

## Reviews

# Essential Tremor and Parkinson's Disease: Exploring the Relationship

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## Abstract

**Background:** There is longstanding controversy surrounding the possible link between essential tremor (ET) and Parkinson's disease (PD). Inconsistent and unreliable diagnostic criteria may in part account for some of the difficulties in defining the relationship between these two common movement disorders.

**Methods:** References for this systematic review were identified using PubMed with the search terms "essential tremor" AND "Parkinson's disease" with articles published in English between 1960 and September 2018 included.

**Results:** In this review we provide evidence that some patients diagnosed with ET have an increased risk of developing PD years or decades after onset of action tremor. There are several still unresolved questions about the link between the two disorders including lack of verifiable diagnostic criteria for the two disorders and marked overlap in phenomenology. Here we review clinical, epidemiologic, imaging, pathologic, and genetic studies that address the ET–PD relationship. Several lines of evidence support the association between ET and PD, including overlapping motor and non-motor features, relatively high prevalence of rapid eye movement sleep behavior disorder (26–43%) in ET patients, increased prevalence of PD in patients with longstanding antecedent ET, increased prevalence of ET in family members of patients with PD, and the presence of Lewy bodies in the brains of some ET patients (15–24%).

**Discussion:** There is a substantial body of evidence supporting the association between ET and PD within at least a subset of patients, although the nature and possible pathogenic mechanisms of the relationship are not well understood.

**Keywords:** Essential tremor, Parkinson's disease

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## Introduction

There has been a longstanding debate among movement disorder specialists as to whether or not essential tremor (ET) confers a greater risk of developing, or is otherwise linked to, Parkinson's disease (PD). This topic has been addressed in the past,<sup>1–5</sup> but it is worth revisiting it in view of recently published data related to this subject, including new diagnostic criteria for ET and PD, and additional studies in imaging, epidemiology, pathology, and genetics.

## Methods

References for this systematic review were identified using PubMed with the search terms "essential tremor" AND "Parkinson's disease" in September 2018, which resulted in 1,180 articles. Articles published

in English between 1960 and September 2018 comparing ET and PD were reviewed in further depth. Additional articles were identified through a review of the authors' own files.

## Results and Discussion

### Diagnosis

First introduced by Buresi (Italy) in 1874 to describe patients with action (postural and kinetic) tremor in the hands and no other neurologic signs, subsequent descriptions have expanded the ET phenotype to include involvement of head, voice, and legs and other movement disorders (e.g., dystonia, myoclonus, parkinsonism, ataxia), response to alcohol and beta-blockers, and hereditary nature.<sup>6,7</sup> This gave rise to numerous debates as to whether ET is a single entity or a syndrome.<sup>8–14</sup>

In the recently published Classification of Tremors by the Task Force on Tremor of the International Parkinson and Movement Disorder Society (IPMDS), ET has been defined in Axis I as a syndrome and divided into “ET” and “ET plus.”<sup>15</sup> According to this classification ET is an isolated action tremor involving both upper limbs, at least 3 years in duration, with or without tremor in other locations, and in the absence of other neurological signs such as dystonia, ataxia, or parkinsonism. Although the statement acknowledges that patients frequently have a family history and alcohol may improve the tremor, the authors concluded that these clinical features are not consistent enough to be included in the definition of ET. ET plus is defined as tremor with the characteristics of ET and additional neurologic signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis. Exclusionary criteria of ET and ET plus require ruling out enhanced physiological tremor, isolated focal tremors (head or voice), orthostatic tremor with frequency greater than 12 Hz, task- and position-specific tremors, and sudden onset and other features suggestive of functional (psychogenic tremor). Complicating the distinction between ET and ET plus is the potential for symptoms to evolve over time (such as with the development of parkinsonism or cerebellar symptoms) that necessitates a change in the patient's diagnosis from ET to ET plus, provided they do not meet criteria for an alternative neurologic diagnosis. Indeed, the consensus statement acknowledges that patients with longstanding ET may ultimately develop other neurologic conditions such as dystonia or PD and that “ET is a syndrome that may evolve into another tremor syndrome.” Thus patients with longstanding ET who later develop a PD phenotype would be referred to as PD with “antecedent ET.” It should be noted that there have been dissenting opinions expressed following the publication of the consensus statement,<sup>7,16</sup> and future revisions are likely.

