Genome Biology

Minireview

Common variants in polygenic schizophrenia

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Abstract

Common variant single-nucleotide polymorphisms at the MHC locus have recently been associated with schizophrenia. Together with known associations with rare copy-number variants affecting many genes, this reveals the highly polygenic etiology of the disease.

Schizophrenia is a devastating mental disorder characterized by reality distortion. Common features are positive symptoms of hallucination, delusion, disorganized speech and abnormal thought process, negative symptoms of social deficit, lack of motivation, inability to experience pleasure, impaired emotion processing and cognitive deficit. Onset of symptoms typically occurs in late adolescence or early adulthood, with approximately 0.5 to 1% of the population affected and heritability estimated at 80% [1]. However, despite strong genetic support for heritability, little progress has been made in uncovering the genetic factors involved in schizophrenia.

The utilization of single nucleotide polymorphisms (SNPs) from DNA sequencing projects such as the Human Genome Project [2] and the 1000 Genomes Project [3] has enabled genome-wide genotyping of between 0.5 and 2 million variations across large sample sets. Studies of linkage disequilibrium have been used to generate haplotypes to inform the genotypes of untyped SNPs by reference to genotyped SNPs. Such studies face many genetic, computational and statistical challenges. The mass of human variation created by evolutionary lineage and population stratification confounds the analysis of large populations, and genomic control must be used to minimize the effects of genomic inflation on the chi-square statistic [4] and reduce the effects of outliers determined by principal components analysis (PCA) or multidimensional scaling (MDS). (The chi-square statistic measures the difference in allele frequency for each SNP between case and control cohorts.) Applying these principles enables genome-wide association studies of large cohorts, such as a recently reported meta-analysis of 8,000 schizophrenia cases and 19,000 controls, in which the MHC locus was associated with the disease [5-7]. These large-scale studies were carried out by three groups: the International Schizophrenia Consortium (ISC) [5], the Molecular Genetics of Schizophrenia (MGS) project [6] and the SGENE project [7].

Meta-analysis of three schizophrenia cohorts

To detect SNPs, the ISC study used the Affymetrix 500K, 5.0 and 6.0 GeneChips, MGS used the Affymetrix 6.0 GeneChip, and SGENE used the Illumina HumanHap300 and HumanHap550 BeadChips. There is relatively little overlap (around 15%) between these platforms and the principal findings of these studies concern 26 newly discovered SNPs in the MHC region with combined *P*-values ranging from 9.27×10^{-7} to 9.50×10^{-9}, with 13, 10 and 7 SNPs being directly genotyped in the ISC, MGS and SGENE cohorts, respectively (Table 1 and Figure 1). The remainder of the SNPs were imputed using different programs in each study. The MGS study, which used just one type of array with all the most recently genotyped SNPs at the same genotyping center, returned the poorest significance for the 26 MHC SNPs, with 20 SNPs at *P* greater than 0.01 and less than 0.1 and 6 SNPs at *P* greater than 0.0006 and less than 0.006.

A threefold variance and a standard deviation of 0.038 is observed in the minor allele frequency of the SNP rs3130375, the most significant SNP in the ISC analysis, among the various case-control subsets of the ISC cohort, indicating some potential sample bias. A similar subsampling bias is seen in the SGENE sample set with *P* less than 0.05 for the SNP rs3131296 from the population subgroups Finland (Helsinki), Scotland, Denmark (Copenhagen), and Germany (Munich), whereas the other 18 subgroups have *P* greater than 0.05. Although sample bias is observed in these schizophrenia samples, all three studies point to association effects in the same direction, which raises the confidence level. These results are in keeping with those from a recently reported meta-analysis for autism, another highly heterogenous neurophsyciatric/neurodevelopmental disorder. Although no *P*-values reached genome-wide significance in the four independent autism cohorts, the combined *P*-values reached genome-wide significance, tagging common variants on 5p14.1 [8]

