

# Penetrance for copy number variants associated with schizophrenia

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Received March 22, 2010; Revised June 10, 2010; Accepted June 21, 2010

The discovery of 'high-risk' *de novo* copy number variants (CNVs) associated with neuropsychiatric disorders such as schizophrenia offers the opportunity to translate these findings into useful tools for clinical geneticists. However, this will require estimation of penetrance for these variants, which has not yet been properly considered. To facilitate this process, we estimated the penetrance of CNVs associated with schizophrenia, at 15q13.3, 1q21.1, 15q11.2, 17p12, 2p16.3, 16p13.1 and 16p11.2 with a novel Bayesian method applied to pooled data from published case–control studies. For these CNVs, penetrance for schizophrenia was between 2 and 7.4%, which contrasts with the much higher penetrance for schizophrenia of the 22q11.2 deletions found in velo-cardio-facial syndrome. The highest penetrance was for 15q13.3 deletion (6–9% in individual studies) and the lowest was for 15q11.2 (2%). **CNVs confer much higher risk for schizophrenia than common variants, but their penetrance is substantially lower than Mendelian disorders or other syndromic conditions.** Since these CNVs predispose to multiple disorders, including epilepsy, autism and intellectual impairment, penetrance estimates will also need to take into account diagnostic specificity, and their overall penetrance for any neuropsychiatric disorder is likely to be much higher. Thus, although CNVs are still far from being clinically useful or relevant to genetic counselling for specific disorders, their detection may hold an important clinical value in predicting negative developmental outcomes.

## INTRODUCTION

Many medical disciplines have been able to benefit from recent technological developments in genetics, and are developing pathways for personalized patient care. Recent progress in the genetics and genomics of psychiatric disorders such as autism and schizophrenia has been impressive, and it is timely to assess the utility of these advances in clinically relevant applications such as diagnostics and genetic counselling. In particular, there has been a flurry of excitement at the emergence of 'high-risk' *de novo* copy number variants (CNVs), a type of genomic variation in which segments of DNA of more than 1000 bp are duplicated or deleted, as genomic risk factor

for common complex brain disorders, including schizophrenia, autism and mental retardation (1–4). One CNV, a deletion of ~3 Mb, on chromosome 22, which causes the 22q11 deletion syndrome (velo-cardio-facial syndrome or VCFS), is well established as a risk factor for schizophrenia and other neuropsychiatric phenotypes (5). More recent findings demonstrate that VCFS is not unique and provide strong support for a model of schizophrenia that includes an excess of rare, *de novo* CNVs across the genome as a whole (6,7), as well as associations at specific loci, including 1q21.1, 15q11.2, 15q13.3, 17p12, 16p11.2, 16p13.1 and the neurexin1 gene (2,3,8–13). **These CNVs are not disorder specific, as they can give rise to a range of phenotypes**, from language disorder

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to epilepsy (4,14). The pleiotropic effects of common CNVs challenge psychiatric diagnoses and current classification systems (15).

These pathogenic CNVs tend to be rare in the population: deletions at 1q21.1, 15q13.3 and 17p12 occur in ~1 in 500 patients with schizophrenia compared with fewer than 1 in 5000 controls without neuropsychiatric illness, whereas the commoner 2p16.3 and 15q11.2 deletions occur in ~1 in 200 patients and 1 in 500 controls. Duplications at 16p13.1 and 16p11.2 occur in ~1 in 300 cases compared with 1 in 1000 and 1 in 3500 controls, respectively. The odds ratio for risk is high; CNVs at 1q21.1, 15q13.3, 17p12 and 16p11.2 confer an approximate 10-fold increased risk of schizophrenia. This is in contrast to the expected pattern of genetic susceptibility for common, complex disorders such as schizophrenia, involving many common, small effect variants: the 'common disease—common variant' model. Over 1000 genetic association studies have been published in schizophrenia based on this model, 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 (16). There are also examples of susceptibility loci emerging from genome-wide association, in the major histocompatibility complex region, and at the ZNF804a, neurogranin and TCF4 genes (17–20), all conferring between 1.1- and 1.24-fold increased risk, which is typical for low-risk variants of common complex diseases (21). Estimates from one of these studies (19) suggests that common, low-risk variants may account collectively for at least one-third of the genetic risk for schizophrenia, but high-risk CNVs and other rare variants are also likely to play a significant role in the susceptibility.

