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A Genome Wide Survey Supports the Involvement of Large Copy Number Variants in Schizophrenia With and Without Intellectual Disability

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Background: Copy number variants (CNVs) have been shown to play a role in schizophrenia and intellectual disability.

Methods: We compared the CNV burden in 66 patients with intellectual disability and no symptoms of psychosis (ID-only) with the burden in 64 patients with intellectual disability and schizophrenia (ID + SCZ). Samples were genotyped on three plates by the Broad Institute using the Affymetrix 6.0 array.

Results: For CNVs larger than 100 kb, there was no difference in the CNV burden of ID-only and ID + SCZ. In contrast, the number of duplications larger than 1 Mb was increased in ID + SCZ compared to ID-only. We detected seven large duplications and two large deletions at chromosome 15q11.2 (18.5–20.1 Mb) which were all present in patients with ID + SCZ. The involvement of this region in schizophrenia was confirmed in Scottish samples from the ISC study (N = 2,114; 1,130 cases and 984 controls). Finally, one of the patients with schizophrenia and low IQ carrying a duplication at 15q11.2, is a member of a previously described pedigree with multiple cases of mild intellectual disability, schizophrenia, hearing impairment, retinitis pigmentosa and cataracts. DNA samples were available for 11 members of this family and the duplication was present in all 10 affected individuals and was absent in an unaffected individual.

Conclusions: Duplications at 15q11.2 (18.5–20.1 Mb) are highly prevalent in a severe group of patients characterized by intellectual disability and comorbid schizophrenia. It is also associated

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with a phenotype that includes schizophrenia, low IQ, hearing and visual impairments resembling the spectrum of symptoms described in "ciliopathies." © 2013 Wiley Periodicals, Inc.

Key words: schizophrenia; intellectual disability; copy number variants; genetics

INTRODUCTION

Recent studies have indicated that copy number variants (CNVs) may be important in genetic disease as CNV regions contain hundreds of genes and disease loci [Iafrate et al., 2004; Sebat et al., 2004; Redon et al., 2006]. CNVs play a role in mental retardation and neuropsychiatric disorders including schizophrenia and autism [Koolen et al., 2009; Grayton et al., 2012; Kirov et al., 2012]. The specific CNVs which contribute to these three disorders show large overlap [Guilmatre et al., 2009].

Patients with schizophrenia and low IQ are a particularly important group for genetic studies in schizophrenia as they represent a severe form of neurodevelopmental disorder. Subjects with mild mental retardation have a higher point prevalence of schizophrenia than the normal population [Turner, 1989]. A community based study of mild intellectual disability in Scotland showed a point prevalence of over 4% for schizophrenia [Cooper et al., 2007]. The higher frequency of schizophrenia in mental retardation was examined by MRI neuroimaging which revealed reductions in the volume of the amygdalo-hippocampal region in the schizophrenia subjects with normal and low IQ, compared to controls whereas the patients with mental retardation alone had amygdalo-hippocampal volumes larger than controls [Sanderson et al., 1999]. These findings were confirmed by reanalysis of the MRI data to calculate gyrification index (i.e., a measure of cortical folding calculated from MRI scans). Subjects with mental retardation had the lowest GI scores in pre-frontal lobes, schizophrenia subjects with low and normal IQ were midway between this and controls and there were no differences between the two schizophrenia groups [Bonnici et al., 2007]. Thus neuroimaging studies provide strong arguments for considering schizophrenia combined with low IQ to be a severe form of schizophrenia rather than a co-morbidity associated with separate risk factors [Doody et al., 1998; Bonnici et al., 2007] raising the possibility that the same neurodevelopmental pathology may be involved in low IQ and the symptoms of psychosis in this group.

The aim of this study is to compare the CNV burden in 66 patients with intellectual disability (IQ $<$ 70) and no symptoms of psychosis (ID-only) with the burden in 64 patients with intellectual disability and schizophrenia (ID + SCZ).

