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Vitamin D Receptor and Binding Protein Gene Variants in Patients with Essential Tremor

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Abstract

Several studies have shown an association between some variants in the *vitamin D receptor* (*VDR*) and the *GC vitamin D binding protein* (*GC*) genes with the risk for Parkinson's disease or other neurological disorders. *VDR* rs2228570 has shown an association with essential tremor (ET) in a previous study. The aim of this study is to look for the association between several common variants in these genes and the risk for ET. We genotyped 272 patients diagnosed with familial ET and 272 age-matched controls using specific TaqMan assays for *VDR* rs2228570, *VDR* rs731236, *VDR* rs7975232, *VDR* rs739837, *VDR* rs78783628, *GC* rs7041, and *GC* rs4588 single nucleotide variants (SNVs). We found an association between *GC* rs7041 SNV and ET using recessive, codominant, and allelic models. Despite our results did not find an association between *VDR* rs2228570 and ET, the pooled data with those by a previous report suggest this association under recessive, codominant, and allelic models. None of the SNVs studied was related to the age at onset of tremor in ET patients. Data from the current study suggest an association between *GC* rs7041 and *VDR* rs2228570 SNVs and ET risk.

Keywords Essential tremor · Genetics · Gene variants: VDR gene · GC vitamin D binding protein gene

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Introduction

Essential tremor (ET), which is characterized from the clinical point of view by the presence of postural and/or kinetic tremor affecting predominantly or exclusively upper limbs (with a variable percentage of patients showing tremor in other body locations, and many of them associating non-motor symptoms or co-morbidities), is a movement disorder of high prevalence, especially in elderly people [1, 2]. Although the etiopathogenesis of ET is not definitively understood, the role of genetic factors, supported by the high positivity of family history of tremor, the higher concordance rates of ET for monozygotic twins compared with dizygotic ones, and the presence of genetic anticipation in ET [3–6], together with descriptions of a possible role of environmental factors, at least in non-familial of sporadic cases of ET [7–9], suggest a contribution of both genetic and environmental factors to ET development.

Data from the contribution of genetic factors to the etiopathogenesis of ET arise from [3–6]: (a) Linkage studies in families with ET, which identified 4 genes/loci without identification of the responsible (s) gene (s); (b) previous

genome-wide association studies (GWAS), which found associations, not confirmed by replication studies, of ET risk with several variants in the *LINGO1*, *SLC1A2*, *STK32B*, *PPARGC1A*, and *CTNNA3* genes [3–6], and a more recent GWAS and meta-analysis involving 7177 ET patients and 475,877 controls, that found association with variants in the *PTGFRN* (rs1127215), *PPARGC1A* (rs17590046), *MIR924HG* (rs1945016), *LOC105379011* (rs28562175), and *LINC00323* (rs9980363) genes [10]; (c) exome sequencing studies in families and case-series of patients with ET, which described associations of many genes, including *FUS*, *HTRA2*, *TENM4*, *SORT1*, *SCN11A*, *NOTCH2NLC*, *NOS3*, *KCNS2*, *HAPLN4*, *USP46*, *CACNA1G*, *SLIT3*, *CCDC183*, *MMP10*, and *GPR151*, with familial ET, but limited each one to a few families; (d) hypothesis-driven case–control studies on candidate genes for ET, which have described associations, non-replicated to date, with several variants in the *CYP2C19* [11], *CYP2C9/CYP2C8* [12], *RIT2* [13], *IL1B* [14], and *VDR* [15] genes, and an increased risk for carriers of the *ALAD* rs1800435 variants in interaction with a variant in the *HMOX2* gene [16] and with serum levels of lead [17].

VDR gene (link http://www.ncbi.nlm.nih.gov/gene/7421; chromosome 12q13.11; MIM 601,769; Gene ID 7421) encodes the nuclear hormone receptor for vitamin D3. This gene has 5 common single nucleotide variants (SNV) in Caucasians: (a) rs2228570 (*Fok1*) causes the amino acid substitution (Met 1, start loss), (b) rs731236 (*Taq1*), a synonymous SNV which does not cause amino acid substitution (Ile352Ile), (c and d) rs739837 and rs78783628, two common variants located in the 3′ untranslated area, and (e) rs7975232 (*Apa1*), a common intronic variant. There are no other SNVs with frequencies higher than 0.0010 and known functional impact affecting the *VDR* gene according to the gnomAD database.

