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# Absence of Mutation Enrichment for Genes Phylogenetically Conserved in the Olivocerebellar Motor Circuitry in a Cohort of Canadian Essential Tremor Cases

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## Abstract

Essential Tremor is a prevalent neurological disorder of unknown etiology. Studies suggest that genetic factors contribute to this pathology. To date, no causative mutations in a gene have been reproducibly reported. All three structures of the olivocerebellar motor circuitry have been linked to Essential Tremor. We postulated that genes enriched for their expression in the olivocerebellar circuitry would be more susceptible to harbor mutations in Essential Tremor patients. A list of 11 candidate genes, enriched for their expression in the olivocerebellar circuitry, was assessed for their variation spectrum and frequency in a cohort of Canadian Essential Tremor cases. Our results from this list of 11 candidate genes do not support an association for Essential Tremor in our cohort of Canadian cases. The heterogenic nature of ET and modest size of the cohort used in this study are two confounding factors that could explain these results.

**Keywords** Essential Tremor · Movement disorder · Genetics · Inferior olive · Cerebellum

## Introduction

Essential Tremor (ET) is a prevalent neurological disorder of unknown etiology that is characterized by the presence of tremors during voluntary motion and affecting primarily the upper limbs [1]. Although non-life threatening, ET can be the cause of social embarrassment as well as functional impairments. The worldwide prevalence of ET is 0.9% in the general population and 4.6% in individuals ≥ 65 years old [2]. Twin studies have shown concordance varying between 60 and 93% in monozygotic twins, which suggests that genetic factors contribute to the pathology [3, 4]. Unfortunately, to date, no causative mutations in a gene have been reproducibly reported [5]. This is partly attributable to the heterogenic nature of the disorder and the fact that the exact pathophysiological origin of ET remains poorly understood. However, mounting

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evidence is pointing to dysfunction affecting the olivocerebellar motor circuitry [6].

Currently, all three structures (Purkinje cell layer, inferior olive, and deep cerebellar nuclei) comprising this circuitry have been linked to ET. Firstly, a common pharmacological rodent model of ET induced by harmaline administration specifically targets neurons populating the inferior olive that subsequently become synchronized with neurons of the deep cerebellar nuclei which in turn affect the onset of behavioral tremor [7, 8]. Secondly, $GABA_A$ receptor $\alpha 1^{-/-}$ mice exhibit an intention tremor phenotype, characteristic of ET, and a profound loss of Purkinje cell response to synaptic or exogenous GABA; interestingly, the "essential-like" tremor phenotype observed in the model is suppressed by the administration of medications used to treat ET patients [9]. Thirdly, in humans, functional imaging studies suggested abnormal activation of the inferior olive neurons in ET [10], whereas pathophysiological studies have demonstrated a reduction in the levels of specific GABA receptor isoforms in the dentate nucleus of post-mortem ET patients [11], and Purkinje cell loss as well as cerebellum abnormalities have been linked to ET [12–18].

Hence, based on these evidences, we postulated that genes enriched for their expression in the olivocerebellar circuitry and phylogenetically conserved from human to mouse would be more susceptible to harbor mutations in ET patients. To provide substantial evidence to this hypothesis, we first generated a list of 11 candidate genes using publicly available tools. These genes were then assessed for their variation spectrum and frequency in a cohort of Canadian ET cases. While our results from this preliminary list of 11 candidate genes do not support an association for ET in our cohort of Canadian cases, it is important to consider that ET is an heterogeneous genetic condition and up to 50% of individuals diagnosed with ET have been suggested to be misdiagnosed [19].

