Isolated and combined genetic tremor syndromes: a critical appraisal based on the 2018 MDS criteria

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Abstract

The 2018 consensus statement on the classification of tremors proposes a two-axis categorization scheme based on clinical features and etiology. It also defines “isolated” and “combined” tremor syndromes depending on whether tremor is the sole clinical manifestation or is associated with other neurological or systemic signs. This syndromic approach provides a guide to investigate the underlying etiology of tremors, either genetic or acquired.

Several genetic defects have been proven to cause tremor disorders, including autosomal dominant and recessive, X-linked, and mitochondrial diseases, as well as chromosomal abnormalities. Furthermore, some tremor syndromes are recognized in individuals with a positive family history, but their genetic confirmation is pending. Although most genetic tremor disorders show a combined clinical picture, there are some distinctive conditions in which tremor may precede the appearance of other neurological signs by years or remain the prominent manifestation throughout the disease course, previously leading to misdiagnosis as essential tremor (ET). Advances in the knowledge of genetically determined tremors may have been hampered by the inclusion of heterogeneous entities in previous studies on ET. The recent classification of tremors therefore aims to provide more consistent clinical data for deconstructing the genetic basis of tremor syndromes in the next-generation and long-read sequencing era.

This review outlines the wide spectrum of tremor disorders with defined or presumed genetic etiology, both isolated and combined, unraveling diagnostic clues of these conditions and focusing mainly on ET-like phenotypes. Furthermore, we suggest a phenotype-to-genotype algorithm to support clinicians in identifying tremor syndromes and guiding genetic investigations.

1. INTRODUCTION

The 2018 consensus statement on tremor classification reiterates that tremor is an involuntary, rhythmic, oscillatory movement of a body part,[1,2] and provides a novel categorization scheme based on clinical features (Axis 1) and etiology (Axis 2).[1] Within Axis 1, tremor syndromes are termed “isolated” and “combined” depending on whether tremor occurs alone or is associated with other neurological or relevant systemic signs.[1] This syndromic approach aims to better delineate tremor phenotypes and investigations of both genetic and acquired tremor syndromes.[1]

Many tremor disorders have a known genetic basis, including autosomal dominant (AD) and recessive (AR), X-linked and mitochondrial diseases, as well as chromosomal abnormalities. Moreover, some patients with tremor have positive family histories, but lack molecular diagnosis,[1] suggesting Mendelian inheritance of hitherto unknown genes or more complex heritability patterns. Most genetic tremor disorders are combined syndromes. However, in some distinctive conditions, tremor may precede other neurological signs by years or remain the sole or prominent manifestation, potentially masquerading as essential tremor (ET).

This review outlines the broad spectrum of isolated and combined tremor syndromes with defined or presumed genetic etiology. Given the numerous genes and chromosomal abnormalities linked to tremor disorders, we focus on ET-like phenotypes and highlight clues to diagnose other distinctive phenotypes. Monogenic disorders are presented first according to their inheritance patterns and chromosomal aberrations thereafter. A phenotype-to-genotype algorithm is provided at the end. Previously unpublished videos (Video 1) and references to previously published videos (Supplementary Table) showing some tremor disorders covered by this review are provided.

2. INHERITED AUTOSOMAL DOMINANT TREMOR DISORDERS

2.1 Essential tremor

ET is an isolated tremor syndrome characterized by bibrachial action tremor with or without tremor in other body parts (e.g., head, larynx, lower limbs).[1] Prevalence is estimated at 1% in the general population and 4-5% in people over 65 years.[3] Age of onset ranges from childhood to late adulthood, with a bimodal distribution showing peaks before 24 years of age, and after 46 years of age.[4] Some affected individuals display alcohol sensitivity.[1,2] Positive family history is present in 20-90% of ET cases, suggesting AD inheritance.[5] Candidate loci and genes associated with ET are listed in Table 1.[6-29] However, no genetic findings have conclusively been replicated, and ET etiology remains controversial. Many factors may have hampered the dissection of genetic underpinnings of ET.[35] First, the longstanding lack of stringent diagnostic criteria and the lack of biomarkers for ET which may have facilitated contamination of ET study cohorts with tremor disorders misdiagnosed with ET (e.g., Klinefelter syndrome (KS), fragile X-related tremor/ataxia syndrome (FXTAS), DYT-*ANO3* (DYT24),[36] and SCA-*PPP2R2B* (SCA12)[36]), or with

“ET plus” syndromes, where additional subtle neurological signs (e.g., mild memory impairment, impaired tandem gait, subtle body posturing) are present.[1] Second, the reduced penetrance of ET observed in ET families. Third, the high rate of phenocopies in ET pedigrees, i.e. people with a similar or identical phenotype resulting from different underlying genotypes or environmental nongenetic factors. Fourth, the possible contribution of multiple risk loci, epigenetic modifications, and environmental influences in the pathogenesis of ET.[35] Finally, the intrinsic limitations of genetic technologies available for ET research over time. For instance, early genetic research on ET was mainly represented by genome-wide association studies (GWAS) whose limitations have recently been reviewed by Tam et al.[37] As another example, next-generation sequencing (NGS) has not allowed to accurately analyze genomic regions carrying structural variation, repetitive sequences, guanine-cytosine rich sequences, or sequences with multiple homologous elements, but the emerging long-read sequencing (LRS) technologies promise to overcome specific limitations of NGS and might shed light on the significance of noncoding genomic regions, complex genomic variants, repeat expansions, and DNA methylation patterns in the pathogenesis of ET.[38,39] Against this background, LRS has recently contributed to identify a GCC trinucleotide repeat expansion in the *NOTCH2NLC* gene in 11 Chinese kindreds with ET,[29] but this finding has not been replicated in independent studies yet.

In summary, ET and ET plus represent clinical syndromes of heterogeneous possibly genetic etiology. In this context, the recent classification of tremors should promote deeper clinical phenotyping to deconstruct genetic tremor syndromes in the NGS and LRS era.[1]

2.2 Autosomal dominant primary dystonias

Tremor is part of the motor phenomenology of dystonia,[40] therefore all genes associated with dystonia may underpin isolated and combined tremor syndromes.[1] Dystonic tremor manifests as a rhythmic, intermittent, patterned movement in body regions which are primarily affected or unaffected by dystonia. It may appear before overt dystonic posturing and abate in response to sensory tricks or null-point positioning.[40] An overview of monogenic primary dystonias is found elsewhere, including the AD dystonia phenotypes related to *TOR1A* (DYT1), *THAP1* (DYT6), and *GNAL* (DYT25) genes.[41-45] Tremor is often reported as a major clinical feature in DYT-*ANO3* and DYT/PARK-*GCH1* (DYT5a),[36] discussed below.

DYT-*ANO3* is caused by a heterozygous mutation in *ANO3*, which maps on chromosome 11p14.2-p14.3 and encodes anoctamin 3, a $Ca2^{+}$-gated chloride channel highly expressed in the striatum.[46] Age of onset ranges between childhood and the sixth decade.[46-48] Tremor involving the head, voice, and upper limbs in various combinations is often the earliest manifestation, and most prominent finding throughout the disease course, mimicking ET or *SCGE*-related myoclonus-dystonia (Supplementary Table); dystonic posturing is often minimal.[49] Contiguous spread over years is possible, but generalization has never been reported.[49] Subcortical myoclonus can also be observed.[49]

DYT/PARK-*GCH1* is a dopa-responsive dystonia caused by a heterozygous mutation in *GCH1*, which maps on chromosome 14q22.1-q22.2 and encodes the enzyme GTP cyclohydrolase 1.[50] Upper-limb postural tremor has been reported, either alone or with parkinsonism, in both childhood- and adult-onset cases.[50,51] Voice, head, chin and parkinsonian rest tremor are also described.[51] Tremor is dopa-responsive and shows diurnal fluctuation.[50] AR inheritance has also been reported in DYT/PARK-*GCH1*.[52]

2.3 Autosomal dominant spinocerebellar ataxias

Tremor is common in AD spinocerebellar ataxias (SCAs). A 2-3 Hz titubatory head or trunk tremor reflects cerebellar dysfunction, and is therefore not indicative of a specific SCA. However, action tremor of the hands resembling ET has been reported as presenting sign in SCA-*PPP2R2B* and SCA-*FGF14* (SCA27),[36] which are herein discussed in detail.[53-55] Palatal tremor is part of the phenotypic spectrum of SCA20 and SCA-*ATXN7* (SCA7),[36] both important differential diagnoses of progressive ataxia with palatal tremor (PAPT; see below).[56-58] Rest tremor is rare in SCAs, usually indicating coexisting parkinsonism, as observed in SCA-*ATXN2* (SCA2) and SCA-*ATXN3* (SCA3).[36,59]

SCA-*PPP2R2B (SCA12)* is caused by a CAG/CTG repeat expansion in the 5' untranslated region of *PPP2R2B*, which maps on chromosome 5q32 and encodes a brain-specific regulatory subunit of the phosphatase PP2A.[60,61] Individuals with more than 46 repeats on one allele develop the disease.[62] Rather than the gait ataxia typical of SCAs, SCA-*PPP2R2B* often presents with prominent or isolated upper-limb and sometimes head action tremor (Video 1, Segment 1).[60] SCA-*PPP2R2B* is particularly common among the Agarwal community from northern India, but also reported in European, American, and non-Indian Asian kindreds.[63] Onset is generally in the fourth decade. Disease progression is slow and patients display varied clinical manifestations, including cerebellar signs (i.e., gait ataxia, limb dysmetria, dysarthria, abnormal eye movements), parkinsonism, dystonia, hyperreflexia, psychiatric symptoms, and, in later stages, cognitive decline.[63] Cerebral and cerebellar atrophy are typical MRI findings.[63] Testing for SCA-*PPP2R2B* should be considered in individuals with ET-like tremor and a positive family history of cerebellar, parkinsonian, pyramidal, and cognitive manifestations, especially if geographical provenance and brain imaging are consistent. Despite being an ET phenocopy at onset, SCA-*PPP2R2B* has not been associated with ET in a large cohort study.[64]

A heterozygous mutation in the gene encoding fibroblast growth factor 14 (*FGF14*) on chromosome 13q34 cause SCA-*FGF14* (SCA27), which usually manifests with childhood-onset hand "trembling" (high-frequency, small-amplitude tremor) exacerbated by emotions and fatigue, and/or head titubation.[65] Tremor is the initial clinical feature in 60% of cases (and present in over 95%), and may precede the appearance of progressive or episodic ataxia, dysarthria, nystagmus, orofacial dyskinesia, psychiatric manifestations and cognitive impairment by many years.[65] Mild to moderate cerebellar atrophy on MRI has been reported in 20% of cases, mainly older individuals.[59,65] The diagnosis should therefore be considered in patients with ataxia who report tremor since childhood, or other associated features, such as episodic ataxia and neuropsychiatric symptoms.

2.4 Autosomal dominant monogenic Parkinson's disease

All genes causing monogenic Parkinson's disease (PD) may be linked with combined tremor syndromes, as rest tremor is a cardinal motor feature. Hand rest tremor in monogenic PD is indistinguishable from the classic pill-rolling tremor observed in idiopathic PD; unilateral leg rest tremor has been reported as a presenting feature in many PARK-*LRRK2* (PARK8; chromosome 12q12), and may precede the appearance of other parkinsonian features by many years.[36,66-67] An overviews of monogenic PD is available elsewhere.[68]

2.5 Neuroferritinopathy

Neuroferritinopathy is an AD neurodegeneration with brain iron accumulation (NBIA) syndrome. Caused by mutations in the ferritin light chain gene (*FTL*; chromosome 19q13.33)[69], it was originally described in families from Northern England, but later also in France, Italy, Japan, and India. Neuroferritinopathy usually begins between the fourth and sixth decade of life with either prominent chorea, dystonia, pyramidal signs, or a bradykinetic-rigid syndrome. Onset with upper-limb postural and kinetic tremor, followed by gait difficulties and progressive cognitive impairment has been reported by several authors.[70-71] Palatal tremor was reported with cognitive decline in affected individuals of British and French ancestry.[70-73] Laboratory investigations reveal low to low-normal serum ferritin levels, with normal iron, hemoglobin and transferrin. Neuroradiological clues include cortical iron deposition (pencil lining sign),[74] bilateral pallidal necrosis, and cystic cavitation of the basal ganglia in advanced stages.[75]

2.6 Tremor related to genes causing frontotemporal dementia with parkinsonism

The genetic landscape of the syndrome of frontotemporal dementia with parkinsonism (and sometimes motor neuron disease) has been clarified in recent decades with the identification of multiple causative genes including *MAPT*, *PRGN*, *TARDP*, *VCP*, *CHMP2B*, and *C9orf72*.[76-82] In this context, parkinsonism generally manifests as an akinetic-rigid syndrome, with typical resting tremor being reported in less than 10% of cases.[77] *FUS* mutations rarely cause parkinsonism associated with a postural tremor resembling ET.[81]

2.7 Hereditary geniospasm

Hereditary geniospasm (HG) is an isolated tremor syndrome characterized by recurrent, paroxysmal elevation-and-depression of the chin and lower lip due to rhythmic mentalis muscle contractions at frequencies between 4-30 Hz.[83,84] It is inherited as an AD trait with approximately 80% penetrance.[83] Episodes occur spontaneously or triggered by stress and last seconds to several hours. HG usually manifests soon after birth or in early childhood but frequency and severity of episodes generally decrease with age. Although the genes responsible for HG remain unknown, a genome-wide linkage analysis mapped some cases to chromosome 9q13-q21, and confirmed the genotypic heterogeneity of the disorder.[83] Despite its

denomination, neurophysiological findings suggest that HG represents a focal brainstem myoclonus rather than tremor.[84]

2.8 Autosomal dominant progressive ataxia with palatal tremor

PAPT is a rare clinical syndrome characterized by progressive cerebellar dysfunction and low-frequency (1-2 Hz) palatal tremor. While increasing evidence suggests that sporadic PAPT represents a novel 4-repeat tauopathy,[85] several genetic disorders are recognized to underlie familial cases of PAPT. These include late-onset Alexander disease,[86] SCA20[56] and SCA-*ATXN7* (SCA7)[36,57] (see Table 2), the AR disorders GM2-gangliosidosis[87] and cerebrotendineous xantomatosis[88] (see Table 3), and mutations in the mitochondrial polymerase gamma gene (*POLG*; see section 5).[89]

Alexander disease is a rare AD leukodystrophy with age of onset from infancy to the early seventh decade. Adult-onset forms manifest with bulbar signs (dysarthria and dysphagia), spasticity, slowly progressive gait ataxia, dysautonomia, sleep disturbances, and cognitive impairment.[86,90] A 2-Hz palatal tremor is reported in around 40% of cases (Supplementary Table).[91] The disease is caused by mutations in *GFAP*, which maps on chromosome 17q21.31 and codes for the glial fibrillary acidic protein.[86] On brain MRI, almost 90% of late-onset cases show severe medullary and cervical spinal cord atrophy, with a preserved basis pontis ('tadpole sign').[92] Although white matter abnormalities may coexist, lesion load is never as high as in early-onset disease.[86]

2.9 Autosomal dominant hereditary spastic paraplegias

Tremor rarely forms part of the spectrum of hereditary spastic paraplegias (HSPs).[93] Orthostatic tremor has been reported as a presenting or additional sign in three independent cases of HSP-*REEP1* (HSP31; Supplementary Table).[36,94,95] Furthermore, hand tremor has been described in HSP-*SPAST* (HSP4).[36,93]

Table 2 provides summaries of the above-mentioned and other AD tremor disorders.[41-86,89-102]

3. INHERITED AUTOSOMAL RECESSIVE TREMOR DISORDERS

3.1 Wilson's disease

Wilson's disease (WD) is an AR disorder of copper metabolism caused by biallelic mutations in *ATP7B* (chromosome 13q14.3),[103] which results in defective copper excretion into the biliary tract, and subsequent toxic accumulation of free copper in different organs, primarily the liver and brain. Hepatic WD typically presents in late childhood, whereas neurological manifestations generally occur in the second or third decade (though cases presenting as young as 6 and as old as 72 years have been reported).[104] Tremor is the presenting manifestation in up to 55% of neurological WD, and may be accompanied by dystonia,

parkinsonism, choreoathetosis, and cerebellar signs with dysphagia, dysarthria, and drooling.[103,104] Although well-known, the classic "wing-beating" tremor of the upper extremities is not the sole tremor type in WD (Supplementary Table). An ET-like tremor involving the arms, head and legs can be the earliest manifestation of neurological WD, as can tongue tremor with dysarthria.[103-106] WD-related tremors (which can be unilateral) may also be 'rubral-like', dystonic or parkinsonian and are generally accompanied by prominent postural and/or kinetic component. Investigations reveal low serum ceruloplasmin, excessive urinary copper excretion, cerebral atrophy with hyperintensity of the basal ganglia on T2-weighted MRI sequences, and Kayser-Fleischer rings. Liver biopsy may confirm the clinical suspicion in challenging cases.[103,104]

