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Update on Genetic Chorea

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ABSTRACT

Hereditary choreas are a clinically and genetically heterogeneous group of monogenic disorders in which chorea constitutes the core or an early-dominant feature. These conditions result from various genetic mutations affecting the structures and pathways involved in movement control, primarily the caudate and putamen, ultimately impairing the basal ganglia circuits involved in the regulation of movement, cognition, and behavior. This review focuses on the main forms of hereditary choreas, including Huntington's disease, neuroacanthocytosis syndromes, Huntington's disease phenocopies, benign hereditary chorea, and other less common genetic disorders presenting with chorea. We discuss the clinical, genetic, and pathophysiological features of each condition, alongside key aspects of phenomenology, examination, and complementary tests—including laboratory findings—to guide phenotype-driven genetic testing. We detail the characteristic features of key disorders while also highlighting less common but emerging conditions. This review aims to assist neurologists in recognizing and diagnosing hereditary choreas efficiently, including guidance on the selection of appropriate genetic tests, thereby reducing diagnostic delays, informing accurate counseling, and facilitating access to disease-specific interventions and clinical trials.

1 | Introduction

Hereditary choreas are a clinically and genetically heterogeneous group of monogenic disorders in which chorea constitutes the core or an early-dominant feature. Chorea is a movement disorder characterized by involuntary, rapid, and irregular movements that unpredictably shift from one part of the body to another. These movements, often described as flowing or dance-like, can interfere significantly with daily activities and are the hallmark of the neurological dysfunction seen in these conditions [1]. Hereditary choreas arise from genetic mutations that impair the function of proteins highly expressed in key brain regions involved in motor control—most notably the caudate nucleus and putamen—leading to dysfunction of the basal ganglia circuits [2, 3].

In addition to the motor symptoms, most hereditary choreas are frequently associated with a range of cognitive and behavioral alterations, adding further complexity to their clinical presentation. Cognitive decline, psychiatric symptoms such as depression and anxiety, and personality changes are common features that can emerge alongside the movement disorder, often complicating both diagnosis and management.

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Differential diagnosis of adult-onset chorea can be challenging, and one of the most informative clinical clues is the temporal pattern of symptom onset. Hereditary choreas typically manifest as slowly progressive, generalized choreic syndromes, whereas acquired etiologies—most often pharmacological, autoimmune, metabolic, or infectious—tend to present with a subacute onset [1, 4, 5]. The distribution of involuntary movements also contributes to diagnostic orientation. Hemichorea–hemiballism syndromes are commonly linked to structural brain lesions, such as vascular events or non-ketotic hyperglycemia. In contrast, hereditary choreas are usually generalized, although specific regions—such as the upper face in Huntington's disease (HD)—may show earlier or more prominent involvement. Age at onset may also help guide the differential diagnosis. A childhood onset presenting as a non-progressive choreic syndrome is more suggestive of one of the benign hereditary chorea (BHC) conditions, whereas paroxysmal choreo-dystonic episodes during childhood are more consistent with paroxysmal dyskinesias (see Table 1) [4–7]. Given the diagnostic complexity of these disorders and the growing number of implicated genes, some patients may reach adulthood without a definitive diagnosis.

The pattern of inheritance, the presence of anticipation due to trinucleotide repeat expansions within a family, and the geographic origin of the patient may also provide valuable diagnostic clues. Among autosomal dominant (AD) forms with anticipation, HD is the most frequent; among autosomal recessive disorders, chorea-acanthocytosis is the most frequent cause, whereas McLeod syndrome is the main representative of X-linked choreas [1, 4, 5]. A number of additional clinical features and neuroimaging findings can further support the diagnostic process, as summarized in Tables 2, 3, 5 and Figure 1.

This article provides a comprehensive review of the primary forms of hereditary choreas with a particular focus on adult-onset presentations. Childhood-onset choreas are not the primary focus of this review, but are briefly discussed when relevant to adult neurology practice. The search methodology is detailed in the Supporting Information. We discuss the clinical, genetic, and pathophysiological aspects of each disorder, highlighting the importance of detailed patient history, thorough neurological examination, and the use of complementary diagnostic tests—including neuroimaging and laboratory studies—to guide genetic diagnosis. For each disorder, we indicate the most appropriate genetic test, emphasizing that many adult-onset choreas cannot be reliably diagnosed through next-generation whole-exome sequencing (NGS-WES) alone, as they are often caused by repeat expansions not detectable by standard WES pipelines. Advanced technologies such as whole-genome sequencing (NGS-WGS) with specific tools like *ExpansionHunter*, or long-read sequencing, may overcome most of these limitations; however, their availability in routine clinical settings remains limited. These approaches are expected to become increasingly accessible in the near future, potentially enabling faster and more accurate diagnoses. Given the clinical overlap and genetic heterogeneity of these disorders, accurate diagnosis is essential for appropriate management, genetic counseling, and timely access to disease-specific treatments and potential clinical trials.

TABLE 1 | Differential diagnosis of chorea.

Differential diagnosis of chorea
Pattern of onset
Acute: Vascular, metabolic
Subacute: Autoimmune (e.g., antiphospholipid syndrome, Sydenham chorea, IGLON5 disease), paraneoplastic (e.g., anti-CV2, anti-Hu), deficiency-related (e.g., nutritional or metabolic deficiencies), pharmacological
Chronic: Typically genetic
Progression
Progressive: Degenerative (HD, NA)
Non-progressive: HBC, *ADCY5*, dyskinetic cerebral palsy
Paroxismal: Paroxismal dykinesias
Distribution
Hemichorea/hemiballismus: Often associated with structural lesions (e.g., stroke, non-ketotic hyperglycemia, infections)
Generalized: HD, NA, BHC
Frontal-predominant: Early stages of HD
BOL: Common in NA, iron accumulation disorders, tardive dyskinesias
Age of onset
Childhood: Benign hereditary chorea (e.g., *NKX2-1/TITF1*, *ADCY5* mutations)
Adulthood: HD, NA, HD-like syndromes (e.g., *C9orf72* expansions, SCA17, DRPLA, HDL1, HDL2)

Note: Differential diagnosis of chorea according to the pattern of onset, clinical course, distribution of involuntary movements, and age at presentation.
Abbreviations: BHC, benign hereditary chorea; BOL, bucco-orolingual; HD, Huntington's disease; NA, neuroacanthocytosis.

2 | Huntington's Disease (HD)

HD is the most common cause of hereditary chorea with a prevalence of approximately 5–12 cases per 100,000 people [8, 9] in populations of European descent, being less prevalent in Asia and Africa.

This neurodegenerative disease is caused by an abnormal expansion of CAG triplets in exon 1 of the *HTT* gene with an AD inheritance pattern [6, 10, 11]. The greater the number of CAG repeats, the earlier the age of onset, which is associated with a worse prognosis. There is a phenomenon of CAG-triplet expansion that can occur in successive generations, particularly when the disease is inherited paternally. The penetrance of the disease is related to the number of CAG repeats, being incomplete with 36–39 repeats and complete with 40 or more repeats. Juvenile-onset (JHD) forms are typically associated with 55 or more repeats [6, 12–14].