MATERIALS AND METHODS

Sample Collection and Ascertainment

The study was approved by the appropriate Multicentre Research Ethics Committee and was carried out in accordance with the Adults with Incapacity Act (Scotland). Patients were over 18 years of age and recruited from the inpatient and outpatient services for Adults with Intellectual Disability of South East Scotland Health Boards. In the UK the health services provided for patients with IQ $<$ 70 have a separate administration within the National Health Service and psychiatrists are involved in the management of many patients regardless of whether or not they have a mental illness. Recruitment was through the "Intellectual Disability Service" within the National Health Service. To be in this service all patients were assessed to have IQ $<$ 70. In this study we did not routinely reassess IQ but relied on case note records. IQ assessment used Wechsler Intelligence Scale for Children (WISC) or Wechsler Adult Intelligence Scale (WAIS) (most patients were part of the Intellectual Disability Service since childhood). The IQs of patients were assessed by clinical psychologists in the Intellectual Disability Service; only patients with an IQ between 50 and 70 were included in this study. In the patients with ID + SCZ, IQ was assessed before the onset of psychosis. Patients with known chromosomal rearrangements and clinically diagnosed "syndromic" ID based on phenotypic evaluation and dysmorphic features were not included in this study.

The patients gave consent to take part in the study; however, if their cognitive level meant they were incapable of giving fully informed consent their welfare guardian or nearest relative was approached to also give consent. Initial contact was through the responsible psychiatrist. Some patients were being treated for schizophrenia and major depression and some had no history of mental illness. Diagnoses according to DSM-IV criteria were reached using the semi-structured interview Psychiatric Assessment Schedule for Adults with a Developmental Disability (PAS-ADD 10) involving the patient and a key informant. Additional clinical information was obtained from hospital case note review. The Social Communication Questionnaire-lifetime version (SCQ-L) provided a screen for autism and high scoring individuals were followed up using the Autism Diagnostic Instrument-Revised (ADI-R).

Genotype data were available from 137 subjects with ID + SCZ or ID only and the final sample after excluding subjects based on quality control criteria of the genotype data comprised 130 subjects. A diagnosis of schizophrenia was reached in 64 subjects and 15 subjects had major depressive disorder. Subjects were divided into two groups: intellectual disability and a clinical diagnosis for schizophrenia (ID + SCZ; N = 64), and intellectual disability with no clinical diagnosis except for depression (ID-only; N = 66). The 15 subjects diagnosed with depression were all included in the ID-only group; the prevalence of depression in this group was 23%.

The mean age of the subjects was not significantly different between the ID-only group (mean age = 53.39; SD = 15.42) and the SCZ + ID groups (mean age = 56.67; SD = 12.98) ($F(1,129) = 1.71$, $P = 0.19$). The minimum age of the subjects was 24 in the ID-only group and 28 in the ID + SCZ group, which implies that the probability that patients in the ID-only group will develop schizophrenia is small. In the ID-only group, 32 subjects (49%) were male; in the SCZ + ID group, 38 subjects (59%) were male. The male–female ratio was not significantly different between groups ($X^2(1) = 1.55$, $P = 0.12$).

A Family With Multiple Cases of Schizophrenia and Mild Intellectual Impairment Also Associated With Retinitis Pigmentosa and/or Progressive Hearing Loss

This Scottish family has been fully described by Sharp and colleagues [Sharp et al., 1994]. There was no evidence of consanguinity and cytogenetic analysis revealed a normal karyotype.

Family members were directly interviewed by a trained psychiatrist and some consented to ophthalmological and audiometric assessment. The phenotype of the ten family members, from whom DNA was available for this study and who each carried the 15q11 duplication, is described in the supplementary information (Sample Collection and Ascertainment Section) and summarized in Figure 2.

Genotyping

Samples were genotyped on three plates by the Broad Institute using the Affymetrix 6.0 array which includes 906,600 SNP and 940,000 copy number probes. CNVs were called using Birdseye [Korn et al., 2008] which identifies rare CNVs by integrating intensity data from neighbouring probes using a hidden Markov model (HMM) on a per-individual basis. For each CNV a LOD score was generated as the logarithm of the relative likelihood of the segment being the stated copy number versus the copy number of the flanking segments.

Quality Control Evaluation of the Intellectual Disability Sample

Birdseye provides a sample-specific measure of noise of SNP and CN probes which reflects the square of the average number of standard deviations a sample is from the expected value. Four subjects showed high relative variances (i.e., >2) consistent with technical errors and were therefore deleted from subsequent analyses. In addition, based on SNP data, duplicate samples were detected by calculating the IBS matrix in PLINK [Purcell et al., 2007] and checking the samples with genome-wide average IBS pairwise identities >0.9. Two duplicate pairs were detected. One of the four samples was already removed due to high SNP variances and the remaining three samples were excluded from subsequent analyses. We also checked for the presence of outliers (>30 events, or total events spanning >10 Mb), but none were present. In total, seven samples (three individuals with ID + SCZ and four with ID only) were excluded.

