Confirmed rare copy number variants implicate novel genes in schizophrenia

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Abstract

Understanding how cognitive processes including learning, memory, decision making and ideation are encoded by the genome is a key question in biology. Identification of sets of genes underlying human mental disorders is a path towards this objective. Schizophrenia is a common disease with cognitive symptoms, high heritability and complex genetics. We have identified genes involved with schizophrenia by measuring differences in DNA copy number across the entire genome in 91 schizophrenia cases and 92 controls in the Scottish population. Our data reproduce rare and common variants observed in public domain data from >3000 schizophrenia cases, confirming known disease loci as well as identifying novel loci. We found copy number variants in *PDE10A* (phosphodiesterase 10A), *CYFIP1* [cytoplasmic FMR1 (Fragile X mental retardation 1)-interacting protein 1], K^+ channel genes *KCNE1* and *KCNE2*, the Down's syndrome critical region 1 gene *RCAN1* (regulator of calcineurin 1), cell-recognition protein *CHL1* (cell adhesion molecule with homology with L1CAM), the transcription factor *SP4* (specificity protein 4) and histone deacetylase *HDAC9*, among others (see http://www.genes2cognition.org/SCZ-CNV). Integrating the function of these many genes into a coherent model of schizophrenia and cognition is a major unanswered challenge.

Introduction

Schizophrenia is a debilitating psychiatric disorder that affects 1 % of the population worldwide. It is characterized by positive psychotic symptoms, such as hallucinations and delusions, and negative symptoms, including cognitive and social impairments [1]. With an estimated heritability coefficient of ~0.8, schizophrenia is thought to have strong genetic components, interacting with a number of environmental, epigenetic and stochastic factors. Identifying genomic variants linked to schizophrenia is therefore a crucial step in understanding the aetiology and pathophysiology of the disorder.

In previous decades, the main strategies used in psychiatric genetics were family linkage and case-control association studies [1–3], complemented by the identification of cytogenetic abnormalities. This led to the discovery of some rare, potentially disease-causing, mutations: for example, disease-related genes or genetic loci such as *DISC1* (disrupted in schizophrenia 1), *NPAS3* [neuronal PAS (Per/Arnt/Sim) domain 3] and 22q11 were identified from balanced translocations or microdeletions. They have subsequently been supported by compelling biological and functional evidence as candidates for contributors to the aetiology of schizophrenia.

More recently, whole-genome screening for CNV (copy number variation) and genome rearrangements has revealed many more structural variations than expected in healthy individuals [4,5]. Furthermore, associations between CNV and neuropsychiatric conditions have been identified [6,7]. For example, studies by the ISC (International Schizophrenia Consortium), the SGENE-plus Consortium, and others have shown significant associations between rare recurrent CNVs and schizophrenia [8–11]. These studies also revealed a higher collective disease burden from rare genic CNVs.

We screened DNA from 91 cases and 92 controls for CNVs using aCGH (array-based comparative genome hybridization). The screen was performed using the WGTP (whole genome tile path) microarray platform. Examination of autosomal CNVs revealed agreement with the ISC dataset at individual loci and confirmation of disease-biased CNV at multiple loci. These results take a first step in pinpointing rare variants that are likely to be functional and demonstrate the usefulness of confirmatory association studies of rare variants in schizophrenia.

Key words: array comparative genome hybridization, copy number variant, psychiatric genetics, schizophrenia.

Abbreviations used: aCGH, array comparative genome hybridization; BIN1, bridging integrator 1; CHL1, cell adhesion molecule with homology with L1CAM; CHRNA7, cholinergic receptor, nicotinic, α_7; CNV, copy number variation; CNVR, CNV region; Cy3, indocarbocyanine; Cy5, indodicarbocyanine; CYFIP1, cytoplasmic FMR1 (Fragile X mental retardation 1)-interacting protein; FAM7A, family with sequence similarity 7A; CHRFAM7A, CHRNA7 and FAM7A fusion; HDAC9, histone deacetylase 9; ISC, International Schizophrenia Consortium; LBC, Lothian Birth Cohort; PDE10A, phosphodiesterase 10A; PITPNA, phosphatidylinositol-transfer protein α; PSD, postsynaptic density; RCAN1, regulator of calcineurin 1; SCZ, Schizophrenia Cohort; SGCE, sarcoglycan ε; WGTP, whole genome tile path.

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aCGH data analysis

CNVs were detected in 91 Scottish individuals with schizophrenia and 92 control Scottish samples from the 1921 LBC (Lothian Birth Cohort) [12].

WGTP array CGH was performed as described previously by Redon et al. [13]. Briefly, each fluorescently labelled [with Cy3 (indocarbocyanine) or Cy5 (indodicarbocyanine)] HapMap DNA sample (200 ng) was hybridized to an oppositely labelled (Cy5 or Cy3) reference genomic DNA (NA10851) (200 ng) in a dye-swap experiment using two BAC (bacterial artificial chromosome) array slides. After 21 h of hybridization, array slides were scanned in an Agilent scanner and analysed using the BlueFuse software and an in-house Perl script for data normalization and GC-content correction.