3.2 Autosomal recessive Parkinson's disease and primary dystonias

Overviews on monogenic PD and primary isolated dystonias are detailed elsewhere.[41-43,45,68] Among AR PD, PARK-*Parkin* (PARK2), PARK-*PINK1* (PARK6), PARK-*DJ-1* (PARK7), PARK-*FBXO7* (PARK15), PARK-*DNAJC6* (PARK19), and PARK-*SYNJ1* (PARK20) may manifest with dystonic and/or parkinsonian rest tremor usually before the age of 40.[36,107-111] DYT/PARK-*SLC6A3* causes infancy-, childhood-, and rarely adult-onset parkinsonism-dystonia with tremor.[36,112] An entity called *benign tremulous parkinsonism of the young*, characterized by rest and/or postural tremor in the legs or hands, sometimes as the sole or prominent feature of PD, has been reported in juvenile PARK-*Parkin*.[113] *PLA2G6*- and *ATP13A2*-related disorders can present as an AR parkinsonian syndrome, including rest tremor, and are reported in details below.[114] AR isolated dystonias related to the *HPCA*, *COL6A3*, and *VPS16* genes are extremely rare. Mutations in the *THAP1* (DYT6) or *GNAL* (DYT25) genes, which are usually dominantly inherited, can also be inherited in an AR manner.[45]

3.3 Autosomal recessive syndromes of neurodegeneration with brain iron accumulation

All genes linked to AR NBIA disorders may underlie combined tremor syndromes, including *PANK2*, *PLA2G6*, *C19orf12*, *COASY*, *FA2H*, *ATP13A2*, and *CP*.[114] Isolated rest or dystonic tremor of the upper limbs is reported as the presenting sign in atypical cases of NBIA/DYT-*PANK2* (PKAN) with late onset (second to fourth decade).[36,115-119] In atypical cases of NBIA/DYT/PARK-*PLA2G6* (PLAN) with onset in late adolescence or early twenties with dystonia-parkinsonism, pill-rolling tremor is present in approximately two thirds of cases along with psychiatric manifestations and rapid cognitive decline.[114,120] The clinical picture of aceruloplasminemia, a disorder resulting from biallelic mutations in the gene coding for ceruloplasmin (*CP*), encompasses different movement disorders including tremor, chorea, ataxia, and/or dystonia alongside psychiatric and cognitive changes, diabetes mellitus and retinopathy.[121,122] Laboratory investigations usually reveal absent or very low serum ceruloplasmin with normal copper excretion and high ferritin. On MRI, iron deposition may be detected in the basal ganglia, red nucleus, and dentate, but also in the liver.[121,122] Intention tremor or parkinsonism with rest tremor have been described alongside dystonia, spasticity, cerebellar signs, neuropathy, and visual failure in

mitochondrial membrane protein-associated neurodegeneration (MPAN), a childhood-onset NBIA syndrome caused by biallelic mutations in *C19orf12* (chromosome 19q12).[123,124] Recently, AD mode of inheritance has also been reported for MPAN.[125]

3.4 Autosomal recessive inborn errors of metabolism

A plethora of AR neurometabolic diseases include tremor in their clinical phenotype,[126] including glutaric aciduria type I, classic galactosemia, and phenylketonuria. In these conditions, tremor may appear in early childhood or as late-onset sequela, regardless of prompt initiation of dietary treatment (Supplementary Table).[126,127] Glutaric aciduria type I is a disorder of lysine and tryptophan metabolism due to mutations in the glutaryl-CoA dehydrogenase gene (*GCDH*; chromosome 19p13). Although the classic phenotype encompasses acute encephalopathic crises precipitated by febrile episodes before the age of 2, bibrachial dystonic tremor with orofacial dyskinesias starting from adolescence or early adulthood have been reported in otherwise asymptomatic individuals.[128] Classic galactosemia is an inborn error of galactose metabolism caused by pathogenic variants in the galactose-1-phospate uridylyltransferase gene (*GALT*; chromosome 9p13). Acute systemic complications are typical of disease presentation in newborns. However, neurological manifestations, including action tremor of the arms and head, dystonia, cerebellar and pyramidal signs, as well as late-onset complications (e.g., premature ovarian failure (POF)) have been reported despite strict dietary galactose restriction since birth.[129]

Table 3 provides brief summaries of the above-mentioned and other AR tremor disorders.[87,88,93,103-136]

4. INHERITED X-LINKED TREMOR DISORDERS

4.1 Fragile X-associated tremor ataxia syndrome

FXTAS is a late-onset neurodegenerative disorder affecting around 40% of males carrying a premutation (CGG trinucleotide expansion of 55-200 repeats) allele in the 5' untranslated region of fragile X mental retardation gene (*FMR1*; chromosome Xq27.3). Estimated prevalence is 1:800 in males and 1:250 in females.[137,138] Onset is generally in the seventh decade with progressive disabling tremor and ataxia, variably associated with parkinsonism, cognitive and behavioral impairment, autonomic dysfunction, peripheral neuropathy, and sleep disturbances. Tremor is the earliest sign in nearly 80% of cases and may precede other symptoms by years. Documented tremor phenotypes include ET-like tremor affecting the hands, axial tremor, and non-isolated unilateral upper-limb rest tremor (Video 1, Segment 2).[138] Due to stochastic X-chromosome inactivation, female premutation carriers rarely develop FXTAS, though a case series reports tremor in nearly 40% of females permutation carriers, and many suffer from POF and depression.[139] A FXTAS-like phenotype has also been reported in fragile X syndrome (>200 repeats). In FXTAS, brain MRI shows T2 hyperintensities in the periventricular white matter and middle cerebellar

peduncles (MCP sign) in 60% of male and 13% of female carriers.[138] The MCP sign on brain MRI along with a family history of mental retardation in male offspring and/or of amenorrhea before the age of 40 in females should prompt fragile X carrier testing.

4.2. Lubag disease

Lubag disease (DYT/PARK-*TAF1*) is an X-linked dystonia-parkinsonism described in males of maternal Filipino descent. Mutations in the noncoding regions within, and close to, the TATA-binding protein-associated factor-1 gene (*TAF1*; chromosome Xq13.1) have been reported as cause of the disease.[140] Age of onset ranges from 12 to 79 years.[141] The classic phenotype is one of focal cranio-cervical dystonia that spreads to other body regions over time, and may combine with, or be replaced by, parkinsonism. Tremor and parkinsonism are common at presentation and may precede or overshadow dystonic features.[142] Tremor in DYT/PARK-*TAF1* dystonia affects the head or limbs, and may appear at rest, on posture and/or during movements. It is often asymmetric and can be misdiagnosed as PD or ET. Lubag patients may also exhibit myorhythmia.[141] Female carriers are mostly asymptomatic, though a small minority manifest dystonia, parkinsonism, and/or chorea. Lubag disease should be suspected when an isolated or combined tremor syndrome occurs in individuals of Filipino ancestry and there is a family history of parkinsonism and/or dystonia consistent with X-linked inheritance.[141]

Table 4 provides brief summaries of the above-mentioned and other X-linked tremor disorders.[137-147]

5. INHERITED MITOCHONDRIAL TREMOR DISORDERS

Defects in maternally inherited mitochondrial DNA (mtDNA) or in nuclear genes (nDNA) encoding respiratory chain subunits may result in isolated and combined tremor syndromes.[89,148-152] Mutations in *POLG* (nDNA) may cause early-onset levodopa-responsive parkinsonism with typical rest tremor with either dominant or recessive inheritance. *POLG*-related parkinsonism usually begins around age 40, but onset has been reported as early as the third decade in some families. *POLG* mutations may also underlie familial PAPT.[89,148] A task-specific dystonic tremor was the presenting feature in a patient with pathogenic variant in *SURF1*-related Leigh syndrome (nDNA).[149] A *C10orf2* TWINKLE variant has been reported in a patient presenting with simultaneous orthostatic tremor and eyelid ptosis.[150] Cytochrome c oxidase deficiency due to mutation in *COX20* gene (mtDNA) causes a childhood-onset cerebellar ataxia with intention tremor and pyramidal signs.[151] An extensive review of mitochondrial disorders is covered elsewhere.[149,151,152]

6. TREMOR DISORDERS RELATED TO CHROMOSOMAL ABNORMALITIES

Sex chromosome aneuploidies

Tremor is a common manifestation of sex chromosome aneuploidies, including KS, Jacobs syndrome (JS), and rarer supernumerary X or Y syndromes (Supplementary Table).[153-159]

KS is the most frequent sex chromosome abnormality among males (1:700 newborns) and the most common cause of infertility in the male population. The clinical picture includes tall stature from puberty, arm span exceeding height, and hypergonadotropic hypogonadism/androgen deficiency.[153] Intention tremor of the upper extremities, sometimes associated with head, voice, and leg tremor, has been reported in up to 75% of individuals with KS (47,XXY karyotype).[154,155]

Unilateral or bilateral rest, postural and/or intention tremor of the arms as well as head tremor is also recognized in JS (47,XYY karyotype). Despite a prevalence of 1:1,000 in the male population, it is estimated that up to 88% of cases remain undiagnosed in their lifetime.[153,156] Clinical clues include tall stature, central adiposity, macrocephaly, macro-orchidism, hypotonia, clinodactyly, and hypertelorism. Half of males with XYY karyotype receive a diagnosis of attention deficit or autistic spectrum disorder.[156]

Postural and/or action tremor of the upper limbs with onset during the first or second decade is reported in 48,XXYY syndrome, which has an estimated prevalence of approximately 1:18,000-1:40,000 among newborn males. Physical features are similar to those seen in KS, although 48,XXYY patients exhibit significantly more neurodevelopmental and psychological features, including dysmorphic features (e.g., long face, epicanthal folds, poor dentition), pes planus, attention deficit disorder, and learning difficulties.[153,157-159]

In summary, males presenting with tremor from an early age with suggestive physical features (tall stature, micro- or macro-orchidism, and rarely, facial dysmorphism), and a history of infertility and/or early developmental delays or learning disabilities should prompt karyotyping to evaluate for sex chromosome aneuploidies.[153-159] As aneuploidies are not inherited, family history is usually unremarkable.

Table 5 provides brief summaries of tremor disorders related to sex chromosome aneuploidies and structural chromosomal abnormalities.[153-161]

7. DISCUSSION

A plethora of gene and chromosomal abnormalities are known to cause isolated and combined tremor syndromes. Details on genetic disorders causing tremor and relevant clues to diagnosis are reported in Tables 2 to 5. Figure 1 provides a phenotype-to-genotype algorithm to guide clinicians in the differential diagnosis and genetic testing options.

Most genetic tremor disorders exhibit a complex clinical picture when their phenotype is fully expressed. However, some (e.g., DYT-*ANO3*, SCA-*PPP2R2B*, FXTAS, KS) may resemble ET both at onset and for many years thereafter. Moreover, some tremor syndromes of uninvestigated or undetermined etiology may be erroneously referred to as ET in clinical practice. By providing a detailed syndromic approach to tremors and strict diagnostic criteria for ET, the 2018 tremor classification allows stratification of patients into phenotypically homogeneous subgroups, and may ultimately contribute to further advances in our understanding of the genetic basis of tremors.

Deconstructing Axis 1 of the recent classification,[1] the differential diagnosis of presumed genetic tremors appears to be largely based on the presence or absence of associated signs, as illustrated in Figure 1. Young age of onset narrows the differential diagnosis, as few genetic tremor disorders manifest in childhood or adolescence (e.g., WD, KS, some monogenic primary dystonias and neurometabolic diseases). Specific patterns of body distribution can aid the diagnostic process (e.g., palatal tremor: Alexander disease, SCA20, *POLG*-related disorders; laryngeal tremor: dystonic conditions, ET). Similarly, rest tremor limits the differential diagnoses mostly to parkinsonian conditions, while intention tremor should prompt a search for other signs of cerebellar involvement, as seen in SCAs and other ataxic syndromes. Abnormal laboratory tests may hint at the diagnosis. These include serum ceruloplasmin and urinary copper levels in WD and aceruloplasminemia, iron studies in neuroferritinopathy and aceruloplasminemia, sex hormone levels in sex chromosome aneuploidies, and CSF analysis in dopa-responsive dystonia and rarer neurometabolic diseases. Specific imaging findings on brain MRI in FXTAS, WD, NBIA, and positive dopamine receptor imaging in PD and other parkinsonian condition can also be directive.

It is noteworthy that genetic tremor syndromes often occur in the absence of a positive family history of tremor. Although being particularly frequent for AR, X-linked, and classic mitochondrial inheritance, this may also occur in AD disorders with incomplete or delayed penetrance, or due to *de novo* mutations. Moreover, sex chromosome aneuploidies are not inherited, and parents of a child with one of these conditions are not at an increased risk of having a second affected child. Geographical provenance may prove useful, suggesting diagnoses such as SCA-*PPP2R2B*, DYT/PARK-*TAF1*, and neuroferritinopathy. A history of intellectual disability in male offspring and/or premature amenorrhea in female family members should prompt clinical suspicion of FXTAS.

Despite the large number of genetic defects which are recognized to cause tremor disorders, a substantial proportion of patients with tremor-dominant clinical pictures encountered in the routine care remain without a definitive molecular diagnosis, even after undergoing NGS-based investigations, such as multigene panels, whole exome sequencing (WES) and whole genome sequencing (WGS).

An exponential growth of genetic knowledge on tremors is expected with the progress and widespread availability of NGS and LRS technologies.[38,39,162-164] Firstly, targeted gene panels allow simultaneous cost-effective testing for several known tremor-related genes and simplify molecular diagnosis of sporadic cases due to *de novo* mutations, when a priori hypotheses on responsible genes may be challenging. Secondly, WES or WGS combined with Sanger sequencing and linkage analysis may identify new genes

responsible for tremor syndromes in individual families. Thirdly, NGS makes large scale exome or genome screening possible, in order to identify new risk loci through approaches such as genome-wide association studies. Finally, LRS may enable the detection of variants in NGS blind genomic spots, reveal large and complex rearrangements, large insertions or deletions, haplotype phasing, and changes in DNA methylation.[38,39] NGS and LRS technologies may therefore shed light on heterogeneous etiologies underlying tremor syndromes currently labeled as ET, and expand the genotypic spectrum of rarer or more complex tremor disorders.[38,39,163,164] Continuous updating on genotype and phenotype of tremor syndromes will be possible with online resources, such as Online Mendelian Inheritance in Man® (https://www.omim.org/), Human GeneReviews® (https://www.ncbi.nlm.nih.gov/books/NBK1116/), Genecards® (http://www.genecards.org), and Movement Disorder Society Genetic mutation database (https://www.mdsgene.org). Nevertheless, thorough phenotyping of patients and targeted investigations remain the cornerstone of clinical decision-making for genetic testing and result interpretation.

All patients provided written informed consent to be videotaped, and to the publication of the videos in both the printed and online modalities.

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References

[1] K.P. Bhatia, P. Bain, N. Bajaj, R.J. Elble, M. Hallett, E.D. Louis, J. Raethjen, M. Stamelou, C.M. Testa, G. Deuschl; Tremor Task Force of the International Parkinson and Movement Disorder Society, Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society, Mov. Disord. 33 (2018) 75-87.

[2] G. Deuschl, P. Bain, M. Brin, Consensus statement of the Movement Disorder Society on tremor. Ad hoc scientific committee, Mov. Disord 13 Suppl. 3 (1998): 2-23.

[3] E.D. Louis, J.J. Ferreira, How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor, Mov. Disord. 25 (2010): 534e541.

[4] E.D. Louis, O. Dogu, Does age of onset in essential tremor have a bimodal distribution? Data from a tertiary referral setting and a population-based study, Neuroepidemiology 29 (2007): 208-212.

[5] F. Hopfner, D. Haubenberger, W.R. Galpern, K. Gwinn, A. Van't Veer, S. White, K. Bhatia, C.H. Adler, D. Eidelberg, W. Ondo, G.T. Stebbins, C.M. Tanner, R.C. Helmich, F.A. Lenz, R.V. Sillitoe, D. Vaillancourt, J.L. Vitek, E.D. Louis, H.A. Shill, M.P. Frosch, T. Foroud, G. Kuhlenbäumer, A. Singleton, C.M. Testa, M. Hallett, R. Elble, G. Deuschl G, Knowledge gaps and research recommendations for essential tremor, Parkinsonism Relat. Disord. 33 (2016): 27-35.

[6] J.R. Gulcher, P. Jónsson, A. Kong, K. Kristjánsson, M.L. Frigge, A. Kárason, I.E. Einarsdóttir, H. Stefánsson, A.S. Einarsdóttir, S. Sigurthoardóttir, S. Baldursson, S. Björnsdóttir, S.M. Hrafnkelsdóttir, F. Jakobsson, J. Benedickz, K. Stefánsson, Mapping of a familial essential tremor gene, FET1, to chromosome 3q13, Nat. Genet. 17 (1997): 84-87.

[7] J.J. Higgins, L.T. Pho, L.E. Nee, A gene (ETM) for essential tremor maps to chromosome 2p22-p25, Mov. Disord. 12 (1997): 859-864.

[8] A. Sazci, E. Ergul, K. Bayulkem, Association of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene in patients with essential tremor in Turkey, Mov. Disord. 19 (2004): 1472-1476.

