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Analysis of copy number variations at 15 schizophrenia-associated loci

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Background
A number of copy number variants (CNVs) have been suggested as susceptibility factors for schizophrenia. For some of these the data remain equivocal, and the frequency in individuals with schizophrenia is uncertain.

Aims
To determine the contribution of CNVs at 15 schizophrenia-associated loci (a) using a large new data-set of patients with schizophrenia (n = 6882) and controls (n = 6316), and (b) combining our results with those from previous studies.

Method
We used illumina microarrays to analyse our data. Analyses were restricted to 520 766 probes common to all arrays used in the different data-sets.

Results
We found higher rates in participants with schizophrenia than in controls for 13 of the 15 previously implicated CNVs.

Conclusions
We strengthen the support for the majority of the previously implicated CNVs in schizophrenia. About 2.5% of patients with schizophrenia and 0.9% of controls carry a large, detectable CNV at one of these loci. Routine CNV screening may be clinically appropriate given the high rate of known deleterious mutations in the disorder and the comorbidity associated with these heritable mutations.

Declaration of interest
None.

Copy number variants (CNVs) are chromosomal rearrangements involving large segments of DNA (from 1000 and up to several million base pairs in length) that can be deleted, duplicated, inverted or translocated. A number of pathogenic CNVs are known to cause clinically recognisable syndromes, such as Williams–Beuren syndrome (WBS), Angelman/Prader–Willi syndrome (AS/PWS) and velocardiofacial syndrome (VCFS). Some CNVs are associated with a highly variable phenotype, which often includes both developmental and neuropsychiatric disorders. For example, 22q11.2 deletions, the first CNV to be associated with schizophrenia, also causes VCFS, which is characterised by intellectual disability and a number of medical problems such as palatal and skeletal anomalies and cardiac defects. Several large and rare CNVs have now been implicated in the aetiology of schizophrenia, reviewed by Malhotra & Sebat. They have been shown to substantially increase risk for the development of the disorder, from twofold to over 60-fold. Most of them have been shown to also increase risk for other disorders, such as autism spectrum disorders, intellectual deficit, developmental delay and epilepsy.

As some of the CNVs are very rare (found in less than 1 in 1000 patients), notwithstanding the relatively large data-sets examined so far (ranging between ~5000 and 14 000 people with schizophrenia), it is not clear that all those that have been implicated are true risk factors for the disorder. Thus, for nine of the loci that have received the strongest support in the literature, fewer than 15 observations have been made in people with schizophrenia. These nine loci are: duplications at 1q21.1, the WBS region, at VIPR2 at 16p13.11 and deletions at 3q29, distal 16p11.2, 17q12 and 17p12. The evidence for six loci is based only on single, albeit very large, studies: deletions at 17q12, distal 16p11.2 and 17p12, and duplications at 1q21.1, AS/PWS region, and at 16p13.11. Moreover, the rate of duplications at 15q11.2 and deletions at 16p11.2 and 16p13.11, has recently been challenged by a study that indicated that the rates among controls might be higher than originally reported, and no excess in individuals with schizophrenia was seen for these two CNVs in one of the largest studies. Finally, each previous report focused on the identification of one, or only a small number of CNV loci, and several reports used partially overlapping data-sets. Consequently, the rate of all previously reported risk CNVs has not yet been evaluated in a single independent data-set that is not biased by the inclusion of the original discovery sample. We set out to evaluate these specific CNVs in a sample of 6882 people with schizophrenia that passed quality control. This represents the largest single CNV data-set yet reported in schizophrenia, and nearly doubles the sample size of patients from the total world literature for many loci. For control individuals, we used publicly available data from 6316 samples genotyped on arrays with a resolution similar to the case group. These data-sets are completely independent from samples used in previous studies or reviews that established the rates of these CNVs in schizophrenia.

Method

Samples
Case group
We collected data on patients with schizophrenia (case group) in two waves, which we call (a) CLOZUK and (b) CardiffCOGS.
Copy number variations at 15 schizophrenia-associated loci

Results

The rates of CNVs among the case and control groups are presented in Table 1. For 13 out of the 15 CNVs, we found higher rates in the case than in the control group. For six of these, the difference was nominally significant in this new sample alone (Table 1).

