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LETTER TO THE EDITOR

rs34331204 regulates *TSPAN13* expression and contributes to Alzheimer's disease with sex differences

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Alzheimer's disease is the most common neurodegenerative disease with complex genetic architecture (Liu *et al.*, 2014). Recently, large-scale genome-wide association studies (GWAS) have been performed and successfully identified more than 40 novel Alzheimer's disease genetic variants (Lambert *et al.*, 2013; Cuyvers *et al.*, 2015; Kunkle *et al.*, 2019). Meanwhile, large-scale GWAS of Alzheimer's disease endophenotypes have also been reported (DemiNg *et al.*, 2017, 2018; Chung *et al.*, 2018; Dumitrescu *et al.*, 2019; Moreno-Grau *et al.*, 2019), and identified sex differences (Deming *et al.*, 2018; Dumitrescu *et al.*, 2019). In 2018, Deming and colleagues conducted sex-specific GWAS of CSF levels of amyloid-β_{42} and tau from 1527 males and 1509 females (Deming *et al.*, 2018). They identified rs316341 (sex-interaction $P = 0.04$) and rs13115400 (sex-interaction $P = 0.002$) to show stronger association with amyloid-β_{42} in females than males (Deming *et al.*, 2018). In 2019, Dumitrescu and colleagues analysed a GWAS dataset with 2701 males and 3275 females (Dumitrescu *et al.*, 2019). They identified variant rs34331204, which showed significant sex-specific association with $P = 2.90 \times 10^{-4}$ (Dumitrescu *et al.*, 2019). The rs34331204 variant minor allele C was associated with a lower risk of neurofibrillary tangles (NFT) in males ($P = 2.50 \times 10^{-8}$) but not females ($P = 0.85$). Interestingly, rs34331204 was also associated with increased hippocampal volume and executive function only in males (Dumitrescu *et al.*, 2019). Hence, their findings provide a male-specific protective genetic variant against tau pathology.

There are still four main concerns to be mentioned, although these are important and interesting findings. First, Dumitrescu and colleagues established the association between rs34331204 variant C allele and reduced NFT burden. It is known that increased NFT burden is a key Alzheimer's disease neuropathology. However, it remains unclear whether the rs34331204 variant is associated with Alzheimer's disease risk, especially in males. Second, the rs34331204 variant is a non-coding variant. Dumitrescu and colleagues conducted an expression quantitative trait loci (eQTL) analysis to identify the candidate genes within the rs34331204 variant, and further evaluate the association between the tau load and the expression of target genes in the

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prefrontal cortex (PFC) (Dumitrescu *et al.*, 2019). Using the Braineac data, eQTL analyses—including the exon-specific level and the transcript level—were carried out. However, they only evaluated the association between target gene expression and tau load at the transcript level. Importantly, these eQTL analyses are based on the average expression profile across all 10 brain tissues in Braineac (Dumitrescu *et al.*, 2019). It remains unclear whether these target genes have different expression in these different brain tissues. Third, ours and other studies have clearly indicated that eQTL analyses vary considerably in different tissue/cell types, and disease statuses (Liu *et al.*, 2016, 2017*a*, 2018, 2019*a*, *b*, 2020; Peters *et al.*, 2016; Soldner *et al.*, 2016; Hu *et al.*, 2017*b*). Hence, a tissue-specific eQTL analysis should be performed, especially in the PFC. Fourth, if one gene is the target gene of the rs34331204 variant in PFC, and its expression shows sex-specific association with tau pathology in PFC, it remains unclear whether there is significant difference regarding differential expression (Alzheimer's disease versus controls) in males and females. These concerns prompted us to further evaluate their findings.

