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Recent advances in genetics of chorea

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Abstract

Purpose of review—Chorea presenting in childhood and adulthood encompasses several neurological disorders, both degenerative and non-progressive, often with a genetic basis. In this review, we discuss how modern genomic technologies are expanding our knowledge of monogenic choreic syndromes and advancing our insight into the molecular mechanisms responsible for chorea.

Recent findings—A genome-wide association study in Huntington Disease identified genetic disease-modifiers involved in controlling DNA repair mechanisms and stability of the CAG repeat expansion. Chorea is the cardinal feature of newly recognized genetic entities, *ADCY5* and *PDE10A*-related choreas, with onset in infancy and childhood. A phenotypic overlap between chorea, ataxia, epilepsy, and neurodevelopmental disorders is becoming increasingly evident.

Summary—The differential diagnosis of genetic conditions presenting with chorea has considerably widened, permitting a molecular diagnosis and an improved prognostic definition in an expanding number of cases. The identification of Huntington Disease genetic-modifiers and new chorea-causing gene mutations has allowed the initial recognition of converging molecular pathways underlying medium spiny neurons degeneration and dysregulation of normal development and activity of basal ganglia circuits. Signalling downstream of dopamine receptors and control of cAMP levels represent a very promising target for the development of new aetiology-based treatments for chorea and other hyperkinetic disorders.

Keywords

Chorea; Genetics; Huntington Disease; Next-Generation Sequencing; Medium Spiny Neurons

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Introduction

Chorea is a hyperkinetic movement disorder characterized by an excess of brief, continuous, unpatterned involuntary movements [1]. Focal lesions of the striatum and degeneration and/or functional dysregulation of medium spiny neurons (MSNs), which constitute ~95% of the striatal cells and form the striatal output projections, are considered to underlie the pathophysiology of choreic movements [2].

A variety of acquired causes may underlie chorea (recently reviewed in [3]). However, genetic aetiologies play a central role in the differential diagnosis of choreic syndromes. Huntington's disease (HD), with a prevalence of up to 1 in 10,000 subjects in Western countries, is not only the most relevant single cause of chorea, but also the most common monogenic neurodegenerative disorder [4]. In recent years, thanks to the advances in DNA sequencing technologies, the list of genetic entities presenting with chorea, both neurodegenerative and non-progressive forms, is rapidly and largely expanding (Table 1).

In this review we will summarise the most relevant recent progresses in the field of genetics of chorea. Furthermore, we will discuss the advances in the understanding of the molecular mechanisms of basal ganglia disorders, gained thanks to the identification of novel monogenic choreic syndromes.

Advances in the genetics of Huntington's disease

Most of the current research efforts in HD genetics are aimed at identifying disease modifiers, which may influence the disease progression and determine the age at onset (AAO) of motor symptoms [5]. The length of the CAG expansion is well known to be the most relevant determinant of the age at onset (AAO), with longer repeats associated with an earlier onset [6]. However, the CAG repeat size accounts for only ~50% of the variation in AAO [7] and a substantial portion of the remaining variance in AAO is highly heritable, strongly indicating the existence of other critical genetic determining factors [5]. Neither the size of the non-expanded *HTT* allele, nor the presence of a second smaller CAG pathological expansion, is able to significantly influence AAO [8]. A recent study showed that a variant (rs13102260; G>A) in the *HTT* promoter, located in the site that regulates binding of the transcription factor NF-κB, exerts a bidirectional effect on HD AAO [9]. The authors showed *in vitro* and *in vivo* that the presence of the A allele determined a lower NF-κB-mediated *HTT* transcriptional activity, resulting in delayed AAO when inherited on the same allele of the pathological expansion (reduced expression of the pathological allele). On the contrary, the A allele was associated with an earlier AAO when located on the non-expanded allele (reduced expression of the normal *HTT*). An important corollary of these results is that therapeutic strategies aimed at lowering the expression of the pathological CAG expansion should take into account that non allele-specific silencing of *HTT* could bear undesired effects by decreasing the expression of the normal allele. The most relevant advance toward the discovery of HD genetic modifiers is the recent publication of the genome-wide association study (GWAS) performed by the Genetic Modifiers of Huntington Disease (GeM—HD) Consortium [10]. The authors identified two GWAS-significant loci, one on chromosome 15 and one on chromosome 8 that significantly modified the AAO of

