

## Advances in the genetics of schizophrenia: will high-risk copy number variants be useful in clinical genetics or diagnostics?

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### Abstract

Schizophrenia is a highly heritable, common mental illness, affecting 1% of the population worldwide. It is currently diagnosed using exclusive clinical criteria, and at present there are no genetic tests to facilitate this process. There are also no reliable means to predict who will develop the disease in later life. Genetic counselling uses crude estimates of risk based on family history, as the strongest predictive factor is having an affected first-degree relative. It has recently become apparent that large *de novo* deletions in the genome (copy number variants, or CNVs) can increase risk of the disease by tenfold or more. The purpose of this report is to assess whether these 'high risk' pathogenic CNVs might be useful in a clinical genetic or diagnostic setting. Routine use of laboratory techniques such as comparative genome hybridisation will reveal these *de novo* CNVs in standard investigative procedures for referrals to clinical genetics. The lack of disease specificity of CNVs presents problems for their use in diagnosis at present. Currently, there is also insufficient evidence in relation to schizophrenia to suggest that clear clinical benefit would be gained from learning one's genetic status pre-symptomatically. However, this is likely to change rapidly in the near future as knowledge of the genetic and environmental basis of schizophrenia accrues and increasingly effective measures for early intervention and risk reduction are developed.

### Introduction and context

Schizophrenia is a severe mental illness, with heritability estimated at over 80% and onset in adolescence or early adulthood [1]. Its aetiology is complex and multifactorial, involving interaction between multiple genetic and environmental factors, and therefore the identification of the underlying genetic basis has proven difficult. The working hypothesis for genetic influences on schizophrenia has been the 'common disease, common allele' model, in which the illness is caused by combinations of genetic variants which are frequent in the populations (for example, a risk allele frequency of more

than 5%), each contributing a modest effect. Over 1,000 genetic association studies have been published, with largely inconsistent results, but a recent meta-analysis has identified 16 genes with nominally significant effects and an average pooled odds ratio of 1.23 [2]. Genome-wide approaches examining common single-nucleotide polymorphisms (SNPs) for association with schizophrenia are also beginning to yield results [for example, an SNP in the *ZNF804A* gene, which has a relative risk of about 1.1] [3]. These variants have extremely low penetrance; that is, the vast majority of those who carry them do not develop schizophrenia. Because of this,

common variants have poor predictive power and limited utility in clinical genetics, at least in isolation.

The alternative 'rare variant' model proposes that genetic variants predisposing to schizophrenia are penetrant mutations, which are of recent origin and individually rare, even specific to single cases or families [4]. A severe mutation such as a deleterious amino acid change on a protein or a deletion in any of the genes involved in neurodevelopmental pathways may lead to a psychopathological phenotype; variable expression or penetrance may arise by genetic or epigenetic 'second hits' or simply by chance [5]. One such mutation is a copy number variant (CNV) on chromosome 22 which deletes 1.5 to 3 million base pairs of DNA and causes 22q11.2 deletion syndrome (velocardiofacial syndrome, or VCFS). This is a well-established risk factor for schizophrenia and other neuropsychiatric phenotypes such as autism spectrum disorders; at least 25% of subjects with a deletion develop psychosis [6]. As discussed below, there is evidence that CNVs such as 22q11.2 deletion may play an important role in the aetiology of schizophrenia [7].

Thus, it is possible to conceptualise the genetics of schizophrenia as a disorder made up of genetic risk conferred by three types of variants: common low-risk sequence variants such as SNPs which increase risk by 1.1- to 2-fold, rare CNVs such as the VCFS deletion which increase the risk of schizophrenia by 3- to 50-fold, and rare deleterious sequence variants such as non-synonymous SNPs. Current commercially available microarrays cannot easily detect association with rare SNP variants [8] and therefore large-scale DNA sequencing is required for their discovery, so less is known about the role of these variants in complex disorders such as schizophrenia. It is possible to speculate that 10-20% of genetic risk is from CNVs, a similar percentage from rare sequence variants, and the remainder from many common low-risk polymorphisms [9]. A better understanding of the genetic (and indeed environmental) basis of schizophrenia may facilitate both risk prediction and diagnosis.

It is theoretically possible to use these various types of genetic susceptibility variants to predict risk. Using Crohn's disease (CD) as a model of a common complex disorder, Lewis *et al.* [10] developed methods to estimate disease risks using both genetic and environmental risk factors. They found that high absolute risks of CD can be obtained by incorporating information on smoking, family history and NOD2 gene mutations. Additional information on genetic risk can be incorporated into this model as it arises to improve risk prediction. This

approach should have utility in the clinical setting for both genetic counselling and behavioural modification to reduce risk (for example, smoking cessation).

