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LETTER TO THE EDITOR

The rs2228570 Variant of the Vitamin D Receptor Gene is Associated with Essential Tremor

Ali Sazci[1] · Nihal Uren[1] · Halil Atilla Idrisoglu[2] · Emel Ergul[1]

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Dear Editor,

Essential tremor (ET) is one of the most common movement disorders of unknown etiology [1, 2], having an overall prevalence of 4% in the general population [2]. The age at onset has been reported to be between 15 years and 20 years, and penetrance to be complete at between 50 years and 70 years. It seems to be a progressive neurological disorder, and can lead to substantial disability in some patients. Although it presents some degree of clinical variability, it occurs in sporadic (SET) and familial (FET) forms with heterogeneity of expression between and within families [3]. ET is characterized essentially by a postural and kinetic tremor most often affecting the arms, but it can also affect other parts of the body [4]. Nonetheless, familial expression of ET has been linked to some loci [5–7].

In ET, Purkinje cell loss is the main neuropathological feature, with an increase in torpedoes in the cerebellum [8]. Moreover, impairment in the ventral intermediate nucleus–motor cortex–cerebellum circuit has also been revealed [9].

Present evidence shows high heritability for ET, but only a few susceptibility loci have been determined thus far. Three susceptibility loci for FET have been localized to *ETM1* on chromosome 3q13 [5], *ETM2* on chromosome 2p25–p22 [6], and *ETM3* on chromosome 6p23 [7]. Genome-wide association studies (GWAS) have revealed that the rs9652490 and rs11856808 variants in intron 3 of the *LINGO1* gene are implicated in ET [10], as well as the intronic rs3794087 variant in the *SLC1A2* gene [2]. Three missense mutations in the *TENM4* gene have been identified as autosomal dominant in ET families [2]. Subsequent GWAS further identified the rs10937625 variant in the *STK32B* gene, the rs17590046 variant in the *PPARGC1A* gene, and the rs12764057, rs10822974, and rs7903491 variants in the *CTNNA3* gene [2]. In addition, the genes *MTHFR* [1], *FUS*, *HTRA2*, *SORT1*, *SCN4A*, *NOS3*, *KCNS2*, *HAPLN4*, *USP46*, and *SCN11A* [2] have been shown to be associated with ET. However replication studies in different populations have reported inconsistent findings [2].

The human vitamin D receptor (*VDR*) gene is located on the long arm of chromosome 12q13.11 and consists of 11 exons, together with introns which span a 75-kb DNA sequence [11]. So far, 63 polymorphisms have been identified in the *VDR* gene, including the rs2228570 variant at the translation initiation site in exon 2. It has been shown that the *VDR* gene rs2228570 variant produces either a 424- or a 427-amino-acid VDR protein, differing only by three amino-acids. The shorter variant is associated with a 1.7-fold higher level of transcriptional activity than the longer variant [11, 12]. The C allele of the shorter variant has a stronger affinity for the active form of vitamin D. The T allele produces a longer VDR protein characterized by lower affinity for active vitamin D that might result in the development of ET.

Given the available data on the involvement of vitamin D and the *VDR* gene in neurological disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and migraine, we performed a case-control genetic association study on the rs2228570 variant (missing or containing a *Fok*I restriction site) in 239 sporadic ET patients and 239 healthy controls to determine

✉ Ali Sazci
alisazci@gmail.com

[1] Department of Medical Biology and Genetics, Faculty of Medicine, University of Kocaeli, 41380 Kocaeli, Turkey

[2] Department of Neurology, Istanbul Faculty of Medicine, University of Istanbul, Capa, 34260 Istanbul, Turkey

whether there is an association between this variant and sporadic ET. The PCR-restriction fragment length polymorphism method was used for genotyping.

A total of 239 unrelated Caucasian SET patients [129 (54%) men and 110 (46%) women, mean age 57.2 years ± 19.9 years, range 18 years–85 years] were included in the study, and diagnosed by a movement disorder specialist using the criteria of differential diagnosis assessment [6, 7]. The age at onset was 45.2 years ± 12.8 years with a disease duration of 13.4 years ± 10.0 years. The body distribution of tremor was 76.79% (182) in both hands; 9.28% (22) right hand; 2.53% (6) predominantly right hand with both sides; 5.91% (14) left hand; 1.69% (4) predominantly left hand with both sides; and 3.80% (9) whole body involvement. Two hundred and thirty nine unrelated, sex- and regionally-matched healthy Caucasian participants served as controls [129 (54%) men and 110 (46%) women; mean age 58.4 years ± 15.8 years, range 18 years–85 years]. All protocols were approved by the Ethics Committee of Kocaeli University. All participants gave written informed consent.

Statistical analysis was performed using SPSS v. 21 for PC (SPSS Inc., Chicago, IL). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression analysis. Statistical significance was considered at the level $P < 0.05$.

In this study, 239 SET patients and 239 healthy controls were analyzed in terms of genotype and allele distributions

Table 1 Allele and genotype distributions of the *VDR* rs2228570 variant (*Fok*I) in sporadic essential tremor patients and controls, and in male and female sporadic essential tremor patients and controls.