Besides the evolution of ET to another or additional movement disorder, the presence of multiple or mixed phenotypes (of ET, PD, and dystonia) within family members of patients with ET also presents a challenge in defining ET. For example in three of our four kindreds examined in detail, in which several members had ET as defined by the presence of bilateral postural tremor involving the hands or forearms that was visible and persistent, lasting longer than 5 years, and without any other additional neurologic symptoms, other members of the family had additional movement disorders, such as dystonia and parkinsonism.<sup>17</sup> Although no gene mutations have been identified in these families, we hypothesized that the various affected family members had different phenotype of the same genetic disorder. Finding specific and sensitive genetic and other biomarkers for ET would clearly help in addressing this important issue of different phenotypes despite the same etiology versus phenocopies associated with different etiologies.

The gold standard for the diagnosis of PD is based on autopsy findings, with neuronal loss in the substantia nigra and the presence of Lewy bodies and Lewy neurites as the pathologic hallmarks of the disease.<sup>18</sup> However, the pathology-based definition of PD has been

challenged and some have proposed that, similar to ET, PD should also be considered a syndrome as it can present in the setting of different motor and non-motor phenomenologies, heterogeneous pathological findings, and with increasingly recognized genetic etiologies. Clinically, PD is characterized by a wide variety of motor symptoms (bradykinesia, rigidity, tremor, gait disturbances, and dystonia among others), and non-motor symptoms (including mood disorders, anosmia, rapid eye movement sleep behavior disorder (RBD), and autonomic dysfunction).<sup>19–21</sup> Some of these non-motor features such as mood disorders and RBD may also occur at a higher frequency in ET patients than controls (as will be discussed later).<sup>22,23</sup> Historically, the UK Brain Bank criteria have been most widely used in clinically diagnosing PD, defined as the presence of bradykinesia with at least one additional feature of muscular rigidity, 4–6 Hz rest tremor, or postural instability; and the absence of exclusionary features (including strokes with stepwise progression of parkinsonism, head injury, neuroleptic treatment at symptom onset, or atypical parkinsonism features), which would suggest an alternative diagnosis.<sup>24</sup> The 2015 MDS clinical diagnostic criteria defined parkinsonism as the presence of bradykinesia with either rest tremor or rigidity, with “clinically established PD” additionally requiring at least two supportive features (which include a clear and dramatic beneficial response to dopaminergic therapy, the presence of levodopa-induced dyskinesias, rest tremor documented on clinical examination, or the presence of either olfactory loss or cardiac sympathetic denervation on metaiodobenzylguanidine scintigraphy) and no exclusionary criteria or “red flags.”<sup>25</sup>

Although we believe, based on our clinical experience following longitudinally patients with ET over decades, that a subset of ET patients has a higher than expected risk for developing PD, we have tried to interpret the literature related to this topic as objectively as possible and without specific bias. One of the major areas of disagreement among experts is the diagnosis of the observed clinical entity. For example, PD patients often present with action tremor prior developing more overt PD signs.<sup>26</sup> Is the postural tremor in these patients ET or an early presentation of PD? If the latency between onset of postural tremor and other features of PD is long (e.g., >10 years) it would be difficult to argue that the postural tremor (in some cases of childhood onset)<sup>2</sup> is an early manifestation of PD. Because it is difficult to diagnose ET in a patient who already has PD (although the presence of head, voice, and writing tremor suggests the diagnosis of coexistent ET), there are no studies to address the possible relationship between antecedent PD in patients who later develop ET.<sup>27</sup> Another challenge is to determine whether additional symptoms in patients with longstanding ET, such as the emergence of rest tremor, bradykinesia, cogwheeling, and postural instability are manifestations of ET plus or the beginnings of PD. Although DaTscan imaging, if abnormal, may provide evidence for underlying PD, ultimately only brain autopsy can answer the question whether the patient has a longstanding but slowly evolving PD, merely ET with age-related changes, or a separate syndrome, a combination of both ET and PD. If it is the latter, then the next question that needs to be addressed is whether the ET–PD

association is coincidental or pathogenically related. We believe that the reported data, reviewed below, provides evidence for the latter.

