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LETTER TO THE EDITOR

Parkinson's Disease Risk Variant rs1109303 Regulates the Expression of *INPP5K* and *CRK* in Human Brain

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Dear Editor,

Parkinson's disease (PD) is the second most common neurodegenerative disease in the elderly [1, 2]. PD affects 1%–2% of the world's population older than 65 years [3–5]. In recent years, large-scale genome-wide association studies (GWAS) have been widely conducted to identify the common genetic risk genes for PD. A number of PD susceptibility genes have been identified, including *SNCA*, *MAPT*, *NUCKS1*, the *HLA* region, *GAK*, *BST1*, *GBA*, *WNT3*, *RIT2*, and *LRRK2* [3–5].

It has been reported that the serum urate level is associated with PD risk and progression [6]. In 2015, Nazeri *et al.* conducted a GWAS and highlighted an association of the rs1109303 variant (T > G) within an intronic region of the *INPP5K* gene with the serum urate level (P = 2.01E-08) [6]. The authors considered that the rs1109303 variant may impact PD progression by affecting the expression of nearby genes (*MYO1C*, *PITPNA*, *SLC43A2*, and *CRK*) [6], but they did not directly investigate this association, which prompted us to investigate their findings further.

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Evidence has shown that some genetic variants have more ubiquitous effects, and others may need factors in a specific tissue, cell, region, or disease to exert their influence on gene expression [4, 5, 7–9]. These variants influencing gene expression are an important class of functional variants, and are named expression quantitative trait loci (eQTLs) [4, 5, 7–9]. Here, we investigated whether the rs1109303 variant regulates the expression of the nearby genes *INPP5K*, *MYO1C*, *PITPNA*, *SLC43A2*, and *CRK* using multiple large-scale eQTL datasets in 22 human brain tissue samples and 34 non-brain tissue samples, including whole blood.

The first eQTL datasets were from the Brain eQTL Almanac (Braineac), which is a web-based resource for access to the UK Brain Expression Consortium dataset (http://peana-od.inf.um.es:8080/UKBECv12/) [10]. The Braineac includes 10 eQTL datasets for tissues from 10 brain regions of 134 neuropathologically normal individuals [10]. The 10 brain tissues are: cerebellar cortex, frontal cortex, hippocampus, medulla (specifically, the inferior olivary nucleus), occipital cortex (primary visual cortex), putamen, substantia nigra, temporal cortex, thalamus, and intralobular white matter [10]. The second eQTL datasets were from the Genotype-Tissue Expression (GTEx) database (version 6), which includes 449 donors with a total of 7051 samples of 44 different tissues, with at least 70 samples of each tissue (https://www.gtexportal.org/home/datasets) [11]. Most donors are neuropathologically normal individuals [11]. The donors with neurological diseases are only ~3.7% of the donors aged 20–39 years, and 2.3% of those aged 60–71 years [11]. In the GTEx dataset, there are 10 human brain tissues (anterior cingulate cortex, caudate basal ganglia, cerebellar hemisphere, cerebellum, cortex, frontal cortex BA9, hippocampus, hypothalamus, nucleus accumbens basal ganglia, and putamen basal ganglia) and

Table 1 rs1109303 variant and gene expression in human tissues.

