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Rare genome-wide copy number variation and expression of schizophrenia in 22q11.2 deletion syndrome

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Disclosures and acknowledgements: The authors have no conflict of interests to declare. The authors would like to thank all of the subjects with 22q11.2 deletion syndrome and their families for their generous contributions to this and related research studies. The authors express gratitude to the students, research assistants, and staff affiliated with the Clinical Genetics Research Program and The Centre for Applied Genomics. Special thanks to Gladys Wong for her help with formatting and referencing.

Grant support: This work was supported the National Institute of Mental Health (5U01MH101723 02), the Canadian Institutes of Health Research (ASB, MOP #97800, MOP #111238), the Canada Research Chairs in Schizophrenia Genetics and Genomic Disorders (ASB), Canada Latin America and Caribbean Research Exchange Grants (LACREG) (ASB and GR), and the University of Toronto McLaughlin Centre (MC 2015 01). Dr. Bassett is supported by the Dalglish Chair at the University Health Network. Ms. Chelsea Lowther is supported by a Frederick Banting and Charles Best Canadian Institutes of Health Research Doctoral Award. Dr. Vorstman was funded for this work by the Brain and Behavior Research Foundation (Young Investigator Award).
ABSTRACT

Objective: 22q11.2 deletion syndrome (22q11.2DS) is associated with a >20 fold increased risk for developing schizophrenia. The aim of this study was to identify additional genetic factors (i.e., ìsecond hitsî) that may contribute to schizophrenia expression. Methods: Through an international consortium we obtained DNA samples from 329 psychiatrically phenotyped subjects with 22q11.2DS. Using a high resolution microarray platform and established methods to assess copy number variation (CNV), we compared the genome wide burden of rare autosomal CNV, outside of the 22q11.2 deletion region, between two groups: with and, at age ³25 years, without a psychotic disorder. We assessed whether genes overlapped by rare CNVs were over represented in functional pathways relevant to schizophrenia. Results: Rare CNVs overlapping one or more protein coding genes revealed significant between group differences. For rare exonic duplications, six of 19 gene sets tested were enriched in the schizophrenia group; genes associated with abnormal nervous system phenotypes remained significant in a step wise logistic regression model (p=0.00062) and showed significant interactions with 22q11.2 deletion region genes in a connectivity analysis. For rare exonic deletions, the schizophrenia group had on average more genes overlapped (p=0.0058). The additional rare CNVs implicated known (e.g., GRM7, 15q13.3, 16p12.2) and novel schizophrenia risk genes and loci. Conclusions: The results suggest that additional rare CNVs overlapping genes outside of the 22q11.2 deletion region contribute to schizophrenia risk in 22q11.2DS, supporting a multigenic hypothesis for schizophrenia. The findings have implications for understanding expression of psychotic illness, and herald the importance of whole genome sequencing to appreciate the overall genomic architecture of schizophrenia.
INTRODUCTION

Chromosomal microarray analysis has made routine the ability to detect pathogenic copy number variations (CNVs), including recurrent CNVs associated with established genomic disorders. Most testing is done postnatally in children with autism spectrum disorder, developmental delay/intellectual disability, and/or multiple congenital anomalies, or prenatally (1). Several commercial laboratories are now providing the means for non invasive prenatal screening of microdeletion syndromes (2). With increased early diagnosis, attention is shifting to understanding the later onset expression of genomic disorders.

Of concern is the association of several genomic disorders with schizophrenia (3-5), a serious psychotic disorder that typically has onset in adolescence or early adulthood and requires lifelong treatment. The recurrent 22q11.2 deletion associated with 22q11.2 deletion syndrome (22q11.2DS) has an estimated prevalence of 1 in 3 4,000 live births and, in addition to risk for several congenital (e.g., cardiac) anomalies, represents one of the strongest known risk factors for schizophrenia (6). Schizophrenia occurs in about 1 in 4 patients with 22q11.2DS, representing a >20 fold increase over the general population risk of 1% (6, 7). Given the high but incomplete penetrance of the 22q11.2 deletion for schizophrenia, there is considerable interest in identifying additional genetic factors that may increase the likelihood of an individual developing this illness (6, 8-11).