### Phenomenology

While ET is characterized by action tremor and PD by rest tremor, some patients have overlapping features that can present a diagnostic challenge. PD patients have been noted to have postural tremor of two phenotypes: 1) a re-emergent postural tremor that appears after a latency of a few seconds when assuming a horizontal (anti-gravity) position of the arms and often responds to levodopa, and 2) a postural tremor without latency that phenomenologically resembles ET.<sup>26,28,29</sup> Some ET patients can develop rest tremor, particularly with longer disease duration.<sup>30</sup> In the authors' personal experience, one of the most common reasons why ET-PD syndrome may not be recognized is because the examiner fails to ask the critical question of a patient with clinically diagnosed PD if they or others ever noted any other tremor prior to the onset of rest tremor. It is remarkable how often patients endorse postural or action tremors from relatively early on in life. Without diligently seeking answer to this critical question one would never suspect pre-existing (antecedent) ET, though some would argue this could also represent earlier motor manifestations of PD.

Several physiological studies have provided evidence for overlap between ET and PD. Both ET and PD show similar impairment in primary motor cortex excitability in response to paired associative stimulation.<sup>31</sup> Another study of 46 PD patients, 34 ET patients, and 56 controls demonstrated slowed reaction times and slower movement velocities in ET (and as expected in PD) patients relative to controls.<sup>32</sup> Some electrophysiological studies have also found distinctions between the two conditions including that the muscle contractions in patients with rest tremor associated with ET are mainly synchronous whereas those in PD-related rest tremor are mainly alternating, though these patterns do not always differentiate the two types of tremor.<sup>33,34</sup> While the cerebellum has been implicated in the pathophysiology of ET, evidence that the cerebellum is the source of ET has not been supported by some recent studies that also found that cortical contribution to PD and ET tremor are similar.<sup>35</sup>

### ET-PD combination

Once patients develop clinical features of PD it is difficult to diagnose coexistent ET although there are some clues, such as the presence of head, voice, and writing tremor; family history of tremor (and/or alcoholism); and improvement with alcohol, where ET may also be suspected.<sup>2,27</sup> In one study involving 53 ET-PD patients and 150 ET patients, it was noted that the ET-PD group showed a male predominance (68%) similar to the 2:1 ratio seen in PD.<sup>27</sup> The mean latency from onset of ET to first sign on neurologic examination of PD was  $14 \pm 15$  years. The mean age at onset of ET symptoms was 51.8 years with the first clinical symptom of PD at 65.8; 30.8% had a long latency (>20 years) between onset of ET and onset of PD symptoms. The more affected side of early tremor correlated with the side later exhibiting more parkinsonian signs such as reduced arm swing (78.6%  $p = 0.009$ ) bradykinesia (71.4%  $p = 0.003$ ), rigidity (56.3%  $p = 0.03$ ) and

rest tremor (73.3%  $p < 0.001$ ).<sup>27</sup> This is similar to our findings in patients with asymmetric, childhood-onset ET.<sup>36</sup> One study involving 621 individuals in families with ET identified 22 patients with isolated PD, 20 of whom (90%) had tremor-dominant PD.<sup>37</sup> The predilection of patients in this population to present with tremor dominant PD over other subtypes highlights the association of this subtype of PD with ET. Another study comparing 25 patients with ET-PD to 125 patients with PD found rest and action tremor to be more prominent in the ET-PD group, which also had a higher prevalence of tremor in first-degree relatives.<sup>38</sup> Other studies also found a stronger family history of ET in the ET-PD group than in the isolated PD group.<sup>39-41</sup> Together these studies demonstrate distinct features of the ET-PD phenotype: tremor-dominant subtype of PD, long duration of tremor before onset of parkinsonism, presence of cerebellar signs, slow progression, and a strong family history of tremor (Table 1).

### Non-motor symptoms

Non-motor symptoms, while traditionally associated with PD, are being increasingly recognized as a part of ET. Impaired neuropsychological performance in ET, particularly in frontal domains such as executive function, have been noted in several studies.<sup>42-45</sup> A large population-based study from Spain demonstrated a greater degree of cognitive decline on the 37 item Mini-Mental State Examination (0.7 points versus 0.11 points  $p = 0.03$ ) in 135 ET patients compared to 2,184 controls,<sup>42</sup> with a more recent follow-up suggesting that this cognitive decline was in a partially overlapping pattern (though to a lesser degree) to that in PD.<sup>43</sup> A study of neuropsychological performance between 32 ET and 32 PD patients also demonstrated deficits in similar areas of cognitive function (particularly with involvement of the prefrontal cortex) when compared to controls ( $n = 32$ ).<sup>44</sup> In a study of 23 ET patients, a subset of eight (35%) patients showed impaired visuomotor control, similar to that seen in PD.<sup>46</sup>

Mood disturbances and apathy, similar to those in PD, have also been reported at an increased frequency in ET patients.<sup>46-50</sup> This, however, may not be specific as there are many other disorders associated with depression and other mood changes.

