

## Genetic studies of schizophrenia: an update

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Schizophrenia (SCZ) is a complex and heterogeneous mental disorder that affects about 1% of global population. In recent years, considerable progress has been made in genetic studies of SCZ. A number of common variants with small effects and rare variants with relatively larger effects have been identified. These variants include risk loci identified by genome-wide association studies, rare copy-number variants identified by comparative genomic analyses, and *de novo* mutations identified by high-throughput DNA sequencing. Collectively, they contribute to the heterogeneity of the disease. In this review, we update recent discoveries in the field of SCZ genetics, and outline the perspectives of future directions.

**Keywords:** schizophrenia; genome-wide association study; copy-number variant; *de novo* mutation; sequencing; genetics

### Introduction

Schizophrenia (SCZ) is a severe neuropsychiatric disorder with a lifetime prevalence of ~1% worldwide<sup>[1]</sup>. Clinically, SCZ is characterized by symptoms traditionally classified as positive (delusions and hallucinations), negative (flattened emotions and social withdrawal), and impairments of cognitive functions<sup>[2–4]</sup>. The age at onset is typically in late adolescence or early adulthood<sup>[5]</sup>. This disorder has a considerable impact not only on patients' health and well-being, but also on society and health services worldwide<sup>[6]</sup>.

SCZ is a complex genetic disorder with a relatively high heritability, exceeding 60% in two national family studies<sup>[7,8]</sup> and 80% in twin studies<sup>[9]</sup>. After decades of frustration, genetic studies of SCZ have made significant progress in recent years with the application of genome-wide association studies (GWASs) and next-generation DNA sequencing technologies. In these studies, a number of genes have been identified with common risk alleles, rare copy-number variations (CNVs), and *de novo* mutations (DNMs). From these studies, we have learned

that the genetic risk for SCZ is highly polygenic: many genes contribute to the development of the disorder but the contribution from individual genes is relatively small. These studies also reveal the complexity of the genetic architecture that includes structural variations (CNVs), common and rare single-nucleotide variations (SNVs), and DNMs. In this brief review, we update recent progress on genetic studies of SCZ, focusing on the common SNVs discovered by GWASs, as well as CNVs and rare SNVs and DNMs discovered by high-throughput DNA sequencing.

### Common Variants Contributing to SCZ

SCZ is now established as a heritable disorder by family and twin studies<sup>[7–9]</sup>. In the early years, the search for genes involved in SCZ by linkage and candidate gene studies did not produce replicable and consistent results<sup>[10,11]</sup>. From 2009 onwards, a number of creditable candidates were identified, largely by GWAS, a linkage disequilibrium-based technique designed to find links between genetic variations and diseases in a homogeneous population without a

*priori* knowledge of the disease. The variants discovered by GWASs are common variants, conventionally defined as those with allele frequencies  $\geq 1\%$ . This is largely due to the design of genotype chips used in GWAS, a design intended to test the “common diseases – common variants” hypothesis. Table 1 summarizes the top findings from GWASs in recent years. Of the loci identified, the region encompassing the major histocompatibility complex (MHC) on chromosome 6p<sup>[12]</sup> is the most significant and consistent. Many markers in this region reach genome-wide significance ( $P \leq 5.0 \times 10^{-8}$ ). The association signals cover an interval of ~6 million base-pairs, including all three classes of MHC regions that encode for >50 genes<sup>[13,14]</sup>. Due to the high linkage disequilibrium and complex genomic structure, it is difficult to determine whether one or multiple genes in this region are involved in the disorder. It has long been speculated that the immune system is involved in SCZ, so the finding that the genetic effects are enriched in the MHC region or even in regions outside the MHC that are also involved in acquired immunity is consistent with this hypothesis. After the first GWAS reporting on the MHC

region, a total of 30 loci across the whole genome were reported to be associated with SCZ by 2013<sup>[15-25]</sup>, including the genes for transcription factor 4 (TCF4), neurogranin (NRGN), and DPYD/MIR317 that are known to play crucial roles in brain development. Of these GWASs, only two used Chinese subjects, one used Japanese subjects and the rest used Caucasian subjects. Most recently, the Psychiatric Genomics Consortium (PGC) SCZ group published the largest SCZ GWAS, identifying 108 independent loci across the genome, including all but 5 loci reported before<sup>[26]</sup>.

