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Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders

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Abstract

Recent studies have established an important role for rare genomic deletions and duplications in the etiology of schizophrenia. This research suggests that the genetic architecture of neuropsychiatric disorders includes a constellation of rare mutations in many different genes. Mutations that confer substantial risk for schizophrenia have been identified at several loci, most of which have also been implicated in other neurodevelopmental disorders, including autism. Genetic heterogeneity is a characteristic of schizophrenia; conversely, phenotypic heterogeneity is a characteristic of all schizophrenia-associated mutations. Both kinds of heterogeneity probably reflect the complexity of neurodevelopment. Research strategies must account for both genetic and clinical heterogeneity to identify the genes and pathways crucial for the development of neuropsychiatric disorders.

A resurgence of the field of schizophrenia genetics

Genes play an important role in the etiology of schizophrenia, with a heritability estimated at ~ 80% 1. Despite intensive effort to discover genetic risk factors for schizophrenia, causal variants have eluded definitive identification 2–5. In the past, linkage studies were confounded by an under-appreciated degree of locus heterogeneity, yielding weak signals at many locations throughout the genome, the bulk of which did not replicate consistently across studies 6. Candidate gene-based analyses of common variants were also largely unsuccessful 2–5, 7. The first wave of genome-wide association studies produced variable results,8–10 confounded by a lack of statistical power and the extremely small effect sizes of common risk alleles.

In the past two years this trend has reversed. Studies by several groups have begun to shed new light on the genetics of schizophrenia. Recent findings have established that both rare mutations of large effect 11–15 and common variants of modest effect 16–19 contribute to genetic risk for schizophrenia. Collectively, these studies show that schizophrenia is characterized by much more genetic heterogeneity than was previously thought. The risk alleles that have been implicated include rare copy number variants (CNVs) and common haplotypes based on single nucleotide polymorphisms (SNPs). Mutations that confer risk are located throughout the genome and involve many different genes.

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What may represent the greatest change in our scientific understanding of schizophrenia is the recognition that individually rare genetic variants at many loci play a role in the etiology of schizophrenia. This discovery is primarily based on findings that emerged from early cytogenetic studies and recent studies of copy number variation (CNV). Here we explore the role of rare structural variants in schizophrenia and discuss the wider implications for psychiatric research.

The CNV-based approach

Copy number variants (CNVs) are large (typically >1000 bp) deletions and duplications of the genome that vary in copy number among individuals in the population 20–22. Other classes of structural variation include balanced rearrangements, such as inversions and balanced translocations. Once considered to be anomalies that were rare among healthy individuals, CNVs are now recognized as a source of inter-individual genetic variation 21–26.

CNV analysis is a mutation discovery approach, similar in nature to other rare variant approaches, such as candidate gene re-sequencing 27–35, Because CNV analysis is typically applied genome-wide, this approach permits researchers to look for disease association in multiple ways. This includes single-marker association (examining the frequencies of individual variants); gene-based association (examining the frequency of multiple individually rare mutations in the same genes); and genome-wide mutational burden analysis (examining the aggregate frequency of all rare CNVs in patients and controls) (Figure 1). Using these technologies, recent studies have shown that individually rare structural variants are associated with schizophrenia 11–13, 36 and other neurocognitive disorders 20–22.

Rare structural variants play an important role in the etiology schizophrenia

Early evidence implicating structural abnormalities in schizophrenia came from cytogenetic studies 37–40. Seminal examples include a translocation of the gene disrupted in schizophrenia (*DISC1*) identified in a large Scottish pedigree 41 and a microdeletion of Chromosome 22q11.2 which is the underlying cause of Velocardiofacial syndrome and confers a substantial risk of schizophrenia42. The evidence for these individual variants was convincing. However, because such mutations accounted for a small proportion of cases, it was not widely anticipated that rare structural variants as a class would contribute significantly to the genetic risk for schizophrenia.