In addition to manual inspection of profile qualities, all hybridization results were monitored with two statistical indicators for quality control. The first is global SDe [5], an estimate of S.D. of all log2 fluorescence ratio signals in the genome for a particular sample profile. The second is the clone retention rate after fusion of dye-swap experimental data. Experiments were accepted for further analysis only if global SDe was <0.06, global clone retention rate was >90 % and clone exclusion rate per individual chromosome was <20 %.

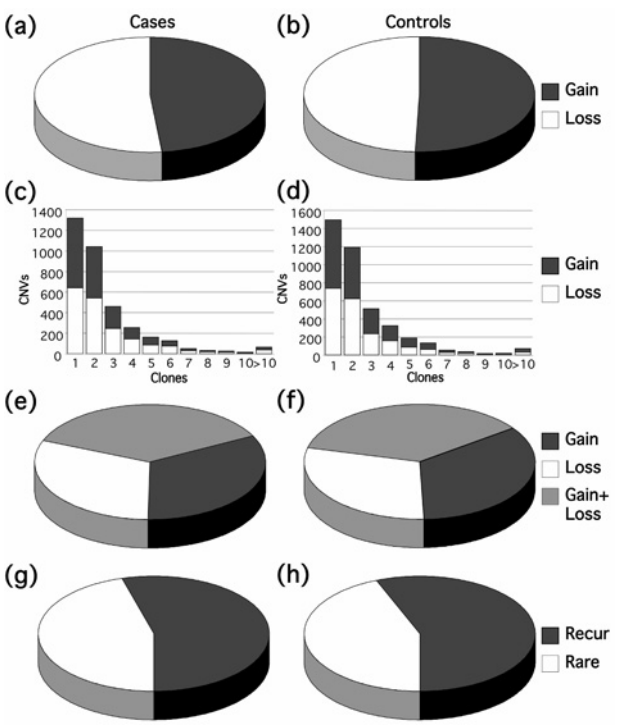
Clones mapping to the X chromosome in females and to the Y chromosome and pseudo-autosomal regions in all individuals were excluded from further analysis. Clones were then excluded further if they were retained in less than 75 % of expected individuals in either SCZ (Schizophrenia Cohort) or LBC. This left a total of 27 980 clones, representing an average of 25 102 clones per individual (range 23 292–25 805). Data for each individual were then normalized to give a median log2 fluorescence ratio of 0.00. Finally, to compensate for CNV in the reference individual, the clonewise median log2 fluorescence ratio was subtracted across all individuals. CNV was detected in each individual using CNVFinder [5]. The reduced variation in the samples enabled more sensitive calling of CNV events, since the CNVFinder algorithm automatically increases sensitivity of detection when the overall sample variance is low.

CNV detection

A CNV dataset was generated from 91 Scottish SCZ and 92 Scottish control (LBC) DNA samples hybridized against a single HapMap reference DNA on the WGTP array platform. Initial normalization on the WGTP data was performed as described previously [5]. Additional normalization and filtering steps, including correction for GC content, and filtering of clones for artefacts are summarized in [14]. One key pre-processing normalization step in which our method differs from earlier methods involved the computation of the median log2 ratio for each clone and subtraction of this median across individuals. This step reduced the S.D. of overall log2-transformed fluorescence ratios in the SCZ samples from 0.052 to 0.043 and in control samples from 0.050 to 0.040.

Figure 1 | Overall characteristics of CNVs and CNVRs found by CNVFinder in cases (a, c, e and g) and controls (b, d, f and h)

Among CNVs (**a**–**d**), similar numbers of gains and losses were observed in each cohort (**a** and **b**), and the number of clones associated with gains and losses of DNA were similar between cohorts (**c** and **d**). CNV regions in cases (**e**) and controls (**f**) had similar fractions of gains, losses and regions of gain and loss. Cases (**g**) and controls (**h**) both had roughly half of CNV regions representing single events within their cohort.



CNVs were detected using CNVFinder [5]. This algorithm automatically increases the sensitivity of detection when the overall sample variance is low. Since the SCZ samples had generally higher variation in fluorescence than LBC samples, CNVFinder detected fewer CNVs in SCZ samples than controls (Figure 1). The total number of CNV calls was 3551 in the cases (1715 gains, 1836 losses, 39 CNVs average per sample) and 4041 in the controls (2038 gains 2003 losses, 44 CNVs average per sample) (Figures 1a and 1b). In each cohort, CNVs from multiple individuals may overlap at the same genomic location. To generate sets of non-overlapping CNV genomic locations, we grouped CNVs for each cohort into CNVRs (CNV regions). For our purposes, we defined CNVRs as clusters of CNVs or singletons isolated by more than 1 Mb from the next adjacent CNV. SCZ samples were found to harbour 449 CNVRs (147 gain only, 138 loss only, 164 gain or loss), whereas controls had 481 (166 gain only, 141 loss only, 174 gain or loss) (Figures 1e and 1f). The CNV length distributions were broadly similar between cases and controls (Figures 1c and 1d), as were ratios of CNVRs representing rare compared with recurrent CNVs. In cases, 204 CNVRs represented rare events, whereas 245 were recurrent; in controls, 211 CNVRs were associated with

rare CNVs compared with 270 regions with recurrent CNVs (Figures 1g and 1h).

