wikipedia.org/, 2011). CNVs contrast with single nucleotide polymorphisms (SNPs) which affect only one single nucleotide base. CNVs may be inherited or caused by de novo mutation. CNVs can be limited to a single gene or include a contiguous set of genes. If a complete gene is affected by a duplication, the expression of the relevant protein can be increased. Copy number variations can be responsible for both physiological behavioral traits and disease susceptibility in humans (http://en.wikipedia.org/, 2011).

The significance of microdeletions in schizophrenia etiopathogenesis has already been signalled long ago, when the 22q11.2 deletion syndrome (Velo-Cardio-Facial Syndrome, VCFS) brings in a 20-fold increase in risk for schizophrenia (Bassett & Chow 2008).

Previous procedures used by psychiatric geneticists, as linkage or association studies, did not clarify the genetic background of schizophrenia in a satisfactory way, so the search for DNA copy number variations is the next logical step in our effort to discover schizophrenia etiology and pathogenesis.

The aim of this review article is to sum up and highlight the current knowledge on CNVs in schizophrenia in order to facilitate further reserach.

METHODS

We searched the PubMed computer database using the key words "schizophrenia AND CNVs" on 26th October 2011 (http://www.ncbi.nlm.nih.gov/pubmed/, 2011). Out of 91 obtained results, we selected the references based on their relevance.

RESULTS

Walsh *et al.* (2008) identified DNA microdeletions and microduplications >100 kilobases from 150 individuals with schizophrenia and 268 ancestry-matched controls. Novel deletions and duplications of genes were present in 5% of controls versus 15% of cases and 20% of young-onset cases, both highly significant differences. The association was independently replicated in patients with childhood-onset schizophrenia as compared with their parents. Mutations in cases disrupted genes related to signalling networks controlling neurodevelopment, including neuregulin and glutamate pathways.

International Schizophrenia Consortium (2008) reported a genome-wide survey of rare CNVs in 3 391 patients with schizophrenia and 3 181 ancestrally matched controls. For CNVs that were observed in less than 1% of the sample and were more than 100 kilobases in length, the total burden was increased 1.15-fold in patients with schizophrenia in comparison with controls. This effect was more pronounced for rarer, single-occurrence CNVs and for those that involved

genes as opposed to those that did not. Deletions were found within the region critical for velo-cardio-facial syndrome. Associations with schizophrenia were also found for large deletions on chromosomes 15q13.3 and 1q21.1.

In a genome-wide search for CNVs associating with schizophrenia, Stefansson *et al.* (2008) used a population-based sample to identify de novo CNVs by analysing 9 878 transmissions from parents to offspring. The 66 de novo CNVs identified were tested for association in a sample of 1 433 schizophrenia cases and 33 250 controls. Three rare deletions at 1q21.1, 15q11.2 and 15q13.3 showing nominal association with schizophrenia in the first sample were followed up in a second sample of 3 285 cases and 7 951 controls. All three deletions were significantly associated with schizophrenia and related psychoses in the combined sample.

Xu *et al.* (2008) examined the possibility that rare de novo copy number mutations with relatively high penetrance contribute to the genetic component of schizophrenia. They carried out a whole-genome scan. Confirmed de novo mutations were significantly associated with schizophrenia (p=0.00078) and were collectively approximately eight times more frequent in sporadic (but not familial) cases with schizophrenia than in unaffected controls. Rare inherited copy number mutations were only modestly enriched in sporadic cases.

Vrijenhoek *et al.* (2008) screened 54 patients with deficit schizophrenia. They identified 90 CNVs in total, 77 of which have been reported previously in unaffected control cohorts. Among the genes disrupted by the remaining rare CNVs are MYT1L (myelin transcription factor 1-like), CTNND2 (catenin delta 2 neural plakophilin-related arm-repeat protein), NRXN1 (neurexin-1-alpha), and ASTN2 (astrotactin 2), genes that play an important role in neuronal functioning but except for NRXN1 have not been associated with schizophrenia before. The authors studied the occurrence of CNVs at these four loci in an additional cohort of 752 patients and 706 normal controls from the Netherlands. They identified eight additional CNVs, of which the four that affect coding sequences were found only in the patient cohort.