For the 130 individuals passing QC, we observed 35,214 regions of copy number other than 2. We selected only those CNVs with a LOD $>$ 10 and physical length >100 kb and restricted analysis to the remaining 1,341 segments. As genotyping was performed on three different plates we compared CNV rates, proportions, total kb of the CNV segments and average kb of the segments between plates. Each plate was compared with the other two plates in separate analyses so in total three comparisons were made. A comparison of CNV rates (>100 kb and >1 Mb) revealed no significant differences between plates.

CNV Burden Analysis

The rate of deletions and duplications was calculated including all CNVs larger than 100 kb and larger than 1 Mb. Two-sided tests were performed to compare rates between ID + SCZ and ID-only and permutation testing of group status was performed to assess statistical significance.

Scottish Samples From the International Schizophrenia Consortium (ISC)

Scottish schizophrenia and control samples included in the Genome-wide association study conducted by the ISC were used as comparison groups. This sample does not allow for a formal replication of reported ID+-SCZ and ID-only differences, as all cases with schizophrenia in the ISC cohort had IQ $>$ 70, but confirmation of the role of a specific CNV in the ISC sample does provide additional evidence for its involvement in causing schizophrenia. All schizophrenia patients and controls in the ISC study were recruited from the same regions using similar procedures as for the ID patients. Patients with schizophrenia and cytogenetic rearrangements were excluded from the cohort of SCZ patients with normal IQ.

All cases and controls gave informed consent and the study was approved by both local and multicentre Research Ethics committees. The Aberdeen sample met the Diagnostic and Statistical Manual for Mental Disorders-IV edition (DSM-IV) and International Classification of Diseases 10th edition (ICD-10) criteria for schizophrenia. Diagnosis was made by a trained psychiatrist based on direct interview and case note review. Operational Criteria Checklist (OPCRIT) was completed. All case participants were outpatients or stable in-patients. Detailed medical and psychiatric histories were collected. Controls were volunteers recruited through general practices in Scotland. Practice lists were screened for potentially suitable volunteers by age and sex and by exclusion of subjects with major mental illness or use of neuroleptic medication. Volunteers who replied to a written invitation were interviewed using a short questionnaire to exclude major mental illness in individual themselves and first-degree relatives. The Edinburgh sample comprised Caucasian individuals contacted through the inpatient and outpatient services of hospitals in South East Scotland. A diagnosis of schizophrenia was based on information from an interview with the patient using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L) supplemented by case note review and frequently by information from medical staff, relatives and care givers. Final diagnoses, based on DSM-IV criteria were reached by consensus between two trained psychiatrists. Cases were excluded if IQ $<$ 70. Ethnically matched controls from the same region were recruited through the South of Scotland Blood Transfusion Service and from hospital staff.

Genotyping the Scottish control samples on Affy-6 arrays at the Broad Institute as part of the ISC [Purcell et al., 2009] was carried out at a different time from the ID samples but methods were otherwise the same. We obtained called CNVs for cases and controls from Aberdeen and Edinburgh, processed in the same manner as reported in the original paper [International Schizophrenia Consortium, 2008], except that CNVs were not filtered based on

TABLE I. Overview of CNV (>100 kb) Rates in 66 Subjects With ID-Only and 64 Subjects With ID + SCZ

	ID + SCZ (N = 64)	ID-only (N = 66)	Empirical *P*-value
Size: >100 kb			
N (rate) total CNV	663 (10.4)	678 (10.3)	0.92
N (rate) deletions	281 (4.4)	316 (4.8)	0.49
N (rate) duplications	382 (6.0)	362 (5.5)	0.44
Size: >500 kb			
N (rate) total CNV	44 (0.69)	46 (0.70)	1
N (rate) deletions	11 (0.17)	16 (0.24)	0.51
N (rate) duplications	33 (0.52)	30 (0.45)	0.72
Size: >1 Mb			
N (rate) total CNV	14 (0.22)	6 (0.09)	0.04
N (rate) deletions	6 (0.09)	5 (0.08)	0.47
N (rate) duplications	8 (0.13)	1 (0.02)	0.01

Rate = number of CNVsM/N of subjects (allowing multiple CNVs per individual).

frequency. The total number of Scottish samples that passed QC was N = 2,114 (1,130 schizophrenia cases and 984 controls). The majority of the subjects were from Aberdeen (N = 1421; 67%) while the remaining subjects were from Edinburgh (N = 693; 33%). Since the ID samples were not genotyped as part of the same experiment there may be confounding factors that cause differences between CNV rates in the ID samples and the ISC schizophrenia cases and controls. To minimize biases introduced by such factors we only used CNVs called in the ISC data that were larger than 1 Mb.