The *GC vitamin D binding protein gene* (link http://www.ncbi.nlm.nih.gov/gene/2638; chromosome 4q13.3; gen ID 2638; MIM 139,200) encodes the vitamin D binding protein. This protein is able to bind to vitamin D and their plasma metabolites and acts as a transporter to target tissues. According to the gnomAD database, two main SNVs in the *GC* gene with frequencies higher than 0.0025 and known functional impact affecting the *GC* gene have been described in Caucasians: (a) rs7041, a missense SNV which causes the amino acid substitution Asp 451 Glu, and (b) and rs4588, another missense SNV which causes the amino acid substitution Thr 455 Lys. The intronic SNV *GC* rs3755967, which is in strong linkage disequilibrium with *GC* rs4588, has been related to vitamin D levels [18–20].

Updated meta-analyses have shown an association of *VDR* rs2228570 [21, 22] and rs7975232 [17] with the risk for Parkinson's disease, at least in the Asian population [22] an association between *VDR* rs731236 and the risk for Alzheimer's disease [21, 22], at least in Caucasians [23]; increased and decreased risk for mild cognitive impairment associated, respectively, with *VDR* rs1544410 (BsmI) and *VDR* rs7975232 [23]; and an association between *VDR* rs7975232 and the risk for multiple sclerosis [24]. Regarding other neurological disorders, some studies described associations of *VDR* rs2228570 and *VDR* rs731236 with migraine without aura [25], *VDR* rs2228570 with ischemic stroke [26], *VDR* rs7975232 with amyotrophic lateral sclerosis [27], and *VDR* rs2228570 and *VDR* rs7975232 with childhood temporal lobe epilepsy [28]. A study found a possible association between *VDR* rs731236 and adult non-thymoma myasthenia gravis with negativity of acetylcholine receptors antibodies [29]. Gezen-Ak et al. [30] reported an association between *GC* rs7041 and the risk for Parkinson's disease. An association of *VDR* rs2228570 and *VDR* rs731236 with the risk for restless legs syndrome reported in one study [31] was not confirmed in another [32]. A lack of association between *GC* rs7041, *GC* rs4588, and *GC* rs2282679 and multiple sclerosis [33], and between *GC* rs7041and *GC* rs4588 and restless legs syndrome [34] has also been reported.

Two previous studies addressed the possible association between *VDR* variants and the risk for ET. While Saczi et al. [15] reported an association between *VDR* rs2228570 and sporadic ET, Cheng et al. [14] did not find an association between *VDR* rs731236 and ET risk (50% of ET patients had familial history of ET). The main aim of our study is to replicate the finding by Saczi et al. [15]. In addition, we studied other common SNVs in the *VDR* and *GC* genes (both associated with the risk for Parkinson's disease) in patients with familial ET and controls.

Patients and Methods

Patients and Controls

The genotype and allelic variants *VDR* rs2228570, *VDR* rs731236, *VDR* rs7975232, *VDR* rs739837, *VDR* rs78783628, *GC* rs7041, and *GC* rs4588 were studied in 272 ET patients and 272 gender-matched controls, all of them of Spanish European ancestry. ET patients (141 men and 131 women, mean age 66.6 ± 15.8 years, mean age at onset of tremor 49.6 ± 25.0 years) were diagnosed with definite ET according to standard diagnostic criteria [34]; all of them had at least one first-degree relative affected with ET, and were included in the study if they had normal thyroid function, absence of other neurological diseases, and absence of family history of Parkinson's disease. Many of these ET patients, that were recruited at the Movement Disorders of four University Hospitals, had participated in previous case–control association studies reported by our group [9, 11, 17, 35–44]. Controls, that were unrelated healthy subjects of Spanish European ancestry who did not have

personal or familial history of movement disorders including tremor or Parkinson's disease (141 men and 131 women, mean age 51.3 ± 14.2 years), were recruited from the University of Extremadura.

Ethical Aspects.

