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Genome-Wide Approaches to Schizophrenia

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Abstract

Schizophrenia (SZ) is a common and severe psychiatric disorder with both environmental and genetic risk factors, and a high heritability. After over 20 years of molecular genetics research, new molecular strategies, primarily genome-wide association studies (GWAS), have generated major tangible progress. This new data provides evidence for: 1) A number of chromosomal regions with common polymorphisms showing genome-wide association with SZ (the major histocompatibility complex, MHC, region at 6p22-p21; 18q21.2; and 2q32.1). The associated alleles present small odds ratios (the odds of a risk variant being present in cases versus controls) and suggest causative involvement of gene regulatory mechanisms in SZ. 2) Polygenic inheritance. 3) Involvement of rare (<1%) and large (>100kb) copy number variants (CNVs). 4) A genetic overlap of SZ with autism and with bipolar disorder (BP) challenging the classical clinical classifications. Most new SZ findings (chromosomal regions and genes) have generated new biological leads. These new findings, however, still need to be translated into a better understanding of the underlying biology and into causal mechanisms. Furthermore, a considerable amount of heritability still remains unexplained (missing heritability). Deep resequencing for rare variants and system biology approaches (e.g., integrating DNA sequence and functional data) are expected to further improve our understanding of the genetic architecture of SZ and its underlying biology.

Keywords

genome-wide association; schizophrenia; polygenic; CNV; rare variant; gene expression; systems biology

1. Overview

The GWAS approach is based on linkage disequilibrium (LD), which is the non-random association of alleles (alternative forms of a polymorphism) at different loci, and is implemented with single nucleotide polymorphism (SNP) arrays that interrogate common variation across the genome. GWAS experiments have been remarkable successful. Over 900 genes have been reported to be associated at genome-wide significant levels ($p < 5 \times 10^{-8}$) [1] to one or more of ~200 complex phenotypes (www.genome.gov/gwastudies as of 02/12/2010 [2,3]). Current array platforms capture ~80% of the common variation in the

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genome for European ancestry (EA) samples [4]. Imputation, the computational prediction of genotypes of untyped SNPs, extends GWAS map coverage [5,6], and enables the combined analysis of samples genotyped with different platforms. The same arrays used for testing SNP associations carry probes designed for the detection of CNVs, but lower accuracy, particularly for duplications.

2. Main GWAS findings in SZ

Table 1 summarizes the published GWAS for SZ [7–13]. No single study detected genome-wide significant association with individual SNPs. Only a meta-analysis of 8,008 EA cases and 19,077 EA controls, in regions with individual study p -values <0.001 , detected a genome-wide significant association at the MHC locus on chromosome 6p [11–13]. The most significant SNP (rs13194053) reached $p=9.54 \times 10^{-9}$ (Table 1). The odds ratios, a measure of effect size, are small (e.g., the strongest associations at the MHC had ORs ranging 1.14–1.16; other associations with common SNPs also show low ORs). The MHC region is very gene-dense, containing over 200 genes. The low recombination rate at the MHC causes long LD blocks within the region [14]. Because of this long range LD and high gene density, it has not yet been determined whether one or more genes or intergenic regions are implicated. The MHC region contains many genes with roles in immunity and self-recognition, and has been implicated by GWAS in multiple common immune diseases, including type 1 diabetes (T1D), multiple sclerosis, Crohn's disease (CD), and rheumatoid arthritis (RA) (see review [2]). Furthermore, one of the three studies also found a suggestive association for SZ with the *FAM69A-EVI-RPL5* gene cluster (1p22) [13], which was previously reported as associated with multiple sclerosis [15]. Consistent with an immune hypothesis of SZ [16], a recent Danish registry study indicated that autoimmune disorders increase the risk for SZ [17]. However, final proof of immune abnormalities in SZ is still missing.

TCF4 (transcription factor 4), located in chromosome 18q21, has also been identified as another novel SZ susceptibility locus [12]. *TCF4* is a neuronal transcription factor essential for neurogenesis [18]. Mutations in *TCF4* cause Pitt–Hopkins syndrome, a disorder characterized by severe motor and mental retardation [19–21].