In stage 1, we conducted a candidate variant study to evaluate the potential association between the rs34331204 variant and Alzheimer's disease risk using three large-scale Alzheimer's disease GWAS datasets. The first dataset was from the International Genomics of Alzheimer's Project (IGAP) (Kunkle *et al.*, 2019). The IGAP stage 1 dataset included 21 982 Alzheimer's disease patients and 41 944 cognitively normal control subjects of European descent from four consortia including the Alzheimer Disease Genetics Consortium (ADGC), Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE), The European Alzheimer's Disease Initiative (EADI), and the Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES) (Kunkle *et al.*, 2019). All Alzheimer's disease patients were diagnosed using the NINCDS-ADRDA criteria or DSM-IV guidelines (Kunkle *et al.*, 2019). Meanwhile, we selected two sex-specific Alzheimer's disease GWAS datasets including one Alzheimer's disease GWAS dataset in males diagnosed by paternal history of Alzheimer's disease (14 338 cases and 245 941 controls), and one Alzheimer's disease GWAS dataset in females diagnosed by maternal history of Alzheimer's disease (27 696 cases and 260 980 controls), both of which were from the UK Biobank (Marioni *et al.*, 2018). Here, we defined the significance threshold to be $P < 0.05$. Using the Alzheimer's disease GWAS dataset in IGAP, we found no significant association between the rs34331204 variant and Alzheimer's disease risk. Interestingly, the sex-specific analysis indicated that rs34331204 variant C allele was associated with reduced Alzheimer's disease risk in males ($P = 0.046$), but not in females ($P = 0.365$), as provided in Supplementary Table 1.

In stage 2, we conducted a gene expression analysis to demonstrate the significant expression difference of the target genes of rs34331204 across the 10 brain tissues in Braineac. Using the Braineac dataset, Dumitrescu and colleagues (2019) identified eight target genes for rs34331204 variant: *BZW2*, *TSPAN13*, *AGR3*, *ANKMY2*, *LRRC72*, *AGR2*, *ISPD*, and *AHR*, and evaluated the association of six genes with tau pathology in PFC by excluding *AGR3* and *LRRC72*. Using the online Braineac database (http://www.braineac.org/), we found that all of these six genes showed significant expression difference across the 10 brain tissues including *TSPAN13* (maximum fold change = 5.8, $P = 2.20 \times 10^{-64}$), *AHR* (maximum fold change = 3, $P = 2.30 \times 10^{-68}$), *ANKMY2* (maximum fold change = 2, $P = 8.80 \times 10^{-44}$), *BZW2* (maximum fold change = 2, $P = 1.00 \times 10^{-37}$), *ISPD* (maximum fold change = 1.6, $P = 3.50 \times 10^{-22}$), and *AGR2* (maximum fold change = 1.1, $P = 5.00 \times 10^{-8}$). A box plot showing the expression of these six genes across the 10 brain tissues in Braineac is provided in Fig. 1. All of these findings indicate that a tissue-specific eQTL analysis is needed, especially in PFC.

In stage 3, we performed an eQTL analysis of the rs34331204 variant in PFC using two independent datasets. The first dataset was from the Religious Orders Study and Memory and Aging Project (ROSMAP), which included 494 human PFC samples (Ng *et al.*, 2017). Ninety-seven per cent of these samples were diagnosed with pathological Alzheimer's disease and clinical Alzheimer's disease (Ng *et al.*, 2017). In ROSMAP, a Spearman's rank correlation was used to perform the eQTL analysis (Ng *et al.*, 2017). The second dataset was from the PsychENCODE Consortium (Wang *et al.*, 2018). There were a total of 1866 PFC individuals including 1039 control individuals [113 from Genotype-Tissue Expression Consortium (GTEx version 7) and 926 from PsychENCODE], and 827 disease samples (558 schizophrenia, 217 bipolar disorder, 44 autism spectrum disorder, and eight affective disorder from PsychENCODE) (Wang *et al.*, 2018). In PsychENCODE, a liner regression analysis was used to conduct the eQTL analysis (Wang *et al.*, 2018). The statistical significance was a Bonferroni-corrected threshold of $P < 0.05/31 = 1.61 \times 10^{-3}$. The results showed that the rs34331204 variant C allele was associated with increased *TSPAN13* expression only in the ROSMAP dataset ($P = 1.23 \times 10^{-3}$) (Table 1).