## Methods

**Patients** Details of the cohort used in this study have been described previously [20]. Briefly, ethics approval for the recruitment and genetic analysis of ET-affected individuals and their families has been granted at the following institutes: MUHC (McGill University Health Centre) (Roubank protocol no.: 14051), CRCHUM (Centre de recherche du Centre hospitalier de l'Université de Montréal) (project no.: ND043076). All diagnoses were reviewed by a senior neurologist. Exclusion criteria included (1) an identified cause of exaggerated physiological tremor, (2) other neurological deficits (Parkinsonisms, polyneuropathies, other) were present, and (3) an orthostatic tremor or (4) a psychogenic-like tremor. To focus our analysis on the hereditary form of ET (as opposed to senile tremor), we selected patients with a reported disease onset at < 50 years of age. Moreover, since ET is an adult onset disease, we only included controls > 70 years old, to control the possibility of including individuals who will develop the disorder later in life.

**Candidate Genes Enrichment Selection** Candidate genes were screened for their enriched expression in either the inferior olivary complex or the cerebellar nuclei in both human and mouse using publicly available genome wide data from the Allen Brain Atlas (http://www.brain-map.org/) [21]. To be retained as a candidate, a gene had to be enriched by a factor of at least two in the tested brain regions ($p$ value ≤ 0.05) and had to be found in both human and mouse enriched populations. Enrichment was evaluated based on the relative expression level compared to the closest adjacent brain structure used as background. In mouse, expression level of genes in the inferior olivary complex was compared to the medulla, whereas the expression level of genes in the cerebellar nuclei was compared to the cerebellum. A similar analysis was performed in human, where the expression level of genes in the inferior olivary complex was compared to their expression in the myencephalon and similarly, the expression level of genes in the cerebellar nuclei was compared to the cerebellum. Candidate genes were further interrogated for their enrichment in relevant gene ontology (GO) terms using the DAVID service (http://david.abcc.ncifcrf.gov/summary.jsp) [22, 23]. A significant $p$ value threshold was applied using a multiple testing correction (Bonferroni, $p$ value < 0.05).

**MIPs Design, Capture, and Post-Sequencing Analysis** MIPs have been designed using scripts and criteria that were described previously [20, 24]. Sequencing and analyses were carried out on our cohort of 266 cases and 287 controls. These comprise enrolled individuals from both French-Canadian and Western Canada descents [20]. Raw sequence data was processed using our bioinformatics pipeline. Overall, 96.4% of all candidate genes coding base pairs were covered by > 50 reads in across samples (coverage per gene, see supplementary Table 1). Based on the average sequencing quality in terms of coverage, we excluded eight individuals below 10X (four controls and four cases).

Raw sequencing has been processed as follows: (1) preprocessing, MIPs IDs were assigned to each raw sequencer read based on the arms sequence and then trimmomatic was used for base quality trimming of raw reads; (2) mapping, reads were aligned to the human reference genome (hg19) using the Burrows-Wheeler Aligner (BWA-MEM algorithm); (3) post-processing of the BWA-MEM alignment was performed using 1000 Genomes Phase I Indel calls; (4) the post-processed reads were compiled to *mpileup*, a format convenient for variant calling by VARSCAN, (5) variant calling was performed by VARSCAN to identify the variants above

**Table 1** 11 Candidate genes list details

| Gene name | Exon number | Gene length (bps) | Number of MIPs |
|---|---|---|---|
| *CACNA1C* | 55 | 13,480 | 191 |
| *CACNA1E* | 48 | 14,972 | 197 |
| *CACNA1G* | 38 | 8075 | 124 |
| *CACNB3* | 18 | 2958 | 50 |
| *CALM3* | 6 | 2277 | 28 |
| *CAMK2A* | 19 | 4918 | 73 |
| *GRIN3A* | 9 | 7771 | 84 |
| *GRM5* | 12 | 7957 | 89 |
| *HT2RC* | 7 | 4774 | 55 |
| *SLC17A6* | 12 | 3938 | 51 |
| *SLC1A1* | 12 | 3757 | 49 |

*bps* base pairs, *MIPs* molecular inversion probes

the mutation frequency of 20%, (6) the called variants were filtered based on their depth ≥ 50 using VCFtools, and (7) gene-based (e.g., protein coding change) as well as filter-based annotations (e.g., variants reported in public databases of healthy individuals (NHLBI Exome Variant Server [NHLBI-EVS]) were performed by ANNOVAR to unravel candidate functionally relevant variants. We performed an overall genotype quality control to exclude the variants that were missing genotypes in > 95% of individuals. Using PLINK29, we extracted the data to create input files for SKAT and tested the polymorphic variants for deviation from Hardy–Weinberg equilibrium (HWE). No deviations from HWE were observed in controls or cases.