### Recent advances

In addition to 22q11.2 deletions, high-risk newly occurring deletions and duplications of DNA (CNVs) have recently emerged as genomic risk factors for common brain disorders, including schizophrenia, autism and mental retardation [7,11,12]. This involves an excess of rare *de novo* CNVs across the genome as a whole [5,13], which at an individual level probably represents the damaging effect of very large mutations on brain function [14]. Some of these may be 'private' pathogenic mutations possibly unique to a single individual. Others appear to be recurrent mutations at specific sites, such as on chromosomes 1q21.1, 15q11.2, 15q13.3 and the neurexin 1 (*NRXN1*) gene at 2p16.3 [14-18]. These CNVs are not specific to any particular psychiatric diagnosis and can give rise to a range of phenotypes, from autism to epilepsy [12,19-22].

These pathogenic CNVs tend to be rare in the population: deletions at 1q21.1 and 15q13.3 occur in about 1/500 patients with schizophrenia compared with 1/5,000 controls without neuropsychiatric illness [15,16]. In idiopathic generalized epilepsy, however, deletions at 15q13.3 occur in as many as 1/100 of cases [21], whereas the 15q11.2 deletion occurs in about 1/200 patients with schizophrenia [15]. These pathogenic CNVs have a high odds ratio for risk, at around 3- to 10-fold increased risk, in contrast to common variants, which show odds ratios between 1 and 2. Thus, the penetrance of the pathogenic CNVs discovered so far is intermediate between common variants and the high-risk variants associated with syndromes commonly used in a clinical genetic setting, at between 2 and 9% for schizophrenia, compared with 11-55% for VCFS deletions [Vassos *et al.*, personal communication]. Given that these variants can give rise to multiple neuropsychiatric phenotypes, the overall penetrance for any disorder is likely to be considerably higher; for example, although the penetrance for 15q13.3 deletions in schizophrenia is 6-9%, penetrance for idiopathic generalized epilepsy is much higher [20, Vassos *et al.*, personal communication].

### Implications for clinical practice

These findings will impact on clinical practice in two areas, diagnosis and risk assessment (genetic counselling). At present, schizophrenia is diagnosed using clinical criteria, which means that because of the low yield of clinically relevant variants (such as the 22q11.2 VCFS deletion) patients with schizophrenia are not commonly assessed by genetic testing. However, this

picture is likely to change as further CNVs are identified and their clinical relevance becomes more widely understood. In addition, children who show idiopathic developmental delay (for example, intellectual disability, language delay or both) or 'chromosomal' phenotype (that is, developmental delay in association with growth retardation, facial dysmorphism and minor or major congenital abnormalities) are usually assessed in a clinical genetic setting. Here, conventional cytogenetic analysis is being replaced by CGH and other DNA-based methods because they have the potential to detect the majority of microscopic and submicroscopic chromosomal abnormalities [23]. This will inevitably lead to the identification of children who carry CNVs associated with the later development of schizophrenia and other paediatric or adult neuropsychiatric phenotypes, which raises ethical and practical issues.

In terms of diagnostics, the observation that CNVs are not disorder-specific but cross diagnostic boundaries presents difficulties, as these pleiotropic effects challenge current psychiatric diagnosis and current classification systems [24]. One option is that these disorders be considered separate syndromes (for example, '2p16.3 deletion syndrome' or 'NRXN1 deletion syndrome'). However, patients with schizophrenia who have pathogenic CNVs are not obviously unusual in their phenotype [17] and to classify them as having separate syndromes, given that the penetrance of CNV mutations is incomplete and that other factors may be involved in the disease, may not make sense. Only when there is a fuller understanding of the role of both CNVs and common and rare sequence variants (for example, SNPs) in susceptibility, together with an understanding of the genetic and environmental factors which modify penetrance and phenotype, may it be possible to diagnose phenotype on the basis of genetics.

In terms of genetic counselling and risk assessment, genetic and environmental factor research is likely to lead to validated clinical tests to assess psychosis risk in the long term, which will gradually replace the current family history-based assessment of risk [25,26]. Genetic counselling is likely to have an important role in bridging research and clinical practice in psychiatry. While there are controversies relating to predictive testing in mental illness that cannot be dismissed [27,28], there may be considerable benefits; these include addressing misconceptions about the illness, reducing guilt and stigma, and introducing adaptive strategies and non-directive support for decision making, resulting in improvements in quality of life, compliance with medication, and reduction in risky behaviours [29]. In a recent study of schizophrenia [30], no affected

individuals and only 1 in 20 relatives had received genetic counselling. However, over 40% indicated that their family planning decisions were influenced by having schizophrenia in their family, and over 70% thought genetic counselling would be useful.