Multinational collaborative recruitment efforts can facilitate appropriately powered research of individually rare CNVs like 22q11.2 deletions. A goal of the International 22q11.2DS Brain and Behavior Consortium (IBBC) (12) is to discover additional genetic factors that contribute to the
high risk for schizophrenia in the 22q11.2DS population. Emerging research suggests that additional rare CNVs elsewhere in the genome may shape the expression of cardiac phenotypes associated with 22q11.2DS (13). In the current study, we used high resolution genome wide microarrays and proven CNV detection methods (14) to identify rare CNVs that may be involved in the expression of schizophrenia in 22q11.2DS. We chose this strategy given the relatively high penetrance (i.e., OR 2 60) of rare genic CNVs for idiopathic schizophrenia (15). This is in contrast to common variants, e.g., single nucleotide polymorphisms (SNPs) that are mostly located in non coding regions and individually associated with small risks for schizophrenia (15). Data from the IBBC 22q11.2DS cohort enabled us to compare genome wide burden and genic content of rare autosomal CNVs, outside of the 22q11.2 deletion region, between individuals with schizophrenia or related psychotic disorders and those with no psychotic disorder at age ³25 years.

SUBJECTS AND METHODS

Ascertainment of samples from 22q11.2DS subjects for CNV analysis

Subjects with a presumed 22q11.2 deletion were recruited from 22 international sites (Table S1) and provided DNA samples that were genotyped using the Affymetrix Genome Wide Human SNP Array 6.0 at the Albert Einstein College of Medicine (13). Informed consent was obtained from all subjects and/or their legal guardian. This study was approved by the local institutional research ethics boards of each site.

Quality control (QC) measures, ancestry and relatedness determination
Similar to our previous studies of CNV (14), all downstream processing and analysis of microarray data, including applying rigorous methods for QC and CNV detection, were completed at The Centre for Applied Genomics (TCAG) in Toronto, Canada. Initially, there were 866 DNA samples available from subjects with a presumed 22q11.2 deletion and psychiatric phenotype data. Of these, 741 (85.6%) samples had high quality CNV data after accounting for batch effects and applying other QC measures (see Supplemental Material for full details).

Phenotype and diagnostic group determination

Of the 666 unrelated 22q11.2DS subjects of European ancestry with genome wide CNV data, n=329 met inclusion criteria for this study. The phenotypic and diagnostic assessment protocol is described elsewhere (12). We first selected subjects who met DSM IV TR diagnostic criteria for a major psychotic disorder; n=15 subjects with an affective psychosis were excluded. The resulting 158 individuals formed the schizophrenia group, and had specific diagnoses of schizophrenia (n=117; 74.1%), schizoaffective disorder (n=12; 7.6%), psychosis not otherwise specified (n=20; 12.7%), or schizophreniform (n=1; 0.6%), delusional (n=2; 1.3%), brief psychotic (n=2; 1.3%) or other psychotic (n=4; 2.5%) disorders. Median age at onset of psychotic illness was 21 (range 7-9) years, with no overall sex difference. We assigned individuals to the non psychotic group (n=171) if they had no history of any psychotic illness when assessed at age ≥25 years (median age 32, range 25-67, years). As expected for 22q11.2DS, given the known impact of ascertainment and disease factors (6), in the non psychotic group compared to the schizophrenia group the proportion of female subjects was higher (n=113, 66.1% vs n=82, 51.9%, respectively; p=0.0089), the proportion of cases with a
congenital cardiac defect where known (n=248) was higher [n=74, 58.3% vs n=49, 40.5%, respectively; p=0.0051), and the median IQ was higher [75, range 34 105 (n=137) vs 69, range 3694 (n=121), respectively; p<0.0001].