Another GWAS reported an association of SZ with zinc finger protein 804A (*ZNF804A*) in 2q32.1 [22]. Although not genome-wide significant for SZ ($p=1.61 \times 10^{-7}$ with rs1344706), the association reached genome-wide significance in the combined analysis of SZ and BP ($p=9.96 \times 10^{-9}$) [22]. In a subsequent meta-analysis of a much larger data set with 18,945 SZ cases, 2,329 BP cases, and 38,675 controls, support strengthened: $p=2.5 \times 10^{-11}$ for SZ and $p=4.1 \times 10^{-13}$ for SZ and BP [23]. *ZNF804A* was reported associated with altered neuronal connectivity in the dorsolateral prefrontal cortex in a functional magnetic resonance imaging study of healthy controls [9].

Thus, several SZ susceptibility loci have emerged from GWAS and meta-analyses thereof. None of the genome-wide significant loci implicated by GWAS span leading pathophysiological SZ candidate genes (e.g., those examined in [24]), and thus may represent new biological leads.

3. Evidence for a polygenic model

Purcell et al. [11] tested the polygenic hypothesis of SZ [25] by evaluating whether many common variants with small effects could explain a large proportion of the variation in disease risk. Based on different thresholds of association p -values in the International SZ Consortium (ISC) dataset, sets of common variants with small effects (“score” alleles”) were first defined. For each set, an aggregate risk score was then generated for each subject from

the Molecular Genetics of SZ (MGS) EA and African American (AA) datasets, and a SZ UK sample [13,22]. Aggregate risk scores in SZ cases were found to be higher than in controls in SZ samples (and also for BP cases from two BP samples [26,27]). Performing the same basic analysis for T1D, T2D, hypertension, CD, RA, and coronary artery disease [11,27] subsequently showed that the result was not an artifact of population stratification, genotyping quality, or other potential systematic biases. Although the variance explained by the observed score alleles derived from ISC study was only ~3%, with simulated datasets, the variance explained by a set of score alleles reached ~1/3. A set of causal alleles with minor allele frequency (MAF) <5% did not fit the model well [11], but a role for rare susceptibility variants could not be excluded. Like for other complex disorders, a large proportion of SZ heritability still remains unexplained by GWAS. Further increasing GWAS sample sizes, including meta-analyses (e.g., the ongoing Psychiatric GWAS Consortium, PGC, for SZ [28]), is expected to provide incremental evidence for the known and as yet undiscovered common loci.

4. Rare CNVs implicated in SZ

About one-quarter of the human genome harbors CNVs, stretches of DNA deletions or duplications ranging from 1kb to several Mb [29]. Multiple CNVs have been suggested associated with SZ (Table 2). So far, only rare (<1%) and large (>100kb) CNVs have been implicated in SZ [10,30–35] as reflected by overall CNV burden (aggregate) and individual CNV loci. Initial genome-wide CNV scans using 200–400 subjects observed 3- to 8-fold over-representation in SZ cases [31,32], but subsequent studies with larger sample sizes (>2,000) revealed smaller effects of CNVs in aggregate (Table 2) [33,34]. A 3Mb 22q11.21 deletion, known as 22q11 deletion syndrome (22qDS), was increasingly linked to SZ in the 1990s [36–38]. 22qDS still is the only CNV that has reached genome-wide significance in a single GWAS of SZ [34]. 22qDS causes DiGeorge or velocardiofacial syndrome (DGS/VCFS), one of the most common anomaly syndromes with 180 variable clinical features, both physical and behavioral, such as congenital heart disease, cleft palate, learning disabilities, facial abnormalities, thymic aplasia, and recurrent infections [39]. Over than 30% of 22qDS carriers develop psychosis, of which 80% manifests as SZ [40] (see also [37,40]). Other SZ susceptibility CNVs, however, seem less penetrant (i.e., some, albeit very few, controls also carried such CNVs), and many candidate CNVs are singletons and their penetrance remains unknown.

Of the individual CNVs, the 2p16.3 deletion has the clearest connection to a single causal gene (i.e., exon disruptions of just one gene: *NRXN1*) [41]. For other CNV regions spanning multiple genes, it is unclear which genes are causative. For example, the 16p11.2 duplication [42] spans 29 genes, of which 22 are brain-expressed and at least 9 (*MAZ*, *CDIPT*, *DOC2A*, *TBX6*, *MAPK3*, *TAOK2*, *QPRT*, *MVP*, *SEZ6L2*) have functions of potential relevance to SZ pathogenesis, such as neuronal differentiation, glutamate neurotransmission, synaptic plasticity, and cognition [43–51]. Similarly, 22qDS spans 51 genes, of which 36 are brain-expressed, and some have been previously studied as SZ candidate genes, including *COMT* (see review [52], *PRODH* (see review [53], *ARVCF* [54], and *GNB1L* [55]; several (*ZDHC8*, *PRODH*, *TBX1*, *COMT*, *DGCR8*, and *GNB1L*) have also been suggested to be linked with a range of cognitive and psychiatric phenotypes as demonstrated by mouse models [56–60].