Further evidence that rare variants contributed to disease risk required the development of more sensitive microarray-based methods for analysis of CNVs 43–46. Multiple independent studies strongly suggest a role for individually rare structural variants in schizophrenia patients. This line of research has uncovered several findings. First, the genome-wide burden of rare structural variants is significantly greater in patients than in healthy controls. Second, recurrent deletions or duplications at different loci are significantly over-represented in schizophrenia. Finally, many of the structural variants that are associated with schizophrenia are not located in 'hotspots' in the genome, but are dispersed throughout the genome and involve many different genes.

Mutational burden analysis

In 2008, a series of studies by multiple groups applied the first systematic tests of the hypothesis that rare copy number variants contribute to risk of schizophrenia. This was done by comparing the total genome-wide mutational burden of rare CNVs in patients with that of matched controls (Figure 1c). Assuming that patterns of rare non-causal variation are similar

in patients and controls, an enrichment of causal rare variants in cases would be predicted to increase the total genomic burden of rare CNVs.

Several studies have shown that the mutational burden of rare structural variants is significantly greater in patients with schizophrenia than in healthy controls. One study, by our group, examined rare CNVs of >100 Kb from constitutional genomic DNA of 150 cases and 258 controls. Rare deletions and duplications were detected in 5% of healthy controls compared with 15% of adult-onset schizophrenia patients and 20% of patients with disease onset by 18 years of age, a 3.4-fold and 4.8-fold enrichment, respectively 11. This result was replicated in a sample of 83 trios (consisting of a patient and both parents), in which a 2.6-fold enrichment of rare structural variants was observed in patients compared with the untransmitted parental chromosomes. An increased mutational burden of rare CNVs in schizophrenia was also observed by two independent groups 12, 13. The International Schizophrenia Consortium (ISC)(http://pngu.mgh.harvard.edu/isc/), studying several independent cohorts, found that affected individuals overall had a 1.15-fold increased risk of harboring a rare CNV compared with ancestry-matched controls. The strongest effects were observed for variants that contained genes and for events found in only one individual 12. These findings have been replicated in more recent studies of schizophrenia 15 and bipolar disorder 47. One study did not replicate the association of rare CNVs with schizophrenia 48 and in another study, the increased frequency of rare CNVs in patients was observed for the largest (>2 Mb) CNVs, but not for all rare variants >100 Kb 49.

In a family-based study, Xu and colleagues observed an 8-fold increase in frequency of *de novo* CNVs in patients from families with sporadic schizophrenia compared with healthy controls 36. By contrast, rare *de novo* CNVs were not observed in any patients from families with multiple cases of schizophrenia. These results are consistent with previous family-based studies of autism spectrum disorders (ASDs) 50, 51, and suggest that rare *de novo* mutations account for some proportion of sporadic cases. In a more recent study by Xu *et al*, the contribution of inherited structural variants in this cohort was found to be greatest in patients with a positive family history of mental illness 52. These results are consistent with rare CNVs playing an etiological role in sporadic and familial schizophrenia.

Thus far, case-control and family-based studies 11, 12, 36, 50 indicate that mutations contributing to schizophrenia are not limited to a small number of “hotspots,” but instead involve many different genes throughout the genome. Some of these rare mutations are recurrent, but most are observed in only a single patient, and it is this latter class of mutations that shows the strongest association with disease 11, 12. These findings are consistent with the idea that individually rare mutations in many different genes, some of which are unique to a single patient, are genetic risk factors for schizophrenia.

Large deletions and duplications confer significant risk for schizophrenia

In large cohorts of patients with schizophrenia, some genomic ’hotspots‘ harbor multiple structural variants strongly associated with the disease. For example, deletions at four different loci, 1q21.112, 13, 15q11.213, 15q13.312, 13 and 22q11.2 12, 37 are significantly over-represented in schizophrenia patients compared with controls. More recent studies have identified significant associations with microduplications of 16p11.2 53, and 16p13.1 54 and microdeletions of the gene neurexin-1 (NRXN1) 14, 55 All of these structural variants were found to confer substantial risk. Reported odds ratios for deletions of 1q21.1 and 15q.13.3 were 6.6–14.8 and 11.5–17.9, respectively (see table 1 for more details). Odds ratios for the microduplications of 16p11.2 and 16p13.1 were 8.3–25.8 and 3.0, respectively. The odds ratio for deletions of neurexin-1 (NRXN1) in schizophrenia was 9.0 14. Several other candidate regions for schizophrenia have been identified based on suggestive evidence from CNV studies. These include deletions of the genes Contactin Associated Protein-like 2