Validation of individual CNVs by secondary platforms

Previous literature proposed the role of rare CNVs in schizophrenia, with an estimated enrichment in cases of up to three times that found in controls. The fact that CNVFinder penalizes the SCZ samples more heavily due to their higher variation makes it less likely that any such enrichment will be found in our dataset. Conversely, it was expected that CNVs detected as specific to the SCZ samples were more likely to represent true rare variants. We therefore validated CNVs that were specific to cases for potential schizophrenia candidate genes.

Validation was performed by quantitative PCR or by using Nimblegen high-density oligonucleotide arrays in 11 individual CNVs, of which ten were technically confirmed (see Supplementary Table S1 at http://www.biochemsoctrans.org/bst/038/bst0380445add.htm). In addition, we compared CNVs from 39 individuals in our study, with CNVs detected by standard genotyping arrays in the same patients, which were included in the ISC study [8]. Of 91 CNVs in 39 individuals, 50 were confirmed in our CNV calls (Supplementary Table S1). We noted that three individuals accounted for fully one third of the 91 ISC calls. When these individuals were excluded, 77 % (46 out of 60) of ISC calls were replicated in our study.

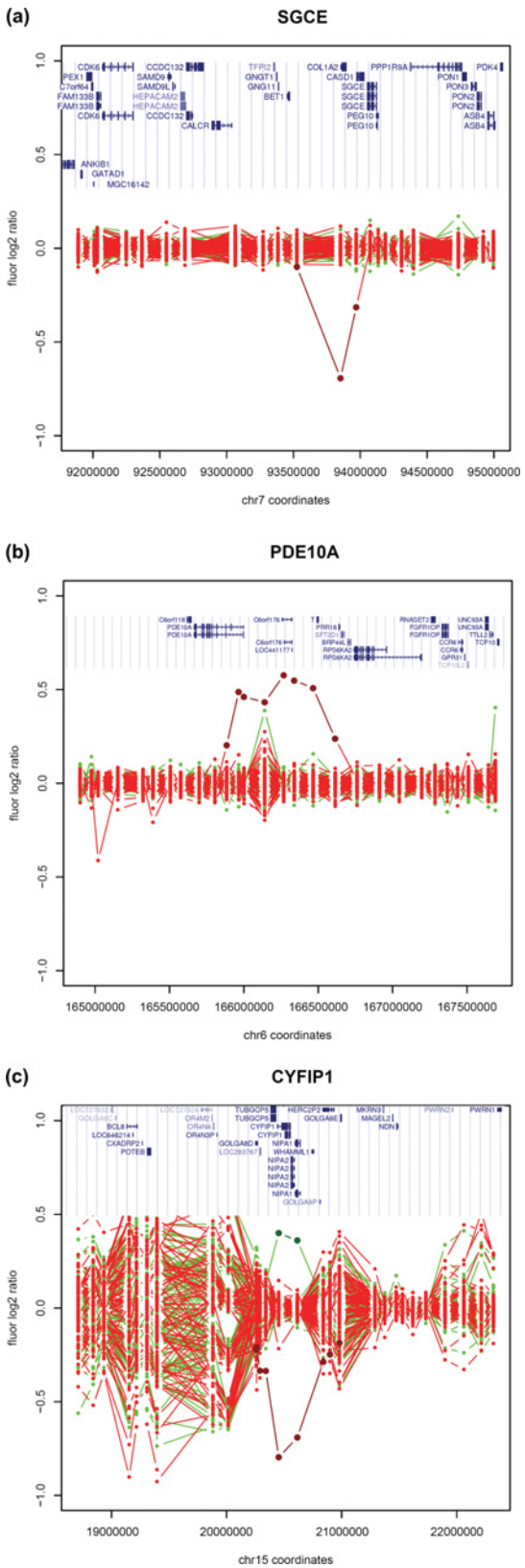
These validated regions (Supplementary Table S1) contain neuronal-related genes or overlap with previously associated psychiatric disorders (Figure 2). These include sarcoglycan ε (*SGCE*), which is associated with Tourette's syndrome and obsessive compulsive disorder; phosphodiesterase 10A (*PDE10A*), which is associated with schizophrenia and bipolar disorder; and the recurrent schizophrenia candidate locus at 15q11.2 encompassing the gene for cytoplasmic FMR1 (Fragile X mental retardation 1)-interacting protein 1, *CYFIP1*. CYFIP1 is involved in the regulation of translation in neurons, with important functions in synaptic plasticity and brain development [15]. This deletion region with *CYFIP1* has been described previously as a statistically significant schizophrenia-associated CNV locus in a large case-control cohort [9], deleted in approx. 0.55 % of cases and 0.2 % of controls.