[9] J.J. Higgins, R.Q. Lombardi, J. Pucilowska, J. Jankovic, E.K. Tan, J.P. Rooney, A variant in the HS1-BP3 gene is associated with familial essential tremor, Neurology 64 (2005): 417-421.

[10] A. Shatunov, N. Sambuughin, J. Jankovic, R. Elble, H.S. Lee, A.B. Singleton, A. Dagvadorj, J. Ji, Y. Zhang, V.E. Kimonis, J. Hardy, M. Hallett, L.G. Goldfarb, Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23, Brain 129 (2006): 2318-2331.

[11] G. Lucotte, J.P. Lagarde, B. Funalot, P. Sokoloff, Linkage with the Ser9Gly DRD3 polymorphism in essential tremor families, Clin. Genet. 69 (2006): 437-440.

[12] H. Stefansson, S. Steinberg, H. Petursson, O. Gustafsson, I.H. Gudjonsdottir, G.A. Jonsdottir, S.T. Palsson, T. Jonsson, J. Saemundsdottir, G. Bjornsdottir, Y. Böttcher, T. Thorlacius, D. Haubenberger, A. Zimprich, E. Auff, C. Hotzy, C.M. Testa, L.A. Miyatake, A.R. Rosen, K. Kristleifsson, D. Rye, F. Asmus, L. Schöls, M. Dichgans, F. Jakobsson, J. Benedikz, U. Thorsteinsdottir, J. Gulcher, A. Kong, K. Stefansson, Variant in the sequence of the LINGO1 gene confers risk of essential tremor, Nat. Genet. 41 (2009): 277-279. Erratum in: Nat. Genet. 41 (2009): 504.

[13] C. Vilariño-Güell, A.I. Soto-Ortolaza, A. Rajput, D.C. Mash, S. Papapetropoulos, R. Pahwa, K.E. Lyons, R.J. Uitti, Z.K. Wszolek, D.W. Dickson, M.J. Farrer, O.A. Ross, MAPT H1 haplotype is a risk factor for essential tremor and multiple system atrophy, Neurology 76 (2011): 670-672.

[14] S. Their, D. Lorenz, M. Nothnagel, C. Poremba, F. Papengut, S. Appenzeller, S. Paschen, F. Hofschulte, A.C. Hussl, S. Hering, W. Poewe, F. Asmus, T. Gasser, L. Schöls, K. Christensen, A. Nebel, S. Schreiber, S. Klebe, G. Deuschl, G. Kuhlenbäumer, Polymorphisms in the glial glutamate transporter SLC1A2 are associated with essential tremor, Neurology 79 (2012): 243-248.

[15] N.D. Merner, S.L. Girard, H. Catoire, C.V. Bourassa, V.V. Belzil, J.B. Rivière, P. Hince, A. Levert, A. Dionne-Laporte, D. Spiegelman, A. Noreau, S. Diab, A. Szuto, H. Fournier, J. Raelson, M. Belouchi, M. Panisset, P. Cossette, N. Dupré, G. Bernard, S. Chouinard, P.A. Dion, G.A. Rouleau, Exome sequencing identifies FUS mutations as a cause of essential tremor, Am. J. Hum. Genet. 91 (2012): 313-319.

[16] H. Unal Gulsuner, S. Gulsuner, F.N. Mercan, O.E. Onat, T. Walsh, H. Shahin, M.K. Lee, O. Dogu, T. Kansu, H. Topaloglu, B. Elibol, C. Akbostanci, M.C. King, T. Ozcelik, A.B. Tekinay, Mitochondrial serine protease HTRA2 p.G399S in a kindred with essential tremor and Parkinson disease, Proc. Natl. Acad. Sci. USA 111 (2014): 18285-18290.

[17] H. Hor, L. Francescatto, L. Bartesaghi, S. Ortega-Cubero, M. Kousi, O. Lorenzo-Betancor, F.J. Jiménez-Jiménez, A. Gironell, J. Clarimón, O. Drechsel, J.A. Agúndez, D. Kenzelmann Broz, R. Chiquet-Ehrismann, A. Lleó, F. Coria, E. García-Martin, H. Alonso-Navarro, M.J. Martí, J. Kulisevsky, C.N. Hor, S. Ossowski, R. Chrast, N. Katsanis, P. Pastor, X. Estivill, Missense mutations in TENM4, a regulator of axon guidance and central myelination, cause essential tremor, Hum. Mol. Genet. 24 (2015): 5677-5686.

[18] S. Ortega-Cubero, O. Lorenzo-Betancor, E. Lorenzo, J.A. Agúndez, F.J. Jiménez-Jiménez, O.A. Ross, I. Wurster, C. Mielke, J.J. Lin, F. Coria, J. Clarimon, M. Ezquerra, L. Brighina, G. Annesi, H. Alonso-Navarro, E. García-Martin, A. Gironell, M.J. Marti, K.C. Yueh, Z.K. Wszolek, M. Sharma, D. Berg, R. Krüger, M.A. Pastor, P. Pastor, TREM2 R47H variant and risk of essential tremor: a cross-sectional international multicenter study, Parkinsonism Relat. Disord. 21 (2015): 306-309.

[19] E. Sánchez, A. Bergareche, C.E. Krebs, A. Gorostidi, V. Makarov, J. Ruiz-Martinez, A. Chorny, A. Lopez de Munain, J.F. Marti-Masso, C. Paisán-Ruiz, SORT1 Mutation resulting in sortilin deficiency and p75(NTR) upregulation in a family with essential tremor, ASN Neuro. 7 (2015).

[20] A. Bergareche, M. Bednarz, E. Sánchez, C.E. Krebs, J. Ruiz-Martinez, P. De La Riva, V. Makarov, A. Gorostidi, K. Jurkat-Rott, J.F. Marti-Masso, C. Paisán-Ruiz, SCN4A pore mutation pathogenetically contributes to autosomal dominant essential tremor and may increase susceptibility to epilepsy, Hum. Mol. Genet. 24 (2015): 7111-7120.

[21] A. Rajput, J.P. Ross, C.Q. Bernales, S. Rayaprolu, A.I. Soto-Ortolaza, O.A. Ross, J. van Gerpen, R.J. Uitti, Z.K. Wszolek, A.H. Rajput, C. Vilariño-Güell, VPS35 and DNAJC13 disease-causing variants in essential tremor, Eur. J. Hum. Genet. 23 (2015): 887-888.

[22] X. Liu, N. Hernandez, S. Kisselev, A. Floratos, A. Sawle, I. Ionita-Laza, R. Ottman, E.D. Louis, L.N. Clark, Identification of candidate genes for familial early-onset essential tremor, Eur. J. Hum. Genet. 24 (2016): 1009-1015.

[23] S.H. Müller, S.L. Girard, F. Hopfner, N.D. Merner, C.V. Bourassa, D. Lorenz, L.N. Clark, L. Tittmann, A.I. Soto-Ortolaza, S. Klebe, M. Hallett, S.A. Schneider, C.A. Hodgkinson, W. Lieb, Z.K. Wszolek, M. Pendziwiat, O. Lorenzo-Betancor, W. Poewe, S. Ortega-Cubero, K. Seppi, A. Rajput, A. Hussl, A.H. Rajput, D. Berg, P.A. Dion, I. Wurster, J.M. Shulman, K. Srulijes, D. Haubenberger, P.

Pastor, C. Vilariño-Güell, R.B. Postuma, G. Bernard, K.H. Ladwig, N. Dupré, J. Jankovic, K. Strauch, M. Panisset, J. Winkelmann, C.M. Testa, E. Reischl, K.E. Zeuner, O.A. Ross, T. Arzberger, S. Chouinard, G. Deuschl, E.D. Louis, G. Kuhlenbäumer, G.A. Rouleau, Genome-wide association study in essential tremor identifies three new loci, Brain 139 (2016): 3163-3169.

[24] X.R. Leng, X.H. Qi, Y.T. Zhou, Y.P. Wang, Gain-of-function mutation p.Arg225Cys in SCN11A causes familial episodic pain and contributes to essential tremor, J. Hum. Genet. 62 (2017): 641-646.

[25] L. Yuan, X. Deng, Z. Song, S. Deng, W. Zheng, P. Mao, H. Deng, Systematic analysis of genetic variants in patients with essential tremor, Brain Behav. 8 (2018): e01100.

[26] A. Sazci, N. Uren, H.A. Idrisoglu, E. Ergul, The rs2228570 variant of the vitamin D receptor gene is associated with essential tremor, Neurosci. Bull. 35 (2019): 362-364.

[27] J. Chen, P. Huang, Y. He, J. Shen, J. Du, S. Cui, S. Chen, J. Ma, IL1B polymorphism is associated with essential tremor in Chinese population, BMC Neurol. 19 (2019): 99.

[28] Z. Odgerel, S. Sonti, N. Hernandez, J. Park, R. Ottman, E.D. Louis, L.N. Clark, Whole genome sequencing and rare variant analysis in essential tremor families, PLoS One 14 (2019): e0220512.

[29] Q.Y. Sun, Q. Xu, Y. Tian, Z.M. Hu, L.X. Qin, J.X. Yang, W. Huang, J. Xue, J.C. Li, S. Zeng, Y. Wang, H.X. Min, X.Y. Chen, J.P. Wang, B. Xie, F. Liang, H.N. Zhang, C.Y Wang, L.F. Lei, X.X. Yan, H.W. Xu, R.H. Duan, K. Xia, J.Y. Liu, H. Jiang, L. Shen, J.F. Guo, B.S. Tang, Expansion of GGC repeat in the human-specific NOTCH2NLC gene is associated with essential tremor, Brain 143 (2020): 222-233.

[30] L.J. Findley, W.C. Koller, Definitions and behavioural classifications, in: L.J. Findley, W.C. Koller (Eds), Handbook of Tremor Disorders, Marcel Dekker, New York, 1995, pp. 1–5.

[31] E.D. Louis, B. Ford, H. Lee, H. Andrews, G. Cameron, Diagnostic criteria for essential tremor. A population perspective, Arch. Neurol. 55 (1998): 823–828.

[32] R.J. Elble, Diagnostic criteria for essential tremor and differential diagnosis, Neurology 54 Suppl. 4 (2000): S2–S6.

[33] M.F. Brin, W. Koller, Epidemiology, genetics of essential tremor, Mov. Disord. 13 Suppl. 3 (1998): S55–S63.

[34] E.D. Louis, R. Ottman, B. Ford, S. Pullman, M. Martinez, S. Fahn, W.A. Hauser, The Washington Heights-Inwood Genetic Study of Essential Tremor: methodologic issues in essential-tremor research, Neuroepidemiology 16 (1997): 124-133.

[35] F. Hopfner, R.C. Helmich, The etiology of essential tremor: genes versus environment, Parkinsonism Relat. Disord. 46 (2018): S92-S96.

[36] C. Marras, A. Lang, B.P. van de Warrenburg, C.M. Sue, S.J. Tabrizi, L. Bertram, S. Mercimek-Mahmutoglu, D. Ebrahimi-Fakhari, T.T. Warner, A. Durr, B. Assmann, K. Lohmann, V. Kostic, C. Klein, Nomenclature of genetic movement disorders: Recommendations of the International Parkinson and Movement Disorder Society task force, Mov. Disord. 32 (2017): 724-725.

[37] V. Tam, N. Patel, M. Turcotte, Y. Bossé, G. Paré, D. Meyre, Benefits and limitations of genome-wide association studies, Nat. Rev. Genet. 20 (2019): 467-484.

[38] T. Mantere, S. Kersten, A. Hoischen, Long-Read Sequencing Emerging in Medical Genetics, Front. Genet. 10 (2019): 426.

[39] M.K. Midha, M. Wu, K.P. Chiu, Long-read sequencing in deciphering human genetics to a greater depth, Hum. Genet. 138 (2019): 1201-1215.

[40] A. Albanese, K. Bhatia, S.B. Bressman, M.R. Delong, S. Fahn, V.S. Fung, M. Hallett, J. Jankovic, H.A. Jinnah, C. Klein, A.E. Lang, J.W. Mink, J.K. Teller, Phenomenology and classification of dystonia: a consensus update, Mov. Disord. 28 (2013): 863-873.

[41] Müller U, The monogenic primary dystonia, Brain 132 (2009): 2005-2025.

[42] B. Balint, K.P. Bhatia, Isolated and combined dystonia syndromes - an update on new genes and their phenotypes, Eur. J. Neurol. 22 (2015): 610-617.

[43] M. Zech, D.D. Lam, L. Francescatto, B. Schormair, A.V. Salminen, A. Jochim, T. Wieland, P. Lichtner, A. Peters, C. Gieger, H. Lochmüller, T.M. Strom, B. Haslinger, N. Katsanis, J. Winkelmann, Recessive mutations in the alpha-3 (VI) collagen gene COL6A3 cause early-onset isolated dystonia, Am. J. Hum. Genet. 96 (2015): 883-893.

[44] N.E. Mencacci, I. Rubio-Agusti, A. Zdebik, F. Asmus, M.H. Ludtmann, M. Ryten, V. Plagnol, A.K. Hauser, S. Bandres-Ciga, C. Bettencourt, P. Forabosco, D. Hughes, M.M. Soutar, K. Peall, H.R. Morris, D. Trabzuni, M. Tekman, H.C. Stanescu, R. Kleta, M. Carecchio, G. Zorzi, N. Nardocci, B.

Garavaglia, E. Lohmann, A. Weissbach, C. Klein, J. Hardy, A.M. Pittman, T. Foltynie, A.Y. Abramov, T. Gasser, K.P. Bhatia, N.W. Wood, A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia, Am. J. Hum. Genet. 96 (2015): 938-947.

[45] B. Balint, N.E. Mencacci, E.M. Valente, A. Pisani, J. Rothwell, J. Jankovic, M. Vidailhet, K.P. Bhatia, Dystonia, Nat. Rev. Dis. Primers 4 (2018): 25.

[46] G. Charlesworth, V. Plagnol, K.M. Holmström, J. Bras, U.M. Sheerin, E. Preza, I. Rubio-Agusti, M. Ryten, S.A. Schneider, M. Stamelou, D. Trabzuni, A.Y. Abramov, K.P. Bhatia, N.W. Wood, Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis, Am. J. Hum. Genet. 91 (2012): 1041-1050.

[47] A. Münchau, E.M. Valente, M.B. Davis, V. Stinton, N.W. Wood, N.P. Quinn, K.P. Bhatia, A Yorkshire family with adult-onset cranio-cervical primary torsion dystonia, Mov. Disord. 15 (2000): 954–959.

[48] P.R. Blackburn, M.T. Zimmermann, J.M. Gass, K.G. Harris, M.A. Cousin, N.J. Boczek, O.A. Ross, E.W. Klee, P.W. Brazis, J.A. Van Gerpen, P.S. Atwal, A novel ANO3 variant identified in a 53-year-old woman presenting with hyperkinetic dysarthria, blepharospasm, hyperkinesias, and complex motor tics, BMC Med. Genet. 17 (2016): 93.

[49] M. Stamelou, G. Charlesworth, C. Cordivari, S.A. Schneider, G. Kägi, U.M. Sheerin, I. Rubio-Agusti, A. Batla, H. Houlden, N.W. Wood, K.P. Bhatia, The phenotypic spectrum of DYT24 due to ANO3 mutations, Mov. Disord. 29 (2014): 928-934.

[50] M. Segawa, A. Hosaka, F. Miyagawa, Y. Nomura, H. Imai, Hereditary progressive dystonia with marked diurnal fluctuation, Adv. Neurol. 14 (1976): 215-233.

[51] I. Trender-Gerhard, M.G. Sweeney, P. Schwingenschuh, P. Mir, M.J. Edwards, A. Gerhard, J.M. Polke, M.G. Hanna, M.B. Davis, N.W. Wood, K.P. Bhatia, Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients, J. Neurol. Neurosurg. Psychiatry 80 (2009): 839-845.

[52] S. Wijemanne, J. Jankovic, Dopa-responsive dystonia--clinical and genetic heterogeneity, Nat. Rev. Neurol. 11 (2015): 414-424.

[53] E. O'Hearn, S.E. Holmes, P.C. Calvert, C.A. Ross, R.L. Margolis, SCA-12: tremor with cerebellar and cortical atrophy is associated with a CAG repeat expansion, Neurology 56 (2001): 299–303.

[54] H.J. Schelhaas, P.F. Ippel, G. Hageman, R.J. Sinke, E.N. van der Laan, F.A. Beemer, Clinical and genetic analysis of a four-generation family with a distinct autosomal dominant cerebellar ataxia, J. Neurol. 248 (2001): 113–120.

[55] J.C. van Swieten, E. Brusse, B.M. de Graaf, E. Krieger, R. van de Graaf, I. de Koning, A. Maat-Kievit, P. Leegwater, D. Dooijes, B.A. Oostra, P. Heutink, A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected], Am. J. Hum. Genet. 72 (2003): 191–199.

[56] M.A. Knight, R.J. Gardner, M. Bahlo, T. Matsuura, J.A. Dixon, S.M. Forrest, E. Storey, Dominantly inherited ataxia and dysphonia with dentate calcification: spinocerebellar ataxia type 20, Brain 127 (2004): 1172–1181.