The study protocol was approved by the Ethics Committees of the University Hospital "Príncipe de Asturias" (Alcalá de Henares, Madrid, Spain), and of the University Hospital "Infanta Cristina" (Badajoz, Spain). The study was performed following the principles of the Declaration of Helsinki, being an obligate requisite for inclusion written and signed informed consent.

Genotyping of VDR rs2228570, VDR rs731236, VDR rs7975232, VDR rs739837, and VDR rs78783628, GC rs7041, and GC rs4588 Variants

The selection of SNVs analyzed was done considering not only the allele frequencies reported in individuals of European descent according to the public database gnomAD (https://gnomad.broadinstitute.org/) but also their functional impact, and their clinical associations. Genotyping of the analyzed variants were performed by using genomic DNA obtained from peripheral leukocytes of venous blood samples of both ET patients and controls, and using specific TaqMan Assays (Life Technologies, Alcobendas, Madrid, Spain) for the SNVs *VDR* rs2228570 (C__12060045_20); *VDR* rs731236 (C__2404008_10); *VDR* rs7975232 (C__28977635_10); *VDR* rs739837 (C___2404007_10); *VDR* rs78783628 (custom-designed TaqMan probes), *GC* rs7041 (C___3133594_30); and *GC* rs4588 (C___8278879_10), as it was previously described elsewhere [31].

Statistical Analysis

Statistical analysis was performed by using the SPSS 27.0 version for Windows (SPSS Inc., Chicago, Illinois, USA). The exploration of the Hardy–Weinberg equilibrium was performed with the online program https://www.snpstats.net/start.htm, and we confirmed this equilibrium for all the variants assessed, both in ET patients and controls. The intergroup comparison values (both for the whole series and for each gender of ET patients and controls) were calculated with the chi-square or Fisher's exact tests where appropriate. We also calculated the 95% confidence intervals (95% CI) [45], and we used the False Discovery Rate (FDR) correction for adjustment for multiple analyses [46]. According to the sample size of this study and using a genetic model that analyzed the minor allele frequencies with an odds ratio (OR) value = 1.5 ($\alpha = 0.05$), the statistical power (two-tailed association) for *VDR* rs2228570, *VDR* rs731236, *VDR* rs7975232, *VDR* rs739837, *VDR* rs78783628, *GC* rs7041, and *GC* rs4588 variant alleles was 90.85%, 91.56%, 90.02%, 90.26%, 91.60%, 90.83%, and 89.71%, respectively. The comparison of the mean ± SD age at onset of tremor across the different genotypes of the SNVs studied was done by using the Student's *T* test.

Results

The Hardy–Weinberg equilibrium was correct by the frequencies of the genotypes and allelic variants of *VDR* rs2228570, *VDR* rs731236, *VDR* rs7975232, *VDR* rs739837, *VDR* rs78783628, *GC* rs7041, and *GC* rs4588 SNVs, both in ET patients and in controls. Table 1 shows the Akaike information criteria (AIC) for the genetic models for all SNVs analyzed. We selected the recessive model because it was the model with best AIC for the SNVs analyzed. The frequency of the rs7041CC genotype was significantly higher in ET patients under the recessive and the codominant models, both in the whole series (Table 1) and in men (Table 2). The same trend was observed in women, but the findings did not reach statistical significance in this subgroup. The frequencies of the genotypes of *VDR* rs2228570, *VDR* rs731236, *VDR* rs7975232, *VDR* rs739837, *VDR* rs78783628, and *GC* rs4588did not differ significantly between ET patients and controls, both considering the whole series (Table 1) or each gender analyzed separately (Table 2). The analysis of the pooled data of the present study with those of Saczi et al. [15] regarding *VDR* rs2228570, which involved a total of 511 ET patients (53.2% with familial ET) and 511 controls, showed significant differences in the genotype (under the recessive and codominant models, but not under the dominant one) between ET patients and controls (Table 3). Since the mean age of control individuals was slightly higher that than of the age at onset of patients, and it was lower that the age at sample collection of patients, we performed a logistic regression to adjust for age. The findings confirm the association of the rs7041 SNV under the recessive model, even after adjustment for age ($p = 0.001$), and it also confirmed a lack of significant association with the rest of SNVs. Therefore, putative differences in age do not modify the findings in this study.

The mean ± SD age at onset of tremor did not differ significantly between the 3 genotypes of each of the variants studied (Table 4).