Confirmed genic mutational biases between studies

By comparing our data with ISC data on >3000 cases and controls (http://pngu.mgh.harvard.edu/isc/isc-r1.cnv.bed), we could cross-validate putative mutational biases between schizophrenia-specific genic CNV gains and losses in the WGTP data. We excluded from the ISC data, CNV coordinates from the 39 individuals that were included in our study and which we used earlier for validation of individual CNV calls. Cross-validation of genic mutational

Figure 2 | Loci confirmed by secondary platforms

Normalized fluorescence ratios for cases (red) and controls (green) are shown. Gene positions (NCBI36) are shown in blue.



bias was then assessed separately for insertions and deletions and was deemed positive if a gene overlapped an indel of the same sense (insertion or deletion) in the same (case or control) cohort in both datasets. We detected 36 autosomal regions demonstrating replicated case-specific gains or losses (see Supplementary Table S2 at http://www.biochemsoctrans.org/bst/038/bst0380445add.htm). Of these regions, harbouring 17 genes, 12 were deletions and 24, overlapping 55 genes, represented insertions. These groups of genes, and especially the deletions, are expected to be enriched in disease candidates. A total of 338 genes in 123 regions had matching case or control skew in their insertion or deletion bias in both studies (results not shown).

In addition to CNVs in our study which overlapped with known schizophrenia-associated regions, our cross-validation analysis identified new candidate loci for schizophrenia. Among known regions, the two CNV regions most robustly validated in the ISC data involved deletions at 15q13 and a duplication at 21q22 (Figure 3). Human chromosome 15q13 is a region shown previously to be associated with schizophrenia [16,17]. CHRNA7 (cholinergic receptor, nicotinic, α_7) is thought to participate in the gating of auditory stimuli and a lack of this receptor has been hypothesized to contribute to auditory hallucinations in schizophrenia [16]. Some 23 deletions were detected overlapping the *CHRNA7* gene in our data in this region, compared with 14 in controls: in the ISC data, this gene was affected by ten deletions in cases and three in controls. It should be noted that the *CHRNA7* locus shows strong nucleotide similarity to that of the *CHRFAM7A* [CHRNA7 and FAM7A (family with sequence similarity 7A) fusion] gene, which represents a fusion between a partially duplicated copy of *CHRNA7* and a copy of the *FAM7A* gene. Owing to the strong similarity between these loci, it is possible that some of the events assigned to *CHRNA7* are a result of changes at the *CHRFAM7A* locus. However, our results duplicate earlier findings by Freedman et al. [16], lending credence to this locus as being subject to disruption in schizophrenia.

A case-specific single duplication in 21q22 was detected in our study (Figure 3c) and was matched by duplication occurring 16 times in ISC patients compared with seven times in controls. The CNV breakpoints are similar in all patients. This ~200 kb duplication harbours two K^+ channel genes, *KCNE1* and *KCNE2*. The *DSCR1* (Down's syndrome critical region 1) gene, also known as *RCAN1* (regulator of calcineurin 1), is located at the 3′ breakpoint of the duplication. *RCAN1* has been linked to Down's syndrome and Alzheimer's disease [18–20]. It encodes calcipressin 1, a regulator of calcineurin (calmodulin-dependent protein phosphatase). *RCAN1* was shown previously to affect the expression of *GSK3B* (glycogen synthase kinase 3β) [21], a candidate gene for schizophrenia and bipolar disorder [22]. Furthermore, knockout mouse models of *RCAN1* showed impairment in spatial learning and memory (in particular long-term potentiation), as well as sensorimotor deficits [18].

Several other variants recurrent in both studies also struck our notice, including case-specific deletions in *SP4* (transcription factor SP4) and *HDAC9* (histone deacetylase 9) (Figures 3d and 3e). SP4 is a transcription factor highly expressed in brain and therefore could reasonably have a large effect through controlling the transcription of many genes. In addition, *SP4* single nucleotide polymorphisms have been linked with schizophrenia and bipolar disorder, as well as sensorimotor gating in mice in other studies [23,24]. Furthermore, SP4 has been shown to be involved in cerebellar granule neuron development by promoting activity-dependent pruning of dendritic processes [25]. HDAC9 is highly expressed in brain and skeletal muscle [26] and was found to contain single schizophrenia-specific deletions in both studies. A decrease in the expression of this gene has been associated with increased neuronal apoptosis [27]. However, its putative role in chromatin modification suggests a potential for broader effects on transcription in neurons.

In addition to *SP4* and *HDAC9*, our study robustly confirmed a rare deletion variant in the *CHL1* (cell adhesion molecule with homology with L1CAM) gene (Figure 3f). CHL1 is a cell-recognition protein with roles in nervous system development, synaptic plasticity and behaviour in mice [28–31]. CHL1 has also been implicated in mental retardation in humans [32]. Other genes having a role in cell–cell interactions, for example *NRG1* (neuregulin 1) [33], have been implicated in schizophrenia.