A CNV may manifest phenotypic effects through a variety of structural and regulatory mechanisms [61]: (1) alteration of gene expression due to a gene dosage effect, gene loss-of-function or gene fusion when a CNV disrupts a gene (thought to be the most common mechanisms underlying disease associations); (2) deletion-related hemizygous expression of a recessive mutation or exacerbation of the effect from a functional variant on the non-

deleted chromosomal segment [62]; 3) abnormal gene expression of a gene outside the CNV, a positional effect [63] or alteration of gene *trans*-regulation (e.g., deletion of the trans-acting regulatory sequence element), a transvection effect [64]. In addition, interactions between CNVs (i.e., a hit in a second CNV that would act as a genetic modifier) should also be considered. About ¼ of the subjects with developmental delay with a large 16p12.1 deletion also carried a 2nd large CNV elsewhere [65]. Furthermore, the 2nd hit accompanying a CNV could also be a common risk variant.

Because the dosage change caused by a duplication (1.5-fold via 2N→3N duplication) is less pronounced than by deletion (2-fold via 2N→1N deletion), duplications are expected to have on average smaller phenotypic effects than deletions. The study of knockout mice (null for single or multiple genes within the CNV) is used to model the effect of deletions. A 22q11.2 deletion mouse exhibits impaired sensorimotor gating (a neurophysiological trait associated with SZ), deficits in working memory, spontaneous sensitization of hyperactivity, and a lack of habituation [58,59], which have been hypothesized as models of clinical SZ characteristics. It is noteworthy that regular knockout or duplication of a syntenic CNV region in the mouse may not always be fully informative of the actual causal mechanisms because a CNV can affect expression of genes as far as ~500kb away from the CNV [66]. Modifying large chromosomal segments [67] will probably be required to unravel the phenotypes associated with most CNVs.

A role for more common, smaller CNVs in SZ pathogenesis remains unknown, largely due to a number of limitations of hybridization-based array platforms for CNV detection and current CNV calling algorithms, including poor probe coverage, low detection sensitivity, and poor reproducibility [68,69]. These technical limitations especially affect duplication-rich regions (because of the cross-hybridization of probes), leading to low sensitivity (18–55%) and specificity (39–77%) there [70]. Other technical artifacts (e.g., plate effects and cell line artifacts) may also confound the estimation of the prevalence of a CNV [71,72]. Next-generation sequencing has been shown to outperform microarrays in sensitivity and specificity of CNV detection [73–75], and thus may provide a more comprehensive and accurate estimation of the contribution of both common and rare CNVs to the genetic basis of common disease.

5. Overlap with BP and autism

SZ and BP

As discussed above, polygenic SZ score alleles were found enriched in BP datasets [11,26,27]. *ZNF804A* [22,23] and *CACNA1C* (calcium channel, voltage-dependent, L type, alpha 1C subunit) are possibly shared by both disorders [9,76]. Family studies have also suggested genetic overlap between SZ and BP [77–83]. A recent large family study, with 35,985 SZ and over 40,487 BP Swedish probands, concluded that ~63% of familial coaggregation between SZ and BP was due to additive genetic effects common to both disorders [83].

SZ and autism

All the individual CNVs implicated in SZ in Table 2 were also reported to be associated with autism (and mental retardation, and some also with seizures) [42,84–94]. Some data from common variation also suggests shared susceptibilities. For example, the MGS EA GWAS had its strongest SNP association ($p=4.6\times10^{-7}$) in *centaurin gamma 2* (*CENTG2*, also known as *AGAPI*), a gene that has been implicated by linkage evidence in autism [95]. The molecular data is consistent with reports of increased rates of SZ in the parents of autism cases [96], and an increased rate of autism in the presence of parental history of SZ-like psychosis [97].