However, this association was not replicated in the PsychENCODE dataset (Table 1). We consider that multiple disease statuses in PsychENCODE may have caused this negative finding, although there was larger sample size compared with ROSMAP. Here, we carried out a further subgroup eQTL analysis of the rs34331204 variant in PFC using the neuropathologically normal samples from two independent datasets. The first dataset was from the Braineac, including 134 PFC samples (Ramasamy *et al.*, 2014). The second dataset was from the GTEx (version 8), including 175 PFC samples (Battle *et al.*, 2017). We first evaluated the association between the rs34331204 variant and *TSPAN13* expression using a liner regression analysis in both datasets. We then extracted the corresponding summary statistics of the rs34331204 variant in both datasets, and determined the heterogeneity of the rs34331204 variant using Cochran's Q

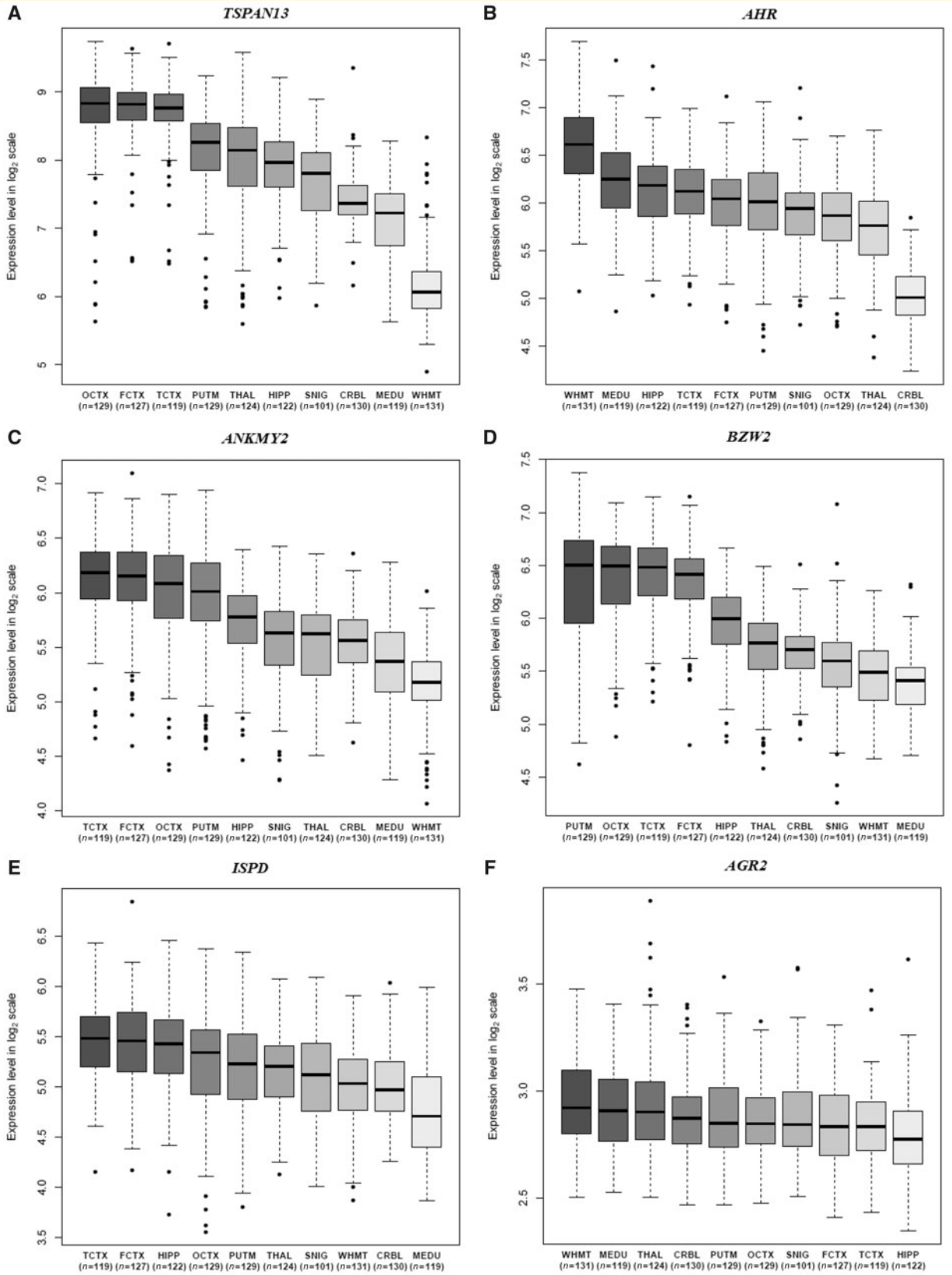

Figure 1 A box plot showing the expression of the six genes across the 10 brain tissues in Braineac. (**A**) Fold change between OCTX and WHMT = 5.8 ($P = 2.20 \times 10^{-64}$) for *TSPAN13*; (**B**) fold change between WHMT and CRBL = 3 ($P = 2.30 \times 10^{-68}$) for *AHR*; (**C**) fold change between TCTX and WHMT = 2 ($P = 8.80 \times 10^{-44}$) for *ANKMY2*; (**D**) fold change between PUTM and MEDU = 2 ($P = 1.00 \times 10^{-37}$) for *BZW2*; (**E**) fold change between TCTX and MEDU = 1.6 ($P = 3.50 \times 10^{-22}$) for *ISPD*; (**F**) fold change between WHMT and HIPP = 1.1 ($P = 5.00 \times 10^{-8}$) for *AGR2*. CRBL = cerebellar cortex; FCTX = frontal cortex; HIPP = hippocampus; MEDU = medulla; OCTX = occipital cortex; PUTM = putamen; SNIG = substantia nigra; TCTX = temporal cortex; THAL = thalamus; WHMT = intralobular white matter.

Table 1 The rs2293871 variant and *HTRA1* expression in human brain tissues

SNP	EA	NEA	Gene symbol	Gencode ID	Beta	*P*-value	Dataset
rs34331204	C	A	*SOSTDC1*	ENSG00000171243.7	–0.0257	5.69×10^{-1}	ROSMAP
rs34331204	C	A	*ANKMY2*	ENSG00000106524.4	0.0372	4.09×10^{-1}	ROSMAP
rs34331204	C	A	*TSPAN13*	ENSG00000106537.7	0.1450	$\mathbf{1.23 \times 10^{-3}}$	ROSMAP