GWASs, as noted above, are designed to discover associations between common variants and diseases. The successful discovery of many risk loci for SCZ provides evidence that its genetic architecture is polygenic by nature, and that individual genes have limited effects on its development. The common variants identified so far have a low genotypic relative risk individually (odds ratios (ORs) 1.1- to 1.5-fold). But collectively, these variants account for >50% of the heritability<sup>[27]</sup>. As we examine these variants closely, it is clear that most do not have known functions, and many of them are not located in protein-coding genes,

**Table 1. The 25 most common variants identified by GWASs**

Index SNP	Chr	Position (hg19)	Allele	OR (95% CI) <sup>a</sup>	P-value <sup>a</sup>	Genes	References
rs115329265	6	27143833- 30174131	AG	1.21 (1.17-1.24)	$3.48 \times 10^{-31}$	MHC class II including HIST1H2BJ, PRSS16, NKAPL, and TRIM26	[12,15,16, 19-21,25,26]
rs1702294	1	97792625- 98559084	TC	0.89 (0.87-0.91)	$3.36 \times 10^{-19}$	DPYD, MIR137 (micro-RNA),	[19,25,26, 108]
rs11191419	10	104423800- 105165583	AT	0.91 (0.89-0.93)	$6.2 \times 10^{-19}$	ARL3, AS3MT, C10orf32, CNNM2, CYP17A1, INA, NT5C2, PCGF6, PDCD11, SFXN2, TAF5, TRIM8, USMG5, and WBP1L	[19,25,26, 108,109]
rs2007044	12	2321860-2523731	AG	0.91 (0.89-0.93)	$3.22 \times 10^{-18}$	CACNA1C	[24-26,108]
rs4129585	8	143309503- 143330533	AC	1.09 (1.07-1.11)	$1.74 \times 10^{-15}$	TSNARE1	[25,26]
chr7_2025096_I	7	1896096-2190096	DI3	0.92 (0.90-0.94)	$8.2 \times 10^{-15}$	MAD1L1	[25,26,110]
rs4391122	5	60499143- 60843543	AG	0.92 (0.90-0.94)	$1.1 \times 10^{-14}$	ZSWIM6	[25,26,110]

To be continued

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rs2851447	12	123448113- 123909113	CG	0.92 (0.89-0.94)	$1.86 \times 10^{-14}$	ABCB9, ARL6IP4, C12orf65, CDK2AP1, MPHOSPH9, OGFOD2, PITPNM2, RILPL2, SBNO1, SETD8	[25,26]
chr2_200825237_I	2	200715237- 200848037	I2D	0.91 (0.89-0.93)	$5.65 \times 10^{-14}$	AC073043.2, C2orf47, C2orf69, and TYW5	[25,26]
rs10791097	11	130714610- 130749330	TG	1.08 (1.06-1.10)	$1.09 \times 10^{-12}$	SNX19	[25,26]
rs11693094	2	185601420- 185785420	TC	0.93 (0.91-0.95)	$1.53 \times 10^{-12}$	ZNF804A	[26,85]
rs7893279	10	18681005- 18770105	TG	1.13 (1.09-1.16)	$1.97 \times 10^{-12}$	CACNB2	[25,26]
rs12129573	1	73766426- 73991366	AC	1.08 (1.06-1.10)	$2.03 \times 10^{-12}$	LRRIQ3	[25,26]
rs6704768	2	233559301- 233753501	AG	0.93(0.91-0.95)	$2.32 \times 10^{-12}$	C2orf82, EFHD1, GIGYF2, KCNJ13, and NGEF	[25,26]
rs55661361	11	124610007- 124620147	AG	0.93 (0.91-0.95)	$2.8 \times 10^{-12}$	ESAM, MSANTD2, NRG1, and VSIG2	[16,26]
rs9636107	18	52747686- 53200117	AG	0.93 (0.91-0.95)	$3.34 \times 10^{-12}$	TCF4	[16,17,19,25, 26,108]
chr11_46350213_D	11	46342943- 46751213	I2D	0.91 (0.88-0.93)	$1.26 \times 10^{-11}$	AMBRA1, ARHGAP1, ATG13, CHRM4, CKAP5, CREB3L1, DGKZ, F2, HARBI1, MDK, and ZNF408	[26,111]
rs11682175	2	57943593- 58502192	TC	0.93 (0.91-0.95)	$1.47 \times 10^{-11}$	FANCL and VRK2	[17,26]
rs2535627	3	52541105- 52903405	TC	1.07 (1.05-1.09)	$4.26 \times 10^{-11}$	GLT8D1, GNL3, ITIH1, and ITIH3	[24,26]
rs111294930	5	151941104- 152797656	AG	1.09 (1.06-1.12)	$1.06 \times 10^{-10}$	GRIA1	[25,26]
rs2905426	19	19374022- 19658022	TG	0.93 (0.91-0.95)	$3.63 \times 10^{-10}$	CILP2, GATAD2A, HAPLN4, MAU2, NCAN, NDUFA13, PBX4, SUGP1, TM6SF2, and TSSK6	[25,26]
rs77149735	1	243503719- 244002945	AG	1.32 (1.20-1.44)	$3.73 \times 10^{-9}$	AKT3 and SDCCAG8	[24,26]
rs59979824	2	193848340- 194028340	AC	0.94 (0.92-0.96)	$8.41 \times 10^{-9}$	PCGEM1	[19,26]
rs10503253	8	4177794-4192544	AC	1.07 (1.05-1.10)	$1.06 \times 10^{-8}$	CSMD1	[19,26,108]
rs7819570	8	89340626- 89753626	TG	1.08 (1.05-1.11)	$1.22 \times 10^{-8}$	MMP16	[19,26]

