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Essential tremor

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Abstract

Essential tremor (ET) is one of the most common neurologic disorders, and genetic factors are thought to contribute significantly to disease etiology. There has been a relative lack of progress in understanding the genetic etiology of ET. This could reflect a number of factors, including the presence of substantial phenotypic and genotypic heterogeneity. Thus, a meticulous approach to phenotyping is important for genetic research. A lack of standardized phenotyping across studies and patient centers likely has contributed to the relative lack of success of genomewide association studies in ET. To dissect the genetic architecture of ET, whole-genome sequencing will likely be of value. This will allow specific hypotheses about the mode of inheritance and genetic architecture to be tested. A number of approaches still remain unexplored in ET genetics, including the contribution of copy number variants, 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 noncoding variation.

INTRODUCTION

Essential tremor (ET) is a chronic, progressive neurologic disease (Louis, 2001). The hallmark motor feature of ET is a 4–12-Hz kinetic tremor (i.e., a tremor that occurs during voluntary movements such as writing or eating) that involves the hands and arms, but which may also eventually spread to involve the head (i.e., neck), voice, jaw, and other body regions (Louis et al., 2013b). Given the presence of etiologic, clinical, pharmacologic response profile and pathologic heterogeneity, there is increasing support for the notion that ET may be a family of diseases whose central defining feature is kinetic tremor of the arms, and which might more appropriately be referred to as "the essential tremors" (Louis, 2013a).

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CLINICAL MANIFESTATIONS

The cardinal feature of ET is kinetic tremor (Louis, 2001). The tremor is typically mildly asymmetric (Louis et al., 1998). In approximately 5% of patients, the tremor is markedly asymmetric or even unilateral (Phibbs et al., 2009). In about 50% of patients (Louis et al., 2009), the tremor has an intentional component. Postural tremor also occurs in ET, and is generally worse in the wing-beat position than when the arms are held straight in front of the patient. The postural tremor of ET is generally greatest in amplitude at the wrist joint rather than more proximal (i.e., shoulder, elbow) or distal (metacarpophalangeal and phalangeal) joints (Sternberg et al., 2013). As a rule, the amplitude of kinetic tremor exceeds that of postural tremor (Louis, 2013b). Tremor at rest, without other cardinal features of parkinsonism, occurs in 20% of patients with ET who are attending a specialty clinic, but in contrast to that of Parkinson disease, it is a late feature and it has only been observed in the arm rather than the arm and leg (Cohen et al., 2003). Aside from tremor, another motor feature of ET is gait ataxia, which is in excess of that seen in similarly aged controls (Singer et al., 1994; Earhart et al., 2009; Kronenbuerger et al., 2009). In most patients, this is mild, although in some it may be of moderate severity (Louis et al., 2013a) and associated with functional problems (Louis et al., 2013a). In several studies, mild saccadic eye movement abnormalities have also been detected in ET patients (Helmchen et al., 2003; Gitchel et al., 2013).

In recent years, an increasing appreciation of the presence of nonmotor features in ET has emerged (Findley, 2004). Sensory changes include diminished hearing in excess of that seen in age-matched controls (Ondo et al., 2003) as well as a mild olfactory deficit in some, though not all, studies (Louis et al., 2002). Cognitive changes are in excess of those seen in similarly aged controls, and range from mild changes across several domains (but especially executive function) to mild cognitive impairment and dementia, both of which occur to a greater extent than seen in age-matched controls (Lombardi et al., 2001; Bermejo-Pareja, 2011; Benito-Leon et al., 2011). Psychiatric manifestations include both secondary anxiety and depression (Louis et al., 2007a). A harm-avoidant personality has been reported in studies that have assessed personality traits (Thenganatt and Louis, 2012).

Initially the tremor may be mild and asymptomatic, but in most individuals the tremor worsens over time (Critchley, 1949). Several patterns of progression have been described (Louis, 2013a). There are few natural history studies, but from these, the best estimates of rate of change suggest that arm tremor worsens by 2–5%/year (Louis et al., 2011). With the progression of time, there is a tendency for the tremor to spread beyond the arms to cranial structures (neck, voice, jaw), particularly in women, among whom the risk of neck tremor is several-fold higher than that of men (Hubble et al., 1997; Hardesty et al., 2004).