Sleep disturbances and RBD are well established in PD, often as prodromal symptoms, but have also been reported at a relatively high frequency in ET patients. One study using the RBD Screening Questionnaire (RBDSQ) showed a high frequency of RBD symptoms (43.5%) in ET patients relative to an estimated 0.5% frequency of RBD in the general population.<sup>47</sup> In another study of 92 ET patients screened by phone questionnaires, the frequency of RBD was 26.4%.<sup>22</sup> In a study of 120 ET patients, 120 controls, and 40 PD patients, ET patients were found to have intermediate Epworth Sleepiness Scale scores compared to controls and PD patients.<sup>48</sup> Increased daytime somnolence, as determined by the Epworth Sleepiness Scale, was found in both ET and PD patients relative to controls (5.75,  $p = 0.009$ , and 6.98,  $p = 0.001$ , respectively versus 2.68).<sup>45</sup>

Collectively these disturbances in cognition, mood, and sleep suggest more widespread neurologic involvement in ET with significant overlap in changes in domains associated with PD. While not symptoms *per se*,

**Table 1. A Summary of Evidence Supporting the Association of ET and PD**

Phenomenologic motor non-motor ET–PD phenotype other	Overlapping clinical motor features, e.g. rest tremor, cogwheeling, postural instability <sup>26,28–30,58</sup> Slowed reaction times <sup>31,32</sup> Preserved olfaction in tremor dominant PD patients with family history of tremor <sup>41</sup> Cognitive dysfunction (primarily frontal/executive problems) <sup>42–46</sup> Increased frequency of anxiety, depression, and apathy <sup>45,47,112,113</sup> Increased frequency of RBD and daytime somnolence <sup>22,45,47,48</sup> Emergence of PD after long-standing ET <sup>27</sup> PD asymmetry correlating with historical tremor asymmetry and severity <sup>27,36</sup> Increased incidence of rest and action tremor in ET–PD group versus PD <sup>38</sup> Increased cerebellar signs and more diffuse tremor in ET–PD patients than isolated PD patients <sup>39</sup> Increased risk of melanoma in PD and ET <sup>49,50</sup> Decreased risk of PD and ET among smokers <sup>51–53</sup>
Epidemiologic	Increased prevalence of PD in ET patients relative to general population <sup>54–57</sup> Increased prevalence of ET in family members of PD patients <sup>60–65</sup> Increased prevalence of tremor dominant PD in ET families <sup>37</sup> Increased family history of tremor in relatives of ET–PD patients than isolated PD patients <sup>38,40</sup>
Imaging	Hyperechogenicity in substantia nigra of ET patients associated with progression to PD <sup>68</sup> Reduced striatal dopamine uptake on DaTscan <sup>69–71</sup>
Pathologic	Overlapping cerebellar pathology of changes in climbing fiber density and torpedoes <sup>74,75,77,78</sup> Lewy bodies in brains of ET patients <sup>75,77</sup>
Genetic (strong family history and putative genes)	<i>LINGO1</i> <sup>93–96</sup> <i>LINGO2</i> <sup>96,97</sup> <i>HS1BP3</i> <sup>98,99</sup> <i>DNAJC13</i> <sup>100</sup> <i>HTRA2</i> <sup>102</sup> <i>NAACP-Rep1</i> <sup>103</sup> <i>CACNA1G (Cav3.1)</i>

Abbreviations: ET, Essential Tremor; PD, Parkinson's Disease; RBD, Rapid Eye Movement Sleep Behavior Disorder.

other similarities between ET and PD populations include a greater risk in developing melanoma,<sup>49,50</sup> and a decreased risk of in both conditions among smokers.<sup>51–53</sup>

### Epidemiology

Epidemiologic studies examining a link between ET and PD have focused either on the co-occurrence of ET and PD, or the occurrence of ET and/or PD in family members of patients with either condition.