motor symptoms as predicted solely by the CAG expansion length. Other suggestive associations, though not passing the stringent GWAS-significance threshold, were observed on chromosomes 3, 5 and 21. Genes located on chromosome 15 locus are *MTMR10* and *FAN1* and on the chromosome 8 locus are *RRM2B* and *UBR5*. Pathway analysis of the GWAS results indicates that HD modifiers may be involved in control of DNA handling and repair mechanisms. Supporting this view, the chromosome 3 locus centred on *MLH1*, a gene previously identified in a HD mouse model as a modifier of somatic instability of the CAG repeats [11].

Huntington's disease-like syndromes

Around 1% of cases with a HD-like presentation does not carry pathogenic expansion in *HTT* (HD-lookalikes, HDLs). These represent a genetically heterogeneous group of progressive heredo-degenerative conditions. Mutations in both dominant and recessive genes can result into HD mimics (recently reviewed in [12]). Amongst the autosomal dominant causes, it is important to consider pathological expansions in the genes encoding the prion protein (*PRNP*), junctophilin 3 (*JPH3*), TATA box-binding protein (*TBP*; also responsible for the dominant spinocerebellar ataxia type 17), atrophin-1 (*ATN1*), mutations in the ferritin light chain gene (the cause of neuroferritinopathy, an adult-onset dominant form of neurodegeneration with brain iron accumulation [NBIA]), and mutations in the genes responsible for idiopathic basal ganglia calcification (*SLC20A2, PDGFB, PDGFRB, XPR1*) [13–18]. Other important neurodegenerative conditions mimicking HD are neuroacanthocytosis, caused by recessive *VPS13A* mutations [19], and Macleod syndrome, an X-linked recessive disease caused by mutations in *XK* [20]. Most of the published cases series indicate that a genetic diagnosis can be reached only in a small minority of HDL cases (~1-3%) [15, 21–24]. Exceptions to this are the high prevalence of the *JPH3* expansion in patients of sub-Saharan African descent [15, 25] and the *ATN1* expansions in Japanese patients [26]. Importantly, pathological *C9orf72* exanucleotide repeat expansions, the most common genetic cause of familial frontotemporal lobar degeneration and amyotrophic lateral sclerosis [27, 28], were recently recognised as the single most prevalent cause of HDL in Caucasians [29]. Hensman-Moss et al. assessed a UK cohort of 514 HDL patients and identified ten subjects (1.95%) who carried the expansion. The spectrum of movement disorders observed in these cases included variable combinations of chorea, dystonia, myoclonus, and parkinsonian signs. Behavioural, psychiatric and cognitive difficulties were observed in most expansion carriers. Prominent signs of upper motorneuron involvement (but not lower motorneuron) were evident in four subjects. The *C9orf72* repeat expansion has been subsequently confirmed to be a relevant cause of HDL also in other cohorts [30, 31].

Chorea as the core feature in patients with mutations in cerebellar ataxia-related genes

Chorea is increasingly observed in patients with pathogenic mutations in genes linked to cerebellar ataxia (other than the aforementioned SCA17 expansion). Patients with bi-allelic *ATM* mutations, the cause of ataxia-telangiectasia (A-T), may present with a broad spectrum

of movement disorders, including chorea [32–34], isolated dystonia [35, 36], DOPA-responsive dystonia [37], and myoclonus-dystonia [38–40]. Patients with variant A-T have milder mutations, which allow a degree of residual protein activity [41]. Meneret and colleagues recently reported a total of 14 consecutive adults with variant A-T, and showed that, compared to patients with the classic presentation, they show a milder disease course and longer survival [42]. Of relevance, patients with *ATM*-related chorea and dystonia may completely lack the classic clinical features of A-T [43]. Chorea has been rarely described also in cases with ataxia with oculomotor apraxia type 1, 2 and 4 [44–46], and Friedrich ataxia [21, 47, 48]. Recently, recessive mutations in *RNF216,* a gene previously associated with cerebellar ataxia and hypogonadotropic hypogonadism [49], were identified in two recessive pedigrees with chorea, behavioural problems, and severe dementia [50].