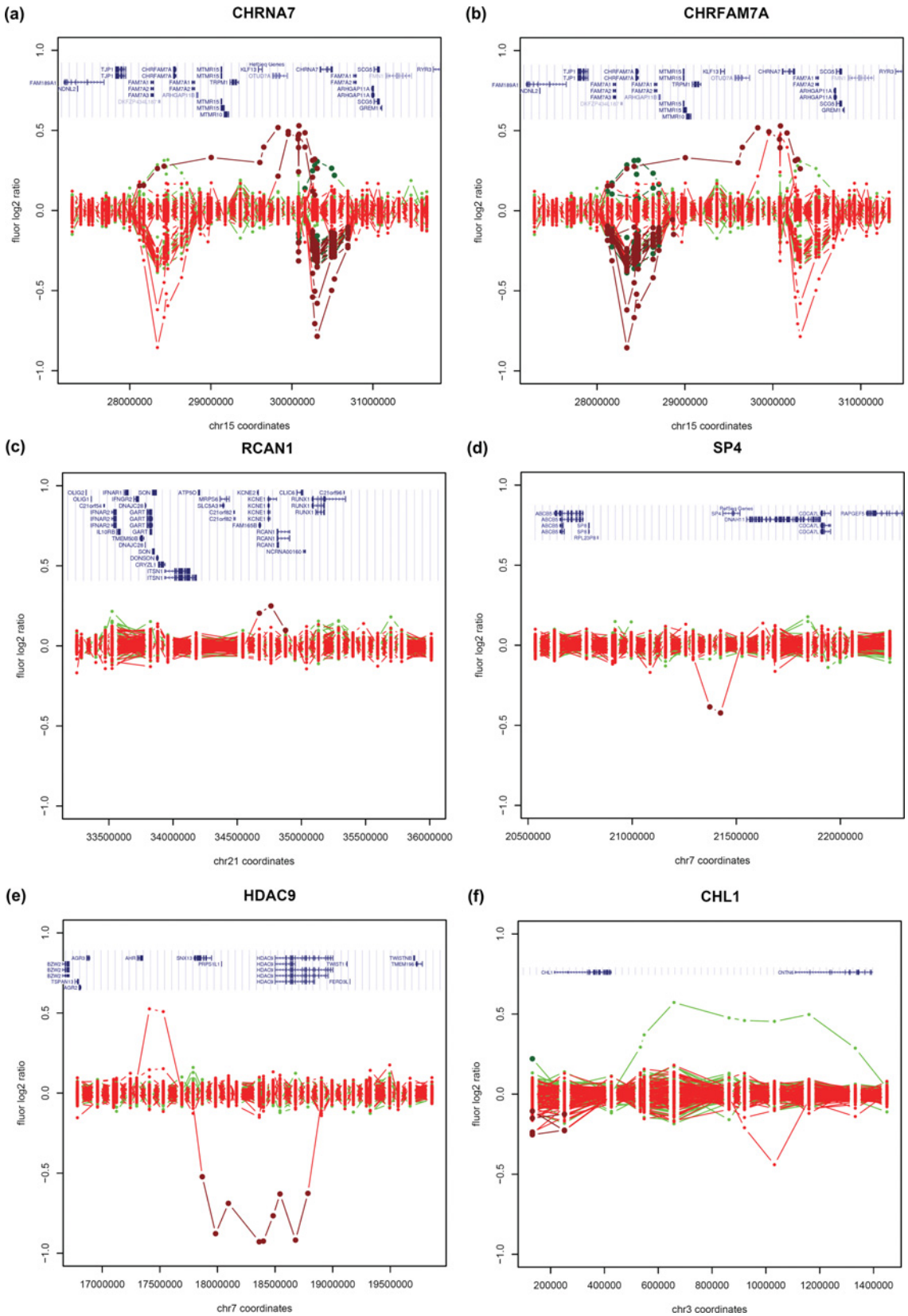
Finally, rare CNVs in our study suggested several novel candidate schizophrenia genes. For example, we found rare single deletions overlapping the *PITPNA* (phosphatidylinositol-transfer protein α) gene in our study and in the ISC study. A mouse knockout of this gene [34] exhibited early-onset tremors and neurodegeneration, indicating its relevance to neural function. Rare insertions were found in several genes, including *BIN1* (bridging integrator 1), which has been found to be important for synaptic vesicle recycling and learning in the mouse [35]. To facilitate the use of these data, we have created a web resource of the CNVs and the genes containing them (http://www.genes2cognition.org/SCZ-CNV).

Discussion

This study illustrates that some of the more common earlier findings of genes associated with schizophrenia are duplicated in smaller-scale studies, suggesting commonality of schizophrenia aetiology across populations. Principally, mutations in *PDE10A* and *CYFIP1*, suggested previously as candidate genes for schizophrenia, were confirmed. *SGCE*, associated with obsessive compulsive disorder, was overlapped by a deletion in one patient in our study. A region containing two K^+ channel genes, *KCNE1* and *KCNE2*, and *RCAN1* was duplicated in one patient. Both *KCNE1* and *KCNE2* mutations have been strongly associated with death owing to heart arrhythmias and related sudden death. Although *KCNE2* is highly expressed in brain, no brain pathology has been associated with this gene in OMIM. Whereas no study to date has implicated RCAN1 in human pathology, in rats an alternative transcript of *Rcan1* is

Figure 3 | **Six loci cross-validated in the ISC dataset**

Normalized fluorescence ratios for cases (red) and controls (green) are shown. Gene positions (NCBI36) are shown in blue.