The typical onset of HD occurs between the ages of 35 and 50, although up to 25% of cases manifest after the age of 60. It leads to a reduced life expectancy, with an average course from

TABLE 2 | Diagnostic clues that can guide genetic testing.

Diagnostic clues
Clinical characteristics—Physical examination
Upper face involvement/frontal corea: HD
Oro-buco-lingual dystonia: NA (ChAc, McLeod syndrome), NBIA, Lubag disease, Wilson's disease, Lesch–Nyhan syndrome
Self-mutilating behavior: ChAc, Lesch–Nyhan syndrome, SCA17
Pyramidal signs and signs of lower motor neuron involvement: *C9orf72*
Polyneuropathy, areflexia: ChAc, McLeod
Myopathy: McLeod, mitochondrial
Seizures: ChAc, DPRLA, SCA17, mitochondrial
Ataxia: SCA17, DRPLA, SCAs and recessive ataxias
Ethnicity
Asians DRPLA; Sub-Saharan Africans HDL2—*JHP3*; Philippines origin, Lubag disease; Northern England, neuroferritinopathy
Neuroimaging
Caudate atrophy: HD, ChAc, McLeod
Cerebellar atrophy: SCA17, DRPLA, SCAs
Cortical atrophy
Fronto-temporal: *C9orf72* expansions, occipital atrophy: HDL2-*JPH3*
Diffusion restriction: HDL1
Leukoencephalopathy: DPRLA
Inherited disorders with metal or mineral deposition
PKAN2: Eye of the tiger
Wilson's disease: Panda eyes
Neuroferrinopathy: Cystic lesions
Aceruloplasminemia: Basal ganglia hypointensity
Farh syndrome: Calcifications on CT scan
Basal ganglia hyperintensity: Glutaric aciduria, HDL1 (diffusion restriction)
Laboratory findings
Acanthocytes: ChAc, McLeod, *JPH3*, PKAN2, aceruloplasminemia
CKs elevation: ChAc, McLeod syndrome, mitochondrial
AST, ALT elevation: ChAc, McLeod syndrome
Ceruloplasmin: Low levels in Wilson disease, absence in aceruloplasminemia
Ferritin: Low ferritin levels in neuroferritinopathy
Alpha-fetoprotein: Ataxia telangiectasia, ataxia with oculomotor apraxia

symptom onset to death ranging 15–20 years [6, 13]. Between 2% and 5% of cases present before the age of 21 and are classified as JHD. The phenotype differs from the classic forms of HD, with a clinical picture dominated by dystonia and parkinsonism from the early stage of the disease [15–17].

HD is characterized by a clinical triad of motor, cognitive, and neuropsychiatric symptoms that can manifest at various stages throughout the course of the disease [6]. Before the onset of established symptoms, there is a prodromal phase characterized by subtle signs of the disease [18, 19].

2.1 | Motor Symptoms

Chorea is the hallmark motor symptom of HD. It typically begins in the facial region, often with a frontal predominance, and progressively generalizes. Tics and vocalizations may also be present [1, 20]. Motor impersistence often co-occurs with chorea [1, 21]. As the disease progresses, chorea will gradually be replaced by dystonia and parkinsonism [22–24]. Hyperreflexia with hung-up knee jerk is characteristic [25, 26]. Oculomotor abnormalities are common, particularly the inability to inhibit the head impulse during eye movements [27, 28]. Gait abnormalities in HD are often difficult to categorize as they typically present with a combination of chorea, motor impersistence, dystonia, parkinsonism, and cerebellar ataxia [29, 30].

2.2 | Cognitive Impairment

The most frequent cognitive alteration is a dysexecutive-attentional syndrome. Although cortical impairment is also common, it is often overshadowed by the prominent impairment of executive functions. Anosognosia is a frequent and clinically significant feature. As the disease progresses, most patients develop dementia [31–35].

2.3 | Neuropsychiatric Symptoms

Neuropsychiatric symptoms are highly prevalent in HD. Apathy is particularly characteristic and tends to progress linearly with the disease. Depression, anxiety, irritability, and aggression are also very common. Less frequently, obsessive-compulsive traits or psychosis may occur. Suicidal ideation and attempts are frequent in HD [36–41].

2.4 | Diagnosis

The genetic diagnosis is based on the detection of an abnormal CAG trinucleotide repeat expansion in the *HTT* gene [42]. This is typically performed using targeted molecular techniques such as triplet-primed PCR (TP-PCR), also referred to as repeat-primed PCR (RP-PCR), which are specifically designed to identify large or interrupted repeat expansions. Although a biological classification system (Huntington's Disease Integrated Staging System [HD-ISS]) [19] has been proposed recently, clinical diagnosis in routine practice still relies primarily on the unequivocal presence of motor symptoms consistent with HD in patients with

TABLE 3 | Main clinical and ancillary test findings in hereditary chorea.

Disease	Gene	Main and characteristic clinical features	Ancillary test
Autosomal dominant			
Huntington's disease	*HTT* (*IT15*) CAG expansion	Frontal chorea, motor impersistence, oculomotor dysfunction, psychiatric and cognitive symptoms, hung up reflexes	MRI: Caudate atrophy
C9orf72	*C9orf72* GGGGCC expansion	Association with DLFT and ALS, pyramidalism, motor neuron symptoms	MRI: Fronto-temporal atrophy
SCA 17 (HDL-4)	*TPB* CAG expansion	Cerebellar ataxia, dystonia, psychiatric symptoms and cognitive impairment	MRI: Cerebellar and cortical atrophy, putaminal rim
DRPLA	*ATN1* CAG expansion	Chorea if onset > 20 years, often accompanied by ataxia, dystonia, parkinsonism, and dementia, < 20 years: progressive myoclonic epilepsy More frequent in Asia	MRI: Olivo-ponto-cerebellar atrophy Leukoencephalopathy
HDL-2	*JPH3* CTG/CAG expansion	Parkinsonism, dementia, psychiatric disturbances, Sub-Saharan ancestry	MRI: Cortical atrophy—occipital Acanthocytes (< 1)
HDL-1	*PRPP* Octapeptide expansion	Rapidly progressive course, myoclonus, dementia	RMI: cortical ribbon 14.3.3 protein
Neuroferritinopathy (NBIA)	*FTLm*	Oro-buco-lingual dystonia	Low ferritin levels MRI: cystic degeneration in the caudate and putamen; and "pencil sign"
Benign hereditary chorea NKX2-1 related disorderes	*NKX2-1* (*TITF-1*)	Non-progressive, may be accompanied by developmental delay, lung and thyroid alterations	Thyroid hormone abnormalities
ADCY-5 related movement disorders	*ADCY5*	Chorea, dystonia, myoclonus, and facial dyskinesias, movement disorder can be paroxysmal	Caffeine response
Autosomal recessive			
Chorea-acanthocytosis	*VPS13A*	Bucco-oro-lingual dystonia, feeding dystonia, PNP, myopathy, psychiatric symptoms, epilepsy, self-mutilation behaviors, areflexia	MRI: Caudate atrophy Acanthocytes Elevated CK levels, AST, ALT
Aceruloplasminemia (NBIA)	*CP*	Dystonia, ataxia, diabetes, retinal degeneration, and anemia	Absence of ceruloplasmin
Wilson's disease	*ATP7B*	Parkinsonism, wing beating, dystonia, psychiatric disturbances, hepatic failure, Kayser–Fleischer ring	MRI: Panda sign Low ceruloplasmin levels, elevated copper levels in 24-h urine
X-linked			
McLeod syndrome	*XK*	Myopathy, cardiomyopathy (2/3), OCB, tics, hepatosplenomegaly	MRI: Caudate atrophy Acanthocytes Elevated CK levels, AST, ALT

