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SLC1A2 rs3764087 does not associate with essential tremor

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Abstract

A recent genome-wide association study of essential tremor (ET) patients from Germany has nominated *SLC1A2* rs3764087 as a novel risk factor for disease. This association was independently replicated in the Chinese population, albeit with an opposite direction of effect. To further define the role of *SLC1A2* in ET we genotyped rs3764087 in a North American series consisting of 1,356 ET patients and controls. Statistical analysis did not identify significant differences in genotype or allele frequencies between healthy controls and ET patients ($p>0.36$). These findings therefore do not support a role for *SLC1A2* rs3764087 in the susceptibility to ET in the North American population. Further studies in ethnically distinct populations of ET patients are necessary to understand whether genetic variability in *SLC1A2* affects disease risk for ET.

Keywords

Essential tremor; SLC1A2; association

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1 Introduction

Essential tremor (ET) is the most common movement disorder of the elderly. To date, two genome-wide association studies (GWAS) for ET have been reported.(Stefansson, et al., 2009, Thier, et al., 2012) The initial study in Icelandic patients identified variants in *LINGO1* associated with disease risk. This finding was confirmed by several studies, however others have not been able to replicate this association.(Jimenez-Jimenez, et al., 2012, Klebe, et al., 2010, Vilarino-Guell, et al., 2010) Their et al. nominated a variant in the *SLC1A2* gene from a second GWAS of ET patients from Germany.(Thier, et al., 2012) Although not initially reaching genome-wide significance, genotyping of additional cases and controls resulted in a significant association of one intronic *SLC1A2* variant (rs3764087) with disease risk. Recently, an independent replication study in ET patients from the Chinese population replicated the association between *SLC1A2* rs3764087 and disease; however, in contrast to the initial study, the minor allele was found to be decreased in patients.(Tan, et al., 2013) To further evaluate the association previously described between ET patients and *SLC1A2* we genotyped rs3764087 in two independent case-control series from North America.

2 Methods

We included 435 ET patients and 912 healthy controls from North America; detailed descriptives are provided in Table 1. All samples were of Caucasian descent, and all patients were examined and observed longitudinally by a movement disorder neurologist, diagnosed according to standard criteria, and satisfied clinical criteria for definite or probable ET. (Louis, et al., 1998) The ethical review board of each institution approved the study and all participants provided informed consent. Genotyping was performed using a TaqMan probe on an ABI7900. Individual genotypic associations and Hardy-Weinberg assessment were investigated by chi-square test.

3 Results

Genotyping frequencies for rs3764087 in patients and controls for both populations were consistent with Hardy-Weinberg equilibrium (p-value > 0.05). The minor allele frequency (MAF) of rs3764087 in the US and Canadian control series was 0.22 and 0.26 respectively, which is similar to those reported in the European (MAF = 0.22) and Asian (MAF = 0.19) populations.(Tan, et al., 2013, Thier, et al., 2012) However, in contrast to previous reports of association between ET and *SLC1A2* rs3764087, we did not observed statistically significant differences in genotype or allele frequencies between healthy controls and ET patients in either population or the combined dataset (Table 1). Power analysis estimates resulted in 86%, 57% and 97% probability of identifying a positive association ($p<0.05$) in the US, Canadian and combined series respectively, assuming an additive model with a genotype relative risk of 1.5, a disease allele frequency of 0.2, and a disease prevalence of 0.001.

4 Discussion

Despite the relatively large number of ET patients and controls examined in this study, our data does not support a role for *SLC1A2* rs3764087 in the susceptibility to ET. Thus our data provides conflicting evidence to the reports from European and Asian populations which identified significant associations between rs3764087 and ET, albeit with an opposite direction of effect.(Tan, et al., 2013, Thier, et al., 2012) Interestingly, the flip-flop of alleles associated with risk of disease between different studies, and conflicting reports of association is reminiscent of studies on *LINGO1* rs9652490 following its initial nomination from a GWAS of ET in the Icelandic population.(Jimenez-Jimenez, et al., 2012, Klebe, et al., 2010, Stefansson, et al., 2009, Vilarino-Guell, et al., 2010) The inconsistencies between replication studies of ET highlight the high level of heterogeneity in the disease resulting in additional challenges for the identification and validation of the genetic components implicated in disease susceptibility. In summary, our replication study in ET patients from the US and Canada does not support the previously described association between *SLC1A2* rs3764087 and risk of ET in the European or Asian populations. Further association analysis and gene sequencing studies in large cohorts of ET patients from ethnically distinct populations is necessary to elucidate whether genetic variability in *SLC1A2* has a true role in disease risk.

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Table 1

Sample descriptives and association analysis of *SLC1A2* rs3794087.

Population	Group	Samples	Gender	Age	Age at onset	rs3794087 n(%)			p-value		Odds ratio
			M:F ratio	mean (SD)	mean (SD)	GG	GT	TT	Genotype	Allele	(95% CI)
US	Patients	256	1:1.1	68.2 (11.9)	50.7 (20.1)	151 (59.0)	95 (37.1)	10 (3.9)	0.627	0.843	1.05 (0.79–1.41)
	Controls	726	1:1.4	65.3 (12.8)	NA	437 (60.2)	258 (35.5)	31 (4.3)			
Canada	Patients	179	1:1.7	73.3 (13.7)	55.3 (17.7)	100 (55.9)	66 (36.9)	13 (7.3)	0.392	0.417	1.14 (0.75–1.73)
	Controls	186	1:2.2	72.2 (12.5)	NA	110 (59.1)	66 (35.5)	10 (5.4)			
Combined	Patients	435	1:1.3	70.2 (12.9)	52.6 (19.3)	251 (57.7)	161 (37.0)	23 (5.3)	0.363	0.374	1.10 (0.87–1.39)
	Controls	912	1:1.5	66.7 (13.1)	NA	547 (60.0)	324 (35.5)	41 (4.5)			