GENETIC ADVANCES IN MOVEMENT DISORDERS

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Introduction

Several genes are well validated as causes of movement disorders, such as Parkinson disease (PD)[1] and dystonia[2, 3], which will be the main focus of this syllabus and presentation. However, known monogenic causes and genetic risk factors only partly explain the observed familial aggregation of PD and dystonia. Not surprisingly, the application of new techniques such as next generation sequencing (NGS) – increasingly also as part of clinical-diagnostic testing - and genome-wide association meta-analyses have allowed for the discovery of new genes and genetic risk factors for both groups of diseases[4]. Furthermore, there has been significant progress in the development of new disease models, particularly through the use of induced pluripotent stem (iPS) cell-derived neurons[5]. These efforts are now starting to be translated into clinical practice with an impact on genetic counseling but also with first emerging clinical trials tailored towards genetic/genomic findings. In this context, clinico-genetic studies remain of key importance to improve genotype-phenotype correlations and to reveal the earliest disease signs.

Of further note, the rapid advances in gene discovery have led to the description of a number of genes and genetic risk factors that did not stand the test of independent replication. Due to the complex nature and very large body of the pertinent literature, it has become increasingly difficult, especially for the busy movement disorder clinician, to keep close track of these developments. Adding another layer of complexity, genetic testing has become widely available both in academic and commercial settings and putative 'novel genes' are usually quickly added to newly developed gene panels, unfortunately, typically without careful prior evaluation whether the respective gene has indeed been confirmed as causative. This has led to an increasing number of reported variants of unknown significance (VUS) in movement disorder genes of questionable causative importance and thus to considerable uncertainty when it comes to interpreting these test results and trying to put them into the patients' clinical context.

Separating the wheat from the chaff: The MDS Nomenclature and Classification Task Force and MDSGene Initiative

This state of affairs led to the foundation of the MDS Task Force for Nomenclature of Genetic Movement Disorders in 2012, which recently published their international consensus recommendations for a new system for naming and classifyting genetically determined PD and other movement disorders[6].

The newly proposed system takes into account the two key notions derived from the genetics of movement disorders: First, there are multiple clinically different forms of movement disorders caused by the same genotype and second, multiple movement disorder genes may cause a similar clinical picture. The Task Force recommendations for the inclusion of genes into the list of confirmed movement disorder genes are as follows:

(i) Genes should only be included when genetic testing is possible. Accordingly, a disorder should only be listed once the causative gene is identified. The exception to this recommendation is when a founder haplotype is diagnostic, as in the case of X-linked dystonia-parkinsonism.

(ii) Previously used number suffixes should be replaced by the gene name, i.e. the PARK designation should be followed by the name of the disease-causing gene (e.g. PARK-*SNCA* [currently PARK1 and PARK4]).

(iii) Only disease-causing genes should be considered in this naming system, whereas genetic risk loci should not be included. For the latter, the PDGene website (http://www.pdgene.org) provides a genome-wide catalogue of genetic association results in PD and highlights established as well as putative PD genetic risk factors[7, 8].

(iv) To avoid inaccuracies and redundancies that currently permeate the lists of locus symbols, the threshold of evidence should be raised before assigning locus symbols according to the guidelines of the US National Human Genome Research Institute: 1. Presence of the variant in multiple unrelated affected individuals, 2. Evidence for segregation, 3. The variant should be conserved across different species and 4. The variant should be predicted to alter the normal biochemical effect of the gene product, if possible as supported by functional evidence in human tissue or well-established cellular or animal models or by other biochemical or histological abnormalities.

Furthermore, MDS has recently launched the MDS Genetic Mutation Database (MDSGene, availablet http://www.mdsgene.org), which systematically assesses the pathogenicity of reported mutations and links them to movement disorder phenotypes and other demographic and clinical information. MDSGene was first launched in June 2016 with an initial set of nine movement disorder genes. The content will be completed with major movement disorder phenotypes and reported causative mutations within a 5-year time frame and content will be updated regularly[9].

