Published in final edited form as:

Rev Neurol (Paris). 2015 ; 171(6-7): 466–474. doi:10.1016/j.neurol.2015.02.015.

Challenges in Essential Tremor Genetics:

Les défis de la génétique du tremblement essentiel

Lorraine N. Clark^{1,2} and Elan D. Louis^{3,*}

¹Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, 650 West 168th Street, New York, NY, 10032, USA

²Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA

³Department of Neurology, Yale School of Medicine, Yale University, New Haven, CT, USA

Abstract

The field of essential tremor (ET) genetics remains extremely challenging. The relative lack of progress in understanding the genetic etiology of ET; however, does not reflect the lack of a genetic contribution, but rather, the presence of substantial phenotypic and genotypic heterogeneity. A meticulous approach to phenotyping is important for genetic research in ET. The only tool for phenotyping is the clinical history and examination. There is currently no ET-specific serum or imaging biomarker or defining neuropathological feature (e.g., a protein aggregate specific to ET) that can be used for phenotyping, and there is considerable clinical overlap with other disorders such as Parkinson's disease (PD) and dystonia. These issues greatly complicate phenotyping; thus, in some studies, as many as 30 – 50% of cases labeled as “ET” have later been found to carry other diagnoses (e.g., dystonia, PD) rather than ET. A cursory approach to phenotyping (e.g., merely defining ET as an “action tremor”) is likely a major issue in some family studies of ET, and this as well as lack of standardized phenotyping across studies and patient centers is likely to be a major contributor to the relative lack of success of genome wide association studies (GWAS). To dissect the genetic architecture of ET, whole genome sequencing (WGS) in carefully characterized and well-phenotyped discovery and replication datasets of large case-control and familial cohorts will likely be of value. This will allow specific hypotheses about the mode of inheritance and genetic architecture to be tested. There are a number of approaches that still remain unexplored in ET genetics, including the contribution of copy number variants (CNVs), ‘uncommon’ moderate effect alleles, ‘rare’ variant large effect alleles (including Mendelian and complex/polygenic modes of inheritance), *de novo* and gonadal mosaicism, epigenetic changes and non-coding variation. Using these approaches is likely to yield new ET genes.

*Correspondence: Dr. Elan Louis, Department of Neurology, Yale School of Medicine, Yale University, 800 Howard Ave # 2, New Haven, CT 06519, USA., Tel: 203 785-6599, elan.louis@yale.edu.

Déclaration d'intérêts

The authors declare that they have no conflicts of interest concerning this article

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Fibromuscular dysplasia; Carotid disease; Subarachnoid haemorrhage; Stroke; Prognosis; Intracranial aneurysm

Introduction

Essential tremor (ET) is a chronic, progressive neurologic disease [1]. Its hallmark motor feature is a 4–12 Hz kinetic tremor. Thus, tremor occurs during voluntary movements such as writing, eating, and drinking. At disease onset, the tremor affects the hands and arms, but it may also eventually spread to involve the head (i.e., neck), voice, jaw and other body regions [2]. Given the presence of etiological, clinical, pharmacological response profile and pathological heterogeneity, there is growing support for the idea that ET may be a family of diseases whose central defining feature is kinetic tremor of the arms, and therefore, it might more appropriately be referred to as “the essential tremors” [3].

The presence of both clinical as well as etiological heterogeneity has hindered gene identification. With a resultant lack of progress in the field of ET genetics, there are no appropriate animal models, and this has greatly hindered progress in the area of experimental therapeutics. Indeed, despite the high prevalence of ET, which is considered among most common movement disorders, and the highly familial nature of the disease, with an apparent Mendelian autosomal dominant pattern of inheritance, the identification of ET genes has remained elusive. The discovery of ET genes would have a major impact on the ET field, and the search for genes is an area of intense research. In this viewpoint article, we summarize the current literature and progress in ET genetics, the current challenges in ET genetics, and novel approaches in ET gene identification.

Etiology of ET – Genetic Vs. Environmental Factors

Both genetic and environmental (i.e., toxic) factors are likely contributors to disease etiology. Many large kindreds show an autosomal dominant pattern of inheritance [4], and in a familial aggregation study, first-degree relatives of ET patients were approximately five times more likely to develop the disease than were members of the general population, and ten times more likely if the proband’s tremor began at an early age [5]. Twin studies provide strong evidence for a genetic contribution to ET with heritability estimates ranging from 45–90% in monozygotic twins [6, 7]. However, the existence of sporadic cases, variability in age at onset in familial cases, and lack of complete disease concordance in monozygotic twins also argues for nongenetic (i.e., environmental) causes as well [8]. A number of environmental toxins are under investigation, including β -carboline alkaloids (e.g., harmaline, a dietary toxin) and lead [8].

Genetics - modes of inheritance and transmission in ET

Introduction

Historically, most studies have assumed a Mendelian inheritance pattern because of the high heritability and aggregation of ET in families [4, 6, 7, 9]. While other modes of inheritance,

including autosomal recessive and complex inheritance patterns are possible, published family and linkage studies suggest an autosomal dominant mode of inheritance with reduced penetrance [10–13]. Echoing this, our own experience with ET pedigrees strongly suggests an autosomal dominant mode of inheritance with reduced penetrance because:

- ET is inherited or transmitted from father to son, which suggests that ET is not an X-linked trait,
- ET is observed and inherited in 3 consecutive generations, which is never observed with recessive traits,
- Males and females are affected with approximately the same probability,
- In some instances, a family member has clearly transmitted the allele to offspring but does not express the disease, suggesting incomplete penetrance.

In reality; however, the genetic architecture of familial and sporadic ET is likely to be explained by several modes of inheritance and transmission including both Mendelian and complex disease patterns. These modes of inheritance and transmission are unlikely to be mutually exclusive, as we have learned from other common complex diseases, including Parkinson's disease (PD) [14], Alzheimer's disease (AD) [15] and schizophrenia [16], and it is likely that in ET both Mendelian/monogenic and complex disease patterns contribute to the genetic architecture.

