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No association between polymorphisms in the glutamate transporter *SLC1A2* and Parkinson disease

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Essential tremor (ET) and Parkinson disease (PD) are clearly distinct disorders. However, there is considerable clinical and pathophysiological overlap.¹ ET patients are at an approximately fourfold risk to develop PD compared to population controls. Both, ET and PD, have a genetic component. For PD numerous monogenic forms are known and genome-wide-association-studies (GWAS) in sporadic patients have uncovered a number of disease associated genetic variants. For ET only two GWAS studies have been performed up to date.^{2,3} In one of them we discovered an association between variants in the major glutamate reuptake transporter of the brain (EAAT2 encoded by the *SLC1A* gene) and ET.³ The strongest association was found for the intronic single nucleotide polymorphism (SNP) *rs3794087*. To investigate whether SNPs in or around the *SLC1A2* gene are also associated with PD we undertook a two-part study. The study was approved by the local ethics committees and written informed consent was obtained from all participants. Firstly, we investigated the association between our ET lead SNP *rs3794087* and PD in three previously described large German PD case/control samples (1798 PD patients, 1482 controls, a detailed description of the samples can be found in reference ⁴). Genotyping was performed using a TaqMan[®] assay. Association was assessed using PLINK.⁵ We calculated Hardy-Weinberg equilibrium (HWE, p-exclusion <0.001) and association in the allelic model. Power calculations can be found in supporting figure 1. The genotyping rate of *rs3794087* was >95% and the SNP was in HWE. No significant p-values were obtained for *rs3794087*, neither in the complete sample (p=0.775), nor in the subsamples from Kiel (p=0.623),

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the region of the *SLC1A* gene typed in the first stage sample of a large GWAS performed for PD (1713 PD patients, 3978 controls, a detailed description of the samples can be found in reference ⁶). All SNPs were in HWE. Two SNPs (*rs12294045*, $p=0.034$; *rs3847618*, $p=0.035$) yielded nominally significant p-values. Both p-values do not withstand Bonferroni correction for multiple testing (Bonferroni corrected alpha-level $p<0.001$). The ET associated lead SNP *rs3794087* was excluded from the GWAS analysis because the samples are partially overlapping with the Tübingen samples from the first analysis. A list of all SNPs with allele frequencies and p-values can be found in supporting table 2. In summary, we conclude that we didn't find any evidence for association between SNPs in the *SLC1A2* gene and PD neither in our three German samples nor in the GWAS-sample which contains American and German samples. A previous GWAS identified association between SNPs in the *LINGO1* gene and ET.² Also in this case most groups, including our own, could not find association of these variants with PD.⁷ *SLC1A2* encodes the predominant glutamate reuptake transporter EAAT2 in the brain which removes glutamate from the synaptic cleft. Interestingly EAAT2 is strongly expressed in the inferior olive, a structure implicated in rhythm generation in ET but not in the substantia nigra which is subject to neurodegeneration in PD. Therefore we hypothesize that *SLC1A2* is an ET specific gene, not involved in the pathogenesis of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association results between SNP rs3794087 and PD

German samples (MAF – minor allele frequency)			
SNP <i>rs3794087</i>	MAF cases	MAF controls	P-value
whole sample	0.252	0.249	0.775
subs. Kiel	0.238	0.229	0.623
subs. Lübeck	0.273	0.273	0.998
subs. Tübingen	0.251	0.256	0.766