[57] G. Modi, M. Modi, I. Martinus, J. Rodda, D. Saffer, The clinical and genetic characteristics of spinocerebellar ataxia type 7 (SCA7) in three black South African families, Acta Neurol. Scand. 101 (2000): 177–182.

[58] M. Samuel, N. Torun, P.J. Tuite, J.A. Sharpe, A.E. Lang, Progressive ataxia and palatal tremor (PAPT): clinical and MRI assessment with review of palatal tremors, Brain 127 (2004): 1252-1268.

[59] J. van Gaalen, P. Giunti, B.P. van de Warrenburg, Movement disorders in spinocerebellar ataxias, Mov. Disord. 26 (2011): 792-800.

[60] S.E. Holmes, E. O'Hearn, R.L. Margolis, Why is SCA12 different from other SCAs?, Cytogenet. Genome Res. 100 (2003): 189-197.

[61] S.E. Holmes, E.E. O'Hearn, M.G. McInnis, D.A. Gorelick-Feldman, J.J. Kleiderlein, C. Callahan, N.G. Kwak, R.G. Ingersoll-Ashworth, M. Sherr, A.J. Sumner, A.H. Sharp, U. Ananth, W.K. Seltzer, M.A. Boss, A.M. Vieria-Saecker, J.T. Epplen, O. Riess, C.A. Ross, R.L. Margolis, Expansion of a novel CAG trinucleotide repeat in the 5 region of PPP2R2B is associated with SCA12, Nat. Genet. 23 (1999): 391-392.

[62] Y. Dong, J.J. Wu, Z.Y. Wu, Identification of 46 CAG repeats within PPP2R2B as probably the shortest pathogenic allele for SCA12, Parkinsonism Relat. Disord. 21 (2015): 398-401.

[63] E. O'Hearn, S.E. Holmes, R.L. Margolis, Spinocerebellar ataxia type 12, Handb. Clin. Neurol. 103 (2012): 535-547.

[64] L.N. Clark, X. Ye, X. Liu, K. Mirzozoda, E.D. Louis, Genetic analysis of ten common degenerative hereditary ataxia loci in patients with essential tremor, Parkinsonism Relat. Disord. 21 (2015): 943-947.

[65] C.L. Groth, B.D. Berman, Spinocerebellar ataxia 27: a review and characterization of an evolving phenotype, Tremor Other Hyperkinet. Mov. (NY) 8 (2018): 534.

[66] N.L. Khan, S. Jain, J.M. Lynch, N. Pavese, P. Abou-Sleiman, J.L. Holton, D.G. Healy, W.P. Gilks, M.G. Sweeney, M. Ganguly, V. Gibbons, S. Gandhi, J. Vaughan, L.H. Eunson, R. Katzenschlager, J. Gayton, G. Lennox, T. Revesz, D. Nicholl, K.P. Bhatia, N. Quinn, D. Brooks, A.J. Lees, M.B. Davis, P. Piccini, A.B. Singleton, N.W. Wood, Mutations in the gene LRRK2 encoding dardarin (PARK8) cause familial Parkinson's disease: clinical, pathological, olfactory and functional imaging and genetic data, Brain 128 (2005): 2786-2796.

[67] C. Paisàn-Ruìz, A. Sàenz, A. Lòpez de Munain, I. Martì, A. Martìnez Gil, J.F. Martì-Massò, J. Pèrez-Tur, Familial Parkinson's disease: clinical and genetic analysis of four Basque families, Ann. Neurol. 57 (2005): 365-372.

[68] A. Puschmann, Monogenic Parkinson's disease and parkinsonism: clinical phenotypes and frequencies of known mutations, Parkinsonism Relat. Disord. 19 (2013): 407-415.

[69] A.R. Curtis, C. Fey, C.M. Morris, L.A. Bindoff, P.G. Ince, P.F. Chinnery, A. Coulthard, M.J. Jackson, A.P. Jackson, D.P. McHale, D. Hay, W.A. Barker, A.F. Markham, D. Bates, A. Curtis, J. Burn, Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease, Nat. Genet. 28 (2001), 350-354.

[70] P.F. Chinnery, D.E. Crompton, D. Birchall, M.J. Jackson, A. Coulthard, A. Lombès, N. Quinn, A. Wills, N. Fletcher, J.P. Mottershead, P. Cooper, M. Kellett, D. Bates, J. Burn, Clinical features and natural history of neuroferritinopathy caused by the FTL1 460InsA mutation, Brain 130 (2007): 110-119.

[71] E. Ohta, T. Nagasaka, K. Shindo, S. Toma, K. Nagasaka, K. Ohta, Z. Shiozawa, Neuroferritinopathy in a Japanese family with a duplication in the ferritin light chain gene, Neurology 70 (2008): 1493–1494.

[72] A. Kubota, A. Hida, Y. Ichikawa, Y. Momose, J. Goto, Y. Igeta, H. Hashida, K. Yoshida, S. Ikeda, I. Kanazawa, S. Tsuji, A novel ferritin light chain gene mutation in a Japanese family with neuroferritinopathy: description of clinical features and implications for genotype-phenotype correlations, Mov. Disord. 24 (2009): 441-445.

[73] A.J. Wills, G.V. Sawle, P.R. Guilbert, A.R. Curtis, Palatal tremor and cognitive decline in neuroferritinopathy, J. Neurol. Neurosurg. Psychiatry 73 (2002): 91-92.

[74] A. Batla, M.E. Adams, R. Erro, C. Ganos, B. Balint, N.E. Mencacci, K.P. Bhatia, Cortical pencil lining in neuroferritinopathy: a diagnostic clue, Neurology 84 (2015): 1816-1818.

[75] E. Ohta, Y. Takiyama, MRI findings in neuroferritinopathy, Neurol. Res. Int. (2012) 2012: 197438.

[76] J.F. Baizabal-Carvallo, J. Jankovic, Parkinsonism, movement disorders and genetics in frontotemporal dementia, Nat. Rev. Neurol. 12 (2016): 175-185.

[77] J. Diehl-Schmid, J. Schūlte-Overberg, J. Hartmann, H. Förstl, A. Kurz, P. Häussermann, Extrapyramidal signs, primitive reflexes and incontinence in fronto-temporal dementia, Eur. J. Neurol. 14 (2007): 860–864.

[78] J. Siuda, S Fujioka, ZK Wszolek, Parkinsonian syndrome in familial frontotemporal dementia, Parkinsonism Relat. Disord. 20 (2014): 957-964.

[79] S. Davion, N. Johnson, S. Weintraub, M.M. Mesulam, A. Engberg, M. Mishra, M. Baker, J. Adamson, M. Hutton, R. Rademakers, E.H. Bigio, Clinicopathologic correlation in PGRN mutations, Neurology 69 (2007): 1113-1121.

[80] B.F. Boeve, K.B. Boylan, N.R. Graff-Radford, M. DeJesus-Hernandez, D.S. Knopman, O. Pedraza, P. Vemuri, D. Jones, V. Lowe, M.E. Murray, D.W. Dickson, K.A. Josephs, B.K. Rush, M.M. Machulda, J.A. Fields, T.J. Ferman, M. Baker, N.J. Rutherford, J. Adamson, Z.K. Wszolek, A. Adeli, R. Savica, B. Boot, K.M. Kuntz, R. Gavrilova, A. Reeves, J. Whitwell, K. Kantarci, C.R. Jr Jack, J.E. Parisi, J.A. Lucas, R.C. Petersen, R. Rademakers, Characterization of frontotemporal dementia and/or

amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72, Brain 135 (2012): 765-783.

[81] J. Yan, H.X. Deng, N. Siddique, F. Fecto, W. Chen, Y. Yang, E. Liu, S. Donkervoort, J.G. Zheng, Y. Shi, K.B. Ahmeti, B. Brooks, W.K. Engel, T. Siddique, Frameshift and novel mutations in FUS in familial amyotrophic lateral sclerosis and ALS/dementia, Neurology 75 (2010): 807-814.

[82] N. Chan, C. Le, P. Shieh, T. Mozaffar, M. Khare, J. Bronstein, V. Kimonis, Valosin-containing protein mutation and Parkinson's disease, Parkinsonism Relat. Disord. 18 (2012): 107-109.

[83] P.R. Jarman, N.W. Wood, M.T. Davis, P.V. Davis, K.P. Bhatia, C.D. Marsden, M.B. Davis, Hereditary geniospasm: linkage to chromosome 9q13-q21 and evidence for genetic heterogeneity, Am. J. Hum. Genet. 61 (1997): 928-933.

[84] A. Macerollo, T.A. Saifee, P. Kassavetis, G. Pilurzi, S.A. Schneider, M.J. Edwards, K.P. Bhatia, Abnormalities of masseteric inhibitory reflex in hereditary geniospasm: evidence for a brainstem myoclonus. Mov. Disord. Clin. Pract. 2 (2015): 49-52.

[85] A.F. Gao, A. Faust-Socher, M. Al-Murshed, M.R. Del Bigio, A.E. Lang, D.G. Munoz, Progressive ataxia and palatal tremor: two autopsy cases of a novel tauopathy, Mov. Disord. 32 (2017): 1465-1473.

[86] M. Brenner, A.B. Johnson, O. Boespflug-Tanguy, D. Rodriguez, J.E. Goldman, A. Messing, Mutation in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease, Nat. Genet. 27 (2001): 117–120.

[87] E. Pretegiani, F. Rosini, P. Federighi, A. Cerase, M.T. Dotti, A. Rufa, Pendular nystagmus, palatal tremor and progressive ataxia in GM2-gangliosidosis, Eur. J. Neurol. 22 (2015): e67-e69.

[88] M. Rossi, M. Cesarini, E.M. Gatto, A. Cammarota, M. Merello, A treatable rare cause of progressive ataxia and palatal tremor, Tremor Other Hyperkinet. Mov. (NY) 8 (2018): 538.

[89] N. Nicastro, E. Ranza, S.E. Antonarakis, J. Horvath, Pure progressive ataxia and palatal tremor (PAPT) associated with a new polymerase gamma (POLG) mutation, Cerebellum 15 (2016): 829-831.

[90] D. Thyagarajan, T. Chataway, R. Li, W.P. Gai, M. Brenner, Dominantly-inherited adult-onset leukodystrophy with palatal tremor caused by a mutation in the glial fibrillary acidic protein gene, Mov. Disord. 19 (2004): 1244–1248.

[91] T. Yoshida, M. Nakagawa, Clinical aspects and pathology of Alexander disease, and morphological and functional alteration of astrocytes induced by GFAP mutation, Neuropathology 32 (2012): 440-446.

[92] M. Namekawa, Y. Takiyama, J. Honda, H. Schimazaki, K. Sakoe, I. Nakano, Adult-onset Alexander disease with typical “tadpole” brainstem atrophy and unusual bilateral basal ganglia involvement: a case report and review of the literature, BMC Neurol. 10 (2010): 21.

[93] T. Lo Giudice, F. Lombardi, F.M. Santorelli, T. Kawarai, A. Orlacchio, Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms, Exp. Neurol. 261 (2014): 518-539.

[94] R. Erro, C. Cordivari, K.P. Bhatia, SPG31 presenting with orthostatic tremor, Eur. J. Neurol. 21 (2014): e34-e35.

[95] M. Picillo, R. Erro, R.P. Munhoz, A. Fasano, When shaking during standing points to hereditary spastic paraplegias, Parkinsonism Relat. Disord. 46 (2018): 92-94.

[96] A. Molloy, O. Kimmich, J. Martindale, H. Moore, M. Hutchinson, S. O'Riordan, A novel CACNA1A mutation associated with adult-onset, paroxysmal head tremor, Mov. Disord. 28 (2013): 842-843.

[97] E. Bernard, E. Broussolle, S. Thobois, Postural tremor as first symptom of Huntington disease, Rev. Neurol. (Paris) 166 (2010): 841-843.

[98] T. Nguyen, T.C. Danaila, G.L. Defer, Isolated postural tremor revealing Huntington's disease [abstract]. Mov. Disord. 27 Suppl. 1 (2012): 172.

[99] T. Konno, O.A. Ross, H.A.G. Teive, J. Sławek, D.W. Dickson, Z.K. Wszolek, DCTN1-related neurodegeneration: Perry syndrome and beyond, Parkinsonism Relat. Disord. 41 (2017): 14-24.

[100] A. Batla, X.Y. Tai, L. Schottlaender, R. Erro, B. Balint, K.P. Bhatia, Deconstructing Fahr's disease/syndrome of brain calcification in the era of new genes, Parkinsonism Relat. Disord. 37 (2017): 1-10.

[101] C. Sundal, S. Fujioka, J.A. Van Gerpen, C. Wider, A.M. Nicholson, M. Baker, E.A. Shuster, J. Aasly, S. Spina, B. Ghetti, S. Roeber, J. Garbern, A. Tselis, R.H. Swerdlow, B.B. Miller, A. Borjesson-Hanson, R.J. Uitti, O.A. Ross, A.J. Stoessl, R. Rademakers, K.A. Josephs, D.W. Dickson, D.

Broderick, Z.K. Wszolek, Parkinsonian features in hereditary diffuse leukoencephalopathy with spheroids (HDLS) and CSF1R mutations, Parkinsonism Relat. Disord. 19 (2013): 869-877.

[102] T.A. Saifee, I. Pareés, P. Kassavetis, D. Kaski, A.M. Bronstein, J.C. Rothwell, A. Sadnicka, M.P. Lunn, H. Manji, J.T. Teo, K.P. Bhatia, M.M. Reilly, M.J. Edwards, Tremor in Charcot-Marie-Tooth disease: no evidence of cerebellar dysfunction, Clin. Neurophysiol. 126 (2015): 1817-1824.

[103] M.T. Lorincz, Neurologic Wilson's disease, Ann. NY Acad. Sci. 1184 (2010): 173-187.

[104] A. Członkowska, T. Litwin, G. Chabik, Wilson disease: neurologic features, Handb. Clin. Neurol. 142 (2017): 101-119.

[105] H. Topaloglu, K Gücüyener, C Orkun, Y Renda, Tremor of tongue and dysarthria as the sole manifestation of Wilson's disease, Clin. Neurol. Neurosurg. 92 (1990): 295-296.

[106] H. El Otmani, T. Benhsain, Z. Abdulhakeem, B. El Moutawakil, M.A. Rafai, Ondulating tongue revealing Wilson's disease, Mov. Dis. Clin. Pract. 6 (2019): 605-607.

[107] S.A. Schneider, K.P. Bhatia, J. Hardy, Complicated recessive dystonia parkinsonism syndromes, Mov. Disord. 24 (2009): 490–499.

[108] E. Lohmann, M. Periquet, V. Bonifati, N.W. Wood, G. De Michele, A.M. Bonnet, V. Fraix, E. Broussolle, M.W. Horstink, M. Vidailhet, P. Verpillat, T. Gasser, D. Nicholl, H. Teive, S. Raskin, O. Rascol, A. Destée, M. Ruberg, F. Gasparini, G. Meco, Y. Agid, A. Durr, A. Brice; French Parkinson's Disease Genetics Study Group; European Consortium on Genetic Susceptibility in Parkinson's Disease, How much phenotypic variation can be attributed to parkin genotype?, Ann. Neurol. 54 (2003); 54: 176-185.

[109] S. Edvardson, Y. Cinnamon, A. Ta-Shma, A. Shaag, Y.I. Yim, S. Zenvirt, C. Jalas, S. Lesage, A. Brice, A. Taraboulos, K.H. Kaestner, L.E. Greene, O. Elpeleg, A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism, PLoS One 7 (2012): e36458.

[110] C.E. Krebs, S. Karkheiran, J.C. Powell, M. Cao, V. Makarov, H. Darvish, G. Di Paolo, R.H. Walker, G.A. Shahidi, J.D. Buxbaum, P. De Camilli, Z. Yue, C. Paisán-Ruiz, The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures, Hum. Mutat. 34 (2013): 1200-1207.

[111] M. Quadri, M. Fang, M. Picillo, S. Olgiati, G.J. Breedveld, J. Graafland, B. Wu, F. Xu, R. Erro, M. Amboni, S. Pappatà, M. Quarantelli, G. Annesi, A. Quattrone, H.F. Chien, E.R. Barbosa; International Parkinsonism Genetics Network, B.A. Oostra, P. Barone, J. Wang, V. Bonifati, Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism, Hum. Mutat. 34 (2013): 1208-1215.

[112] J. Ng, J. Zhen, E. Meyer, K. Erreger, Y. Li, N. Kakar, J. Ahmad, H. Thiele, C. Kubisch, N.L. Rider, D.H. Morton, K.A. Strauss, E.G. Puffenberger, D. D'Agnano, Y. Anikster, C. Carducci, K. Hyland, M. Rotstein, V. Leuzzi, G. Borck, M.E. Reith, M.A. Kurian, Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood, Brain 137 (2014): 1107-1119.

[113] E. Mulroy, B. Balint, E. Menozzi, A. Latorre, K.P. Bhatia, Benign tremulous parkinsonism of the young - consider Parkin, Parkinsonism Relat. Disord. 65 (2019): 270-271.

[114] S.J. Hayflick, M.A. Kurian, P. Hogarth, Neurodegeneration with brain iron accumulation, Handb. Clin. Neurol. 147 (2018): 293-305.

