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Review

How Have Advances in Genetic Technology Modified Movement Disorders Nosology?

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Abstract
The role of genetics and its technological development has been fundamental in advancing the field of movement disorders, opening the door to precision medicine. Starting from the revolutionary discovery of the locus of the Huntington disease gene, we review the milestones of genetic discoveries in movement disorders and their impact on clinical practice and research efforts. Before the 1980s, early techniques did not allow the identification of genetic alteration in complex diseases. Further advances increasingly defined a large number of pathogenic genetic alterations. Moreover, these techniques allowed epigenomic, transcriptomic, and microbiome analyses. In the 2020s, these new technologies are poised to displace phenotype-based classifications towards a nosology based on genetic/biological data. Advances in genetic technologies are engineering a reversal of the phenotype-to-genotype order of nosology development, replacing convergent clinicopathologic disease models with the genotypic divergence required for future precision medicine applications.
1. Introduction

"The success of any genetic linkage project depends in large part on the quality of family material available for the study. We initially invested considerable effort in identifying a useful family [...]" [1]. This statement, extracted from the manuscript presenting the discovery of the mutation responsible for Huntington disease (HD), represents a milestone in the history of medicine: the first genetic disease mapped without any *a priori* knowledge of its localization was discovered [1, 2]. This event represented a watershed in the genetics of movement disorders between the first era, characterized by a few successes, and a new one marked by an ever-increasing number of genetic discoveries.

This quote, while accurate, encompasses the old paradigm in the approach to genetic analysis, based on the flow of information from phenotype to genotype where a comprehensive assessment and description of family history was essential to generate the genetic causal hypotheses needed to identify the genetic abnormality responsible for the observed phenotype. This approach reflected the technological limitations in the DNA analysis at that time, for which a clear mode of genetic inheritance and evidence for a monogenic disease trait were necessary, limiting the knowledge to rare or low penetrance conditions.

Toward the end of the first decade of this century, as the initial phase of the Human Genome Project concluded [3], and with breakthrough advances in DNA sequencing technologies, a "blind" analysis of a single patient DNA became possible. In this era, the flow of information is reversed, genotypes are obtained beforehand phenotypes and our approach to proving a causal genetic hypothesis is inverted as well. This technological development came along with advances in the knowledge of the complexity of genetic interactions, such as the impact of regulatory elements on coding variants [4] or the stochastic effect of aging on somatic mutations [5], adding challenges to the interpretation of novel genetic findings.

We here review the milestones of genetic discoveries in movement disorders and how these altered the clinical management of patients and the design of clinical and research programs. We also draw attention to the interface of biomarker discovery programs, ushering the era of “precision medicine” for movement disorders [6, 7].
2. Before 17 November 1983: Cytogenetic and HLA analysis

After the major discovery of the 20th century, namely the description of the human DNA by Watson and Crick in 1953 [8], genetic studies emerged as a crucial component in scientific research. However, it was not until 1956 when the number and structure of human chromosomes were first described [9]. Soon after these two discoveries, Down syndrome became the first disease recognized as associated with aberrant chromosomes [10]. However, cytogenetics was still inadequate to detecting causal genetic factors in movement disorders, leading to limited applicability. For the first and limited applicability in movement disorders, we had to wait until the discovery of the physical localization of the human leukocyte antigen system (HLA) loci on chromosome 6 and, with it, to serve as a map for genomic location [11, 12] using linkage analyses, intragenic recombination, and chromatography techniques [13, 14]. HLA linkage analysis first suggested that the spinocerebellar ataxia 1 (SCA1) gene locus might be located on chromosome 6 near the HLA loci, based on studies of a family of five patients with the previously called Marie’s ataxia [15, 16]. Later on, in 1977, Jackson et al. [17] refined the location of the SCA1 locus on chromosome 6 at a 12 cM distance from the HLA loci.

However, the possibility to obtain information related only to the HLA locus limited our knowledge for a vast majority of the diseases. Subsequently, in the 1980s, further improvements in gene mapping were based on restriction fragment length polymorphisms (RFLP), which allowed the analysis of the whole genome [18].

