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Chorea: An Update on Genetics

Jean-Marc Burgunder[a, b, c, d]

[a]Department of Neurology, University of Bern, Bern, Switzerland; [b]Swiss HD Center, Neurozentrum Siloah AG, Gümligen, Switzerland; [c]Department of Neurology, West China University, Chengdu, China; [d]Department of Neurology, Sun Yat Set University, Guangzhou, China

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Abstract
Background: Chorea may be present in a number of diseases including hereditary disorders. Major advances have occurred in our understanding of the genetic background of those disorders, and the present short review aims at highlighting the most salient ones. ***Summary:*** Chorea is one of the major manifestations of Huntington's disease. However, there are a number of other diseases, in which chorea is present as well and their list is in constant increase thanks to the availability of advanced molecular genetic diagnostic techniques. Finding of new genes followed by the investigation of further cases with part of the phenotype first described often leads to the recognition of additional aspects of the disorders, thus widening the scope of investigation and management. Likewise, assessment of genetic variations associated with specific aspects of the phenotype, in a way similar to approaches established in nongenetic disorders, has improved our understanding of phenotype variation. Knowledge on genetic background of chorea has ameliorated our diagnostic approaches. Furthermore, it opens new therapeutic strategies aimed at modifying expression both of the genes primarily implicated as the ones involved in further phenotype modification. ***Key messages:*** Recent research on the genetic background of disorders with chorea has provided data, which can now better guide differential diagnostic investigations in practical ways. Furthermore, they provide avenues for research on the disease mechanisms opening the door for clinical therapeutic trials.

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Introduction

Chorea is the major phenotypic aspect of a number of disorders, foremostly including Huntington's disease (HD), more appropriately called in this way instead of Huntington's chorea since movement disorder is only a part of the syndrome. Other such disorders with predominant chorea include Huntington-like syndromes and benign hereditary chorea, but the abnormal movement can also be present in cases due to a large number of further disorders. Algorithms to guide through differential diagnostic workout of diseases with chorea have been published. Recommendations include a thorough clinical description of the syndrome, including information from family history, and physical examination followed by additional investigations including MRI, laboratory workup, and molecular genetic investigations [1–3]. It is important not to miss treatable causes of chorea and other hyperkinetic disorders, which have recently been reviewed [4]. An important increase in our knowledge

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Correspondence to:
Jean-Marc Burgunder, jmburgunder@bluewin.ch

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about the genetic background of disorders with chorea has taken place in recent years. This includes the discovery of new genes involved in the causation of disorders with chorea, but also the recognition of genetic factors modifying their presentation, some of which are now being explored as therapeutic targets. This brief account reviews the most salient recent findings in this topic.

Huntington's Disease

HD was one of the first neurogenetic disorders in which the causative mutation was found. HD is due to an elongation of a CAG repeat element in the exon 1 of the *HTT* gene [5]. The age at onset is inversely correlated with the number of repeats [6] in European ancestry populations but also in China, where the prevalence is much lower [7]. People with more than 39 CAG repeats will be affected, those below 35 not, and those between the two numbers with a less penetrant phenotype. Disease manifestation may occur in earlier ages over the next generations, phenomenon described as anticipation, a concept that had been suggested already in the early 20th century [8]. Genetic anticipation is due to instability of the CAG repeat with the tendency to increase over generation [9]. However, the CAG repeat numbers account only for about 60% of the variation of the age at motor symptoms onset and the onset age may vary over more than 2 decades with the same CAG number. This may be due to the difficulty to precisely assess age at onset, but the suggestion had earlier been formulated that modifying genetic factors may play a role. Based on this hypothesis, a continuous stream of genome-wide association studies has been pursued by the GeM-HD consortium. The group has taken benefit of large patient cohorts availability, in particular Pharos [10] and Cohort [11], run by the Huntington Study Group, and Registry [12], established by the European Huntington's Disease Network and continued into Enroll-HD, a global observational study sponsored by CHDI [13]. In a combined study with more than 4,000 participants, several loci associated with a variation in the age at motor onset were found. Two were located on a chromosome 15 locus: one associated with a 1.4 years later onset, and another one with a 6 years earlier onset, and a further locus on chromosome 8 was associated with 1.6 years earlier onset [14]. These findings were confirmed in a later study with more than 9,000 participants [14]. The increased power offered by the larger sample size has allowed to demonstrate the presence of additional loci, associated with hastened, respectively, delayed motor onset. Furthermore, the data have shown that the onset is not dependent on the size of the polyglutamine tract, but on the size of the uninterrupted CAG repeat sequence. Genes found in at least six genetic modifier loci are involved in DNA maintenance, among them *MSH3*, and a role for this gene is substantiated by other studies. Track HD was a prospective cohort study aimed at deep phenotyping of pre- and early manifest gene carriers over the course of 3 years [15, 16]. Data from this study and from the EHDN Registry study [17] gave a good correlation of progression measures and age at onset. This has allowed to perform a meta-analysis in the search for loci associated with disease progression. A signal was found on chromosome 5, and out of three genes, the one with the most significant signal was *MSH3*, even after correction for age at onset [18]. Variation in *MSH3*, specifically in exon 1, has been shown to influence somatic expansion [19]. In line with genetic instability mentioned above, data from tissue samples in animal models and in human have shown that there is also an expansion in somatic cells, including striatum [20], but also in blood [21]. Somatic expansion is an age-related phenomenon both in animal models [22] and in human brain [21]. These data are compatible with a two-sequential component model of disease pathogenesis [23], the inherited CAG repeat expansion being followed by onset, and progression of the disease in the context of somatic expansion.