CNV detection and annotation
Similar to previous studies (14), we used CNV methods that ensure high (>90%) validation using a second laboratory method (16) (Table S2). Genome wide CNVs were identified with a multiple algorithm approach using Birdsuite (17), iPatiory (18), and Affymetrix Genotyping Console (http://www.affymetrix.com/) to maximize CNV call accuracy. We included CNVs for analyses only if: (i) identified by two or three of the CNV calling algorithms, (ii) spanning 10 consecutive array probes for deletions or duplications, and (iii) <75% overlap with sequence from segmental duplications. We used 9,611 independent population based controls of European ancestry (Table S2) to adjudicate CNV rarity, designating CNVs found in <0.1% of the population controls as ‘rare’ in the 22q11.2DS subjects. CNVs were adjudicated for microRNA (miRNA) content using miRBase (19), and for genic content using RefSeq. CNVs were deemed exonic if they overlapped at least one base pair (bp) of coding sequence.

CNV burden analysis and statistical approach
For CNV burden analyses, we compared the proportion of subjects with one or more rare autosomal CNVs >10 kb (all, deletions, duplications, and restricting to those overlapping a gene, exon or miRNA) between the schizophrenia and non psychotic groups. Fisher’s exact tests, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using SAS or R 3.3.1 software. All tests were two sided with p<0.05 defined for statistical significance.
Gene-set enrichment analysis

To assess whether genes overlapped by rare CNVs in the schizophrenia group were over represented in functional pathways related to schizophrenia, we evaluated 19 gene sets (Table S3) similar to those used in a recent schizophrenia consortium (PGC) study (16). These comprised genes with roles in human neurodevelopment, neuronal function, or synaptic function (7 sets), or human orthologs of mouse genes whose disruptions cause neurobehavioral or nervous system abnormalities (3 sets). Given evidence for miRNA mechanisms in schizophrenia and the role of DGCR8 in genome wide miRNA buffering (9, 20), we also examined genes predicted to be targets of miRNAs showing differential gene expression with haploinsufficiency of DGCR8 in a mouse model (1 set) (9, 10, 20). Eight further gene sets involved genes associated with abnormal phenotypes in non brain organ systems (7 sets), or causing prenatal or perinatal lethality (1 set), in mice (16).

The gene set burden analysis used a logistic regression deviance test (21) [R/Bioconductor package cnvGSA: Gene Set Analysis of (Rare) Copy Number Variants (version 1.18.0)] (https://www.bioconductor.org/packages/release/bioc/html/cnvGSA.html) to evaluate if the number of genes overlapped by rare exonic deletions or duplications in each subject for each gene set (i.e., gene set specific genic burden) is predictive of the subject being a member of the schizophrenia or non psychotic group. We report the regression coefficients after standardizing the gene set gene count. Sex was used as a covariate. Similar to our previous whole genome sequencing study of 22q11.2DS (9), we also performed a secondary gene set burden analysis that included each original gene set after restricting to just the genes that are predicted to be targets of
DGCR8 (9). Multiple testing correction (Benjamini Hochberg False Discovery Rate, BH FDR) was performed separately for each gene set group (with and without DGCR8 restriction) and CNV type (deletions, duplications). Gene sets with a BH FDR <10% and p value <0.05 were considered to be significantly enriched (9). To account for overlap between the gene sets we retested the burden following a step wise logistic regression approach that used the same regression deviance test and covariates after ranking the gene sets based on most to least significant p values.

Network connectivity test and network construction

We performed an absolute connectivity test by treating the 46 protein coding genes (n=42 with network data) in the 22q11.2 deletion region genes as "bait" and the 41 genes from the mouse abnormal nervous system gene set overlapped by duplications in the 22q11.2DS schizophrenia group (n=39 with network data) as "prey". For each bait gene, the top 200 interaction neighbors (prey) were retrieved using GeneMANIA physical protein protein interaction and pathway interaction networks (22). Since each of the networks contains different information, they require weighting based on their capability to predict gene functions as defined by Gene Ontology (GO) (22). Accordingly, we used the weighting procedure implemented in GeneMania and selected GO Biological Process functional annotations to pre weight the selected protein interaction networks (22), as more representative of pathways than GO Cellular Component and Molecular Function. We determined a connectivity score for each bait gene using the average of the respective preysí GeneMANIA scores and performed an empirical test to compare this connectivity score to that for the 15,824 genes outside the 22q11.2 deletion region. Nominal p values were then corrected using Benjamini Hochberg FDR. We generated a gene interaction
proximity network using the results from the network connectivity analysis, and linker genes identified using GeneMANIA (22), visualizing the resulting network in Cytoscape (23).