Discussion

Among their physiological roles, vitamin D has several important actions on dopaminergic and, to a lesser extent, on the noradrenergic and serotoninergic systems [31]. In addition, VDR has shown a high expression in dopaminergic

Table 1 *VDR* and *GC* genotypes of patients with ET and healthy volunteers

Gene	Genotype	ET PATIENTS (N = 272, 544 alleles)	CONTROLS (N = 272, 544 alleles)	Akaike information criteria (AIC) for genetic models. (codominant, dominant, recessive, over dominant, additive)	OR recessive model (95% CI); P; Pc
VDR	rs2228570 (G/G)	117 (43.0; 37.1–48.9)	110 (40.4; 34.6–46.3)	757.99, 757.77, 756.02, 758.03, 756.81	0.68 (0.40–1.15); 0.146; 0.280
VDR	rs2228570 (G/A)	128 (47.1; 41.1–53.0)	124 (45.6; 39.7–51.5)		
VDR	rs2228570 (A/A)	27 (9.9; 6.4–13.5)	38 (14.0; 9.9–18.1)		
VDR	rs731236 (A/A)	110 (40.4; 34.6–46.3)	86 (31.6; 26.1–37.1)		
VDR	rs731236 (A/G)	125 (46.0; 40.0–51.9)	139 (51.1; 45.2–57.0)	755.26, 753,54, 756.73, 756.70, 753.63	0.75 (0.47–1.20); 0.235; 0.329
VDR	rs731236 (G/G)	37 (13.6; 9.5–17.7)	47 (17.3; 12.8–21.8)		
VDR	rs7975232 (C/C)	61 (22.4; 17.5–27.4)	51 (18.8; 14.1–23.4)		
VDR	rs7975232 (C/A)	138 (50.7; 44.8–56.7)	132 (48.5; 42.6–54.5)	757.53, 757.02, 755.89, 757.88, 755.63	0.75 (0.52–1.09); 0.133; 0.280
VDR	rs7975232 (A/A)	73 (26.8; 21.6–32.1)	89 (32.7; 27.1–38.3)		
VDR	rs739837 (G/G)	56 (20.7; 15.8–25.5)	51 (18.8; 14.1–23.4)		
VDR	rs739837 (G/T)	146 (53.9; 47.9–59.8)	137 (50.4; 44.4–56.3)	756.77, 756.44, 754.78, 756.09, 755.21	0.76 (0.53–1.11); 0.160; 0.280
VDR	rs739837 (T/T)	69 (25.5; 20.3–30.6)	84 (30.9; 25.4–36.4)		
VDR	rs78783628 (A/A)	67 (24.9; 19.7–30.1)	80 (29.4; 24.0–34.8)		
VDR	rs78783628 (A/−)	147 (54.6; 48.7–60.6)	134 (49.3; 43.3–55.2)	754.15, 752.58, 753.91, 752.40, 753,60	0.94 (0.63–1.43); 0.802; 0.802
VDR	rs78783628 (−/−)	55 (20.4; 15.6–25.3)	58 (21.3; 16.5–26.2)		
GC	rs7041 (A/A)	36 (13.3; 9.3–17.4)	52 (19.1; 14.4–23.8)		
GC	rs7041 (A/C)	128 (47.4; 41.5–53.4)	149 (54.8; 48.9–60.7)	745.89, 752.01, 744.65, 752.42, 744.77	1.82 (1.27–2.63); **0.001; 0.007**
GC	rs7041 (C/C)	106 (39.3; 33.4–45.1)	71 (26.1; 20.9–31.3)		
GC	rs4588 (G/G)	132 (48.9; 42.9–54.9)	118 (43.4; 37.5–49.3)		
GC	rs4588 (G/T)	111 (41.1; 35.2–47.0)	131 (48.2; 42.2–54.1)	754.61, 753.71, 754.98, 752.64, 754.85	1.20 (0.67–2.17); 0.534; 0.623
GC	rs4588 (T/T)	27 (10.0; 6.4–13.6)	23 (8.5; 5.1–11.8)		

Among cases, the genotype call rates were 99.6% for rs739837, 98.9% for rs78783628, and 99.3% for rs7041 and rs4588, whereas the call rates for the rest of genotypes were 100%. Among controls, the rate was 100% for all genotypes

nuclei such as the nucleus accumbens and the striatum, and other human brain areas [47]. In contrast, the expression of vitamin D-binding protein is relatively low in the rodent's brain [48]. While several studies suggested the possibility that vitamin D could have protective and symptomatic effects In Parkinson's disease (although this issue is controversial) [49, 50], to our knowledge, there are no reports regarding serum vitamin D levels or the effects of vitamin D treatment in ET.