(*CNTNAP2)* 56, a duplication spanning the Amyloid beta (A4) Precursor Protein-Binding A2 (*APBA2)* 55, and balanced translocations of the genes Phosphodiesterase 4B (*PDE4B)* 39 and Neuronal PAS-domain protein 3 (*NPAS3)* 40. These and other findings provide promising avenues for further research.

All CNVs that have shown a significant and replicated association (see Table 1) are located within regions of genome that are unstable. Disease-associated mutations are observed frequently at these loci because they are subject to high rates of structural mutation (as high as one mutation in 10 000 individuals) 23. Regions of instability at 1q21.1, 15q11,1, 15q13.3, 16p11.2, 16p13.1 and 22q11.2 are flanked by tandem segmental duplications, which mediate rearrangements by non-allelic homologous recombination (NAHR) 23, 37, 57–59. Recurrent *de novo* rearrangements have been detected in families at all 5 of these loci 60, 61, 50, 62–64 and the same is true for the gene NRXN1 at 2p16.3 14, 65, 66. These results suggest that the high frequency of CNVs that are observed at these loci in patients is due to a high rate of spontaneous mutation.

Collectively, these seven hotspots account for a small but measurable fraction of schizophrenia cases (~2–4%, Table 1). However, these few loci do not account for most of the increased CNV burden in schizophrenia. For example, when the most significant individual loci in the ISC study were removed from the mutational burden analysis, the effect was not greatly diminished 12. This suggests that CNVs at other loci account for most of the effect. In other words 'warm spots', with low or intermediate rates of mutation (10^{-6}–10^{-5}) could outnumber the 'hotspots' with high mutation rates (10^{-5}–10^{-4}). The prevalence of causal CNVs at any one such region is likely to be less than one in 500 patients. Therefore, very large family-based and case-control studies are needed to provide statistical evidence for the involvement of any single event.

Implications for the genetic architecture of schizophrenia

One disorder involves a multiplicity of genes and risk alleles

Rare mutations at many loci throughout the genome contribute to the etiology of schizophrenia. These findings are consistent with a multiple rare variant (MRV) model of schizophrenia 2, 30, 67, and have contributed to a shift in the prevailing view. An exclusively polygenic model that explains the genetic basis of this disease by the combined action of common genetic variants with modest effects 68 is no longer realistic.

Although, the identification of common risk alleles in schizophrenia has been a challenge, this endeavor has yielded some intriguing new findings. Statistical evidence for the contribution of common genes of small effect has come from recent large GWAS studies. The major histocompatibility (MHC) locus on 6p22.1 was implicated in three different studies 16–18. In addition, one study has reported a genome-wide significant association of the transcription factor ZNF804A with schizophrenia 19. Furthermore, the study by Purcell et al 16 addressed the aggregate role of common polygenic variation. By defining a large number of 'score' alleles (i.e. putative risk alleles) based on modest statistical evidence from a primary sample, Purcell *et al.* 16 estimated that the same SNPs explained ~30% of the variance in risk in multiple independent cohorts of schizophrenia (based on Nagelkerke's pseudo R-squared from logistic regression). These results, if correct, suggest that the population of individuals with schizophrenia is enriched for a large number (hundreds or possibly thousands) of different common alleles, each contributing a very modest effect.

