Genomewide Association Analysis Followed by a Replication Study Implicates a Novel Candidate Gene for Neuroticism

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Classification genetic study designs such as family and twin studies provide evidence for familial aggregation and the magnitude of genetic component. Furthermore, linkage studies map susceptible regions for diseases. Genomic regions that are identified by linkage analyses are likely to contain genes influencing one disorder or including pleiotropic loci and can then be targeted for more extensive gene identification, namely candidate gene association study. Due to the rapid advances in genotyping technology, genome-wide association studies (GWAS) with hundreds of thousands of markers are now becoming popular. The GWAS is a hypothesis free method which densely genotypes SNPs (single nucleotide polymorphism) and CNVs (copy number variations) along the whole genome without prior hypotheses of candidate genes for the diseases. These large scale genetic studies offer great promise to expedite the discovery of the common genetic variants affecting common diseases or traits of interest. In the recent few years, the GWAS has demonstrated to be a successful strategy because there have been multiple successes with the identification of highly compelling candidate genes, such as age-related macular degeneration, body mass index, inflammatory bowel disease, and type 2 diabetes mellitus.

In the last decades, great efforts have been put in searching for genes which predispose individuals to emotional disturbance. From public health point of view, mood disorders cause a large proportion of burden of disease according to the World Health Organization report and are expected to be on the top list of cause of disability worldwide for individuals of all ages by the year of 2020. In Taiwan, mood disorders are also evolving problems with increasing annual treated incidence and high recurrent rate clinically. Among general population samples, past studies have suggested that individuals with high Neuroticism personality trait have increased likelihood of developing major depressive disorder than individuals with low neuroticism. Neuroticism is a trait that reflects a tendency toward negative mood states. It has long been linked to internalizing psychiatric conditions, such as anxiety, depression, panic
disorder, and phobia. Large-scale twin studies demonstrated that genetic factors shared with neuroticism accounted for between roughly one-half of the genetic risk across several internalizing disorders. The genetic correlations between neuroticism and internalizing disorders were high. Therefore, neuroticism may account for much of the substantial comorbidity seen between emotional related disorders. To identify common genetic variants that affect neuroticism can provide a way to better understand the etiology of a broad range of psychiatric disorders and to develop effective treatments in the future.

We conducted a GWAS for the purpose mentioned above to identify genetic loci for neuroticism. The original sample consisted of 1227 healthy individuals ascertained from a US national sampling frame supported by National Institute of Mental Health with the measure of neuroticism using self-report questionnaire. More than 500,000 genetic SNP markers were tested for their association with neuroticism. Detailed quality control procedures for genotyping were employed to remove unqualified markers for following analyses. In total, the data reduced to 420,287 SNPs. The first run of association tests including both single marker and multi-markers have brought us some interesting regions for further validation and replication. The most promising markers were then subsequently tested in a German replication sample comprising 1880 healthy individuals. Replication of results in an independent sample can provide a more convincing evidence for the association between identified genes and neuroticism. Here, a strict definition of replication was used, which required an association in the replication study with (1) the same phenotype, (2) the same SNP, and (3) the same direction of effects for tested SNPs.

In the massive data sets, we estimated the proportion of markers without true effects ($p_0$) and the effect sizes ($\Delta$) of markers with effects (Kuo et al., 2007a), which provides information about how relevant the genotyped markers are for the outcome trait. To control the risk of false discoveries among large number of tests, we used the Q value threshold of .1 for declaring significance (Note: A Q value is an estimate of the proportion of false discoveries among all significant markers when the corresponding $P$ value is used as the threshold for declaring significance). This implies that, on average, we allow 10% of the SNPs that are declared significant to be false discoveries.

The most promising results in the GWAS and replication samples were SNPs in the gene \textit{MAMDC1}. Consistent with a strict definition of replication, the replication involved the same phenotype, the same SNPs, and the same direction of effects. All 4 SNPs in \textit{MAMDC1} were in very high linkage disequilibrium. These SNPs all tagged the same 2 haplotypes (accounted for 94% of all the haplotypic variation) and had small $P$ values of $10^{-5}$ to $10^{-6}$ in the GWAS sample and of .006 to .02 in the replication sample. In the combined analysis of original and replication samples, these SNPs in gene \textit{MAMDC1} were significant according to the threshold that allows for 10% false positive findings.

Although our previous linkage study for neuroticism did not find significant linkage signals for the region of \textit{MAMDC1} locus (Kuo et al., 2007b), two bipolar disorder linkage scans have previously implicated the region where \textit{MAMDC1} is located. The \textit{MAMDC1} (also known as \textit{MDGA2}) expressed in a variety of human tissues, including the nervous system, and is proposed to be involved in regulating neuronal migration and axonal guidance. \textit{MAMDC1} is one of the members of the immunoglobulin domain cell adhesion molecule subfamily, which includes neural cell adhesion molecules. Although the function of \textit{MAMDC1} is not well understood, other neuronal cell adhesion molecules have been implicated in psychiatric disorders, neuronal stress response, and specifically, depression. In conclusions, we identified a novel locus for personality trait neuroticism, which perceived to be an
endophenotype for multiple psychiatric conditions. Although the small effect sizes of MAMDC1 SNPs may limit the prognostic, diagnostic, and therapeutic use of these SNP markers in the current stage, we have demonstrated the use of a GWAS to discover potentially important pathogenic pathways for which clinically more powerful biomarkers may eventually be developed in the future.

References:


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