The fact that several variants in the *VDR* and in the *GC-binding protein* genes have shown an association with the risk of other conditions that could be associated with ET such as Parkinson's disease [51], Alzheimer's disease-dementia-mild cognitive impairment [52, 53], and restless legs syndrome [54] makes reasonable to evaluate their influence in the risk of developing ET. Regarding the pathogenicity of the SNVs analyzed in this study, among *VDR* SNVs, rs2228570 been classified as pathogenic. It causes start loss and was classified a probably damaging according to PolyPhen, and as deleterious with low confidence by Sorting Intolerant From Tolerant (SIFT). Our findings, when combined with previous findings, indicate relationship with the risk of developing ET in agreement with the expected functional impact of this SNV. The rest of *VDR* SNVs were classified as non-pathogenic. Regarding *GC* SNVs, both cause amino acid substitutions, although both were classified as benign by PolyPhen and as tolerated by SIFT. However, one of these SNVs, rs7041, is strongly related to ET risk in our study and, therefore, this study raises the hypothesis that it might be pathogenic for ET, provided that our findings are confirmed by independent studies.

The main result of the present case–control association study was the association between the *GC* rs7041C allele and the risk of developing ET (this was found in the whole series but, after correction for multiple comparisons, was not significant when analyzed each gender separately, likely due to the sample size), similarly to the previously reported association of this variant with the risk for Parkinson's disease [30], although data from both studies need to be replicated. Despite that, in the current study, we did not find an association between *VDR* rs2228570 and ET, the pooled data of our series with that reported by Saczi et al. [15] suggest that carriers of the minor allele of this variant show decreased risk for ET. Data regarding *VDR* rs731236 showing lack of association with ET were in agreement with those of a previous study [14]. The lack of association of *VDR* rs731236,

Table 2 *VDR* and *GC* genotypes and allelic variants of patients with ET and healthy volunteers distributed by gender. The values in each cell represent number (percentage; 95% confidence intervals)