In the paragraphs below we summarize the studies to date. Family and linkage studies have been largely unsuccessful at identifying ET genes [10, 11, 13], which may reflect the technological and analytic limitations of these studies, which were performed in 1997 and 2001 before the era of whole exome sequencing (WES) and whole genome sequencing (WGS). We also suspect that it reflects, in large measure, the challenges in phenotyping.

Genome wide association studies (GWAS) do not overwhelmingly support the common disease common variant (CDCV) hypothesis, with only two significant genes identified from two published GWAS [17, 18]. To date, a complex disease rare variant (CDRV) model has not been tested in ET studies.

Mendelian Inheritance and Monogenic Genes: Family Studies and Linkage

Many studies indicate that on the order of 30 – 70% of ET patients have a family history, with the vast majority (>80%) of young-onset (< 40 years old) cases reporting 1 affected first-degree relative [19]. To date, only three published genome wide linkage scans have been performed, all in north American or Icelandic ET families [10, 11, 13]. These studies led to the identification of genetic loci harboring ET genes on chromosomes 3q13 (ETM1; OMIM:190300) [10], 2p22-p25 (ETM2; OMIM:602134) [11], and 6p23 (ETM3; OMIM: 611456) [13]. Several studies have attempted to replicate linkage to ETM1 [12, 20, 21], ETM2 [12, 22, 23] and ETM3, without success (no LOD score >2.0), and the genes and causal mutations for these loci (ETM1, ETM2 and ETM3) have yet to be identified despite the reporting of linkage over a decade ago. Recently, using a linkage and WES approach, a p.Q290X mutation in the *fused in sarcoma/translated in liposarcoma (FUS/TLS)* gene was identified as the cause of ET in a large Quebec family [24]. Subsequent studies [25–27],

including our own, suggest that mutations in FUS are an extremely rare or family-specific cause of ET, and without functional studies, the pathogenicity of mutations identified so far (p.Q290X [24] and R377W reported in 1 patient with family history of ET [28]) is unknown. More recently, in a six-generation consanguineous Turkish kindred with both ET and PD, the mitochondrial serine protease HTRA2 p.G399S variant was shown to segregate with both phenotypes (PD and ET). The authors pointed out that all of the patients with the mixed phenotype (ET+PD) had severe ET and that the ET had been present for many years prior to the onset of PD. This makes it unlikely that the action tremor (“ET”) was merely an early motor sign of an evolving PD diagnosis. It also makes it less likely that the diagnosis was tremor-predominant PD rather than ET+PD. The diagnosis of PD required at least two cardinal features, which makes it less likely that these were merely longstanding ET cases who had developed isolated rest tremor. All affected individuals in the family were either heterozygous or homozygous for the HTRA2 variant and homozygosity was associated with earlier age at onset of tremor ($p < 0.0001$), more severe postural tremor ($p < 0.0001$), and more severe kinetic tremor ($p = 0.0019$) [29]. Follow up studies in ET family and case-control studies will be needed to determine whether HTRA2 represents a major ET susceptibility gene.

Complex Disease Inheritance Pattern: CDCV Hypothesis

Candidate Gene Studies—Since 2006, numerous genes have been evaluated as candidates for ET [30–53], based on either localization to linkage intervals or function (reviewed in Testa 2013 [30] and Jiménez-Jiménez 2013 [31]). These genes (table 1) provide at best weak evidence of association or no association at all (odds ratio [OR] range = 0.6 – 1.5; p range = 0.94 – 0.01). We and others have also evaluated additional genes that are associated with other neurodegenerative disease such as PD, dystonia, spinocerebellar ataxias and Fragile X Tremor Ataxia Syndrome. We did not observe an association with the PD genes *synuclein*, *alpha (non A4 component of amyloid precursor) (SNCA)* [52], *Leucine-rich repeat kinase 2 (LRRK2)* [53], *Glucosidase, beta, acid (GBA)* [53] or *Microtubule-associated protein tau (MAPT)* [42], nor did we identify pathogenic repeat expansions in the 10 common spinocerebellar ataxia loci (*SCA-1 (ATXN1)*, *SCA-2 (ATXN2)*, *SCA-3 (ATXN3)*, *SCA-6 (CACNA1A)*, *SCA-7 (ATXN7)*, *SCA-8 (ATXN8OS)*, *SCA-10 (ATXN10)*, *SCA-12 (PPP2R2B)*, *SCA-17 (TBP)* and *DRPLA (ATN1)* or *FRAXA* (unpublished results).

Genome Wide Association Studies (GWAS)—There are two published GWAS, which variably identify single nucleotide polymorphisms (SNPs) in the *Leucine rich repeat and Ig domain containing 1 (LINGO1)* gene or an intronic variant in the *SLC1A2* gene, with increased risk for ET (see below).

LINGO1: A genome-wide SNP association study of ET in an Icelandic population identified an association with a marker in the *LINGO1* gene [17]. Since the initial report, numerous studies, including our own, have replicated the association in independent ET case-control samples worldwide [54–64]. Collectively, these data suggest that the *LINGO1* SNP rs9652490 confers modest risk, with ORs in the range of 1.2 – 1.7, across different studies and populations. Although the majority of studies positively replicate the *LINGO1*

SNP rs9652490 association, some studies did not observe an association [59, 60, 62, 64]. One explanation for this lack of association may be allelic heterogeneity, and that rs9652490 does not confer risk in these populations, and that other variants in *LINGO1* are risk factors. Alternatively, clinical and genetic heterogeneity in ET may explain the lack of association. We and others have also shown that a highly related *LINGO1* family member (61% amino acid identity), the *leucine-rich repeat (LRR) and Ig domain containing two genes (LINGO2)*, might also be a risk factor for ET and PD, providing further evidence that the *LRR* gene pathway may be perturbed in ET pathogenesis [55]. To date, SNPs in *LINGO1* provide the strongest evidence for association with ET; however, data are not completely consistent.

SLC1A2: More recently, the SNP, rs3794087, located in *SLC1A2*, was identified in a two-stage European GWAS in a total of 990 ET cases and 1,537 controls, with an OR of ~1.4 [18]. To date, four studies have attempted to replicate the association of rs3794087 with ET in different populations, with conflicting results, some of which are positive (Chinese, Taiwanese) and others of which are negative (Spanish, North American) [37–39]. While further studies in different populations are needed to confirm the role of *SLC1A2* in ET, rs3794087 is unlikely to represent a major risk factor for ET.

