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COMMENTARY

A commentary on the gender-specific association of TSNAX/DISC1 locus for schizophrenia and bipolar affective disorder in South Indian population

Shusuke Numata

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The disrupted-in-schizophrenia-1 (*DISC1*) gene was originally identified from the breakpoint of a chromosomal translocation (1;11) (q42.1;q14.3) in a large Scottish family with major mental disorders, including schizophrenia (SCZ), bipolar affective disorder (BPAD) and recurrent major depression.[1,2] Subsequently, many genetic evidences for the involvement of *DISC1* in SCZ have been reported in different populations,[3] and *DISC1* has become one of the putative susceptibility genes for SCZ. In this issue, Ram Murthy *et al.*[4] reported a gender-specific *DISC1* contribution in SCZ, BPAD and combined samples in South Indian population.

The first concern is the risk alleles and the haplotypes identified. Although the results of genetic replication studies between SCZ and the *DISC1* gene must be interpreted with extreme caution,[5] a critical issue in positive *DISC1* association studies is a lack of replication for the same alleles in the same direction and the same haplotypes across the studies. In addition, recent genome-wide association studies (GWAS)[6,7] as well as a large association study[8] and a meta-analysis of variants in the *DISC1* gene[9] failed to replicate significant associations of the *DISC1* gene with SCZ. The second concern is a gender-specific association of *DISC1* in SCZ. A meta-analysis of published literature has demonstrated a sex difference in the risk of developing SCZ,[10] and several studies have demonstrated sex-specific associations of *DISC1* in SCZ.[3] However, the GWAS has produced evidence that the genetic basis of SCZ is the same in males and females.[11] When the data are subdivided on the basis of sex in genetic association studies, one major problem that arises is the lack or reduction of power, and another is to claim nominal statistical significance, which may be occurred by chance. The sample size of the present study was small, and most of their sex-specific findings did not remain significant after correction for multiple comparisons.[4] Patsopoulos *et al.*[12] empirically evaluated observational 432 studies claiming to have found sex-related differences in genetic effects for common diseases and traits, and demonstrated that the majority of these claims were insufficiently documented or spurious. The third concern is a genetic overlap between SCZ and BPAD in the *DISC1* gene. As described above, the translocation event involving *DISC1* increases the risk of both SCZ and BPAD.[1,2] Lichtenstein *et al.*[13] reported that first-degree relatives of probands with either SCZ or BPD were at increased risk of these disorders, and half-siblings had an increased risk, but lower than that of the full-siblings, suggesting that SCZ and BPD partly share a common genetic cause. Similar to this epidemiological study, the GWAS revealed that common polygenic variation contributed to the risk of SCZ and BPD.[6] From this point of view, the present study's finding of a genetic overlap between SCZ and BPAD in the *DISC1* gene[4] is not surprising.

In conclusion, the majority of previous genetic association studies of SCZ, including GWAS, have been underpowered to detect common risk alleles with small effect sizes. To determine whether common *DISC1* genetic variants are truly implicated in SCZ, association studies using large samples and meta-analyses of previous literature are essential. Recent GWAS analyses of large collaborative samples have been remarkably successful for other common diseases, such as Crohn's disease and type 2 diabetes. For psychiatric disorders, the Psychiatric Genomewide Association Study Consortium (PGC) was organized. PGC is extending its samples and is performing large scale collaborative analyses using both traditional disorder categories and non-traditional analyses that cut across diagnostic categories (cross-disorder analyses).[6,7] It is still difficult to come to a conclusion of the involvement of common *DISC1* variants in SCZ in the general population, and there is a possibility that other mechanisms, such as copy number variants, epigenetics (histone and DNA modifications) and microRNAs, could explain the involvement of *DISC1* in SCZ in the future. Dr Sawa,[14] one of the most distinguished *DISC1* researchers, said that the molecular pathways involving *DISC1* seem to be implicated in unique endophenotypes that underlie many distinct mental disorders labelled by current diagnostic manuals, thus, *DISC1* biology may possibly provide a hint for constructing new diagnostic criteria for mental disorders at a more biological, and probably more relevant.

Dr S Numata is at the Department of Psychiatry, Course of Integrated Brain Sciences, Medical Informatics, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan.
E-mail: shu-numata@umin.ac.jp

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