Ongoing trials to slow disease progression in targeting the Huntington gene transcript harboring repeat expansion by intrathecal application of antisense oligonucleotides are ongoing, although recent developments have reminded that the way is going to be a long one [24]. The accumulation of data about modifying genetic factors has already led to the suggestion to also manipulate their function as an additional potential therapeutic approach. This includes gene expression-modulated functional modification in gene-repairing proteins found in the course of above-mentioned studies [25]. The large set of data with clinical and genetic information will also allow further discoveries in complex genetic modification in the course of the disorders for other aspects of the phenotype. Meanwhile, and also in the future, symptomatic treatment remain important [26].

HD Phenocopies

About 1% of the patients presenting with the typical HD phenotype including a motor syndrome (mainly chorea but also other abnormal movements and pyramidal

signs), with cognitive impairment (mainly an early executive disorder with apathy in later stages) alongside of psychiatric disturbances, do not have the typical CAG triplet repeat number increase [27]. In a recent publication, we have suggested a set of guidance to assess these disorders based on a literature review and an expert opinion consensus process [28]. Traditionally, the first group of those HD phenocopies has been named "Huntington-like disease (HDL)" disorders; however, other, newly discovered genes including *C9orf72* are more frequently involved but are not mentioned as such, mostly due to the recognition of a more diverse phenotype. Furthermore, while the presence of chorea without triplet elongation in the Huntington gene had been the motivation to search for other genetic causes leading to the use of HDL as syndromatic description, further studies have shown that the phenotype is more complex in a large number of other ones. Traditional HDL disorders include two dominant diseases, HDL1 due to prion protein (*PrP*) mutations and HDL2 to mutations in the junctophilin-3 (*JPH3*) gene. HDL3 has been used to designate a very rare recessive disorder [29] suggested to be linked to 4 p15.3 [30]. HDL4 has been suggested for cases with a CAA/CAG repeat elongation in the TATA-binding protein (*TBP*) gene also found in SCA17 [31]. This is another illustration of the risk in defining names early in the discovery process since the understanding of the predominant aspects may change after study of larger cohorts with the same mutation. A number of other diseases also present with chorea but are still named according to the historical data, including Wilson, Fahr disease, McLeod syndrome, or to salient aspects of the presentation, including chorea-acanthocytosis and neuroferritinopathy. Finally, newly discovered syndromes are still named according to the gene or locus involved, like *RNF216*-mediated neurodegeneration, *FRRS1L*-mediated chorea, or the already mentioned *C9orf72*. Importantly, these diseases need to be considered in disorders presenting with predominant chorea.

PrP-Related Disorders

Mutations in the *PrP* gene may lead to variable overlapping phenotypes including prominent chorea, confirming old observations about familial occurrence of a rapid course spongiform encephalopathy [32]. These include hereditary Creutzfeld-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and familial insomnia, which are spongiform encephalopathies with similar pathogenesis like sporadic or rarely transmitted Creutzfeld-Jakob disease [33]. The age at onset is typically in the sixth decade of life, rarely earlier, and the course over 4 to rarely up to 10 years, longer than in sporadic or transmitted forms. Hereditary forms occur in about 15% of the cases and are due to point mutations or to the insertion of an octapeptide repeat in the *PrP*. The phenotype is partially correlating with the mutation but also influenced by the sequence at codon 129 and the type of glycosylation in a similar way as in the sporadic form. Some mutations, for example, the octapeptide repeat insertion, are more frequently associated with chorea than other [32]. In a large series of cases with spongiform encephalopathies in China including 218 cases (accounting to 11% of the total number of cases) due to mutations in the *PrP* gene, nineteen different subtypes were recognized [34]. There was a large variation in the phenotype according to the particular mutation; movement disorders including myoclonus and pyramidal and extrapyramidal disorders were found up to 80% in some mutations. Interestingly, chorea is not mentioned as such suggesting additional ethnic factors modifying the phenotype.