Chr, chromosome; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism. <sup>a</sup>All ORs and *P*-values are from the most recent PGC study<sup>[26]</sup>.

suggesting that most of the identified variants are not causal. Therefore, even though GWASs have identified >100 variants associated with SCZ, we still cannot be certain to what extent common variants contribute to the etiology of SCZ. Another lesson learned from GWASs is that a stringent threshold requires a huge sample size to reliably identify risk genes. From the incremental PGC studies<sup>[19,25,26]</sup>, it is clear that when the sample size reaches a critical value, every addition of 1 000 samples leads to the identification of 2–3 more new loci. The same trend is observed in studies of other complex diseases and traits, such as obesity, height, and blood lipids<sup>[28–30]</sup>. This trend demands collaborative work from many investigators to ensure the successful discovery of risk genes for complex diseases. In the case of SCZ studies, the PGC includes almost all existing samples of Caucasian ancestry worldwide.

Since we have good reasons to believe that there are other unidentified risk genes for SCZ, and that continuing to increase the sample size is not sustainable in the long run, other approaches must be considered. Based on this rationale, we and others have explored alternative approaches to discover risk genes for SCZ. With a two-stage design, by integrating data-mining and functional analyses of a selected number of candidates from GWAS datasets, we found that two markers in the CMYA5 gene are associated with SCZ<sup>[31]</sup>; one of the markers (rs10043986) changes a proline to leucine in the protein sequence. Using a convergent functional genomics approach, which utilizes poly-evidence scoring and pathway analyses, Ayalew *et al.* identified several genes involved in SCZ, including *DISC1* and *TCF4*<sup>[32]</sup>. By combining gene expression profiling and GWAS data, Luo *et al.* showed that *CAMKK2* is differentially expressed in SCZ and controls, and a marker in the gene, rs1063843, is associated with the expression and diagnosis of SCZ in a large GWAS dataset<sup>[33]</sup>.

### Copy-Number Variations and SCZ

Changes of DNA copy involving insertion/deletion (indel) or duplication (dup) are known as CNVs. Indels can be as small as a few hundred base-pairs or as large as an entire chromosome, and about one-quarter of the human genome harbors CNVs<sup>[34]</sup>. As a result, CNVs can change the dosage of one or more genes in the regions covered

by CNVs, and therefore exert a profound effect on the expression of the genes. Most studies of CNVs in SCZ are based on the analyses of signal intensity from GWAS microarrays. The assumption is that most parts of the genome (except for the X and Y chromosomes) have two copies, and the signal intensity of markers along the chromosome is approximately the same when smoothed across a reasonable number of markers or genomic distance. When the signal intensity changes consistently and continuously for a reasonable genomic interval (hundreds of kilobase-pairs or more), a copy-number change can be inferred. Typically, these inferred CNVs need to be verified experimentally *via* real-time quantitative PCR or other techniques.