Genomic rearrangements have long been associated with rare genetic syndromes that include psychiatric manifestations, most notably VCFS for which the penetrance for schizophrenia is estimated to be 25% (22). For autistic spectrum disorders, penetrance is >40% in 15q duplication, Angelman syndrome, and 90% in Potocki–Lupski syndrome (23). However, unlike clinical geneticists dealing with penetrant disorders caused by high-risk variants, complex disease geneticists do not usually consider the issue of penetrance, as for common, low-risk alleles this will be vanishingly small. The larger odds ratios of *de novo* CNVs (3,24,25) have potential implications in the conceptualization of novel disease models, diagnosis and genetic counselling, because they are expected to be more predictive of disease status than common variants. Even though causal relationship to psychiatric disorders has not been proved so far, CNVs can be of particular interest to clinical geneticists as the use of genome-wide arrays CGH tests, which are able to routinely detect them, is now commonplace in clinical genetic settings (26). However, the clinical utility of the recent findings will require proper estimation of penetrance, especially for use in genetic counselling and risk prediction.

## RESULTS

Data from six studies were used in the estimation of penetrance for CNVs associated with schizophrenia (2,3,9–12). Our method shows that the penetrance is moderate, at

between 2 and 7.4% for most CNVs and most data sets, with 95% credible intervals from the larger data sets, indicating that penetrance is unlikely to be >20% (Table 1 and Supplementary Material, Table S1). These penetrance estimates are much lower than for syndromic conditions with psychiatric manifestations: for VCFS, we estimate penetrance to be 55%, based on data from pooled studies, although credible intervals are broad, as no CNVs are observed in control cohorts. The distributions for penetrance for other CNVs are tight, indicating that data provide good information for an accurate estimation of penetrance.

Since the size and the number of disrupted genes differed between the seven CNVs studied, we examined potential association of these factors with our penetrance estimates. We did not observe significant association of penetrance with the CNV size ( $P = 0.61$ ) nor with the number of genes affected ( $P = 0.30$ ).

Studies of these CNVs in other neuropsychiatric disorders (1,4,14,27–31) used diversely ascertained clinical samples and complex co-morbid phenotypes, such as autism plus dysmorphic features or intellectual impairment plus epilepsy. Thus, estimates of prevalence for the case ascertainment criteria are unavailable, and we were unable to estimate CNV penetrance for these disorders (Table 2). CNVs associated with both schizophrenia and other neuropsychiatric disorders have similar frequency in cases across disorders (between 0.2 and 0.6%), with the exception of the 15q13.3 deletion, which was more common (1%) in cases with idiopathic generalized epilepsy (28). Since these CNVs are not disorder specific, future estimates of risk will need to take into account not only the penetrance for each individual disorder, but also the overall risk of developing any neuropsychiatric phenotype.

## DISCUSSION

On the basis of our penetrance estimations, we can conceptualize CNVs as genetic variants that bridge the gap between highly penetrant mutations in Mendelian, single-gene diseases and the common low-risk genetic variants typically associated with complex genetic disorders. The CNVs we describe are neither necessary nor sufficient for the development of a neuropsychiatric disorder, but they substantially increase the risk of disease. The variable expressivity and incomplete penetrance suggest that their impact is modified by other genetic loci or environmental factors (32). The level of penetrance of the CNVs described in this study is not sufficient for them to be considered as useful clinical tools in genetic counselling and testing, as well as in diagnosis at present. Before this can be implemented, more detailed information on the factors that modulate penetrance and diagnostic specificity are required. If these parameters can be established, then specific benefits to patients would include (i) improved diagnostic validity, (ii) enhanced prognostic accuracy, (iii) personalized care planning and (iv) individualized risk assessment and genetic screening/counselling.

Modulation of the penetrance of CNV deletions could involve a number of factors, such as the exposure of recessive alleles on the intact chromosome because of the

**Table 1.** Frequency and penetrance estimates of CNVs for schizophrenia

CNV	Genes ( <i>n</i> )	Position (Mb)	Observed CNVs		Penetrance	95% CI
			Cases	Controls		
1q21.1 deletion	10	143.8–146.6	17/7918	11/46 502	0.061	0.03–0.12
2p16.3 deletion	1	50.7–51.3	12/2977	49/33 746	0.020	0.01–0.04
15q11.2 deletion	4	20.3–20.8	49/7918	103/46 497	0.020	0.01–0.03
15q13.3 deletion	6	28.2–30.6	15/7413	8/45 103	0.074	0.03–0.16
16p13.1 duplicat.	12	15.0–18.0	16/4816	38/37 871	0.024	0.01–0.04
16p11.2 duplicat.	26	29.5–30.2	26/8590	8/28 406	0.069	0.03–0.14
17p12 deletion	8	14.0–15.4	8/5089	6/38 884	0.067	0.03–0.17
22q11 deletion	43	17.1–19.9	18/7038	0/44 602	0.553	0.18–0.97