3. After 17 November 1983: Mapping of Huntington Disease Gene

This day marked the beginning of a revolution for the medical field: the first gene was mapped analyzing the entire DNA without a priori knowledge of its physical localization [1, 2]. Since the 1970s, HD was considered a neurodegenerative autosomal dominant genetic disorder [19]. Blood group A was initially found to be associated with HD [20] but large population studies failed to confirm this association. At that time, neither gross morphology nor number alteration of chromosomes were detected in HD [21]. With the advent of RFLP analysis, it became finally possible to identify the specific HD locus. This result gave a significant boost in genetics, allowing the
discovery of further loci responsible for other conditions, such as SCA1 in 1987 [22], Friedreich's ataxia in 1988 [23], and early onset generalized dystonia (DYT1) in 1989 [24]. However, several years elapsed before further technical developments facilitated the identification of the specific mutation responsible for each of these conditions. This step was made thanks to the possibility to capture and amplify specific regions of the genome by the polymerase chain reaction (PCR) technique in the 1990s [25] together with advances in Sanger sequencing [26]. In 1993, the exact mutations responsible for HD and SCA1 [27, 28] were identified, followed by many other such successes, such as for Friedreich's ataxia in 1996 [29], and DYT1 in 1997 [30].

A special mention deserves the identification of the genetic mutation responsible for an autosomal dominant form of Parkinson's disease (PD), namely SNCA (PARK1). The first localization of this gene on chromosome 4 (4q21.3-q22) was documented by Chen et al. in 1995 [31]. At the time, it was called the non amyloid component of Alzheimer's disease (AD) plaques (NAC), given that it was the second most common component found in the amyloid plaques of Alzheimer's disease pathology [32]. In two years, the first genetic variant (Ala to Thr substitution at position 53 - Ala53Thr) was found in the “Contursi family” [33]. In the same year, Spillantini and coworkers in 1997 [34] found the expression of the protein coded by this gene as the molecule constituting Lewy bodies (LB) in patients with PD and dementia with Lewy bodies. Notably, a causal implication was readily given to these findings, as stated by Spillantini and coworkers in their original publication: "α-Synuclein aggregation and Lewy-body formation may be important in the aetiology and pathogenesis of all cases of Parkinson's disease." The demonstration of the first genetic form of PD was interpreted as informing the whole of the clinicopathologic construct of PD. Separately in the same year, Japanese investigators identified the Parkin gene as a genetic variant responsible for a recessive form of PD (PRKN, PARK6) [35]. Interestingly, some of the mutation positive patients had been previously been shown to have no LB pathology on autopsy [35, 36, 37]. If the Contursi kindred had carried PRKN instead of SNCA, there may not have been a pathogenic premise for α-synuclein and Spillantini's discovery would not have framed pathology as equating etiology. Nevertheless, the pathogenic centrality α-synuclein became enshrined in most subsequent research efforts.
Although the expectation that discoveries of genetic variants in parkinsonisms and dystonia, for instance, may inform therapeutic management, there have been no disease-modifying treatments established to date. Some genetic variants have been associated with different outcomes in device-aided therapies, such as deep brain stimulation (DBS) [38]. For example, a recent meta-analysis showed a higher post-DBS reduction in levodopa-equivalent daily dose in LRRK2- and PRKN-(around 60%) compared with GBA-associated parkinsonism (around 20%) [38]. Conversely, GBA-mutated patients demonstrated a higher rate of cognitive impairment after DBS compared to other genetic parkinsonisms [38]. Differential clinical responses to DBS have also been ascertained for dystonia, where, for example, response is more favorable in TOR1A compared to other variants [39].

Many other discoveries were made in movement disorders in the 1990s and 2000s (Tables 1-4; Figure 1) [28, 40-62]. The approach during this period was disease centered rather than patient centered: data on many patients with the same conditions and within the same families were necessary to describe the possible loci of disease related genes, to meet the technological needs. Finally, in the 2000s, with the advent of "Next generation sequencing" (NGS), a personalized genetic approach became possible. A full reversal of the phenotype to genotype approach was finally engineered, enabling the study of a single patient, one for whom the phenotype could not inform a locus, let alone a gene.