[115] B. Zhou, S.K. Westaway, B. Levinson, M.A. Johnson, J. Gitschier, S.J. Hayflick, A novel pantothenate kinase gene (PANK2) is defective in Hallervorden–Spatz syndrome, Nature Genetics 28 (2001): 345–349.

[116] S. Yamashita, Y. Maeda, H. Ohmori, Y. Uchida, T. Hirano, K. Yonemura, E. Uyama, M. Uchino, Pantothenate kinase-associated neurodegeneration initially presenting as postural tremor alone in a Japanese family with homozygous N245S substitutions in the pantothenate kinase gene, J. Neurol. Sci. 225 (2004): 129–133.

[117] A. Aggarwal, S.A. Schneider, H. Houlden, M. Silverdale, R. Paudel, C. Paisan-Ruiz, S. Desai, M. Munshi, D. Sanghvi, J. Hardy, K.P. Bhatia, M. Bhatt, Indian-subcontinent NBIA: unusual phenotypes, novel PANK2 mutations, and undetermined genetic forms. Mov. Disord. 25 (2010): 1424-1231.

[118] W.T. Yoon, W.Y. Lee, H.Y. Shin, S.T. Lee, C.S. Ki, Novel PANK2 gene mutations in Korean patient with pantothenate kinase-associated neurodegeneration presenting unilateral dystonic tremor, Mov. Disord. 25 (2010): 245–247.

[119] M. Rohani, G. Shahidi, A. Alavi, A.E. Lang, N. Yousefi, S. Razme, A. Fasano, Tremor-dominant pantothenate kinase-associated neurodegeneration, Mov. Dis. Clin. Pract. 4 (2017): 772-774.

[120] S. Karkheiran, G.A. Shahidi, R.H. Walker, C. Paisán-Ruiz, PLA2G6-associated dystonia-parkinsonism: case report and literature review, Tremor Other Hyperkinet. Mov. (NY) 5 (2015): 317.

[121] H. Miyajima, Y. Takahashi, S. Kono, Aceruloplasminemia, an inherited disorder of iron metabolism, Biometals 16 (2003): 205e213.

[122] L.H.P. Vroegindeweij, J.G. Langendonk, M. Langeveld, M. Hoogendoorn, A.J.A. Kievit, D. Di Raimondo, J.H.P. Wilson, A.J.W. Boon, New insights in the neurological phenotype of aceruloplasminemia in Caucasian patients, Parkinsonism Relat. Disord. 36 (2017): 33-40.

[123] M. Hartig, H. Prokisch, T. Meitinger, T. Klopstock, Mitochondrial membrane protein-associated neurodegeneration (MPAN), Int. Rev. Neurobiol. 110 (2013): 73-84.

[124] R. Horvath, E. Holinski-Feder, V.C. Neeve, A. Pyle, H. Griffin, D. Ashok, C. Foley, G. Hudson, B. Rautenstrauss, G. Nürnberg, P. Nürnberg, J. Kortler, B. Neitzel, I. Bässmann, T. Rahman, B. Keavney, J. Loughlin, S. Hambleton, B. Schoser, H. Lochmüller, M. Santibanez-Koref, P.F. Chinnery, A new phenotype of brain iron accumulation with dystonia, optic atrophy, and peripheral neuropathy, Mov. Disord. 27 (2012): 789-793.

[125] A. Gregory, M. Lotia, S.Y. Jeong, R. Fox, D. Zhen, L. Sanford, J. Hamada, A. Jahic, C. Beetz, A. Freed, M.A. Kurian, T. Cullup, M.C.M. van der Weijden, V. Nguyen, N. Setthavongsack, D. Garcia, V. Krajbich, T. Pham, R. Woltjer, B.P. George, K.Q. Minks, A.R. Paciorkowski, P. Hogarth, J. Jankovic, S.J. Hayflick, Autosomal dominant mitochondrial membrane protein-associated neurodegeneration (MPAN), Mol. Genet. Genomic Med. 7 (2019): e00736.

[126] F. Sedel, J.M. Saudubray, E. Roze, Y. Agid, M. Vidailhet, Movement disorders and inborn errors of metabolism in adults: a diagnostic approach, J. Inherit. Metab. Dis. 31 (2008): 308-318.

[127] H.S. Singer, J.W. Mink, D.L. Gilbert, J. Jankovic, Inherited metabolic disorders with associated movement abnormalities, in: H.S. Singer, J.W. Mink, D.L. Gilbert, J. Jankovic (Eds.), Movement Disorders in Childhood 2nd Edition, Elsevier Inc., USA, 2016, pp. 337-406.

[128] S. Külkens, I. Harting, S. Sauer, J. Zschocke, G.F. Hoffmann, S. Gruber, O.A. Bodamer, S. Kölker, Late-onset neurologic disease in glutaryl-CoA dehydrogenase deficiency, Neurology 64 (2005): 2142-2144.

[129] I. Rubio-Agusti, M. Carecchio, K.P. Bhatia, M. Kojovic, I. Parees, H.S. Chandrashekar, E.J. Footitt, D. Burke, M.J. Edwards, R.H. Lachmann, E. Murphy, Movement disorders in adult patients with classical galactosemia, Mov. Disord. 28 (2013): 804-810.

[130] M. Beaudin, C.J. Klein, G.A. Rouleau, N, Systematic review of autosomal recessive ataxias and proposal for a classification, Cerebellum Ataxias 4 (2017): 3.

[131] J.G. Hou, J. Jankovic, Movement disorders in Friedreich's ataxia, Neurol. Sci. 206 (2003): 59-64.

[132] A. Méneret, Y. Ahmar-Beaugendre, G. Rieunier, N. Mahlaoui, B. Gaymard, E. Apartis, C. Tranchant, S. Rivaud-Péchoux, B. Degos, B. Benyahia, F. Suarez, T. Maisonobe, M. Koenig, A. Durr, M.H. Stern, C. Dubois d'Enghien, A. Fischer, M. Vidailhet, D. Stoppa-Lyonnet, D. Grabli, M. Anheim, The pleiotropic movement disorders phenotype of adult ataxia-telangiectasia, Neurology 83 (2014): 1087-1095.

[133] A. Levy, A.E. Lang, Ataxia-telangiectasia: a review of movement disorders, clinical features, and genotype correlations, Mov. Disord. 33 (2018): 1238-1247.

[134] M. Anheim, B. Monga, M. Fleury, P. Charles, C. Barbot, M. Salih, J.P. Delaunoy, M. Fritsch, L. Arning, M. Synofzik, L. Schöls, J. Sequeiros, C. Goizet, C. Marelli, I. Le Ber, J. Koht, J. Gazulla, J. De Bleecker, M. Mukhtar, N. Drouot, L. Ali-Pacha, T. Benhassine, M. Chbicheb, A. M'Zahem, A. Hamri, B. Chabrol, J. Pouget, R. Murphy, M. Watanabe, P. Coutinho, M. Tazir, A. Durr, A. Brice, C. Tranchant, M. Koenig, Ataxia with oculomotor apraxia type 2: clinical, biological and genotype/phenotype correlation study of a cohort of 90 patients, Brain 132 (2009): 2688-2698.

[135] M. Stamelou, K. Tuschl, W.K. Chong, A.K. Burroughs, P.B. Mills, K.P. Bhatia, P.T. Clayton, Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder, Mov. Disord. 27 (2012): 1317-1322.

[136] K. Tuschl, E. Meyer, L.E. Valdivia, N. Zhao, C. Dadswell, A. Abdul-Sada, C.Y. Hung, M.A. Simpson, W.K. Chong, T.S. Jacques, R.L. Woltjer, S. Eaton, A. Gregory, L. Sanford, E. Kara, H. Houlden, S.M. Cuno, H. Prokisch, L. Valletta, V. Tiranti, R. Younis, E.R. Maher, J. Spencer, A. Straatman-Iwanowska, P. Gissen, L.A. Selim, G. Pintos-Morell, W. Coroleu-Lletget, S.S. Mohammad, S. Yoganathan, R.C. Dale, M. Thomas, J. Rihel, O.A. Bodamer, C.A. Enns, S.J. Hayflick, P.T.

Clayton, P.B. Mills, M.A. Kurian, S.W. Wilson, Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia, Nat. Commun. 7 (2016): 11601.

[137] E. Apartis, A. Blancher, W.G. Meissner, L. Guyant-Maréchal, D. Maltête, T. De Broucker, A.P. Legrand, H. Bouzenada, H.T. Thanh, M. Sallansonnet-Froment, A. Wang, F. Tison, C. Roué-Jagot, F. Sedel, P. Charles, S. Whalen, D. Héron, S. Thobois, A. Poisson, G. Lesca, A.M. Ouvrard-Hernandez, V. Fraix, S. Palfi, M.O. Habert, B. Gaymard, J.C. Dussaule, P. Pollak, M. Vidailhet, A. Durr, J.C. Barbot, V. Gourlet, A. Brice, M. Anheim, FXTAS: new insights and the need for revised diagnostic criteria, Neurology 79 (2012): 1898-1907.

[138] R.J. Hagerman, P. Hagerman, Fragile X-associated tremor/ataxia syndrome - features, mechanisms and management, Nat. Rev. Neurol. 12 (2016): 403-412.

[139] D. Hall, K. Todorova-Koteva, S. Pandya, B. Bernard, B. Ouyang, M. Walsh, T. Pounardjian, C. Deburghraeve, L. Zhou, M. Losh, M. Leehey, E. Berry-Kravis, Neurological and endocrine phenotypes of fragile X carrier women, Clin. Genet. 89 (2016): 60-67.

[140] D.C. Bragg, K. Mangkalaphiban, C.A. Vaine, N.J. Kulkarni, D. Shin, R. Yadav, J. Dhakal, M.L. Ton, A. Cheng, C.T. Russo, M. Ang, P. Acuña, C. Go, T.N. Franceour, T. Multhaupt-Buell, N. Ito, U. Müller, W.T. Hendriks, X.O. Breakefield, N. Sharma, L.J. Ozelius, Disease onset in X-linked dystonia-parkinsonism correlates with expansion of a hexameric repeat within an SVA retrotransposon in TAF1, Proc. Natl. Acad. Sci. USA 114 (2017): E11020-E11028.

[141] V.G. Evidente, J. Advincula, R. Esteban, P. Pasco, J.A. Alfon, F.F. Natividad, J. Cuanang, A.S. Luis, K. Gwinn-Hardy, J. Hardy, D. Hernandez, A. Singleton, Phenomenology of "Lubag" or X-linked dystonia-parkinsonism, Mov. Disord. 17 (2002): 1271-1277.

[142] V.G. Evidente, D. Nolte, S. Niemann, J. Advincula, M.C. Mayo, F.F. Natividad, U. Müller, Phenotypic and molecular analyses of X-linked dystonia-parkinsonism ("Lubag") in women, Arch. Neurol. 61 (2004): 1956-1959.

[143] G.R. Wilson, J.C. Sim, C. McLean, M. Giannandrea, C.A. Galea, J.R. Riseley, S.E. Stephenson, E. Fitzpatrick, S.A. Haas, K. Pope, K.J. Hogan, R.G. Gregg, C.J. Bromhead, D.S. Wargowski, C.H. Lawrence, P.A. James, A. Churchyard, Y. Gao, D.G. Phelan, G. Gillies, N. Salce, L. Stanford, A.P. Marsh, M.L. Mignogna, S.J. Hayflick, R.J. Leventer, M.B. Delatycki, G.D. Mellick, V.M. Kalscheuer,

P. D'Adamo, M. Bahlo, D.J. Amor, P.J. Lockhart, Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with α-synuclein pathology, Am. J. Hum. Genet. 95 (2014): 729-735.

[144] T. Temudo, M. Santos, E. Ramos, K. Dias, J.P. Vieira, A. Moreira, E. Calado, I. Carrilho, G. Oliveira, A. Levy, C. Barbot, M. Fonseca, A. Cabral, P. Cabral, J. Monteiro, L. Borges, R. Gomes, G. Mira, S.A. Pereira, M. Santos, A. Fernandes, J.T. Epplen, J. Sequeiros, P. Maciel, Rett syndrome with and without detected MECP2 mutations: an attempt to redefine phenotypes, Brain. Dev. 33 (2011): 69-76.

[145] R. Hanajima, Y. Terao, S. Nakatani-Enomoto, M. Hamada, A. Yugeta, H. Matsumoto, T. Yamamoto, S. Tsuji, Y. Ugawa, Postural tremor in X-linked spinal and bulbar muscular atrophy, Mov. Disord. 24 (2009): 2063-2069.

[146] S.J. Hayflick, M.C. Kruer, A. Gregory, T.B. Haack, M.A. Kurian, H.H. Houlden, J. Anderson, N. Boddaert, L. Sanford, S.I. Harik, V.H. Dandu, N. Nardocci, G. Zorzi, T. Dunaway, M. Tarnopolsky, S. Skinner, K.R. Holden, S. Frucht, E. Hanspal, C. Schrander-Stumpel, C. Mignot, D. Héron, D.E. Saunders, M. Kaminska, J.P. Lin, K. Lascelles, S.M. Cuno, E. Meyer, B. Garavaglia, K. Bhatia, R. de Silva, S. Crisp, P. Lunt, M. Carey, J. Hardy, T. Meitinger, H. Prokisch, P. Hogarth, β-Propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation, Brain 136 (2013): 1708-1717.

[147] Y.B. Hong, J.M. Park, J.S. Yu, D.H. Yoo, D.E. Nam, H.J. Park, J.S. Lee, S.H. Hwang, K.W. Chung, B.O. Choi, Clinical characterization and genetic analysis of Korean patients with X-linked Charcot-Marie-Tooth disease type 1, J. Peripher. Nerv. Syst. 22 (2017): 172-181.

[148] S. Rahman, W.C. Copeland, POLG-related disorders and their neurological manifestations, Nat. Rev. Neurol. 15 (2019): 40-52.

[149] S.R. Schreglmann, F. Riederer, M. Galovic, C. Ganos, G. Kägi, D. Waldvogel, Z. Jaunmuktane, A. Schaller, U. Hidding, E. Krasemann, L. Michels, C.R. Baumann, K. Bhatia, H.H. Jung HH, Movement disorders in genetically confirmed mitochondrial disease and the putative role of the cerebellum, Mov. Disord. 33 (2018): 146-155.

[150] M. Milone, B.T. Klassen, M.L. Landsverk, R.H. Haas, J.J. Wong, Orthostatic tremor, progressive external ophthalmoplegia, and Twinkle, JAMA Neurol. 70 (2013): 1429-1431.

[151] R. Ghaoui, C.M. Sue, Movement disorders in mitochondrial disease, J. Neurol. 265 (2018): 1230-1240.

[152] C. Tranchant, M. Anheim, Movement disorders in mitochondrial diseases, Rev. Neurol. (Paris) 172 (2016): 524-529.

[153] D.S. Hong, A.L. Reiss, Cognitive and neurological aspects of sex chromosome aneuploidies, Lancet Neurol. 13 (2014): 306-318.

[154] T.L. Harlow, P. Gonzalez-Alegre, High prevalence of reported tremor in Klinefelter syndrome, Parkinsonism Relat. Disord. 15 (2009): 393-395.

[155] M. Koegl-Wallner, P. Katschnig-Winter, T. Pendl, B. Melisch, M. Trummer, E. Holl, U. Werner, R. Schmidt, P. Schwingenschuh, Tremor associated with Klinefelter syndrome--a case series and review of the literature, Parkinsonism Relat. Disord. 20 (2014): 323-327.

[156] M.Z. Bardsley, K. Kowal, C. Levy, A. Gosek, N. Ayari, N. Tartaglia, N. Lahlou, B. Winder, S. Grimes, J.L. Ross, 47,XYY syndrome: clinical phenotype and timing of ascertainment, J. Pediatr. 163 (2013): 1085-1094.

[157] N. Tartaglia, N. Ayari, S. Howell, C. D'Epagnier, P. Zeitler, 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome, Acta Paediatr. 100 (2011): 851-860.

[158] N. Tartaglia, S. Davis, A. Hench, S. Nimishakavi, R. Beauregard, A. Reynolds, L. Fenton, L. Albrecht, J. Ross, J. Visootsak, R. Hansen, R. Hagerman, A new look at XXYY syndrome: medical and psychological features, Am. J. Med. Genet. 146A (2008): 1509-1522.

[159] N. Tartaglia, M. Borodyanskaya, D.A. Hall, Tremor in 48,XXYY syndrome, Mov. Disord. 24 (2009): 2001-2007.

[160] E. Boot, A.S. Bassett, C. Marras, 22q11.2 deletion syndrome–associated Parkinson's disease, Mov. Dis. Clin. Pract. 6 (2018): 11-16.

[161] E.K. Tan, Chromosomal deletion at 22q11.2 and Parkinson's disease, Lancet Neurol. 15 (2016): 538-540.

[162] M. Carecchio, N.E. Mencacci, Emerging monogenic complex hyperkinetic disorders, Curr. Neurol. Neurosci. Rep. 17 (2017): 97.

[163] C. Reale, C. Panteghini, M. Carecchio, B. Garavaglia, The relevance of gene panels in movement disorders diagnosis: a lab perspective, Eur. J. Paediatr. Neurol. 22 (2018): 285-291.

