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Investigating the association and causal relationship between restless legs syndrome and essential tremor

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The genetic etiology of a common movement disorder, essential tremor (ET), has not been fully characterized. The ET phenotype consists of involuntary rhythmic shaking during voluntary movements in different regions of the body [1]. Another common movement disorder, restless legs syndrome (RLS), has been shown to occur comorbidly with ET [2,3]. With the introduction of the omnigenic model, a growing number of studies have begun investigating pleiotropy of genetic variants between many complex phenotypes. Given the clinical overlap of RLS and ET, a recent study investigated whether twenty RLS-associated genetic variants conferred ET risk in a Chinese population [4]. This study identified an ET-associated *MAP2K5/SKOR1* haplotype containing five SNPs: rs4489954, rs3784709, rs2241420, rs1026732, and rs6494696 [2]. The haplotype is positioned between two genes implicated in RLS, suggesting a genetic link between the two diseases. In the present study, we examined the same haplotype and SNPs genotyped in a large cohort of ET patients and controls to determine whether the same association exists within an ET North-Western European (CEU) population. Additionally, we used mendelian randomization (MR) to determine whether RLS—the top 20 SNPs from the recent RLS genome-wide association study (GWAS) were used as instruments [3]—is causative for ET.

The association between RLS variants and the risk of ET was investigated using the discovery stage genotypic data from the largest ET GWAS to date [5]. Briefly, samples were genotyped using the Axiom Genome-Wide North-Western European (CEU) 1 Array Plate (Affymetrix, California, United States) after obtaining ethical approval and informed consent. After appropriate quality controls, the filtered case and control cohorts consisted of 1778 ET patients and 5376 controls of CEU ancestry. Markers not directly genotyped were imputed using the Sanger Institute Imputation Service. Briefly, phasing was performed with EAGLE2 and imputation was done with PWBT using the Haplotype Reference Consortium Panel. Association testing between the phenotype and SNPs was done using PLINK v.1.90 following an additive logistic regression adjusted for sex and population stratification using the first ten dimensions of a multidimensional scaling matrix. Haplotype analysis was also done using PLINK v.1.90. Linkage disequilibrium (LD) was calculated between the previously reported haplotype SNPs using LDLink. Mendelian randomization was done using an inverse-variance weighted method to test for functional connectivity. A Bonferroni-corrected significance was set at $P = 0.00125$ (0.05/40).

None of the SNPs had a missingness rate greater than 2%, and all SNPs were in Hardy-Weinberg Equilibrium (SNPs removed if $P < 0.000001$). Of the 20 variants studied by Chan et al. [4], none were found to be significantly associated with ET (Table 1). All SNPs had a power > 0.95, following an additive model. Although a *MAP2K5/SKOR1* haplotype has previously been associated with ET in Chinese cohort, the GCGGG haplotype frequency (rs4489954, rs3784709, rs2241420, rs1026732, rs6494696 did not significantly differ between our ET cases (0.6727) and controls (0.6696) ($P = 0.7347$). All five haplotype SNPs had a $D' = 1$ and were completely linked ($P < 0.0001$). Next, we investigated whether RLS was a causal factor for ET through MR with the top 20 RLS GWAS SNPs as instruments (Supplementary Table 1). The SNPs were not heterogenous for Cochran's Q test ($Q = 14.993$, $P = 0.723$). RLS was found to not be a causal factor for ET ($\beta = -0.008$, CI = −0.327, 0.311, $P = 0.960$). The MR had a power of 0.82.

Our results do not suggest common variant pleiotropy between ET and RLS based on the GWAS-identified SNPs and mendelian randomization investigation. The complete LD between the haplotype SNPs and the lack of significant association with ET suggests that no RLS haplotype at this locus is associated with our ET cohort. Our study did not replicate the previously reported association between the *MAP2K5/SKOR1* haplotype and ET. This could be due to different ethnic populations having variable variant frequencies for the genes of interest or the large difference in cohort sizes. Moreover, the MR results do not provide evidence for a causal relationship between RLS and ET. However, we note that some RLS GWAS SNPs had lower imputation scores for our data.

There were some limitations with our investigation. First, power might be decreased when comparing European and Asian LD structures.