200 years after James Parkinson's first description of Parkinson's Disease: Advances in Monogenic Parkinson's disease
The year 2017 not only marks the 200th anniversary of the 'Essay on the Shaking Palsy' by James Parkinson but also the 20th anniversary of the discovery of the first gene causing a monogenic form of Parkinson's disease (PD), i.e. *alpha-Synuclein* (*SNCA*). However, only a minority (i.e. ~5%) of cases is currently attributed to well-defined genetic causes (**Table 1**). Indeed, post-encephalitic and MPTP-induced parkinsonism, lack of convincing concordance rates among twins, and the identification of environmental risk factors had long supported the hypothesis of an exogenous cause of PD until the identification of monogenic forms of PD in 1997 dismantled the previously held dogma of an exclusively non-genetic etiology.

The identification of mutations in at least six genes (*SNCA*, *LRRK2*, *VPS35*, *Parkin*, *PINK1*, and *DJ-1*) causing 'classical PD' and several others involved in related parkinsonian phenotypes have broadened our understanding of the pathophysiological and molecular mechanisms underlying PD. While about 5% of patients suffer from these monogenic forms of the disease, the majority of PD ('idiopathic PD') is genetically complex, i.e. it is caused by the combined action of comparatively common DNA sequence variants (e.g. single-nucleotide polymorphisms [SNPs]) of low penetrance in concert with environmental factors. Via utilizing genome-wide screening methods, 26 PD risk variants have been established to date. Similar to other genetically complex diseases, these show only moderate effects on PD risk. Increasing this etiologic complexity, many of the involved genetic and environmental risk factors likely interact in an intricate fashion.

A total of 20 genes and loci have been assigned a 'PARK' designation. For ten of these, a gene has not yet been unequivocally identified (e.g., PARK3). Two 'PARK' designations refer to the same gene (PARK1 and PARK4 are both related to the SNCA gene) and parkinsonism is a rare and inconsistent feature of mutations in carriers of PLA2G6 mutations who usually present with infantile neuroaxonal dystrophy (INAD).

According to the recently revised system of the genetic nomenclature of PD, there are ten confirmed monogenic forms of parkinsonism (**Table 1**). Three follow an autosomal dominant mode of inheritance, and seven are recessively inherited. The most common forms are late-onset autosomal dominant parkinsonism with mutations in the *LRRK2* gene and early-onset parkinsonism caused by mutations in the *Parkin* gene. The three dominant forms and three of the seven recessive forms of parkinsonism (*Parkin*, *PINK1*, *DJ-1*) are associated with a clinical picture closely resembling that of idiopathic Parkinson's disease with its cardinal motor features of bradykinesia, resting tremor, rigidity and postural instability. The remaining four recessive forms (*ATP13A2*, *FBOX07*, *DNAJC6*, and *SYNJ1*) usually have a juvenile onset and present with atypical, multisystem features including early dementia, eye movement abnormalities, pyramidal signs etc. However, parkinsonism is a key clinical feature linked to all four of these.

PARK-*SNCA*
Although mutations in *SNCA* are an extremely rare cause of PD, *SNCA* is likely the most intensely investigated PD gene, not only with respect to causative mutations[7, 10] but also to risk variants, as well as function of the gene and the encoded protein. Unifying features of all *SNCA* mutations comprise an overall earlier age of disease onset than that seen in iPD, a faster decline of motor symptoms that are mostly levodopa-responsive, however, with a less sustained alleviation of symptoms than in iPD and with early occurrence of motor fluctuations, and presence of prominent non-motor features[11]. Compared to the other PD-causing genes, the observation of mutation (type)-specific clinical expression appears to be rather unique to *SNCA*. *SNCA* triplication carriers have

an about 10-year earlier onset than duplication carriers. In accordance with a dosage effect, *SNCA* triplication carriers also have a more severe phenotype and faster disease progression than duplication carriers with an about 8-year shorter duration from symptom onset to death. Importantly, other PD-related genes, such as *LRRK2* and *GBA* (acid beta-glucosidase) have also been linked to alterations of *SNCA* levels. Accumulation of SNCA can lead to inhibition of wild-type GBA by interfering with endoplasmic reticulum-to-Golgi trafficking of GBA, which, in turn, leads to decreased GBA activity and increasing accumulation of SNCA[12]. α-Synuclein-induced lysosomal dysfunction has recently been shown to occur through disruptions in protein trafficking[13]. While cell-to-cell transmission of α-synuclein has been demonstrated in both cell culture and animal models (e.g.[14]), the exact sequence and molecular mechanisms of propagation of PD's neuropathology throughout the human brain remain elusive[15].