Data for 1q21.1, 15q11.2, 15q13.3, 17p12 and 22q11 were taken from Kirov *et al.* (11) which combined observations from Stefansson *et al.* (2), ISC (3) and new data; 2p16.3 from Rujescu *et al.* (10), 16p11.2 from McCarthy *et al.* (13) and for 16p13.1 we combined data from Ingason *et al.* (12) and Kirov *et al.* (11). The number of genes intersecting CNVs was taken from UCSC genome browser built 36, except from 22q11 which was taken from the ISC study. When the CNV end points differed between studies we took the broader limits. CI, credible intervals.

**Table 2.** Frequency of CNVs in various neuropsychiatric disorders

Disorder	CNV	Reference	Cases		Controls	CNV frequency
			Observed CNVs	CNV frequency	Observed CNVs	CNV frequency
MR, autism	1q21.1 del	Mefford <i>et al.</i> (4)	25/5218	0.00479	0/4737	0
MR, autism	1q21.1 dup	Mefford <i>et al.</i> (4)	9/5218	0.00173	1/4737	0.00021
MR, epilepsy and dysm.	15q13.3 del	Sharp <i>et al.</i> (27)	6/2082	0.00288	0/2962	0
MR, autism, dysm.	15q13.3 del	Miller <i>et al.</i> (14)	5/1445	0.00346	0/1420	0
Epilepsy	15q13.3 del	Helbig <i>et al.</i> (28)	12/1223	0.00981	0/3699	0
Autism	16p11.2	Marshall <i>et al.</i> (29)	4/427	0.00937	0/1652	0
Autism (and MR)	16p11.2 del	Weiss <i>et al.</i> (1)	13/2252	0.00577	5/22082	0.00023
Autism (and MR)	16p11.2 dup	Weiss <i>et al.</i> (1)	7/2252	0.00311	5/22082	0.00023
Autism	16p11.2 del	Kumar <i>et al.</i> (30)	4/712	0.00562	0/837	0
Autism and DD	16p11.2 dup	McCarthy <i>et al.</i> (13)	10/2172	0.00460	6/28406	0.00024
MR, dysmorph	16p13.11 del	Hannes <i>et al.</i> (31)	5/1027	0.00487	0/2014	0
MR, dysmorph	16p13.11 dup	Hannes <i>et al.</i> (31)	5/1027	0.00487	5/2014	0.00248

MR, mental retardation; DD, developmental delay; dysmorph, dysmorphic features; del, deletion; dup, duplication.

resulting hemizygoty, the effects of genetic background, environmental or epigenetic factors. Penetrance of a specific CNV may depend on the functionality of the genes within the locus, with loci containing dose-sensitive critical genes being less tolerant to any disruption and having greater penetrance (33). For example, in HFE-related haemochromatosis, mediation of the penetrance appears to result from concomitant mutations in other genes that influence iron metabolism (34). Likewise, in a mouse model of 22q11.2 deletion syndrome, genetic background also appears to have a substantial effect on the penetrance of various malformations seen in the syndrome; mutations in *Crkl*, which lies within 22q11.2, and in *Fgf8* and *chordin*, which lie elsewhere, both modulate the developmental phenotype by enhancing the effects of a *Tbx1* null mutation on craniofacial abnormalities (35–37). Thus, for CNVs predisposing to neuropsychiatric disorders, it should be possible to identify modifier genes through the careful analysis of related biological pathways and the use of mouse models. The clinical utility of these CNVs will be enhanced by further understanding of their interactions with common genetic variants, and the roles of environmental and epigenetic risk factors.

A limitation of our study is that the accuracy of the penetrance estimation depends on the quality of the original studies. Although the associations with schizophrenia are almost certainly robust, given the rarity of CNVs their frequency estimates still lack precision, despite the large sample sizes. With the current detection methods it is difficult to define accurately the CNV breakpoints. The studies reviewed identified CNVs with dosage detection methods using the intensities from single nucleotide polymorphism probes on Illumina Bead-Arrays or Affymetrix Gene-Chips and provide adequate quality control evaluation. Since these detection methods have low resolution and potential issues with measurement precision, the CNVs identified may be an underestimation of the total number of CNVs. However, if there is no systematic bias in the detection of CNVs (i.e. use of same detection method in both cases and controls), a proportional inflation of CNVs would not substantially change the penetrance estimations.