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Table 1
Haplotype-investigated SNPs in 1778 Essential tremor patients and 5376 controls.

CHR:POS	NT	rsID	Gene	MAF (A)	MAF (U)	P	OR(95% CI)	INFO (R^2)
2:66750017	TG	rs4544423	*MEIS1*	0.4064	0.3993	0.3044	1.0430 (0.9624–1.13)	0.970961
2:66758422	GA	rs6710341	*MEIS1*	0.1597	0.1533	0.1739	1.0790 (0.9669–1.204)	–
2:66764308	GA	rs12469063	*MEIS1*	0.2368	0.2377	0.7031	1.0180 (0.9275–1.118)	0.990409
2:66781453	GT	rs2300478	*MEIS1*	0.2413	0.2415	0.6594	1.0211 (0.9304–1.121)	–
2:68070225	AG	rs6747972	intergenic	0.4398	0.4473	0.7959	0.9895 (0.9133–1.072)	–
6:38365841	CT	rs9296249	*BTBD9*	0.2134	0.2269	0.2889	0.9497 (0.8632–1.045)	–
6:38365873	CT	rs9357271	*BTBD9*	0.2151	0.2281	0.308	0.9515 (0.8649–1.047)	–
6:38440970	GA	rs3923809	*BTBD9*	0.3037	0.3068	0.7812	0.9878 (0.906–1.077)	0.93024
9:8570779	CT	rs10977209	*PTPRD*	0.1347	0.1381	0.3447	0.9457 (0.8424–1.062)	–
9:8846955	AG	rs1975197	*PTPRD*	0.1682	0.1576	0.1094	1.0910 (0.9806–1.215)	–
9:9261737	AG	rs4626664	*PTPRD*	0.1597	0.1491	0.169	1.0791 (0.9681–1.204)	–
15:68036852	AG	rs12593813	*MAP2K5/SKOR1*	0.3383	0.3439	0.129	0.9370 (0.8614–1.019)	0.960339
15:68037578	AG	rs11635424	*MAP2K5/SKOR1*	0.3383	0.3439	0.129	0.9370 (0.8614–1.019)	0.96002
15:68072075	TG	rs4489954	*MAP2K5/SKOR1*	0.3102	0.3171	0.07606	0.9250 (0.8489–1.008)	–
15:68072275	TC	rs3784709	*MAP2K5/SKOR1*	0.3262	0.3299	0.1837	0.9440 (0.867–1.028)	–
15:68082816	AG	rs2241420	*MAP2K5/SKOR1*	0.2219	0.2301	0.01989	0.8913 (0.8091–0.982)	0.998803
15:68095085	AG	rs1026732	*MAP2K5/SKOR1*	0.3301	0.3326	0.2136	0.9477 (0.8707–1.031)	–
15:68103206	CG	rs6494696	*MAP2K5/SKOR1*	0.3301	0.333	0.1987	0.9459 (0.8691–1.03)	0.999549
16:52624738	TG	rs3104767	*TOX3*	0.4184	0.4186	0.4738	0.9713 (0.8968–1.052)	0.977201
16:52638503	CT	rs3104788	*TOX3*	0.4176	0.4166	0.5516	0.9760 (0.9009–1.057)	0.981049

Abbreviations: A, affected; CHR, chromosome; CI, confidence interval; MAF, minor allele frequency, NT, nucleotides; OR, odds ratio; POS, position (hg19); U, unaffected.

Second, incomplete penetrance of ET risk alleles, phenocopies and potential misdiagnosis could have reduced our statistical power to detect association. Third, we did not consider the effect of rare variants and copy number variants involving these genes as a cause of ET. In conclusion, our results suggest that common RLS-associated variants and the *MAP2K5/SKOR1* haplotype is not associated with ET and RLS is not a causal factor for ET.

Author's role

C.L. analyzed data, performed statistical analyses and drafted the manuscript. G.H. and Q.H. helped with analysis and revised the manuscript. S.L.G. helped with collecting data. A.D.L. helped with data analysis. P.A.D. oversaw the study design and revised the manuscript. G.A.R. supervised the study and revised the manuscript.