RESULTS

22q11.2 deletions

There was no significant between group difference in the distribution of 22q11.2 deletions ($c^2=0.18$, df=1, $p=0.68$). The majority of subjects had LCR A D 22q11.2 deletion (schizophrenia n=147, 93.0%; non psychotic n=157, 91.8%; Figure S1), three subjects (1.9%) in the schizophrenia group had a known proximal variant of the LCR A D deletion and the remainder had a LCR A B (schizophrenia n=7, 4.4%; non psychotic n=11, 6.4%) or LCR A C (schizophrenia n=1, 0.6%; non psychotic n=3, 1.8%) deletion (Figure S1).

Quantitative genome-wide burden of additional rare CNVs

In the overall sample of 329 subjects with a 22q11.2 deletion, there were 726 additional rare genome wide autosomal CNVs in 291 (88.4%) subjects (schizophrenia n=142, 89.9%; non psychotic n=149, 87.1%; Table S4, S5). The proportion of schizophrenia subjects (n=16, 10.1%) with one or more rare CNVs overlapping a miRNA was non significantly greater than that of the non psychotic group (n=8, 4.7%; $p=0.0878$).

There were 272 rare CNVs (173 duplications, 99 deletions) that overlapped at least 1 bp of coding sequence in 182 (55.3%) subjects. Those with exon duplication (schizophrenia n=68, 43.0%; non psychotic n=59, 34.5%) outnumbered those with exon deletions (schizophrenia n=38, 24.1%; non psychotic n=47, 27.5%) in both subject groups. There were no overall...
between group differences in the total number of rare CNVs (deletions and/or duplications, Table S4), or in the total genomic length of rare CNVs per subject (median: 173 kb, range: 12 kb–3.6 Mb, vs median: 184 kb, range: 11 kb–1.9 Mb for schizophrenia and non-psychotic groups, respectively; p=0.48). Restricting to rare exonic CNVs showed similar results (data not shown).

However, when examining the total number of genes (regardless of function) overlapped by the additional rare CNVs, there were significantly more genes overlapped by rare exonic deletions in the schizophrenia group (median: 2 genes, range: 1–18) compared to the non-psychotic group (median: 1 gene, range: 1–14; p=0.0058) (Table 1). There was no such significant finding for duplications. There was no significant difference in the IQ scores of individuals with and without an additional rare exonic deletion in either the schizophrenia or non-psychotic groups (data not shown). Multigenic rare deletions in the schizophrenia group included a 410 kb 1q21.1 deletion (at the TAR locus) and a 600 kb 16p12.2 deletion, both previously associated with schizophrenia in general population samples (3).

Functional burden of additional rare CNVs

We performed a gene set enrichment analysis in order to identify between group differences in the burden of rare CNVs overlapping functionally related genes (i.e., gene sets or pathways). Compared to the non-psychotic group, after multiple test correction (BH FDR<10% and nominal p value <0.05), the schizophrenia group had significantly more individuals with rare exonic duplications overlapping genes from six of the 19 gene sets assessed (Table 2). There were no between group differences for deletions. Of the six significantly enriched gene sets, only the top
ranking Nervous System Phenotype gene set remained significant (p=0.00062) in the stepwise logistic regression model (Table 2); overlap of the gene signal with the other five gene sets is shown in Table S6. Secondary gene set analyses, restricting to genes predicted to be affected by DGCR8 haploinsufficiency (9, 20), showed significant improvement in the burden analysis results over that for the full gene set only for the Muscle/Cardiovascular gene set, after permutation to account for gene set size (data not shown).