Another limitation is that the penetrance estimation depends on the characteristics of cases and controls used in the original studies. One consideration is whether cases are representative of the clinical population as a whole. Cases in research studies are usually screened with structured interviews and probably

have 'cleaner' phenotypes than patients in clinical practice. If the cases included in the studies represent the more severe end of the spectrum, one may hypothesize that penetrance is overestimated. On the other hand, given the pleiotropic effects of CNVs, exclusion of cases with congenital malformations, learning disability or neurological symptoms would have led to underestimation of penetrance. In all studies, cases fulfilled DSM-IV or ICD10 criteria for schizophrenia and explicit description of phenotypic characteristics of cases with CNVs, when available, were comparable with the general schizophrenic patient population. As regard to controls, in some samples, they were screened to exclude schizophrenia, while in others, controls were drawn from the population without psychiatric screening and possibly include some schizophrenia cases. We repeated the analyses assuming population sampling for controls, and obtained very similar penetrance estimates (data presented in Supplementary Material, Table S1).

Patients with schizophrenia and their family members may want to avail themselves of genetic counselling and require more information about the risk of developing schizophrenia (38). The CNVs identified to date account for only a small proportion of genetic susceptibility to schizophrenia, but many more are likely to be discovered over the next few years (25). Ideally, to overcome the limitations of case ascertainment and to be able to explore the whole spectrum of phenotypes associated with CNVs, future studies should investigate large birth cohorts followed up prospectively beyond the risk period for the development of associated phenotypes. Since the predictive value of genetic variants depends on their penetrance, our study shows that the recently discovered CNVs are still far from being clinically useful or relevant to genetic counselling for specific disorders. CNVs are neither necessary nor sufficient for specific diseases and current evidence does not support the referral of patients with schizophrenia for genetic screening. However, once better characterized and more precisely associated with diseases, their detection may hold important clinical value in predicting negative developmental outcomes. They may be useful in contributing to the formulation of empiric risk models and perhaps, more importantly, have a role in the understanding of genetic and biological processes underpinning the development of schizophrenia and other neuropsychiatric disorders.

## MATERIALS AND METHODS

### Data sources

We identified all published case-control studies that investigate the association of CNVs with schizophrenia and other neuropsychiatric disorders. For each study, we extracted the inclusion criteria for cases and controls, the number of observed CNVs and the total number of participants in each cohort. Criteria for study selection for our analyses were the association of CNVs at specific loci (as opposed to measurement of the collective burden of rare CNVs) and the presence of more than one observation of each CNV in cases. For studies with overlapping samples, we analysed data from the larger study and for studies that included meta-analyses we used the pooled numbers. The sizes and location of CNVs

were variable and the end points differed between studies. For our analysis, we took the straightforward approach of counting all CNVs in each locus as equivalent events, irrespective of their size and exact position.

### Statistical analysis

Using the observed CNV frequencies from published data, we employed a Bayesian approach to derive posterior distributions of likely values for the frequency of CNVs in case and control cohorts. We then sampled pairs of CNV frequencies from these distributions, and calculated the penetrance, i.e. the probability of developing schizophrenia (disease,  $D$ ) for individuals carrying the CNV (genotype,  $G$ ), from

$$P(D|G) = \frac{P(G|D)P(D)}{P(G|D)P(D) + P(G|\bar{D})P(\bar{D})},$$

where  $\bar{D}$  represents controls, who do not have schizophrenia, and  $P(D)$  the lifetime morbid risk for schizophrenia. For the estimation of penetrance of schizophrenia, we adopted the conservative median global value for lifetime morbid risk ( $P(D)$  above) of 0.72% from a comprehensive meta-analysis (39). Simulation was performed using the R statistical package (<http://cran.r-project.org/>), with 2.5, 50 and 97.5% quantiles extracted to obtain the median penetrance, and its ~95% credible intervals. Complete details of the statistical methods are given as Supplementary Material.

## SUPPLEMENTARY MATERIAL

Supplementary Material is available at *HMG* online.

*Conflict of Interest statement.* None declared.

## FUNDING

This work was supported by EU grant LSHM-CT-2006-037761 (Project SGENE), Guy's and St Thomas' Charity grant, and NARSAD Young Investigator Award (E.V.). The author's work was independent from the funders.

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