[164] S. Yohe, B. Thyagarajan, Review of clinical next-generation sequencing, Arch. Pathol. Lab. Med. 141 (2017): 1544–1557.

Table 1. Summary of loci and genes which have hitherto been associated with essential tremor in chronological order

Locus/*Gene*	Chromosome	Gene product	Study type^	Study population	Criteria to define ET in the study	Reference
ETM1	3q13	- (see *DRD3*)	GWS+LA	16 small Icelandic families (75 ET)	TRIG criteria for definite ET.[2, 30] Bilateral postural tremor, with or without kinetic tremor, of the hands or forearms which was visible and persistent and had lasted for at least five years. Absence of other neurological signs, including dystonia.	[6]
ETM2	2p22-p25	- (see *HS1BP3*)	GWS+LA	1 large Czech/American family (18 ET)	Bilateral postural tremor, with or without kinetic tremor, that was visible and persistent in the hands or forearms and had moderate (2- to 4- cm excursion) or coarse (>4-cm excursion) tremor amplitudes and slow tremor frequency (4 to 10 Hz).	[7]
MTHFR	1p36.22	Methylenetetrahydrofolate reductase	CG+CCGAS	158 unrelated Caucasian ET and 246 unrelated Caucasian HC	Criteria for ET according to [31] and [32].	[8]
HS1-BP3	2p24.1	Hematopoietic lineage cell specific protein binding protein 3	FM	2 unrelated US families	Definite or probable ET according to [30]. Bilateral postural tremor of the hands or forearms which was visible and persistent with at least 1- to 2-cm excursions in at least one arm. Absence of parkinsonism, dystonia, myoclonus, peripheral neuropathy, or restless legs syndrome.	[9]
ETM3	6p23	-	GWS+LA	7 North American families (65 ET)	Definite ET according to [33]. Bilateral tremor of minimum 5-year duration and severity grades three or four with secondary causes of tremor excluded.	[10]
DRD3	3q13.31	Dopamine receptor D3	CG+LA	30 unrelated ET French families	Definite or probable familial ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2]	[11]
LINGO1	15q24.3	Leucine-rich repeat and Ig domain containing 1	GWAS	First stage: 452 Icelandic ET and 14,394 HC. Second stage: 301 ET and 1,419 HC of European (Austria, Germany, Iceland) or US origin.	Icelandic families: TRIG criteria for definite ET,[2, 30] i.e. bilateral postural tremor, with or without kinetic tremor, of hands or forearms, visible and persistent and lasting for at least five years. Absence of abnormal neurological signs, including dystonia and Parkinson's disease. Austrian families: ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2] Exclusion of subjects with the co-occurrence of PD and ET. German families: not specified. American families: definite or probable ET according to the guidelines of the 1998 MDS Consensus Statement[2] and TRIG criteria.[30]	[12]
MAPT	17q21.31	Microtubule-associated protein tau	CG+CCGAS	356 Caucasian ET and 409 Caucasian HC from North America	Not specified.	[13]
SLC1A2	11p13	Excitatory amino acid transporter 2	GWAS	First stage: 436 ET and 928 HC of German origin. Second stage: 554 ET and 609 HC of European (Germany, Denmark, Austria) origin.	ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2]	[14]
***FUS* (ETM4)**	16p11.2	Fused in sarcoma/translated in liposarcoma	WES	First stage: 1 large French-Canadian family (23 ET, 12 HC). Second stage: 270 ET.	Definite ET according to the guidelines of the 1998 MDS Consensus Statement.[2]	[15]

HTRA2	2p13.1	Mitochondrial serine protease	WES	First stage: 1 large Turkish family (11 ET, 5 ET+PD, 8 HC). Second stage: 25 other Turkish ET families (each including multiple ET) and 364 HC.	ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2] Five subjects were reported to have co-existence of PD and ET.	[16]
***TENM4* (ETM5)**	11q14.1	Teneurin transmembrane protein 4	WES	First stage: 3 Spanish families (23 ET, 12 HC). Second stage: 299 unrelated Spanish ET.	ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2]	[17]
TREM2	6p21.1	Triggering receptor expressed on myeloid cells 2	CG+CCGAS	First stage: 456 ET and 2,715 HC of Spanish origin. Second stage: 897 ET and 1,449 HC from Germany, Italy, America, and Taiwan. Third stage: 14,777 HC from Spain, Italy, Germany, North America, China.	Definite or probable ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2]	[18]
SORT1	1p13.3	Sortilin 1	WES	1 small Spanish family (2 ET, 4 HC)	ET according to the guidelines of the 1998 MDS Consensus Statement[2] and the WHIGET clinical criteria.[34]	[19]
SCN4A	17q23.3	Voltage-gated sodium channel, type 4, alpha subunit	WES	First stage: 1 large Spanish family with ET and epilepsy (7 ET). Second stage: 76 sporadic and 25 familial ET.	Not specified, but apparently not isolated tremor syndrome in the index family (one subject had postural tremor of both hands, head tremor, mild resting tremor and a mild ataxic gait; one subject had myoclonus, postural tremor of both hands and head tremor). In the second stage, ET according to the guidelines of the 1998 MDS Consensus Statement[2] and the WHIGET criteria clinical criteria were comprehensively reviewed by the Consensus Statement of the Movement Disorder Society on Tremor.[34]	[20]
DNAJC13	3q22.1	DnaJ (Hsp40) homolog, subfamily C, member 13	WES	571 ET of European descent from North America	ET according to standard diagnostic criteria.[31]	[21]
NOS3	7q36.1	Nitric oxide synthase 3	WES	37 families with 3 to 7 ET enrolled in the US	ET according to the WHIGET criteria clinical criteria.[34]	[22]
HAPLN4	19p13.11	Hyaluronan and proteoglycan link protein 4				
USP46	4q12	Ubiquitin-specific protease 46				
KCNS2	8q22.2	Voltage-gated potassium channel subunit Kv9.2		37 families with 3 to 7 ET enrolled in the US and 95 unrelated ET		
STK32B	4p16.2	Serine/threonine kinase 32B	GWAS	First stage: 1,778 ET and 5,376 HC of North-Western European ancestry. Second stage: 1,029 ET and 1,065 HC of North-Western European ancestry.	Definite or probable ET according to the guidelines of the 1998 MDS Consensus Statement.[2] Postural and action tremor in the arms exceeding the amplitude seen in enhanced physiological tremor and not attributable to other causes (PD, dystonia, medication).	[23]
PPARGC1A	4p15.2	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha				
CTNNA3	10q21.3	Catenin alpha 3				
SCN11A	3p22.2	Voltage-gated sodium channel subunit alpha Nav1.9	WES	1 Chinese family with ET and recurrent pain attacks (8 ET)	Postural and action tremor localized to both upper limbs, without tremor of the voice, head or other body parts. Rest tremor gradually developing with age.	[24]
MC1R	16q24.3	Melanocortin 1 receptor	CG+CCGAS	200 Han Chinese ET and 432 Han Chinese matched HC	ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement[2] and [31].	[25]
VDR	12q13.11	Vitamin D receptor	CG+CCGAS	239 Caucasian sporadic ET and 239 unrelated matched Caucasian HC	ET according to [30] and [33], no further details provided.	[26]

IL1B	2q14.1	Interleukin 1-beta	CG+CCGAS	200 Chinese ET and 229 Chinese HC	ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2] Exclusion of parkinsonism, drug induced tremor, cerebellar tremor, dystonia and tremors with hyperthyroidism.	[27]
CACNA1G	17q21.33	Calcium voltage-gated channel subunit alpha1 G	WGS	8 families (31 ET, 9 HC) enrolled in the US	Definite, probable, or possible ET according to the WHIGET criteria.[34]	[28]
SLIT3	5q34-q35	Slit guidance ligand 3				
KARS	16q23.1	Lysyl-tRNA synthetase				
KIF5A	12q13.3	Kinesin family member 5A				
NTRK1	1q23.1	Neurotrophic receptor tyrosine kinase 1				
NOTCH2NLC	1q21.2	Notch 2 N-terminal like C	WES+LRS+RP-PCR+GC-PCR	197 ET pedigrees of Chinese origin and 1305 Chinese HC	ET diagnosed according to the guidelines of the 1998 MDS Consensus Statement.[2]	[29]

Legend: CCGAS = case-control genetic association study; CG = candidate gene approach; ET = subjects with essential tremor; FM = fine mapping; GC-PCR = GC-rich polymerase chain reaction; GWAS = genome-wide association study; GWS = genome-wide scan; HC = healthy controls; LA = linkage analysis; LRS = long-read sequencing; MDS = Movement Disorder Society; PD = Parkinson's disease; RP-PCR = repeat-primed polymerase chain reaction; TR = targeted resequencing; TRIG = Tremor Investigation Group; WES = whole-exome sequencing; WGS = whole-genome sequencing; WHIGET = Washington Heights–Inwood Genetic Study of Essential Tremor; ^ Original genetic study; replication studies not reported.

Table 2. Main autosomal dominant inherited disorders which can present with tremor

Tremor disorder	OMIM®	Chromosome	Gene	Age of onset	Main phenotype^	Tremor as rare sign§	Laboratory and imaging findings
Primary dystonias[1]							
DYT-*TOR1A* (DYT1)	128100	9q34.11	*TOR1A*	First-third decade	Early-onset mostly generalized dystonia, usually involving lower limbs at onset. **Isolated writing tremor, head tremor, late onset rest tremor reported**.		-
DYT/PARK-*GCH1*[2] (DYT5a)	128230	14q22.2	*GCH1*	First-sixth decade	Progressive dopa-responsive dystonia with diurnal fluctuation. **Upper-limb postural and kinetic tremor reported**. Sometimes combined with parkinsonism (including **rest tremor**), pyramidal signs, scoliosis, anxiety, depression, obsessive–compulsive disorder, sleep disturbances.		Blood tests: high post-load phenylalanine. CSF: low neopterin, biopterin, 5-HIAA, low or normal HVA.
DYT-*THAP1*[2]	602629	8p11.21	*THAP1*	Second-third decade	Early-onset mostly generalized dystonia, usually involving neck and upper limbs at onset. **Head or upper limb tremor reported as isolated or presenting sign.**		-
PxMD-*SLC2A1* (DYT9, Glut1 Deficiency Syndrome)	601042 (606777)	1p34.2	*SLC2A1*	Childhood	Paroxysmal exercise-induced dystonia with or without epilepsy. **Cerebellar action tremor** frequently reported.		CSF: low glucose and lactate. Reduced CSF to blood glucose ratio.
DYT-*ANO3* (DYT24)	615034	11p14.3-p14.2	*ANO3*	Fourth-fifth decade	Focal or segmental dystonia. **Head and/or arm tremor often precedes overt dystonia**. Sometimes combined with myoclonic jerks.		-
DYT-*GNAL*[2]	615073	18p11.21	*GNAL*	Childhood to fourth decade	Focal or segmental and occasionally generalized dystonia. **Pure dystonic tremor of the upper limbs may precede or follow the onset of dystonia.**		
Spinocerebellar ataxias[3]							
SCA-*ATXN2* (SCA2)	183090	12q24.12	*ATXN2*	Third-fourth decade	Slowly progressive ataxia, slow saccades, parkinsonism (including **rest tremor**), **postural tremor**, sensory symptoms.		Brain MRI: marked cerebellar atrophy; atrophy of the pons, medulla oblongata, spinal cord, parietal cortex, and thalamus. DaTscan: possible reduced tracer uptake.
SCA-*ATXN3* (SCA3)	109150	14q32.12	*ATXN3*	Third-fourth decade	Ataxia, ophthalmoplegia, parkinsonism (including **rest tremor**), dystonia, chorea, spasticity, sensory symptoms, amyotrophy.		Brain MRI: ponto-cerebellar atrophy. DaTscan: possible reduced tracer uptake.
SCA-*CACNA1A* (SCA6)	183086	19p13.13	*CACNA1A*[4]	Adulthood (usually >50 years)	Usually pure cerebellar syndrome with ataxia and **postural tremor**; rarely parkinsonism (including **rest tremor**).		Brain MRI: moderate-severe atrophy of the vermis; mild atrophy of the cerebellar hemispheres; mild, diffuse atrophy of cortical areas in some cases.
SCA-*ATXN7* (SCA7)	164500	3p14.1	*ATXN7*	Adolescence	**Palatal tremor**, ataxia, visual disturbances, ophthalmoplegia, spasticity.		Brain MRI: severe pontine and cerebellar atrophy.
SCA-*PPP2R2B* (SCA12)	604326	5q32	*PPP2R2B*	Childhood or adulthood (8 to 62 years)	**Action tremor of the arms or head**, mild or absent ataxia and/or limb dysmetria, pyramidal signs. Parkinsonism (including **rest tremor**) reported.		Brain MRI: cerebral and/or cerebellar (vermis>hemispheres) atrophy. DaTscan: reduced tracer uptake in reported cases with parkinsonism.
SCA-*ITPR1* (SCA15/SCA16)	606658	3p26.1	*ITPR1*	Fifth decade	Pure cerebellar ataxia, **head tremor** and cognitive impairment.		Brain MRI: cerebellar atrophy (mainly of the vermis).

	SCA20	608687	11q12.2-12.3	unknown	Adulthood (19-64 years)	Dysarthria, slowly progressive ataxia, **palatal tremor** (2/3 of cases), laryngeal dystonia, hypermetric horizontal saccades, minor pyramidal signs, **postural tremor of the arms with or without involvement of the head**.		Brain CT/MRI: early dentate calcification, sometimes along with pallidal calcification; mild to moderate cerebellar atrophy; increased inferior olivary T2-weighted signals in cases with symptomatic palatal tremor.
	SCA-*FGF14* (SCA27)	609307	13q33.1	*FGF14*	Adolescence	Ataxia, orofacial dyskinesia, cognitive impairment, **hand tremor**, cognitive decline.		Brain MRI: atrophy of the cerebellar vermis and hemispheres.
Parkinson's disease[5]								
	PARK-*SNCA* (PARK1/PARK4)	168601/ 605543	4q22.1	*SNCA*	Usually fourth-fifth decade	Parkinsonism (including **rest tremor**), cognitive impairment.		DaTscan: reduced tracer uptake.
	PARK-*LRRK2* (PARK8)	607060	12q12	*LRRK2*	Usually >50 years	Slowly progressive parkinsonism (including **rest tremor**) with good response to levodopa.		DaTscan: reduced tracer uptake.
	PARK-*VPS35* (PARK17)	614203	16q11.2	*VPS35*	Usually fifth-sixth decade	Parkinsonism (including **rest tremor**) with good response to levodopa.		DaTscan: reduced tracer uptake.
Frontotemporal dementia								
	***MAPT*-FTD**	600274	17q21.31	*MAPT*	Third-seventh decade	FTD, parkinsonism (including **rest tremor**) can precede FTD, rarely MND.	×	Brain MRI: selective frontal and/or temporal lobe atrophy. DaTscan: reduced tracer uptake (in cases with parkinsonism).
	***C9orf72*-FTD**	105550	9q21.2	*C9orf72*	Fourth-seventh decade	FTD, MND, akinetic-rigid parkinsonism, rarely associated with **postural or rest tremor**.	×	Brain MRI: selective frontal and/or temporal lobe atrophy. DaTscan: reduced tracer uptake (in cases with parkinsonism).
	***PRNG*-FTD**	607485	17q21.31	*PRNG*	Sixth-ninth decade	FTD, parkinsonism (including **rest tremor**) can precede FTD, rarely MND.	×	Blood tests: low progranulin. CSF: low progranulin. Brain MRI: selective frontal and/or temporal lobe atrophy. DaTscan: reduced tracer uptake (in cases with parkinsonism).
	***FUS*-FTD**	608030	16p11.2	*FUS*	Fourth-fifth decade	FTD, MND, rarely parkinsonism typically associated with **postural tremor**.	×	Brain MRI: striking caudate atrophy; frontal and/or temporal lobe atrophy. DaTscan: reduced tracer uptake (in cases with parkinsonism).
	***TARDP*-FTD**	612069	1p36.22	*TARDP*	Usually sixth decade	FTD, MND, parkinsonism (including **rest tremor**).	×	Brain MRI: selective frontal and/or temporal lobe atrophy. DaTscan: reduced tracer uptake (in cases with parkinsonism).
Huntington disease		143100	4p16.3	*HTT*	Usually fourth decade	Chorea, psychiatric features, cognitive impairment. Akinetic-rigid parkinsonism rather than chorea in juvenile-onset forms. **Isolated postural hand and head tremor** rarely reported as presenting sign.	×	Brain MRI: caudate atrophy. DaTscan: normal tracer uptake.
Perry syndrome		168605	2p13.1	*DCTN1*	Fourth-fifth decade	Parkinsonism (including **rest tremor**), weight loss, central hypoventilation, psychiatric features (apathy, hallucinations). Family history of parkinsonism and sudden death.	×	DaTscan: reduced tracer uptake.
Hereditary spastic paraplegias								
	HSP-*SPAST* (HSP4)	182601	2p22.3	*SPAST*	Infancy to seventh decade	Pure (mostly) or complex HSP (cognitive impairment, epilepsy, ataxia, distal amyotrophy, ataxia, **postural hand tremor**, neuropathy)		Brain MRI: white matter abnormalities, posterior fossa abnormalities.