In 32 subjects with 22q11.2DS schizophrenia, there were 37 rare duplications that contributed to the Nervous System Phenotype gene set result (Tables 2, 3). For individuals with IQ data available, there was no significant difference in the median IQ between those with (n=23) and without (n=104) a rare duplication contributing to this gene set result (68 vs. 70, p=0.41). Four (10.8%) duplications were recurrent, flanked by segmental duplications, and previously associated with idiopathic schizophrenia (Table 3). These included two 22q11.2DS schizophrenia subjects with 1.9-2.0 Mb duplications at 15q13.2 q13.3 (BP4 BP5) (24), one with a 1.5 Mb duplication at 17q12 (25), and one with a 1.3 Mb duplication at 22q11.23 (26). Eighteen (48.6%) of the 37 CNVs overlapped a single gene, including several genes implicated in idiopathic schizophrenia by rare variant studies, such as RYR2 (3, 21), GRM7 (3, 27), DOK7 (3, 28), and CACNA2D1 (3, 29). In silico breakpoint analysis indicated that the majority (n=28; 65.1%) of the genes implicated in the rare duplication gene set results had coding sequence that was disrupted by the CNV (data not shown).

Potential mechanisms of rare CNV-related risk for schizophrenia in 22q11.2DS
We attempted to identify potential mechanisms contributing to the schizophrenia risk posed by the additional rare duplications overlapping genes from the Nervous System Phenotype gene set (Tables 3). Using protein protein interaction data available from GeneMANIA (22), we empirically tested whether genes in the 22q11.2 region (n=46 total, 42 with network data) were more connected to the Nervous System Phenotype genes overlapped by rare duplications in the schizophrenia group (n=41 total, 39 with network data), when compared to 15,824 other protein coding genes in the genome. This analysis revealed four 22q11.2 deletion region genes with significant interactions at FDR<20% (nominal p value <0.02): P2RX6, SEPT5, RTN4R and CLTCL1 (Table S7; Figure 1). The a priori probability of randomly extracting 42 genes from the genome with at least four genes achieving significant connectivity at FDR<20% is <0.0098, providing further support for this result.

The interaction proximity network constructed using the four 22q11.2 deletion region genes and the genes implicated by the duplication gene set findings suggested a diverse set of pathways potentially related to schizophrenia pathogenesis (Figure 1). Four interaction clusters were characterized by the presence of a significant gene from the 22q11.2 deletion region and/or at least one schizophrenia only gain gene: axon guidance and neuronal adhesion (UNC5D, DSCAM), axon guidance and nerve growth factor signalling (RTN4R; TNFRSF19), purinergic receptors and calcium channels (P2RX6; CACNA2D1), and glutamatergic and adenosine receptors, synaptic trafficking (CLTCL1; ADORA2A, GRM7) (Figure 1).

DISCUSSION
The results of the current study provide new data relevant to a key knowledge gap in our understanding of the association between genomic disorders like 22q11.2DS, and a profoundly increased risk for developing major psychotic illnesses such as schizophrenia. For the first time, there are sufficient data to support additional rare CNVs that overlap protein coding sequence as contributing factors to this increased risk. These comprise both rare duplications that overlap genes involved in neuronal function and rare loss CNVs that tend to overlap more genes in those who develop schizophrenia. The findings suggest the possibility that additional information captured by chromosomal microarray at the time of initial diagnosis of a 22q11.2 deletion could eventually help in identifying some of those at greatest risk for schizophrenia.