**Statistical Analysis** Details of the statistical method have been described previously [20]. Briefly, we assessed for enrichment of potentially deleterious variants in ET cases by performing three different rare variants association tests. We first used the burden method that collapses all the rare variants located in our candidate gene regions into a single value, which is then tested for association with the phenotype [25]. We also carried out the sequence kernel association test (SKAT) [26] and an optimal unified SKAT (SKAT-O) [27] test. Gender identity or sex was also considered as a co-variate since one of the genes in our list was found on the X-chromosome (HTR2C). Statistical analyses were performed using the SKAT package 30 in R statistical software v.3.2.3 and results were considered statistically significant when $p$ values were ≤ 0.05 after Bonferroni correction.

## Results

Our list of candidate genes enriched for their expression in the olivocerebellar pathway was mined using the criteria described in the "Methods" section. Two lists of candidate genes were retained, with one comprising 53 candidate genes enriched for their expression in the inferior olivary complex and another comprising 246 additional candidate genes enriched for their expression in the cerebellar nuclei. Further investigations using gene ontology enrichment analyses performed with the DAVID service (http://david.abcc.ncifcrf.gov/summary.jsp) allowed to hone our list to 64 candidate genes significantly enriched in synaptic transmission categories (Bonferroni, $p < 0.05$) [22, 28].

Of these 64 candidate genes, 11 genes found in calcium and glutamate signaling pathways were retained for initial investigation in our cohort of ET patients (gene details, see Table 1). Calcium pathway-related genes were retained as highly plausible candidates based on the evidences supporting calcium-

**Table 2** 11 Candidate genes association test summary on missense variants only

| Gene name | Missense variants | *P* value SKAT | *P* value SKAT corrected | *P* value burden | *P* value burden corrected | *P* value SKAT-O | *P* value SKAT-O corrected |
|---|---|---|---|---|---|---|---|
| *CACNA1E* | 9 | 5.22E−01 | 1.00E+00 | 6.96E−01 | 1.00E+00 | 7.16E−01 | 1.00E+00 |
| *CAMK2A* | 1 | 1.67E−01 | 1.00E+00 | 1.67E−01 | 1.00E+00 | 1.67E−01 | 1.00E+00 |
| *SLC1A1* | 2 | 9.45E−02 | 8.50E−01 | 9.32E−02 | 8.39E−01 | 4.66E−02 | 4.19E−01 |
| *GRIN3A* | 11 | 1.00E+00 | 1.00E+00 | 7.89E−01 | 1.00E+00 | 1.00E+00 | 1.00E+00 |
| *SLC17A6* | 3 | 8.61E−01 | 1.00E+00 | 5.41E−01 | 1.00E+00 | 7.10E−01 | 1.00E+00 |
| *GRM5* | 0 | NA | NA | NA | NA | NA | NA |
| *CACNA1C* | 3 | 4.24E−01 | 1.00E+00 | 7.64E−01 | 1.00E+00 | 5.64E−01 | 1.00E+00 |
| *CACNB3* | 0 | NA | NA | NA | NA | NA | NA |
| *CACNA1G* | 4 | 8.74E−01 | 1.00E+00 | 6.40E−01 | 1.00E+00 | 8.01E−01 | 1.00E+00 |
| *CALM3* | 0 | NA | NA | NA | NA | NA | NA |
| *HTR2C* | 1 | 1.93E−02 | 1.74E−01 | 1.93E−02 | 1.74E−01 | 1.93E−02 | 1.74E−01 |
| Total | 34 | | | | | | |