Table 1

Chromosome 6 *P*-values from ISC, MGS, SGENE and combined analysis

SNP	Position	*P* (ISC)	*P* (MGS)	*P* (SGENE)	*P* combined	Gene	Distance
rs6939997*	25929203	5.66×10^{-4}	1.40×10^{-1}	2.85×10^{-4}	4.90×10^{-7}	*SLC17A1*	0
rs13199775*	25936761	5.66×10^{-4}	5.12×10^{-2}	2.57×10^{-4}	1.19×10^{-7}	*SLC17A1*	0
rs9461219*	25944906	2.68×10^{-3}	4.99×10^{-2}	5.52×10^{-4}	4.72×10^{-7}	*SLC17A1*	6130
rs1324087	25949387	6.30×10^{-2}	4.30×10^{-2}	2.90×10^{-3}	6.90×10^{-5}	*SLC17A3*	3920
rs9467626*	25981725	7.47×10^{-4}	5.32×10^{-2}	2.68×10^{-4}	1.65×10^{-7}	*SLC17A3*	0
rs13198474	25982402	6.00×10^{-2}	9.50×10^{-2}	1.30×10^{-4}	2.50×10^{-5}	*SLC17A3*	0
rs2072806*	26493072	2.80×10^{-4}	5.91×10^{-3}	3.40×10^{-2}	9.27×10^{-7}	*BTN2A2*	0
rs2072803*	26500494	2.80×10^{-4}	5.53×10^{-3}	3.23×10^{-2}	8.19×10^{-7}	*BTN2A2*	0
rs6904071*†	27155235	3.00×10^{-4}	1.20×10^{-2}	3.70×10^{-4}	1.80×10^{-8}	*HIST1H2BJ*	45506
rs926300*†	27167422	3.00×10^{-4}	1.20×10^{-2}	2.10×10^{-4}	1.10×10^{-8}	*HIST1H2BJ*	33319
rs7745603	27198383	-	3.00×10^{-2}	6.70×10^{-4}	8.70×10^{-5}	*HIST1H2BJ*	2358
rs6913660*‡	27199404	3.00×10^{-4}	1.70×10^{-2}	3.40×10^{-4}	2.40×10^{-8}	*HIST1H2BJ*	1337
rs13219181*†	27244204	3.00×10^{-4}	1.50×10^{-2}	2.10×10^{-4}	1.30×10^{-8}	*HIST1H2AH*	20879
rs13194053*†§	27251862	3.00×10^{-4}	1.50×10^{-2}	1.50×10^{-4}	9.50×10^{-9}	*HIST1H2AH*	28537
rs13219354*†	27293643	5.11×10^{-4}	3.59×10^{-2}	4.39×10^{-4}	1.12×10^{-7}	*PRSS16*	29844
rs3800307*†	27293771	3.40×10^{-3}	1.30×10^{-2}	6.10×10^{-5}	4.40×10^{-8}	*PRSS16*	29716
rs13212921	27313401	5.76×10^{-4}	3.09×10^{-2}	5.53×10^{-4}	1.28×10^{-7}	*PRSS16*	10086
rs4452638	27337244	3.96×10^{-4}	4.51×10^{-2}	1.11×10^{-3}	2.68×10^{-7}	*PRSS16*	5015