The associations of a SNP or a CNV to both SZ and BP, or to SZ and autism, can be explained by pleiotropy, which refers to situations where more than one major independent phenotype is associated with a single gene. Pleiotropy is common [98], and in humans, the evidence includes the associations of the same gene with functionally related traits such as body weight and height [99], as well as seemingly unrelated disorders such as T2D [100] and prostate cancer [101] (both associated with *JAZF1*), and colon/lung cancer and familial Parkinson's disease (both associated with *PARK2*) [102]. Alternatively, a common association of two disorders to a single gene can be explained by shared phenotypic characteristics (for example, psychosis in BP and in SZ). The integrated analysis of GWAS and other genome-wide approaches (e.g., expression) [103] may disentangle the different alternatives. For example, a pleiotropic effect would be supported if the associated gene was shown to preferentially regulate different gene expression modules in each disorder. It is possible that the association of SZ-implicated CNVs with mental retardation, seizures, and autism, although still challenging the clinical classification, reflects a phenomenon mainly occurring on a subset of subjects with SZ at the clinical boundaries of the core disorder (i.e., CNVs appear to be less common in the more mainstream SZ presentation with less cognitive impairment and absence of seizures).

6. What to do next?

Study of rare variants

The genetic architecture of SZ is still elusive, likely involving a combination of both common and rare risk variants, but with non-linear phenotype-genotype correlations. It has been suggested that endophenotypes, such as neurophysiological, neuroimaging, and cognitive traits [104], are more informative to index the underlying genetic effects than dichotomous diagnostic assessments of SZ [105], but none of the proposed endophenotypes shows stronger heritability than the typical heritability estimates for SZ [106,107], and association studies of endophenotypes have not produced any stronger associations with SZ than using categorical SZ diagnosis [108]. The common and rare variations identified up-to-now show substantial clinical phenotype overlap across the different types of identified genetic loci, but also substantial differences (such as an enrichment of cognitive impairment and seizures in SZ cases with CNVs). Rare variants have been hypothesized to constitute the bulk of mutations for SZ [109]. Negative selection predicts removal of most risk alleles with major deleterious effects, which is consistent with the small effect of common susceptibility loci and the rarity of mutations of larger penetrance (such as CNVs). As SZ is associated with decreased fertility [110], SZ risk alleles are likely under negative selection. Rare risk variants are either of recent origin if highly penetrant, or older mutations with smaller effect that have not yet been eliminated by selection. Rare risk variants not present in parental genomes are known as *de novo* mutations, and if only identified in a single individual, they are referred as “private” mutations. It has been proposed that many rare risk variants from a large genetic interval may explain associations first detected with common variants (“synthetic associations”) [111].

The common disease/rare variant (CDRV) hypothesis for SZ has not been robustly tested yet since rare mutations are not reliably captured by current GWAS SNP panels or imputed with high accuracy, and awaits for deep genomic resequencing studies (i.e., sequencing of a large number of individuals). Rapid advances in next generation sequencing technology [112] have made the study of rare variants feasible in principle, at least in the exome (the exons in the aggregate). The 1,000 genomes project will deliver a comprehensive reference catalog with LD maps of sequence and structural DNA variants (MAF>1%) in the general population [113,114], which will be instrumental for the testing of the CDRV hypothesis.

Conventional single-marker based association testing with rare variants has little statistical power (because few subjects have each mutation), but the analysis in the aggregate is more robust [115,116]. It is important to distinguish functional from nonfunctional DNA variation since collapsing nonfunctional and functional variants also diminishes statistical power (e.g., cases may be enriched for functional variants, but including in the analysis nonfunctional variants will dilute that signal) [115,116]. Non-synonymous mutations (altering amino acids) are relatively straightforward to interpret by using programs such as PolyPhen and SIFT [117,118] to predict the functional effect of non-synonymous SNPs. However, many other non-coding DNA changes are more difficult to interpret, largely due to the lack of extensive functional annotation of sequence elements within noncoding regions [2].

Systems biology approaches

Whether biological interpretations relying only on single genes will be likely to capture the fundamental genetic architecture of most complex human traits is a matter of active controversy. Instead, it merits a systems biology approach (integration of genomic, transcriptomic, and proteomic data, metabolomics, gene networks, epigenetics, and environmental factors), where gene expression profiling is an important component of the gene networks [119]. The genetic regulation of gene expression is central to most biological processes. A gene variant may modify the transcript abundances of other genes from the same network or modify protein-protein interactions. Often associated variants are located in intronic (45%) and intergenic (43%) regions [2], and if functional, these variants are thought to regulate gene expression [120]. Even coding polymorphisms may alter transcript levels through affecting mRNA stability [121–126] or mRNA splicing [127]. A genetic variant within a microRNA (miRNA, 19~22 nt small noncoding RNA mostly transcribed from intronic or intergenic sequences) or in an miRNA targeting site may impair the inhibitory effect of miRNA on expression of ~30% of human genes [128]. Interestingly, miRNAs are known to play a pivotal role in regulating synaptic development and function [129], providing relevancy to SZ pathogenesis.