Chorea secondary to *NKX2-1* mutations

Mutations in *NKX2-1*, encoding a transcription factor essential for striatal development, cause benign hereditary chorea (BHC) [51, 52], an autosomal dominant choreic syndrome with onset in infancy or early childhood, relatively scarce progression of symptoms and absence of other major neurological deficits, in particular progressive cognitive decline [53]. To date ~190 cases and ~100 *NKX2-1* mutations have been reported, allowing a better definition and an expansion of the phenotype associated with mutations in this gene [54–56]. *NKX2-1* mutations lead to a complex multi-systemic disease, featuring not only chorea, but also thyroid and pulmonary defects (*brain-lung-thyroid* syndrome) in ~80% of cases [54, 56]. It was recently proposed to abandon the term BHC [57] given that (i) 60% of the identified *NKX2-1* mutations are de novo (hence, the disease is not hereditary)[54]; (ii) *NKX2-1*-mutated cases commonly present with a variety of neurological symptoms other than chorea (i.e. hypotonia, neurodevelopmental delay, dystonia, myoclonus, tics and ataxia) [54, 58–61]; (iii) patients with *NKX2-1* mutations may present various degrees of non-progressive intellectual disability, as well as behavioural and psychiatric symptoms (recently reviewed in [62]). Furthermore, while the term BHC is often used to imply the presence of *NKX2-1* mutations, a significant number of families with BHC do not carry mutations in this gene [63, 64]. Thorwarth and colleagues recently published an extensive clinical and genetic study in a large cohort of BHC cases [56]. Pathogenic *NKX2-1* mutations were present in only 26.7% of cases (27/101; 17 point mutations and 10 large deletions), indicating the existence of other undetected pathogenic variants in the *NKX2-1* non-coding regions and/or mutations in other closely functionally related genes. Intriguingly, two of the detected deletions spared the coding region of *NKX2-1,* involving only the neighbouring chromosomal region, which encompasses the *MBIP* gene. The pathogenic mechanism of these deletions is currently not clear. The deletions may remove regulatory elements essential for *NKX2-1* transcription and critically affect *NKX2-1* expression. Alternatively, *MBIP* haploinsufficiency may represent a novel cause of a *NKX2-1* deficiency-like presentation [56].

Chorea secondary to *ADCY5* and *PDE10A* mutations

Recently, mutations in *ADCY5* and *PDE10A* have been identified as important causes of chorea. The first pathogenic *ADCY5* missense mutation (A726T) was identified in a large

kindred with an autosomal dominant movement disorder, mainly characterized by early onset of dyskinesias (chorea and dystonia) and facial myokymias [65]. Subsequently, *ADCY5* mutations have been recognized as the cause of a broad range of hyperkinetic movement disorders, mainly including chorea, but also dystonia and myoclonus [66–69]. So far, eight different mutations (de novo or with autosomal dominant transmission) have been reported in 27 unrelated subjects. Mutations affecting the amino acid residues R418 and A726 are recurrent, highlighting a particular relevance of these residues for disease mechanisms. Looking at patients published so far, subjects with the common p.R418W mutation seem to have a more severe presentation, with axial hypotonia and delayed motor milestones. Furthermore, somatic mosaicism may be at least in part responsible for intra-familial clinical variability in these subjects [67, 68]. Red flags for the diagnosis of *ADCY5*-related dyskinesias are (i) an onset of symptoms in the first years of life, (ii) the absence of significant cognitive involvement, (iii) prominent facial twitches, (iv) a marked fluctuations of symptoms (some patients presenting frank paroxysmal attacks, though without specific triggers [70]), (v) a marked exacerbation of the dyskinesias at night and upon awakening. Although *ADCY5*-related chorea is a non-degenerative condition, others and we have observed that the clinical picture of *ADCY5*-mutated cases can evolve, with chorea being more evident during childhood and dystonic and myoclonic elements becoming more prominent over the years [66, 67].