(Continues)

TABLE 3 | (Continued)

Disease	Gene	Main and characteristic clinical features	Ancillary test
Lesch–Nyhan syndrome	*HPRT1*	Dystonia predominantly of the lower facial part, self-mutilation behaviors	Elevation of uric acid in the blood
Lubag disease	*TAF1*	Hemidystonia, oromandibular dystonia, parkinsonism, Philippines ancestry	Dopa responsive parkinsonism
Other genetic conditions			
Genetic ataxias	SCA1, 2, 3, 8, 48 (*ATXN1*, *ATXN2*, *ATXN3*), *ATXN8* (*STUB1*), *AF* (*FXN*), AT (*ATM*), AOA1 (*APTX*), AOA2 (*SETX*), *CANVAS* (*RFC1*)...	Predominant cerebellar ataxia, Chorea is more commonly reported in SCA48, AT, AOA, whereas in other ataxias it is uncommon and typically emerges later in the disease course	MRI: Cerebellar atrophy
Metabolic conditions	Glutaric aciduria (*GCDH*)	Acute onset, in childhood triggers—infections, fever	Characteristic MRI
	Mitochondrial disease	Myopathy, seizures, ophthalmoparesis, movement disorders are present in 20%–30% patients although chorea is uncommon	CKs, GDF15 elevation

confirmed genetic mutations or a family history of genetic confirmation [19, 43, 44]. Neuroimaging tests can assist in the differential diagnosis. In classic forms of HD, brain MRI typically reveals atrophy of the caudate and putamen. In JHD forms, a characteristic hyperintensity in the putamen on T2/FLAIR sequences may be observed (Figure 1). PET-FDG scans can show hypometabolism in the caudate and putamen [12, 19, 45–47].

2.5 | Treatment

The management of HD should be multidisciplinary, addressing the treatment of motor, cognitive, and psychiatric symptoms in an integrated manner. Chorea is primarily managed with vesicular monoamine transporter type 2 (VMAT2) inhibitors [48, 49], although antipsychotics are commonly used in routine clinical practice to manage both chorea and psychiatric symptoms, while antidepressants are frequently employed to treat psychiatric disorders [48, 49].

3 | Neuroacanthocytosis

Neuroacanthocytosis refers to a group of disorders that present neurological symptoms and acanthocytes in peripheral blood (Table 4) [50–52]. These syndromes can be categorized into "core" neuroacanthocytosis syndromes—such as chorea-acanthocytosis and McLeod syndrome—where chorea is a key clinical feature, and other neurological conditions in which acanthocytes may also appear but chorea is not the predominant manifestation.

3.1 | Chorea-Acanthocytosis (ChAc)—Levine-Critchley Syndrome

It is the most common cause of neuroacanthocytosis, as well as the most frequent form of autosomal recessive (AR) hereditary chorea [51]. It is caused by variants in the *VPS13A* gene, which leads to the absence of chorein—a protein expressed in both neurons and erythrocytes [51, 53, 54]. The estimated prevalence is less than one case per million. Symptom onset typically occurs in the third or fourth decade of life, and the life expectancy is approximately 15–20 years from onset [55].

The phenotype closely resembles that of HD, presenting with a pattern of generalized chorea [52, 54, 56]. However, several distinctive features help differentiate it from HD. There is a marked predilection for involvement of the buccolingual region, including oromandibular dystonia and the characteristic "feeding dystonia." Self-injurious behaviors—particularly tongue and lip biting—are common and may lead to significant mutilation. Tics are very common, particularly vocalizations, grunting, belching, and echolalia. A particularly distinctive motor symptom is intermittent head drop [52, 54, 56]. Additional neurological findings include axonal sensorimotor polyneuropathy and myopathy with hypo- or areflexia [57]. The gait is described as "rubber-person" attributed to a combination of motor impersistence, dystonia, and myopathy. Parkinsonism may also occur. Approximately one-third of patients also experience generalized epileptic seizures [29]. Neuropsychiatric symptoms include prominent OCD, along with apathy and frontal behavioral changes. Cognitively, patients experience progressive deterioration, primarily with executive dysfunction, which may ultimately progress to dementia [54, 56, 58].

The genetic diagnosis is based on the identification of biallelic pathogenic variants in the *VPS13A* gene. Full gene sequencing using targeted NGS panels or WES is commonly employed and can detect most point mutations. However, up to 20%–30% of pathogenic *VPS13A* alleles correspond to large deletions or duplications that may escape detection by standard sequencing. In such cases, complementary techniques such as multiplex ligation-dependent probe amplification (MLPA) or WGS may be necessary.

