Whole Exome Sequencing in Essential Tremor


Background

Essential tremor (ET) is a common movement disorder affecting about 5% of the population older than 65 years of age. The etiology of ET remains unclear. Given that up to 75% of patients have a positive family history and there is high concordance among monogenetic twins, ET is likely to have a genetic etiology. However, the search for genes has largely proven elusive. Genes previously implicated in ET are shown in Table 1, but most require replication.

Whole exome sequencing (WES) is a promising tool to elucidate the genetics of ET, potentially identifying genetic variants that could contribute to ET pathophysiology. Identifying genes associated with ET can aid in diagnosis, risk prediction and possibly targeted therapeutic strategies.

In this study, we performed WES in families and individual cases with ET and analyzed for pathogenic variants that may be associated with disease.

Subjects / Families

Our familial ET WES cohort of 20 cases (55% female) includes six subjects from three families (two related subjects per family) and 14 individual cases (one subject per family). The median age at tremor onset is 19.5 years (range 4-57 years) and the median age at enrollment was 52.5 years (range 38-75 years).

Methods

Three families and 14 individual ET cases were included in our WES cohort. We initially evaluated the presence of variants in genes previously described in the literature (Table 1). None were detected in our cohort. Next, we focused on two related subjects from each of three families. The common variants in each family were then filtered and ranked.

The variant filtering strategy is described in Figure 1. First, we identified shared variants among subjects from individuals in the same family. We identified frameshift insertions/deletions, stopgain single nucleotide variants (SNVs), non-synonymous SNVs, and splicing variants. Next, population-level filters were applied to enrich for rare variants. Cohorts with healthy controls (ARIC- Atherosclerosis Risk in Communities) and individuals not known to have a diagnosis of ET (ExAC-Exome Aggregation Consortium) were used to determine the frequency of candidate variants. Only variants with ARIC scores <10 and allele frequencies <0.001 in ExAC were included. Then, the Genotype-Tissue Expression (GTEx) project was used to select genes expressed in the brain.

Subsequently, non-synonymous SNVs variants were ranked based on in silico predictions of pathogenicity (SIFT, Polyphen2, Mutation Taster, LRT). Within each group, the variants were further ranked by Phylop score (>2.0), based on conservation of protein in 46 vertebrate species and by known function of the protein product. Variants were ranked in order of distance from the closest exon because variants closer to the exon are expected to be more deleterious.

Individual cases were evaluated for variants in the top prioritized genes within each family.

Table 1. Genes associated with ET.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>ExAC freq</th>
<th>Function</th>
<th>Present in members of the cohort</th>
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</table>

Conclusions / Future Directions

- We identified several promising candidate variants potentially associated with ET.
- Family-based WES analysis of subjects with ET is a promising approach to discover variants that contribute to disease.
- Additional sequencing of affected and unaffected family members as well as larger ET cohorts will be required to determine if the variants have a definite role in disease risk.

References


Funding source: RDINS037362 (NH / NINDS)