Gene	Genotype	*ET women (N = 141, 272 alleles)*	*Control women (N = 141, 272 alleles)*	OR recessive model (95% CI), P; Pc	*ET men (N = 131, 262 ALLELES)*	*Control men (N = 131, 262 ALLELES)*	OR recessive model (95% CI); P; Pc
VDR	rs2228570 (G/G)	60 (42.6; 34.4–50.7)	57 (40.4; 32.3–48.5)		57 (43.5; 35.0–52.0)	53 (40.5; 32.1–48.9)	
VDR	rs2228570 (G/A)	63 (44.7; 36.5–52.9)	64 (45.4; 37.2–53.6)	0.87 (0.44–1.72); 0.692; 0.969	65 (49.6; 41.1–58.2)	60 (45.8; 37.3–54.3)	0.46 (0.20–1.08); 0.067; 0.235
VDR	rs2228570 (A/A)	18 (12.8; 7.3–18.3)	20 (14.2; 8.4–19.9)		9 (6.9; 2.5–11.2)	18 (13.7; 7.8–19.6)	
VDR	rs731236 (A/A)	59 (41.8; 33.7–50.0)	45 (31.9; 24.2–39.6)		51 (38.9; 30.6–47.3)	41 (31.3; 23.4–39.2)	
VDR	rs731236 (A/G)	62 (44.0; 35.8–52.2)	72 (51.1; 42.8–59.3)	0.81 (0.42–1.54); 0.512; 0.896	63 (48.1; 39.5–56.6)	67 (51.1; 42.6–59.7)	0.70 (0.35–1.39); 0.303; 0.487
VDR	rs731236 (G/G)	20 (14.2; 8.4–19.9)	24 (17.0; 10.8–23.2)		17 (13.0; 7.2–18.7)	23 (17.6; 11.0–24.1)	
VDR	rs7975232 (C/C)	33 (23.4; 16.4–30.4)	26 (18.4; 12.0–24.8)		28 (21.4; 14.4–28.4)	25 (19.1; 12.4–25.8)	
VDR	rs7975232 (C/A)	71 (50.4; 42.1–58.6)	68 (48.2; 40.0–56.5)	0.71 (0.43–1.19); 0.193; 0.676	67 (51.1; 42.6–59.7)	64 (48.9; 40.3–57.4)	0.80 (0.47–1.37); 0.417, 0.487
VDR	rs7975232 (A/A)	37 (26.2; 19.0–33.5)	47 (33.3; 25.6–41.1)		36 (27.5; 19.8–35.1)	42 (32.1; 24.1–40.1)	
VDR	rs739837 (G/G)	29 (20.7; 14.0–27.4)	26 (18.4; 12.0–24.8)		27 (20.6; 13.7–27.5)	25 (19.1; 12.4–25.8)	
VDR	rs739837 (G/T)	74 (52.9; 44.6–61.1)	72 (51.1; 42.8–59.3)	0.82 (0.49–1.37); 0.450; 0.896	72 (55.0; 46.4–63.5)	65 (49.6; 41.1–58.2)	0.71 (0.41–1.22); 0.215; 0.487
VDR	rs739837 (T/T)	37 (26.4; 19.1–33.7)	43 (30.5; 22.9–38.1)		32 (24.4; 17.1–31.8)	41 (31.3; 23.4–39.2)	
VDR	rs78783628 (A/A)	36 (25.7; 18.5–33.0)	41 (29.1; 21.6–36.6)		31 (24.0; 16.7–31.4)	39 (29.8; 21.9–37.6)	
VDR	rs78783628 (A/–)	75 (53.6; 45.3–61.8)	70 (49.6; 41.4–57.9)	0.97 (0.54–1.72); 0.908; 1.000	72 (55.8; 47.2–64.4)	64 (48.9; 40.3–57.4)	0.93 (0.51–1.69); 0.809; 0.809
VDR	rs78783628 (–/–)	29 (20.7; 14.0–27.4)	30 (21.3; 14.5–28.0)		26 (20.2; 13.2–27.1)	28 (21.4; 14.4–28.4)	
GC	rs7041 (A/A)	18 (12.8; 7.3–18.3)	27 (19.1; 12.7–25.6)		18 (14.0; 8.0–19.9)	25 (19.1; 12.4–25.8)	
GC	rs7041 (A/C)	70 (49.6; 41.4–57.9)	76 (53.9; 45.7–62.1)	1.64 (0.98–2.70); 0.056; 0.392	58 (45.0; 36.4–53.5)	73 (55.7; 47.2–64.2)	2.08 (1.22–3.45); **0.006; 0.042**
GC	rs7041 (C/C)	53 (37.6; 29.6–45.6)	38 (27.0; 19.6–34.3)		53 (41.1; 32.6–49.6)	33 (25.2; 17.8–32.6)	
GC	rs4588 (G/G)	73 (51.8; 43.5–60.0)	61 (43.3; 35.1–51.4)		59 (45.7; 37.1–54.3)	57 (43.5; 35.0–52.0)	
GC	rs4588 (G/T)	55 (39.0; 31.0–47.1)	67 (47.5; 39.3–55.8)	1.00 (0.45–2.22); 1.000; 1.000	56 (43.4; 34.9–52.0)	64 (48.9; 40.3–57.4)	1.47 (0.63–3.45); 0.361; 0.487
GC	rs4588 (T/T)	13 (9.2; 4.4–14.0)	13 (9.2; 4.4–14.0)		14 (10.9; 5.5–16.2)	10 (7.6; 3.1–12.2)	

VDR rs7975232, *VDR* rs739837, *VDR* rs78783628, and *GC* rs4588 variants with ET found in this study has not been previously reported. Despite the association reported in the current study, the possibility of a direct biological evidence to the role of the vitamin D receptor or GC vitamin D binding protein in ET is difficult to explain. According to the previously mentioned data, we could speculate with the idea that *GC* rs4588, which is in strong linkage disequilibrium with *GC* rs3755967, could indirectly affect vitamin D levels and cause alterations in dopaminergic, noradrenergic, and serotoninergic systems [30].