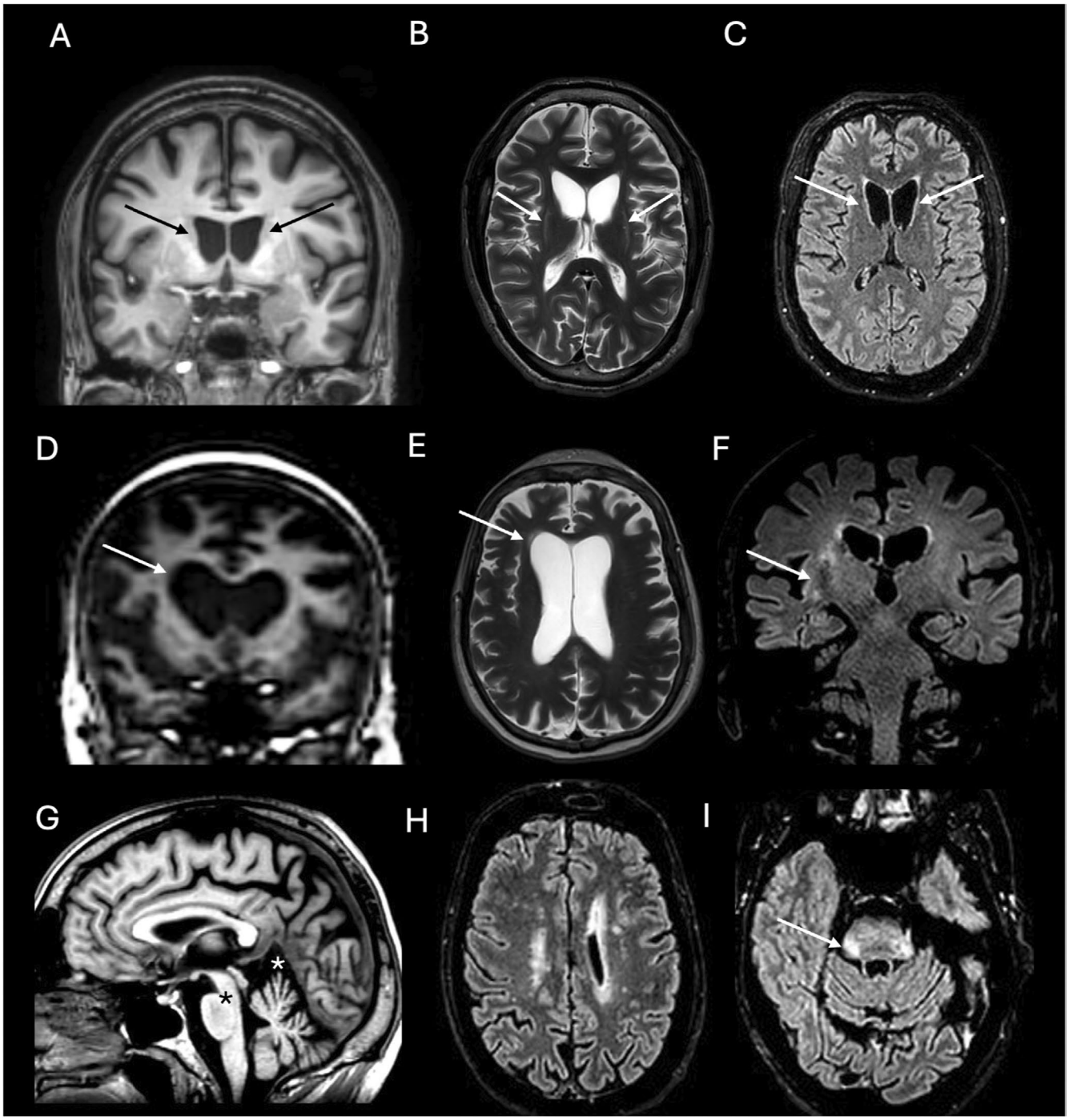

FIGURE 1 | MRI images from patients with genetic choreas (A–I). (A) T1-weighted MRI of a patient with early-stage Huntington's disease showing mild caudate atrophy (arrows). (B) T2-weighted MRI of a patient with the Westphal variant of Huntington's disease showing characteristic hyperintensity in the putamen associated with caudate atrophy. (C) FLAIR MRI demonstrating caudate atrophy in a patient with neuroacanthocytosis due to a VPS13A mutation. (D, E) Coronal T1-weighted and axial T2-weighted images showing asymmetric atrophy, predominantly in the right frontal lobe, in a patient with a C9orf72 mutation, chorea, and frontotemporal cognitive decline. (F) FLAIR MRI of a patient with SCA17 presenting with ataxia, parkinsonism, and chorea, showing a right putaminal rim and cerebellar and caudate atrophy. (G–I) MRI of a patient with DRPLA: (G) T1-weighted image showing hypointensity in the pons and cerebellar atrophy, (H) FLAIR image showing characteristic white matter hyperintensities, and (I) FLAIR image showing hyperintensity in the superior cerebellar peduncle and brainstem pathways.

Western blot analysis of erythrocyte proteins can be performed to demonstrate chorein deficiency, providing supportive diagnostic evidence [53, 59]. Additional laboratory findings that may assist in diagnosis include creatine kinase (CK) and liver enzymes. Acanthocytes may be present on a peripheral blood smear, although sensitivity is limited and repeated testing (ideally three times) on freshly prepared samples is recommended to improve detection. Brain MRI reveals atrophy of the caudate and putamen, while ^{18}F-FDG PET may show corresponding striatal hypometabolism (Figure 1) [54, 57, 60].

TABLE 4 | Neuroacanthocytosis syndromes.

"Core" neuroacanthocytosis syndromes
Choreoacanthocytosis (ChAc)
McLeod syndrome
Neurodegenerative diseases that may present with acanthocytes in peripheral blood and chorea
Pantothenate kinase-associated neurodegeneration (PKAN)
Aceruloplasminemia
Huntington like-2 (HDL-2)
Diseases with decreased lipoproteins in the blood and acanthocytes
Abetalipoproteinemia
Hypobetalipoproteinemia

Note: Acanthocytes are spiculated red blood cells that acquire this shape due to alterations in the membrane proteins of erythrocytes.

Pharmacological management is similar to HD, with the particularity that good responses to deep brain stimulation in the internal globus pallidus (DBS-GPi) have been described, as well as botulinum toxin injections for the management of oromandibular dystonia [61, 62].

3.2 | McLeod Syndrome

It primarily affects males due to its X-linked recessive inheritance, although there have been some cases reported in homozygous women or those with X chromosome inactivation, who tend to have milder symptoms. The syndrome is caused by a mutation in the *XK* gene that contains a single coding exon and encodes the Kell protein responsible for carrying the Kx antigen on red blood cells [63, 64]. The prevalence of this condition is even lower than ChAc, with fewer than 1000 cases reported worldwide.

The onset of symptoms usually occurs later in life, typically between the ages of 40 and 60 [55]. The phenotype includes generalized chorea. Tics may be predominant. Self-injurious behaviors are less common than in ChAc. Axial myopathy, sensory-motor axonal polyneuropathy with areflexia, and epileptic seizures are common [63, 65]. OCD and other neuropsychiatric symptoms, such as perseveration, behavioral changes, and cognitive decline, may also be present [58, 64, 66]. Regarding systemic symptoms, the presence of cardiomyopathy (up to 70% of patients), arrhythmias, and the risk of sudden death should be considered [55, 67]. These patients may experience severe adverse reactions after receiving a blood transfusion without the McLeod phenotype starting from the second exposure [66].

The genetic diagnosis of McLeod syndrome relies on the identification of pathogenic variants in the *XK* gene. *XK* is covered in most neuroacanthocytosis gene panels and WES. However, as previously mentioned for ChAc, large deletions may also escape detection by WES; in such cases, confirmation with MLPA or array-CGH focused on Xp21 is recommended.

The absence of the Kx antigen and weakened Kell antigen expression in red blood cells provides a useful hematological clue that supports the diagnosis and should prompt genetic confirmation. As for ChAc, blood tests may show elevated CK levels, and acanthocytes may be present [68]. MRI shows caudate atrophy. The electromyogram may reveal a pattern consistent with sensory-motor axonal polyneuropathy and myopathy, which can also be confirmed through muscle biopsy or muscle MRI [69].

4 | Phenocopies of Huntington's Disease: Huntington Disease-Like (HD-Like or HDL)

The term "HD-like" generally refers to patients presenting a phenotype resembling HD, characterized by the triad of motor, cognitive, and neuropsychiatric symptoms, but testing negative for CAG repeat expansion in the *HTT* gene [4, 7, 70].

4.1 | C9orf72-Associated Disease

It is considered the most common genetic cause of HD-like syndromes in the Western population [71, 72]. It is caused by a GGGGCC hexanucleotide repeat expansion (> 60 repeats) located in the first intron and promoter region of the *C9orf72* gene. It follows an AD inheritance with age-dependent incomplete penetrance [73, 74].

The average age at onset is 55–60 years. The disease is characterized by a combination of motor, cognitive, and psychiatric symptoms with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) as the most frequent phenotypes. From a motor perspective, signs of both upper and lower motor neuron involvement are typically present, with pyramidal signs on examination. Parkinsonism is also common, while chorea is a less frequent symptom, primarily affecting the buccolingual region. Cognitive decline is accompanied by pronounced behavioral symptoms, although suicidal ideation is less frequent than in HD [72, 73, 75].