To summarize, there is a lack of consistent and robust associations from candidate gene studies and GWAS.

Complex Disease Inheritance Pattern: CDRV Hypothesis

To date, there is only one published study, as described above, which performed WES (combined with linkage); the investigators studied a single large ET family from Quebec and identified a nonsense mutation in the *FUS/TLS* gene. There are no published studies that have performed WGS in ET families.

Current challenges in ET genetics

Why has the field of ET genetics made so little progress? Despite significant efforts to identify genes for ET, the field has made little progress. There are a number of possible explanations, some of which we highlight below.

Phenotyping

We would rank this as perhaps the top problem. A meticulous approach to phenotyping is critical for genetic research in ET. The ET diagnosis relies on clinical evaluation. The only tool for phenotyping is clinical. Thus, there is currently no serum/imaging biomarker or defining neuropathological feature (e.g., a protein aggregate specific to ET or a distinctive imaging finding) that can be used for diagnosis, and there is clinical overlap with other disorders such as PD and dystonia. These issues greatly complicate the diagnosis of ET; thus, in some studies, as many as 30 – 50% of cases labeled as “ET” have later been found to carry other diagnoses (e.g., dystonia, PD, and other disorders) rather than ET [65]. Poor attention to phenotyping (e.g., merely defining ET as an “action tremor”) is likely a major issue in some family studies of ET, and this as well as lack of standardized phenotyping across studies and patient centers is likely to be the major contributor to the lack of success

of GWAS. We have focused a great deal of attention on detailing the phenotypic characteristics that set ET apart. To begin with, in ET, the tremor itself is not merely a featureless, nondescript action tremor (although it is often viewed as such, and consequently there is a tendency to label many non-ET tremors as “ET”). Studies show that 30–50% of “ET” cases do not have ET [65–67]. Close inspection indicates that the tremor of ET is characterized by a definable and specific pattern of clinical features:

- kinetic tremor is nearly always greater than postural tremor [68, 69],
- the tremor involves movement at particular joints in specific directions [70, 71],
- the tremor is regularly recurrent and without directionality,
- the arm tremor is generally slightly asymmetric [72, 73],
- when drawing a spiral, a single tremor orientation axis is identifiable rather than multiple axes [74],
- intention tremor of the arms is seen on finger-nose-finger maneuver in approximately 50% of cases [75–77],
- rest tremor occurs in the arms (however, not the legs) in as many as 20% of cases [78],
- arm tremor precedes cranial tremor [79, 80],
- head (i.e., neck) tremor, unless very severe, generally resolves while supine [81],
- patients are often unaware of their head tremor, esp. if it is mild [82],
- the prevalence of neck tremor is greater than that of other cranial tremors [82, 83],
- and there is a tendency for tremor severity to increase over time [3, 84, 85].

These clinical features distinguish the tremor of ET from that of PD, dystonia, and drug-induced tremor [85].

Dystonia requires some additional discussion, as there are unresolved issues and some of the boundaries between ET and dystonia are unclear. The presence of mild dystonic movement or postures in the hands/arms (i.e., slight dystonic features) is not uncommon in ET patients, and it is questionable whether this physical finding merits any change in diagnosis, especially when in the presence of advanced, long-standing ET. By contrast, the presence of more marked dystonic features in the hands/arms or the presence of cranial dystonias (blepharospasm, torticollis) is considered an indicator of a mixed phenotype (ET + dystonia) [86]. The presence of more marked dystonia is even interpreted by some as an indicator that the patient has only dystonia, and that the “ET” is actually dystonic tremor [87, 88]. For genetic studies, the safest course is to separate patients with ANY dystonia from those with pure ET.

A related issue is the possibility, as discussed above, is that ET may represent a family of diseases rather than a single clinical-pathological entity.

Mode of inheritance

Mendelian and complex disease inheritance patterns may play a role in ET. While most studies have assumed an autosomal dominant mode of inheritance with reduced penetrance, other modes of inheritance including complex disease inheritance patterns may be important.

Genetic heterogeneity and sample size

Linkage and GWAS provide evidence for genetic heterogeneity in ET. Genetic heterogeneity has been observed in other neurodegenerative disorders such as PD, but does not preclude the identification of ET gene(s). One method to deal with the effects of genetic heterogeneity is to increase the sample size.

Molecular methods and statistical analysis of rare variants

A major roadblock to gene discovery, until recently, has been the lack of technological and analytical advances in genome wide sequencing and statistical models for multiple rare variants. Recent advances in Next generation sequencing (NGS) techniques, particularly for WGS, sequence data processing, decreased cost of WGS and faster computational power, together with new analytical methods to study rare variants, means that WGS and rare variant analysis is now feasible. While WES identifies on the order of ~20,000 coding variants per exome sequenced, WGS provides more uniform coverage and captures a range of genetic variation to allow analysis of both coding and noncoding variants in addition to indels and structural variation, with on average of ~4,000,000 variants per genome.

Novel approaches to ET gene identification

In understanding the genetic architecture of ET and novel approaches that can be used in gene identification, we turn to approaches being used to identify genes in other common complex diseases such as neuropsychiatric and neurodegenerative disease (AD and PD), and child neurodevelopmental disorders (e.g., autism).

To dissect the genetic architecture of ET, WGS in carefully characterized and well-phenotyped discovery and replication datasets of large case-control and familial cohorts is needed. This will allow specific hypotheses about the mode of inheritance and genetic architecture to be tested. As we outline in the following paragraphs, there are a number of approaches that still remain unexplored in ET genetics, including copy number variants (CNVs), the contribution of 'uncommon' moderate effect alleles, 'rare' variant large effect alleles (including Mendelian and complex/polygenic modes of inheritance), *de novo* and gonadal mosaicism, epigenetic changes and the contribution of non-coding variation. These approaches are likely to yield new ET genes.