Over the years, many CNVs have been found to increase the risk for SCZ. Most of these involve multiple genes, while some involve a single gene or do not have known genes in the interval. For example, 2p16.3 del only affects the NRXN1 gene<sup>[35–42]</sup>, and 7p36.3 dup only affects the VIPR2 gene<sup>[38,43,44]</sup>. CNVs that alter the expression of multiple genes include 1q21.1 del/dup (34 genes)<sup>[36–39,41,45–47]</sup>, 3q29del/dup (21 genes)<sup>[38–40,44,48,49]</sup>, 15q13.3del (12 genes)<sup>[38,39,44,46,47,49]</sup>, 16p13.1dup (11 genes)<sup>[40,41,50,51]</sup>, and 22q11.2del/dup (53 genes)<sup>[38,39,44,46,47,51–56]</sup>, *etc.* (see Table 2 for more details). For the involved genes, the effect is more pronounced<sup>[34,57–59]</sup>. The large 22q11.21 locus (3 Mb), also known as DiGeorge and velo-cardio-facial syndrome critical region, was first reported to be associated with SCZ in the 1990s<sup>[60]</sup>, and this was verified in many later studies<sup>[38,39,44,46,47,51–55]</sup>. Most of the studies show that deletion of this region increases the risk of SCZ. A recent study indicates that a duplication of this same region is protective against SCZ<sup>[56]</sup>, demonstrating a dosage effect on the development of SCZ. As this region contains >50 genes, it is still not clear which are involved and how they contribute to SCZ<sup>[61,62]</sup>. There is evidence that the total burden of rare CNVs (numbers of CNVs per individual in combination with the number of genes per CNV) is increased in SCZ patients at both the whole-genome and specific loci levels<sup>[37,46,47]</sup>.

In general, CNVs have relatively low frequencies (typically less than 1 in 1 000 individuals), but account for a substantially higher risk (OR 2.7 to infinity)<sup>[63]</sup>. Although it is uncertain which gene(s) are responsible for the effects, as multiple genes are involved in most CNVs, evidence shows that the risky CNVs most likely affect genes involved