Kirov *et al.* (2008) sought to determine the relevance of CNVs to the etiology of schizophrenia. Whole-genome comparative genomic hybridization was employed to test DNA from 93 individuals with schizophrenia. Common DNA copy number changes that are unlikely to be directly pathogenic in schizophrenia were filtered out by comparison to a reference dataset of 372 control individuals. A total of 13 aberrations satisfied the authors´ criteria. Two of them are very likely to be pathogenic. The first one is a deletion at 2p16.3 that was present in an affected sibling and disrupts NRXN1. The second one is a de novo duplication at 15q13.1 spanning APBA2 (amyloid beta (A4) precursor protein-binding, family A, member 2). The proteins of these two genes interact directly and play a role in synaptic development and function.

Bassett *et al.* (2008) assessed CNV content and the parental origin of 22q11.2 deletions in a cohort of 100 adults with 22q11.2 deletion syndrome (44 with schizophrenia) and controls. 22q11.2 deletion syndrome subjects with schizophrenia failed to exhibit de novo CNVs or any excess of novel inherited CNVs outside the 22q11.2 region. There were no significant effects of parental origin of the 22q11.2 deletion, deletion length, parental age or family history on expression of schizophrenia. There was no evidence for a general increase of de novo CNVs in 22q11.2 deletion syndrome. A novel finding was the relative paucity of males with de novo 22q11.2 deletions of paternal origin (p=0.019).

Kirov *et al.* (2009) investigated the involvement of rare (<1%) copy number variants in 471 cases of schizophrenia and 2 792 controls. Large CNVs >1 Mb were 2.26 times more common in cases (p=0.00027), with the effect coming mostly from deletions. Two large deletions were found in two cases each, but in no controls – at 22q11.2 and 17p12. The authors also provided the support for an association between deletions at 15q11.2 and schizophrenia (p=0.026).

Guilmatre *et al.* (2009) investigated 28 candidate loci previously identified by comparative genomic hybridization studies for gene dosage alteration in 247 cases with mental retardation, 260 cases with autism spectrum disorders, 236 cases with schizophrenia or schizoaffective disorder, and 236 controls. Recurrent or overlapping CNVs were found in cases at 39.3% of the selected loci. The collective frequency of CNVs at these loci was significantly increased in cases with autism, schizophrenia, and mental retardation compared with controls (p<0.001, p=0.01, and p=0.001, respectively). Most of these de novo CNVs, which contain genes involved in neurotransmission or synapse formation and maintenance, were present in the three pathological neurodevelopmental conditions, supporting the existence of shared biologic pathways.

Xu *et al.* (2009) combined linkage analysis with studies of fine-level chromosomal variation in families recruited from the Afrikaner population in South Africa. The authors demonstrated that individually rare inherited copy number variants are more frequent in cases with familial schizophrenia as compared to unaffected controls and affect almost exclusively genic regions. They also found that while the prevalence of rare structural variants is similar in familial and sporadic cases, the type of variants is markedly different. In addition, Xu *et al.* (2009) identified a region on chromosome 13q34 that shows genome-wide significant linkage to schizophrenia and showed that in the families not linked to this locus, there is evidence for linkage to chromosome 1p36. No causative CNVs were identified in either locus. The results highlighted differences in the genetic architecture of the familial and sporadic forms of schizophrenia.

McCarthy *et al.* (2009) reported the association of 16p11.2 microduplications with schizophrenia in two large cohorts. The microduplication was detected in 12/1 906 (0.63%) cases and 1/3 971 (0.03%) controls (p=1.2×10^{-5}, OR=25.8) from the initial cohort, and in 9/2 645 (0.34%) cases and 1/2 420 (0.04%) controls (p=0.022, OR=8.3) of the replication cohort. The 16p11.2 microduplication was associated with a 14.5-fold increased risk of schizophrenia (95% CI 3.3–62) in the combined sample.

Rujescu *et al.* (2009) examined the neurexin 1 gene (2p16.3) for copy number variants in 2 977 schizophrenia patients and 33 746 controls from seven European populations. They found 66 deletions and 5 duplications in NRXN1, including a de novo deletion: 12 deletions and 2 duplications occurred in schizophrenia cases (0.47%) compared to 49 and 3 (0.15%) in controls. The CNVs varied from 18 to 420 kb. The authors performed a Cochran-Mantel-Haenszel exact test to estimate association between all CNVs and schizophrenia (p=0.13; OR=1.73; 95% CI 0.81–3.50). Because the penetrance of NRXN1 CNVs may vary according to the level of functional impact on the gene, Rujescu *et al.* (2009) next restricted the association analysis to CNVs that disrupt exons (0.24% of cases and 0.015% of controls). These were significantly associated with a high odds ratio (p=0.0027; OR=8.97, 95% CI 1.8–51.9) for schizophrenia.