4. Next generation sequencing era

With the end of the Human Genome Project, the sequence of the entire human DNA was finally available [3]. However, the cost and the time to sequence the entire genome were limiting steps for clinical applicability [63]. With NGS, a term that refers to a number of different techniques capable of analyzing fragments of DNA in parallel [64], these two major limitations have been, at least partially, overcome. In 2008, the genome of the DNA pioneer J. Watson was the first to be sequenced with NGS [65] with a significant reduction in cost (100th less expensive) and time (4.5 months vs. 4 years) [66]. NGS was not only important in discovering new gene variants associated with movement disorders [67] but was also fundamental in revisiting already known genetic conditions (Figure 2). An emblematic example is the paroxysmal disorders (Table 4), for a long period classified exclusively as channelopathies and now considered as a more complex spectrum of genetic diseases [68]. The
discovery of new genes not coding for ion channels shifted the pathophysiology understanding of these conditions and has opened the door to novel therapeutic opportunities [68]. For instance, the identification of mutations in SLC2A1 affect the glucose type-1 transporter, prompting a consideration of a ketogenic diet for the individualized therapeutic approach to these patients [68].

Another advantage of NGS is the possibility to combine with previous techniques, such as linkage analysis, which can be a useful approach for the analysis of genetic conditions with a clear familial predisposition. In these cases, we can use linkage analysis and select only a few regions that can be subsequently analyzed with NGS, thus reducing the coverage required for the analysis. An important success using this combination was the discovery of COQ2 variants in multiple system atrophy [69].

Importantly, NGS techniques have extended their reach beyond the genome, becoming fundamental in the analysis of other biological data, such as epigenetic alterations of the DNA, the transcriptome (the analysis of the mRNA), and the characterization of metagenomes [70]. The possibility to deeply analyze the complexity of biological interactions directly challenges clinical based disease classifications allowing the advent of an era in which the biological data represent the “gold standard” for reassessing clinical nosology and disease modification efforts of complex diseases [71]. Indeed, the traditional genetic classification of diseases into polygenic and monogenic is under revision [72]; the effects of the regulatory variants can modulate the penetrance of coding variants [73]. Therefore, a reconstruction process in genetic movement disorders should treat as independent variables those genomic variants with larger effects (i.e., the classical disease causing mutations in genes such as GBA or LRRK2) [74, 75], and as co-variates a vast number of factors acting as penetrance modifiers. Regulatory variants have been shown to be important in neurodevelopmental processes, affecting not only the penetrance but also the clinical presentation of several conditions [76]. Moreover, patients harboring more than one gene mutation in certain monogenic parkinsonisms have been described, adding layers of complexity to the diagnosis and future treatment approaches [77].

Some important genetic variants have been validated as risk factors for movement disorders. For instance, the GBA p.E365K variant has been associated with a higher risk of cognitive impairment
and rapid eye movement sleep behavior disorders in patients with PD, whereas other variants of the same gene, such as p.N370S and p.T408M have been associated with higher motor disability [78]. Many other genetic variants have been associated to varying degrees with the development of PD, such as \textit{TMEM230}, which encodes a trans-membrane protein involved in vesicles trafficking [79], \textit{SLC6A3}, which encodes human dopamine transporter gene [80], or catechol-O-methyltransferase (COMT) haplotypes [81]. In dystonias, the rs1801968 \textit{TOR1A} variant increases the risk of a focal phenotype (writer’s cramp) [82]. Furthermore, selected variants in genetic variants associated with an increased risk of PD are opening the possibility of exploring lysosomal (\textit{GUSB}, \textit{GRN}, and \textit{NEU1}) and endocytic pathways (\textit{VAMP4} and \textit{NOD2}) [83]. The analysis of single nucleotide polymorphisms could help future therapeutic developments in suitable patients using strategies based on drug repurposing [84]. Large cohorts and data driven analyses will assist in identifying genetic and/or biological alterations in a range of phenotypes, helping us transition from a phenotypic-based classification of diseases to a biologically driven one.