PARK-*LRRK2*
Mutations in *LRRK2* are the most common pathogenic changes linked to autosomal dominant PD[8, 16]. They account for 3-41% of familial cases and are also found at a lower rate in apparently sporadic cases[17]. The phenotype of LRRK2 p.G2019S mutations is indistinguishable from that of iPD, although tremor is more common and leg tremor may be a useful diagnostic clue[18]. *LRRK2* is a large gene that consists of 51 exons encoding the 2527-amino acid cytoplasmic LRRK2 protein. There are at least seven recurrent, confirmed pathogenic mutations (p.N1437H, p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S, p.I2020T). The p.G2019S mutation is by far the most prevalent; due to a founder effect, the p.R1441G is frequent in Basques and p.I2020T in Japanese patients. LRRK2 has a guanosine-5-triphosphate (GTP)-regulated serine/threonine kinase activity with pathogenic LRRK2 variants increasing autophosphorylation or kinase activity, raising potential not only for a mechanistic understanding of the effect of LRRK2 mutations but also for the development of biomarkers[19, 20] and of LRRK2 kinase inhibitors to be employed as neuroprotective agents in PD.

PARK-*VPS35*
Two independent studies utilized whole-exome sequencing in a Swiss and an Austrian kindred to identify the same p.D620N (c.1858G>A) mutation in the *vacuolar protein sorting 35 homolog* (*VPS35*) gene as the cause of autosomal dominant PD[21, 22]. This mutation was subsequently found in several additional families but is an overall rare cause of PD with a frequency <0.1%[23]. The p.D620N mutation co-segregates with a phenotype similar to iPD and has incomplete, age-associated penetrance. VPS35 is a component of the retromer complex and is involved in retrograde transport from the endosomes to the trans-Golgi network. VPS35 localizes to dendritic spines and is involved in the trafficking of excitatory AMPA-type glutamate receptors. Fundamental neuronal processes, including excitatory synaptic transmission and synaptic recycling are altered by VPS35 overexpression[24].

PARK-*Parkin*
Parkin mutations are the major cause of autosomal recessive and early-onset PD[25], accounting for up to 77% of isolated PD with an age of onset <20 years[26] and for 10-20% of early-onset PD patients in general. The disease typically starts in the third or fourth decade of life (but can have childhood-onset, especially in Asian patients), is slowly progressive, responds well to dopaminergic treatment[27], is commonly complicated by dystonia but very rarely by dementia[28]. The clinical phenotypes of *Parkin*-, *PINK1*-, and *DJ-1*-linked PD are similar; however, despite large data gaps, published phenotypic information on *Parkin* is the most comprehensive[28]. A large number and broad spectrum of Parkin mutations have been identified, including alterations in all 12 exons across various ethnic groups. Mutations comprise exchanges of single nucleotides, small deletions, and exonic deletions and duplications[29]. Parkin codes for a 465-amino-acid protein which functions as an E3 ubiquitin ligase in the process of ubiquitination and with a critical role in maintaining mitochondrial function and integrity[30, 31].

PARK-*PINK1*
Mutations in the *PTEN-induced putative kinase 1* (*PINK1*) gene are the second most common cause of autosomal recessive early-onset PD[32]. The frequency of *PINK1* mutations in patients is in the range of 1-9% with considerable variation across different ethnic groups[33]. *PINK1* mutation carriers have a similar phenotype to Parkin mutation carriers with the possible exception of a greater incidence of psychiatric and cognitive symptoms. Most of the affected have a disease onset in the fourth decade of life and a typical parkinsonian phenotype with asymmetric onset, slow progression, and an excellent response to levodopa[34]. In contrast to *Parkin*, the majority of the reported *PINK1* mutations are either missense or nonsense mutations, whereas only very few families with whole-exon deletions have been reported. PINK1 is a 581-amino-acid ubiquitously expressed protein kinase with most of the PINK1 mutations affecting the kinase domain. Parkin and PINK1 act in a common pathway of mitochondrial quality control.