Need *et al.* (2009) examined CNVs in 1 013 schizophrenia cases and 1 084 controls of the European ancestry, and a further set of 60 cases and 64 controls of the African ancestry. They found that eight cases and zero controls carried deletions greater than 2 Mb, of which two, at 8p22 and 16p13.11-p12.4, were newly reported. A further evaluation of 1 378 controls identified no deletions greater than 2 Mb, suggesting a high prior probability of disease involvement when such deletions are observed in cases. The authors provided further evidence for some smaller, previously reported, schizophrenia-associated CNVs, such as those in NRXN1 and APBA2.

Ikeda *et al.* (2010) investigated the role of rare CNVs in 575 patients with schizophrenia and 564 control subjects from Japan. There was a nonsignificant trend for excess of rare CNVs in schizophrenia (p=0.087), however, the authors did not confirm the previously implicated association for very large CNVs (>500 kilobase) in this population. Ikeda *et al.* (2010) provided support for three previous findings in schizophrenia, as they identified one deletion in a case at 1q21.1, one deletion within NRXN1, and four duplications in cases and one in a control subject at 16p13.1.

Magri *et al.* (2010) undertook a systematic search for CNVs in 172 patients with schizophrenia and 160 healthy controls of Italian origin. They found five patients with a CNV occurring in one of the regions most convincingly implicated as risk factors for schizophrenia: NRXN1 and the 16p13.1 regions were found to be deleted in single patients and 15q11.2 in 2 patients, whereas the 15q13.3 region was duplicated in one patient. Furthermore, the authors found three distinct patients with CNVs in 2q12.2, 3q29 and 17p12 loci, respectively. Magri *et al.* (2010) also found 5 large CNVs (>900 kb) in 4q32, 5q14.3, 8q23.3, 11q25 and 17q12 in five different patients that could include some new candidate schizophrenia susceptibility genes.

Ono *et al.* (2010) searched CNVs in monozygotic twins discordant for schizophrenia to identify susceptible loci for schizophrenia. Three pairs of monozygotic twins discordant for schizophrenia were subjected to analysis. Validations by quantitative polymerase chain reaction and DNA sequencing revealed that none of the regions had any discordance between the three twin pairs. The results support the hypothesis that epigenetic changes or fluctuation in developmental process triggered by environmental factors may contribute to the pathogenesis of schizophrenia.

Mulle *et al.* (2010) reported a genome-wide analysis of 245 schizophrenia cases and 490 controls of Ashkenazi Jewish descent. They limited the analysis to deletions over 500 kb in size. The authors observed seven large, rare deletions in cases, with 57% of these being de novo. Mulle *et al.* (2010) focused on one 836 kb de novo deletion at chromosome 3q29 that falls within a 1.3–1.6 Mb deletion previously identified in children with intellectual disability and autism. By combining their data with prior CNV studies of schizophrenia and analysis of the data of the Genetic Association Information Network, the authors identified six 3q29 deletions among 7 545 schizophrenic subjects and one among 39 748 controls, resulting in a statistically significant association with schizophrenia (p=0.02) and an odds ratio estimate of 17 (95% CI 1.36–1 198.4). This 3q29 deletion region implicates 20 annotated genes, including PAK2 (p21 protein (Cdc42/Rac)-activated kinase 2) and DLG1 (discs, large homolog 1).

Amar *et al.* (2010) analyzed selenium binding-protein1 (SELENBP1; 1q21.3) copy number variation in blood DNA from 49 schizophrenia patients and 49 controls (cohort A). They also investigated SELENBP1 copy number variants in age-, sex- and postmortem interval-matched cerebellar DNA samples from 14 patients and 14 controls (cohort B). Furthermore, the authors analyzed CNV of the SELENBP1 locus in blood DNA from 26 trios of schizophrenia probands and their healthy parents (cohort C). SELENBP1 mRNA (messenger ribonucleic acid) levels were measured by real-time polymerase chain reaction. In the cohort A, reduced copy number of the SELENBP1 locus was found in four patients but in none of the controls. In the cohort B, Amar *et al.* (2010) found reduced copy number of the SELENBP1 locus in two patients but in none of the controls. In the cohort C, three patients exhibited copy number reduction, not present in their parents, indicating a de-novo mutation. A reduction in SELENBP1 mRNA levels in the postmortem cerebellar samples of schizophrenia patients was also found.