The results are consistent with emerging research suggesting that rare deleterious variants elsewhere in the genome, in addition to the 22q11.2 deletion, are likely to be involved in the variability of neuropsychiatric and other developmental expression of this microdeletion syndrome (6, 8 11). This finding has potential implications for the schizophrenia risk associated with other genomic disorders, such as the 3q29 deletion (30) or 16p11.2 duplication (31). The results are also in keeping with data from the general population of individuals with neurodevelopmental disorders, where ~4% have two rare contributing genetic mutations or genetic diagnoses (32). Although there are case reports of two rare CNVs in patients with schizophrenia (33, 34), there are few previous studies of genome wide CNVs in patients with typical 22q11.2 deletions, and these involved small samples and/or used low resolution arrays or various methods to assess CNVs and their rarity (8, 33 3). Only two of these small studies compared schizophrenia and non psychotic groups within 22q11.2DS (8, 35).
The results of this study are in line with findings supporting an association between large, usually multigenic, rare duplications and schizophrenia in the general population (5, 14). Similarly, the results for enriched burden of genes overlapped by rare deletions in 22q11.2DS schizophrenia also appear consistent with studies of schizophrenia in the general population (16), and with a recent rare CNV study reporting a higher number of overlapped genes in a large schizophrenia cohort compared with controls (36). Within 22q11.2DS, the structural variant results in the current study complement those of pilot whole genome sequencing findings for 22q11.2DS using an extreme phenotype approach to study additional genome wide rare sequence variants affecting schizophrenia expression (9). In that pilot study there was a significantly enriched burden of high quality non synonymous deleterious missense and loss of function sequence variants brain related genes in the schizophrenia cases (9). Genes involved included RYR2 (3, 37) and BSN (38), the latter encoding a pre synaptic scaffolding protein, bassoon (9). Results of the current study (Table 3) further implicate these more novel genes and pathways for schizophrenia. The RYR2 gene and two genes (DLC1 and ABCA4) encoding members of a BSN superfamily of neuronal transmembrane proteins that regulate neurotransmitter release at the synapse were overlapped by very rare duplications in subjects with 22q11.2DS and schizophrenia. BSN was also implicated in the synaptic network derived from a large CNV study of schizophrenia (16), as were some of the network connections in the current study (Figure 1).

The significant genetic interactions between 22q11.2 deletion region genes and duplication locus genes implicate other pathways of potential interest to schizophrenia pathogenesis. These include the RTN4R gene encoding the Nogo receptor and its co receptor, TNFRSF19, involved in
mediating axonal growth inhibition, regeneration and plasticity, and limiting excitatory synapse number during brain development (39). Similarly, the P2RX6 related functional gene cluster includes RYR2 and CHRNA7 and CACNA1C, previously implicated in schizophrenia pathogenesis (40). Several of the genes in the network (Figure 1) have also been implicated as targets of 22q11.2 region miRNAs or of miRNAs dysregulated by DGCR8 haploinsufficiency (10). Interestingly, there is also some evidence from a recent brain expression study implicating RTN4R and P2RX6 down regulation in the pathogenesis of idiopathic schizophrenia (41), further supporting the potential generalizability of the findings in the current study.

The 22q11.2 deletion may lower the threshold for expression of the multiple mechanisms and/or pathways involved in causing schizophrenia, within and between individuals (9, 10). The results of the current study primarily implicate additional genome wide rare CNVs that affect protein coding sequence of genes in the expression of schizophrenia in the context of a 22q11.2 deletion. Effect sizes may be smaller for other mechanisms. For example, non coding regulatory regions and/or miRNAs (at the trend level in this study) may also play important roles in schizophrenia, including in 22q11.2DS, as suggested by rare sequence variant findings for 22q11.2DS supporting DGCR8 haploinsufficiency and altered miRNA buffering mechanisms (9, 20). Power may also be an issue for the difference observed in additional rare CNV findings in 22q11.2DS between those for duplications and deletions. A more neuro specific effect for deletions could perhaps become apparent if the sample size were larger. However, mechanisms for expression of deletions and duplications may differ (1), and penetrance is, on average, higher for deletions than duplications (33). In the presence of the 22q11.2 deletion, additional rare deletions may be more likely to potentially implicate pleiotropic genes in expression of schizophrenia, whereas
duplications could require genes having greater specific impact on neuronal functioning. Notably, the rare duplication burden in 22q11.2DS schizophrenia was enriched for genes associated with mouse neurobehavioral phenotypes, similar to results in a recent large case control study of schizophrenia, though the latter involved somewhat smaller effect sizes (OR 1.18, 1.68, respectively) and deletions, including most commonly the 22q11.2 deletion (16). Results from the current study provide some evidence for the expression of schizophrenia in 22q11.2DS involving network interactions that include genes in the 22q11.2 deletion region and genes overlapped by other rare structural variants outside this locus.

