SLC6A15 rs1545853 and depression: implications from brain imaging data

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TO THE EDITOR: Major depression (MD) is a common neuropsychiatric disorder involving genetic components. A recent genome-wide association study has identified a risk SNP rs1545853 in SLC6A15 (1), which encodes a sodium dependent branched chain amino acid transporter. The risk SNP also showed associations with alterations in hippocampal volume, neuronal integrity and SLC6A15 expression (1), but it is still unclear how rs1545853 affects brain development, causing deficit of a specific brain region, and eventually leads to MD susceptibility.

An informative way of dissecting the functional role of the risk SNP is to test its associations with brain structures using *in vivo* magnetic resonance imaging methods. We recruited 278 unrelated healthy Han Chinese subjects without alcohol dependence, mental disorders, drug abuse, or brain injury. Structural images were acquired using a Philips MRI scanner operating at 3 Tesla, and a voxel-based morphometry (VBM) method was used to provide voxel-wise assessment of volumetric difference. Detailed information about sample, MRI acquisition, image preprocessing and genotyping were provided in **Supplemental Material**. The effect of genotype was examined utilizing linear regression, and p-values were computed for family-wise error (FWE) correction over the brain.

We observed brain-wide significant association of rs1545853 with the gray matter volume in median cingulate gyrus (FWE-corrected, voxel-wise p=0.031, cluster-wise p=0.0071, **Figure 1**). The cingulate cortex is a structurally heterogeneous brain region mainly involved in emotion and cognition processes (2), and deficits in patients with MD have been frequently reported in this brain region. Also, smaller gray matter volumes of regional cingulate gyrus was observed in MD patients (3), although anterior cingulate gyrus was reported more frequently, while median cingulate gyrus was rarely studied and the biology effects of this brain region on MD is still unclear. However, we did not find significant association in hippocampus as described in Kohli et al. (1), and the discrepancy is possibly due to the sample difference. Both MD patients and healthy controls were used in their study, and we only used healthy subjects.

In summary, our results provided evidence for a potential role of rs1545853 in the

brain, implying a possible pathophysiological mechanism underlying MD susceptibility, and further studies are warranted.

Supplemental material cited in this study is available online.

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Figure 1. Results of the association study for rs1545843. The most significant associated foci locate in the median cingulate gyrus (MNI coordinate [0 -18 34]). P < 0.001 uncorrected significant voxels (i.e., voxels survive the cluster-forming threshold) are in blue. Lower p-values have lighter blue color. Whole-brain FWE-corrected significant voxels are in yellow.