JPH3-Related Disorders

HDL2 has a quite similar presentation like HD but is found almost exclusively in people from African origin [35]. The mutation in the *JPH3* gene is a highly penetrant CAG/CTG repeat expansion. Affected people share a common haplotype of three single-nucleotide polymorphisms, and the disease can be traced back to 2000 years [36]. The disease onset is the fourth decade, the phenotype is sometimes very similar to HD, and death occurs after about 20 years. Pathology is also similar to HD with a severe atrophy of the caudate.

Chorea Associated with Spinocerebellar Ataxias

SCA17 was discovered in a study of 4 Japanese families with autosomal dominant ataxia, and an elongation of a CAG triplet in the TATA-binding box (*TBP*) was found [37]. Movement disorders including dystonia and chorea were present in some of the cases. In a cohort from Korea including 661 patients with ataxia and 98 with chorea not diagnosed with SCA1, 2, 3, 6, 7, dentato-rubro-pallidoluysian atrophy (DRPLA), or HD, 2 patients had both ataxia and chorea [38]. In a cohort of 285 patients with HD phenocopies, 5 had an elongation of the CAG repeat in *TBP,* which is more than mutations in *PrP,JPH3*, or the

other genes included in that study [39]. Besides the presentation with chorea, sometimes overlapping, and ataxia, a number of variable other symptoms may occur and incomplete penetrance has also been seen [40]. Chorea may also be present in other genes involved in spinocerebellar ataxia, albeit less frequently [41]. Chorea and ataxia may also be present in small elongations between 41 and 49 repeats, suggesting to consider this in sporadic cases [42].

Dentato-Rubro-Pallidoluysian Atrophy

DRPLA [43] is a disorder due to a triplet repeat elongation in exon 5 of *atrophin 1* found mainly in Japanese. Inheritance is autosomal dominant, and major features in presentation include choreoathetosis, myoclonus, seizures, ataxia, and dementia. There is a correlation between the number of triplet repeats, and younger onset is often characterized by myoclonus epilepsy and cognitive decline, while adult-onset case closer resembles HD [44]. In a recent review, published cases from outside of Japan have been collected and similar findings are described as in Japanese cases [45].

C9orf72

The study of a large family with an autosomal dominant form of fronto-temporal dementia with amyotrophic lateral sclerosis linked to chromosome 9p21 leads to the discovery of an hexanucleotide repeat (GGGGCC) expansion in the *C9orf72* gene [46]. The same mutation was found in 16 of 26 families with a similar main phenotype and also in 59 patients belonging to clinically and pathologically well-defined North American cohorts of 696 cases, 22 one of them without family history [46]. The same expansion was also found in a study of a Finnish cohort, including 46% of familial ALS and 21.1% of sporadic ALS in that population, and also in 38% of European descent families with familial ALS [47]. Shortly after the discovery of this mutation, other cohorts were examined, and the phenotype description expanded. In a large study of 2,974 cases of neurodegenerative disorders, including frontotemporal dementia, ALS Alzheimer, and HD-like disease, among other, 85 had expansions in *C9orf72* [48]. They were found in FTLD (7.5%) and ALS (8.1%) but also present in HDL (1.7%) and other neurodegenerative disorders (2%) (48). The use of modified southern blots allowed to specify the range of repetition numbers, which can reach up to 800, or even 4,400 in rare cases. The age at onset, typically in adulthood, did not differ between the disease groups but correlated with the expansion size [48]. In another study focused on HD phenocopies including 514 patients, 2% had an expansion [49] suggesting that they are the most frequent cause. The movement disorder is complex with dystonia, myoclonus, tremor, rigidity accompanying chorea [49]. In a recently published cohort of 40 patients with expansions in *C9orf72,* 17 had movement disorders, in one third as presenting symptom [50]. Chorea with predominant orofacial dyskinesia was present in 5 of the 17 patients. However, the prevalence of *C9orf72* expansions in HDL syndromes may actually be quite low. In a systematic review and meta-analysis including 1123 HDL cases, 1% carried the expansion, and 3% had intermediate alleles [51]. However, further studies are needed, since only 9 out of 219 studies were selected for the detailed analysis. The mechanisms leading to the variable phenotype even with similar number of expansions in *C9orf72* remain unclear. It is of note that neuronal malfunction is present before degeneration and is suggested to be linked to changes in synaptic and network properties. Neurodegeneration is probably due to haploinsufficiency of the protein and to aberrant protein species [52].