5. Influence on biomarkers development programs for neurodegenerative diseases

The century old view of neurodegenerative diseases as single if complex entities has been useful for the development of symptomatic treatments to compensate for the deficiency of neurotransmitters resulting from degeneration of vulnerable neurons, a convergent outcome of many processes, presumably different in different individuals. The characterization of the unique genetic and biological features of each patient is expected to translate into the first disease modifying successes when therapies will be applied not to groups of clinically defined cohorts but only to individuals biologically suited to benefit, the basis of precision medicine [6, 7]. To answer this need, some biomarker initiatives have been launched in recent years to assess the extent to which genetic and biological/molecular abnormalities may affect patterns of disease progression. Starting from 2011, many cohorts, such as the Parkinson’s Progression Markers Initiative [85], the Luxembourg cohort [86], and the Personalized Parkinson Project [87], have been built with the aim to establish a wide ranging set of clinical, imaging, and biological data to define biomarkers of the clinical PD progression and for possible therapeutic strategies. However, these cohorts aim at the identification of
biomarkers explaining the clinical diagnosis of PD as the independent variable, with biological measures as the dependent variables.

In 2019, the University of Cincinnati launched the Cincinnati Cohort Biomarker Program (CCBP) with the aim to identify biomarkers of subtypes regardless of clinical classifications (e.g., PD like/AD like conditions) (Methods paper in advanced stages of preparation). In this phenotype agnostic cohort, the biological signals are considered the independent variables, whereas the clinical phenotypes the dependent variable. CCBP is a population based longitudinal study of patients with a wide range of neurodegenerative diseases and healthy controls to be followed for up to 10 years. Genetic and biological/molecular analyses and deployment of bioassays of already available therapies will allow the repurposing of these to patients with suitable biology.

6. Five-year view

The increased knowledge in the role of noncoding gene regions (e.g., due to splicing alteration) [88] will be anticipated to further reshape the nosology of movement disorders. For instance, an intronic biallelic pentanucleotide expansion in chromosome 4 has been recently associated with cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) [89]. New insights in the functional interaction between coding and noncoding regions, and the development of new technologies, such as long-read next generation sequencing to identify noncoding variants will improve the discovery of new genetic variants associated with movement disorders, which must go hand in hand with the development in the computational frameworks. Noncoding regions analysis stand to become increasingly important in the regular workflows of clinicians.

7. Challenges and conclusions

Despite the important revolution new genetic technologies have ushered in the field of movement disorders, there are some obstacles to their utilization. First, although costs have been reducing, NGS remain prohibitively expensive for deployment in routine clinical setting [90]. In addition, the accuracy for identifying repeat expansions, copy number variations, and structural rearrangements of short read NGS are limited. For instance, considering that repeat expansions are frequent in SCAs
[91], when suspecting one of these conditions it is extremely important also to test for the most frequent underlying variants (e.g., SCA1, SCA2, SCA3, SCA 6, DRPLA); this approach should also be extended in sporadic SCAs [92]. At the same time, interpreting the vast amount of rare noncoding and missense variants in individual genomes can still be challenging on clinical grounds. Additionally, NGS studies can be affected by findings of unknown significance or false positives. For instance, \textit{CACNA1B} R1389H variant was associated with the myoclonus-dystonia syndrome, but this result was not confirmed by analyzing a large multicentric cohort of myoclonus-dystonia cases [93]. The creation of shared large databases could accelerate and facilitate the increasing of knowledge on the role played by these variants. Furthermore, a number of underpowered candidate-based gene association studies conducted over the last few decades have yielded a number of false positive findings from which corrections continue to be necessary [94]. The development of better designed GWAS studies during the last decade have assisted the understanding of the complex genetics of movement disorders.