Of the loci where previous evidence was modest, the most striking result was for AS/PWS duplications, where we found eight in patients and none in controls (P=0.0055). When combined with previous data (Table 2, for a more detailed version that includes results from previous studies see online Table D56), this CNV is now a strongly supported schizophrenia risk variant. Moreover, as this is an imprinted locus, we tested the parental origin of our eight duplications, and all were shown to be maternal in origin, similar to the original publication. Duplication at 16p13.11, another previously weakly associated CNV, now also shows strong evidence in the combined data (Table 2).
The only instances in our study where CNVs were more common in the control than in the case group concern duplications at VIPR2 and deletions at distal 16p11.2. In neither case is the excess of CNVs in the control group significant. In the case of VIPR2, meta-analysis is no longer supportive, whereas the evidence for association at distal 16p11.2 remains nominally significant (Table 2 and Table DS6). Analysis of only individuals of European descent gave essentially the same results. The distribution of CNVs in the different data-sets and ethnic groups is presented in Table DS3.

In the present sample, which is not subject to the potential bias of including the original studies that discovered the associations, about 2.5% of the case group and 0.9% of the control group carry one of the CNVs in Table 1, a highly significant excess \( (P = 1.4 \times 10^{-12}) \). Only four individuals in the case group carry two of these CNVs (online supplement, section 6).

In the analysis of all 15 loci in the combined data (Table 2), all but one of the CNVs showed significant evidence of association. For 11 of these, the significance surpasses the threshold for multiple testing correction that we suggest in the Method \( (P < 4.1 \times 10^{-4}) \). For many of them the statistical significance is greatly improved compared with the previous results, most strikingly for 15q11.2, AS/PWS, 16p13.11, 16p11.2 and 22q11.2, where the \( P \)-values were strengthened by several orders of magnitude.

## Discussion

In an analysis of the largest single schizophrenia sample to date, we establish more accurate estimates of risk from individual CNVs in an independent sample, and estimate the total burden of susceptibility conferred by this group of CNVs. The vast majority

<table>
<thead>
<tr>
<th>Locus</th>
<th>Frequency, % (n/N)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21.1 del</td>
<td>0.021 (17/81 821)</td>
<td>8.35 (4.65–14.99)</td>
<td>4.1 \times 10^{-13}</td>
</tr>
<tr>
<td>1q21.1 dup</td>
<td>0.037 (24/64 046)</td>
<td>3.45 (1.92–6.20)</td>
<td>9.9 \times 10^{-5}</td>
</tr>
<tr>
<td>NR007 del</td>
<td>0.020 (10/51 161)</td>
<td>9.01 (4.44–18.29)</td>
<td>1.3 \times 10^{-11}</td>
</tr>
<tr>
<td>3q29 del</td>
<td>0.004 (1/69 965)</td>
<td>57.65 (7.58–438.44)</td>
<td>1.5 \times 10^{-1}</td>
</tr>
<tr>
<td>WBS dup</td>
<td>0.063 (3/47 686)</td>
<td>13.20 (3.72–46.77)</td>
<td>5.6 \times 10^{-6}</td>
</tr>
<tr>
<td>VIPR2 dup</td>
<td>0.069 (17/24 815)</td>
<td>1.54 (0.77–3.09)</td>
<td>0.27</td>
</tr>
<tr>
<td>15q11.2 del</td>
<td>0.028 (227/81 802)</td>
<td>2.15 (1.71–2.68)</td>
<td>2.5 \times 10^{-10}</td>
</tr>
<tr>
<td>AS/PWS dup</td>
<td>0.0063 (3/47 686)</td>
<td>13.20 (3.72–46.77)</td>
<td>5.6 \times 10^{-6}</td>
</tr>
<tr>
<td>15q13.3 del</td>
<td>0.019 (15/80 422)</td>
<td>7.52 (3.98–14.19)</td>
<td>4.0 \times 10^{-5}</td>
</tr>
<tr>
<td>16p13.11 dup</td>
<td>0.03 (13/69 289)</td>
<td>2.30 (1.57–3.36)</td>
<td>5.7 \times 10^{-6}</td>
</tr>
<tr>
<td>16p11.2 distal del</td>
<td>0.018 (5/27 045)</td>
<td>3.39 (1.21–9.52)</td>
<td>0.017</td>
</tr>
<tr>
<td>16p11.2 dup</td>
<td>0.03 (19/60 368)</td>
<td>11.52 (6.86–19.34)</td>
<td>2.9 \times 10^{-14}</td>
</tr>
<tr>
<td>17p12 del</td>
<td>0.026 (17/65 402)</td>
<td>3.62 (1.73–7.57)</td>
<td>0.0012</td>
</tr>
<tr>
<td>17q12 del</td>
<td>0.044 (8/74 447)</td>
<td>6.64 (1.78–24.72)</td>
<td>0.0072</td>
</tr>
<tr>
<td>22q11.2 del</td>
<td>0.00 (0/77 055)</td>
<td>NA (28.27–∞)</td>
<td>4.4 \times 10^{-80}</td>
</tr>
</tbody>
</table>
of patients in this study were recruited on the basis that they have a diagnosis of treatment-resistant schizophrenia according to their psychiatrist and were taking clozapine for that indication. The availability of clinician diagnoses allowed us to exclude the limited number of samples from individuals with diagnoses other than schizophrenia. The convention for psychiatric samples has been that patient inclusion is based on research diagnoses arrived at following detailed interview and phenotyping procedures (as is the case in the CardiffCOGS sample in this study). As genome analysis has become more affordable than the establishment of a formal research diagnosis, the latter has now become the limiting step for exploiting the microarray technology. The CLOZUK sampling method offers a pragmatic approach to recruit unusually large numbers of patients with schizophrenia, and nearly doubles the number of patients with schizophrenia analysed in the previous literature. The use of such samples is supported by evidence that with the use of operationalised criteria, clinician diagnoses of schizophrenia have high specificity and positive predictive values when validated against research-based approaches.\textsuperscript{30,31} Furthermore, we have reported findings that support the validity of the individuals in CLOZUK as a schizophrenia sample with genetic data, by demonstrating that of the most strongly associated schizophrenia alleles in the Psychiatric Genetics Consortium Stage 1, 85% (66/78) showed the same direction of effect in the CLOZUK sample, sign test \( P = 1.7 \times 10^{-10}. \)\textsuperscript{21} In the present study, the findings of very similar rates of susceptibility CNVs in the CLOZUK sample compared with previous samples (Table D56), recruited using conventional methods, support the comparability of the two types of samples.