Benign Hereditary Chorea

Benign hereditary chorea is a rare autosomal dominant disorder with childhood onset chorea, without or with slow progression, sometimes with a tendency to improve in adulthood. The disease was linked to 14q13 [53], and mutations in the *TTF1* (*TITF1, NKX2-1*) gene were described [54]. However, such mutations are only rarely found in sporadic cases [55]. Analysis of further cases has documented broader phenotype, including other movement disorders, attention deficit and hyperactivity disorder, learning difficulties, but also lung and thyroid pathologies [56]. Morphological pituitary changes have also been described [57, 58], and variants of the *TTF1* gene are associated with thyroid cancer.

Wilson's Disease

Wilson's disease has a broad phenotype including a wide array of neurological and systemic signs and symptoms [59]. It is there always important to search for Wilson's disease, especially in chorea manifesting before the age of 40–50, since therapeutic options are available for this disorder. Chorea, among other neuropsychiatric and

neurological symptoms and signs, together with liver disease and Kayser-Fleischer rings are typical of the disorder, which can be confirmed by low ceruloplasmin and elevated urine and hepatic copper [60]. Wilson's disease has a high prevalence in China, and results from a large cohort of 1,366 patients have been recently published [61]. At onset and during course, neurological involvement was more frequent than hepatic involvement (n: 665, respective: 276). Movement disorders were the most frequent neurological manifestations, mostly dystonia, tremor, and gait abnormalities, interestingly all three more frequent in males. However, chorea and athetosis are not mentioned, which are known to occur in published cohorts [62], probably mostly from European ancestry, suggesting an ethnic variation in the phenotype.

Newly Discovered Genes

Recessive mutations in the AMPA receptor outer-core protein, *FRRS1L*, lead to a progressive disorder with prominent choreoathetosis and epilepsy in infants and children. Sustained dysfunction of glutamatergic transmission causes a severe encephalopathy [63]. A large family has been recently reported confirming the findings, with children growing up to adolescence but with severe impairment [64].

Dominant and more rarely recessive mutations in *ADCY5* cause chorea together with other movement disorders infantile to adolescent; besides chronic involvement, exacerbations are typical and may be triggered by several factors [65]. The distribution prominent in the face and upper extremities and less in the legs and the manifestation is very much variable. Mutations in the same gene may present with severe developmental impairment [66].

Genes related to mainly paroxysmal chorea, often accompanied by other paroxysmal neurological disorders in particular migraine or epilepsy, have recently been reviewed [67]. Some are also accompanied by a progredient neurological phenotype; genes involved include, besides *ADCY5*, also *FGF14, PRRT2, TBC1D24, ATP1A3, CACN1A, PDE2A, SLC2A1, KCNMA1*, and *RHOBTB2*.

Diagnostic Investigations

In a typical presentation of chorea along with cognitive impairment and psychiatric symptoms, especially in the context of a positive family history, the first step is to search for the CAG repeat elongation in the HTT gene [68]. This has to be done according to established guidance during a genetic counselling workout including the family and with appropriate laboratory quality controls [69]. If this turns out to be negative, brain MRI will guide further investigations. In case of additional frontal and cerebellar atrophy besides the expected one in the basal ganglia, genetic testing could include in a first step *C9orf72*, SCA17, followed by SCA1-3, SCA17, DRPLA, and *PrP*. Specific changes in basal ganglia could be followed by laboratory tests, including ferritin and ceruloplasmin in cases of iron deposit; copper and ceruloplasmin in the presence of hyperintensities; and calcium metabolism in case of calcium deposits. Direct genetic testing can follow, for example, ATP7B in the suggestion of Wilson's disease. In other cases, genetic panels, customized according to those results, or global for chorea can be used.

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Conflict of Interest Statement

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Author Contributions

Jean-Marc Burgunder has conceived and written the review paper.

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