The relative importance of common variants and rare variants in the etiology of schizophrenia is not known, and the scientific debate over this issue is polarized. Thus, the results of GWAS studies have been met with excitement by some and with skepticism by

others in the community (http://www.schizophreniaforum.org/new/detail.asp?id=1532). The truth will ultimately be determined based on empirical evidence. Having demonstrated a genetic contribution from both classes of variation is only the first step. We must keep in mind that the value of these two genetic approaches will also be judged based on how much the risk variants they uncover teach us about disease process. It is now essential to determine the underlying biological mechanisms by identifying more of the individual loci involved and determining how variation (whether rare or common) at these loci influence the function genes and neurobiological pathways.

The rare variant and polygenic models should therefore be regarded as complementary rather than as mutually exclusive. Rare variants play a role in disease etiology, and include mutations that confer high risk, but these are not classical mendelian causes of disease. Schizophrenia is a multifactorial disorder. One or more mutations of large effect can exert a major influence on the disease phenotype in an individual patient. The disease phenotype of the same individual may[s1] [E2]also be influenced by common genetic variants and other factors, including epigenetic variation and environmental exposures. In our view, such modifiers, whether environmental, epigenetic, or genetic, will be easier to characterize after the genes of major effect are identified and their biological actions are better understood.

One mutation can lead to multiple disorders

Some structural variants confer risk for schizophrenia and for other disease phenotypes, suggesting that there is high phenotypic variability even for mutations with high odds ratios. For instance, phenotypic variability has been observed among mutation carriers within the same family. In a large Scottish pedigree harboring a translocation of *DISC1*, clinical presentation was variable among the 29 relatives with the translocation and included people with schizophrenia, bipolar disorder, major depressive disorder and those without mental illness 41. Within the families of five schizophrenic patients with microduplications of 16p11.2, other mutation carriers had diagnoses of schizophrenia, bipolar disorder, psychosis-NOS and major depression 53.

The clinical variability of schizophrenia-associated CNVs is also evident from the fact that some CNVs are associated with disease in studies of different neuropsychiatric or developmental disorders. All of the CNVs that are statistically over-represented in schizophrenia are also significantly associated with other disease phenotypes, as listed in table 1. For example, the 22q11 microdeletion is associated with schizophrenia and Velocardiofacial syndrome 42, as well as anxiety, depression, attention-deficit hyperactivity disorder, obsessive-compulsive disorder and autism spectrum disorders 69. This is also the case for other CNVs that have been recently identified. Deletions and duplications at 1q21 are associated with schizophrenia 12, 13 and multiple pediatric phenotypes, including developmental delay and congenital malformations 60, 70. Deletions at 15q13.3 are associated with schizophrenia, generalized epilepsy 71, 72 and mental retardation 73. Similarly, microduplications of 16p11.2 were recently found to be significantly associated with schizophrenia, autism, and bipolar disorder 53, 62. One study has examined a set of 28 candidate loci across multiple disorders and found CNVs at these loci to be significantly enriched in autism, schizophrenia and mental retardation compared with controls 74. These results are consistent with the idea that schizophrenia and other disorders share overlapping biological pathways.

It is intriguing that some of the same mutations are associated with pediatric developmental disorders and adult neuropsychiatric disorders, suggesting that the phenotype of the individual might in part be dependent on the age at ascertainment. Prior to the onset of schizophrenia, 'prodromal' symptoms of cognitive impairment could meet criteria for another clinical diagnosis, such as autism. This is clearly the case for patients with

microdeletion of 22q11.2 and Velocardiofacial syndrome. The same might be true for other schizophrenia-associated microdeletions and microduplications discussed in this review.

Given the complexities of neurodevelopment, it is not surprising that the impact of structural variants is variable. In principle, expressivity could be modified by additional genetic events, either gene-specific or global epigenetic events, environmental exposures, or stochastic events during development. It will be important to determine how severe mutations and their modifiers combine to influence variable expressivity.

Implications for psychiatric research

Strategies for gene discovery

The growing evidence for the role of rare variants in psychiatric disorders comes predominantly from studies of relatively large structural variants (CNVs >100 Kb). A large CNV might represent only one of several types of risk alleles that can affect the same locus. The others are likely to be sequence variants, indels or smaller CNVs. Therefore, to further explore the rare genetic causes of schizophrenia, it will be necessary to capture a greater fraction of all genetic variation.