In sum, the advances in genetic technologies has altered the approach to classifying and, to a lesser extent, treating patients with movement disorders. From an earlier primacy of the phenotype-to-genotype paradigm, fueled by a convergent clinicopathologic model of disease, newer technologies are moving us closer to a reversed genotype-to-phenotype sequence. This realignment has the potential of ushering a systems biology model to bring the first success in precision medicine for patients with movement disorders.
Data availability statement: No data sharing is applicable given that no new data were created or analyzed for this narrative review

Key points

- Genetics of movement disorders have experienced exponential growth after the mapping of the Huntington’s disease gene.
- Advances in genetic technologies are engineering a reversal of the phenotype-to-genotype and a reconsideration of the clinico-pathologic paradigm on which movement disorders nosology has been based.
- Next generation sequencing techniques have accelerated the transition toward precision medicine, with the identification of genetic etiologies in ever rarer movement disorders.
Figure legends

**Figure 1.** Schematic historical perspective of genetic analysis in spinocerebellar ataxias. NGS, next generation sequencing; STRs, short tandem repeats; SCA, spinocerebellar ataxia; SNPs, single nucleotide polymorphisms; WGS, whole genome sequencing; WES, whole exome sequencing. This figure was drafted according to the following references [28, 57-62].

**Figure 2.** The milestones in genetics of movement disorders and the reversal of the phenotype-to-genotype developmental order. The main discoveries in the field of movement disorders, shown in chronological timeline, demonstrate the increasing power of the detection of pathogenic mutations in individuals with no family history in a phenotype-agnostic manner. DNA, Deoxyribonucleic acid; SCA1, Spinocerebellar ataxia type 1; RFLP, Restriction Fragment Length Polymorphism; PCR, Polymerase Chain Reaction; WGS, Whole Genome Sequencing; HLA, Human Leukocyte Antigen; RNA, Ribonucleic acid.
References


41. https://www.mdsgene.org/ (accessed 01/19/2020)


**Table 1. Preferred genetic approach for selected genetic parkinsonian disorders.**

<table>
<thead>
<tr>
<th>Name and modality of inheritance</th>
<th>Year of first reported mutation</th>
<th>Suggested Genetic Diagnostic Approach</th>
<th>Key clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNCA (PARK1, PARK4)</strong> AD</td>
<td>1997</td>
<td>Single Gene Analysis (Sanger Seq) or Multigene Panel</td>
<td>Early-onset levodopca-responsive parkinsonism, cognitive, behavioral and/or autonomic symptoms, myoclonus</td>
</tr>
<tr>
<td><strong>PRKN (PARK2)</strong> AR</td>
<td>1997</td>
<td>Single Gene Analysis (Sanger Seq and MLPA) or Multigene Panel and MLPA</td>
<td>Early-onset levodopa-responsive parkinsonism; low risk for cognitive impairment</td>
</tr>
<tr>
<td><strong>PINK1 (PARK6)</strong> AR</td>
<td>2005</td>
<td>Multigene Panel or WES</td>
<td>Early-onset levodopa-responsive parkinsonism; possible cognitive and/or behavioral manifestations</td>
</tr>
<tr>
<td><strong>DJ-1 (PARK7)</strong> AR</td>
<td>2003</td>
<td>Multigene Panel or WES</td>
<td>Rare, early-onset levodopa-responsive parkinsonism; low risk for cognitive manifestations</td>
</tr>
<tr>
<td><strong>LRRK2 (PARK8)</strong> AD</td>
<td>2004</td>
<td>Single Gene Analysis (Sanger Seq) or Multigene Panel</td>
<td>Sporadic PD-like AAO, levodopa-responsive parkinsonism with less incidence of cognitive decline. Highly variable pathology</td>
</tr>
<tr>
<td><strong>ATP13A2 (PARK9)</strong> AR</td>
<td>2001</td>
<td>Multigene Panel or WES</td>
<td>Rare, juvenile-onset levodopa-responsive dystonia and atypical parkinsonism; possible eye-movement abnormalities and pyramidal signs. Wide clinical spectrum ranging from parkinsonism to hereditary spastic paraplegia</td>
</tr>
<tr>
<td><strong>FBXO7 (PARK15)</strong></td>
<td>2008</td>
<td>Multigene Panel or WES</td>
<td>Rare, spasticity followed by juvenile-onset levodopa-responsive atypical</td>
</tr>
<tr>
<td>Gene</td>
<td>Year</td>
<td>Methodology</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
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<td>----------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>VPS35</td>
<td>2011</td>
<td>Multigene Panel or WES</td>
<td>Rare, early-onset levodopa-responsive parkinsonism with possible cognitive and/or behavioral symptoms</td>
</tr>
<tr>
<td>DNAJC6</td>
<td>2012</td>
<td>Multigene Panel or WES</td>
<td>Rare, juvenile atypical parkinsonism with cognitive impairment, epilepsy and pyramidal signs; high phenotypic variability</td>
</tr>
<tr>
<td>SYNJ1</td>
<td>2013</td>
<td>Multigene Panel or WES</td>
<td>Rare, juvenile atypical parkinsonism; cognitive impairment and/or seizures</td>
</tr>
<tr>
<td>VPS13C</td>
<td>2016</td>
<td>Multigene Panel or WES</td>
<td>Rare, early-onset atypical parkinsonism with rapid progression and early cognitive impairment</td>
</tr>
</tbody>
</table>