The term “benign essential tremor” is no longer considered appropriate (Louis and Okun, 2011). Indeed, the majority of patients have some tremor-related disability, and 15–25% of ET patients are disabled by the high-amplitude shaking and cannot continue to work (Rautakorpi et al., 1982; Busenbark et al., 1991; Bain et al., 1993).

ET and Parkinson disease seem to co-occur (Tan et al., 2008; Fekete and Jankovic, 2011), and epidemiologic studies indicate that ET patients have a fourfold increased risk of developing incident Parkinson disease (Benito-Leon et al., 2009).

EPIDEMIOLOGY

ET is among the most prevalent adult-onset movement disorders. It may occur at any age, and pediatric cases have been reported (Louis et al., 2001a), yet most cases arise later in life. In a recent metaanalysis of data from 28 population-based prevalence studies in 19 countries, the pooled prevalence of ET across all ages was 0.9% (Louis and Ferreira, 2010). This prevalence increases markedly with age (Dogu et al., 2003). In the metaanalysis, prevalence among persons aged 65 years and older was 4.6%, and in some studies, the prevalence among persons aged 95 and older reached values in excess of 20% (Louis and Ferreira, 2010). The rate at which new ET cases arise (i.e., the incidence rate of ET) has been estimated to be 619 per 100,000 person-years among individuals aged 65 and older, and incidence rises with age (Rajput et al., 1984; Benito-Leon et al., 2005). Established risk factors for ET include older age and family history of ET (Louis et al., 2013c).

PATHOPHYSIOLOGY

The traditional model of ET, the olivary model, was first proposed in the early 1970s; the model posited that a tremor pacemaker in the inferior olivary nucleus was responsible for ET (Llinas and Volkind, 1973). However, there are major problems with this model, and its relevance to ET has been increasingly called into question (Louis, 2014). Recent mechanistic research on ET has focused more on the cerebellum and the role it plays in the biology of this disorder. Interest in the cerebellum was initially motivated by neuroimaging studies, which strongly implicate the importance of this brain region in ET (Wills et al., 1994; Pagan et al., 2003; Quattrone et al., 2008; Passamonti et al., 2012), and clinical studies, which have consistently noted the presence of cerebellar signs in patients with ET (Singer et al., 1994; Bares et al., 2012). More recently, controlled postmortem studies have revealed an array of changes in the cerebellar cortex, primarily involving the Purkinje cell and surrounding neuronal populations, in the majority of ET cases (Louis et al., 2007b; Babij et al., 2013). In some studies, there is actual Purkinje cell loss. A smaller group of ET cases demonstrate a pattern of Lewy bodies that are relatively restricted to the locus coeruleus (Louis et al., 2007b). Of mechanistic interest is that the noradrenergic neurons of the locus coeruleus project to the cerebellum and synapse with Purkinje cells, suggesting that the cerebellum and its outflow tracts may be the final common pathway for this disease. The notion that ET is a degenerative disease or diseases, linked to the cerebellum, has gained increasing momentum in recent years (Louis, 2009; Bonuccelli, 2012; Grimaldi and Manto, 2013).

ETIOLOGY – GENETIC VS. ENVIRONMENTAL FACTORS

Both genetic and environmental (toxic) factors are likely contributors to disease etiology. Many large kindreds show an autosomal-dominant pattern of inheritance (Bain et al., 1994), and in a familial aggregation study, first-degree relatives of ET patients are approximately

five times more likely to develop the disease than are members of the general population, and 10 times more likely if the proband's tremor began at an early age (Louis et al., 2001b). Twin studies reveal a concordance of approximately 60% in monozygotic twins (Tanner et al., 2001; Lorenz et al., 2004). However, the existence of sporadic cases, variability in age at onset in familial cases, and lack of complete disease concordance in monozygotic twins all argue for nongenetic (i.e., environmental) causes as well (Louis, 2008). A number of environmental toxins are under investigation, including β-carboline alkaloids (e.g., harmane, a dietary toxin) and lead (Louis, 2008), and the search for ET genes is ongoing and intensive (Tan and Schapira, 2008). The remainder of this chapter will focus on the genetics of ET, as the disease clearly has a strong familial component.