PARK-*DJ-1*

Mutations in *DJ-1* were first identified in two consanguineous families of Dutch and Italian origin, respectively[35], and are a rare cause of autosomal recessive PD (1-2% of early-onset PD cases)[36]. The seven exons of the DJ-1 gene encode a 189-amino-acid ubiquitous highly conserved protein, which functions as a cellular sensor of oxidative stress. Loss of DJ-1 has recently been shown to lead to an impaired antioxidant response by altered glutamine and serine metabolism and is accompanied by a constitutive pro-inflammatory activation of microglia[37].

Recent novel Parkinson's disease candidate genes

In addition to the established monogenic genes reviewed in detail above, a number of additional causative PD genes have been proposed recently. This includes *DNAJC13* (*DnaJ heat shock protein family (Hsp40) member C13*; assigned 'PARK21')[38] for a dominant form of PD, *CHCHD2* (*coiled-coil-helix-coiled-coil-helix-domain-containing protein 2*; assigned 'PARK22')[39], *VPS13C* (*vacuolar protein sorting protein 13C*; assigned 'PARK23') for an early onset, recessive form of PD with early cognitive decline[40], and *RAB39B* (member RAS oncogene family 39B) for X-linked early-onset PD with intellectual disability[41]. Importantly, independent validation data for any of these genes are currently either missing or not unequivocally supportive. Thus, additional data are needed to determine whether these genes can be considered as established causative PD genes.

Table 1: The proposed new list of hereditary PD

New designation and Phenotypic subgroup	Additional Phenotypic notes	Inheritance pattern	Previous locus symbol
Classical parkinsonism			
PARK-SNCA	Frequent dementia	AD	*PARK1*
PARK-LRRK2	Indistinguishable from idiopathic PD	AD	*PARK8*
PARK-VPS35	Similar to idiopathic PD	AD	*PARK17*
Early-onset parkinsonism			
PARK-PARKIN†	Dystonia common, dementia rare	AR	*PARK2*
PARK-PINK1	Psychiatric features common	AR	*PARK6*
PARK-DJ1		AR	*PARK7*
Atypical parkinsonism or complex phenotypes			
PARK-ATP13A2	Kufor Rakeb syndrome	AR	*PARK9*
PARK-FBX07	Early onset parkinsonism with pyramidal signs	AR	*PARK15*
PARK-DNAJC6	Mental retardation and seizures may be part of the phenotypic spectrum	AR	*PARK19*
PARK-SYNJ1	Seizures, cognitive decline, abnormal eye movements, and dystonia may be part of the phenotypic spectrum	AR	*PARK20*

~100 years after Hermann Oppenheim's first description of hereditary dystonia: Advances in Monogenic dystonia

Even in the first publication that coined the term 'dystonia', Hermann Oppenheim – despite the absence of an obvious family history – suspected that 'hereditary burden likely plays a major role' of the disease[42].

Although genetic causes of dystonia - especially for adult-onset focal forms - are largely elusive, a positive family history has been reported in about 20% of the patients. In the past three decades more than 200 genes have been linked to different, mainly childhood-onset, generalized forms of dystonia. This includes forms in which dystonia is the only disease manifestation with the exception of tremor ("isolated dystonia"), forms in which dystonia co-occurs with another movement disorder such as parkinsonism or myoclonus ("combined dystonia")

and disorders in which dystonia is often less prominent and usually one of several disease manifestations ("complex dystonia"). Notably, most of the genetic forms belong to the latter phenotypic group which, however, also represents the most heterogeneous class in terms of clinical expression and will not be reviewed in detail in this syllabus.