**Table 2. Top CNVs in SCZ**

CNV	Position (Mb)	Size (Mb)	Types	CNV frequency		OR (95% CI)	<i>P</i> -value	Genes	References <sup>a</sup>
				Cases	Controls				
1q21.1	144.6–148.0	3.4	Del/dup	0.00176 (20/11372)	0.00021 (10/47311)	8.3 (3.7–19.9)	$2.2 \times 10^{-8}$	34	[36,37, <b>38</b> ,39,41,45–47]
2p16.3	49.9–51.5	0.02–0.42	Exon del	0.00182 (23/12627)	0.00022 (10/45284)	8.2 (3.8–19.4)	$5.5 \times 10^{-9}$	1 (NRXN1)	[35–37, <b>38</b> ,39–42]
3q29	197.2–198.8	0.84–1.6	Del	0.00080 (6/7539)	0.00003 (1/39747)	17.0 (1.4–1198.4)	$9.7 \times 10^{-3}$	19	[38–40, <b>48</b> ,49]
3q29	196.8–196.9	0.05	Dup	0.00121 (10/8280)	<0.00013 (0/7431)	Inf (1.6–Inf)	$1.0 \times 10^{-2}$	2	[39, <b>44</b> ]
7q36.3	158.5–158.8	0.12–0.36	Exon dup	0.00191 (14/7322)	0.00047 (7/14814)	4.0 (1.5–11.9)	$2.0 \times 10^{-3}$	1 (VIPR2)	[ <b>38</b> ,43,44]
15q11.2	20.3–20.8	0.5	Del	0.00551 (26/4692)	0.00192 (79/41115)	2.7 (1.5–4.9)	$6.0 \times 10^{-4}$	4	[40, <b>47</b> ,49,51]
15q11.2-13.1	20.3–26.4	4.1–9.0	Mat dup	0.00053 (4/7578)	0.00007 (3/41367)	7.3 (1.2–50.0)	$1.0 \times 10^{-2}$	13–24	[49, <b>112</b> ]
15q13.3	28.7–30.3	1.5	Del	0.00193 (21/10866)	0.00020 (9/45913)	9.9 (4.3–24.4)	$2.0 \times 10^{-9}$	12	[ <b>38</b> ,39,44,46,47,49]
16p11.2	29.4–30.1	0.7	Dup/Del	0.00313 (31/9859)	0.00027 (8/29589)	11.6 (5.6–29.3)	$1.5 \times 10^{-12}$	29	[37, <b>38</b> ,39,44,49,55, 113–115]
16p13.1	14.6–18.7	1.16	Dup	0.00299 (13/4332)	0.00091 (32/35047)	3.3 (1.3–7.9)	$7.1 \times 10^{-3}$	11	[40,41, <b>50</b> ,51]
17p12	14.1–15.4	0.93–1.31	Del	0.00151 (8/5292)	0.00015 (6/39213)	9.9 (3.4–28.5)	$5.0 \times 10^{-5}$	15	[40, <b>51</b> ]
17q12	34.8–36.2	1.4	del/Dup	0.00073 (5/6882)	0.00018 (2/11255)	4.2 (1.3–Inf)	$1.8 \times 10^{-2}$	18	[ <b>39</b> ,116]
22q11.2	17.1–20.2	1.4–2.5	Del	0.00307 (35/11365)	<0.00002 (0/45361)	Inf (35.9–Inf)	$<1.0 \times 10^{-16}$	53	[ <b>38</b> ,39,44,46,47,51–55]
22q11.2	18.9–21.9	1.5–3.0	Dup	0.014% (3/21 138)	0.085% (22/25 867)	0.2 (0.1–0.6)	$8.6 \times 10^{-4}$	31	[ <b>39</b> ,56]

<sup>a</sup>For each CNV case-control frequency, ORs and *P*-values are from the bolded study. CI, confidence interval; CNV, copy-number variant; Del, deletion; Exon del, exonic deletion; Dup, duplication; Exon dup, exonic duplication; Inf, infinite; Mat dup, maternally-derived duplication; OR, odds ratio.

in specific brain functions<sup>[64]</sup>. In addition, most CNVs are not SCZ-specific; in contrast, many have effects in multiple neurodevelopmental disorders<sup>[65]</sup>.

### De Novo Mutations in SCZ

It is known that SCZ patients have a reduced reproductive rate<sup>[66,67]</sup>, which is a negative selection pressure in evolution.

However, the incidence rate of SCZ remains stable worldwide at ~1%. Therefore, there must be a genetic mechanism to supply causal factors to balance the negative selection. DNMs, defined as mutations arising sporadically either in the germ-line of the parents or at an early stage of embryonic development so that the mutations are only detected in affected individual but not in the parents, was proposed many years ago as a mechanism to offset the

negative selection<sup>[68]</sup>. This proposition was based on the epidemiological observation that paternal age is associated with an increased risk of SCZ<sup>[69-71]</sup>. This hypothesis did not receive much attention in genetic studies until recently, when high-throughput DNA sequencing of SCZ families provided direct evidence that affected offspring have excess DNMs across the genome<sup>[72,73]</sup>. Further studies of DNMs in individual genes<sup>[74,75]</sup>, a particular set of genes<sup>[76,77]</sup>, or the exome<sup>[78-80]</sup>, also provided evidence that DNMs are enriched in SCZ patients. Direct measurement also indicates that SCZ patients have a higher mutation rate<sup>[76]</sup>.

It should be pointed out that DNMs can be CNVs<sup>[48,81]</sup>, but the overwhelming majority are SNVs. Due to their low frequencies, DNMs are mostly classified as rare mutations. The difference between DNMs and other rare mutations is that DNMs occur only in the offspring, not in the parents. Since the frequencies of DNMs are extremely low, most tests of association are performed at the level of selected genes (gene sets or pathways). Tests can also be conducted on the basis of functional classification of the DNMs: coding *versus* non-coding sequences, *versus* non-synonymous, and neutral *versus* deleterious. Detailed analyses of DNMs in affected offspring reveal an excess of missense and disrupting mutations in protein-coding sequences, especially those involved in synaptic functions<sup>[77,79]</sup>. While most DNMs are unique events, some are recurrent<sup>[79]</sup>. Analyses of rare mutations reach the same conclusion that the polygenic burden of rare disruptive mutations is excessive in SCZ patients<sup>[80]</sup>. The converging results from DNMs, CNVs and SNVs support the notion that these mutations are likely enriched in the same pathways and thus play similar pathological roles in the etiology of SCZ.