*SKAT* sequence kernel association test, *SKAT-O* sequence kernel association test-optimal, *NA* non-applicable

dependent pathways in the generation of neuronal oscillations, resonance, and pacemaker activities [29–31]. Furthermore, one of our candidate genes, the $Ca_v3.1$ T-type $Ca^{2+}$ channel (*CACNA1G*), is implicated in modulating tremor rhythm pacemaker activity in the inferior olive, a phenomenon highly relevant to ET [8]. Glutamate signaling pathway members have been retained based on the alleviation of harmaline-induced tremors using NMDAR agonists, implicating glutamatergic signaling pathway and the inferior olive in ET [32, 33]. Furthermore, abnormal glutamatergic excitatory synaptic transmission between climbing fiber and Purkinje cells in ET patient cerebellar cortex has been observed [34].

A total of 74 single nucleotide variations (SNVs) in the protein coding region of our list of 11 genes were found by targeted re-sequencing in our curated cohort of 262 unrelated ET cases and 283 controls. Of these 74 variants, 34 were predicted to produce an incorrect amino acid incorporation in the gene coding sequence. Details of the number of variants per gene are highlighted in supplementary Table 2. A total of 55 cases and 51 unaffected individuals were carrier of at least one synonymous or non-synonymous mutation with a minor allele frequency < 0.01 in ExAC. We performed three separate gene-based association tests as previously described to jointly analyze the multiple variants identified in our study and to establish if one of our candidate genes could be considered as a risk factor for ET [20].We also performed an analysis using sex as a co-variate since *HTR2C* is found on the X-chromosome. Briefly, none of the tests used here reached a significantly statistical threshold (detailed results, see Table 2 and supplementary Tables 3, 4, and 5).

## Discussion

In this manuscript, we sought to test the hypothesis that genes, phylogenetically enriched for expression in the olivocerebellar circuitry in both human and mouse, are more susceptible to harbor mutations in ET patients. This assumed that phylogenetic conservation of expression would imply a similar function. As a discovery study, we chose an approach employing targeted high-throughput re-sequencing of a selected list of 11 candidate genes in a cohort of 266 cases and 287 controls of French-Canadian and Western Canada origin [20].

This initial investigation failed to reach significance for any of the candidate genes chosen in our list. The heterogenic nature of ET and modest size of the cohort used in this study are two confounding factors that could explain these results. Extending the current study to a larger list of genes enriched in the olivocerebellar circuitry and a larger cohort could help resolve this issue. This is especially important since more and more evidences from post-mortem studies are supporting the fact that a disruption in the olivocerebellar circuitry could explain the etiology of ET, a phenomenon that has failed to be reproducibly explained using conventional genetics approaches [35].

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## Compliance with Ethical Standards

Ethics approval for the recruitment and genetic analysis of ET-affected individuals and their families has been granted at the following institutes: MUHC (McGill University Health Centre) (Roubank protocol no.: 14051), CRCHUM (Centre de recherche du Centre hospitalier de l'Université de Montréal) (project no.: ND043076).