Confirmation of CNVs Using Multiplex Amplicon Quantification

To explore for CNVs in Chr 15q11.2 region, we used Multiplex Amplicon Quantification (MAQ) [Suls et al., 2006; Sleegers et al., 2006] in nine subjects for whom genome-wide SNP data indicated the presence of CNVs in this region and for the 10 individuals in the extended pedigree. We utilized the You-MAQ assay service and kit (purchased from Multiplicon N.V., Belgium; www.multiplicon.com) to analyze our CNV region of interest (Chr 15q11.2). Using this system we generated three primer pairs that were purchased from Sigma–Aldrich (see Table SI). These multiplex primers were used with Multiplicon's You-MAQ control assay kit (Product No.-YM-0090) containing Taq Polymerase and primers targeting six control amplicons on six different chromosomes (see Table SI). Subsequent fragment analysis was carried out on an ABI 3730 DNA analyzer (Applied Biosystems). The comparison of normalized peak areas between patient and control individuals results in a dosage quotient (DQ) of the target amplicon. Four target amplicons and six reference amplicons were amplified in MAQ-assays (Table SI). The YOU-MAQ-reactions were performed on 20 ng genomic DNA following the kit protocol. Dosage quotients were calculated using multiplex amplicon quantification software package (MAQ-S; http://www.vibgeneticservicefacility.be/MAQ.htm). These amplicons provide reliable information as they directly lie within genes affecting message and protein. For example amplicons 1 and 2 lie within genes LOC646214 and LOC3481200, respectively, and amplicon 3 lies close to OR4N3P.

RESULTS

CNV Burden Analysis in 66 Subjects With ID Only and 64 Subjects With ID + SCZ

For CNVs larger than 100 kb, there was no difference in the CNV burden of ID-only and ID + SCZ (rate ID-only = 10.3; rate ID + SCZ = 10.4, empirical $P = 0.92$; see Table I). Restricting the comparison to CNVs larger than 1 Mb, CNV burden was increased in ID + SCZ compared to ID-only (rate in ID-only = 0.09; rate in ID + SCZ = 0.22; empirical $P = 0.04$; see Table I) which was mainly explained by an increase in the number of duplications (rate in ID-only = 0.02; rate in ID + SCZ = 0.16; empirical $P = 0.01$) while the number of deletions was not significantly increased (rate in ID-only = 0.08; rate in ID + SCZ = 0.09; empirical $P = 0.47$). In the total sample of 130 subjects, we detected 22 CNVs larger than 1 Mb. A full overview of the locations of these CNVs is provided in Table II. It is interesting to note that four CNVs were located in previously identified regions of interest, including 1q21.1 (N = 1) and 22q11.2 (N = 3). One individual with ID + SCZ carried three large duplications at chromosome 9p11–p13 but as it was difficult to show these were separate duplications, the comparison of CNV burdens was done under the conservative assumption that this patient carried a single duplication on chromosome 9.

The most striking result was the detection of seven large duplications and two large deletions at chromosome 15q11.2 which were all present in patients with ID + SCZ. The rate of this CNV was 0.14 in ID + SCZ and 0.00 in ID only patients (OR[1] = 20.8, 95%

[1]The OR was calculated by replacing the value of the empty cell with 0.5.

TABLE II. Overview of CNVs (>1 Mb) Detected in 130 Subjects With Intellectual Disability