MODES OF INHERITANCE AND TRANSMISSION IN ESSENTIAL TREMOR

Introduction

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 disease (Gasser et al., 2011), Alzheimer disease (Karch et al., 2014) and schizophrenia (Gratten et al., 2014), and it is likely that in ET both Mendelian/monogenic and complex disease patterns contribute to the genetic architecture. Historically, most studies have assumed a Mendelian inheritance pattern because of the high heritability and aggregation of ET in families (Bain et al., 1994; Findley, 2000; Tanner et al., 2001; Lorenz et al., 2004). Aggregation 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 (Louis and Dogu, 2007). 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 (Gulcher et al., 1997; Higgins et al., 1997; Kovach et al., 2001; Shatunov et al., 2006). Echoing this, our own experience with ET pedigrees strongly suggests an autosomal-dominant mode of inheritance with reduced penetrance.

Progress in ET genetics has been limited and the slow rate of ET gene identification may be due to a number of confounding factors that we discuss later in this chapter (Clark and Louis, 2015). As of 2015, only a handful of genes and risk factors have been identified in ET families and ET case-control cohorts (Fig. 15.1).

Mendelian inheritance and monogenic genes: family studies and linkage

To date, only three published genomewide linkage scans have been performed, all in north American or Icelandic ET families (Gulcher et al., 1997; Higgins et al., 1997; Shatunov et al., 2006). These studies led to the identification of genetic loci harboring ET genes on chromosomes 3q13 (ETM1; OMIM: 190300) (Gulcher et al., 1997), 2p22-p25 (ETM2; OMIM: 602134) (Higgins et al., 1997), and 6p23 (ETM3; OMIM: 611456) (Shatunov et al., 2006). Several studies have attempted to replicate linkage to ETM1 (Kovach et al., 2001; Illarioshkin et al., 2002; Lucotte et al., 2006), ETM2 (Higgins et al., 1998, 2005; Kovach et

al., 2001), and ETM3, without success (no logarithm of the odds 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 many years ago. Using a linkage and whole-exome sequencing 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 (Merner et al., 2012). Subsequent studies (Labbe et al., 2013; Ortega-Cubero et al., 2013; Parmalee et al., 2013) 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 (Merner et al., 2012)andR377Wreportedin1patientwithafamilyhistory of ET (Rajput et al., 2014)) is unknown. More recently, in a six-generation consanguineous Turkish kindred with both ET and Parkinson disease, the mitochondrial serine protease HTRA2 p.G399S variant was shown to segregate with both phenotypes (Parkinson disease and ET). 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 ($p = 0.0019$) (Unal Gulsuner et al., 2014). Follow-up studies in ET family studies and case-control studies will be needed to determine whether *HTRA2* represents a major ET susceptibility gene (Clark and Louis, 2015).

Genetic association studies of candidate genes

Although numerous genes have been evaluated as positional or functional candidates for ET, the majority of genes tested do not provide evidence of association (reviewed in Testa, 2013 and Jiménez-Jiménez et al., 2013). However, more recently a rare variant (p.R47H) in *TREM2* was identified as a risk factor for ET in a Spanish population and this gene may turn out to be a promising candidate in other populations as well. A rare amino acid substitution (p.R47H; rs75932628) in the TREM2 protein (triggering receptor expressed on myeloid cells 2; OMIM: 605086) has been identified as a risk factor for several neurodegenerative diseases, including Alzheimer disease (Jonsson et al., 2013; Ruiz et al., 2014), Parkinson disease (Benitez et al., 2013), fronto-temporal dementia (Ruiz et al., 2014; Thelen et al., 2014), and amyotrophic lateral sclerosis (Cady et al., 2014). A large cross-sectional multicenter international study that included a discovery ET case-control cohort from Spain ($n = 456$ ET and $n = 2715$ controls) and a replication case-control series from different populations (Italy, Germany, North America, and Taiwan; $n = 897$ ET and $n = 1449$ controls) reported a significant association between *TREM2* p.R47H and ET in the Spanish cohort (odds ratio (OR), 5.97; 95% confidence interval, 1.2–29.6; $p = 0.042$). However, the association was not replicated in the other populations, which may suggest population-specific differences, and allelic heterogeneity at *TREM2* (Ortega-Cubero et al., 2015). Resequencing of *TREM2* in different ET case-control ethnic populations may lead to the identification of other rare variants that are risk factors in specific populations.