Glessner *et al.* (2010) performed a whole-genome CNV analysis on a cohort of 977 schizophrenia cases and 2 000 healthy adults of European ancestry who were genotyped with 1.7 million probes. Positive findings were evaluated in an independent cohort of 758 schizophrenia cases and 1 485 controls. The Gene Ontology synaptic transmission family of genes was notably enriched for CNVs in the cases (p=1.5×10^{-7}). Among these, CACNA1B (calcium channel, voltage-dependent, N type, alpha 1B subunit) and DOC2A (double C2-like domains, alpha), both calcium-signalling genes responsible for neuronal excitation, were deleted in 16 cases and duplicated in 10 cases, respectively. In addition, RET (ret proto-oncogene) and RIT2 (ras-like without CAAX 2), both ras-related genes important for neural crest development, were significantly affected by CNVs. RET deletion was exclusive to seven cases, and RIT2 deletions were overrepresented common variant CNVs in the schizophrenia cases.

Lee *et al.* (2010) conducted genome-wide screening for DNA copy number variations for ten pairs, a total of 20 cases, of siblings affected with schizophrenia. They found that negative symptoms were significantly more severe (p<0.05) in the subgroup that harbored more genetic imbalance (number of CNVs disrupted genes >13) as compared with the subgroup with fewer CNVs (number of CNVs disrupted genes <6), indicating that the degree of genetic imbalance may influence the severity of the negative symptoms of schizophrenia. Four central nervous system related genes including CCAAT/enhancer binding protein, delta (CEBPD, 8q11.21), retinoid x receptor, alpha (RXRA, 9q34.2), LIM homeobox protein 5 (LHX5, 12q24.13) and serine/threonine kinase 11 (STK11, 19p13.3) were recurrently disrupted by CNVs.

Rodriguez-Santiago *et al.* (2010) targeted 140 previously reported and putatively relevant gene-containing CNV regions in 654 schizophrenic patients and 604 controls. Most genotyped CNVs (95%) showed very low (<1%) population frequency. A few novel rare variants were only present in patients suggesting a possible pathogenic involvement, including 1.39 Mb overlapping duplications at 22q11.23 found in two unrelated patients, and duplications of the somatostatin receptor 5 gene (SSTR5) at 16p13.3 in three unrelated patients. Furthermore, among the few relatively common CNVs observed in patients and controls, the combined analysis of gene copy number genotypes at two glutathione S-transferase (GST) genes, GSTM1 (glutathione S-transferase mu 1) (1p13.3) and GSTT2 (glutathione S-transferase theta 2) (22q11.23), showed an association of the genotypes at both loci with an additive effect for increased vulnerability to schizophrenia (p=0.0008, OR=1.92).

Melhem *et al.* (2011) reported on copy number variants found in Palauan subjects ascertained for schizophrenia and related psychotic disorders. They compared CNVs found in this Oceanic population with those seen in other samples, typically of European ancestry. DNA samples from 197 subjects affected with schizophrenia and related psychotic disorders, 185 of their relatives, and 159 control subjects were characterized for CNVs. Copy number variants thought to be associated with risk for schizophrenia and related disorders also occur in affected individuals in Palau, specifically 15q11.2 and 1q21.1 deletions, partial duplication of IL1RAPL1 (interleukin 1 receptor accessory protein-like 1, Xp21.3), and chromosome X duplications (Klinefelter's syndrome). Partial duplication within A2BP1 (ataxin 2-binding protein 1) appears to convey an eightfold increased risk in male subjects (95% CI 0.8–84.4) but not female subjects (OR=0.4, 95% CI 0.03–4.9).

Buizer-Voskamp *et al.* (2011) investigated 834 Dutch schizophrenia patients and 672 Dutch control subjects. In total, 2 437 CNVs were identified with an average number of 2.1 CNVs/subject for both cases and control subjects. The authors observed significantly more deletions but not duplications in schizophrenia cases versus control subjects. The CNVs identified coincide with loci previously reported in the literature (1q42 and 22q11.2) as related to schizophrenia. Buizer-Voskamp *et al.* (2011) also found a potentially novel locus on chromosome 5q35.1.