Dystonia is generally characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. two main axes of dystonia classification currently considered most relevant are clinical and etiological. On clinical grounds, the updated classification proposes characterization by age of onset (infancy, childhood, adolescence, early and late adulthood), body distribution (focal, segmental, multifocal and generalized), temporal pattern (static or progressive; persistent, action-specific, diurnal or paroxysmal presentation), and association with additional features (isolated or combined with other movement disorders). Formerly, isolated dystonia was referred to as 'primary dystonia' and combined dystonia as 'dystonia-plus'. The proposed new list of isolated and combined dystonias is based on association with additional features (**Table 2**). As almost all known forms of dystonia are inherited in autosomal dominantly, unlike in PD, mode of transmission does not appear to be a useful feature to categorize familial dystonias.

In the following, selected monogenic forms of isolated and combined dystonia will briefly be reviewed.

DYT-*TOR1A*

Mutations in the *TOR1A* gene (torsin family 1 member A) encoding TorsinA, a member of the AAA+ superfamily (ATPases associated with a variety of cellular activities) are a cause of early-onset generalized dystonia. The first and currently only clearly established mutation is a 3-base pair deletion in the *TOR1A* gene (c.904_906delGAG; p.302delGlu)[43]. This mutation is frequently found among Ashkenazi Jewish patients due to a founder effect[44]. DYT-*TOR1A* dystonia usually presents as dystonia in an extremity in childhood. The symptoms later progress to other body parts but typically spare the face and neck[44]. There is variable expressivity ranging from severe childhood-onset generalized to late-onset focal dystonia and about two thirds of the mutation carriers remain unaffected throughout their life (reduced penetrance)[45]. Despite linking a mutation in *TOR1A* to dystonia 20 years ago, the role of TorsinA is still largely elusive. TorsinA is mainly located in the endoplasmatic reticulum and the perinuclear space and due to its function as a triple AAA+ protein, is thought to act as a molecular chaperone[46].

DYT-*THAP1*

Mutations in the *THAP1* gene (*THAP domain-containing, apoptosis associated protein 1*) encoding the transcription factor THAP1 are a cause of adolescent-onset dystonia with mixed phenotype (previously referred to as DYT6)[47]. About 100 different mutations have been reported in *THAP1* including missense, nonsense, and frameshift mutations[48, 49]. DYT-*THAP1* dystonia usually presents with dysphonia or writer´s cramp in late childhood or adolescence. Over the course of the disease, dystonia spreads to other body parts with prominent cranio-cervical involvement[50]. As for DYT-*TOR1A*, the penetrance of DYT-*THAP1* is highly reduced (to about 50%) and there is variable expressivity. As in most other dystonia forms, there seems to be no neurodegeneration and no specific disease-related pathology in DYT-*THAP1*[51]. THAP1 has a DNA-binding THAP domain at the N-terminus as well as a nuclear localization signal (NLS) and several protein-protein interaction motifs towards the C-terminus. Due to posttranslational modification, several THAP1 species exist including a neuron-specific form that may be a key player in controlling neuronal gene transcription[52].

DYT-*GNAL*

Heterozygous mutations in the *GNAL* gene (*guanine nucleotide-binding protein subunit alpha L*) encoding the stimulatory α subunit of the heterotrimeric G protein G_{olf} ($Gα_{olf}$) cause cervical or cranial dystonia with a mean onset in the thirties[53]. *GNAL* mutations seem to be highly but not fully penetrant[54]. Functional characterization of the homozygous *GNAL* mutation revealed impaired $Gα_{olf}$ functional coupling to dopamine D1 receptors[55], while previously described *GNAL* mutations pointed to a strict loss-of-function mechanism[56].

DYT-*ANO3*

Mutations in the *ANO3* gene (*anoctamin 3*) have first been reported in 2012 in patients with predominantly cranio-cervical dystonia with a broad range of ages of onset[57]. Mutations were detected in about 1% of dystonia patients including small families with segregation of *ANO3* variants. Notably, a large number of missense variants can be found in variant databases and in healthy individuals[58]. However, the presence of *de-novo* mutations in *ANO3* usually supports pathogenicity of the variant[59]. *ANO3* encodes a transmembrane protein that belongs to a family of calcium-activated chloride channels and thus may play a role in signal transduction, an important pathway involved in dystonia[3].