Candidate genes that have been tested with null findings in ET are summarized in Table 15.1. We and others have also evaluated additional genes that are associated with other neurodegenerative diseases, such as Parkinson disease, dystonia, spinocerebellar ataxias, and fragile X tremor ataxia syndrome. We did not observe an association with the Parkinson disease genes synuclein, alpha (non A4 component of amyloid precursor) (*SNCA*) (Ross et

al., 2011), leucine-rich repeat kinase 2 (*LRRK2*) (Clark et al., 2010a), glucocerebrosidase (*GBA*) (Clark et al., 2010a), or microtubule-associated protein tau (*MAPT*) (Clark et al., 2014), nor did we identify pathogenic repeat expansions in the 10 common degenerative 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) (Clark and Louis, 2015).

Genomewide association studies (GWAS) and risk gene identification

To date, two published GWAS variably identified single-nucleotide polymorphisms (SNPs) in the leucine-rich repeat and Ig domain containing 1 (*LINGO1*) gene or an intronic variant in the *SLC1A2* gene, which reached genomewide significance and are associated with increased risk for ET.

LINGO1—A genomewide SNP association study of ET in an Icelandic population identified an association with a marker in the *LINGO1* gene (Stefansson et al., 2009). Since the initial report, numerous studies have replicated the association in independent ET case-control samples worldwide (Tan et al., 2009; Clark et al., 2010b; Thier et al., 2010; Vilarino-Guell et al., 2010a, b, c; Zuo et al., 2010; Wu et al., 2011; Bourassa et al., 2011; Lorenzo-Betancor et al., 2011; Jiménez-Jiménez et al., 2012; Radovica et al., 2012; Clark et al., 2010b). 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 (Zuo et al., 2010; Lorenzo-Betancor et al., 2011; Wu et al., 2011; Radovica et al., 2012). 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 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*), is also a risk factor for ET and Parkinson disease, providing further evidence that the *LRR* gene pathway may be perturbed in ET pathogenesis (Vilarino-Guell et al., 2010b). To date, SNPs in *LINGO1* provide the strongest evidence for association with ET; however, data are not completely consistent.

SLC1A2—The SNP, rs3794087, located in *SLC1A2*, was identified in a two-stage European GWAS in a total of 990 ETcases and 1537 controls, with an OR of ~1.4 (Thier et al., 2012). 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) (Garcia-Martin et al., 2013; Tan et al., 2013; Ross et al., 2014). 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. Furthermore, the paucity of genomewide significant SNP associations from GWAS argues against the common disease common variant hypothesis in ET, and that

common SNPs with small effect are unlikely to contribute to the heritability of ET (Clark and Louis, 2015).

CONFOUNDING FACTORS IN GE'NE IDENTIFICATION IN ESSENTIAL TREMOR

Why has the field of ET genetics made so little progress? Despite significant efforts to identify genes for ET there has been a slow rate of gene identification. There are a number of possible explanations, some of which we highlight below (Clark and Louis, 2015).

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 neuropathologic 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 Parkinson disease 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, Parkinson disease, and other disorders) rather than ET (Jain et al., 2006). 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. A related issue is the possibility, as discussed above, that ET may represent a family of diseases rather than a single clinical-pathologic entity.

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 Parkinson disease, 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.

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.

Molecular methods and statistical analysis of rare variants

A major roadblock to gene discovery, until recently, has been the lack of technologic and analytic advances in genomewide sequencing and statistical models for multiple rare variants. Recent advances in next-generation sequencing techniques, particularly for whole-genome sequencing (WGS), sequence data processing, decreased cost of WGS, and faster computational power, together with new analytic methods to study rare variants, mean that

WGS and rare variant analysis are now feasible. While whole-exome sequencing 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 (Clark and Louis, 2015).