The genetic diagnosis, as with HD, requires specific techniques such as TP-PCR. Neuroimaging typically reveals frontotemporal atrophy and frontotemporal hypometabolism on PET-^{18}FDG scans (Figure 1) [72, 73, 75].

4.2 | SCA17 (HDL-4)

It is considered the second most common cause of HD-like syndrome in Western populations [71]. It is caused by a CAG/CAA polyglutamine expansion in the *TBP* gene and follows an AD inheritance pattern. Alleles with 41–45 repeats exhibit reduced penetrance while those with 46–66 repeats are fully penetrant [76–78]. Recent evidence suggests that mutations in the *STUB1* gene may modify disease expression in individuals carrying *TBP* alleles within the reduced penetrance range, resulting in a digenic inheritance pattern [76, 79, 80].

The usual age at onset ranges from 30 to 50 years, with later onset observed in carriers of reduced penetrance alleles [76, 77]. Clinical presentation is dominated by a progressive ataxia syndrome [76, 79]. Up to one-third of patients present with chorea;

they can also present with parkinsonism, dystonia, and myoclonus. Progressive cognitive decline and psychiatric symptoms are common, especially the presence of schizophrenia-like delusional ideation and depression. Additionally, patients may experience epileptic seizures [76–78].

Genetic diagnosis requires specific techniques such as TP-PCR. In cases with intermediate repeat lengths, sequencing of the *STUB1* gene by NGS or Sanger methods is recommended. Brain MRI shows cerebellar, basal ganglia, and cortical atrophy; a hyperintense rim in the putamen has also been described (Figure 1) [76, 81, 82].

4.3 | Dentato-Rubro-Pallido-Luysian Atrophy (DRPLA)—Naito-Oyanagi Disease

Is the main differential diagnosis of HD in the Asian population, particularly in Japan. It is caused by a CAG repeat expansion in the *ATN1* gene and follows an AD inheritance pattern. It exhibits a significant phenomenon of meiotic expansion, particularly with paternal inheritance. Alleles with 35 and 47 repeats exhibit reduced penetrance, while those with >48 are fully penetrant. Juvenile-onset cases, often presenting as progressive myoclonic epilepsy, are typically associated with more than 70 CAG repeats [83–86].

Typical age at onset ranges from 30 to 50 years [84, 87]. Cerebellar ataxia is the hallmark feature, along with other motor symptoms such as chorea, dystonia, parkinsonism, spasticity, and myoclonus. Chorea and cognitive decline tend to predominate in adult-onset cases with fewer repeats, while myoclonus, epilepsy, and psychomotor delay are more common in juvenile forms with larger expansions [84, 85, 88]. Behavioral disturbances, psychosis, confabulation, depression, and apathy can occur. Seizures are also commonly present [87, 88].

As in other polyglutamine disorders, the genetic diagnosis relies on specific techniques such as TP-PCR. MRI shows cerebellar and pontine tegmentum atrophy with hypointensity in T1-weighted sequences. Additionally, symmetric and diffuse hyperintensities in the white matter, corona radiata, centrum semiovale, and superior cerebellar pedunculus on T2-weighted sequences and ventricular dilatation are characteristics (Figure 1) [82, 85, 87].

4.4 | Huntington Disease-Like 1 (HDL-1)-Familial Prion Disease

HDL-1 is a rare AD prionopathy [89] caused by an octapeptide repeat expansion in the prion protein gene (*PRNP*). The number of repeats influences the phenotype, disease onset, and progression. Expansions of 2–5 repeats are associated with later onset and rapidly progressive Creutzfeldt-Jakob-like disease evolving in less than 24 months (point mutations in *PRNP* can also result in this Creutzfeldt-Jakob-like phenotype). Insertions of 6–12 repeats lead to the HDL-1 phenotype with earlier onset (20–40 years) and slower progression (>24 months) [90, 91]. Fewer than 200 cases have been reported globally, with predominance in Scandinavian populations [90].

The phenotype includes rapidly progressive cognitive decline with cortical features—apraxia, amnesia, and executive dysfunction—accompanied by early behavioral changes, psychosis, depression, and apathy. Motor signs include ataxia, parkinsonism, chorea, and myoclonus [90, 92].

As in other repeat expansion disorders, genetic diagnosis requires targeted analysis of the *PRNP* gene using specific TP-PCR. Supportive diagnostic tools include CSF 14-3-3 protein test—although this may be negative in HDL-1—and real-time quaking-induced conversion (RT-QuIC), which offers superior sensitivity. Brain MRI may show cortical and basal ganglia hyperintensities or diffuse atrophy, although imaging may be normal or reveal cerebellar atrophy in longer expansions.

4.5 | Huntington Disease-Like 2 (HDL-2)

HDL-2 is an AD form of HD-Like caused by a CTG repeat expansion in the *JPH3* (Junctophilin-3) gene. It is the most frequent HD phenocopy in individuals of sub-Saharan African ancestry [93, 94].

Symptom onset typically occurs between 40 and 45 years [93, 95]. Regarding motor aspects, patients may experience chorea, dystonia, and parkinsonism. Chorea tends to predominate in individuals with smaller expansions, whereas higher repeat sizes may be associated with dystonia and parkinsonian features. A progressive subcortical dementia is observed, and neuropsychiatric disturbances such as depression, anxiety, and apathy may occur [93, 95, 96].

Genetic confirmation requires detection of the *JPH3* CTG expansion. TP-PCR or Southern blot is required for accurate sizing. Additional diagnostic clues include the presence of acanthocytes (in 10% of cases) and the MRI pattern, showing striatal and predominantly occipital atrophy [51, 95, 96].

4.6 | Huntington Disease Like 3 (HDL-3)

HDL-3 is a rare AR disorder mapped to chromosome 4p.15.3 and described in a single consanguineous Saudi Arabian family [97]. Symptom onset is in early childhood (4–5 years) with a clinical presentation resembling JHD. Features include chorea, dystonia, spasticity, pyramidal signs, psychomotor regression, mutism, and epileptic seizures [97].

Brain MRI shows caudate and frontal lobe atrophy [7, 97].

5 | Childhood-Onset Chorea Formerly Labeled as 'Benign Hereditary Chorea' (BHC)

The term *benign hereditary chorea* (BHC) has been historically used to describe childhood-onset, non-neurodegenerative choreas with stable or slowly progressive courses. However, this term is misleading, as some patients may develop significant disability related to motor symptoms, psychiatric comorbidities, cognitive dysfunction, or systemic involvement.

Several genes have been described that can result in a benign hereditary chorea (BHC) phenotype. However, BHC classically refers to patients with mutations in the *NKX2-1*/*TITF-1* gene [98]. Mutations in the *ADCY5* gene have been more recently described as a cause of benign hereditary chorea [99]. Other genes associated with paroxysmal dyskinesias can also manifest as non-progressive chorea [100].

5.1 | NKX2-1-Related Disorders ("Classic" BHC)

NKX2-1 mutations, formerly *TITF-1*, cause an AD childhood-onset chorea that often improves with age. With a prevalence of less than one case per million, it is characterized by choreiform movements, often accompanied by respiratory and endocrine involvement [98, 101]. It belongs to the brain–lung–thyroid syndrome spectrum, although only 30%–40% of patients exhibit the full triad. Congenital hypothyroidism, recurrent respiratory infections, obstructive lung disease, and increased neoplastic risk have been reported [101–103].