Advantages and limitations

Despite having the largest sample of 22q11.2DS subjects with and without a psychotic disorder to study the impact of additional rare CNVs on expression, power was limited by the available cohort size. However, the signal related to schizophrenia expression imparted by additional rare genome wide CNVs produced significant results. This is remarkable, given the virtually ubiquitous presence of any neurodevelopmental phenotype in 22q11.2DS (42), and the likelihood that some subjects in the non psychotic group may go on to develop schizophrenia. It is expected that some of the rare CNVs associated with schizophrenia and the genes implicated may also be involved in expression of other neurodevelopmental disorders, consistent with the literature supporting overlap of pathways (15). However, the results do not support intellect as a primary driver of the findings, and while most subjects were not systematically assessed for the presence of autism spectrum disorder, this was documented for a few subjects (n=18; 5.5%). The ability to recruit more adults with no psychotic illness and individuals with schizophrenia within the 22q11.2DS population could provide the means to identify the strength of the relationship
between each additional CNV and the risk for schizophrenia, as well as other mechanisms for schizophrenia expression where the effect sizes are lower. In future studies, larger samples of 22q11.2DS may also assist in determining the role of X chromosome variants and whether, as in autism and ID (43), the X chromosome may provide some protective capacity for schizophrenia expression in the context of a 22q11.2 deletion.

The IBBC proband only 22q11.2DS sample provides no capability of examining inheritance, parent of origin, or segregation data for the 22q11.2 deletion or the additional CNVs, or the family history of schizophrenia, all of which are factors of interest in disease expression (11). In smaller samples, the parental origin and inheritance status of the 22q11.2 deletion have not appeared to play a role in schizophrenia expression, however (8), and one can expect that >90% of the 22q11.2 deletions would be de novo mutations (6).

Conclusions

The results suggest that additional rare CNVs overlapping genes outside of the 22q11.2 deletion region contribute to schizophrenia risk in 22q11.2DS. The fact that these results involved fewer than half of the subjects with schizophrenia supports the likelihood that other yet to be identified variants and mechanisms also play a role in expression. The recurrent 22q11.2 deletion is known to occur as a de novo event in >90% of cases and at any parental age (6, 8), but the inheritance of additional genome wide CNVs remains to be determined. The findings support a multigenic hypothesis for schizophrenia, and further illustrate the value of a 22q11.2DS model for identifying genome wide rare variants to help delineate the genetic architecture of idiopathic schizophrenia. Lessons learned from 22q11.2DS may be applicable to other recurrent CNVs that
contribute to risk for schizophrenia in the general population (14). Whole genome sequencing will allow for more detailed assessment of CNV breakpoints, and the overall genetic architecture and proposed mechanisms of schizophrenia (9, 20).
FIGURE LEGEND

Figure 1: Gene interaction proximity network based on physical and pathway interactions. Circles correspond to genes: 22q11.2 deletion genes with significant connectivity (CLTCL1, P2RX6, RTN4R, and SEPT5, purple), genes with mouse abnormal nervous system phenotypes overlapped by duplications exclusively in the 22q11.2DS schizophrenia group (red), and linker genes (gold). The initial sets comprised the four 22q11.2 deletion region genes with significant connectivity and the 39 genes overlapped by duplications found exclusively in schizophrenia subjects and within the nervous system phenotype gene set. Important linker genes were identified by retrieving the top 25 interaction neighbours of these genes in GeneMANIA, using the same protein-protein interaction and pathway interaction networks used in the connectivity test, and then subsetting to those found connected to at least two different bait genes and belonging to the nervous system phenotype gene set (86 genes). Connections correspond to interaction proximity obtained from GeneMANIA, setting the limit to the top 50 interactors; the connection line thickness is proportional to the GeneMANIA score (22). The resulting network is visualized in Cytoscape (23). The network suggests the presence of four interaction clusters, characterized by the presence of one gene from the 22q11.2 deletion region with significant connectivity results and at least one schizophrenia only duplication related gene (see text for details).
REFERENCES