A wide spectrum of genetic variants, common and rare, can be ascertained using whole-genome sequence data from an individual 75. The availability of next generation sequencing platforms and whole genome sequence data from multiple individuals 76–78 (http:www.1000genomes.org), has spurred a rapid development of new methods for the detection of point mutations 16, 17, 76–78, indels 18, 76–78, and structural variants large and small 18, 25, 79–82. These advances have brought the goal of complete genome sequencing in large patient samples within reach. However, given the cost of a single 20X genome, which is ~ $10 000–$20 000 (as of August 2009), the cost for an ambitious 'schizophrenia genome project' involving thousands of samples would require an investment of hundreds of millions of dollars. Cheaper alternatives could also be considered. A more focused and more affordable approach would be to sequence a set of candidate genes. The development of new methods for capturing and sequencing targeted subsets of the genome 83, 84 has made it feasible to re-sequence either specific candidate regions or the complete human exome. The candidate gene resequencing approach has proven effective in identifying rare variants that influence colorectal cancer risk 33, HDL cholesterol levels 31 and hypertension 27. Based on the success of the CNV-based mutation discovery approach, there is now a strong rationale for applying the complementary sequencing-based approach to schizophrenia and other psychiatric disorders.

Strategies for studying the neurobiology of disease

Mutations that confer high risk for brain disorders are well suited for the development of genetic model systems. A severe mutation in a gene, such as a deletion, frameshift, or stop mutation can be readily introduced into an animal model. Furthermore, a mutation associated with a severe human phenotype, such as significant cognitive impairment, might be more likely to produce a recognizable phenotype in an animal. For these reasons, disease-associated CNVs have inspired the development of new model systems for the study of the disease process. For example, a chromosome-engineered transgenic mouse has been developed for the 22q11.2 microdeletion, and this mouse shows significant impairments in fear conditioning and spatial learning 85. In addition, analysis of gene expression in the prefrontal cortex and hippocampus of the 22q11.2 mouse has showed evidence for alterations in microRNA biogenesis that might be due to haploinsufficiency of the gene DGCR8 85. Chromosome-engineered mouse models have been made for other genomic disorders, including the deletion of 17q11.2 in Smith-Magenis Syndrome (SMS)86,

duplication of 17p12 in Charcot Marie Tooth disease (CMT1A) 87 and duplication of 15q11-13 in autism 88. These models recapitulate some aspects of the human clinical phenotype associated with each mutation.

Studies of individual gene knockouts have also proven helpful in characterizing the biological effects of structural variants. For example, characterization of individual gene knockouts in 17q11.2 has identified a dosage sensitive gene, RAI, that is likely responsible for developmental abnormalities in SMS 86, 89. A mouse knockout of *NRXN1* displays abnormalities in neurotransmitter release 90, and these effects could have relevance to psychiatric phenotypes associated with this gene. Mouse knockouts of Methyl-CpG-binding protein 2 (*MECP2*) 91 and Fragile X Mental Retardation Protein-1 (*FMR1*) 92 recapitulate in mouse aspects of the human phenotype of Rett's Syndrome and Fragile X syndrome, respectively.

Animal models of structural variants have also been used to test new therapeutic strategies. For instance, it has been shown that ascorbic acid normalizes impaired locomotor activity in *CMT1A* mice 93 by inhibiting cAMP dependent overexpression of Peripheral Myelin Binding Protein-22 (*PMP22*) 94. Potential therapeutics have also been identified using single gene knockouts. Using a FMR1 knockout model of fragile-X syndrome, multiple groups have shown that inhibition of the Metabotropic Glutamate Receptor-5 (mGluR5) rescues aspects of the fragile-X phenotype 95–97. This finding has led to the identification of the mGluR5 inhibitor, MPEP, as a potential treatment for Fragile X syndrome 95. Thus, compounds that have therapeutic effects in animal models could make promising leads for drug development.