NOVEL APPROACHES TO ESSENTIAL TREMOR 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, 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. A number of approaches remain unexplored in ET genetics, including copy number variants, 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 noncoding variation. These approaches are likely to yield new ET genes (Clark and Louis, 2015).

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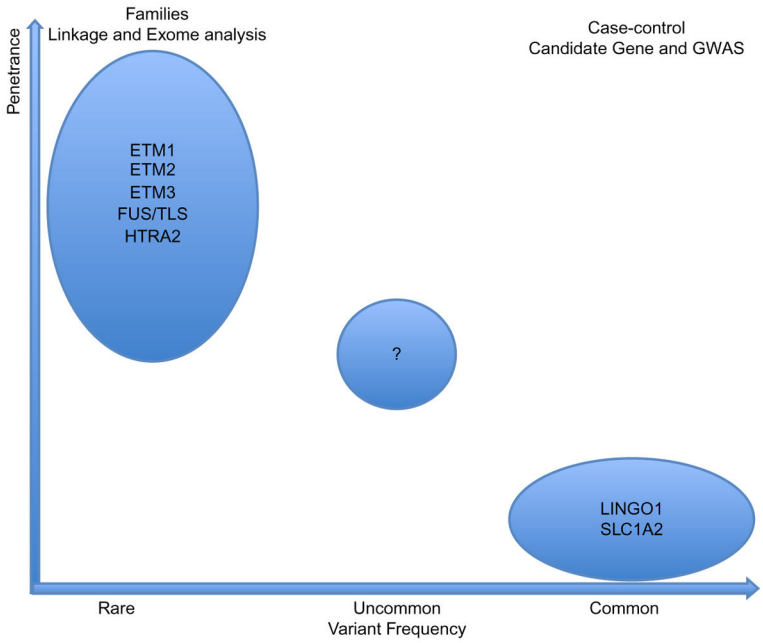

Fig. 15.1.

Schematic summarizing essential tremor (ET) genes identified to date. The penetrance (*y*-axis) and variant frequency (*x*-axis; rare, uncommon, and common variants) are indicated. *FUS/TLS,* fused in sarcoma/translated in liposarcoma; *GWAS*, genomewide association studies. (Adapted from Verstraeten A, Theuns J, Van Broeckhoven C (2015) Progress in unraveling the genetic etiology of Parkinson disease in a genomic era. Trends Genet 31: 140–149.)