rs34331204	C	A	*BZW2*	ENSG00000136261.10	–0.0213	6.37×10^{-1}	ROSMAP
rs34331204	C	A	*AC006041.1*	ENSG00000229379.1	0.0097	7.45×10^{-1}	PsychENCODE
rs34331204	C	A	*RP11-196O16.1*	ENSG00000273477.1	0.0002	9.95×10^{-1}	PsychENCODE
rs34331204	C	A	*RPL36AP29*	ENSG00000224683.1	–0.0111	8.41×10^{-1}	PsychENCODE
rs34331204	C	A	*CRPPA-AS1*	ENSG00000229688.3	0.0218	4.56×10^{-1}	PsychENCODE
rs34331204	C	A	*ISPD*	ENSG00000214960.5	0.0132	5.26×10^{-1}	PsychENCODE
rs34331204	C	A	*SOSTDC1*	ENSG00000171243.7	0.0394	1.55×10^{-1}	PsychENCODE
rs34331204	C	A	*GS1-166A23.1*	ENSG00000272537.1	0.0032	9.32×10^{-1}	PsychENCODE
rs34331204	C	A	*LRRC72*	ENSG00000205858.5	–0.0335	4.16×10^{-1}	PsychENCODE
rs34331204	C	A	*AC005014.5*	ENSG00000224280.1	0.0265	3.92×10^{-1}	PsychENCODE
rs34331204	C	A	*GS1-166A23.2*	ENSG00000272361.1	0.0176	6.90×10^{-1}	PsychENCODE
rs34331204	C	A	*ANKMY2*	ENSG00000106524.4	0.0060	6.92×10^{-1}	PsychENCODE
rs34331204	C	A	*BZW2*	ENSG00000136261.10	0.0160	3.55×10^{-1}	PsychENCODE
rs34331204	C	A	*AC073333.8*	ENSG00000235837.1	0.0662	2.29×10^{-1}	PsychENCODE
rs34331204	C	A	*TSPAN13*	ENSG00000106537.7	0.0012	9.54×10^{-1}	PsychENCODE
rs34331204	C	A	*AC073333.1*	ENSG00000267906.1	0.0356	4.31×10^{-1}	PsychENCODE
rs34331204	C	A	*AGR2*	ENSG00000106541.7	–0.0370	4.04×10^{-1}	PsychENCODE
rs34331204	C	A	*RP11-455J15.1*	ENSG00000270593.1	–0.0329	2.63×10^{-1}	PsychENCODE
rs34331204	C	A	*RAD17P1*	ENSG00000232400.1	0.1042	2.24×10^{-2}	PsychENCODE
rs34331204	C	A	*AGR3*	ENSG00000173467.4	0.0305	4.95×10^{-1}	PsychENCODE
rs34331204	C	A	*AC098592.2*	ENSG00000227965.1	–0.0135	4.72×10^{-1}	PsychENCODE
rs34331204	C	A	*AC098592.1*	ENSG00000223867.1	–0.0466	1.51×10^{-1}	PsychENCODE
rs34331204	C	A	*BRWD1P3*	ENSG00000232841.1	0.0200	6.50×10^{-1}	PsychENCODE
rs34331204	C	A	*AC073332.1*	ENSG00000237773.1	0.0418	3.41×10^{-1}	PsychENCODE
rs34331204	C	A	*AHR*	ENSG00000106546.8	0.0229	3.23×10^{-1}	PsychENCODE
rs34331204	C	A	*AC019117.1*	ENSG00000236318.1	0.0019	9.71×10^{-1}	PsychENCODE
rs34331204	C	A	*AC019117.1*	ENSG00000236039.1	–0.0421	1.93×10^{-1}	PsychENCODE
rs34331204	C	A	*AC017060.1*	ENSG00000226598.1	–0.0209	2.54×10^{-1}	PsychENCODE