Another potential approach to studying the functional effects of disease mutations is through the use of human cells derived from patients that carry specific mutations. For instance, studies of gene expression have been carried out using lymphocytes derived from patients with Fragile-X syndrome and microduplications of 15q11-13 98. However because lymphocytes may not be the ideal tissue for the study of brain disorders, other approaches are being considered. For example, new methods for deriving pluripotent cells from human tissue have made it possible to obtain induced plutipotent stem cells (iPSCs) from humans 99, 100. Human iPS cells can in turn be differentiated into several different neuronal cell types, which would make it possible to study cultured neurons from specific patients. To this end some groups have used this approach to derive cells from patients with known disorders, such as Rett Syndrome 101. The same approach could be applied to specific groups of patients with neuropsychiatric disorders who share a risk variant identified from CNV studies.

Implications for clinical research

Phenotypic heterogeneity among patients has been a major factor confounding clinical research on brain disorders. Inconsistent results from human studies of cognition 102, 103 and brain imaging 104, 105 could in part be explained by the underlying genetic heterogeneity and corresponding phenotypic heterogeneity. Therefore, stratifying patients by specific CNV genotypes could enhance power to identify clinical correlates of individual mutations. Intensive clinical studies of patients who share a specific structural variant have helped to define novel microdeletion syndromes 73, 106, 107 that were not recognizable based on symptomatology. The same principle could be applied within any heterogenous patient group, including a schizophrenia cohort.

Two groups have recently analyzed clinical data from individuals with rearrangements of, 1q21.1 60 and 16p11.2 53. Remarkably, both studies observed that the reciprocal rearrangements at these loci were associated with changes in head circumference.

Microdeletions and microduplications of 1q21.1 were associated with microcephaly and macrocephaly respectively 60, and microdeletions of 16p11.2 were associated with a significantly increased head size 53. These results suggest that changes in brain volume might be related to the psychiatric phenotype in patients that carry these mutations.

More generally, these studies demonstrate that some schizophrenia-associated CNVs can be associated with specific clinical endophenotypes. However, in this context, the analysis strategy differs from the classical endophenotype approach 108. For rare variants, researchers tend to follow a traditional cytogenetics approach, where analysis of clinical data is performed retrospectively on a small genetically-defined patient group. This approach is effective because genetic heterogeneity is reduced considerably within a small group of patients who share a disease-associated rare CNV.

Concluding remarks

The recent identification of mutations that confer substantial risk for schizophrenia has generated much excitement within the field. However, there is much more to be learned. Very few of the individual rare variants have been definitively identified. In addition, the relative contributions of rare variants of large effect and common alleles with modest effects are not known. It is clear, however, that the role of rare variants is not limited to a small percentage of patients. Further studies on a much larger scale are needed to uncover the rare genetic variants that underlie schizophrenia.

Statistical power to detect the association of rare variants in a gene depends not only on sample size, but also on the sensitivity of a method to detect mutations. To understand the contribution of rare variants to schizophrenia, it is first necessary to ascertain the full spectrum of structural variants as well as other classes of variation including point mutations and indels. This could best be achieved through whole-genome sequencing. As the power and cost of genome-wide screening technologies improves, we anticipate that many more critical genes will be identified. These discoveries may include loci that are hotspots, with mutation rates of one in 10,000, as well as many other genes and genomic regions with lower mutation rates (e.g. one in 100,000) and lower overall frequencies. Although the cost of whole-genome sequencing in a large patient sample is substantial, a significant investment could be justified given the power of the data derived from these methods to transform the field of psychiatric genetics.

The discovery of rare schizophrenia-associated CNVs and other mutations that confer substantial risk of disease would, for the first time, identify single mutations that have reasonable predictive value, with potential to improve the clinical diagnosis of patients. First, the clinical relevance of the individual mutations must be definitively established and the penetrance for a variety of clinical phenotypes must be understood. This can be achieved by intensive clinical studies of patients and their families who share a disease mutation.