rs6938200	27339129	2.40×10^{-3}	5.28×10^{-2}	1.51×10^{-4}	3.02×10^{-7}	*PRSS16*	6900
rs6932590*‡	27356910	2.20×10^{-3}	3.40×10^{-3}	8.50×10^{-4}	7.10×10^{-8}	*PRSS16*	24681
rs3800316*†	27364081	3.50×10^{-3}	7.20×10^{-4}	1.10×10^{-3}	3.80×10^{-8}	*PRSS16*	31852
rs7746199*†	27369303	8.80×10^{-4}	6.80×10^{-4}	5.70×10^{-3}	5.00×10^{-8}	*PRSS16*	37074
rs3800318*†	27371620	8.80×10^{-4}	2.80×10^{-3}	2.30×10^{-3}	6.40×10^{-8}	*PRSS16*	39391
rs16897515*	27385999	6.40×10^{-4}	1.22×10^{-2}	2.16×10^{-3}	1.83×10^{-7}	*DKFZp686G2037*	47582
rs13195040*	27521903	3.00×10^{-5}	1.04×10^{-1}	2.82×10^{-3}	2.50×10^{-7}	*ZNF184*	4603
rs10484399*	27642507	8.58×10^{-6}	1.09×10^{-1}	8.69×10^{-3}	3.50×10^{-7}	*ZNF184*	93644
rs17693963*	27818144	6.00×10^{-5}	2.87×10^{-2}	8.85×10^{-3}	2.81×10^{-7}	*BC035101*	33229
rs7776351*†	27834710	1.13×10^{-4}	2.83×10^{-2}	6.51×10^{-3}	3.22×10^{-7}	*HIST1H2BL*	48526
rs12182446*	27853717	7.17×10^{-5}	2.99×10^{-2}	1.22×10^{-2}	4.77×10^{-7}	*HIST1H2BL*	29519
rs149990	28106237	5.00×10^{-4}	3.80×10^{-1}	2.60×10^{-3}	2.60×10^{-5}	*ZNF165*	48314
rs13211507	28365356	2.60×10^{-4}	1.30×10^{-1}	2.70×10^{-3}	5.20×10^{-6}	*PGBD1*	0
rs3130375¶	30429711	3.66×10^{-7}	8.60×10^{-2}	1.40×10^{-1}	-	*RPP21*	7100
rs3130544	31166319	1.30×10^{-2}	3.80×10^{-1}	3.30×10^{-4}	8.20×10^{-5}	*C6orf15*	20660
rs3815087	31201566	7.70×10^{-2}	2.20×10^{-1}	1.30×10^{-4}	6.70×10^{-5}	*PSORS1C1*	0
rs3131296#	32280971	1.30×10^{-3}	1.40×10^{-1}	1.10×10^{-3}	9.80×10^{-6}	*NOTCH4*	0
rs2076537	32425613	1.20×10^{-2}	-	1.60×10^{-3}	5.50×10^{-5}	*C6orf10*	0
rs9272219†	32710247	2.20×10^{-5}	1.30×10^{-2}	1.00×10^{-2}	6.90×10^{-8}	*HLA-DQA1*	2914
rs9272535†	32714734	2.50×10^{-5}	1.60×10^{-2}	9.90×10^{-3}	8.90×10^{-8}	*HLA-DQA1*	0