expressed during nervous system development, suggesting a possible role for RCAN1 in brain development. *CHL1*, a haploinsufficient gene [36] located on the short arm of human chromosome 3, was also associated previously with schizophrenia [37]. Our study also suggests novel candidate genes for schizophrenia: for example, mutations in *Pitpna* and *Bin1* in the mouse have been associated with neuropathology and learning deficits respectively. Numerous other genes implicated in schizophrenia are in the postsynaptic proteome and interact in multiprotein complexes with neurotransmitter receptors [38,39]. For example, the multiprotein complex associated with PSD (postsynaptic density) -95 protein, identified using affinity purification, is highly enriched in known schizophrenia candidate genes [38]. Most recently, identification of the human PSD from fresh cortical tissue and related analysis revealed that, among known schizophrenia candidate genes annotated in public databases, the human PSD is highly enriched in these genes relative to the rest of the genome, and even relative to the rest of brain-expressed genes identified by proteomic techniques [40]. This insight may help identify likely candidate sets of genes in the future and help to narrow down lists of candidate genes. The present study also highlights the necessity for and utility of confirmatory studies to validate variants found by others. Finally, several novel candidate genes for schizophrenia are identified; however, determining how they act together with other susceptibility genes to produce the disease remains an unanswered challenge.

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SUPPLEMENTARY ONLINE DATA

Confirmed rare copy number variants implicate novel genes in schizophrenia

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Table S1 | **Technical confirmations of CNV calls**

n/a, not applicable; n/f, not found; qPCR, quantitative PCR.

Patient ID	CNV co-ordinates (NCBI36)	CNVFinder	qPCR result	Nimblegen result	ISC co-ordinates (NCBI36)
3409	12:17761730–18154145	Loss	Okay	n/a	n/a
5324	6:22212251–22607763	Loss	Okay	n/a	n/a
1085	6:97469365–98475130	Loss	Okay	n/a	n/a
ED1176	7:17795286–18873121	Loss	Okay	n/a	n/a
4203	7:93658283–94064936	Loss	Okay	n/a	n/a
3789	8:9670799–9988807	Loss	n/f	Okay	n/a
3766	1:71346768–71893785	Gain	Okay	n/a	n/a
3584	3:139094479–139416525	Gain	n/f	n/f	n/a
4179	9:137112070–137464520	Gain	Okay	Okay	n/a
5386	3:86998287–87223753	Gain	n/a	Okay	n/a
5386	5:61438895–61723574	Loss	n/a	Okay	n/a
3857	13:112568275–112939870	Gain	n/a	n/a	13:112541419–112904310
3857	17:21109148–22170347	Gain	n/a	n/a	17:21482690–22159778
621	2:24873682–25870859	Loss	n/a	n/a	2:25485729–25865666
621	2:24873682–25870859	Loss	n/a	n/a	2:24949186–25085976
621	2:24873682–25870859	Loss	n/a	n/a	2:25191977–25321842
ED0903	21:34576662–34958227	Gain	n/a	n/a	21:34644865–34827865
ED0903	3:6098521–6274110	Loss	n/a	n/a	3:6052172–6244704
1085	6:97469365–98475130	Loss	n/a	n/a	6:97426034–98410421
ED0908	11:31339431–31549584	Gain	n/a	n/a	11:31312028–31554033
1295	5:25051484–25333181	Gain	n/a	n/a	5:25121394–25405536
1295	7:88344724–88962788	Loss	n/a	n/a	7:88292092–88731204
3141	n/f	n/a	n/a	5:17553826–17675250	
3199	n/f	n/a	n/a	1:120784371–120956136	
3409	12:17761730–18154145	Loss	n/a	n/a	12:17776260–18038013
3443	n/f	n/a	n/a	19:6847380–7057724	
3559	15:29725770–30375195	Gain	n/a	n/a	15:29801634–30299513
3584	11:4012521–4399615	Gain	n/a	n/a	11:4077830–4303386
3584	n/f	n/a	n/a	9:38979378–39305037	