DYT-GCH1

Heterozygous mutations in the *GCH1* gene (*GTP cyclohydrolase 1*) encoding the rate-limiting enzyme in the biosynthesis of dopamine via the biopterin pathway, are a cause of childhood-onset dopa-responsive dystonia (DRD) with diurnal fluctuation[60]. Parkinsonian features often co-occur or may be the only finding[61] and even be associated with a presynaptic dopaminergic deficit as evidenced by SPECT[62]. To date, more than 100 different mutations have been reported including missense, nonsense, frameshift, and splice-site mutations, as well as whole-exon or whole-gene deletions[61, 63]. *GCH1* mutation carriers show a penetrance of around 50% which is considerably higher in women compared to men. Recessively inherited (biallelic) mutations in *GCH1* result in a much more severe clinical phenotype including developmental delay and infantile onset[64]. Due to the enzymatic defect in the levodopa biosynthesis, there is a life-long response of DRD to levodopa therapy.

DYT-*SGCE*

Mutations in the *SGCE* gene (sarcoglycan epsilon) coding for the ε member of the sarcoglycan family, are a frequent cause of myoclonus-dystonia (M-D) characterized by predominant, action-induced, alcohol-responsive myoclonic jerks[65, 66]. Myoclonus as well as dystonia most commonly involve the neck or arms/hands. Onset is usually in childhood or adolescence[67]. Additionally, many carriers of *SGCE* mutations develop psychiatric features such as anxiety-related disorders and alcohol dependence, which is important for counseling and specific treatment[68]. About 80 different mutations have been reported in *SGCE*, many of which are loss-of-function mutations due to frameshift, splice site, nonsense mutations, or deletions of whole exons or even the entire gene. The latter type of mutation often also involves loss of adjacent genes leading to additional clinical features such as joint problems[65]. As for all autosomal dominantly inherited isolated and combined dystonias, M-D also shows reduced penetrance - but in contrast to the other forms - for *SGCE* the underlying mechanism has been elucidated: Penetrance of *SGCE* mutations is only reduced upon maternal transmission due to maternal genomic imprinting of the *SGCE* gene[69]. This impacts on genetic counseling since it is very unlikely that offspring who inherited the mutation from the mother will develop the disease because only the wildtype allele from the father will be expressed and the mutated, maternal allele will be inactive due to the imprinting mechanism. The exact function of ε-Sarcoglycan has not yet been identified at the cellular level. It is known to have a transmembrane domain and to be located at the cytoplasma membrane. Other sarcoglycans form the dystrophin-glycoprotein complex that links the cytoskeleton to the extracellular matrix and mutations in these genes cause limb-girdle muscular dystrophies[70].

Table 2: The proposed new list of isolated and combined hereditary dystonia

New designation and phenotypic subgroup	Additional phenotypic notes	Inheritance pattern	Previous locus symbol
Isolated dystonias			
DYT-TOR1A	Early-onset generalized dystonia	AD	*DYT1*
DYT-THAP1	Adolescent-onset dystonia of mixed type	AD	*DYT6*
DYT-GNAL	Adult onset cranial-cervical dystonia	AD	*DYT25*
Combined dystonias			
Dystonia plus parkinsonism			
DYT-GCH1	Dopa-responsive dystonia	AD	*DYT5a*
DYT-TH	Dopa-responsive dystonia	AR	*DYT5b*
DYT-ATP1A3	Rapid-onset dystonia-parkinsonism	AD	*DYT12*
DYT-PRKRA	Dystonia with mild parkinsonism	AR	*DYT16*
DYT-TAF1*	Dystonia-parkinsonism	X-linked	*DYT3*
Dystonia plus myoclonus			
DYT-SGCE	Myoclonus-dystonia	AD	*DYT11*
Paroxysmal dystonia plus other dyskinesia			
DYT-PRRT2	Paroxysmal kinesigenic dyskinesia	AD	*DYT10 or DYT19*
DYT-MR-1	Paroxysmal non-kinesigenic dyskin.	AD	*DYT8*
DYT-SLC2A1	Paroxysmal exertion-induced dyskin.	AD	*DYT18 or DYT9*

*Due to a founder effect, genetic testing is possible. The pathogenicity of the TAF1 gene is not absolutely confirmed, however testing of selected variants in this gene is sufficient for the diagnosis.

Further reading

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