Vacic *et al.* (2011) reported the significant association of copy number gains at chromosome 7q36.3 with schizophrenia. Microduplications with variable breakpoints were detected in 29 of 8 290 (0.35%) patients versus 2 of 7 431 (0.03%) controls. All duplications overlapped or were located within 89 kilobases upstream of the vasoactive intestinal peptide receptor gene VIPR2.

Ingason *et al.* (2011b) examined 4 345 schizophrenia patients and 35 079 controls from 8 European populations for duplications and deletions at the 16p13.1 locus. They found a threefold excess of duplications and deletions in schizophrenia cases compared with controls, with duplications present in 0.30% of cases versus 0.09% of controls (p=0.007) and deletions in 0.12 % of cases and 0.04% of controls (p>0.05). Candidate genes in the region include NTAN1 (N-terminal asparagine amidase) and NDE1 (nudE nuclear distribution gene E homolog 1).

Levinson *et al.* (2011) analyzed CNVs in the Molecular Genetics of Schizophrenia study (MGS) and additional available data. MGS data for 3 945 subjects with schizophrenia or schizoaffective disorder and 3 611 screened comparison subjects were available for analysis of rare CNVs (<1% frequency). In analyses of MGS data combined with other available data sets, odds ratios of 7.5 or greater were observed for previously reported deletions in chromosomes 1q21.1, 15q13.3, and 22q11.21, duplications in 16p11.2, and exon-disrupting deletions in NRXN1. The most consistently supported candidate associations across data sets included a 1.6 Mb deletion in chromosome 3q29 (21 genes, transfer-

rin receptor TFRC to 3-hydroxybutyrate dehydrogenase, type 1 BDH1), exonic duplications in the gene for vasoactive intestinal peptide receptor 2, and exonic duplications in C16orf72. The case subjects had a modestly higher genome-wide number of gene-containing deletions (>100 kb and >1 Mb) but not duplications.

Ingason *et al.* (2011a) scanned 7 582 patients with schizophrenia or schizoaffective disorder and 41 370 comparison subjects without known psychiatric illness for copy number variants at 15q11-q13 and determined the parental origin of duplications. Duplications were found in four case patients and five comparison subjects. All four case patients had maternally derived duplications (0.05%), while only three of the five comparison duplications were maternally derived (0.007%), resulting in a significant excess of maternally derived duplications in schizophrenia patients (OR=7.3).

DISCUSSION

The CNVs at genome loci 1q21.1 (candidate gene e.g. 5'-AMP-activated protein kinase subunit beta-2, PRKAB2), 2p16.3 (candidate gene e.g. neurexin 1, NRXN1), 3q29 (candidate genes e.g. D-beta-hydroxybutyrate dehydrogenase, BDH1; disks large homolog 1, DLG1; p21 activated kinase, PAK2; transferrin receptor protein 1, TFRC), 15q11.2 (candidate gene e.g. cytoplasmic FMRP interacting protein 1, CYFIP1), 15q13.3 (candidate gene e.g. neuronal acetylcholine receptor subunit alpha-7, CHRNA7), 16p13.1 (candidate genes e.g. N-terminal asparagine amidase, NTAN1; nuclear distribution protein nudE homolog 1, NDE1) and 22q11.2 (candidate genes e.g. catechol-O-methyltransferase, COMT; glutathione S-transferase theta 2, GSTT2; proline dehydrogenase 1, PRODH) were associated with schizophrenia most frequently.

The data provide evidence for low prevalent, but highly penetrant CNVs associated with schizophrenia. CNVs may involve multiple genes and/or regulatory regions. CNV deletions show higher penetrance than duplications. Larger CNVs often have higher penetrance than smaller CNVs (Bassett *et al.* 2010). Although the vast majority of CNVs are inherited, CNVs that have newly occurred as de novo (spontaneous) mutations have more readily been implicated in diseases. De novo CNVs may be responsible for the presence of schizophrenia in only one of the two monozygotic twins, who otherwise have identical genomes (Maiti *et al.* 2011).