Gene	Cases	Controls	χ^2	*P* value	OR (95%CI)
VDR rs2228570	239 (100.0%)	239 (100.0%)	5.206	0.074	
CC	129 (54.0%)	114 (47.7%)	1.883	0.170	1.286 (0.898–1.842)
CT	99 (41.4%)	102 (42.7%)	0.077	0.781	0.950 (0.661–1.366)
TT	11 (4.6%)	23 (9.6%)	4.560	0.033	0.453 (0.216–0.952)
CC + CT dominant	228 (95.4%)	216 (90.4%)	4.560	0.033	2.207 (1.051–4.636)
CT + TT recessive	110 (46%)	125 (52.3%)	1.883	0.170	0.778 (0.543–1.114)
Allele frequency					
C allele	357 (75%)	330 (69%)	4.560	0.033	2.207 (1.051–4.636)
T allele	121 (25%)	148 (31%)	1.883	0.170	0.778 (0.543–1.114)
HWE (exact)	0.17	1.0			
SP	0.31	0.31			
Gene	Male cases	Male controls	χ^2	*P* value	OR (95% CI)
VDR rs2228570	129 (100.0%)	129 (100.0%)	7.962	0.019	
CC	75 (58.1%)	57 (44.2%)	5.026	0.025	1.754 (1.072–2.872)
CT	50 (38.8%)	59 (45.7%)	1.287	0.257	0.751 (0.458–1.232)
TT	4 (3.1%)	13 (10.1%)	5.101	0.024	0.286 (0.091–0.901)
Allele frequency					
C allele	200 (78%)	173 (67%)	5.101	0.024	3.502 (1.110–11.047)
T allele	58 (22%)	85 (33%)	5.026	0.025	0.570 (0.348–0.933)
HWE (exact)	0.31	0.84			
SP	0.51	0.51			
Gene	Female cases	Female controls	χ^2	*P* value	OR (95%CI)
VDR rs2228570	110 (100.0%)	110 (100.0%)	1.002	0.606	
CC	54 (49.1%)	57 (51.8%)	0.164	0.686	0.897 (0.528–1.521)
CT	49 (44.5%)	43 (39.1%)	0.673	0.412	1.252 (0.732–2.141)
TT	7 (6.4%)	10 (9.1%)	0.574	0.449	0.680 (0.249–1.855)
Allele frequency					
C allele	157 (71%)	157 (71%)	0.574	0.449	1.471 (0.539–4.017)
T allele	63 (29%)	63 (29%)	0.164	0.686	1.115 (0.657–1.893)
HWE (exact)	0.48	0.64			

SP Statistical power, *HWE* Hardy–Weinberg equilibrium, *VDR* vitamin D receptor.

(Table 1). Both cases and controls were in Hardy-Weinberg equilibrium for the rs2228570 variant.

The TT genotype of the rs2228570 variant was associated with SET (χ^2 = 4.560; P = 0.033; OR = 0.453; 95% CI = 0.216–0.952). Similarly, the C allele of this variant was associated with SET with an increased risk of 2.2-fold (χ^2 = 4.560; P = 0.033; OR = 2.207; 95% CI = 1.051–4.636). After stratification analysis, the rs2228570 variant was associated with ET in male patients (χ^2 = 7.962; P = 0.019). The CC genotype rendered a 1.8-fold increased risk for SET (χ^2 = 5.026; P = 0.025; OR = 1.754; 95% CI = 1.072–2.872). The TT genotype showed protection against SET (χ^2 = 5.101; P = 0.024; OR = 0.286; 95% CI = 0.091–0.901). On the contrary, the *VDR* rs2228570 variant was not associated with SET in the female patients (χ^2 = 1.002; P = 0.606) (Table 1).

In the present study, the rs2228570 variant of the *VDR* gene was significantly associated with the risk of SET. This is the first study to show an association between the *VDR* rs2228570 variant and SET. Although the statistical power was 0.31 for overall cases and controls, the statistical power for male ET was 0.51. It was difficult to collect so many ET patients at one time. Although it would be preferable to have a statistical power of 0.80, we still managed to obtain statistically important data for overall and male ET patients.

Vitamin D may play a role in brain function. Differences in its levels have been associated with cognitive decline and may result in diseases of the nervous system. Vitamin D has a neuroprotective effect and may be responsible for the regulation of inflammation in the brain. Vitamin D levels are environmentally modifiable as they are generally determined by diet and sunlight. The enzyme 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase) converts the storage form 25-hydroxyvitamin D (25 [OH] D) to the biologically-active vitamin D form, 1,25-dihydroxyvitamin D3. When binding to 1,25-dihydroxyvitamin D3, the VDR is activated and interacts with vitamin D-responsive elements in the promoters of vitamin D target genes to modulate their expression. Within the brain, the expression of VDR and 1 α-hydroxylase is located especially in the hypothalamus and in the dopaminergic neurons within the substantia nigra which are vulnerable in AD [13] and in PD [14]. *VDR*-null mice have impaired locomotor activity [15]. Consequently, the expression pattern of VDR and 1 α-hydroxylase supports an important role of vitamin D in the etiology of PD and ET [13, 14]. The expression level of *VDR* mRNA has been identified as a potential blood biomarker for PD. Genetic studies on *VDR* polymorphisms have indicated its involvement in neurological disorders [16], including MS, AD, PD, and migraine. Moreover, additional studies are required to determine the biological mechanisms underlying the observed association and their potential relationship with SET.

In conclusion, we demonstrated for the first time that the rs2228570 variant of the *VDR* gene is associated with SET overall and in male patients. Therefore, the *VDR* rs2228570 variant is a genetic risk factor for SET.

Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

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