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Table S1 | **(Contd.)**

Patient ID	CNV co-ordinates (NCBI36)	CNVFinder	qPCR result	Nimblegen result	ISC co-ordinates (NCBI36)
3652	15:30191187–30773871	Loss	n/a	n/a	15:30318608–30664277
3703	n/f	n/a	n/a	7:21150024–21270602	
ED0994	19:53868624–54100313	Gain	n/a	n/a	19:53999273–54114243
ED0994	4:8933742–9123666	Loss	n/a	n/a	4:9046959–9155615
3751	n/f	n/a	n/a	5:99347065–99474076	
3815	6:1994541–2304998	Gain	n/a	n/a	6:2001510–2293508
3815	n/f	n/a	n/a	9:74633392–75300129	
3857	n/f	n/a	n/a	9:95716985–95909472	
3945	3:189546565–189761158	Loss	n/a	n/a	3:189564871–189682182
3945	4:28210870–28570510	Loss	n/a	n/a	4:28415433–28541944
ED1024	2:127449511–127814482	Gain	n/a	n/a	2:127182184–127688195
4100	14:74945402–75396561	Gain	n/a	n/a	14:75046923–75379455
4111	18:1734176–1905685	Loss	n/a	n/a	18:1715758–1828113
4179	21:30092743–30395434	Loss	n/a	n/a	21:30189767–30289965
4179	n/f	n/a	n/a	9:135377617–135535293	
ED1080	17:21191534–21340796	Gain	n/a	n/a	17:21269272–21488331
ED1080	3:162804591–163099220	Loss	n/a	n/a	3:162898816–163031692
4710	3:143326112–143612526	Gain	n/a	n/a	3:143303643–143554513
4710	6:57644936–58888125	Gain	n/a	n/a	6:57764260–58190911
4710	6:62001974–62186548	Gain	n/a	n/a	6:61987979–62181322
4716	20:14561835–14926976	Loss	n/a	n/a	20:14650902–14813485
4748	4:11678443–11990799	Loss	n/a	n/a	4:11838410–11948682
5307	1:12596978–13667714	Gain	n/a	n/a	1:12776194–12949762
5307	n/f	n/a	n/a	21:44730300–44890569	
5446	2:97054767–97399962	Loss	n/a	n/a	2:97166222–97295196
5446	7:75511690–76633111	Gain	n/a	n/a	7:75780381–75933685
ED1176	16:18834998–19066807	Gain	n/a	n/a	16:18811897–19027203
ED1176	7:17795286–18873121	Loss	n/a	n/a	7:17674099–18634682
ED1176	8:13581607–13896999	Loss	n/a	n/a	8:13684044–13829803
5562	19:59359391–59464094	Gain	n/a	n/a	19:59432547–59539400
ED1213	8:6046013–6339195	Gain	n/a	n/a	8:6115399–6290920
ED1213	n/f	n/a	n/a	21:13516106–14009921	
6638	13:113166605–113658050	Loss	n/a	n/a	13:113051168–113366491
6638	13:113166605–113658050	Loss	n/a	n/a	13:113525792–113654850
6638	15:99707205–100036184	Gain	n/a	n/a	15:99764132–99956872
6667	20:9592231–9923810	Gain	n/a	n/a	20:9685413–9834501
6667	5:17286078–17757290	Loss	n/a	n/a	5:17369993–17568802
7132	n/f	n/a	n/a	4:93752699–93865582	
7183	15:28080236–30412040	Gain	n/a	n/a	15:28608929–30599822
7294	10:80945468–81607519	Gain	n/a	n/a	10:81475459–81588070
7294	n/f	n/a	n/a	3:50339490–50452892	
7294	n/f	n/a	n/a	11:63498551–63605997	
5758	6:165840859–166673790	Gain	n/a	n/a	6:165893867–166666551
5758	n/f	n/a	n/a	11:66646290–67038667	
5758	n/f	n/a	n/a	9:135377617–135537967	
5758	n/f	n/a	n/a	11:65426675–65585941	
5758	n/f	n/a	n/a	9:137495692–137862491	
5758	n/f	n/a	n/a	1:151959187–152132074	
297	n/f	n/a	n/a	5:104437565–104653030	
297	n/f	n/a	n/a	7:125354682–125517636	
297	n/f	n/a	n/a	1:195349228–195455619	
297	n/f	n/a	n/a	2:194527820–194654919	

Table S1 | (Contd.)

Patient ID	CNV co-ordinates (NCBI36)	CNVFinder	qPCR result	Nimblegen result	ISC co-ordinates (NCBI36)
297	n/f	n/a	n/a	6:102421721–102577471	
297	n/f	n/a	n/a	7:118870202–119151500	
297	n/f	n/a	n/a	13:86534961–86680013	
297	n/f	n/a	n/a	7:108960973–109127453	
297	n/f	n/a	n/a	21:19222152–19326789	
297	n/f	n/a	n/a	8:114240032–114397512	
297	n/f	n/a	n/a	2:70019722–70390224	
297	n/f	n/a	n/a	21:19996804–20119037	
297	n/f	n/a	n/a	7:44379457–44481778	
3766	1:68325266–68897278	Gain	n/a	n/a	1:68334011–68755246
3766	1:71346768–71893785	Gain	n/a	n/a	1:71379226–71687039
3766	21:13556403–13942143	Loss	n/a	n/a	21:13610220–13985450
3766	n/f	n/a	n/a	19:18037250–18203869	
3766	n/f	n/a	n/a	19:846638–1231660	
3766	n/f	n/a	n/a	19:16292361–16581261	
3766	n/f	n/a	n/a	11:62107734–62354294	
3766	n/f	n/a	n/a	11:72061419–72225335	
3766	n/f	n/a	n/a	13:17924949–18160113	
3766	n/f	n/a	n/a	19:13761432–14159634	
3766	n/f	n/a	n/a	20:33710437–33886157	
3766	n/f	n/a	n/a	9:136571119—136733304	