*Main findings of the meta-analysis. †Data presented in two papers with similar values. ‡Data presented in three papers with similar values. §SNP of most focus in MGS. ¶SNP of most focus in ISC. #SNP of most focus in SGENE. A dash (-) indicates data not available.

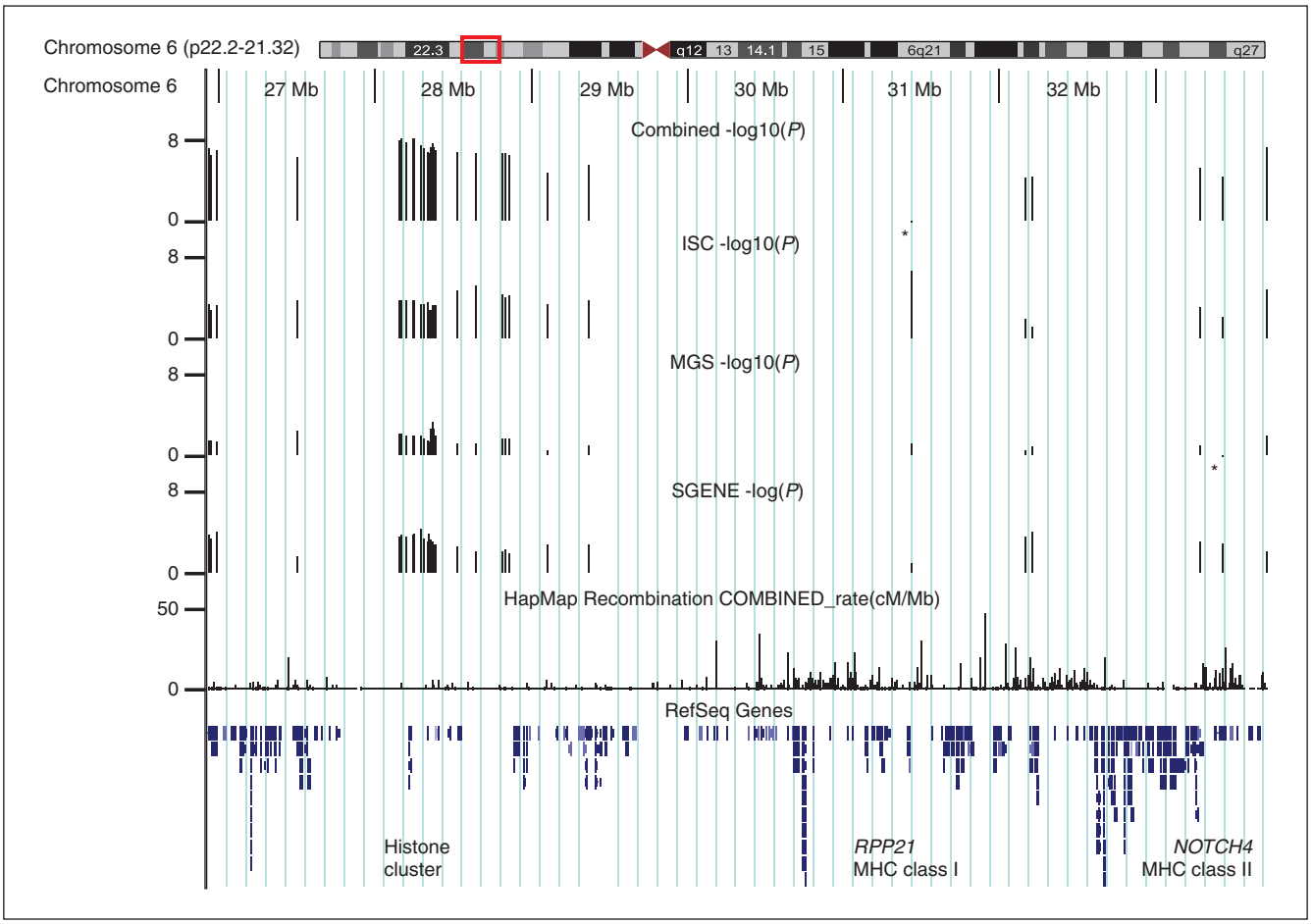

Figure 1

Associations with the MHC in schizophrenia. The significance of case-control association studies, including those from three contributing groups (ISC, MGS, and SGENE), at the MHC region are shown. Recombination rate and gene annotation are also provided. The region shown is chromosome 6: 25-32 Mb. Only SNPs with *P*-values provided in meta-analysis are shown, although coverage and calculated *P*-values exist for many more SNPs in the MHC region. Although consensus from the meta-analysis associates chromosome 25.9-27.8 Mb near histone genes (rs13194053), ISC analysis shows rs3130375 to be most significant, whereas SGENE associates rs3131296. *Data not available.

with minor allele frequencies being comparable in all cohorts.

Resolving the MHC association

All three schizophrenia studies [5-7] report association with the MHC region. However, the location of the best association signals differs between the three. ISC shows greatest significance at SNP rs3130375 (Figure 2), which affects the *RPP21* gene (this encodes a subunit of nuclear ribonuclease P, which processes the 5' leader sequences of precursor tRNAs). The MGS survey points to SNP rs13194053 (within a histone gene cluster) and the SGENE study to rs3131296, which lies within the *NOTCH4* locus (encoding a transmembrane receptor of the Notch family). Moreover, recent genome-wide association scans in type 1 diabetes, celiac disease and systemic lupus erythematosus show a significant association with a SNP in this region in strong linkage disequilibrium to rs3131296, in which the protective allele in schizophrenia is the risk allele for autoimmune disease.

These genes have been implicated in schizophrenia by other studies. In cell and animal studies, the anti-psychotic drug valproic acid is a potent inhibitor of histone-deactylating enzymes, and treatment with this drug results in increased levels of acetylated histones [9]. Hyper-methylation of *RPP21* has been significantly associated with schizophrenia and bipolar disorder in an analysis using CpG-island microarrays to identify changes in DNA methylation in the frontal cortex and germline of patients [10]. *NOTCH4* has previously been associated with schizophrenia by linkage in British schizophrenia families