**Conflict of Interest** The authors declare that they have no conflict of interest.

## References

1. Deuschl G, Bain P, Brin M (1998) Consensus statement of the Movement Disorder Society on tremor. Ad hoc scientific committee. Mov Disord 13(Suppl 3):2–23
2. Louis ED, Ferreira JJ (2010) How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord 25(5):534–541. https://doi.org/10.1002/mds.22838
3. Tanner CM, Goldman SM, Lyons KE, Aston DA, Tetrud JW, Welsh MD, Langston JW, Koller WC (2001) Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. Neurology 57(8):1389–1391
4. Lorenz D, Frederiksen H, Moises H, Kopper F, Deuschl G, Christensen K (2004) High concordance for essential tremor in monozygotic twins of old age. Neurology 62(2):208–211
5. Schmouth JF, Dion PA, Rouleau GA (2014) Genetics of essential tremor: from phenotype to genes, insights from both human and mouse studies. Prog Neurobiol 119-120:1–19. https://doi.org/10.1016/j.pneurobio.2014.05.001
6. Bares M, Husarova I, Lungu OV (2012) Essential tremor, the cerebellum, and motor timing: towards integrating them into one complex entity. Tremor Other Hyperkinet Mov 2
7. de Montigny C, Lamarre Y (1973) Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. Brain Res 53(1):81–95
8. Park YG, Park HY, Lee CJ, Choi S, Jo S, Choi H, Kim YH, Shin HS et al (2010) Ca(V)3.1 is a tremor rhythm pacemaker in the inferior olive. Proc Natl Acad Sci U S A 107(23):10731–10736. https://doi.org/10.1073/pnas.1002995107
9. Kralic JE, Criswell HE, Osterman JL, O'Buckley TK, Wilkie ME, Matthews DB, Hamre K, Breese GR et al (2005) Genetic essential tremor in gamma-aminobutyric acidA receptor alpha1 subunit knockout mice. J Clin Invest 115(3):774–779. https://doi.org/10.1172/JCI23625
10. Boecker H, Wills AJ, Ceballos-Baumann A, Samuel M, Thompson PD, Findley LJ, Brooks DJ (1996) The effect of ethanol on alcohol-responsive essential tremor: a positron emission tomography study.