Conflicts of interest

All authors report no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.022.

References

[1] D. Haubenberger, M. Hallett, Essential tremor, N. Engl. J. Med. 378 (19) (2018) 1802–1810.
[2] G. Ondo William, D. Lai, Association between restless legs syndrome and essential tremor, Mov. Disord. 21 (4) (2005) 515–518.
[3] B. Schormair, C. Zhao, S. Bell, E. Tilch, A.V. Salminen, B. Pütz, Y. Dauvilliers, A. Stefani, B. Högl, W. Poewe, D. Kemlink, K. Sonka, C.G. Bachmann, W. Paulus, C. Trenkwalder, W.H. Oertel, M. Hornyak, M. Teder-Laving, A. Metspalu, G.M. Hadjigeorgiou, O. Polo, I. Fietze, O.A. Ross, Z. Wszolek, A.S. Butterworth, N. Soranzo, W.H. Ouwehand, D.J. Roberts, J. Danesh, R.P. Allen, C.J. Earley, W.G. Ondo, L. Xiong, J. Montplaisir, Z. Gan-Or, M. Perola, P. Vodicka, C. Dina, A. Franke, L. Tittmann, A.F.R. Stewart, S.H. Shah, C. Gieger, A. Peters, G.A. Rouleau, K. Berger, K. Oexle, E. Di Angelantonio, D.A. Hinds, B. Müller-Myhsok, J. Winkelmann, B. 23andMe Research Team, P. DESIR study group, E. Eschwège, F. Rancière, F. Alhenc-Gelas, Y. Gallois, A. Girault, F. Fumeron, M. Marre, R. Roussel, F. Bonnet, A. Bonnefond, S. Cauchi, P. Froguel, J. Cogneau, C. Born, E. Caces, M. Cailleau, O. Lantieri, J. Moreau, F. Rakotozafy, J. Tichet, S. Vol, M. Agee, B. Alipanahi, A. Auton, R.K. Bell, K. Bryc, S.L. Elson, P. Fontanillas, N.A. Furlotte, D.A. Hinds, B.S. Hromatka, K.E. Huber, A. Kleinman, N.K. Litterman, M.H. McIntyre, J.L. Mountain, C.A. Northover, S.J. Pitts, J.F. Sathirapongsasuti, O.V. Sazonova, J.F. Shelton, S. Shringarpure, C. Tian, J.Y. Tung, V. Vacic, C.H. Wilson, Identification of novel risk loci for restless legs syndrome in genome-wide association studies in individuals of European ancestry: a meta-analysis, Lancet Neurol. 16 (2017) 898–907, https://doi.org/10.1016/S1474-4422(17)30327-7.
[4] J. Chen, P. Huang, Y. He, J. Shen, J. Du, S. Cui, P. Cui, S. Chen, J. Ma, A Haplotype of MAP2K5/SKOR1 Was Associated with Essential Tremor in Chinese Population, Parkinsonism & related disorders, 2018.
[5] S.H. Muller, S.L. Girard, F. Hopfner, N.D. Merner, C.V. Bourassa, D. Lorenz, L.N. Clark, L. Tittmann, A.I. Soto-Ortolaza, S. Klebe, M. Hallett, S.A. Schneider, C.A. Hodgkinson, W. Lieb, Z.K. Wszolek, M. Pendziwiat, O. Lorenzo-Betancor, W. Poewe, S. Ortega-Cubero, K. Seppi, A. Rajput, A. Hussl, A.H. Rajput, D. Berg,

P.A. Dion, I. Wurster, J.M. Shulman, K. Srulijes, D. Haubenberger, P. Pastor, C. Vilarino-Guell, R.B. Postuma, G. Bernard, K.H. Ladwig, N. Dupre, J. Jankovic, K. Strauch, M. Panisset, J. Winkelmann, C.M. Testa, E. Reischl, K.E. Zeuner, O.A. Ross, T. Arzberger, S. Chouinard, G. Deuschl, E.D. Louis, G. Kuhlenbaumer, G.A. Rouleau, Genome-wide association study in essential tremor identifies three new loci, Brain: J. Neurol. 139 (Pt 12) (2016) 3163–3169.

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