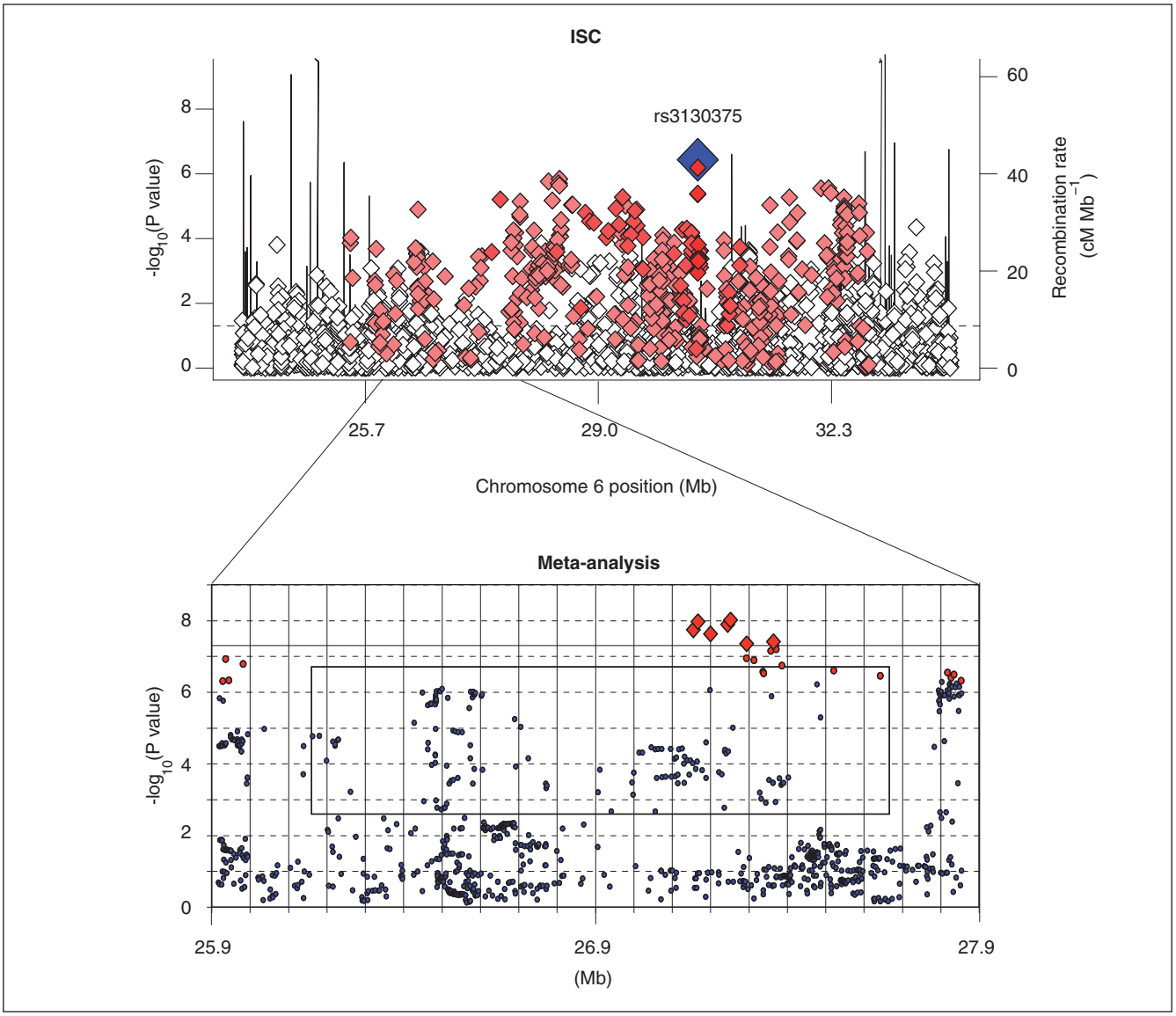

Figure 2

Continuous *P*-values observed in ISC and meta-analysis. The upper panel shows association results across the MHC region. Results are presented as -log10(*P*-value) for genotyped SNPs. The most significant SNP is shown with a blue diamond. The color of the markers reflects r^2 with rs3130375, light pink, $r^2 > 0.1$, red, $r^2 > 0.8$. The recombination rate from the CEU HapMap (second *y*-axis) is plotted in light blue (upper panel). The lower panel shows a zoomed-in presentation of chromosome 6p22.1 genetic association results in meta-analysis. Genome-wide significant evidence for association ($P < 5 \times 10^{-8}$, threshold shown by red line, SNPs by large red diamonds) was observed at seven SNPs across 209 kb. *P*-values are shown for all genotyped and imputed SNPs (25,900,000-27,875,000 bp) for the meta-analysis of European-ancestry MGS, ISC and SGENE samples (8,008 cases, 19,077 controls). Red circles indicate other SNPs with $P < 5 \times 10^{-7}$. Adapted from [5] and [6]. SGENE figure not available.

[11], and a haplotype in *NOTCH4* has been associated with schizophrenia in African Americans [12].

The extremely high level of polymorphism and heterozygosity within the MHC region provides the immune system with a selective advantage against the diversity and variability of pathogens, albeit also providing a clear predisposition to autoimmunity. However, given the complexity of the region, there is also a greater chance of making spurious associations. It is noteworthy that more than 100 diseases, including type 1 diabetes, rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disease and various autoimmune disorders, have been associated with the MHC region [13]. The MHC region has also been associated with central nervous system disorders such as Alzheimer's disease [14], autism [15] and multiple sclerosis [16].