15. Harrison PJ Recent genetic findings in schizophrenia and their therapeutic relevance. J Psychopharmacol. 2015; 29:85 96


Table 1. Average number of genes overlapped by additional rare exonic autosomal CNVs in 22q11.2DS

<table>
<thead>
<tr>
<th>Deletion or duplication</th>
<th>Median</th>
<th>Range</th>
<th>Median</th>
<th>Range</th>
<th>Z</th>
<th>p</th>
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<td>1-14</td>
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All rare (0.1%) CNVs >10kb and <6.5Mb were included in the analysis. The 22q11.2 deletion region, sex chromosomes, and CNVs overlapping >75% of a segmental duplication were excluded. See Methods for details. \(^a\)Sample sizes represent those 22q11.2DS subjects in each group (142/158 (89.9%) schizophrenia; 149/171 (87.1%) non-psychotic) with one or more additional rare CNVs. \(^b\)Deletions that overlapped exons were present in 38 (24.1%) 22q11.2DS subjects with schizophrenia and 47 (27.5%) of those with no psychotic illness.
Table 2. Gene-sets showing significant enrichment in the 22q11.2DS-schizophrenia group for rare exonic duplications

<table>
<thead>
<tr>
<th>Gene-set</th>
<th>Total genes</th>
<th>Number of CNVs</th>
<th>Subjects n</th>
<th>Subjects %</th>
<th>Number of CNVs</th>
<th>Subjects n</th>
<th>Subjects %</th>
<th>p</th>
<th>FDR-BH</th>
<th>OR</th>
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</thead>
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<td>32</td>
<td>22.5</td>
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<td>29.6</td>
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<td>Endocrine/Exocrine/Reproduction Phenotype (MGI)</td>
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*Sample sizes represent those 22q11.2DS subjects in each group with one or more rare CNV (142/158 (89.9%) schizophrenia, 149/171 (87.1%) non-psychotic. Rare (0.1%) CNVs >10kb and <6.5Mb; CNVs in the chromosome 22q11.2 region and on the X chromosome and/or overlapping a segmental duplication by >75% were a priori excluded from analyses.

n / %, The number and percent of unrelated 22q11.2DS individuals with schizophrenia or non-psychotic with at least one duplication contributing to the gene-set result; p, logistic regression model comparison deviance test p-value; The p value for the Nervous system phenotype gene-set represents the gene-set result remaining significant after stepwise model construction (i.e., when gene-sets were serially added to an increasingly larger regression model, starting with this gene-set; see Methods for details); FDR-BH: Benjamini-Hochberg false discovery rate (significance level set at <0.10); OR: Odds ratio, calculated by taking the exponential of the regression coefficient value; MGI: Mouse Genome Informatics; GO: Gene Ontology.
Table 3. Genes contributing to Nervous System gene-set rare genome-wide duplication results significantly enriched in the 22q11.2DS schizophrenia group

<table>
<thead>
<tr>
<th>CNV</th>
<th>Subject</th>
<th>Chr</th>
<th>Cytoband</th>
<th>Start</th>
<th>Size</th>
<th>Number of genes</th>
<th>Very rare CNV</th>
<th>Flanking LCR</th>
<th>All genes overlapped by CNV</th>
<th>Gene(s) contributing to Nervous System gene-set results</th>
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**Table 3 continued...**

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*a Results for the 22q11/2DS-non-psychotic group appear in Table S5.

b CNVs 19 and 32 overlapped with CNVs also found in 22q11.2DS-Non-psychotic subjects (Table S5); *CNVs 28 and 29, and CVN 32, are recurrent CNVs of uncertain pathogenicity (44, 45); LCR, low-copy repeats.