Interestingly, in SZ GWAS, *TCF4* and *ZNF804A* [12,22] are transcription factors that may regulate expression of many genes. Many of the best GWAS hits in the MHC and other regions are intergenic, and may also affect gene transcription through either *cis*-regulatory sequence (e.g., enhancers) or through noncoding RNAs transcribed from intergenic regions (e.g., enhancer RNAs) [130,131]. This raises the interesting possibility that common variation may confer susceptibility to SZ, at least in part, by affecting gene expression regulation. It has been shown that regulatory variants are over-represented in GWAS findings [132], for instance, in celiac disease >50% of the associated risk variants influence immune gene expression [133]. This might be particularly relevant to psychiatric disorders, as genetic regulation of gene expression has been shown to be more important than protein functional changes, such as amino acid substitutions, in shaping human-specific brain function [134,135]. Indeed, a recent follow up study of *ZNF804A* suggested that the SNP (rs1344706) associated with SZ is also associated with gene expression changes in lymphocytes [23], suggesting a regulatory mechanism underlying the GWAS association.

GWAS data provide a static and linear correlation between individual risk variants and disease status [136]. Integrating GWAS and gene expression variation (expression quantitative trait loci, eQTL mapping) data has been successfully used to locate causal genes. For example, in a 206kb region with 19 genes and strong LD, eQTL mapping showed that the asthma-associated SNPs were strongly associated with transcript abundance of *ORMDL3*, suggesting *ORMDL3* as the gene explaining this association [137,138]. It is encouraging that, for some central nervous system disorders, there are consistent gene expression patterns in both lymphocytes and the brain for some loci with strong genetic evidence, e.g., the Parkinson disease susceptibility gene *α-synuclein* [139–141] and the

Alzheimer's disease susceptibility gene *APOE* [142–144]. High throughput sequencing-based transcriptome profiling (RNA-seq), compared to traditional hybridization-based microarray platforms, gives absolute quantification of RNA transcripts with higher sensitivity and larger dynamic range [145], enabling the detection of more eQTL [146,147], novel transcripts [131,148], widespread alternative splicing [149,150], and even proteome profiling through quantifying ribosome-associated RNA transcripts [151]. Pathway analyses of GWAS data and gene expression profiles are important for understanding the causal mechanisms underlying GWAS associations, because complex disorders likely result from dynamic and higher order perturbations of pathways at a systems level [136]. Pathway analysis translates the effects of individual SNPs or genes to a set of genes known *a priori* to have related functions. Furthermore, integrating gene co-expression and protein-protein interaction data into pathway analysis adds directional information within and between pathways [98,136], thus leading to a more comprehensive view of the disease causal mechanism (e.g., interconnected pathways may imply a pleiotropy effect). Animal models (e.g., knockout of a gene or introduction of a putative causal variant) will still remain important for interpreting the phenotypic effect of a genetic variant, although all animal models of SZ suffer from the absence of any unequivocally demonstrated neurobiological features of SZ and a clear definition of a SZ-like behavioral phenotypes [152]. Animal models may also be used to test genetic interactions through crossing animals bearing different mutations, or to examine the interactions with developmental stage or environmental factors through temporal and spatial control of gene expression (see review [153]). In addition, the recent development of induced pluripotent stem cells (iPS) derived from somatic cells, followed by neuronal re-differentiation, may offer a cellular model suitable for studying psychiatric phenotypes (see review [154]).

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Table 1

Top genes or genomic regions identified in recent SZ GWAS.