**Co-occurrence of ET and PD.** There are no longitudinal prospective studies of patients with ET to determine the incidence of subsequent parkinsonism. Furthermore, the question of the nature of parkinsonism in such patients has not been fully addressed. Do these patients have ET and later go on to develop PD, have PD with “antecedent tremor,” have parkinsonism related to ET (ET plus), or is the coexistence of the two disorders purely coincidental, by chance alone? There are currently no definite answers to these critical questions. There are,

however, several epidemiological studies to support the notion that combination of ET and parkinsonism is not purely coincidental. In a population-based study from Spain, six (3%) of 201 patients with ET developed PD as compared to 0.4% of 3,574 controls, supporting the notion that ET patients have a higher risk for developing PD.<sup>54</sup> In a study by the Essential Tremor Study Group of 678 patients, 6.1% of ET patients were found to have PD,<sup>55</sup> while in another study involving 130 patients with ET, 25 (20.8%) were noted to have coexistent PD.<sup>56</sup> In one large study of 600 patients, a higher occurrence of ET in PD patients (5.9%) was noted than in healthy controls (0.5%), or in “diseased” controls with hemifacial spasm (1%).<sup>57</sup> In one study involving 22 PD patients with a history of childhood-onset ET (before age 20, mean age at onset 13.8 years), 11 patients (50%) reported asymmetric childhood ET, with 10 (91%) of these patients reporting PD symptoms developing on the same side as the more prominent childhood tremor.<sup>36</sup> Lastly, in a retrospective study of 350 ET patients from the same center, 20.2% were noted to display at least three of the four cardinal signs of PD.<sup>58</sup>

Although genetic factors most likely play a pivotal role in the development of ET–PD syndrome, other possible explanations for the increased risk of PD in patients with pre-existing ET have been offered. For example, some investigators have recently proposed that beta-blockers used in the treatment of ET may increase the risk of developing PD. This hypothesis is based on a large registry study, utilizing data from the Norwegian public health registry ( $n = 4$  million), which found an association between use of the beta2-adrenergic agonist salbutamol and the beta2-adrenergic antagonist propranolol and the risk of developing PD.<sup>59</sup> Further studies found that beta2-adrenergic antagonists may increase alpha-synuclein, the toxic protein implicated in the pathogenesis of PD, and thus have detrimental effects on dopaminergic neurons. Although this is an intriguing hypothesis to explain the relationship between ET and PD, further studies are needed to further explore this association.

### ET and PD in family members

There are very few family studies in which all affected and unaffected family members have been examined.<sup>17</sup> One study in which first-degree relatives of PD patients and controls were interviewed and screened for tremor showed a trend toward increased risk of ET among family members of patients with PD, with 4.8% of relatives of PD patients having ET versus 3.5% of controls, though this did not reach statistical significance ( $p = 0.08$ ).<sup>60</sup> The risk increased with younger onset of PD (5.8% of relatives had ET when PD onset was  $\leq 66$  years  $p = 0.006$ ) and with tremor-dominant or mixed forms of PD. Similar results of younger onset PD being more closely associated with ET has also been reported in another study of 2,980 relatives of 372 PD patients,<sup>61</sup> however, the focus of this study was on Alzheimer's disease, and it was not adequately powered to assess the strength of this PD and ET relationship. In a study from Crete, where an examination was performed on all first-degree relatives endorsing neurological symptoms, 8.6% of first-degree relatives of 303 PD patients were noted to have ET compared to 3.2% of controls ( $p = 0.015$ ).<sup>62</sup> In another study involving ET, PD, and ET–PD patients, there was a higher occurrence of ET reported in relatives of PD patients (11.5% versus 2.8% in controls  $p = 0.002$ ) but there was no difference in the occurrence of PD in relatives of ET patients.<sup>63</sup> One study of 487 PD patients, 409 controls, and 5,563 relatives found a higher incidence of action tremor in relatives of tremor-dominant PD (6.5%  $p < 0.001$ ) than relatives of controls (3.1%) or those of patients with postural instability and gait disorder PD (3.4%).<sup>64</sup> In a study of 391 patients with PD, 140 with ET, 125 with ET/PD, 99 with progressive supranuclear palsy (PSP), and 104 age-matched controls, a higher incidence of family history of tremor was seen in the ET (70%), ET–PD (64%), and PD (20.7%) populations than the PSP (11.1%) and control (10.6%) populations.<sup>65</sup>

Several studies have examined ET and PD within large multigenerational families. In one large family with a mixed history of ET and PD, 11 family members had limb/head tremor that presented early (second decade) of life. Three brothers in the family (two being identical twins) went on to develop PD in their 50s, and on autopsy

showed cell loss in the substantia nigra and Lewy body formation characteristic of PD.<sup>66</sup> Another study of a multigenerational family provided data on 138 individuals including 65 that were examined, 11 of whom were noted to have PD including six with likely coexistent ET and PD, and an additional 19 individuals with ET.<sup>67</sup> The presence of multiple cases of both ET and PD in these families argues strongly for a genetic component, while the coexistence of both conditions within each family favor the concept of phenotypic variation of a common gene rather than two separate genetic conditions.