In order to reduce the potential bias of using different arrays, we used only Illumina platforms and only analysed those probes common to all arrays. We used the z-score method to both validate each CNV and check whether any CNV in the regions in Table 1 had been missed.

The current study provides support for most previously implicated CNVs, as we found higher rates in the case group than in the control group for 13 of the 15 loci. The support is particularly strong for duplications at 16p11.2 (\( P = 2.3 \times 10^{-14} \)) and at the AS/PWS critical region (\( P = 0.0055 \)) and for deletions at 22q11.2 (\( P = 2.2 \times 10^{-6} \)), 1q21.1 (\( P = 0.0027 \)), \textit{NRXN1} (\( P = 7.7 \times 10^{-6} \)) and 15q11.2 (\( P = 0.046 \)). All eight duplications at the AS/PWS region were of maternal origin (online supplement, section 5), thus supporting the original report.\textsuperscript{8} Two loci: deletions at 15q11.2 and duplications at 16p13.11, that were not supported in two recent papers,\textsuperscript{5,10} also receive support in the current study and the statistical significance of their overall association with schizophrenia is strengthened by several orders of magnitude (Table 2).

Four of the loci in Table 2 do not surpass a significance threshold that corrects for the multiple testing of large recurrent CNVs (\( P < 4.2 \times 10^{-5} \)), or for individual genes (\( P < 2.5 \times 10^{-6} \)) (see Method): duplications at \textit{VIPR2}, and deletions at distal 16p11.2, 17p12 and 17q12.

### Burden of schizophrenia-associated CNVs

Overall, 2.5% of the case group vs. 0.9% of the control group carry one or more of these CNVs. This is highly significant in this completely independent data-set (\( P = 1.4 \times 10^{-14} \)). They are associated with a range of odds ratios and each locus clearly makes a different contribution to the increase in risk (Table 2). They are also known to increase risk for other disorders, such as epilepsy (15q11.2\textsuperscript{23} and 15q13.3\textsuperscript{35}), congenital heart disease (1q21.1\textsuperscript{34} and 22q11.2\textsuperscript{35}), attention-deficit hyperactivity disorder (16p13.11\textsuperscript{36}) and obesity (distal 16p11.2\textsuperscript{25}), and all but two (at \textit{VIPR2} and 17p12) increase risk for developmental delay and autism spectrum disorders.\textsuperscript{1} The overall contribution is modest but the effect size is sufficiently large to suggest that if seen in a patient, it is very likely to be relevant to the disorder, although not sufficient to account for the disease.

### Summary of the findings for the individual loci

**1q21.1 deletions and duplications**

Deletions at 1q21.1 were among the first implicated loci.\textsuperscript{6,38} Our new data provide strong support for their role in schizophrenia (\( P = 0.0027 \)), with a frequency in the case group identical to that in previous reports (0.17%),\textsuperscript{14} confirming an approximately eightfold excess of deletions among patients, with an extremely strong statistical support of \( P = 4.1 \times 10^{-15} \) in the combined literature (Table 2). Duplications at this locus have only been implicated in one study,\textsuperscript{40} but with the addition of our data (although not significant on its own), the evidence for duplications at this locus in schizophrenia is now stronger (\( P = 9.9 \times 10^{-5} \)).