Ann Neurol 39(5):650–658. https://doi.org/10.1002/ana.410390515
11. Paris-Robidas S, Brochu E, Sintes M, Emond V, Bousquet M, Vandal M, Pilote M, Tremblay C et al (2012) Defective dentate nucleus GABA receptors in essential tremor. Brain 135(Pt 1):105–116. https://doi.org/10.1093/brain/awr301
12. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, Pahwa R, Lyons KE et al (2007) Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 130(Pt 12):3297–3307. https://doi.org/10.1093/brain/awm266
13. Babij R, Lee M, Cortes E, Vonsattel JP, Faust PL, Louis ED (2013) Purkinje cell axonal anatomy: quantifying morphometric changes in essential tremor versus control brains. Brain 136(Pt 10):3051–3061. https://doi.org/10.1093/brain/awt238
14. Louis ED, Babij R, Lee M, Cortes E, Vonsattel JP (2013) Quantification of cerebellar hemispheric purkinje cell linear density: 32 ET cases versus 16 controls. Mov Disord 28(13):1854–1859. https://doi.org/10.1002/mds.25629
15. Erickson-Davis CR, Faust PL, Vonsattel JP, Gupta S, Honig LS, Louis ED (2010) "Hairy baskets" associated with degenerative Purkinje cell changes in essential tremor. J Neuropathol Exp Neurol 69(3):262–271. https://doi.org/10.1097/NEN.0b013e3181d1ad04
16. Louis ED (2015) Linking essential tremor to the cerebellum: neuropathological evidence. Cerebellum 15:235–242. https://doi.org/10.1007/s12311-015-0692-6
17. Benito-Leon J, Labiano-Fontcuberta A (2016) Linking essential tremor to the cerebellum: clinical evidence. Cerebellum 15(3):253–262. https://doi.org/10.1007/s12311-015-0741-1
18. Filip P, Lungu OV, Manto MU, Bares M (2016) Linking essential tremor to the cerebellum: physiological evidence. Cerebellum 15(6):774–780. https://doi.org/10.1007/s12311-015-0740-2
19. Schrag A, Munchau A, Bhatia KP, Quinn NP, Marsden CD (2000) Essential tremor: an overdiagnosed condition? J Neurol 247(12):955–959
20. Houle G, Schmouth JF, Leblond CS, Ambalavanan A, Spiegelman D, Laurent SB, Bourassa CV, Panisset M et al (2017) Teneurin transmembrane protein 4 is not a cause for essential tremor in a Canadian population. Mov Disord 32:292–295. https://doi.org/10.1002/mds.26753
21. Ng L, Bernard A, Lau C, Overly CC, Dong HW, Kuan C, Pathak S, Sunkin SM et al (2009) An anatomic gene expression atlas of the adult mouse brain. Nat Neurosci 12(3):356–362. https://doi.org/10.1038/nn.2281
22. Huang da W, Sherman BT, Lempicki RA (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 4(1):44–57. https://doi.org/10.1038/nprot.2008.211
23. Schmouth JF, Arenillas D, Corso-Diaz X, Xie YY, Bohacec S, Banks KG, Bonaguro RJ, Wong SH et al (2015) Combined serial analysis of gene expression and transcription factor binding site prediction identifies novel-candidate-target genes of Nr2e1 in neocortex development. BMC Genomics 16:545. https://doi.org/10.1186/s12864-015-1770-3
24. O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A et al (2012) Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science 338(6114):1619–1622. https://doi.org/10.1126/science.1227764
25. Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X (2010) Powerful SNP-set analysis for case-control genome-wide association studies. Am J Hum Genet 86(6):929–942. https://doi.org/10.1016/j.ajhg.2010.05.002
26. Wu MC, Lee S, Cai T, Li Y, Boehnke M, Lin X (2011) Rare-variant association testing for sequencing data with the sequence kernel association test. Am J Hum Genet 89(1):82–93. https://doi.org/10.1016/j.ajhg.2011.05.029
27. Lee S, Emond MJ, Bamshad MJ, Barnes KC, Rieder MJ, Nickerson DA, Christiani DC, Wurfel MM et al (2012) Optimal unified approach for rare-variant association testing with application to small-sample case-control whole-exome sequencing studies. Am J Hum Genet 91(2):224–237. https://doi.org/10.1016/j.ajhg.2012.06.007
28. Dennis G Jr, Sherman BT, Hosack DA, Yang J, Gao W, Lane HC, Lempicki RA (2003) DAVID: database for annotation, visualization, and integrated discovery. Genome Biol 4(5):P3
29. Huguenard JR (1996) Low-threshold calcium currents in central nervous system neurons. Annu Rev Physiol 58:329–348. https://doi.org/10.1146/annurev.ph.58.030196.001553
30. Kim D, Song I, Keum S, Lee T, Jeong MJ, Kim SS, McEnery MW, Shin HS (2001) Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha(1G) T-type Ca(2+) channels. Neuron 31(1):35–45
31. McCormick DA, Bal T (1997) Sleep and arousal: thalamocortical mechanisms. Annu Rev Neurosci 20:185–215. https://doi.org/10.1146/annurev.neuro.20.1.185
32. Du W, Aloyo VJ, Harvey JA (1997) Harmaline competitively inhibits [3H]MK-801 binding to the NMDA receptor in rabbit brain. Brain Res 770(1–2):26–29
33. O'Hearn E, Molliver ME (2004) Administration of a non-NMDA antagonist, GYKI 52466, increases excitotoxic Purkinje cell degeneration caused by ibogaine. Neuroscience 127(2):373–383. https://doi.org/10.1016/j.neuroscience.2004.04.058
34. Lin CY, Louis ED, Faust PL, Koeppen AH, Vonsattel JP, Kuo SH (2014) Abnormal climbing fibre-Purkinje cell synaptic connections in the essential tremor cerebellum. Brain 137(Pt 12):3149–3159. https://doi.org/10.1093/brain/awu281
35. Wang J, Kelly GC, Tate WJ, Li YS, Lee M, Gutierrez J, Louis ED, Faust PL et al (2016) Excitatory amino acid transporter expression in the essential tremor dentate nucleus and cerebellar cortex: a post-mortem study. Parkinsonism Relat Disord 32:87–93. https://doi.org/10.1016/j.parkreldis.2016.09.003