The current study has as the main limitation the limited sample size. The controls were matched by sex and with the age at onset of patients, although the mean ± SD age of controls is slightly higher (51.3 years) than that of the age at onset of tremor (49.6 years) in ET patients. Although it

Table 3 *VDR* rs2228570 genotypes of patients with ET and healthy volunteers. Pooled data from the present study and the report by Saczi et al. [15]

Gene	Genotype	ET PATIENTS (N = 511, 1022 alleles)	CONTROLS (N = 511, 1022 alleles)	OR recessive model (95% CI); P
VDR	rs2228570 (G/G)	246 (48.1; 43.8–52.5)	224 (43.8; 39.5–48.1)	
VDR	rs2228570 (G/A)	227 (44.4; 40.1–48.7)	226 (44.2; 39.9–48.5)	0.59 (0.39–0.91); **0.015**
VDR	rs2228570 (A/A)	38 (7.4; 5.2–9.7)	61 (11.9; 9.1–14.7)	

Table 4 Age at onset or tremor according to the *VDR* and *GC* genotypes

Gene	Genotype	Age at onset (mean ± SD)	T-test compared to the non-mutated genotype (*P* value)
VDR	rs2228570 (G/G)	54.00 ± 19.03	Reference
VDR	rs2228570 (G/A)	49.06 ± 18.32	0.269
VDR	rs2228570 (A/A)	47.90 ± 21.68	0.246
VDR	rs731236 (A/A)	49.63 ± 19.75	Reference
VDR	rs731236 (A/G)	48.35 ± 20.02	0.646
VDR	rs731236 (G/G)	49.37 ± 19.82	0.949
VDR	rs7975232 (C/C)	47.15 ± 20.30	Reference
VDR	rs7975232 (C/A)	49.58 ± 19.09	0.436
VDR	rs7975232 (A/A)	49.76 ± 21.01	0.501
VDR	rs739837 (G/G)	49.70 ± 20.29	Reference
VDR	rs739837 (G/T)	49.89 ± 19.42	0.954
VDR	rs739837 (T/T)	46.26 ± 20.45	0.386
VDR	rs78783628 (A/A)	48.85 ± 20.22	Reference
VDR	rs78783628 (A/-)	50.03 ± 19.50	0.713
VDR	rs78783628 (-/-)	45.81 ± 19.95	0.448
GC	rs7041 (A/A)	52.41 ± 16.99	Reference
GC	rs7041 (A/C)	50.45 ± 18.63	0.596
GC	rs7041 (C/C)	46.01 ± 21.79	0.135
GC	rs4588 (G/G)	48.16 ± 21.04	Reference
GC	rs4588 (G/T)	49.67 ± 19.03	0.592
GC	rs4588 (T/T)	50.08 ± 17.41	0.673

should be possible that, eventually, some control individuals could develop ET, if we consider the prevalence of ET in Spain [55], it is unlikely that the percentage of subjects with the risk genotypes would develop ET in the time lapse between the mean age of controls and the mean age of cases, and therefore, it is unlikely that this could significantly affect the results. This is confirmed by the logistic regression analyses as described under results. Taking into consideration these limitations, our results suggest a possible role of *GC* rs7041 and *VDR* rs2228570 in the risk for ET.

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Data Availability All data related to the current study, intended for reasonable use, is available from J.A.G. Agúndez (University Institute of Molecular Pathology Biomarkers, University of Extremadura -UNEx ARADyAL Instituto de Salud Carlos III, Av/ de la Universidad S/N, E10071 Cáceres, Spain) and F.J. Jiménez-Jiménez (Section of Neurology, Hospital del Sureste, Arganda del Rey, Madrid, Spain).

Declarations

Ethical Approval and Consent to Participate The study was approved by the corresponding Ethics Committees of the Hospitals involved. Specifically, the Ethics Committees of University Hospital "Príncipe de Asturias," Universidad de Alcalá, Alcalá de Henares (Madrid, Spain) and University Hospital "Infanta Cristina" (Badajoz, Spain). Written informed consent was obtained from all the participants before study enrollment.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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