However, there are considerable ethical issues to be considered, especially as schizophrenia commonly occurs during adolescence or early adulthood. In some cases, schizophrenia may be preceded by idiopathic developmental delay in childhood [31] and therefore the implications of genetic testing of children must be considered. Since, unlike in Mendelian disorders, no definite genetic factors that predict the development of schizophrenia have been established so far and since there are considerable ethical and societal issues relating to mental illness and prenatal diagnosis, prenatal testing is not appropriate in this context.

Questions of ethics most commonly centre on whether there is a clear clinical benefit to be gained from learning the genetic status of the patient, before symptoms of schizophrenia or another disorder develop. Genetic testing is most likely to occur in high-risk groups, such as children with idiopathic 'non-chromosomal' intellectual and motor developmental delay [31,32] who might present to clinical genetic services, those at high genetic risk because of family history of the disease (about 10% risk) [33], or people who have prodromal symptoms (30% risk of conversion to full-blown psychosis) [34]. Delays and/or abnormalities in motor and language development, intellectual and cognitive impairment, disturbances in emotional and behavioural functioning as well as social and interpersonal maladjustment are all childhood antecedents of schizophrenia [32] which might trigger genetic screening and the identification of pathogenic CNVs; perhaps 5% of children referred to clinical genetic testing for these reasons will later develop schizophrenia.

Genetic testing may be beneficial in a clinical genetic context for families with a history of schizophrenia. In these families, the identification of a case who has an isolated *de novo* CNV not present in the parents would indicate a reduction in risk for other family members, as the *de novo* mutation is a rare event and unlikely to re-occur. On the other hand, if a parent carried the CNV, risk would be higher as it could be passed on to offspring. Family history of psychosis may also have a significant impact on penetrance of CNVs, as is seen in haemochromatosis gene (HFE)-related haemochromatosis. In a scenario in which an unaffected parent is found to carry the mutation, the risk of disease to future offspring is modulated by family history; there is an

approximately 1% risk of clinical disease in a female offspring who is homozygous for C282Y mutation and has no family history compared with 10% if there is a closely related affected relative, with the same HFE haplotype in both cases. This mediation of the penetrance appears to result from concomitant mutations in other iron master genes [35]. Thus, in a family with a history of schizophrenia and a pathogenic CNV, the risk to offspring of a carrier of a pathogenic CNV may be substantially higher than indicated by the population prevalence.

Predictive testing might be conceived as useful if it were able to stratify risk and act as an 'early warning' system for intervention; this could be used in a preventative sense in order, for example, to reduce harmful behaviour in those at high risk or to attempt to reduce the duration of untreated psychosis (DUP), which averages 1-2 years for people who develop schizophrenia [36]. A reduction of DUP may confer clinical benefits [37]. In addition, better predictive tools in certain high-risk groups, such as prodromal patients in whom antipsychotic medication is being trialled to prevent onset of psychosis or improve course [38], have the potential to better target medications and reduce their unnecessary use. However, the benefits of drug treatment in prodromal psychosis are as yet unclear, and in any case, the implications of a pathogenic *de novo* CNV for progression to full-blown psychosis are at present unknown, and this will need careful assessment given their low penetrance. Thus, while these are potential areas of clinical use, there is little good evidence that, at present, clear clinical benefit would be gained from learning the genetic status of the patient. Despite this, commercial genetic testing companies are marketing tests directly to consumers based on discoveries from genome-wide association studies. This may carry some benefits (for example, in relation to lung cancer or obesity risk, in which lifestyle changes such as smoking cessation or exercise are very effective). However, in the absence of evidence of clinical validity or utility this may be premature, especially for diseases such as schizophrenia that are severe or carry stigma, and has led to calls for greater discussion of the policy implications [39,40].

The complex ethical issues, coupled with the potential for adverse psychological effects that might accompany genetic testing and the risk of stigmatisation of individuals at 'high risk', need to be weighted against the potential benefits (genetic counselling and psychoeducation of patients and relatives, early detection of illness and implementation of treatment, and minimisation of risk behaviours) [26,27,29,30]. Knowledge of these dilemmas is a first step to resolving them, something

that the medical profession will need to attend to in the near term [41].

### Abbreviations

CD, Crohn's disease; CGH, comparative genome hybridisation; CNV, copy number variant; DUP, duration of untreated psychosis; HFE, haemochromatosis gene; NOD2, nucleotide-binding oligomerization domain containing 2; *NRXN1*, neurexin 1; SNP, single-nucleotide polymorphism; VCFS, velocardiofacial syndrome.

### Competing interests

The authors declare that they have no competing interests.

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