AAO, age at onset; PD, Parkinson disease; WES, whole-exome sequencing, AD, autosomal dominant; AR, autosomal recessive; MLPA, Multiplex ligation-dependent probe amplification.

This table was drafted according to the following references [40, 41, 42]
<table>
<thead>
<tr>
<th>Name and modality of inheritance</th>
<th>Year of first reported mutation</th>
<th>Suggested Genetic Diagnostic Approach</th>
<th>Chief clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOR1A</strong> <em>(DYT1)</em> AD</td>
<td>1989</td>
<td>Single Mutation Analysis or Multigene Panel</td>
<td>Childhood or adolescent-onset generalized dystonia usually starting in one limb (leg), without other systemic involvement (isolated). Most common form</td>
</tr>
<tr>
<td><strong>TAF1</strong> <em>(DYT3)</em> XR</td>
<td>2007</td>
<td>WGS</td>
<td>Adult-onset dystonia characterized by dystonia and parkinsonism with associated neurodegeneration. Endemic in the Philippines</td>
</tr>
<tr>
<td><strong>TUBB4</strong> <em>(DYT4)</em> AD</td>
<td>2013</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset Cranio-cervical dystonia with prominent spasmodic dysphonia (“Whispering dysphonia”). May include leukoencephalopathy</td>
</tr>
<tr>
<td><strong>GCH1</strong> <em>(DYT5a)</em> AD</td>
<td>1993</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset (in general onset at first decade) dopa-responsive dystonia. Lower body dystonia with gait impairment and development of parkinsonian features. Sleep and mood disorders as non-motor features</td>
</tr>
</tbody>
</table>
| **TH** *(DYT5b)* AR              | 1995                             | Multigene Panel or WES               | Infant-onset dopa-responsive dystonia. Lower limb onset with gait difficulties. Fluctuations of symptoms (better in the
<table>
<thead>
<tr>
<th>Gene</th>
<th>Type</th>
<th>Year</th>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
</table>
| **SPR**    | AR   | 2001 | Multigene Panel or WES         | Childhood-onset partially dopa-responsive dystonia with motor and speech delay.  
<p>| <strong>(DYT5b)</strong>|      |      |                                 | Hypotonia, intellectual disability, psychiatric symptoms, autonomic dysfunction, and sleep disturbance can be present. |
| <strong>THAP1</strong>  | AD   | 2009 | Multigene Panel or WES         | Adolescent-onset dystonia of mixed type, mainly affecting cranial, cervical, and laryngeal areas. It may be generalized. |
| <strong>SGCE</strong>   | AD   | 2001 | Single Gene Analysis (Sanger Seq) or Multigene Panel or WES | Childhood-onset myoclonus-dystonia, affecting neck, upper limb, and trunk. Possible association with psychiatric symptoms (Klein, 2014; Klein et al., 2017). |
| <strong>PRKRA</strong>  | AR   | 2008 | Multigene Panel or WES         | Infancy/childhood-onset dystonia, in particular oromandibular, associated with parkinsonism, dysphagia, and retrocollis. No response to levodopa. |
| <strong>ANO3</strong>   | AD   | 2012 | Multigene Panel or WES         | Adult-onset focal or segmental dystonia with predominantly cranial-cervical dystonia. |</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Year</th>
<th>Method</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNAL (DYT25)</td>
<td>2013</td>
<td>Multigene Panel or WES</td>
<td>Adult-onset segmental cranial-cervical dystonia</td>
</tr>
<tr>
<td>KMT2B (DYT28)</td>
<td>2016</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset (first decade) generalized dystonia with prominent cervical, cranial, and laryngeal involvement. Psychiatric symptoms, skull abnormality, skin and eye movement abnormalities</td>
</tr>
</tbody>
</table>