First author and year	Sample	Gene or region	Lowest <i>p</i> -values	OR	Reference
Lencz 2007	178/144 (EA)	<i>CSF2RA</i> , <i>SHOX</i>	3.7×10^{-7}	3.23	[7]
Sullivan 2008	738/733 (EA)	<i>AGBL1</i>	1.71×10^{-6}	6.01	[8]
O'Donovan 2008	Discovery: 479/2,937 (EA) Follow up: 6,829/9,897 (EA)	<i>ZNF804A</i>	1.61×10^{-7}	1.12	[22]
Need 2009	Discovery: 871/863 (EA) Follow up: 1,460/12,995 (EA)	<i>ADAMTSL3</i>	1.35×10^{-7}	0.68	[10]
Purcell 2009 (ISC)	3,322/3,587 (EA)	MHC region ^a <i>MYO18B</i>	9.5×10^{-9} 3.4×10^{-7}	0.82	[11]
Stefansson 2009 (SGENE)	Discovery: 2,663/13,498 (EA) Follow up: 4,999/15,555 (EA)	MHC region ^b <i>NRGN</i> ^b <i>TCF4</i> ^b	1.4×10^{-12} 2.4×10^{-9} 4.1×10^{-9}	1.16 ^c 1.15 1.23	[12]
Shi 2009 (MGS)	2,681/2,653 (EA) 1,286/973 (AA)	MHC region ^a <i>CENTG2</i> (in EA only) <i>ERBB4</i> (in AA only)	9.5×10^{-9} 4.59×10^{-7} 2.14×10^{-6}	0.88 1.23 0.73	[13]

^aCombined analysis of ISC, SGENE, and MGS GWAS.

^bCombined analysis of ISC, SGENE (including SGENE follow up samples) and MGS.

^cOR is for common allele of the associated SNP, which is different from that in ISC and MGS.

Summary of recent genome-wide CNV studies of SZ.

Table 2

Study	Sample	Assay platform	Major findings	CNVs in case/control (interval in Mb and longest interval indicated; NA=data not available)						Reference
				1q21.1	2p16.3 (NRXN1)	15q11.2	15q13.2	16p11.2	22q11.21	
Kirov 2008	93 SZ trios	Array CGH	Two CNVs likely to be pathogenic	NA	1 del (51.14–51.32)	NA	1 dup (26.94–28.01)	NA	NA	[30]
Walsh 2008	150 cases/268 controls; 92 childhood onset SZ cases	Array CGH	Rare CNVs in 15% cases vs. 5% controls	1/0 del (144.94–146.29)	1/0 del (50.02–50.14)	NA	NA	2/0 dup (29.65–30.23)	NA	[31]
	359 SZ trios as screening sample; 152 cases/159 controls		In sporadic cases, frequency of rare <i>de novo</i> CNVs was 10% vs. 1.3% in controls	1/0 del (144.32–144.44)	NA	NA	NA	3/0 del (17.05–19.99)	[32]	
Xu 2008	1433 cases / 33,250 controls; 3 CNVs (1q21.1, 15q11.2 and 15q13.3) were followed up in 3,285 cases / 7,951 controls	Affy 5.0								
Stefansson 2008		Varies	Three rare CNVs (1q21.1, 15q11.2, and 15q13.3) showed nominal association	11/8 del (144.94–146.29)	0/2 del (50.95–51.16)	26/79 del (20.3–20.8)	7/8 del (28.72–30.30)	2/11 del (29.56–30.09)	8/0 del	[33]
			Rare (<1%) and large CNVs (>100kb) are enriched in cases (1.15-fold); 3 regions (1q21.1, 15q13.2, and 22q11.21) showed significant association	10/1 del (143.72–146.95)	5/6 del (50.8–51.50)	26/11 del (20.3–20.8)	9/0 del (28.0–31.0)	NA	13/0 del (17.11–19.92)	[34]
ISC 2008	3,391 cases / 3,181 controls	Affy 5.0/6.0		0/2 del (144.9–146.3)	1/3 del	4/14 del (20.3–20.8)	0/0 del	NA	2/0 del (17.3–19.8)	[35]
Kirov 2009	471 cases / 2,792 controls	Affy 500K	Large CNVs (>1Mb) were 2.26 times over-represented in cases	1/0 del (144.1–146.3)	3/1 del	NA	NA	4/0 del (16.4–19.8)		[10]
Need 2009	1,013 cases / 1,084 controls	HumanHi p300, 550, or 610	Large CNVs (>2Mb) are enriched in cases	0.23% vs. 0.02% (del)	0.17% vs. 0.03% (del)	0.65% vs. 0.22% (del)	0.18% vs. 0.02% (del)	0.19% vs. 0.003% (dup)	0.44% vs. 0% (del)	
			Summary frequency of implicated CNV (case vs. control)							