Copy Number Variants

To date there are no published studies that have evaluated the contribution of CNVs to ET case-control studies or familial studies. As in other neurodegenerative disease [89, 90] and autism [91], CNVs are likely to play a significant role and be key contributors to the ET disease phenotype.

Uncommon Moderate Effect Alleles

GWAS of ET to date and the small number of significant loci (*LINGO1* and *SLC1A2*) do not explain the fraction of heritability of ET. GWAS designs and SNP genotyping arrays typically evaluate ‘common’ SNPs but exclude SNPs with MAF <5%. Therefore SNPs with MAF in the range 1–5% representing ‘uncommon’ moderate effect alleles are excluded from analysis. Re-evaluation of existing ET GWAS datasets together with rigorous clinical phenotyping of ET cases may yield new genome wide significant genes.

Rare Variant Large Effect Alleles

Mendelian—As we outline in the section ‘Mendelian Inheritance and Monogenic Genes: Family Studies and Linkage’, family studies and linkage approaches have been largely unsuccessful in identifying ET genes. As we note in the previous section, only two genes, *FUS* and *HTRA2*, have been identified in single ET families and, although further studies are needed to determine the contribution of *HTRA2* to ET, several studies including our own suggest *FUS* mutations are extremely rare and possibly isolated to this single Quebec family. In fact, our own experience with linkage and exome analysis of 50 early onset ET families, representing the largest familial and exome study to date, and that of others (including Dr. Coro Paisan Ruiz *pers. commun.*), suggests a substantial amount of genetic heterogeneity with no single mutation or different mutations within the same gene being shared across families. Our data suggest that either private mutations contribute to ET in these families or that a different mode of inheritance plays a role. To demonstrate that private mutations in single ET families do indeed contribute to the ET phenotype, functional studies will be needed to determine pathogenicity.

Complex/Polygenic Modes of Inheritance—As with ET, common genetic variants do not contribute to the genetic etiology of autism spectrum disorders (ASD), and recent studies have focused on the role of rare causal variants and de novo mutations [92, 93]. For ET, this approach remains largely unexplored. Like ET, ASD is a highly heritable disorder with a high monozygotic twin concordance rate for ASD at 70 to 90%. There are two possible explanations for this high heritability: a polygenic model involving several genes and environmental factors or *de novo* mutations with limited transmission. In the complex/polygenic model rare variant ‘burden’ analysis assessing the contribution of both inherited and *de novo* rare variants in genes in families may help in the identification of new genes. Most *de novo* mutations will occur in affected individuals and will not be transmitted, but exceptions include maternal transmission of mutations on the X chromosome to male offspring or gonadal mosaicism, which together would result in higher sibling recurrence rate. Pathway and gene network analysis of genes with rare variants may identify the functional impact, gene sets and connected pathways.

Epigenetic Changes

Epigenetic changes are likely to play a role in sporadic ET. Environmental exposures in both prenatal and postnatal life can lead to epigenetic changes. Although the number of published studies linking epigenetic changes to neurodegenerative disease such as PD and AD is rapidly increasing, a recent search of NCBI Pubmed found no published papers in this area

in ET. Exposure to environmental factors that have already been shown to effect and alter brain gene expression, such as dietary factors (Vitamin B-12 and myelination of the nervous system), metal exposure (lead, aluminium, zinc, iron, copper and mercury have all previously been linked to neurodegenerative disease), pesticides (organophosphates, organochlorines and carbamates), exercise, smoking and drug and chemical exposure (caffeine, alcohol, harmaline etc.) may all contribute to epigenetic changes in ET. Studying differences in patterns of histone acetylation and DNA methylation in ET case-control studies may identify genes that are subject to epigenetic changes in ET.

Contribution of non-coding Variation

One area of complex disease genetics that is gaining popularity, as we exhaust the findings in coding regions of the genome together with completion of the ENCODE project, is the identification of causal and risk variants outside the protein coding exome that affect gene transcription (promoter, enhancer elements), transcription of coding and non-coding RNAs or RNA functions and processing. This will be another important area of focus in ET genetics which, again, to date remains largely unexplored.

Conclusion

The field of ET genetics remains extremely challenging. The lack of progress; however, does not reflect the lack of genetic contribution, but rather, substantial phenotypic and genotypic heterogeneity. Dissecting the genetic architecture of ET using novel approaches such as WGS, CNVs and epigenetics is likely to help unravel the puzzle of ET genetics and identify genes and pathways that can be targeted for therapeutic intervention.

References

1. Louis ED. Clinical practice. Essential tremor. *N Engl J Med*. 2001; 345:887–891. [PubMed: 11565522]
2. Louis ED, Gerbin M, Galecki M. Essential tremor 10, 20, 30, 40: clinical snapshots of the disease by decade of duration. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2013; 20:949–954.
3. Louis ED. 'Essential Tremor' or 'the Essential Tremors': Is This One Disease or a Family of Diseases? *Neuroepidemiology*. 2013; 42:81–89. [PubMed: 24335621]
4. Bain PG, Findley LJ, Thompson PD, Gresty MA, Rothwell JC, Harding AE, Marsden CD. A study of hereditary essential tremor. *Brain*. 1994; 117 (Pt 4):805–824. [PubMed: 7922467]
5. Louis ED, Ford B, Frucht S, Barnes LF, MXT, Ottman R. Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. *Ann Neurol*. 2001; 49:761–769. [PubMed: 11409428]
6. Tanner CM, Goldman SM, Lyons KE, Aston DA, Tetrud JW, Welsh MD, Langston JW, Koller WC. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. *Neurology*. 2001; 57:1389–1391. [PubMed: 11673577]
7. Lorenz D, Frederiksen H, Moises H, Kopper F, Deuschl G, Christensen K. High concordance for essential tremor in monozygotic twins of old age. *Neurology*. 2004; 62:208–211. [PubMed: 14745055]
8. Louis ED. Environmental Epidemiology of Essential Tremor. *Neuroepidemiology*. 2008; 31:139–149. [PubMed: 18716411]
9. Findley LJ. Epidemiology and genetics of essential tremor. *Neurology*. 2000; 54