### Imaging

A number of different imaging modalities have demonstrated changes in brains of ET patients suggestive of coexistent PD. In one European study of 54 patients with ET, those demonstrating hyperechogenicity of the substantia nigra by transcranial ultrasonography showed an increased risk of developing PD (seven out of 18). Interestingly, nine of the total 54 ET patients (17%) went on to develop PD (with a mean onset of parkinsonism at 5.3 years and a mean follow-up of 6.2 years),<sup>68</sup> a higher incidence than would be expected in the general population. In a study involving single photon emission computed tomography (SPECT) with <sup>123</sup>I-ioflupane (DaTscan) imaging of 28 patients with ET and 28 healthy controls, semi-quantitative analysis demonstrated a reduction in striatal dopamine in the ET group (though this was not appreciated qualitatively).<sup>69</sup> Another DaTscan study of 32 ET patients, 47 PD patients, and 31 controls demonstrated ET patients to have reductions in striatal dopamine uptake at intermediate levels between PD and control patients.<sup>70</sup> Finally, in one study, two independent radiologists “blinded” to the clinical diagnosis examined <sup>123</sup>I-ioflupane SPECT scans in 39 ET patients (22 with isolated ET, nine with ET and mild parkinsonism, and eight with ET–PD) and 13 healthy controls, visually and by a semi-quantitative method.<sup>71</sup> As expected, ET–PD patients had the lowest striatal binding ratios, but pure ET patients were noted to have a trend towards slightly lower striatal binding ratios than healthy controls. However, in contrast to PD, the dopamine transporter density was lower in the caudate nucleus rather than the putamen, and these differences did not reach statistical significance.

### Pathology

In addition to difficulties defining ET clinically, the reports of pathological examinations of the brains of patients with ET have generated conflicting data. In contrast to studies by Rajput et al.,<sup>72,73</sup> those by Louis and colleagues<sup>74–78</sup> have found pathologic features in autopsied brains of patients with clinically defined ET. The pathological abnormalities in brains of patients with ET showed a reduction of Purkinje cells (PCs), a greater incidence of PC axonal swellings (torpedoes), and additional axonal changes.<sup>75,77</sup> One study examining brains of ET patients demonstrated lower climbing fiber (CF) synaptic density, which was associated with lower numbers of PCs, and a higher percentage of CFs in parallel fiber territory in ET patients than in controls.<sup>74</sup> This change was consistent across several ET “subtypes” including familial versus sporadic ET, and those with and without



head tremor.<sup>76</sup> An increase in CFs in parallel fiber territory has also been seen in PD,<sup>78</sup> as have PC “torpedoes.”<sup>75</sup> By comparison, a study of 12 ET patients and 41 PD patients, and six controls showed no significant difference in cerebellar PC counts between groups.<sup>72</sup> Another study involving 56 ET patients and 62 controls also failed to show a significant difference in PC linear density between the two groups.<sup>79</sup> Despite these conflicting pathologic findings, cerebellar atrophy by volumetric analysis of magnetic resonance imaging scans has been demonstrated in ET patients relative to PD patients and controls.<sup>80</sup>