HSP-*REEP1* (HSP31)	610250	2p11.2	*REEP1*	Second to seventh decade	Complex HSP with axonal neuropathy, cerebellar ataxia, cognitive impairment. **Orthostatic tremor** reported in few cases.		-
HSP-*REEP2* (HSP72)	615625	5q31.2	*REEP2*	Infancy	Spastic paraparesis, mild **postural tremor**.		-
NBIA/CHOREA-*FTL* (Neuroferritinopathy)	606159	19q13.33	*FTL*	Usually adulthood (second to sixth decade)	Progressive chorea and dystonia (mainly affecting the orofacial region), **palatal tremor**, cognitive decline, psychiatric features.		Blood tests: low ferritin, liver function tests may be abnormal. Brain MRI: iron deposition in the basal ganglia and dentate; cystic degeneration of putamen and globus pallidus; cortical lining sign.
HSP/NBIA-*C19orf12* (HSP43, MPAN)[2]	614298	19q12	*C19orf12*	Childhood	Spastic paraparesis, dysarthria, dystonia, parkinsonism, neuropathy, psychiatric features, optic atrophy.	×	Brain MRI: iron deposition in the globus pallidus and substantia nigra.
Adult-onset Alexander disease	203450	17q21.31	*GFAP*	≥13 years to seventh decade	Bulbar (dysarthria, dysphonia, dysphagia) and pyramidal signs, slowly progressive cerebellar ataxia, **palatal tremor**, dysautonomia, sleep disturbances, cognitive decline. **Slow orthostatic tremor** reported in one case.		Brain MRI: mild to severe atrophy of the medulla oblongata extending caudally to the cervical spinal cord (tadpole sign) in almost 90% of cases; white matter abnormalities. Neuropathology: eosinophilic inclusions containing intermediate filament of GFAP (Rosenthal fibers) localized in astrocyte cytoplasm.
Primary familial brain calcification (Fahr disease)	213600	8p11.21	*SLC20A2*	Third-fourth decade	Progressive parkinsonism (including **rest tremor**), dystonia, **action tremor**, psychiatric features, headache, seizures.		Brain CT/MRI: basal ganglia and dentate calcification.
	615007	5q32	*PDGFRB*				
	615483	22q13.1	*PDGFB*				
	616413	1q25.3	*XPR1*				
Hereditary diffuse leukoencephalopathy with spheroids	221820	5q32	*CSF1R*	Usually fourth decade	Personality changes, cognitive impairment, seizures, parkinsonism (including **rest tremor**), **kinetic tremor**, spasticity.	×	Brain CT-MRI: brain calcification in the white matter. Brain MRI: cerebral white matter lesions, cerebral atrophy manifesting as enlarged ventricles. Neuropathology: non-inflammatory myelin loss, reactive astrocytosis, and axonal spheroids in the white matter.
Charcot-Marie-Tooth disease[7]	Various	Various	Various genes (i.e. *PMP22, MPZ, NEFL*)	Usually second to third decade	Sensory-motor neuropathy, pes cavus, peroneal muscular atrophy, **postural tremor**.	×	NCS: MCVs ranging from demyelinating to axonal.

Legend: 5-HIAA = 5-hydroxyindoleacetic acid; CSF = cerebrospinal fluid; CT = computed tomography; FTD = frontotemporal dementia; HSP = hereditary spastic paraparesis; HVA = homovanillic acid; MCV = motor conduction velocity; MND = motor neuron disease; MRI = magnetic resonance imaging; NCS = nerve conduction study; OMIM® = Online Mendelian Inheritance in Man.

^ Tremor features are reported in bold. § Tremor is rarely part of the clinical spectrum. [1] All autosomal dominant primary dystonias may include tremor as part of their phenotype. [2] Autosomal recessive inheritance also reported. [3] All autosomal dominant spinocerebellar ataxias may include tremor as part of their cerebellar

syndrome. [4] Anecdotal reports on CACNA1A-related adult-onset paroxysmal head tremor. [5] All autosomal dominant forms of Parkinson's disease may include tremor as part of their phenotype. [6] Autosomal recessive inheritance also reported. [7] When tremor was a major feature, Charcot-Marie-Tooth disease was referred to as Roussy-Lévy syndrome in previous literature.

Table 3. Main autosomal recessive inherited disorders which can present with tremor

Tremor disorder	OMIM®	Chromosome	Gene	Age of onset	Main phenotype^	Tremor as rare sign§	Laboratory and imaging findings
Wilson disease	277900	13q14.3	*ATP7B*	Adolescence or early adulthood	Combined dystonia with **tremor (action tremor, wing-beating tremor)**, parkinsonism (including **rest tremor**), cerebellar signs, neuropsychiatric and cognitive features, sunflower cataracts, Kayser-Fleischer ring, chronic liver disease. Anecdotal reports on **tongue tremor** as presenting sign.		Blood tests: low serum copper and ceruloplasmin, abnormal liver function. Urine tests: high urinary copper. MRI: high T2 signal in the basal ganglia, "face of the giant panda" or "double panda" signs.
Parkinson's disease[1]							
PARK-*Parkin* (PARK2)	600116	6q26	*PRKN*	Fourth decade	Young-onset parkinsonism (including **rest tremor**) with dystonic features (including **dystonic tremor**), mild pyramidal signs.		DaTSCAN: reduced tracer uptake.
PARK-*PINK1* (PARK6)	605909	1p36.12	*PINK1*	Third-fourth decade	Young-onset parkinsonism (including **rest tremor**) with dystonic features (including **dystonic tremor**). Pyramidal signs also reported.		DaTSCAN: reduced tracer uptake.
PARK-*DJ1* (PARK7)	606324	1p36.23	*DJ1*	Third-fourth decade	Young-onset parkinsonism (including **rest tremor**), areflexia, psychiatric features.		DaTSCAN: reduced tracer uptake.
PARK-*FBOX7* (PARK15)	260300	22q12.3	*FBOX7*	Third decade	Dystonia-parkinsonism-pyramidal syndrome.		DaTSCAN: reduced tracer uptake.
PARK-*SYNJ1* (PARK20)	615530	21q22.11	*SYNJ1*	Third decade	Young-onset parkinsonism (including **rest tremor**), dystonia, cognitive decline, seizures, eyelid apraxia.		DaTSCAN: reduced tracer uptake.
DYT/PARK-*SLC6A3* (Dopamine transporter deficiency syndrome)	613135	5p15.33	*SLC6A3*	Infancy	Infantile parkinsonism-dystonia, including **rest and action tremor**.		CSF: high HVA, normal neopterin, biopterin, 5-HIAA. DaTSCAN: absent or reduced tracer uptake.
Infantile parkinsonism-dystonia type 2	618049	10q25.3	*SLC18A2*	Infancy	Severe psychomotor disability, axial hypotonia, dystonia, parkinsonism (including **rest tremor**), oculogyric crises.		DaTSCAN: absent or reduced tracer uptake.
Primary dystonias[2]							
DYT-*GCH1*[3] (DYT5a)	128230	14q22.2	*GCH1*	First-sixth decade	Progressive dopa-responsive dystonia with diurnal fluctuation. Sometimes combined with parkinsonism (including **rest tremor**) and pyramidal signs.		Blood tests: high post-load phenylalanine. CSF: low neopterin, biopterin, 5-HIAA, low or normal HVA.
DYT-*TH* (DYT5b)	191290	11p15.5	*TH*	Infancy to adolescence	Dystonia–parkinsonism, oculogyric crisis (paroxysmal, conjugate, tonic upward deviation of the eyes), autonomic disturbance, tremor and myoclonus.		CSF: low HVA, normal neopterin, biopterin, 5-HIAA.
Autosomal recessive hereditary ataxias[4]							
Friedreich ataxia	229300	9q21.11	*FXN*	First-second decade (late onset reported)	Cerebellar/sensory ataxia, areflexia, muscle weakness, **postural or kinetic tremor**, **head tremor**. Chorea and dystonia also reported.		NCS: generally show MCV greater than 40 m/s with reduced or absent SNAP with an absent H reflex. Brain and spine MRI: often normal in early stages, atrophy of the cervical spinal cord and cerebellum in advanced stages.
Ataxia telangiectasia	208900	11q22.3	*ATM*	Infancy (late onset reported)	Cerebellar ataxia, oculomotor apraxia, conjunctival telangiectasias, immune defects, predisposition to malignancy. **Tremor** reported since early stages. Parkinsonism including **rest tremor** may be present in late stages.		Blood tests: high alpha-fetoprotein. Brain MRI: cerebellar atrophy.
Ataxia with oculomotor apraxia type 1	208920	9p21.1	*APTX*	First-second decade (late onset reported)	Phenotype similar to ataxia telangiectasia with sensorimotor neuropathy and cognitive impairment. Chorea, dystonia, and parkinsonism including **rest tremor** reported.		Blood tests: low albumin; high serum cholesterol. Brain MRI: cerebellar atrophy.
Ataxia with oculomotor apraxia type 2	606002	9q34.13	*SETX*	First-second decade (late onset reported)	Phenotype similar to ataxia with oculomotor apraxia type 1. Chorea, dystonia, and parkinsonism including **rest tremor** reported.		Blood tests: high alpha-fetoprotein. Brain MRI: cerebellar atrophy.

	Hereditary ataxia with vitamin E deficiency	277460	8q12.3	*TTPA*	First-second decade	Friedreich-like phenotype with visual impairment or retinitis pigmentosa. **Dystonic head tremor reported as presenting feature.**		Blood tests: low vitamin E.
	Abetalipoproteinemia	200100	4q23	*MTTP*	First-second decade	Friedreich-like phenotype, retinitis pigmentosa, hypocholesterolemia, malabsorption.		Blood tests: absent or extremely low LDL-cholesterol, triglyceride, and apolipoprotein B plasmatic levels; acanthocytosis; low vitamin E.
	Cerebrotendinous xanthomatosis	213700	2q35	*CYP27A1*	First-second decade (late onset reported)	Cerebellar ataxia, cognitive impairment, juvenile cataract, tendon xanthomas. Rarely parkinsonism, including **rest tremor**. Chronic diarrhea, psychiatric symptoms, peripheral neuropathy, dystonia, myoclonus, spastic paraplegia, pseudobulbar palsy, seizures.		Blood tests: high cholestanol, absent 27-OH. Brain MRI: variable cerebellar atrophy, cerebellar or cerebral leukodystrophy.
NBIA								
	NBIA/DYT-*PANK2* (PKAN)	234200	20p13	*PANK2*	Childhood (late onset reported)	Parkinsonism (including **rest tremor**), behavioural changes, pigmentary retinopathy in 50% of cases.		Brain MRI: iron deposition in the basal ganglia with "eye of the tiger" sign.
	NBIA/DYT/PARK-*PLA2G6* (PLAN)	256600	22q13.1	*PLA2G6*	Childhood (late onset reported)	Parkinsonism (including **rest tremor**), pyramidal signs, cognitive decline, cerebellar ataxia.		Brain MRI: usually iron deposition in the globus pallidus and substantia nigra; cerebellar atrophy in late-onset forms.
	HSP/NBIA-*C19orf12* (HSP43, MPAN)[3]	614298	19q12	*C19orf12*	Childhood	Spastic paraparesis, dysarthria, dystonia, parkinsonism, neuropathy, psychiatric features, optic atrophy.		Brain MRI: iron deposition in the globus pallidus and substantia nigra.
	CoPAN	615643	17q21.2	*COASY*	Childhood	Global developmental delay, ataxia, pyramidal signs, dystonia, parkinsonism.		Brain MRI: iron deposition in the globus pallidus and substantia nigra.
	HSP/NBIA-*FA2H* (HSP35, FAHN)	234200	20p13	*FA2H*	First-second decade	Spastic paraparesis, ataxia, dystonia.		Brain MRI: iron deposition in the basal ganglia (not constant), pontocerebellar atrophy, white matter hyperintensities.
	Kufor-Rakeb disease (PARK-*ATP13A2*)	606693	1p36.13	*ATP13A2*	Second-third decade	Early-onset levodopa-responsive parkinsonism (including **rest tremor**), pyramidal features, supranuclear upgaze palsy, cognitive impairment.		Brain MRI: generalized atrophy, putaminal and caudate iron deposition.
	NBIA/DYT/PARK-*CP* (Aceruloplasminemia)	604290	3q24-q25	*CP*	Middle adulthood	Retinal degeneration, diabetes, neurological features (dystonia, parkinsonism including **rest tremor**, ataxia).		Blood tests: absent serum ceruloplasmin, high serum ferritin. Brain MRI: iron deposition in the basal ganglia and dentate.
Glutaric aciduria type 1		231670	19p13.13	*GCDH*	Infancy or adulthood	Infancy: acute systemic complications, generalized dystonia. Later in life: **action tremor of the arms and head**, dystonia, cerebellar and pyramidal signs, premature ovarian failure in females.		Routine newborn screening in some countries.
Classic galactosemia		230400	9p13.3	*GALT*	Neonatal period to adulthood	Infancy: acute encephalopathic crises precipitated by febrile episodes. Later in life: **bibrachial dystonic tremor** along with orofacial dyskinesias.		Routine newborn screening in some countries.
Manganese transportopathies								
	SLC30A10 deficiency	613280	1q41	*SLC30A10*	Childhood or adulthood	Liver disease, polycythemia. Childhood: limb dystonia, dysarthria, **fine tremor**, bradykinesia, spastic paraparesis. Adulthood: parkinsonism, including **rest tremor**.	×	Blood tests: abnormal liver function, polycythemia. Brain MRI: T1 hyperintensities of the basal ganglia.

	SLC39A14 deficiency	617013	8p21.3	*SLC39A14*	Infancy	Loss of developmental milestones, dystonia, bulbar signs, spasticity.	×	Brain MRI: T1 hyperintensities of the basal ganglia.
Hereditary spastic paraplegias								
	HSP-*KIAA1840* (HSP11)	604360	15q21.1	*KIAA1840*	Infancy or adolescence (late onset reported)	Complex HSP. Cerebellar signs, polyneuropathy, seizures, cognitive impairment, abnormal eye signs, amyotrophy, parkinsonism (including **rest tremor)**, maculopathy, action tremor, mental retardation, upper limb weakness.		Brain MRI: white matter abnormalities, cerebellar atrophy, thin corpus callosum, "ears of the lynx" sign.
	HSP-*DSTYK* (HSP23)	270750	1q32.1	*DSTYK*	Childhood	Cognitive impairment, Lison syndrome, pigmentary skin abnormalities, facial and skeletal dysmorphism, **tremor**.		-
	HSP-*GJC2* (HSP44)	613206	1q42.13	*GJC2*	Adulthood	Pes cavus and a late onset slowly progressive paraplegia, dysarthria, loss of finger dexterity, dysmetria, **intention tremor**, scoliosis, upper limb involvement, and cognitive impairment.		Brain MRI: hypomyelinating leukodystrophy and TCC in all three patients
	HSP-*PGAP1* (HSP67)	N.A.	2q33.1	*PGAP1*	Infancy	Severe developmental delay, Distended abdomen, borderline intelligence, ACC, vermis hypoplasia, defective myelination	×	Brain MRI: agenesis of corpus callosum, hypomyelination.
	HSP-*REEP2* (HSP72)[5]	615625	5q31.2	*REEP2*	Early childhood	Spastic paraparesis, mild **postural tremor**.		-
Charcot-Marie-Tooth disease[6]		Various	Various	Various genes (i.e. *MFN2*, *NEFL*)	Usually second to third decade	Sensory-motor neuropathy, pes cavus, peroneal muscular atrophy, **postural tremor**.	×	NCS: MCVs ranging from demyelinating to axonal.

Legend: 5-HIAA = 5-hydroxyindoleacetic acid; CSF = cerebrospinal fluid; CT = computed tomography; HSP = hereditary spastic paraparesis; HVA = homovanillic acid; MCV = motor conduction velocity; MND = motor neuron disease; MRI = magnetic resonance imaging; N.A. = not available; NBIA = neurodegeneration with brain iron accumulation; NCS = nerve conduction study; OMIM® = Online Mendelian Inheritance in Man; SNAP = sensory nerve action potential.

^ Tremor features are reported in bold. § Tremor is rarely part of the clinical spectrum. [1] All autosomal recessive forms of Parkinson's disease may include tremor as part of their phenotype. [2] All autosomal recessive primary dystonias may include tremor as part of their phenotype. [3] Autosomal dominant inheritance also reported. [4] All autosomal recessive spinocerebellar ataxias may include tremor as part of their cerebellar syndrome. [5] Autosomal dominant inheritance also reported. [6] When tremor was a major feature, Charcot-Marie-Tooth disease was referred to as Roussy-Lévy syndrome in previous literature.