Chr	Start (Mb)	End (Mb)	Type	N probes	Chromosome band	Size (Mb)	Scz
1	**144.6**	**146.3**	**Deletion**	**703**	**1q21.1**	**1.7**	**Yes**
1	245.3	246.8	Deletion	940	1q44	1.5	No
4	137.7	143.9	Deletion	4,168	4q28.3–q31.21	6.2	No
6	115.5	123.2	Deletion	4,520	6q22.1–q22.3	7.7	No
7	104.4	106.8	Deletion	1,502	7q22.2–q22.3	2.4	No
8	9.3	10.5	Deletion	965	8p23.1	1.2	Yes
9[a]	38.8	46.2	Duplication	261	9p11.2–p13.1	7.4	Yes
15	18.7	19.8	Deletion	270	15q11.2	1.1	Yes
15	18.8	20.1	Duplication	343	15q11.2	1.2	Yes
15	18.7	19.8	Duplication	280	15q11.2	1.1	Yes
15	18.7	20.1	Duplication	394	15q11.2	1.4	Yes
15	18.5	19.5	Duplication	280	15q11.2	1	Yes
15	19.1	20.1	Duplication	307	15q11.2	1	Yes
15	18.5	19.5	Duplication	281	15q11.2	1.1	Yes
15	18.5	20.1	Duplication	406	15q11.2	1.5	Yes
15	18.7	19.8	Deletion	269	15q11.2	1.1	Yes
17	31.9	33.4	Deletion	989	17q12	1.5	No
22	**17.3**	**19.9**	**Deletion**	**1,634**	**22q11.21**	**2.7**	**Yes**
22	**17.3**	**18.7**	**Duplication**	**921**	**22q11.21**	**1.5**	**No**
22	**17.3**	**18.7**	**Deletion**	**921**	**22q11.21**	**1.5**	**Yes**

Note: CNVs printed in bold are located in a candidate CNV region for schizophrenia.
[a]The CNV located at chromosome 9 was called as three separate events in a single individual (38.8–40.6 Mb; 42–43.7 Mb; 45–46.2 Mb). Treating it as a single CNV in the statistical analysis is a more conservative approach.

CI = 1.2–366.8). An overview of the genes in this region is provided in Figure 1. These genes have not previously been found to be associated with any disease according to the Genetic Association Database [Becker et al., 2004]. Note that the CNVs that we have detected were located between 18.5 and 20.1 Mb (NCBI36/hg18) which does not overlap with the known candidate region at 15q11.2 (20.3–20.8 Mb). The duplications and deletions were all confirmed using the PCR based assay, MAQ. Furthermore, the intensity plots of the 130 subjects were manually inspected to verify the positive and negative calls. Even though the CNVs at 15q11.2 overlap with known structural variations as reported in the database of genomic variants (DGV), it was striking that all nine individuals with this CNV had schizophrenia with low IQ. To investigate whether these nine individuals had additional CNVs of interest, we performed additional analyses focusing on this group. The nine individuals with large CNVs at 15q11.2 did not have large CNVs remote from 15q11.2. We also tested whether these nine subjects had significantly increased rates of CNVs compared to the remaining 55 individuals. No statistically significant differences were found genome-wide for CNVs >100 kb or CNVs >500 kb. The rates of CNVs larger than

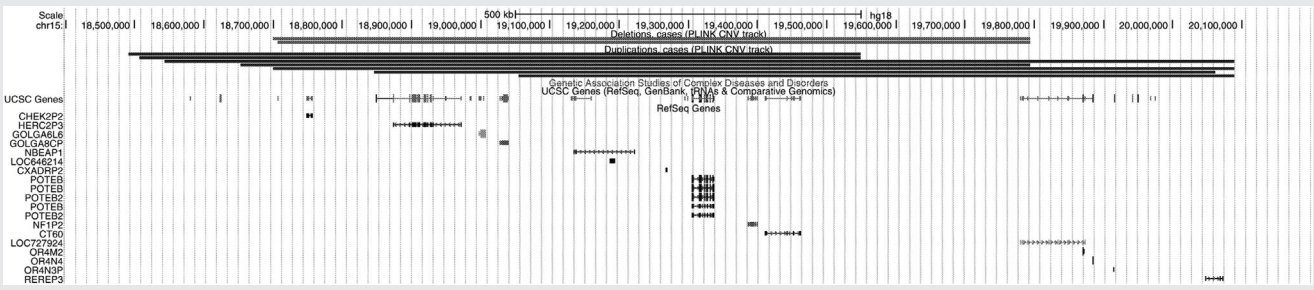

FIG. 1. A graphical overview of the rearrangements (>1 Mb) detected in nine subjects with ID + SCZ. The figure further shows genes (black bars) in the chromosome 15 region (18.5–20.1 Mb).