EA = effect allele; EAF = effect allele frequency; NEA = non-effect allele. Beta is the regression coefficient based on the effect allele. Beta > 0 and Beta < 0 means that this effect allele increase and reduce disease or phenotype, respectively. The statistical significance for eQTL analysis was a Bonferroni-corrected threshold of $P < 0.05/31 = 1.61 \times 10^{-3}$.

test. Finally, we conducted a meta-analysis to evaluate the association between the rs34331204 variant and *TSPAN13* expression using R Package (meta: General Package for Meta-Analysis) (Hu *et al.*, 2017*a*). The overall odds ratio (OR) was calculated by the fixed effect model (Mantel-Haenszel) or random-effect model (DerSimonian-Laird), which is determined by the heterogeneity (Hu *et al.*, 2017*a*; Liu *et al.*, 2017*b*). The statistical significance was 0.05. Interestingly, we found no significant heterogeneity with $P = 0.7425$. A meta-analysis using the fixed effect model highlighted a significant association between the rs34331204 variant C allele and reduced *TSPAN13* expression (beta = –0.15, $P = 0.0107$). Hence, all of these findings indicate that the directions regarding the effect of rs34331204 variant C allele on *TSPAN13* expression are different in neuropathologically normal samples and neurodegenerative disease individuals.

In stage 4, we performed an Alzheimer's disease control gene expression analysis of *TSPAN13* in males and females, respectively. We selected the gene expression dataset from the Harvard Brain Tissue Resource Center (HBTRC), including 129 (62 males and 67 females) Alzheimer's disease samples and 101 (82 males and 19 females) non-demented healthy control samples in human PFC (Zhang *et al.*, 2013). Here, we selected $P < 0.05$ to define the differential expression of *TSPAN13* in Alzheimer's disease and healthy control subjects. Using the online Bioconductor R package GEO2R, we found that *TSPAN13* indicated stronger differential expression in males (fold change = 0.81 for Alzheimer's disease versus control, $P = 2.90 \times 10^{-16}$) than females (fold change = 0.82 for Alzheimer's disease versus control, $P = 3.20 \times 10^{-4}$).

Taken together, Dumitrescu and colleagues identified the rs34331204 variant C allele to be significantly associated with the reduced NFT in males (Dumitrescu *et al.*, 2019). However, four main concerns remained unclear. Here, we performed a multi-stage analysis to answer these questions. In stage 1, we identified the rs34331204 variant C allele to be associated with reduced Alzheimer's disease risk only in males. In stage 2, we demonstrated the different expression of the target genes of rs34331204 across the 10 brain tissues in Braineac. In stage 3, we found that the rs34331204 variant only regulated *TSPAN13* expression in PFC, and in stage 4, we identified stronger differential expression of

TSPAN13 in males than females in the PFC. We believe that these findings provide important supplementary information regarding the role of the rs34331204 variant in Alzheimer's disease.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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