## Conclusions and Future Directions

Some important conclusions can be drawn from the above description. First, SCZ is a polygenic and heterogeneous disorder and its genetic basis involves defects in many genes. These defects can include common SNVs, common and rare CNVs, and rare and recurrent DNMs. Overall, more than one hundred common variants and many more rare variants (including both CNVs and DNMs) are associated with SCZ. The discovery of these loci confirms that a substantial number of genetic defects may be

required for the manifestation of the disease and each individual gene has a limited effect. Currently, it is not clear what proportion of these variants is common and what proportion is rare. Given that the number of genes involved is likely to be more than hundreds, the genes responsible in individual patients may or may not overlap. This genetic heterogeneity not only imposes great challenges to the discovery of risk variants, but also demands individualized treatment for optimal effect. This explains why the commonly-used antipsychotics have very different effects on different patients.

Second, many of the common variants, CNVs, and DNMs identified in recent years are not specific to SCZ. Polygenic scores calculated from risk variants for SCZ can predict bipolar disorder<sup>[12]</sup>, suggesting some sharing of genetic risks between these disorders. Further examination of bipolar disorder, major depression, autism, and attention deficit and hyperactivity disorder indicates broader sharing of genetic liabilities among these disorders<sup>[82-84]</sup>. For example, ZNF804A and TCF4, loci first identified by SCZ GWASs, are associated with bipolar disorder as well<sup>[83,85]</sup>. MIR137 targets multiple genes involved in SCZ, bipolar disorder, and autism<sup>[86-88]</sup>. While the extent of sharing between these disorders may differ, the pleiotropic effects seem to extend beyond these traditional psychiatric disorders<sup>[89-92]</sup>. The extent and the identity of the variants specific to SCZ remain unknown.

Third, most variants identified so far are non-functional and non-causal. In the largest SCZ GWAS that reported 108 independent loci, 15 loci had no known genes nearby, and 36 loci had >3 genes<sup>[26]</sup>. For each of these loci, tens to hundreds of SNVs are involved. This implies that most of the variants showing association signals are most likely not causal. The functional variants at these loci remain unknown and much effort is needed to discover their mechanisms, and thus to improve our understanding of the biological mechanisms involved in disease etiology<sup>[93]</sup>. Rare variants (including CNVs and DNMs) may be pathologically causal. Unfortunately, due to the extremely low frequencies of these rare variants, only a few are reported in cases<sup>[36,78-80]</sup>. For example, the largest exome sequencing project reported a significantly higher rate of rare (frequency <0.1%), disruptive mutations in cases compared to controls among gene sets that had previously been associated with SCZ<sup>[80]</sup>. Those variants found only or overwhelmingly



in affected individuals present a realistic opportunity to establish causal relationships in functional and animal model studies.

Fourth, although we cannot be sure of their relative proportions, both common and rare variants contribute to the development of SCZ. Given that SCZ is negatively selected in evolution but maintains a stable incidence rate, we would argue that rare mutations are more likely the driving force in SCZ, and DNMs are the main counter-event to balance negative selection<sup>[94-96]</sup>. This note is consistent with the polygenic nature and heterogeneity of SCZ.

Based on what we have learned from these recent studies, future studies require extensive collaboration among investigators and across disciplines. Collaborations and consortia of investigators are necessary to assemble the sample sizes required to detect common variants with small effects and rare variants with low frequencies. SCZ GWASs organized by the PGC are successful examples of the discovery of common variants and rare CNVs associated with the disease<sup>[23,25,26,46,97]</sup>. The same model has been adapted for exome sequencing to discover rare variants<sup>[80]</sup>. Multi-disciplinary collaboration is also a current trend. Geneticists need to work more closely with clinicians, statisticians, informaticians, and computer programmers to improve the processing, integration, and analysis of large genetic, phenotypical/clinical, and genomic datasets. This is because more and more studies use the systems biology approach to collect data, and more and more studies incorporate data and information from different fields. These studies produce ever-increasingly large datasets that require specialized techniques and expertise to process and analyze. To some extent, the success of a study depends on the capability and efficiency of data processing, integration, curation, and analysis.

