Genetic variant rs9848497 up-regulates MST1R expression, thereby influencing leadership phenotypes

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In PNAS, Song et al. (1) conduct a genome-wide association study (GWAS) for leadership phenotypes (leadership position and managing demands). They identify nine genome-wide significant single-nucleotide polymorphism (SNP) signals for leadership phenotypes ($P < 5E-08$), and find several top signals overlapping with known loci for bipolar disorder (miR-2113/POUSF2 and LINCO1239) and schizophrenia (ZSWIM6) (1). Although the findings of them are encouraging, how these top SNPs influence leadership phenotypes remains unknown.

Substantial studies have shown that many genetic variants affect complex traits by modulating gene expression (2–5). These variants may regulate the expression of certain genes in the brain region, leading to stronger leadership. Here, we test our hypothesis from two aspects. First, we investigate the cis-regulated effects of the nine top SNPs in the genes (1) they located in 13 types of normal brain tissues from Genotype-Tissue Expression (GTEx, version 8) (amygdala, anterior cingulate cortex, caudate basal ganglia, cerebellar hemisphere, cerebellum, cortex, hippocampus, hypothalamus, frontal cortex, nucleus accumbens basal ganglia, putamen basin ganglia, spinal cord cortical, and substantia nigra) (6). In the GTEx dataset, eQTL (expression quantitative trait loci) analysis was performed by applying linear regression based on an additive model. The statistically significant association after multiple testing is defined as $P < 0.05/(\text{number of loci} \times \text{number of tissues})$. Second, integrating GWAS data for leadership phenotypes with gene expression measurements for brain tissues in GTEx, we implement a transcriptome-wide association scan (TWAS) to identify genes whose cis-regulated expression was associated with leadership phenotypes (1, 2, 6). The significant association after multiple testing is defined as $P < 0.05/(\text{number of genes})$.

As a result, we found that seven of the nine genome-wide significant SNPs (rs7035099, rs4665237, rs9848497, rs7719676, rs1487441, rs4977839, and rs76915478) are involved in regulating the expression of leadership genes in brain regions. However, only the $P$ values for the regulation of rs7035099 on ZNF618 expression and rs9848497 on MST1R expression passed multiple testing (Table 1). Specifically, rs7035099 significantly up-regulated ZNF618 expression in the cerebellar hemisphere and cerebellum, and rs9848497 significantly up-regulated MST1R expression in the anterior cingulate cortex, caudate, cerebellar hemisphere, cerebellum, cortex, nucleus accumbens, and spinal cord. Furthermore, by integrating GWAS data for leadership phenotypes with eQTL data for brain tissues, we identify six gene candidates (MST1, MST1R, RNF123, UBA7, FAM212A, and APEH) whose expression is significantly associated with managing demands after multiple testing (Table 2). These significant association signals are all located in chromosome 3p21.3. Interestingly, MST1R replicates the significant signal in the original GWAS, and is also the most significant signal in TWAS ($Z_{\text{Cerebellum} = 6.30}, P_{\text{Cerebellum} = 3.02E-10}$). However, none of the genes for leadership position

**Table 1. Leadership-related genetic variants and gene expression in brain tissues**

| SNP        | Gene   | Beta    | $P$ value | Tissue               |
|------------|--------|---------|-----------|----------------------|
| rs7035099  | ZNF618 | 0.34    | 0.000014  | Cerebellar hemisphere |
| rs7035099  | ZNF618 | 0.31    | 0.000019  | Cerebellum            |
| rs9848497  | MST1R  | 0.39    | 0.000023  | Anterior cingulate cortex |
| rs9848497  | MST1R  | 0.34    | 2.30E-13  | Cerebellar hemisphere |
| rs9848497  | MST1R  | 0.49    | 5.00E-19  | Cerebellum            |
| rs9848497  | MST1R  | 0.54    | 1.10E-08  | Cortex                |
| rs9848497  | MST1R  | 0.42    | 2.50E-09  | Nucleus accumbens     |
| rs9848497  | MST1R  | 0.47    | 0.000025  | Spinal cord           |

Beta is the regression coefficient of the SNP on gene expression. Beta > 0 and Beta < 0 mean that this effect allele of SNP regulates increased and reduced gene expression, respectively. The statistically significant association after multiple testing is defined as $P < 0.05/(10 \times 13) = 0.000385$. Only variants and their expression levels that passed multiple testing are shown in the table.
passed multiple testing. Similar to the results of Song et al. (1), the genes we identify are also involved in brain function or psychiatric disorders. For instance, down-regulation of MST1 protects against impairment of working memory via regulating neural activity in depression-like mice.  

In summary, our findings highlight that rs9848497 influences leadership phenotypes by modulating MST1 expression, which may provide important information about the biological mechanism of rs9848497 in leadership phenotypes.

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