Both de novo dominant and recessive *PDE10A* mutations have been recently described in patients with childhood-onset chorea. Two different de novo mutations (p.F300L and p.F334L) were identified in three unrelated cases with a very similar clinical presentation of childhood-onset chorea (AAO between 5-10 years) and characteristic brain MRI showing symmetrical T2-hyperintense bilateral striatal lesions [71]. Recessive homozygous mutations (p.Y107C and p.A116P) were detected in two consanguineous pedigrees [72]. The phenotype in these cases was more severe, with a much earlier AAO (< 1 year), severe dysarthria, axial hypotonia, cognitive and language development delay. Of interest, despite a more severe neurological involvement, the MRI of the cases with recessive mutations did not show the same abnormal signal observed in the cases with dominant mutations.

ADCY5 and *PDE10A* encode the main enzymes regulating the synthesis (adenyl cyclase 5; AC5) and degradation (phosphodiesterase 10A; PDE10A) of cyclic adenosine monophosphate (cAMP) in MSNs. AC5 activity, and consequently cAMP synthesis in MSNs, is promoted by the stimulation of the G protein-coupled dopamine receptors type 1 and adenosine receptors 2A. Hence dopamine and adenosine-mediated modulation of MSNs activity largely relies on cAMP signalling [73]. *In vitro* and *in vivo* assessment of the effect of the identified PDE10A substitutions showed that both dominant and recessive variants lead to a loss-of-function [71] or reduced protein levels [72]. These data, together with the fact that *ADCY5* pathogenic mutations may increase the AC5 enzymatic activity and the synthesis of cAMP [74], suggest that increased intracellular cAMP levels in MSNs is critical for chorea pathogenesis. Pharmacological modulation of PDE10A is a primary target in pharmacological research of basal ganglia disorders, including HD and Parkinson disease [75] and a phase II clinical study (the Amaryllis study) of a PDE10A inhibitor is currently ongoing in HD. Importantly, the identification of loss-of-function *PDE10A* mutations as a cause of chorea suggests that pharmacological inhibition of PDE10A may not be the best

option for the treatment of hyperkinetic movement disorders. Mutations in *GNAL* [76] and *GPR88* [77], coding for G proteins almost exclusively expressed in MSNs and coupled with dopamine receptors, have been recently linked to dystonia and chorea, respectively, further implicating intracellular signalling downstream of dopamine receptors in MSNs in the pathogenesis of chorea and other hyperkinetic movement disorders.

Chorea in carriers of epileptic encephalopathy genes

An overlap between hyperkinetic movement disorders and epileptic/neurodevelopmental syndromes is emerging. A rapidly expanding number of mutations in genes originally reported in severe early-onset epileptic encephalopathies are now recognised in a spectrum of conditions ranging from isolated movement disorders (most frequently chorea, but also dystonia and stereotypies) to more catastrophic presentations.

GNAO1 mutations, first described in a type of severe epileptic encephalopathy with developmental delay (Ohtahara syndrome; [78]), are described also in cases presenting with a progressive choreic movement disorder, often in absence of epilepsy [79–82]. Mutations in *FOXG1*, a gene which plays a crucial role in the development of the foetal telencephalon, lead to a distinct phenotype manifesting in infancy and early childhood with microcephaly, epilepsy, delayed milestones and severe intellectual disability without language development (congenital Rett-like syndrome) [83]. Movement disorders have now been recognized as a core feature of this disorder, being present in 100% of cases in a series of 28 patients recently published [84]. Chorea is the most frequent movement disorder in *FOXG1* mutation carriers (88%), followed by orolingual/facial dyskinesias, dystonia, myoclonus and stereotypies, present in various combinations. Importantly, patients with missense mutations (instead of severe truncating mutations) may display a milder phenotype, with independent ambulation, spoken language, and normocephaly [84]. A single missense mutation (p.E1483K) in *SCN8A*, encoding a voltage gated Na-channel subunit widely expressed in the CNS, has recently been linked to paroxysmal kinesigenic dyskinesia and benign familial infantile seizures [85]. This observation expands the phenotypic spectrum associated with mutations in this gene, which also includes severe epileptic encephalopathy and a neurodevelopmental disorder [86]. A *de novo* missense variant in *SYT1*, encoding Synaptotagmin-1, a protein essential for synaptic vescicle fusion, has been recently associated with severe developmental delay and an early onset, paroxysmal dyskinetic movement disorder worsening at night (as seen in *ADCY5*-mutated patients), but only a single patient has been described to date [87].