Table S2 | **Genic case-specific ISC CNVs confirmed by CNVFinder**

HGNC Symbol	Locus (NCBI36)	SCZ91	LBC92	ISC cases	ISC controls	Indel	Gene region
FAM87B	1:742614–745077	1	0	1	0	ins	1
FAHD2B	2:97113051–97124309	1	0	1	0	del	2
BIN1	2:127522073–127581334	1	0	1	0	ins	3
CYP27C1	2:127657888–127694124	1	0	1	0	ins	3
ERCC3	2:127731336–127768222	1	0	1	0	ins	3
ZNF804A	2:185171932–185512457	1	0	1	0	ins	4
GULP1	2:188864641–189168898	1	0	1	0	ins	5
CHL1	3:213650–426098	5	0	1	0	del	6
EHHADH	3:186391108–186454531	1	0	1	0	ins	7
PDS5A	4:39500879–39655971	3	0	2	0	ins	8
TRIML1	4:189297592–189305643	1	0	2	0	del	9
GMDS	6:1569040–2190845	1	0	4	0	ins	10
RREB1	6:7052829–7197212	1	0	1	0	ins	11
NUDT3	6:34363982–34468419	1	0	1	0	ins	12
RPS10	6:34493209–34501814	1	0	1	0	ins	12
RPS10P11	6:34493209–34501814	1	0	1	0	ins	12
RPS10P13	6:34493209–34501814	1	0	1	0	ins	12
RPS10P22	6:34493209–34501814	1	0	1	0	ins	12
RPS10P4	6:34493209–34501814	1	0	1	0	ins	12
TBP	6:170705384–170723869	1	0	1	0	ins	13
PDCD2	6:170728375–170735673	1	0	1	0	ins	13
HDAC9	7:18501894–19003518	1	0	1	0	del	14
SP4	7:21434214–21520674	1	0	2	0	del	15
BET1	7:93430021–93471626	1	0	1	0	del	16
COL1A2	7:93861809–93898480	1	0	1	0	del	16
CASD1	7:93977120–94024215	1	0	1	0	del	16
TNKS	8:9450855–9677266	1	0	1	0	del	17
MSRA	8:9949189–10323803	1	0	1	0	del	17
DMRT1	9:831690–959088	1	0	1	0	ins	18
KCNT1	9:137733859–137826386	1	0	1	0	ins	19
NACC2	9:138038204–138126952	3	0	1	0	ins	19
MUC2	11:1064875–1088828	1	0	1	0	ins	20
MUC5AC	11:1152663–1178504	1	0	1	0	ins	20
MUC5B	11:1200872–1239982	1	0	1	0	ins	20
OR52K2	11:4427146–4452507	2	0	1	0	del	21
OR52K3P	11:4453046–4453699	2	0	1	0	del	21
OR52K1	11:4466707–4467651	2	0	1	0	del	21
MPHOSPH8	13:19105880–19144638	1	0	1	0	ins	22
GPC6	13:92677711–93853948	1	0	1	0	del	23
TTLL5	14:75197374–75491174	1	0	1	0	ins	24
MKRN3	15:21361547–21364653	2	0	1	0	del	25
HISPPD2A	15:41612952–41764218	1	0	1	0	ins	26
CATSPER2	15:41707993–41747608	1	0	1	0	ins	26
CKMT1A	15:41772376–41778712	1	0	1	0	ins	26
PDIA3	15:41825882–41852093	1	0	1	0	ins	26
ELL3	15:41852107–41857033	1	0	1	0	ins	26
SERF2	15:41856590–41881572	1	0	1	0	ins	26
SERINC4	15:41873652–41888067	1	0	1	0	ins	26
MFAP1	15:41884025–41904243	1	0	1	0	ins	26
ZNF205	16:3102564–3110517	1	0	1	0	ins	27
ZNF213	16:3125140–3132805	1	0	1	0	ins	27
OR1F1	16:3194248–3195189	1	0	1	0	ins	27

Table S2 | **(Contd.)**

HGNC Symbol	Locus (NCBI36)	SCZ91	LBC92	ISC cases	ISC controls	Indel	Gene region
ZNF200	16:3212326–3225412	1	0	1	0	ins	27
ATP2C2	16:82959634–83055293	1	0	2	0	ins	28
COTL1	16:83156738–83209203	1	0	1	0	ins	28
CA5A	16:86479126–86527613	1	0	2	0	ins	29
BANP	16:86542539–86668425	1	0	2	0	ins	29
PITPNA	17:1368037–1412835	1	0	1	0	del	30
WSCD1	17:5914658–5968469	1	0	2	0	del	31
UNC45B	17:30498949–30540477	1	0	1	0	ins	32
AMAC1	17:30543652–30545560	1	0	1	0	ins	32
SLFN5	17:30594199–30618852	1	0	1	0	ins	32
ANKRD12	18:9126758–9275206	1	0	1	0	ins	33
CCDC102B	18:64616297–64873406	1	0	1	0	ins	34
ELAVL1	19:7929458–8415925	1	0	1	0	ins	35
LASS4	19:8180257–8233302	1	0	1	0	ins	35
CD320	19:8273011–8279239	1	0	1	0	ins	35
NDUFA7	19:8282234–8292280	1	0	1	0	ins	35
KANK3	19:8293469–8314146	1	0	1	0	ins	35
ANGPTL4	19:8335011–8345257	1	0	1	0	ins	35
RAB11B	19:8361301–8375318	1	0	1	0	ins	35
FPR2	19:56955995—56965572	1	0	1	0	ins	36

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