論文題目：A Genome-Wide Scan for Susceptibility Variants to Autism Spectrum Disorder

（自閉症スペクトラム障害の疾患感受性多型の探索）

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Autism Spectrum Disorder (ASD) is a severe neurodevelopmental disorder characterized by impairment in social interaction, language deficits and repetitive and restricted behaviors. ASD has a very strong genetic factor. However, the underlying genetic mechanism is still elusive. In addition, genetics of ASD in East Asian populations has not been well explored and there is no reported genome wide genetic study for ASD in East Asian populations. To address these issues, in the current study, a two-stage genome wide association study (GWAS) and genome wide copy number variation (CNV) study were conducted in East Asian populations.

In the discovery stage of GWAS, 166 ASD families (500 subjects) and 425 healthy controls were genotyped with the Affymetrix Genome-Wide Human SNP array 6.0 chip (Affymetrix, Santa Clara, CA, USA). A novel method which combines the *P* value of family based association study (FBAT) and case-control was used in prioritizing SNPs for replication study. A total of 86 SNPs were selected for replication and genotyped in independent 205 Japanese ASD trios and 410 Taiwanese ASD trios. A number of nominal associations were observed within or near genes including *GPC6, NTN4, JARID2, AIM2, ROR2, CNTN4*. No single SNP was found to be associated with ASD at a genome-wide significance level ($P=5\times10^{-8}$) in both FBAT and case-control analysis. Furthermore no SNP was replicated either in the Japanese or the Taiwanese trios. The results indicated that ASD has a very complicated genetic architecture and the current sample size might not be sufficient to detect common variants with modest effect.

In the genome wide CNV study, after stringent quality control, a total of 158 cases, 306 parents and 349 controls from the Japanese population were used for CNV calling by three algorithms including PennCNV, QuantiSNP and Birdsuite. Ten putative rare *de novo* CNVs were identified and were validated by qPCR assay. Eight CNVs out of 10 from 8 ASD probands were confirmed. In which, a 5Mb *de novo* 15q11.2 duplication was found. The frequency of this CNV is 1/158 in the Japanese population, which is similar to the frequency reported in Caucasians (1%). Two novel genes were indentified in the *de novo* loci and have critical functions in central nervous system. These two genes may serve as novel ASD candidate genes for further functional study. In addition, 8 Inherited CNVs (5 duplication and 3 deletions) were found overlap with known ASD loci or ASD candidate genes. Of these CNVs, 16p11.2, *NLGN4X* and *MCPH1* are already well-established in association with ASD. 22q11.21 and 17p12 have been reported in a variety of neuropsychiatric disorders including ASD. *PRKCB1* and *SLC25A12* were both ASD candidate genes but no CNV have been previously reported affecting these two genes. The current CNV study confirmed a number of known ASD loci and also identified several novel *de novo* loci which may contain ASD candidate genes.

In conclusion, GWAS and genome-wide CNV analyses were done to explore the genetic architecture of ASD in East Asian populations. The results suggest that common variations may have a more subtle role in the pathogenesis of ASD than expected. Also the lack of association is likely to have been caused by insufficient statistical power of the small sample size. Future GWAS with large sample size were recommended to confirm the findings of the current study. By CNV analysis, a number of rare inherited or *de novo* CNVs have been identified in ASD patients. The results confirmed the significant contribution of CNV in the etiology of ASD and also identified novel loci which worth further study. These results provide a comprehensive genetic landscape of ASD in East Asian populations and also shed new light into the pathogenesis of ASD.