Table 15.1

Candidate genes for essential tremor

Gene	Function/pathway	Published citation	Variant/SNP frequency	Significance
Dopamine receptor D3 (DRD3)	Dopamine receptor, activity mediated by G proteins which inhibit adenyl cyclase/dopamine neurotransmitter receptor activity	Jeanneteau et al. (2006); Lucotte et al. (2006); Tan et al. (2007); Blair et al. (2008); Vitale et al. (2008); Garcia-Martin et al. (2009); Lorenz et al. (2009)	Ser9Gly variant of DRD3	Jeanneteau et al. (2006): $p = 0.039$ Garcia-Martin et al. (2009): $p<0.017$ (genotype) and $p<0.005$ (allele) All other studies not significant
HS1-binding protein 3 (HS1BP3)	May be a modulator of IL-2 signaling (by similarity)	Deng et al. (2005); Shatunov et al. (2005)	Ala265Gly variant of HS1BP3	Not significant
Solute carrier family 1 (glial high-affinity glutamate transporter) member 2 (SLC1A2)	Solute transporter. Clears excitatory neurotransmitter glutamate at synapses in CNS	Thier et al. (2012); Garcia-Martin et al. (2013); Tan et al. (2013); Ross et al. (2014)	rs3794087	Thier et al. (2012): $p = 6.95\ 3\ 10^{-5}$ Tan et al. (2013): $p = 0.009$ Other studies not significant
Microtubule-associated protein 2 (MAPT)	Promotes microtubule assembly and stability. MAPT gene mutations and risk SNPs associated with several neurodegenerative diseases	Vilarino-Guell et al. (2011); Garcia-Martin et al. (2012); Clark et al. (2014)	rs1052553	Clark et al. (2014): metaanalysis of published studies not significant
Methylene tetrahydrofolate reductase (NAD(P)H) (MTFHR)	Catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate	Sazci et al. (2004)	MTHFR 677T allele	$p = 0.005$
Cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19)	Member of the cytochrome P450 family of enzymes. Monooxygenase that catalyzes reactions involved in drug metabolism, synthesis of cholesterol, steroids, and other lipids	Alonso-Navarro et al. (2006)	CYP2C19 allelic variants	$p = 0.0044$
Cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9)	Member of the cytochrome P450 family of enzymes	Martinez et al. (2007b)	CYP2C9 allelic variants	CYP2C9*2: $p = 0.05$ CYP2C9*3: $p = 0.07$
Cytochrome P450, family 2, subfamily C, polypeptide 8 (CYP2C8)	Member of the cytochrome P450 family of enzymes	Martinez et al. (2007b)	CYP2C8 allelic variants	CYP2C8*3: $p = 0.006$
Alcohol dehydrogenase 1B, beta polypeptide (ADH2)	Alcohol dehydrogenase family member. Metabolizes several substrates, including ethanol, retinol, aliphatic alcohols, hydroxysteroids, lipid peroxidation products	Martinez et al. (2007a)	ADH2*1/ADH2*2	Not significant
Glutathione S-transferase pi 1 (GSTP1),	GSTP1: conjugation of reduced glutathione to a number of exogenous and endogenous hydrophobic electrophiles	Martinez et al. (2008)	GSTP1Val allele (rs1695)	Not significant
Gamma-aminobutyric acid (GABA) receptor genes	Ligand-gated chloride channels that bind GABA, the major inhibitory neurotransmitter in the brain	Deng et al. (2006); Garcia-Martin et al. (2011); Thier et al. (2011)	Tagging SNPs	Not significant
Fused in sarcoma/translated in liposarcoma (FUS/TLS)	Component of the heterogeneous nuclear riboprotein (hnRNP) complex. Mutations in FUS/TLS associated with amyotrophic lateral sclerosis	Merner et al. (2012); Labbe et al. (2013); Ortega-Cubero et al. (2013); Parmalee et al. (2013)	Complete or partial gene sequencing	Merner et al. (2012): Fus p.Gln290* in a single essential tremor family. Other published studies no evidence for pathogenic

Gene	Function/pathway	Published citation	Variant/SNP frequency	Significance
				mutations or association of SNPs/variants in FUS/TLS in essential tremor cases
Synuclein, alpha (non-A4 component of amyloid precursor) (SNCA)	Localizes to and enriched at synapses and lipid-rich membrane structures. Mutations in SNCA associated with PD	Ross et al. (2011)	20 different variants at the SCNA locus	Not significant
Leucine-rick repeat kinase 2 (LRRK2)	Large multidomain protein kinase. May play a role in phosphorylation of proteins central to PD. Mutations in LRRK2 associated with PD	Clark et al. (2010a)	6 LRRK2 mutations: G2019S, I2020T, R1441C, Y1699C, L1114L and I1122V and 19LRRK2 SNPs	Not significant
Glucosidase, beta, acid (GBA)	Hydrolase that catalyzes the cleavage of glucosylceramide. Homozygous mutations in GBA cause Gaucher disease. Heterozygous mutations in GBA associated with PD and dementia with Lewy bodies	Clark et al. (2010a); Sun et al. (2013)	Clark et al. (2010a): all GBA exons sequenced Sun et al. (2013): L444P mutation only	Not significant
Triggering receptor expressed on myeloid cells 2 (TREM2)	Encodes a membrane protein that forms a receptor signaling complex with the TYRO protein tyrosine kinase-binding protein	Ortega-Cubero et al. (2015)	rs75932628 (p.R47H)	$p = 0.042$

CNS, central nervous system; PD, Parkinson disease; SNP, single-nucleotide polymorphism.