**NRXN1 deletions**

The gene \textit{NRXN1} encodes for a presynaptic cell adhesion protein, which binds with postsynaptic proteins called neuroligins and plays a vital role in the formation, maintenance and release of neurotransmitters in synapses.\textsuperscript{39} Exonic deletions disrupting this gene have been consistently implicated in schizophrenia,\textsuperscript{9,10,13,40} and autism spectrum disorder.\textsuperscript{41} The current study confirms their role, as we found 11 exonic deletions in the case group (0.16%) and none in the control group, \( P = 7.7 \times 10^{-4} \). This brings the overall significance in the combined literature to \( P = 1.3 \times 10^{-11} \) (easily surpassing our multiple testing correction threshold for individual genes of \( P < 2.5 \times 10^{-6} \)), with approximately a ninefold excess in the case group (Table 2). The positions of exon-disrupting CNVs at this locus in our new data-set are shown in the online supplement, section 4.

**3q29 deletions**

The role of this CNV in schizophrenia was first reported by Mulle \textit{et al.}\textsuperscript{12} and confirmed by Levinson \textit{et al.}\textsuperscript{10} The finding of four individuals in the case group with deletions and none in the control group just fails to reach significance in our independent sample (\( P = 0.074 \)) but can be regarded as supportive independent confirmation. With an overall significance of \( P = 1.5 \times 10^{-5} \), it is another locus where the evidence for a role in schizophrenia is very strong. Only one such deletion has been found in nearly 70,000 controls, indicating it is highly penetrant (Table 2).

**WBS duplications**

The reciprocal duplication of the WBS region was first implicated as increasing the risk for autism.\textsuperscript{42} The region was implicated in schizophrenia after the finding of a \textit{de novo} duplication\textsuperscript{26} and reached statistical support in a large collaborative study.\textsuperscript{16} The finding of three individuals in the case group with deletions and none in the control group (\( P = 0.006 \)) but with the addition of our data (although not significant on its own), the evidence for duplications at this locus in schizophrenia is now stronger, at \( P = 6.9 \times 10^{-5} \).

**VIPR2 duplications**

The evidence for duplications disrupting this gene comes from two studies that used largely overlapping samples.\textsuperscript{30,37} The overall evidence from the previous literature was modest: \( P = 0.086 \).\textsuperscript{14} As we found duplications in six people in the control group and only one in the case group, the evidence in favour of this locus is no longer significant in the combined literature (\( P = 0.27 \)). The
positions of CNVs at this locus in our new data-set are shown in the online supplement (section 4). Most CNVs at this gene are large and covered with a high number of probes on the arrays (medians of 381 kb and 66 probes, details in online Table DS4), therefore they should be called reliably on these arrays. We also examined the region with all available probes for CNV calling on the different arrays, and with the z-score method, and found no additional CNVs that had been missed. The rate in our control group is slightly higher than in previous studies (0.095% v. 0.059%, Table 1 and Table DS6), although this difference is not significant ($P = 0.4$).

15q11.2 deletions

This was one of the first CNVs implicated in schizophrenia. However, a recent report of a higher rate in controls than that reported in the original paper and the lack of support in the study by Levinson et al clearly indicated the need for replication. Here we found independent significant evidence for association ($P = 0.046$), that strengthens the evidence in the combined analysis to $P = 2.5 \times 10^{-10}$ (Table 2).

AS/PWS duplications

The modest prior evidence for the role of this duplication of the AS/PWS critical region in schizophrenia comes from a single publication with just four observations in patients. We found another eight CNVs in our case group and none in the control group ($P = 0.0055$), thus substantially strengthening this finding. Even more notably, by using DNA methylation-sensitive high-resolution melting-curve analysis of the SNRPN locus, which does not require DNA from the parents, we found that all eight duplications are of maternal origin, as in the original study. These findings further underline the importance of imprinting genes (those genes subject to parent of origin specific epigenetic regulation) in the aetiology of psychosis and other neurodevelopmental disorders.

These duplications are among the most common genetic susceptibility factors for autism spectrum disorder, where they are found in nearly 1:500 cases.

