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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 *LINC01239*) 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 basal ganglia, spinal cord cervical, 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 $P < 0.05/(\text{number of loci} * \text{number of tissues})$. 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-related 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 ($Z_{Cerebellar\ hemisphere} = -6.30$, $P_{Cerebellar\ hemisphere} = 3.02E-10$) (1). However, none of the genes for leadership position

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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	5.70E-06	Caudate
rs9848497	*MST1R*	0.49	2.30E-13	Cerebellar hemisphere
rs9848497	*MST1R*	0.54	5.00E-19	Cerebellum
rs9848497	*MST1R*	0.42	1.10E-08	Cortex
rs9848497	*MST1R*	0.40	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 $P < 0.05/(10 * 13) = 0.000385$. Only variants and their expression levels that passed multiple testing are shown in the table.

Table 2. *Cis*-regulated genes associated with managing demands based on TWAS in brain tissues

Tissue	Gene	Chr	HSQ	Z	*P* value
Amygdala	*RNF123*	3	0.16	−4.87	1.13E-06
Anterior cingulate cortex	*RNF123*	3	0.12	−5.11	3.29E-07
	MST1R	3	0.19	−5.74	9.64E-09
Caudate basal ganglia	*UBA7*	3	0.06	5.91	3.43E-09
	MST1R	3	0.11	−4.95	7.3E-07
Cerebellar hemisphere	*FAM212A*	3	0.35	−4.88	1.06E-06
	RNF123	3	0.27	−4.88	1.08E-06
	MST1R	3	0.37	−6.30	3.02E-10
Cerebellum	*RNF123*	3	0.41	−5.45	4.97E-08
	FAM212A	3	0.47	−4.9	9.79E-07
Cortex	*RNF123*	3	0.18	−5.26	1.45E-07
	MST1R	3	0.13	−5.97	2.31E-09
Hypothalamus	*MST1*	3	0.18	4.54	5.69E-06
	MST1R	3	0.09	−5.42	6.07E-08
	RNF123	3	0.17	−5.41	6.24E-08
Frontal cortex	*RNF123*	3	0.13	−4.87	1.13E-06
	MST1R	3	0.15	−4.56	5.21E-06
	MST1	3	0.21	4.91	8.99E-07
Nucleus accumbens basal ganglia	*MST1R*	3	0.15	−5.72	1.09E-08
	RNF123	3	0.17	−4.87	1.13E-06
	MST1	3	0.19	4.90	9.4E-07
	RNF123	3	0.10	−5.31	1.1E-07
Spinal cord cervical	*RNF123*	3	0.15	−5.15	2.57E-07
	APEH	3	0.13	5.13	2.97E-07
	MST1R	3	0.10	−5.79	6.83E-09

Chr, chromosome; HSQ, heritability of the gene; Z, Z score of TWAS test. The statistically significant association after adjusting for multiple testing is defined as $P_{Amygdala} < 0.05/2633 = 1.90E\text{-}05$, $P_{Anterior\ cingulate\ cortex} < 0.05/3482 = 1.44E\text{-}05$, $P_{Caudate\ basal\ ganglia} < 0.05/5078 = 9.85E\text{-}06$, $P_{Cerebellar\ hemisphere} < 0.05/6141 = 8.14E\text{-}06$, $P_{Cerebellum} < 0.05/7330 = 6.82E\text{-}06$, $P_{Cortex} < 0.05/5645 = 8.86E\text{-}06$, $P_{Hippocampus} < 0.05/3576 = 1.40E\text{-}05$, $P_{Hypothalamus} < 0.05/3581 = 1.40E\text{-}05$, $P_{Frontal\ cortex} < 0.05/4557 = 1.10E\text{-}05$, $P_{Nucleus\ accumbens\ basal\ ganglia} < 0.05/5039 = 9.92E\text{-}06$, $P_{Putamen\ basal\ ganglia} < 0.05/4325 = 1.16E\text{-}05$, $P_{Spinal\ cord\ cervical} < 0.05/3148 = 1.59E\text{-}05$, and $P_{Substantia\ nigra} < 0.05/2278 = 2.19E\text{-}05$.

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 stress-induced depression-like behaviors (7, 8). *RNF123*, a biomarker of depression, is overexpressed in the cingulate cortex of depressed patients (9, 10).

In summary, our findings highlight that rs9848497 influences leadership phenotypes by modulating *MST1R* expression, which may provide important information about the biological mechanism of rs9848497 in leadership phenotypes.

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