Table 4. Main X-linked inherited disorders which can present with tremor

Tremor disorder	OMIM®	Chromosome	Gene	Age of onset	Main phenotype^	Tremor as rare sign§	Laboratory and imaging findings
Fragile X tremor/ataxia syndrome	300623	Xq27.3	*FMR1*	Middle-late adulthood (usually >50 years)	**Intention or action tremor**, cerebellar ataxia, cognitive decline, neuropathy, vestibular and autonomic dysfunction. **Postural and rest tremor** also reported. Family history: intellectual disability in male relatives; premature ovarian failure in female relatives.		Brain MRI: middle cerebellar peduncle sign, moderate to severe brain atrophy, cerebral and cerebellar white matter abnormalities.
DYT-*TAF1* (DYT3, Lubag syndrome)	314250	Xq13.1	*TAF1*	Third-fourth decade	Dystonia, parkinsonism, including **rest tremor**.		Brain MRI: hyperintense putaminal rim, then atrophy of the caudate head or putamen.
Waisman syndrome	311510	Xq28	*RAB39B*	Early adulthood (<45 years)	Intellectual disability, early-onset parkinsonism, including **rest tremor**.		-
Adrenoleukodystrophy	300100	Xq28	*ABCD1*	Childhood/Adulthood	Spastic paraparesis, adrenal insufficiency, bladder and bowel dysfunction.		Blood tests: high very long chain fatty acids, high adrenocorticotropic hormone. Brain MRI: white matter abnormalities.
Rett syndrome	312750	Xq28	*MECP2*	Infancy (6-18 months)	Occurs almost exclusively in females. Developmental arrest and regression, poor sociability, lack of communication, irritability, anxiety, dystonia, **tremor**, respiratory pauses, loss of hand skills, deceleration of head growth, progressive motor deterioration and stereotypies.		-
Lesch-Nyhan syndrome	300322	Xq26.2-26.3	*HPRT1*	Infancy (3-6 months)	Dystonia (including **dystonic tremor**), choreoathetosis, ballismus, cognitive and attentional deficits, self-injurious behaviors.		Blood tests: high uric acid.
Spinal and bulbar muscle atrophy (Kennedy disease)	313200	Xq12	*AR*	Third-fifth decade (may appear earlier)	Lower motor neuron disease (muscle weakness and atrophy, fasciculations, decreased or absent tendon reflexes) involving the limbs and bulbar region (dysarthria and dysphagia); cramps; sensory neuropathy; gynecomastia; sexual dysfunction (testicular atrophy, decreased fertility, erectile dysfunction); partial metabolic syndrome (diabetes mellitus, non-alcoholic fatty liver disease). **High-frequency postural tremor of the hands, which may precede the onset of muscle weakness. Postural leg tremor also reported.** A minority of female carriers have mild symptoms (cramps; tremor).		Blood tests: elevated CPK; hyperglycemia; hyperlipidemia. EMG/NCS: signs of acute and chronic diffuse denervation; low SNAP amplitudes.
Pelizaeus-Merzbacher disease	312080	Xq22.2	*PLP1*	Early childhood	Pyramidal dysfunction, cerebellar ataxia, **head tremor**, progressive nystagmus, psychomotor delay.	×	Brain MRI: hypomyelination.
NBIA/PARK-*WDR45* (BPAN)	300894	Xp11.23	*WDR45*	Early childhood	First stage (early childhood): developmental delay, intellectual disability, epilepsy, stereotypies, dysfunctional sleep, ocular defects. Second stage (adolescence or early adulthood): rapidly progressive parkinsonism and cognitive decline. **Rest tremor may be part of parkinsonism.** Both males and females present with a similar phenotype.		Brain MRI: in the first stage normal or nonspecific brain atrophy; in the second stage iron accumulation in the substantia nigra and globus pallidus (hypointense on T2); on T1 hyperintense "halo" surrounding a thin line of hypointensity in the substantia nigra and cerebral peduncles.
Cabezas syndrome	300354	Xq24	*CUL4B*	Infancy	Intellectual disability; speech delay; short stature; cervicodorsal kyphosis; hyperextensible joints; truncal obesity; abnormal gait; prominent lower lip; hypogonadism;		Brain MRI: cortical dysplasia; ventriculomegaly; loss of cerebral white matter; thin corpus callosum.

					muscle wasting in the lower legs; small feet. **Constant fine tremor in the upper extremities with intention component.** Female carriers are normal or minimally affected.		
CMTX (*GJB2*)[1]	302800	Xq13.1	*GJB2* (90% CMTX)	Second to third decade	Males more severely affected than females. Sensory-motor neuropathy. **Postural tremor** reported.	×	NCS: MCV ranging from demyelinating to axonal.

Legend: EMG = electromyography; MCV = motor conduction velocity; MRI = magnetic resonance imaging; NCS = nerve conduction study; OMIM® = Online Mendelian Inheritance in Man.

^ Tremor features are reported in bold. § Tremor is rarely part of the clinical spectrum. [1] When tremor was a major feature, CMT has been referred to as Roussy-Lévy syndrome in previous literature.

Table 5. Main chromosomal abnormalities which may include tremor in their clinical picture

Tremor disorder	Karyotype	Age of symptom onset	Main phenotype^	Laboratory and imaging findings
Quantitative chromosomal abnormalities				
Klinefelter syndrome	47,XXY	Puberty. Tremor usually begins during childhood, but may appear later in life.	**Intention tremor of the upper extremities, sometimes associated with head, voice, and leg tremor**, tall stature, arm span exceeding height, hypergonadotropic hypogonadism/androgen deficiency (infertility due to azoospermia, painless bilateral gynecomastia, decreased libido and potency, very low testicular volume and firm consistency of the testes).	Blood tests: hypergonadotropic hypogonadism/androgen deficiency. Spermiogram: azoospermia.
Jacobs syndrome	47,XYY	First decade	**Intention tremor of the arms, either unilateral or bilateral**, sometimes with **postural and/or mild resting tremor of the arms** as well as **head tremor**. Tall stature starting from childhood, a tendency toward central adiposity, macrocephaly, macro-orchidism starting in early puberty, hypotonia, clinodactyly, and hypertelorism. Asthma, dental problems, and seizures are more frequent than in the pediatric population. Attention deficit or autistic spectrum disorder. Developmental delays and language disorders are common.	-
Other supernumerary X or Y syndromes	48,XXYY	First decade	**Postural and/or action tremor of the upper** limbs, tall stature, micro-orchidism, and hypergonadotropic hypogonadism, dysmorphic features (long face, epicanthal folds, poor dentition), pes planus, allergies, asthma, attention deficit disorder, and learning difficulties.	Blood tests: hypergonadotropic hypogonadism/androgen deficiency. Spermiogram: azoospermia.
Qualitative chromosomal abnormalities				
Chromosome 22q11.2 deletion syndrome		First decade	Various combinations of congenital heart defects (particularly conotruncal malformation), palatal abnormalities, facial dysmorphic features, development delays and learning difficulties, immune deficiency, endocrine dysfunctions, hypocalcemia. Less frequent manifestations include psychiatric illness (psychosis, schizophrenia, attention deficit disorder, anxiety), skeletal malformations, esophageal dysmotility and structural gastrointestinal anomalies, renal anomalies, seizures (idiopathic or associated with hypocalcemia), ophthalmologic abnormalities, and reproductive issues, parkinsonism (including **rest tremor**).	DaTscan: reduced tracer uptake.

^ Tremor features are reported in bold.

Figure 1. Phenotype-to-genotype algorithm for genetic tremor syndromes

Overview: main tremor disorders discussed in this review arranged according to their syndromic classification and mode of inheritance. *Rarer presentations are mentioned in small print. The underlying genes are given in italic.

GENETIC TREMOR DISORDERS

ISOLATED TREMOR SYNDROMES (ET-like syndromes)

AD
DYT-*ANO3* (DYT24)
SCA12-*PPP2R2B* (SCA12)

AR
Glutaric aciduria type 1 (*GCDH*)
Galactosemia (*GALT*)
Phenylketonuria (*PAH*)

XL
FXTAS (*FMR1*, premutation)

CHR
KS (47,XXY)

COMBINED TREMOR SYNDROMES

ET PLUS SYNDROMES

Tremor with the features of ET and additional neurological signs of uncertain significance, such as:
- impaired tandem gait
- subtle dystonic posturing
- memory impairment
- other mild neurologic signs of uncertain significance,

that do not suffice to make an additional syndrome classification or diagnosis, including ET plus rest tremor.

TREMOR COMBINED WITH

DYSTONIA

AD
DYT-*TOR1A* (DYT1)
DYT-*THAP1* (DYT6)
DYT-*SCGE* (DYT11)
DYT-*KMT2B* (DYT28)
DYT-*GCH1* (DYT5a)
DYT-*ATP1A3* (DYT12)
DYT-*PRKRA* (DYT16)
DYT-*SLC2A1* (DYT18)
DYT-*CIZ1* (DYT23)
DYT-*ANO3* (DYT24)
DYT-*GNAL* (DYT25)
Neuroferritinopathy (*FTL*)
Primary familial brain calcification (*SLC20A2*, *PDGFRB*, *PDGFB*, *XPR1*)
Alexander disease (*GFAP*)

AR
WD (*ATP7B*)
DYT-*GCH1* (DYT5a)
DYT-*TH* (DYT5b)
Syndromic tremulous dystonia (*CAMTA2*)
PKAN (*PANK2*)
PLAN (*PLA2G6*)
MPAN (*C19orf12*)
CoPAN (*COASY*)
FAHN (*FA2H*)
Kufor-Rakeb disease (*ATP13A2*)
Aceruloplasminemia (*CP*)

XL
DYT-*TAF1* (DYT3)
BPAN (*WDR45*)

PARKINSONISM

AD
PARK-*SNCA* (PARK1/PARK4)
PARK-*LRRK2* (PARK8)
POLG
MAPT
PGRN
C9orf72
Neuroferritinopathy (*FTL*)
PARK-*UCHL1* (PARK5)
PARK-*GIGYF2* (PARK11)
PARK-*HTRA2* (PARK13)
PARK-*RAB7LI* (PARK16)
PARK-*VPS35* (PARK17)
PARK-*EIF4GI* (PARK18)
VCP
CHMP2B
TARBP

AR
PARK-Parkin (PARK2)
Gaucher disease (*GBA*)
WD (*ATP7B*)
PARK-*PINK1* (PARK6)
PARK*DJ1* (PARK7)
PARK9/Kufor-Rakeb disease (*ATP13A2*)
PARK14 (*PLA2G6*)
PARK15 (*FBXO7*)
PARK19 (*DNAJC6*)
PARK 20 (*SYNJI*)
Infantile parkinsonism-dystonia (*SLC6A3*)

XL
FXTAS (*FMR1*, premutation)
Waisman syndrome (*RAB39B*)

CHR
Chr 22q11.2 deletion syndrome
PARK16/Distal partial trisomy 1q syndrome (1q32q42)

CEREBELLAR FEATURES

AD
POLG
SCA-*ATXN1* (SCA1)
SCA-*ATXN2* (SCA2)
SCA-*ATXN3* (SCA3)
SCA-*CACNA1A* (SCA6)
SCA-*ATXN7* (SCA7)
SCA-*ATXN8* (SCA8)
SCA-*PPP2R2B* (SCA12)
SCA-*ITPR1* (SCA15/16)
SCA-*FGF14* (SCA27)
Alexander disease (*GFAP*)

AR
Friedreich ataxia (*FXN*)
WD (*ATP7B*)
Ataxia telangiectasia (*ATM*)
Ataxia with oculomotor apraxia type 1 (*ATX*)
Ataxia with oculomotor apraxia type 2 (*SETX*)
Cerebrotendinous xanthomatosis (*CYP27*)
Ataxia with vitamin E deficiency (*TTPA*)
Abetalipoproteinemia (*MTTP*)
GM2-gangliosidosis (*HEXA*, *HEXB*, *GM2A*)

XL
FXTAS (*FMR1*, premutation)

CHR
Chr 22q11.2 deletion syndrome
PARK16/Distal partial trisomy 1q syndrome (1q32q42)

PYRAMIDAL FEATURES

AD
HSP-*SPAST* (HSP4)
HSP-*ZFYE26* (HSP15)
HSP-*REEP1* (HSP31)
HSP-*ATP13A2* (HSP78)
SCA-*PPP2R2B* (SCA12)
MAPT
PGRN
C9orf72
VCP
CHMP2B
TARBP
Neuroferritinopathy (*FTL*)
Alexander disease (*GFAP*)

AR
PARK-*Parkin* (PARK2)
PARK-*PINK1* (PARK6)
PARK-*FBOX7* (PARK15)
PKAN (*PANK2*)
PLAN (*PLA2G6*)
MPAN (*C19orf12*)
CoPAN (*COASY*)
FAHN (*FA2H*)
Kufor-Rakeb disease (*ATP13A2*)
Aceruloplasminemia (*CP*)
HSP-*Spactasin* (HSP11)

XL
Adrenoleukodystrophy (*ABCD1*)

OTHER

AD
WITH NEUROPATHY:
Roussy-Lévy syndrome (*MPZ*, *PMP22*, *NEFL*)
WITH COGNITIVE IMPAIRMENT:
MAPT, *PGRN*, *C9orf72*, *VCP*, *CHMP2B*, *TARBP*
Alexander disease (*GFAP*)

AR
WITH COGNITIVE IMPAIRMENT:
GBA

XL
FXTAS (*FMR1*, premutation)

CHR
WITH HYPOGONADISM:
KS (47,XXY syndrome)
47,XYY syndrome
48,XXYY syndrome

Legend: AD = autosomal dominant; AR = autosomal recessive; XL = X-linked; CHR = chromosomal abnormality.

Video Legend

Video 1. Segment 1: tremor in a case of SCA-*PPP2R2B* (SCA12). Segment 2: tremor in a case of fragile X tremor-ataxia syndrome (FXTAS).

Supplementary File Legend

Supplementary Table. Video collection of some tremor disorders reviewed in this article. Previously unpublished videos (Video) or references to previously published videos (Supplementary Table) are provided.

Tremor disorder	**Reference to Video**
DYT-*TOR1A* (DYT1)	[S1]
DYT-*ANO3* (DYT24)	[S2]
SCA-*PPP2R2B* (SCA12)	Video, Segment 1
HSP-*REEP1* (HSP31)	[S3]
Adult-onset Alexander disease	[S4]
Wilson disease	[S5]
Glutaric aciduria type 1	[S6]
Classic galactosemia	[S7]
Fragile X tremor/ataxia syndrome	Video, Segment 2
Spinal and bulbar muscle atrophy (Kennedy disease)	[S8]
Klinefelter syndrome	[S9]
Jacobs syndrome	[S10]
48,XXYY syndrome	[S11]

Supplementary References

[S1] F. Magrinelli, R. Bacchin, M. Tinazzi, M. Gambarin, Twelve-year follow-up of a large Italian family with atypical phenotypes of DYT1-dystonia, Mov. Disord. Clin. Pract. 30 (2018): 166-170.

[S2] M. Stamelou, G. Charlesworth, C. Cordivari, S.A. Schneider, G. Kägi, U.M. Sheerin, I. Rubio-Agusti, A. Batla, H. Houlden, N.W. Wood, K.P. Bhatia, The phenotypic spectrum of DYT24 due to ANO3 mutations, Mov. Disord. 29 (2014): 928-934.

[S3] M. Picillo, R. Erro, R.P. Munhoz, A. Fasano, When shaking during standing points to hereditary spastic paraplegias, Parkinsonism Relat. Disord. 46 (2018): 92-94.

[S4] J.R. Sebesto, J.A. van Gerpen, Teaching Video NeuroImages: Palatal tremor in adult-onset Alexander disease, Neurology 86 (2016): e252.

[S5] R. Mahajan, U. Zachariah, Images in clinical medicine. Wing-beating tremor, N. Engl. J. Med. 371 (2014): e1.

[S6] E. Fernandez-Alvarez, A. Garcia-Cazoria, A. Sans, C. Boix, M.A. Vilaseca, C. Busquets, A. Ribes, Hand tremor and orofacial dyskinesia: clinical manifestations of glutaric aciduria type I in a young girl, Mov. Disord. 18 (2003): 1076-1079.

[S7] I. Rubio-Agusti, M. Carecchio, K.P. Bhatia, M. Kojovic, I. Parees, H.S. Chandrashekar, E.J. Footitt, D. Burke, M.J. Edwards, R.H. Lachmann, E. Murphy, Movement disorders in adult patients with classical galactosemia, Mov. Disord. 28 (2013): 804-810.

[S8] I. Aicua, O. Verhagen, N. Arenaza, E. Cubo, Head and arm tremor in X-linked spinal and bulbar muscular atrophy, Tremor Other Hyperkinet. Mov. (NY) 4 (2014): 265.

[S9] M. Koegl-Wallner, P. Katschnig-Winter, T. Pendl, B. Melisch, M. Trummer, E. Holl, U. Werner, R. Schmidt, P. Schwingenschuh, Tremor associated with Klinefelter syndrome--a case series and review of the literature, Parkinsonism Relat. Disord. 20 (2014): 323-327.

[S10] J.L. Davis, J.A. Kurek, J.C. Morgan, K.D. Sethi, Tremor and dystonia in Jacob's Syndrome (47,XYY), Mov. Disord. Clin. Pract. 7 (2019): 107-108.

[S11] N. Tartaglia, M. Borodyanskaya, D.A. Hall, Tremor in 48,XXYY syndrome, Mov. Disord. 24 (2009): 2001-2007.