The explanation of the biologic significance of CNVs, whether a deletion or a duplication, may be that the "dosage" of gene expression is tightly controlled during neurodevelopment and that abnormalities of levels of gene expression, too much or too little transcription of a given gene, can perturb brain development and lead to neurodevelopmental disorders (Morrow 2010). Although disorders may emerge from too little or too much gene expression, increases in gene dosage may be less deleterious than decreases. The phenotypic effects of copy number variants associated with schizophrenia are pleiotropic and imply the existence of shared biologic pathways among multiple neurodevelopmental conditions.

Clinical heterogeneity is typical in schizophrenia. Schizophrenia is not a disease but a cluster of symptoms. Schizophrenia is a diagnosis made entirely on clinical grounds (symptoms, course) without the use of any biological markers. The data suggest that very few schizophrenia patients share identical genomic causation. The evidence for SNPs associated with schizophrenia agrees with the "common disease-common variant" model. On the other hand, the role of CNVs supports the "common disease-rare variant" model of the genetic background of schizophrenia. Both these models are probably coexistent, they need not be mutually exclusive (Tam *et al.* 2009).

Genes by themselves are not sufficient to induce schizophrenia, they operate in interplay with the environment. Maternal pregnancy complications, prenatal maternal infection, paternal age, quality of early rearing environment, abuse in childhood, urban environment, cannabis use, migration, stressful life events or traumatic brain injury belong to the most important environmental factors (van Winkel *et al.* 2010).

CNVs have emerged as strong susceptibility factors not only in schizophrenia, but also in autism, mental retardation, bipolar disorder, attention deficit hyperactivity disorder, and epilepsy (Merikangas *et al.* 2009; Morrow 2010; Vissers *et al.* 2010; Mulley & Mefford 2011). In some cases, there is a genetic overlap among these clinical states (Lionel *et al.* 2011).

Recent studies assessing copy number variation in autistic spectrum disorder (ASD) and schizophrenia have repeatedly observed heterozygous deletions eliminating exons of the neurexin-1α gene (but not the neurexin-1β gene) in patients with ASD and schizophrenia. The neurexins are synaptic adhesion proteins that are known to play a key role in synaptic formation and maintenance. The genetic disruption of neurexin-1α may underpin the neuropathology contributing to these distinct neurodevelopmental disorders (Reichelt *et al.* 2011).

Variation at ZNF804A (zinc finger protein 804A, 2q32.1) is associated with risk of both schizophrenia and bipolar disorder. Some rare CNVs in this location are also associated with risk of autism and epilepsy (Craddock *et al.* 2009).

Since 2008, multiple studies have reported on copy number variations in schizophrenia. Many identified regions are unique with minimal overlap between studies. This makes it difficult to gain a comprehensive overview of all CNVs involved in the etiology of schizophrenia (Buizer-Voskamp *et al.* 2011). Also the relevant genes and neurobiological mechanisms are recently not well understood. These facts limit the potential use of the results of schizophrenia CNVs studies in the clinical practice.

However, our findings could represent a decisive step towards understanding the causes of severe mental disorders including schizophrenia as well as developing new potential treatments. Spontaneous (or inherited) copy number variations can be identified in a hypothesis-free genome-wide approach (Rujescu & Collier 2009). Subsequently, the researchers will be able to find the matching neurobiological pathways relevant to schizophrenia. The recent genetic findings may also lead to changes in psychiatric terminology. It will be based not only on clinical symptoms of mental disorders, but also on biological markers.

The identification of genetic vulnerability factors should involve a comprehensive survey of the entire human genome. Future technologies will be better designed to assay common CNVs reliably. Next genetic research of schizophrenia should also involve epigenetics, transcriptomics, metabolomics, intermediate phenotypes and gene-environment interactions. Large, well phenotyped patient samples as well as smaller but homogenous case samples will be necessary for further research. Genetic and phenotype data from the families will also be important. Geneticists, statisticians, epidemiologists, radiologists, psychiatrists and neuropsychologists should collaborate in this effort. Recent development of a database of CNVs in a cohort of healthy individuals by Shaikh *et al.* (2009) will facilitate more reliable discrimination of CNVs with etiological effects. The replication of genetic findings in schizophrenia will also be crucial.

CONCLUSIONS

Identifying large, rare CNVs in schizophrenia can lead to changes in the treatment and genetic counselling helpful to the patient, family, and clinicians. Last but not least, our recent knowledge on the genetic background of neurodevelopmental disorders may reduce stigma in schizophrenia, autism, and mental retardation.

Declaration of interest

The authors declare no conflict of interest related to this manuscript.

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