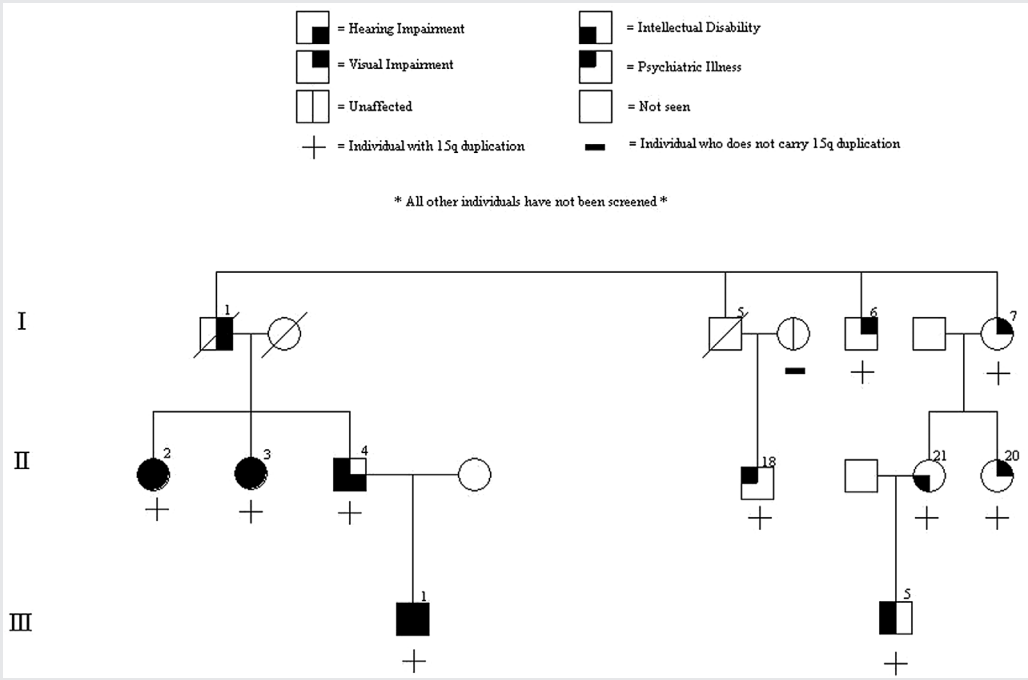

FIG. 2. Segregation of the 15q11 (18.5–20.1 Mb) duplication in an extended pedigree. DNA was available from 11 family members and the duplication was present in all 10 related individuals (marked by +) and was absent in a healthy married-in individual, the wife of I.5 (marked −). All carriers are heterozygous for the duplication. DNA samples were not available to test for the duplication in other family members (based on the pedigree published in Sharp et al. [1994]; the identifiers are the same as those in the original publication).

100 kb at chromosome 15 was also similar in both groups (1.7 in SCZ + ID with a CNV at 15q11.2 vs. 1.3 in SCZ + ID with no CNV at 15q11.2; $P = 1.00$). Finally, the rates of CNVs larger than 500 kb at chromosome 15 appeared to be different (1.11 vs. 0.13) but the difference was non-significant and nine out of 10 large CNVs in the SCZ + ID group with a CNV were located at 15q11.2 so the apparent difference in rates is entirely explained by the CNV of interest. Therefore, second hits do not seem to explain the association between a CNV at 15q11.2 and clinical status.

CNV Burden Analysis in Scottish Samples of the International Schizophrenia Consortium

We used the Scottish samples of the ISC to test whether the CNV rate in this region was increased in cases with schizophrenia and normal IQ (>70) compared to controls [International Schizophrenia Consortium, 2008]. The CNV was not reported in the original paper, since the authors had excluded CNVs with a frequency >1% [International Schizophrenia Consortium, 2008]. The Scottish ISC and ID cases and controls were all recruited from the same area by the same clinical team. In the Edinburgh and Aberdeen samples (N = 2,114; 1,130 cases and 984 controls), the CNV rate was not significantly different between SCZ cases and controls for CNVs >100 kb (empirical $P = 0.17$) or for CNVs larger than 500 kb (empirical $P = 0.15$). However, as in the intellectual disability sample, a difference was reported for CNVs larger than 1 Mb. The CNV rate in the 18.5–20.1 Mb 15q11.2 region was significantly higher in schizophrenia cases (rate = 0.088) compared to controls (rate = 0.066; one-sided empirical $P = 0.037$; OR = 1.4; 95% CI = 0.98–1.88). The difference could be attributed to an increased rate of duplications in cases (rate = 0.051) compared to controls (rate = 0.036) (one-sided empirical $P = 0.049$; OR = 1.47; 95% CI = 0.96–2.25) while the rate of deletions in this region was not significantly different between groups (one-sided empirical $P = 0.27$; OR = 0.67; 95% CI = 0.44–1.03).