Looking forward, to understand the genetic mechanism of SCZ, we should focus on the following areas. The first is functional studies aiming at the discovery and understanding of causal variants at identified loci. As described above, many loci have been identified by GWASs, most of which should contain genuine variants contributing to the development of SCZ. Therefore, the time is ripe to pursue functional studies to understand the mechanism. Since most of the loci discovered by GWASs encompass large genomic intervals and contain multiple genes, deep sequencing of a substantial number of subjects is a

necessary first step to discover the causal variants at these loci. Deep sequencing can provide a catalog of variants with potentially deleterious functions. By combining functional genomics analyses with molecular, cellular, and animal model studies, we hope to demonstrate that a variant, or a group of variants, causes functional changes of a gene, leading to changes of the properties of neurons such as migration, communication, and differentiation. While it may be difficult to prove the causality of the variants in SCZ, we can reasonably interpret the effects of the variants if they have functional consequences at the level of neurons or lead to behavioral and cognitive changes in animal models similar to SCZ patients. Since a single variant may not be sufficient to cause observable changes resembling SCZ, cellular and animal models accommodating multiple variants should be explored.

The second direction is to continue the search for new risk loci. There is a good reason to believe that more loci await discovery. Given the small effect sizes of common variants and modest effects at best even for rare variants or DNMs, further searching for new loci requires a significant increase of power, to which there are several approaches. The simple approach is to increase sample sizes. Since most of the well-studied Caucasian samples have been included in PGC studies, there is not much room to expand the sample size, and the collection of new samples takes time, so this is not sustainable in the long run. For samples from other understudied ethnicities, organizing consortia and collaboration will be the most effective approach to discover novel risk loci. Integration of information from independent sources, including genome-wide functional genomic data such as biological pathways, gene expression, and DNA/chromatin modification, is another approach to improving power. These functional data can be used to exclude unlikely genes/loci, effectively reducing the number of tests needed for unbiased searches across the genome, thus improving the power to discover novel loci. For rare variants, pathway- and network-based analyses are essential. Furthermore, refinement of phenotype and the use of endophenotype and multiple related phenotypes to purify samples provide another approach to improving power. As discussed above, SCZ is genetically heterogeneous, so if we combine clinical information and functional endophenotypes (such as cognitive functions and immunological responses) to screen samples and define

biologically-based disease subgroups, we can reduce the heterogeneity within the group and thus improve power. A benefit of having a biologically-defined phenotype is that it can provide insights into the underlying mechanism and provide options for treatment of the disease.

A third direction is to study gene-environment interactions. It has long been speculated that the immune system is involved in SCZ. As the immune system is the primary defense against environmental pathogens, infection with pathogens leads to the activation/dysfunction of immune responses, which can modulate the risk of developing SCZ. This is consistent with increased incidence in individuals who are migrants, have an urban upbringing<sup>[98]</sup>, are exposed to maternal infection during pregnancy<sup>[99,100]</sup>, and suffer childhood infection<sup>[101]</sup>. While the specifics of the interaction remain largely unknown, some studies have implicated specific genes that can serve as a model for studying gene-environment interactions<sup>[102,103]</sup>. Another well-known fact is that there is a small but consistent difference of incidence between males and females. This difference can be seen as a special case of gene-environment interaction where sex hormones are the most likely mediators. The study of gene-sex interaction can follow the models of other sexually dimorphic diseases<sup>[104]</sup>. In SCZ, the RELN gene has been shown to have sexually different effects<sup>[105–107]</sup>. Other environmental factors, such as stressful/traumatic life events and substance use may also alter the risk of developing SCZ. Systematic examination of the interactions between these environmental factors and genetic variants would provide insights into how environmental factors modulate and mediate the risk of SCZ, thus improving our understanding of the pathology of this disorder.

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