10. Gulcher JR, Jonsson P, Kong A, Kristjansson K, Frigge ML, Karason A, Einarsson IE, Stefansson H, Einarsson AS, Sigurthorsson S, et al. Mapping of a familial essential tremor gene, FET1, to chromosome 3q13. *Nature genetics*. 1997; 17:84–87. [PubMed: 9288103]
11. Higgins JJ, Pho LT, Nee LE. A gene (ETM) for essential tremor maps to chromosome 2p22-p25. *Movement disorders: official journal of the Movement Disorder Society*. 1997; 12:859–864. [PubMed: 9399207]
12. Kovach MJ, Ruiz J, Kimonis K, Mueed S, Sinha S, Higgins C, Elble S, Elble R, Kimonis VE. Genetic heterogeneity in autosomal dominant essential tremor. *Genet Med*. 2001; 3:197–199. [PubMed: 11388761]
13. Shatunov A, Sambuughin N, Jankovic J, Elble R, Lee HS, Singleton AB, Dagvadorj A, Ji J, Zhang Y, Kimonis VE, et al. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. *Brain*. 2006; 129:2318–2331. [PubMed: 16702189]
14. Gasser T, Hardy J, Mizuno Y. Milestones in PD genetics. *Movement disorders: official journal of the Movement Disorder Society*. 2011; 26:1042–1048. [PubMed: 21626549]
15. Karch CM, Cruchaga C, Goate AM. Alzheimer's disease genetics: from the bench to the clinic. *Neuron*. 2014; 83:11–26. [PubMed: 24991952]
16. Gratten J, Wray NR, Keller MC, Visscher PM. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature neuroscience*. 2014; 17:782–790. [PubMed: 24866044]
17. Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsson IH, Jonsdottir GA, Palsson ST, Jonsson T, Saemundsdottir J, Bjornsdottir G, et al. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. *Nature genetics*. 2009; 41:277–279. [PubMed: 19182806]
18. Thier S, Lorenz D, Nothnagel M, Poremba C, Papengut F, Appenzeller S, Paschen S, Hofschulte F, Hussl AC, Hering S, et al. Polymorphisms in the glial glutamate transporter SLC1A2 are associated with essential tremor. *Neurology*. 2012; 79:243–248. [PubMed: 22764253]
19. Louis ED, Dogu O. Does age of onset in essential tremor have a bimodal distribution? Data from a tertiary referral setting and a population-based study. *Neuroepidemiology*. 2007; 29:208–212. [PubMed: 18043006]
20. Illarioshkin SN, Rakhmonov RA, Ivanova-Smolenskaia IA, Brice A, Markova ED, Miklina NI, Kliushnikov SA, Limborskaia SA. Molecular genetic analysis of essential tremor. *Genetika*. 2002; 38:1704–1709. [PubMed: 12575458]
21. Lucotte G, Lagarde JP, Funalot B, Sokoloff P. Linkage with the Ser9Gly DRD3 polymorphism in essential tremor families. *Clin Genet*. 2006; 69:437–440. [PubMed: 16650084]
22. Higgins JJ, Loveless JM, Jankovic J, Patel PI. Evidence that a gene for essential tremor maps to chromosome 2p in four families. *Movement disorders: official journal of the Movement Disorder Society*. 1998; 13:972–977. [PubMed: 9827627]
23. Higgins JJ, Lombardi RQ, Pucilowska J, Jankovic J, Tan EK, Rooney JP. A variant in the HS1-BP3 gene is associated with familial essential tremor. *Neurology*. 2005; 64:417–421. [PubMed: 15699368]
24. Merner ND, Girard SL, Catoire H, Bourassa CV, Belzil VV, Riviere JB, Hince P, Levert A, Dionne-Laporte A, Spiegelman D, et al. Exome sequencing identifies FUS mutations as a cause of essential tremor. *American journal of human genetics*. 2012; 91:313–319. [PubMed: 22863194]
25. Parmalee N, Mirzozoda K, Kisselev S, Merner N, Dion P, Rouleau G, Clark L, Louis ED. Genetic analysis of the FUS/TLS gene in essential tremor. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2013; 20:534–539.
26. Ortega-Cubero S, Lorenzo-Betancor O, Lorenzo E, Alonso E, Coria F, Pastor MA, Fernandez-Santiago R, Marti MJ, Ezquerra M, Valleoriola F, et al. Fused in Sarcoma (FUS) gene mutations are not a frequent cause of essential tremor in Europeans. *Neurobiology of aging*. 2013; 34:2441 e2449–2441 e2411. [PubMed: 23731953]
27. Labbe C, Soto-Ortolaza AI, Rayaprolu S, Harriott AM, Strongosky AJ, Uitti RJ, Van Gerpen JA, Wszolek ZK, Ross OA. Investigating the role of FUS exonic variants in Essential Tremor. *Parkinsonism & related disorders*. 2013