The neurological clinical picture includes hypotonia associated with hyperkinetic movement disorders such as chorea, myoclonus, ataxia, tremor, and dystonia. Patients usually present with mild, non-progressive psychomotor delay and psychiatric disorders within the spectrum of attention-deficit/hyperactivity disorder (ADHD) and OCD.

Pathogenic variants include point mutations and larger deletions; the latter may be missed by standard NGS and require complementary techniques such as MLPA or array-CGH for detection [101]. Neuroimaging frequently reveals pituitary abnormalities, although it can also be normal. Blood tests may reveal thyroid hormone abnormalities [102].

Some patients may respond to treatment with levodopa [104].

5.2 | ADCY5-Related Movement Disorders

ADCY5 mutations cause AD hyperkinetic movement disorders [99, 105] often arising de novo, with high penetrance and marked phenotypic variability. Described phenotypes include BHC, nocturnal paroxysmal dyskinesia, and kinesigenic and non-kinesigenic dyskenisias [105, 106]. The estimated prevalence is below one case per million [99, 106]. Patients may also present with some degree of psychomotor delay [99, 106].

The onset age is typically in childhood, although there are mildly symptomatic cases diagnosed in adulthood. The phenotype includes facial chorea, dystonia, and myoclonus with paroxysmal exacerbations, often triggered by sleep–wake transitions (especially early morning), stress, or fatigue [99, 107]. During exacerbations, patients may exhibit orofacial and cervical dystonia, generalized chorea, and ballism.

Somatic mosaicism is frequent and may influence severity. It can go undetected by standard NGS requiring high-depth sequencing when suspected [108]. Neuroimaging is usually normal. A sustained response to caffeine or theophylline has been reported in up to 40% of patients [109]. Selected cases may benefit from DBS-GPi [110, 111].

5.3 | Other Genes With BHC-Like Phenotypes

- *PDE2A*: AR early onset chorea with paroxysmal exacerbations, progressive cognitive symptoms, and epilepsy [112].
- *PDE10A*: AD childhood chorea (ages 5–10), associated with bilateral striatal hyperintensity on MRI and intellectual disability [113].
- *GNAO1*: AD gain-of-function mutations lead to non-progressive childhood chorea; loss-of-function mutations are associated with Ohtahara syndrome [114].

6 | Paroxysmal Dyskinesias

These are a group of genetic disorders characterized by sudden episodes of hyperkinetic choreo-dystonic movements triggered by specific factors. Patients typically exhibit a normal interictal examination, and symptoms often improve with age. Although these disorders typically present with paroxysmal symptoms beginning in childhood, there is increasing recognition of their overlap with choreic syndromes. A single gene can give rise to a spectrum of phenotypes, including forms that resemble hereditary chorea. Moreover, many cases remain undiagnosed until adulthood, and these disorders should therefore be considered in the differential diagnosis of genetic choreas, particularly in cases with paroxysmal or fluctuating symptoms [115, 116]. A comprehensive review of all genetic causes of paroxysmal dyskinesias exceeds the scope of this article and is addressed in detail in dedicated reviews [115, 116].

7 | Inherited Disorders With Metal or Mineral Deposition

This group includes rare genetic conditions characterized by abnormal accumulation of metals or minerals in the brain, often producing distinctive neuroimaging findings that can guide diagnosis. Chorea may be present, although often as part of a broader movement disorder spectrum.

7.1 | Primary Familial Brain Calcification (PFBC)

PFBC, formerly known as Fahr disease, is defined by bilateral calcium deposition in the basal ganglia and cerebellum best visualized on CT scan [117]. It is most frequently caused by AD mutations in the *SLC20A2* gene, with variable penetrance and expressivity. Other AD genes include *PDGFB*, *PDGFRB*, and *XRP1* [117, 118]. Clinically, the syndrome is primarily characterized by parkinsonism and ataxia, although choreoathetosis may also be present in up to 12%–16% of genetically confirmed cases. Additionally, neuropsychiatric alterations and cognitive decline are observed [117]. Genetic diagnosis relies on NGS or WES panels including both AD and AR PFBC genes, with CNV analysis, after excluding metabolic mimics such as hypoparathyroidism or vitamin D deficiency.

7.2 | Wilson's Disease

Wilson's disease (AR, *ATP7B*) is a treatable disorder of copper metabolism. Neurological presentations include parkinsonism, dystonia (often with risus sardonicus), tremor ("wing-beating" tremor), psychiatric symptoms [119, 120] with chorea in only 5%–10% of cases [121] The Kayser- Fleischer ring is a hallmark finding in patients with neurological symptoms [119, 120, 122]. Diagnosis begins with low serum ceruloplasmin and elevated 24-h urinary copper excretion. Genetic confirmation requires full sequencing of *ATP7B* with MLPA if needed. Brain MRI may show the classic "face-of-the-panda" midbrain sign [119, 122].

7.3 | Neurodegeneration With Brain Iron Accumulation (NBIA)

NBIA syndromes are genetically heterogeneous disorders characterized by basal ganglia iron accumulation visible on brain MRI using T2-weighted gradient-echo or susceptibility-weighted