Conclusions

Chorea is observed in an expanding number of genetic diseases. Mutations in *ADCY5* and *PDE10A* represent novel important causes of chorea, frequently featuring also myoclonus and dystonia. Furthermore, mutations in genes classically associated with other neurological disorders, such as ataxias, developmental delay, and epileptic encephalopathies, are increasingly detected in patients with chorea. Vice versa, mutations in *NKX2-1*, the cause of BHC, are now recognised in patients with a range of movement disorders (i.e. myoclonus, dystonia and ataxia) other than chorea. Importantly, this substantial genetic and clinical

overlap suggests that disruption of similar circuits and/or molecular pathways may underlie these neurological conditions.

While individually rare, clinical recognition and molecular diagnosis of monogenic causes of chorea is crucial to define precisely the prognosis and offer a correct genetic counselling to patients with chorea. Furthermore, the identification of genetic HD modifiers and of a growing number of mutations in novel genes linked to chorea is allowing the definition of converging biological pathways likely to be essential for the survival and physiological activity of MSNs. Different types of disease mechanisms can affect MSNs and clinically lead to chorea, including degenerative processes (e.g. HD and HDL), developmental abnormalities (e.g. *NKX2-1* and *FOXG1*-related choreas) and disrupted post-receptorial intracellular signalling (*ADCY5* and *PDE10A*-related choreas). A better understanding of the molecular mechanisms responsible for these conditions will be the key step to develop specific disease-modifying treatments.

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Key points

- The results of the first GWAS in Huntington's disease identified novel genetic modifiers of age at onset located on chromosome 8 and 15 and suggest that DNA handling and repair mechanisms are crucial in controlling the somatic stability of the CAG expansion.
- Thanks to the discovery of mutations in *ADCY5* and *PDE10A* as novel causes of chorea, abnormal cAMP metabolism in medium spiny neurons is emerging as a central molecular mechanism underlying the pathogenesis of basal ganglia disorders
- The *C9orf72* exanucleotide expansion has been recognised as the most common cause of Huntington disease-like syndrome in Caucasian populations
- While mutations in *NKX2-1* have been identified in patients with a range of movement disorders other than chorea, more than to 70% of benign hereditary chorea (BHC) cases do not have mutations in *NKX2-1,* prompting to abandon the use of the term BHC to label patients with *NKX2-1* mutations.
- An expanding genetic and phenotypic overlap between chorea (and other hyperkinetic movement disorders) and other neurological syndromes, including developmental delay, epilepsy and ataxia, is emerging.

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Table 1

List of monogenic causes of chorea

Gene	Main associated phenotype	Gene product	Inheritance	Age of onset	Diagnostic clues
HTT	Huntington disease	Huntingtin	AD (CAG expansion)	Childhood to late adulthood	Cognitive decline, psychiatric disturbances Progressive course MRI: caudate nucleus head atrophy
PRNP	HDL1	Prion protein	AD (octapeptide coding repeat expansion)	Adulthood	Dementia and psychiatric features Possible parkinsonism at onset and longer survival than HD
JPH3	HDL2	Junctophilin 3	AD (CAG/CTG expansion)	Adulthood	Parkinsonism may be first manifestation High frequency in people with black African ancestry
TBP	- HDL4 - Spinocerebellar ataxia type 17	TATA box-binding protein	AD (CAG expansion)	Childhood to adulthood	Ataxia and cognitive decline Frequent parkinsonism MRI: cerebellar atrophy
ATN1	Dentatorubral-pallidoluysian atrophy	Atrophin-1	AD (CAG expansion)	Childhood to adulthood	Seizures, myoclonus and cognitive decline MRI: Cerebellar and brainstem atrophy (especially pons) High frequency in Japan
C9orf72	FTD/MND	Chromosome 9 Open Reading Frame 72	AD (GGGGCC expansion)	Childhood to adulthood	Prominent cognitive and psychiatric features Pyramidal signs MRI: diffuse cerebral atrophy
FTL	Neuroferritinopathy	Ferritin light chain	AD	Teenage to late adulthood	Action-specific facial dystonia Reduced ferritin plasma levels MRI: iron deposition in basal ganglia and cortical pencil lining
SLC20A2 *PDGFB* *PDGFRB* *XPR1*	Idiopathic Basal Ganglia Calcification (IBGC)	Na-dependent phosphate transporter type 2 Platelet-derived growth factor βpolypeptide Platelet-derived growth factor receptor, β Xenotropic and polytropic retroviruses receptor	AD	Symptoms: early to late adulthood Calcium deposition: childhood to adolescence	CT scan: basal ganglia, cerebellar dentate nuclei and subcortical white matter calcification
VPS13A	Chorea-acanthocytosis	Chorein	AR	Early adulthood	Severe oromandibular dystonia with lip and tongue biting Head drops Peripheral axonal neuropathy Elevated serum CK MRI: caudate nucleus head atrophy
XK	Macleod syndrome	Kell blood group protein	X-linked recessive	Adulthood	Peripheral sensorimotor neuropathy Cardiomyopathy