28. Rajput A, Rajput AH, Rajput ML, Encarnacion M, Bernales CQ, Ross JP, Farrer MJ, Vilarino-Guell C. Identification of FUS p.R377W in essential tremor. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2014; 21:361–363.
29. Unal Gulsuner H, Gulsuner S, Mercan FN, Onat OE, Walsh T, Shahin H, Lee MK, Dogu O, Kansu T, Topaloglu H, et al. Mitochondrial serine protease HTRA2 p.G399S in a kindred with essential tremor and Parkinson disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2014; 111:18285–18290. [PubMed: 25422467]
30. Testa CM. Key issues in essential tremor genetics research: Where are we now and how can we move forward? *Tremor and other hyperkinetic movements*. 2013; 3
31. Jimenez-Jimenez FJ, Alonso-Navarro H, Garcia-Martin E, Lorenzo-Betancor O, Pastor P, Agundez JA. Update on genetics of essential tremor. *Acta neurologica Scandinavica*. 2013; 128:359–371. [PubMed: 23682623]
32. Tan EK, Prakash KM, Fook-Chong S, Yih Y, Chua E, Lum SY, Wong MC, Pavanni R, Zhao Y. DRD3 variant and risk of essential tremor. *Neurology*. 2007; 68:790–791. [PubMed: 17339592]
33. Blair MA, Ma S, Phibbs F, Fang JY, Cooper MK, Davis TL, Hedera P. Reappraisal of the role of the DRD3 gene in essential tremor. *Parkinsonism & related disorders*. 2008
34. Vitale C, Gulli R, Ciotti P, Scaglione C, Bellone E, Avanzino L, Lantieri F, Abbruzzese G, Martinelli P, Barone P, et al. DRD3 Ser9Gly variant is not associated with essential tremor in a series of Italian patients. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2008; 15:985–987.
35. Lorenz D, Klebe S, Stevanin G, Thier S, Nebel A, Feingold J, Frederiksen H, Denis E, Christensen K, Schreiber S, et al. Dopamine receptor D3 gene and essential tremor in large series of German, Danish and French patients. *European journal of human genetics: EJHG*. 2009; 17:766–773. [PubMed: 19092771]
36. Shatunov A, Jankovic J, Elble R, Sambuughin N, Singleton A, Hallett M, Goldfarb L. A variant in the HS1-BP3 gene is associated with familial essential tremor. *Neurology*. 2005; 65:1995. author reply 1995. [PubMed: 16380635]
37. Tan EK, Foo JN, Tan L, Au WL, Prakash KM, Ng E, Ikram MK, Wong TY, Liu JJ, Zhao Y. SLC1A2 variant associated with essential tremor but not Parkinson disease in Chinese subjects. *Neurology*. 2013; 80:1618–1619. [PubMed: 23596072]
38. Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P, Ortega-Cubero S, Lopez-Alburquerque T, Agundez JA, Jimenez-Jimenez FJ. No association of the SLC1A2 rs3794087 allele with risk for essential tremor in the Spanish population. *Pharmacogenetics and genomics*. 2013; 23:587–590. [PubMed: 23949322]
39. Ross JP, Rayaprolu S, Bernales CQ, Soto-Ortolaza AI, van Gerpen J, Uitti RJ, Wszolek ZK, Rajput A, Rajput AH, Rajput ML, et al. SLC1A2 rs3794087 does not associate with essential tremor. *Neurobiology of aging*. 2014; 35:935 e939–910. [PubMed: 24139280]
40. Vilarino-Guell C, Soto-Ortolaza AI, Rajput A, Mash DC, Papapetropoulos S, Pahwa R, Lyons KE, Uitti RJ, Wszolek ZK, Dickson DW, et al. MAPT H1 haplotype is a risk factor for essential tremor and multiple system atrophy. *Neurology*. 2011; 76:670–672. [PubMed: 21321341]
41. Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P, Lopez-Alburquerque T, Samaranch L, Lorenzo E, Agundez JA, et al. H1-MAPT and the Risk for Familial Essential Tremor. *PloS one*. 2012; 7:e41581. [PubMed: 22911817]
42. Clark LN, Liu X, Parmalee NL, Hernandez N, Louis ED. The microtubule associated protein tau H1 haplotype and risk of essential tremor. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2013
43. Sazci A, Ergul E, Bayulkem K. Association of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene in patients with essential tremor in Turkey. *Movement disorders: official journal of the Movement Disorder Society*. 2004; 19:1472–1476. [PubMed: 15390052]
44. Xiao Y, Zhang BS. Association of the polymorphism in alpha-2 macroglobulin gene with essential tremor and Parkinson's disease. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2006; 23:84–85. [PubMed: 16456795]

45. Alonso-Navarro H, Martinez C, Garcia-Martin E, Benito-Leon J, Garcia-Ferrer I, Vazquez-Torres P, Puertas I, Lopez-Alburquerque T, Agundez JA, Jimenez-Jimenez FJ. CYP2C19 polymorphism and risk for essential tremor. *Eur Neurol*. 2006; 56:119–123. [PubMed: 16960452]
46. Martinez C, Garcia-Martin E, Alonso-Navarro H, Jimenez-Jimenez FJ, Benito-Leon J, Garcia-Ferrer I, Vazquez-Torres P, Puertas I, Zurdo JM, Lopez-Alburquerque T, et al. Changes at the CYP2C locus and disruption of CYP2C8/9 linkage disequilibrium in patients with essential tremor. *Neuromolecular medicine*. 2007; 9:195–204. [PubMed: 17627038]
47. Martinez C, Garcia-Martin E, Alonso-Navarro H, Benito-Leon J, Puertas I, Rubio L, Lopez-Alburquerque T, Agundez JA, Jimenez-Jimenez FJ. Alcohol dehydrogenase 2 genotype and allelic variants are not associated with the risk for essential tremor. *Clin Neuropharmacol*. 2007; 30:196–200. [PubMed: 17762315]
48. Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Puertas I, Rubio L, Lopez-Alburquerque T, Agundez JA, Jimenez-Jimenez FJ. Paraoxonase 1 (PON1) polymorphisms and risk for essential tremor. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2010; 17:879–881.
49. Deng H, Xie WJ, Le WD, Huang MS, Jankovic J. Genetic analysis of the GABRA1 gene in patients with essential tremor. *Neuroscience letters*. 2006; 401:16–19. [PubMed: 16530959]
50. Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P, Puertas I, Rubio L, Lopez-Alburquerque T, Agundez JA, et al. Gamma-aminobutyric acid (GABA) receptor rho (GABRR) polymorphisms and risk for essential tremor. *Journal of neurology*. 2011; 258:203–211. [PubMed: 20820800]
51. Thier S, Kuhlenbaumer G, Lorenz D, Nothnagel M, Nebel A, Christensen K, Schreiber S, Deuschl G, Klebe S. GABA(A) receptor- and GABA transporter polymorphisms and risk for essential tremor. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2011; 18:1098–1100.
52. Ross OA, Conneely KN, Wang T, Vilarino-Guell C, Soto-Ortolaza AI, Rajput A, Wszolek ZK, Uitti RJ, Louis ED, Clark LN, et al. Genetic variants of alpha-synuclein are not associated with essential tremor. *Movement disorders: official journal of the Movement Disorder Society*. 2011; 26:2552–2556. [PubMed: 22025277]
53. Clark LN, Kisselev S, Park N, Ross B, Verbitsky M, Rios E, Alcalay RN, Lee JH, Louis ED. Mutations in the Parkinson's disease genes, Leucine Rich Repeat Kinase 2 (LRRK2) and Glucocerebrosidase (GBA), are not associated with essential tremor. *Parkinsonism & related disorders*. 16:132–135. [PubMed: 19527940]
54. Tan EK, Teo YY, Prakash KM, Li R, Lim HQ, Angeles D, Tan LC, Au WL, Yih Y, Zhao Y. LINGO1 variant increases risk of familial essential tremor. *Neurology*. 2009; 73:1161–1162. [PubMed: 19805735]
55. Vilarino-Guell C, Wider C, Ross OA, Jasinska-Myga B, Kachergus J, Cobb SA, Soto-Ortolaza AI, Behrouz B, Heckman MG, Diehl NN, et al. LINGO1 and LINGO2 variants are associated with essential tremor and Parkinson disease. *Neurogenetics*.
56. Thier S, Lorenz D, Nothnagel M, Stevanin G, Durr A, Nebel A, Schreiber S, Kuhlenbaumer G, Deuschl G, Klebe S. LINGO1 polymorphisms are associated with essential tremor in Europeans. *Movement disorders: official journal of the Movement Disorder Society*. 2010; 25:717–723. [PubMed: 20310002]
57. Vilarino-Guell C, Ross OA, Wider C, Jasinska-Myga B, Cobb SA, Soto-Ortolaza AI, Kachergus JM, Keeling BH, Dachsel JC, Melrose HL, et al. LINGO1 rs9652490 is associated with essential tremor and Parkinson disease. *Parkinsonism & related disorders*. 2010; 16:109–111. [PubMed: 19720553]
58. Clark LN, Park N, Kisselev S, Rios E, Lee JH, Louis ED. Replication of the LINGO1 gene association with essential tremor in a North American population. *European journal of human genetics: EJHG*.
59. Wu YW, Rong TY, Li HH, Xiao Q, Fei QZ, Tan EK, Ding JQ, Chen SD. Analysis of Lingo1 variant in sporadic and familial essential tremor among Asians. *Acta neurologica Scandinavica*. 2011; 124:264–268. [PubMed: 21158743]
60. Lorenzo-Betancor O, Garcia-Martin E, Cervantes S, Agundez JA, Jimenez-Jimenez FJ, Alonso-Navarro H, Luengo A, Coria F, Lorenzo E, Irigoyen J, et al. Lack of association of LINGO1