SNP	Study	Tissue	Gene	Experiment ID	Alleles	*N*	Effect allele	Z-score	Beta	*P*
rs1109303	Braineac [10]	Brain occipital cortex	CRK	t3740171	G/T	134	G	2.78	0.122	6.30E-03
rs1109303	GTEx [11]	Brain anterior cingulate cortex BA24	INPP5K	ENSG00000132376.15	G/T	72	G	3.04	0.318	3.75E-03
rs1109303	GTEx [11]	Artery tibial	ABR	ENSG00000159842.10	G/T	285	G	2.75	0.100	6.50E-03
rs1109303	GTEx [11]	Heart atrial appendage	DBIL5P	ENSG00000231784.4	G/T	159	G	2.76	0.312	6.61E-03
rs1109303	GTEx [11]	Spleen	FAM57A	ENSG00000167695.10	G/T	89	G	−2.97	−0.347	4.10E-03
rs1109303	GTEx [11]	Artery aorta	INPP5K	ENSG00000132376.15	G/T	197	G	−2.89	−0.183	4.37E-03
rs1109303	GTEx [11]	Stomach	INPP5K	ENSG00000132376.15	G/T	170	G	−2.76	−0.220	6.56E-03
rs1109303	GTEx [11]	Artery aorta	MIR22HG	ENSG00000186594.8	G/T	197	G	−2.80	−0.092	5.75E-03
rs1109303	GTEx [11]	Adrenal gland	MYO1C	ENSG00000197879.10	G/T	126	G	2.79	0.313	6.35E-03
rs1109303	GTEx [11]	Esophagus mucosa	MYO1C	ENSG00000197879.10	G/T	241	G	3.06	0.217	2.51E-03
rs1109303	GTEx [11]	Esophagus muscularis	MYO1C	ENSG00000197879.10	G/T	218	G	2.79	0.090	5.79E-03
rs1109303	GTEx [11]	Artery aorta	PITPNA	ENSG00000174238.10	G/T	197	G	−3.14	−0.124	2.04E-03
rs1109303	GTEx [11]	Heart left ventricle	PITPNA	ENSG00000174238.10	G/T	190	G	3.02	0.136	2.94E-03
rs1109303	GTEx [11]	Artery aorta	RNMTL1	ENSG00000171861.6	G/T	197	G	2.72	0.166	7.18E-03
rs1109303	GTEx [11]	Pancreas	SCARF1	ENSG00000074660.11	G/T	149	G	2.87	0.242	4.88E-03
rs1109303	GTEx [11]	Adrenal gland	SERPINF2	ENSG00000167711.9	G/T	126	G	−3.17	−0.351	1.99E-03
rs1109303	GTEx [11]	Heart atrial appendage	SGSM2	ENSG00000141258.8	G/T	159	G	−2.70	−0.114	7.96E-03
rs1109303	GTEx [11]	Colon transverse	SMYD4	ENSG00000186532.7	G/T	169	G	2.82	0.214	5.47E-03
rs1109303	GTEx [11]	Artery coronary	TIMM22	ENSG00000177370.4	G/T	118	G	2.84	0.235	5.54E-03
rs1109303	GTEx [11]	Testis	YWHAE	ENSG00000108953.12	G/T	157	G	−2.62	−0.109	9.86E-03
rs1109303	[12]	Whole blood	PITPNA	6590243	G/T	5311	G	−4.14	NA	3.50E-05
rs1109303	[12]	Whole blood	SKIP	2640678	G/T	5311	G	−3.38	NA	7.34E-04
rs1109303	[14]	Whole blood	INPP5K	3740264	G/T	5257	G	−8.29	−0.021	1.43E-16
rs1109303	[13]	Whole blood	INPP5K	ENSG00000132376	G/T	2116	G	−9.04	NA	1.58E-19
rs1109303	[13]	Whole blood	PITPNA	ENSG00000174238	G/T	2116	G	−5.25	NA	1.51E-07
rs1109303	[13]	Whole blood	PITPNA-AS1	ENSG00000236618	G/T	2116	G	−5.25	NA	1.51E-07

Significance level $P < 0.01$; rs1109303, chr17:1403477 (hg19); NA, not available; Z-score = effect (beta)/standard error; Beta is the regression coefficient based on the effect allele. Beta > 0 and Beta < 0 mean that this effect allele increases or reduces gene expression, respectively.

34 non-brain tissues including whole blood (n = 338) [11]. The third eQTL datasets for whole blood included 5311 individuals [12], 2116 individuals [13], and 5257 individuals [14]. More detailed information is described in the original studies [12–14].