15q13.3 deletion

This is also among the first implicated CNVs in schizophrenia, and received further strong support in the study by Levinson et al. It was found at a ~tenfold higher rate in patients with schizophrenia, with a strong statistical support in the previous literature, $P = 2.1 \times 10^{-11}$. Although we found only a twofold excess in our case group in our new sample, at 0.058% v. 0.032%, $P = 0.38$, its role as a susceptibility factor for schizophrenia remains very strong in the combined literature ($P = 4.0 \times 10^{-10}$). This locus also increases the risk for epilepsy.

16p13.11 duplication

The previous evidence for this CNV comes mostly from a single study and the overall number of analysed patients with schizophrenia so far, at 5147 individuals, is smaller than in our new data-set. Two recent studies weakened the evidence for this locus, and in the recent review by Mallhotra & Sebat it had very weak statistical support, $P = 0.03$. Here we found 24 CNVs in the case group and 12 in the control group, an excess that just fails to reach significance, $P = 0.056$. Combined with the earlier data, our study strengthens the statistical support for this locus in schizophrenia to $P = 5.7 \times 10^{-5}$. This CNV has also been implicated in attention-deficit hyperactivity disorder.

16p11.2 duplication

This is our strongest finding, with a $P = 2.3 \times 10^{-8}$ in the discovery sample alone, and a combined evidence at $P = 2.9 \times 10^{-24}$, with an odds ratio of over 11. This duplication is also one of the strongest autism spectrum disorder CNV risk factors.

16p11.2 distal deletion

This CNV was suggested to confer susceptibility to schizophrenia by Guha et al. We found no support for this locus in the present study, with two deletions in the control group and none in the case group. However, the lack of deletions among our case group could be as a result of ascertainment bias. Obesity is found in at least 50% of 16p11.2 distal deletion carriers. Clozapine produces the most severe weight gain among all antipsychotics and the most common cause for the reluctance of UK psychiatrists to prescribe clozapine is the potential weight gain. It is therefore possible that psychiatrists are less likely to give clozapine to carriers of 16p11.2 distal deletion (as such patients are more likely to be obese already), thus potentially reducing the frequency of this CNV in the CLOZUK sample. The combined result from the literature retains the statistical support for the role of this locus ($P = 0.017$), but it clearly requires testing in further data-sets.

17p12 deletion

This deletion causes the neurological disorder hereditary neuropathy with liability to pressure palsies and was implicated in schizophrenia on the basis of only eight observations in the original case group. Although the overall statistical evidence is still in favour of it increasing the risk for schizophrenia ($P = 0.0012$), the support is not compelling, raising the need for further replication. It does not increase the risk for either developmental delay or autism, unlike most other loci discussed here, and it is possible that the original report was a false-positive finding.

17q12 deletion

Originally this locus had been known to cause renal cysts and diabetes. It was identified as a susceptibility CNV for schizophrenia with only four observations in the case group in a study that also implicated its role in autism spectrum disorder. We found only one deletion in a patient, a rate a quarter of that in the original study. Although we found no deletions in the control group, the overall $P$-value of all data is not sufficiently robust to definitively conclude that this is a schizophrenia susceptibility locus ($P = 0.0072$). Therefore, this locus also requires testing in further schizophrenia data-sets.

22q11.2 deletion

This was the first CNV implicated in schizophrenia and has received extensive replication over the years. It affects ~40 genes and leads to a variety of physical anomalies. The latest review found a rate of 0.30% in patients and 0% in controls. This rate is practically identical to our new sample, where we found 20 carriers in the case group (0.29%) and none in the control group. It remains the most significantly associated CNV in schizophrenia: $P = 4.4 \times 10^{-40}$.

Implications

Out of 15 previously implicated CNV loci, 11 are now strongly associated with schizophrenia from the combined results of the previous literature and our new data. The evidence for the remaining four loci should be regarded as still equivocal and requiring further investigation. Our findings indicate that approximately 2.5% of individuals with schizophrenia carry at least one known pathogenic CNV. The odds ratios of these CNVs
in relation to schizophrenia range between −2 and >50 and nearly all of them are also associated with a range of other neurodevelopmental disorders, such as autism spectrum disorder and intellectual deficit. Moreover, a number of the individual pathogenic CNVs are associated with particular physical disease phenotypes, such as hypothyroidism (15p11.2), congenital heart disease (1q21.1 and 22q11.2), microcephaly (1q21.1, 3q29 and 16p11.2) and obesity (16p11.2 distal),\(^1\)\(^{-}\)\(^{1.3,5,15}\)\(^{51}\) Given their frequency, these findings therefore suggest that routine screening for CNVs should be made available and that the results will have immediate implications for genetic counselling, and given their comorbidity with other medical disorders, for patient management as well. The robust identification of 11 relatively high comorbidity with other medical disorders, for patient management as well. The robust identification of 11 relatively high

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