Further differences between the three papers associating MHC with schizophrenia [5-7] relate to their secondary focus. On the basis of a deeper examination of nominally significant SNPs, ISC proposes a common polygenic variant model for schizophrenia. MGS presents significant findings within their cohort in the hope of future replication of the significance of loci additional to those of the MHC, including *CENTG2*, *NTRK3*, *EML5*, *MXRA5*, *ADIPOR2*, *PTPN21*, *ZNF518* and *JARID2* in subjects of European ancestry and *ERBB4*, *CBX2*, *DDX31*, *RNLS*, *GTF3C4*, *TRPA1*, *NRG1*, *ELP3* and *TNIK* in subjects of African-American ancestry. SGENE (SGENE-plus has 658 additional samples) presents *NRGN* and *TCF4* as intriguing candidates for brain development, memory and cognition.

The ISC study [5] rapidly moves on from the MHC association to a description of an aggregate test of large numbers of common alleles, weighted by their odds ratios in a single-SNP association analysis of the sample. Increasing proportions of the relative risk are picked up at increasingly liberal significance thresholds (P_T) - for example, $P_T < 0.1$ or $P_T < 0.5$ - where a significant increase in variance is explained in both schizophrenia (ISC [5], MGS [6] and O'Donovan [17]) and bipolar disorder from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and Wellcome Trust Case-Control Consortium (WTCCC) studies, but not in six other case-control cohorts for a different disease (coronary artery disease, Crohn's disease, hypertension, rheumatoid arthritis, type 1 and type 2 diabetes) from the WTCCC. A simulation showed that this observation is significantly above hypothetical variance. Genomic control values are minimal and stratified populations do not show bias. In total, common polygenic variation accounts for roughly one-third of the total variation in schizophrenia, which may be a conservative estimate based on simulation of linkage disequilibrium, SNPs in linkage disequilibrium with causal variants, allele frequency and effect size.

Rare copy number variation is enriched in schizophrenia cases

Three other reports, published in 2008, have highlighted large rare copy-number variants affecting many different genes enriched in neurodevelopmental pathways [18-20]. Two of these studies utilized the same ISC and SGENE cohorts as the SNP genotype association study and one used microarray comparative genomic hybridization, which provides intensity data alone. Specifically, novel deletions and duplications of genes were reported in 15% of cases versus 5% of controls ($P = 0.0008$) [18]. However, a study of copy number variation in Chinese schizophrenia patients detected no significant difference in rare variants between cases and controls [21]. Another study of 1,013 schizophrenia cases and 1,084 controls of European ancestry also failed to find more rare copy-number variants of more than 100 kb in patients or enrichment of copy-number variants in neurodevelopmental pathways [22]. Although confidence is lower and statistical correction higher if small copy number variants are included, the 100 kb size threshold excludes many copy number variants that are informative and could affect many of the loci presented as novel to cases. Nevertheless, this enrichment of rare copy number variants affecting many different genic loci bolsters the polygenic variation model for schizophrenia proposed by ISC, although these large copy number variants are rare as opposed to the common SNP-genotype variants. A comparable pattern has also been identified in autism, with rare highly penetrant copy number variants in ubiquitin genes as well as common variants overrepresented in neuronal development [23].

The conclusion from all these studies is that rare copy number variants and common genotypic variants are significantly enriched, providing polygenic evidence for the etiology of schizophrenia. The characterization of the contributing loci and the perturbed biological processes in schizophrenia is left for future study. MHC SNPs were associated at genome-wide significance levels ($P < 10 \times 10^{-8}$) via a meta-analysis of SNPs in all three studies ($P < 1 \times 10^{-3}$). This emphasizes the need for collaborative sharing of most significant results between centers since such individual studies with no SNPs meeting genome-wide significance provide low confidence individually. It is important, however, that adequate time is allowed for follow-up analysis and evaluation of confounders in meta-analysis. Taken together, association of schizophrenia with the MHC locus underscores the important contribution of common genotype variants in this disease, a finding in keeping with other complex disorders [24]. In addition, the polygenic inheritance of these variants and their contribution to the overall phenotype diversity and disease state suggests significant genetic variation, and that both common and rare variants may be underlying psychiatric illness.

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