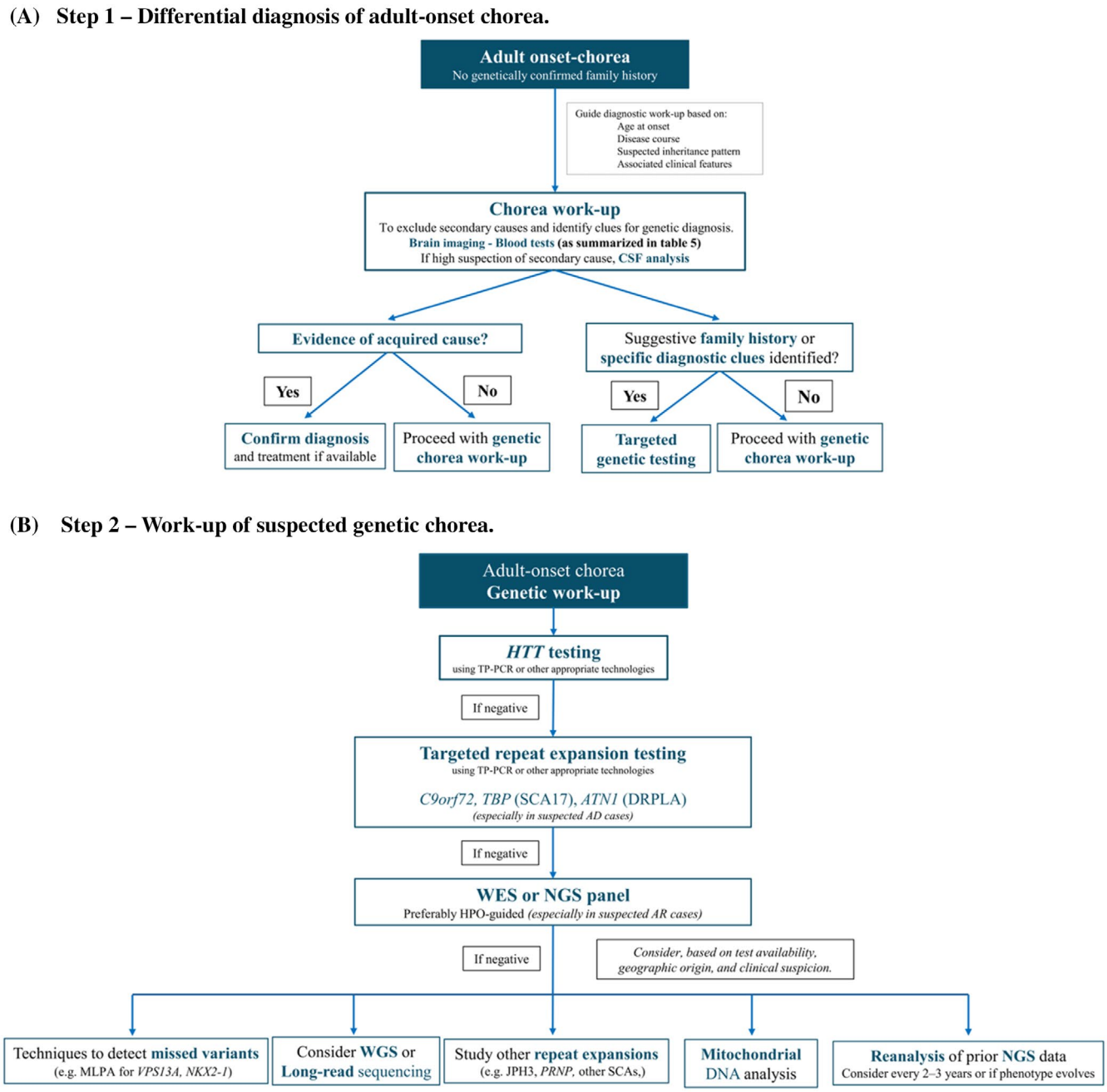

FIGURE 2 | Diagnostic approach to adult-onset chorea. Stepwise diagnostic algorithm for patients presenting with chorea. The initial evaluation focuses on excluding acquired causes through clinical history, laboratory studies, neuroimaging, and cerebrospinal fluid analysis when appropriate. In chronic or progressive cases, a genetic etiology should be suspected [(A) Step 1—Differential diagnosis of adult-onset chorea]. Targeted genetic testing is recommended in the presence of specific diagnostic clues (e.g., acanthocytosis, MRI findings, systemic involvement). In the absence of such clues, broader approaches including repeat expansion testing and phenotype-guided next-generation sequencing panels should be considered [(B) Step 2—Work-up of suspected genetic chorea]. See Tables 1, 3, and 5 for detailed clinical and ancillary test correlations.

imaging (SWI) sequences [123–125]. Chorea is rare overall but may be a prominent feature in specific forms such as neuroferritinopathy, aceruloplasminemia, and pantothenate kinase-associated neurodegeneration (PKAN) [126].

Other NBIA subtypes (e.g., *PLA2G6*, *FA2H*, *C19orf12*) rarely cause chorea and are not detailed here. Hypermagnesemia syndromes (*SLC30A10*, *SLC39A14*), which may include chorea and are treatable with chelation, can be considered in selected cases with compatible imaging and systemic findings.

7.3.1 | Neuroferritinopathy

Mutation of the *FTL* gene, being the only iron deposition disorder transmitted in a dominant manner. It is more prevalent in the north of England, specifically in the Cumbria region [127]. Chorea, dystonia with orofacial component, cognitive decline, and neuropsychiatric alterations starting in middle age, around 50 years old. On MRI, we may observe pallidal necrosis with cystic degeneration. In laboratory tests, low plasma ferritin levels can be found [127].

7.3.2 | Aceruloplasminemia

Mutation in the *CP* gene, AR inheritance that leads to a deficiency of the protein ceruloplasmin, which is essential for copper metabolism [128]. The clinical spectrum may include cranio-cervical dystonia, parkinsonism, chorea, ataxia, diabetes mellitus, hemolytic anemia, and retinal degeneration. Cognitive decline and psychiatric disturbances are also commonly observed [128, 129]. In MRI, hypointensity will be observed in the striatum and dentate nucleus. In laboratory tests, low or undetectable ceruloplasmin levels, elevated ferritin, and anemia with hemolytic characteristics will be noted [129].

7.3.3 | Pantothenate Kinase-Associated Neurodegeneration (PKAN)

Mutations in the *PKAN2* gene with AR inheritance. Disease generally begins in childhood or adolescence, although it can also manifest in adulthood. Symptoms include chorea (although this is an uncommon presentation) in the head and upper limbs, which may then generalize. However, dystonia with orofacial involvement and parkinsonism are more common [123, 124]. On MRI, the characteristic "tiger eye sign" can be observed. Additionally, approximately 10% of patients present acanthocytes in peripheral blood examination [51, 123, 124].

8 | Other Genetic Neurological Disorders That May Present With Chorea

To date, up to 249 genes have been associated with the chorea phenotype according to the Human Phenotype Ontology database (https://hpo.jax.org/browse/term/HP:0002072). Many genetic disorders may present with chorea, although it is often not the primary clinical feature. In most of these conditions, chorea may emerge in the context of a broader neurological or multisystemic syndrome, underscoring the importance of careful phenotyping and targeted genetic testing in the diagnostic workup. Examples include genetic ataxias beyond the more common SCA17 and DRPLA, such as SCA48, ataxia telangiectasia, ataxia with oculomotor apraxia, *RFC1 related diseases*; mitochondrial diseases due to mitochondrial DNA mutations (e.g., MELAS) or nuclear DNA gene defects (e.g., *POLG*); inborn errors of metabolism (e.g., glutaric aciduria type I, Lesch-Nyham syndrome); and nucleotide excision repair disorders (NERDND). A comprehensive review of all these genetic entities exceeds the scope of this article. However, Table 3 provides a brief overview of some of the most relevant and prevalent

TABLE 5 | Recommended diagnostic workup for potentially treatable causes of chorea and hereditary chorea.

Category	Recommended tests
Blood tests	Complete blood count, liver enzymes (AST, ALT), renal function tests (creatinine, urea) creatine kinase (CK), thyroid and parathyiroid function tests, ceruloplasmin, copper (serum and 24 h urine), ferritin, acanthocytes
Autoimmune	ANA, anti-dsDNA, ASLO, antiphospholipid antibodies, ENA panel (SSA, SSB, ACE...)
Paraneoplastic	Autoimmune encephalitis and onconeural antibody panel (commonly associated antibodies include: anti-CV2, anti-NMDA, anti-Hu, anti-Ri, anti-GAD, anti-IgLON5, LGI1, CASPR2, etc.)
Metabolic/ nutritional/ pharmacological	Electrolyte panel (Na^+, K^+, calcium, magnesium), vitamin B12, folate, homocysteine, ammonia, lactate, glucose, renal function tests (creatinine, urea), alpha-fetoprotein, GDF15 (if mitochondrial disease is suspected) Toxicology screen (including antipsychotics, stimulants)
Infectious	HIV, VDRL/TPHA, hepatitis B/C serologies, tuberculosis (quantiferon or PPD), toxoplasma IgG/IgM, herpesvirus serologies (HSV, VZV, ...)
Neuroimaging	MRI brain with T1, T2, FLAIR, DWI, SWI/BOLD sequences; CT brain (calcifications, non-ketotic hyperglycemia)
CSF analysis	Cell count, protein, glucose, oligoclonal bands, 14-3-3 protein/RT-QuIC (if prion disease suspected), surface neuronal antibodies and onconeural antibody panel, PCR and serologies if CNS infection is suspected

disorders in which chorea may be part of the clinical phenotype [4, 117, 125, 130–146].