- rs9652490 and rs11856808 SNPs with familial essential tremor. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2011; 18:1085–1089.
61. Bourassa CV, Riviere JB, Dion PA, Bernard G, Diab S, Panisset M, Chouinard S, Dupre N, Fournier H, Raelson J, et al. LINGO1 variants in the French-Canadian population. *PloS one*. 2011; 6:e16254. [PubMed: 21264305]
 62. Radovica I, Inashkina I, Smeltere L, Vitols E, Jankevics E. Screening of 10 SNPs of LINGO1 gene in patients with essential tremor in the Latvian population. *Parkinsonism & related disorders*. 2012; 18:93–95. [PubMed: 21741293]
 63. Jimenez-Jimenez FJ, Garcia-Martin E, Lorenzo-Betancor O, Pastor P, Alonso-Navarro H, Agundez JA. LINGO1 and risk for essential tremor: results of a meta-analysis of rs9652490 and rs11856808. *Journal of the neurological sciences*. 2012; 317:52–57. [PubMed: 22425540]
 64. Zuo X, Jiang H, Guo JF, Yu RH, Sun QY, Hu L, Wang L, Yao LY, Shen L, Pan Q, et al. Screening for two SNPs of LINGO1 gene in patients with essential tremor or sporadic Parkinson's disease in Chinese population. *Neuroscience letters*. 2010; 481:69–72. [PubMed: 20600614]
 65. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? *Arch Neurol*. 2006; 63:1100–1104. [PubMed: 16908735]
 66. Schrag A, Muenchau A, Bhatia KP, Quinn NP, Marsden CD. Overdiagnosis of essential tremor. *Lancet*. 1999; 353:1498–1499. [PubMed: 10232326]
 67. Schrag A, Munchau A, Bhatia KP, Quinn NP, Marsden CD. Essential tremor: an overdiagnosed condition? *Journal of neurology*. 2000; 247:955–959. [PubMed: 11200689]
 68. Brennan KC, Jurewicz EC, Ford B, Pullman SL, Louis ED. Is essential tremor predominantly a kinetic or a postural tremor? A clinical and electrophysiological study. *Movement disorders: official journal of the Movement Disorder Society*. 2002; 17:313–316. [PubMed: 11921117]
 69. Louis ED. The primary type of tremor in essential tremor is kinetic rather than postural: cross-sectional observation of tremor phenomenology in 369 cases. *European journal of neurology: the official journal of the European Federation of Neurological Societies*. 2013; 20:725–727.
 70. Thenganatt MA, Louis ED. Distinguishing essential tremor from Parkinson's disease: bedside tests and laboratory evaluations. *Expert review of neurotherapeutics*. 2012; 12:687–696. [PubMed: 22650171]
 71. Sternberg EJ, Alcalay RN, Levy OA, Louis ED. Postural and Intention Tremors: A Detailed Clinical Study of Essential Tremor vs. Parkinson's Disease. *Front Neurol*. 2013; 4:51. [PubMed: 23717300]
 72. Louis ED, Wendt KJ, Pullman SL, Ford B. Is essential tremor symmetric? Observational data from a community-based study of essential tremor. *Arch Neurol*. 1998; 55:1553–1559. [PubMed: 9865800]
 73. Phibbs F, Fang JY, Cooper MK, Charles DP, Davis TL, Hedera P. Prevalence of unilateral tremor in autosomal dominant essential tremor. *Movement disorders: official journal of the Movement Disorder Society*. 2009; 24:108–111. [PubMed: 18973247]
 74. Louis ED, Yu Q, Floyd AG, Moskowitz C, Pullman SL. Axis is a feature of handwritten spirals in essential tremor. *Movement disorders: official journal of the Movement Disorder Society*. 2006; 21:1294–1295. [PubMed: 16673396]
 75. Deuschl G, Wenzelburger R, Loffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. *Brain*. 2000; 123 (Pt 8):1568–1580. [PubMed: 10908187]
 76. Louis ED, Frucht SJ, Rios E. Intention tremor in essential tremor: Prevalence and association with disease duration. *Movement disorders: official journal of the Movement Disorder Society*. 2009
 77. Leegwater-Kim J, Louis ED, Pullman SL, Floyd AG, Borden S, Moskowitz CB, Honig LS. Intention tremor of the head in patients with essential tremor. *Movement disorders: official journal of the Movement Disorder Society*. 2006; 21:2001–2005. [PubMed: 16960854]
 78. Cohen O, Pullman S, Jurewicz E, Watner D, Louis ED. Rest tremor in patients with essential tremor: prevalence, clinical correlates, and electrophysiologic characteristics. *Arch Neurol*. 2003; 60:405–410. [PubMed: 12633153]