The well-established pathologic hallmark of PD is a neuronal loss in the substantia nigra and a widespread presence of Lewy bodies and Lewy neurites,<sup>18</sup> although pathologic changes in the cerebellum and basal ganglia–cerebellum connections have been also described.<sup>81</sup> In one study of the brains of 33 ET patients, eight (24.2%) were found to have a substantial presence of Lewy bodies (the presence of which were rated as moderate or severe on a semi-quantitative scale), primarily localized to the locus ceruleus. These patients were noted to be older than the other ET patients. In contrast, those without Lewy bodies showed primarily cerebellar pathologic changes and were found to have a younger age at onset of tremor, higher proportion of gait difficulty, and family history of ET.<sup>77</sup> A subsequent study by the same group again demonstrated a subset of ET patients with Lewy bodies, albeit at a lower frequency (15%).<sup>75</sup> In contrast, another study of brains of ET patients found no significant difference in the frequency of Lewy bodies compared to controls, though it should be noted that the average age of patients in this study was 86.2 years with a mean tremor duration of 11.1 years;<sup>82</sup> a substantially later age of onset than typical ET. Furthermore, since the investigators excluded patients with longstanding ET who later developed parkinsonism, this pathological study was not suited to address the ET–PD relationship. It should also be noted that the methodology differed between contrasting studies in these two groups, with Lewy bodies in the former being relatively abundant, and observed with a hematoxylin and eosin stain,<sup>77</sup> while a more sensitive alpha synuclein stain was used in identifying incidental Lewy bodies in the latter group's study.<sup>82</sup>

## Genetics

Although ET is well recognized as a familial condition, the causative gene or genes have not yet been identified. While a number of studies have failed to identify causative gene(s),<sup>83–92</sup> there have been some cases in which genes appear to have an overlapping role in the risk of developing ET and PD. *LINGO1*, a gene that plays a potential role in the pathophysiology of ET,<sup>93</sup> has been also suggested to play a role in the pathophysiology of some cases of PD.<sup>94–96</sup> Variants in *LINGO2* have been also associated with an increased risk of developing both ET and PD.<sup>96,97</sup> Variants in *HS1BP3*, a gene that plays a role in catecholamine and serotonin metabolism, have also been associated both with ET and PD.<sup>98,99</sup> One study of 571 ET patients identified a variant in *DNAJC13*, found to be associated with PD, in two ET patients (0.3%).<sup>100</sup> This variant had previously been undetectable in a large control population.<sup>101</sup> A variant in the gene *HTRA2*, which codes for a mitochondrial serine protease, has also been associated with both

ET and PD in one Turkish kindred.<sup>102</sup> An allele in the non-amyloid component of plaques (*NACP*-Rep1, which serves as a promoter region for alpha synuclein, and has a known association with an increased risk of PD, was also shown to occur at an increased frequency in patients with ET relative to controls.<sup>103</sup> One study of *LRRK2* variants that are thought to be protective in the development of PD failed to demonstrate a similar protective effect in the risk of developing ET, but did show a trend towards a reduced incidence.<sup>104</sup> “Functional” variants have been recently identified in *CACNA1G* (*Cav3.1*) gene in three ET families (Clark, personal communication, 2018). Although electrophysiologic studies by whole cell patch clamp recordings in HEK293T cells expressing the Cav3.1 mutant channels showed significant differences in the gating of the mutant Cav3.1 channels compared to the wild-type channel, it is not yet clear whether this variant represents a pathogenic mutation. While the search for causative gene(s) in ET has been thus far unsuccessful,<sup>105</sup> the application of new techniques may provide better insights into the genetics of ET.

In contrast to ET, PD has traditionally been considered mostly a sporadic disease, with cases demonstrating clear Mendelian inheritance patterns representing only about 10% of PD as a whole. In addition to the over 20 genes identified in such cases, there has increasingly been an identification of risk factor genes, such as *GBA*, *LRRK2*, *MAPT*, and *SNCA* in PD patients.<sup>106,107</sup> Genetic abnormalities found in sporadic and familial PD have been also evaluated in patients with ET, though without an association thus far. For example, the mutations in gene for glucocerebrosidase (*GBA*), recognized as a common genetic risk for PD,<sup>108,109</sup> have not been observed in ET.<sup>110,111</sup> Nevertheless, due to noted overlapping features, genetic research into PD may provide new pathways and better insights into identifying the elusive causative gene or genes in ET.

## Conclusion

While a wealth of literature supports the relationship between ET and PD (as summarized in Table 1), the association is not yet fully defined or understood. This may be due to differences in populations studied and the absence of a “gold standard” for the diagnosis of ET or PD. Because of the clinical (and likely pathogenic) heterogeneity of ET, future studies should consider categorizing ET into distinct subtypes rather than simply referring to this entity as a “syndrome” and dividing it into only two categories: ET and ET plus. Phenotype-specific physiological, genetic, and pathological biomarkers are needed to provide a pathogenesis-based categorization, and eventually treatment, of ET.

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