9 | Discussion

The spectrum of genetic disorders associated with chorea is broad, with HD being the most common cause worldwide. In clinical practice, the diagnostic approach for a patient presenting with chorea and no previously genetically confirmed family diagnosis should be guided by several factors: age at onset (childhood vs. adult), disease course (acute, subacute, or chronic), family history, suspected inheritance pattern, and associated clinical features (Table 1) [1, 4, 5]. A chronic and progressive course is more suggestive of a hereditary etiology. In cases with a genetically confirmed family history, confirmatory testing for the known pathogenic variant is indicated [1, 4]. Furthermore, genetic testing of asymptomatic individuals at risk requires thorough genetic counseling to address the psychological, ethical, and medical implications of predictive testing [42].

The first step in the workup patients without a genetically confirmed family history, as detailed in Figure 2, involves ruling out acquired causes through neuroimaging, blood tests, and, when clinically indicated, cerebrospinal fluid analysis, particularly in cases with subacute onset. Differential diagnosis should consider autoimmune and paraneoplastic, vascular, metabolic, or infectious etiologies [1, 4, 5]. Laboratory screening should also include CK, peripheral blood smear for acanthocytes, serum ceruloplasmin and 24 h urinary cooper, thyroid function tests and plasma manganese, that may provide diagnostic clues suggestive of hereditary choreas (Table 5 summarizes the recommended laboratory tests and neuroimaging findings). Similarly, brain MRI may reveal disease-specific patterns such as caudate nucleus atrophy (commonly observed in HD and neuroacanthocytosis), iron deposition in the globus pallidus ("eye of the tiger" sign in PKAN), or cerebellar atrophy suggestive of SCA17, DRPLA, or other ataxic disorders [1, 5, 82]. These clinical, biochemical, and radiological features are summarized in Tables 3 and 4, and can serve as key elements to orient the differential diagnosis.

When specific diagnostic indicators are identified (e.g., acanthocytosis, Kayser–Fleischer rings, or disease-specific MRI findings), targeted genetic testing should be prioritized.

In the absence of such findings, a stepwise approach is recommended. This should begin with analysis of *HTT*, followed by testing for the most frequent known repeat expansions in *C9orf72*, *TBP*, *ATN1*, *JPH3* using RP-PCR or TP-PCR. If negative, broader sequencing strategies should be considered. NGS-WES is commonly employed, although it may fail to detect CNVs, such as those found in *VPS13A*, *NKX2-1*, or *PDGFB*, as well as variants in mitochondrial DNA (mtDNA), or deep intronic variants which require specific complementary assays (e.g., MLPA, mtDNA analysis, WGS) [4, 7, 70].

In specialized centers, WGS with tailored bioinformatic pipelines (as *ExpansionHunter*) is increasingly available. WGS enables simultaneous interrogation of SNVs, CNVs, deep intronic variants, and, when appropriately analyzed, repeat expansions. However, long-read sequencing technologies remain the only approach capable of fully resolving complex tandem repeats and structural rearrangements in a single continuous read. While

TABLE 6 | Treatment of hereditary chorea.

Etiology	First-line treatment	Second-line adjunct options	Comments
HD	VMAT-2 inhibitors (e.g., tetrabenazine, deutetrabenazine, valvenazine)	Atypical antipsychotics (e.g., aripiprazole, olanzapine, risperidone)	Consider psychiatric profile; antipsychotics useful if comorbid psychosis or agitation Avoid tetrabenazine if depression/suicide risk
NA (ChAc, McLeod)	VMAT-2 inhibitors, antipsychotics	GPi deep brain stimulation (DBS), botulinum toxin for oromandibular dystonia and feeding dystonia	Self-injury and orolingual dystonia may respond to focal botulinum toxin, use antipsychotics with caution if associated cardiomyopathy
Benign hereditary chorea (NKX2-1, ADCY5, etc.)	Levodopa (in NKX2-1), caffeine/theophylline (in ADCY5)	DBS in selected cases Levetiracetam may be considered in patients with associated myoclonus	Often non-progressive; treat comorbid ADHD/OCD symptoms if present
Paroxysmal chorea/dyskinesias	Responsive to anticonvulsants (carbamazepine, clonazepam)	Lifestyle adjustment (e.g., avoid triggers)	Episodes often decrease with age without treatment
Wilson's disease	Chelation (D-penicillamine, trientine), zinc supplementation	Symptomatic therapy for chorea (e.g., tetrabenazine, antipsychotics)	Avoid dopamine antagonists early due to risk of worsening parkinsonism

Note: Therapeutic approaches for the management of chorea according to etiology and clinical context. The table summarizes pharmacological and interventional strategies for chorea, based primarily on the available evidence from clinical experience and trials conducted in HD. Where applicable, disease-specific therapeutic recommendations are included for other causes. Treatment decisions should be individualized based on symptom severity, comorbidities, and underlying etiology.

currently restricted to research settings, long-read platforms are expected to become integral to clinical diagnostics in the near future.

In unresolved cases, periodic reanalysis of WES/WGS data is recommended every 2–5 years, or earlier if the phenotype evolves, as both gene discovery and bioinformatic pipelines continue to advance. Selected cases may benefit from referral to research programs offering long-read sequencing to improve diagnostic yield. When a genetic diagnosis is reached, genetic counseling should be offered to the patient and family members to plan their lives and future offspring.

Due to the constellation of cognitive, psychiatric, and systemic symptoms that often accompany genetic choreas, management requires a multidisciplinary approach. Chorea treatment depends on etiology, comorbidities, and severity. While evidence is limited beyond HD, VMAT2 inhibitors and antipsychotics are commonly used; DBS may help in refractory cases. Specific recommendations are summarized in Table 6, and detailed reviews are available elsewhere [48, 49, 147].

Author Contributions

Jesús Pérez-Pérez: conceptualization, methodology, resources, visualization, writing – original draft preparation, writing – review and editing (lead). **Gonzalo Olmedo-Saura:** conceptualization, methodology, resources, visualization, writing – original draft preparation (lead). **Saül Martínez-Horta:** writing – original draft preparation, writing – review and editing (supporting). **Sara Bernal:** methodology, original draft preparation (supporting). **Javier Pagonabarraga:** writing – methodology, review and editing (supporting). **Jaime Kulisevsky:** conceptualization methodology, writing – review and editing (equal).

Ethics Statement

The MRI data are fully anonymized. All images, videos, and data were obtained with appropriate ethical committee approval and informed consent from participants, in compliance with the principles outlined in the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The MRI data discussed in this article are part of the Movement Disorders Unit's repository of videos and images, collected for educational purposes. These materials, have not been previously published elsewhere, and their use complies with ethical guidelines and relevant policies.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ene70357-sup-0001-DataS1.docx.