The ultimate goal of psychiatric genetic research is to identify and characterize neurobiological pathways and processes that are disrupted in individuals with mental disorders. Although schizophrenia might arise from a multitude of different causes, it is likely that these will influence a more limited number of key brain systems or pathways. A thorough characterization of these critical pathways will make a substantial contribution to our understanding of pathophysiology and provide important targets for treatment.

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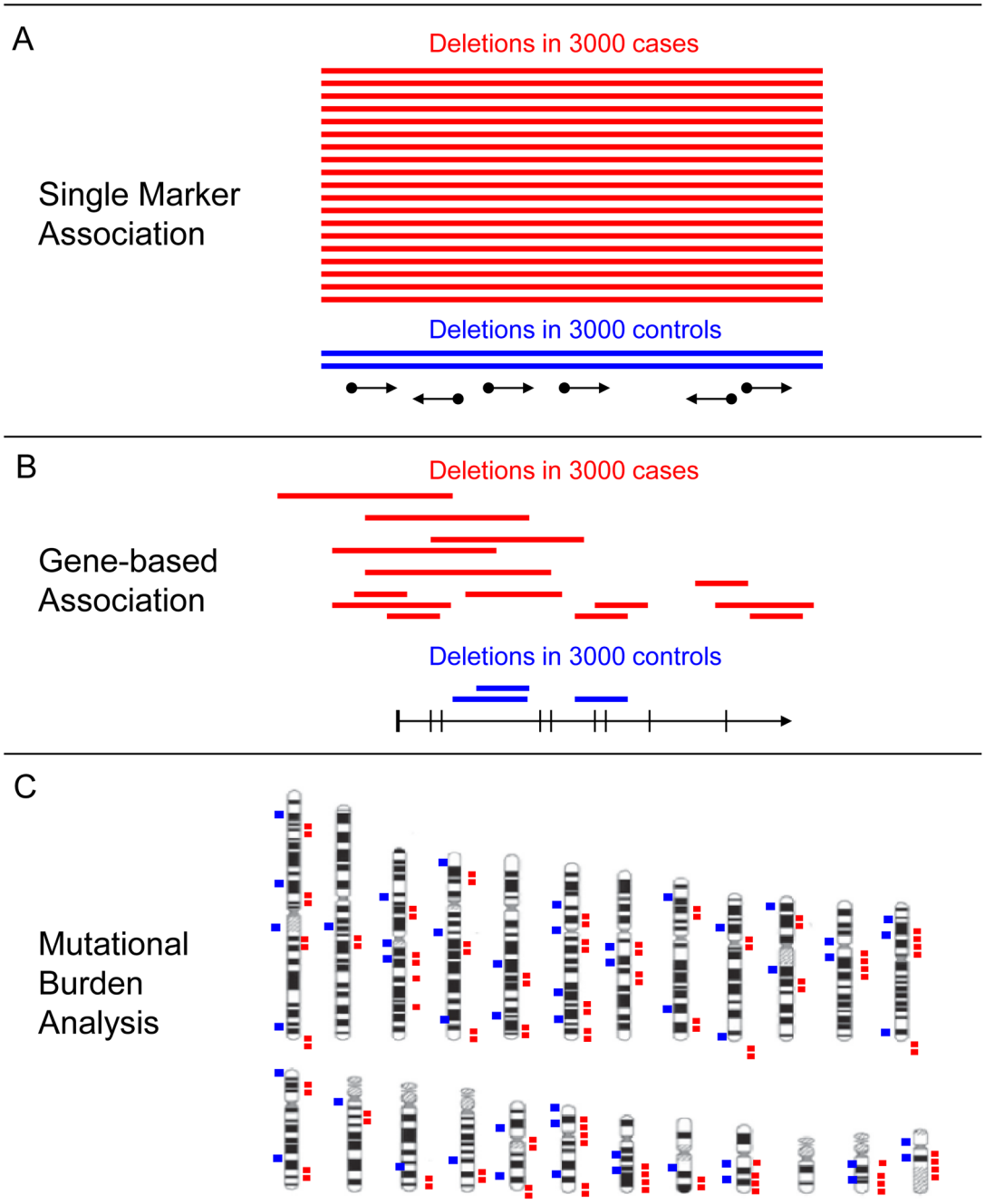