WES, whole-exome sequencing; WGS, whole-genome sequencing; AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

This table was drafted according to the following references [41, 43-54].
Table 3. Preferred genetic approach for selected genetic choreas.

<table>
<thead>
<tr>
<th>Name and modality of inheritance</th>
<th>Year of first reported mutation</th>
<th>Suggested Genetic Diagnostic Approach</th>
<th>Chief clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD AD</td>
<td>1983</td>
<td>Single Mutation Analysis (Repeat Expansion Assesment)</td>
<td>Adult-onset progressive chorea associated with irritability, depression, and cognitive impairment. Juvenile form (Westphal) has faster progression</td>
</tr>
<tr>
<td>ADCY5 AD</td>
<td>2012</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset chorea with dystonia, myoclonus and delayed motor and/or language milestones. Axial hypotonia common. No response to levodopa</td>
</tr>
<tr>
<td>NKX2-1 AD</td>
<td>2002</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset chorea with possible dysarthria, axial dystonia and gait disturbances. No response to levodopa</td>
</tr>
<tr>
<td>PDE10A AR, AD</td>
<td>2016</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset chorea with characteristic symmetrical bilateral striatal lesions on imaging</td>
</tr>
</tbody>
</table>

WES, whole-exome sequencing; AD, autosomal dominant; AR, autosomal recessive.

This table was drafted according to the following references [41, 55].
<table>
<thead>
<tr>
<th>Name and modality of inheritance</th>
<th>Year of first reported mutation</th>
<th>Suggested Genetic Diagnostic Approach</th>
<th>Chief clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRRT2 AD</td>
<td>2011</td>
<td>Single gene analysis (Sanger Seq) or Multigene Panel or WES</td>
<td>Childhood-onset paroxysmal kinesigenic dyskinesia associated with epilepsy. General brief chorea/dystonia episodes, less than 1 minute</td>
</tr>
<tr>
<td>PNKD AD</td>
<td>2004</td>
<td>Multigene Panel or WES</td>
<td>Childhood-onset dystonic and choreic episodes with dysarthria, dysphagia, oculogyric crises; episodes last hours</td>
</tr>
<tr>
<td>SLC2A1 AD</td>
<td>2008</td>
<td>Multigene Panel or WES</td>
<td>Variable age-onset (often in second decade) of choreic and dystonic attacks triggered by sustained exercise. Ataxia and epilepsy can be associated</td>
</tr>
<tr>
<td>ECHS1 AR</td>
<td>2016</td>
<td>Multigene Panel or WES</td>
<td>Infant-onset paroxysmal exercise-induced dystonia. Episodes last 30-60 minutes with dystonia/opisthotonus. Leigh syndrome can be associated</td>
</tr>
<tr>
<td>KNCMA1 AD</td>
<td>2005</td>
<td>Multigene Panel or WES</td>
<td>Infant-onset paroxysmal non-kinesigenic dyskinesia. Attacks are brief. Often associated with epilepsy and mental retardation</td>
</tr>
</tbody>
</table>
WES, whole-exome sequencing; AD, autosomal dominant; AR, autosomal recessive.

This table was drafted according to the following references [56].