The Role of the Novel CNV (15q11.2, 18.5–20.1) in an Extended Pedigree With Multiple Cases of Schizophrenia and Mild Intellectual Impairment

One of the patients with schizophrenia and low IQ carrying the novel duplication located at 15q11.2, is a member of a previously described pedigree with multiple cases of mild intellectual disability, schizophrenia, hearing impairment, retinitis pigmentosa and cataracts occurring in combination or alone [Sharp et al., 1994]. DNA samples were available for 11 members of this family and the duplication was present in all 10 affected individuals (three with IQ < 70, schizophrenia, deafness and visual impairment; one with IQ < 70, unspecified psychosis and deafness; three with visual impairment; one with IQ < 70; one with recurrent depression;

one with IQ < 70 and childhood behavioral disorder with drug and alcohol abuse) and absent in a healthy married-in subject (Fig. 2). The novel 15q11.2 duplication thus appears to be associated with neurodevelopmental disorders expressed as a range of phenotypes.

DISCUSSION

We have found that CNV rates are increased in cases with ID + SCZ compared to ID-only, but only when analysis was restricted to very large CNVs (>1 Mb). For CNVs >100 kb no difference was found which may reflect that CNVs of this size have increased rates in both ID + SCZ and ID-only. At the extreme end of the disorder, with subjects being affected both in the intellectual and psychiatric domain, genetic differences seem to be reflected in the increased rate of extremely large CNVs.

The increased rate of >1 Mb duplications in cases with ID + SCZ compared to ID-only mainly reflects a novel CNV region at chromosome 15q11.2 (18.5–20.1 Mb). The CNV rate in this region was 0.14 in subjects with intellectual disability and schizophrenia and 0.00 in the intellectual disability only group. ISC data revealed CNV rates of 0.088 and 0.066 in Scottish schizophrenia cases and controls, respectively. The finding that the rate of this novel CNV is increased both in patients with SCZ + ID and in patients with SCZ with normal IQ, supports our hypothesis that SCZ + ID is a severe form of SCZ and not a comorbid condition or a separate diagnostic category.

A potential causal role for this locus for ID + SCZ should be interpreted with caution recognizing that the CNV has been reported in the DGV [Zhang et al., 2006]. Furthermore, this region is covered with low copy repeats of various sizes, which are known to confound CNV identification. Finally, we cannot rule out the possibility of population stratification, although we have been very careful to reduce this by recruitment strategy. All cases were recruited by the same clinical teams in the same geographical regions in Scotland through National Health Service clinics. As this duplication has also been observed in healthy controls, it is unlikely that this CNV is a sufficient risk factor for schizophrenia with or without ID. However, it may be a genetic factor which increases the risk for schizophrenia, possibly acting together with additional genetic risk factors.

Despite these difficulties, we believe that our finding is potentially important for the following reasons. First, the CNV calls were confirmed by MAQ assay and manual inspection of the intensity plots. Second, a potential role for this region in the etiology of schizophrenia was confirmed in an independent Scottish cohort of schizophrenia with normal IQ and was found in several members of a single family with a phenotype, originally described as similar to Usher syndrome that includes hearing and visual impairment, low IQ and mental illness, resembling the spectrum of symptoms found in "ciliopathies" caused by defects in primary cilia of neurons and specialized sensory cells [Lee and Gleeson, 2010].

Third, even though it is unlikely that this CNV is a sufficient risk factor for low IQ or schizophrenia, given the fact that it has been reported in the DGV, our results do suggest that it increases the risk for schizophrenia. The rate of duplications is higher in ISC schizophrenia cases (rate = 0.051) compared to controls (rate = 0.036) and is highly prevalent in severely affected subjects with low IQ and psychosis (rate = 0.14). The fact that this duplication is rather common in the normal population, may explain the relatively low OR of ~1.4 (e.g., the well-known 16p11.2 duplication is associated with a 14.5-fold increased risk of schizophrenia) [McCarthy et al., 2009]. Therefore, even though this finding needs further replication, we report on a novel finding which deserves further study. Functional analysis of genes within the duplication may identify risk factors shared by schizophrenia, intellectual disability, and specific sensory impairments.

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