79. Hubble JP, Busenbark KL, Pahwa R, Lyons K, Koller WC. Clinical expression of essential tremor: effects of gender and age. *Movement disorders: official journal of the Movement Disorder Society*. 1997; 12:969–972. [PubMed: 9399222]
80. Hardesty DE, Maraganore DM, Matsumoto JY, Louis ED. Increased risk of head tremor in women with essential tremor: longitudinal data from the Rochester Epidemiology Project. *Movement disorders: official journal of the Movement Disorder Society*. 2004; 19:529–533. [PubMed: 15133816]
81. Agnew A, Frucht SJ, Louis ED. Supine head tremor: a clinical comparison of essential tremor and spasmodic torticollis patients. *Journal of neurology, neurosurgery, and psychiatry*. 2012; 83:179–181.
82. Louis ED, Pellegrino KM, Rios E. Unawareness of head tremor in essential tremor: A study of three samples of essential tremor patients. *Movement disorders: official journal of the Movement Disorder Society*. 2008
83. Louis ED, Rios E, Applegate LM, Hernandez NC, Andrews HF. Jaw tremor: prevalence and clinical correlates in three essential tremor case samples. *Movement disorders: official journal of the Movement Disorder Society*. 2006; 21:1872–1878. [PubMed: 16941462]
84. Putzke JD, Whaley NR, Baba Y, Wszolek ZK, Uitti RJ. Essential tremor: predictors of disease progression in a clinical cohort. *Journal of neurology, neurosurgery, and psychiatry*. 2006; 77:1235–1237.
85. Louis ED, Agnew A, Gillman A, Gerbin M, Viner AS. Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. *Journal of neurology, neurosurgery, and psychiatry*. 2011; 82:761–765.
86. Louis ED, Hernandez N, Alcalay RN, Tirri DJ, Ottman R, Clark LN. Prevalence and features of unreported dystonia in a family study of “pure” essential tremor. *Parkinsonism & related disorders*. 2012
87. Quinn NP, Schneider SA, Schwingenschuh P, Bhatia KP. Tremor--some controversial aspects. *Movement disorders: official journal of the Movement Disorder Society*. 2011; 26:18–23. [PubMed: 21322015]
88. Defazio G, Gigante AF, Abbruzzese G, Bentivoglio AR, Colosimo C, Esposito M, Fabbrini G, Guidubaldi A, Girlanda P, Liguori R, et al. Tremor in primary adult-onset dystonia: prevalence and associated clinical features. *Journal of neurology, neurosurgery, and psychiatry*. 2012
89. Liu X, Cheng R, Ye X, Verbitsky M, Kisselev S, Mejia-Santana H, Louis E, Cote L, Andrews H, Waters C, et al. Increased Rate of Sporadic and Recurrent Rare Genic Copy Number Variants in Parkinson’s Disease Among Ashkenazi Jews. *Molecular genetics & genomic medicine*. 2013; 1:142–154. [PubMed: 24073418]
90. Guffanti G, Torri F, Rasmussen J, Clark AP, Lakatos A, Turner JA, Fallon JH, Saykin AJ, Weiner M, et al. Initiative, A.t.A.s.D.N. Increased CNV-region deletions in mild cognitive impairment (MCI) and Alzheimer’s disease (AD) subjects in the ADNI sample. *Genomics*. 2013; 102:112–122. [PubMed: 23583670]
91. Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, et al. Strong association of de novo copy number mutations with autism. *Science*. 2007; 316:445–449. [PubMed: 17363630]
92. Iossifov I, O’Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, Stessman HA, Witherspoon KT, Vives L, Patterson KE, et al. The contribution of de novo coding mutations to autism spectrum disorder. *Nature*. 2014; 515:216–221. [PubMed: 25363768]
93. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, Kou Y, Liu L, Fromer M, Walker S, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*. 2014; 515:209–215. [PubMed: 25363760]

Table 1

Candidate Genes for ET

Gene	Published Citation
Dopamine receptor D3 (DRD3)	21, 32–35
HS1 binding protein (HS1BP)	36
solute carrier family 1 (glial high affinity glutamate transporter) member 2 (SLC1A2)	18, 37 – 39
microtubule associated protein 2 (MAPT)	40–42
methylenetetrahydrofolate reductase (NAD(P)H)(MTFHR)	43
alpha-2 macroglobulin (A2M)	44
Cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19)	45
Cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9)	46
Cytochrome P450, family 2, subfamily C, polypeptide 8 (CYP2C8)	46
alcohol dehydrogenase 4 (class II) pi polypeptide (ADH2)	47
glutathione S-transferase pi 1 (GSTP1), paraoxonase 1 (PON1)	48
gamma-aminobutyric acid (GABA) receptor genes	49–51
fused in sarcoma/translated in liposarcoma (FUS/TLS)	24–27
synuclein, alpha (non A4 component of amyloid precursor) (SNCA)	52
Leucine-rich repeat kinase 2 (LRRK2),	53
Glucosidase, beta, acid (GBA)	53
Microtubule-associated protein tau (MAPT)	42