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Gene	Main associated phenotype	Gene product	Inheritance	Age of onset	Diagnostic clues
					Elevated serum CK
ATM	Ataxia-telangiectasia	Ataxia-telangiectasia mutated gene	AR	Childhood to adulthood	Oculocutaneous telangiectases Sensorimotor neuropathy Elevated serum alpha-fetoprotein Predisposition to malignancy MRI: cerebellar atrophy
APTX *SETX* *PNKP*	Ataxia with oculomotor apraxia (AOA) type 1, 2, and 4	Aprataxin Senataxin Polynucleotide kinase 3'-phosphatase	AR	Childhood to adulthood	Sensorimotor neuropathy Hypoalbuminemia in AOA1 Hypercholesterolemia in AOA1 and AOA4 Elevated alpha-fetoprotein in AOA2 and AOA4 MRI: cerebellar atrophy
RNF216	Gordon-Holmes syndrome	Ring finger protein 216	AR	Adulthood	Hypogonadism MRI: cerebellar atrophy
NKX2-1	*NKX2-1*-related chorea	Thyroid transcription factor 1	AD/De novo	Infancy	Non-progressive course Hypotonia and early falls Learning difficulties Frequent pulmonary and thyroid dysfunction
ADCY5	*ADCY5*-related chorea	Adenylate cyclase 5	AD/De novo	Infancy to childhood	Normal cognition Dystonia and myoclonus may become prominent with age Severe diurnal and nocturnal exacerbations Axial hypotonia and delayed milestones in most severe cases
PDE10A	*PDE10A*-related chorea	Phosphodiesterase 10A	De novo/AR	Infancy to childhood	Delayed milestones and language development and dysarthria in cases with recessive mutations MRI: symmetrical T2-hyperintense bilateral striatal lesions in cases with dominant de novo mutations
GPR88	*GPR88*-related chorea	G protein-coupled receptor 88	AR	Childhood	Language delay and learning disabilities
GNAO1	Early infantile epileptic encephalopathy type 17 (Ohtahara syndrome)	Gαo	De novo	Infancy to childhood	Progressive and severe movement disorder associated with developmental delay, with or without seizures
FOXG1	Congenital Rett disease	Forkhead Box G1	De novo	Infancy to early childhood	Severe intellectual disability, absent language, acquired microcephaly MRI: corpus callosum abnormalities, frontal or frontotemporal underdevelopment mild cerebellar hypoplasia, and delayed myelination.

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Gene	Main associated phenotype	Gene product	Inheritance	Age of onset	Diagnostic clues
SYT1	Severe motor delay and intellectual disability	Synaptotagmin-1	De novo	Infancy	Severe delayed motor development without seizures
SCN8A	- Early infantile epileptic encephalopathy type 13 - BFIS	NaV1.6α-subunit of voltage-gated Na channels	AD/De novo	Infancy to childhood	Paroxysmal dystonia/chorea triggered by sudden movements or emotional stress Focal EEG abnormalities during attacks

AD: autosomal dominant; **AR**: autosomal recessive; **BFIS**: Benign familial infantile seizures; **HDL**: Huntington's disease-like.