Figure 1. Detecting the association of rare structural variants (SVs) with disease

Three different approaches to detecting the association of rare SVs with disease are shown. The association of rare structural variants with disease can be determined by comparing cases and controls with respect to the frequency of an individual mutation (single marker association, Panel a), the aggregate frequency of multiple mutations within a single gene or region (gene-wise mutational burden, Panel b), or the aggregate frequency of all rare structural variants (genome-wide mutational burden, Panel c). Panels A and B depict a typical genome browser view displaying tracks for SVs and annotated genes, c depicts an ideogram displaying the distribution of SVs genome-wide.

Table 1

Genomic regions implicated by rare structural variants in schizophrenia[a].

Locus[b]	Gene(s)[c,d]	copy number change	Frequency in SCZ (%)	OR	Reference	Other Associated Disorders[d]
Replicated significant associations from case-control studies						
1q21.1	~10 genes	deletion	0.23–0.32	6.6–14.8	[12,13]	DD, CM60, 70
15q13.3	~10 genes	deletion	0.17–0.3	11.5–17.9	[12,13]	GE71, 72, MR73
16p11.2	>25 genes	duplication	0.3	8.3–25.4	[11,53]	ASD, BD, MD, P-NOS53, 62, VCFS42, Anxiety, Depression, ADHD, OCD69
22q11.2	>25 genes	deletion	0.5–2.0	30	[12,13,37]	
2p16.3	NRXN1	deletion	0.47	9.0	[14,55]	ASD 65, 66, 109
Significant association reported in individual studies						
15q11.2	~10 genes	deletion	0.55	2.73	[13]	ASD, DD 110
17p12	~10 genes	deletion	0.13	7.8	[15]	HNPP 111
16p13.1	~14 genes	duplication	0.30	3.3	[54]	DD64, 112
1q42.2	DISC1	balanced translocation	NA	NA	[38]	BD, MDD41
Nonsignificant associations reported in individual studies						
1p31.3	PDE4B	balanced translocation	NA	NA	[39]	
14q13.1	NPAS3	balanced translocation	NA	NA	[40]	
7q35	CNTNAP2	deletion	NA	NA	[56]	ADHD113, ASD 114–116
15p13.1	APBA2	duplication	NA	NA	[55]	

[a]Abbreviations: Autism Spectrum Disorder (ASD), Developmental Delay (DD), Congenital Malformations (CM), Generalized Epilepsy (GE), Mental Retardation (MR), Bipolar Disorder (BD), Psychosis Not Otherwise Specified (P-NOS), Velo-Cardio-Facial Syndrome (VCFS), Attention-Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), Hereditary Neuropathy with Liability to Pressure Palsies (HNPP), Major Depressive Disorder (MD)

[b]Approximate genomic coordinates (hg18) for the six large CNV regions are chr1:144,900,000–146,000,000 (1q21.1), chr15:20300000–20700000 (15q11.2), chr15:28,800,000–30,300,000 (15q13.3), chr16:29,500,000–30,100,000 (16p11.2), chr16:14,890,000–16,390,000 (16p13.1), chr17:14,000,000–15,500,000 (17p12), and chr22:17,200,000–18,700,000 (22q11.2).

[c]Number of genes is approximate because breakpoints of the rearrangements fall within complex clusters of duplicated genes, and the exact boundaries of the rearrangements vary between patients.

[d]The full names of genes in Table 1 are Neurexin-1 (*NRXN1*), Disrupted in Schizophrenia-1 (*DISC1*), Phosphodiesterase 4B (*PDE4B*), Neuronal PAS Domain Protein 3 (*NPAS3*), Contactin Associated Protein-2 (*CNTNAP2*) and Amyloid A4 Precursor Protein-Binding, Family A, Member 2 (*APBA2*).