In brief, linear regression analysis or Spearman rank correlation was applied to evaluate the potential association between the eQTLs and gene expression under an additive model [10–14]. In Braineac, we downloaded the gene expression data and the genotype data of generic variants with 1 Mb upstream of the transcription start site and 1 Mb downstream of the transcription end site [10]. We used the R program (http://mirrors.tuna.tsinghua.edu.cn/CRAN/, TUNA Team, Tsinghua University, Beijing, China) to evaluate the association between rs1109303 and nearby gene expression in each of the 10 brain regions. Meanwhile, we downloaded the summary results from the online GTEx database (version 6) to evaluate the potential association between rs1109303 and the expression of nearby genes [11]. Here, we downloaded the summary results [14], or used the online eQTL databases [12, 13] to evaluate the potential effect of the rs1109303 variant on the expression of nearby genes in human whole blood.

In the 10 brain regions in the Braineac dataset, the G allele of the rs1109303 variant was significantly associated with the increased *CRK* expression in the occipital cortex with beta = 0.122 and P = 6.30E-03. In the 10 human brain regions in the GTEx dataset, the G allele of the rs1109303 variant was only significantly associated with increased expression of *INPP5K* in the anterior cingulate cortex BA24 with beta = 0.318 and P = 3.75E-03. More detailed information is provided in Table 1.

In the 34 non-brain tissues in the GTEx dataset, the G allele of the rs1109303 variant was significantly associated with increased *MYO1C* gene expression in adrenal gland (beta = 0.313), esophagus mucosa (beta = 0.217), and esophagus muscularis (beta = 0.090), reduced *INPP5K* expression in artery aorta (beta = –0.183) and stomach (beta = –0.220), reduced *PITPNA* expression in artery aorta (beta = –0.124), and increased *PITPNA* expression in heart left ventricle (beta = 0.136). Meanwhile, rs1109303 significantly regulated the expression of other nearby genes including *ABR*, *DBIL5P*, *FAM57A*, *MIR22HG*, *RNMTL1*, *SCARF1*, *SERPINF2*, *SGSM2*, *SMYD4*, *TIMM22*, and *YWHAE* (Table 1).

In whole blood, the G allele of the rs1109303 variant is significantly associated with reduced *PITPNA* expression with P = 3.50E-05 [12] and P = 1.51E-07 [13], and reduced *INPP5K* expression with P = 1.43E-16 [14] and P = 1.58E-19 [13]. Meanwhile, the results indicated that rs1109303 significantly regulates the reduced expression of other nearby genes including *SKIP* with P = 7.34E-04 [12] and *PITPNA-AS1* with P = 1.51E-07 [13] (Table 1).

In summary, Nazeri *et al.* identified the *INPP5K* rs1109303 (T > G) variant to be significantly associated with the serum urate level [6]. Here, we evaluated the potential association between the rs1109303 variant and the expression of nearby genes using multiple large-scale eQTL datasets in multiple human tissues and whole blood. Our findings indicated that the G allele of the rs1109303 variant influenced the expression of nearby genes in diverse human tissues and different diagnostic groups. Hence, it is difficult to conclude that the *INPP5K* rs1109303 variant regulates the expression of a specific gene, such as *CRK*.

PD is a common neurodegenerative disease. We further focused on the two genes *CRK* and *INPP5K*, which were regulated by rs1109303 in the occipital cortex and anterior cingulate cortex BA24, respectively (Table 1). It has been reported that the human chromosome 17p13.3 region often shows genomic instability, including deletion or duplication of the region, and is linked to rare neurodevelopmental genetic diseases [15]. The *CRK* gene is located on chromosome 17p13.3. *CRK* encodes a signaling protein involved in cell proliferation, differentiation, migration, and axonal growth [15]. *CRK* plays an important role in neuronal migration and contributes to neurodevelopmental genetic diseases when microdeletions or microduplications occur [15]. *INPP5K* encodes a protein with 5-phosphatase activity on polyphosphate inositol. Nazeri *et al.* have identified the rs1109303 variant of the *INPP5K* gene to be associated with the serum urate level (P = 2.01E-08) in PD [6]. Hence, we believe that these findings may explain the potential mechanisms by which rs1109303 could affect the expression of nearby genes, PD risk, and PD progression.

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Compliance with Ethical Standards

Competing financial interests The authors declare no competing financial interests.

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