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18 *Current Genomics,* **2014**, *15,* **18-27**

Genetic Variants in Diseases of the Extrapyramidal System

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Abstract: Knowledge on the genetics of movement disorders has advanced significantly in recent years. It is now recognized that disorders of the basal ganglia have genetic basis and it is suggested that molecular genetic data will provide clues to the pathophysiology of normal and abnormal motor control. Progress in molecular genetic studies, leading to the detection of genetic mutations and loci, has contributed to the understanding of mechanisms of neurodegeneration and has helped clarify the pathogenesis of some neurodegenerative diseases. Molecular studies have also found application in the diagnosis of neurodegenerative diseases, increasing the range of genetic counseling and enabling a more accurate diagnosis. It seems that understanding pathogenic processes and the significant role of genetics has led to many experiments that may in the future will result in more effective treatment of such diseases as Parkinson's or Huntington's. Currently used molecular diagnostics based on DNA analysis can identify 9 neurodegenerative diseases, including spinal cerebellar ataxia inherited in an autosomal dominant manner, dentate-rubro-pallido-luysian atrophy, Friedreich's disease, ataxia with oculomotorapraxia, Huntington's disease, dystonia type 1, Wilson's disease, and some cases of Parkinson's disease.

Received on: June 15, 2013- Revised on: November 12, 2013- Accepted on: November 28, 2013

Keywords: Ataxia, Dystonia, Huntington's disease, Parkinson's disease, Wilson's disease.

INTRODUCTION

The field of movement disorders, which are also known as extrapyramidal disorders, is growing rapidly. Knowledge on the genetics of movement disorders has advanced significantly in recent years. It is now recognized that disorders of the basal ganglia have a genetic basis and it is believed that molecular genetic data will provide clues to the pathophysiology of normal and abnormal motor control [1].

An understanding of pathogenic processes and the significant role of genetics has led to many experiments that, perhaps, in the future will result in more effective treatment of diseases such as Parkinson's (PD) or Huntington's disease (HD). However, the unclear pathogenesis of many neurodegenerative diseases and the lack of simple and readily available indicators of the early period of these diseases remain crucial issues in the causal treatment of these diseases.

Progress in molecular genetic studies, leading to the detection of genetic mutations and loci, has contributed to the understanding of mechanisms of neurodegeneration and to clarify the pathogenesis of some neurodegenerative diseases. Molecular studies have also found application in the diagnosis of neurodegenerative diseases, increasing the range of genetic counseling and enabling more accurate diagnosis. Currently, diagnostic tests, including the exploration of known inherited disease-causing mutations in an autosomal dominant or autosomal recessive manner, are carried out in patients with a clinical diagnosis of a particular disease. Tests prior to the onset of a disease are performed at the request of adult individuals with families in which molecular studies have previously identified a genetic mutation linked to the disease in question. Moreover, prenatal diagnosis is carried out if one of the parents is known to have the disease.

Currently used molecular diagnostics based on DNA analysis can identify 9 neurodegenerative diseases, namely spinal cerebellar ataxia inherited in an autosomal dominant manner, dentate-rubro-pallido-luysian atrophy (DRPLA), Friedreich's disease, ataxia with oculomotorapraxia induced mutation of aprataxin gene (APTX), HD, dystonia type 1 (DYT1), Wilson's disease (WD), and some cases of PD caused by gene mutations [1-3].

The Online Mendelian Inheritance in Man (OMIM) database lists over 500 entries for disorders of which ataxia or a movement disorder is a component, but this paper presents only selected issues on the molecular basis and diagnostic capabilities of certain diseases of the extrapyramidal system [4].

PARKINSON'S DISEASE AND PARKINSONISM SYNDROMES

Parkinson's disease is a progressive disorder of the central nervous system (CNS), manifesting a clinical slowdown in mobility, muscle rigidity and tremor at rest, resulting from loss of midbrain *substantia nigra* (SN) cells, which results in a dramatic reduction of the neurotransmitter dopamine in the striatum [5].

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1875-5488/14 $58.00+.00

Parkinson's disease is one of the most common degenerative diseases of the CNS. According to estimates of the World Health Organization (WHO), approximately 5 million people suffer from PD. In Europe, this degenerative disease affects approximately 1.2 million people. Aprroximately 1 million Americans and about 100 000 British suffer from PD [6, 7]. As is clear from epidemiological studies in the United States, on average, every nine minutes a new case of PD is diagnosed, which makes about 60 000 cases annually. The average age of PD onset is 58 years. However, there are cases of much earlier onset, called early-onset parkinsonism (before 40 years of age) and juvenile parkinsonism, onset before 30 years. Moreover, it has been shown that men suffer more frequently than women. It is also known that the incidence of PD is about 20 in 100 000 each year [8-11].

The four main symptoms of PD are resting tremor, slowness of movement, muscle rigidity, and altered postural stability. Most often the first clinical symptom of PD is a tremor of one hand. Some patients also experience imbalance and postural instability at the beginning. In addition to the tremors, disability in one upper limb or dystonic setting for walking may occur [12]. Characteristic of PD is also inclined silhouette of the body due to increased paraspinal muscle tension, and patients walk using small steps. A reduction of the amplitude of movement has also been observed, manifested by micrographia and hypomimia. Over time, there are disturbances of balance that can lead to frequent falls [10, 12]. As is well known in PD, in addition to the movement disorders patients also present with neuropsychiatric disorders and autonomic dysfunction [12].

The role of genetic factors in the etiology of PD has been controversial for many years. It is currently believed that the etiology of PD is multifactorial, indicating the contribution of both environmental and genetic factors. Results of studies conducted by Lazzarini *et al.* indicate that the risk of developing PD in the general population over 80 years of age is about 2%, and increases to about 5-6% if the disease is present in a parent or sibling. If the symptoms of the disease occur in two family members, the risk is 20-40% [13]. Marder *et al.* [14] showed that the risk of developing of PD in first degree relatives of patients within a geographical area for age 75 was 2% while in the control group was 1%. Epidemiological studies in a group of 203 sibling pairs have showed PD manifestation in all subjects. Furthermore, a PET study on 17 twins estimated a concordance of 45% in monozygotes and 29% in dizygotes, supporting the genetic hypothesis of PD pathogenesis [15]. A greater risk of PD manifestation has been shown among biological relatives than among spouses [16]. For many familial forms of PD (FPD), the genes or loci responsible for the manifestation of the disease have been identified and described. It is known that FPD, depending on the causal mutations, can be inherited in either an autosomal dominant or in an autosomal recessive manner. However, it is believed that certain genetic variants may also play a role in the modulation of the risk for the sporadic form of PD (SPD).

The first genetic mutation, located on the long arm of chromosome 4, was detected in a large Italian-American family, coming from the Contrusi village in the province of Salerno in southern Italy, with typical for PD clinical and neuropathological symptoms [17]. Since then, numerous further genes and mutations involved in the pathogenesis of PD have been described [18]. The currently identified genes associated with the occurrence of FPD are shown in (Table **1**). It is now believed that genetic diagnostic testing can be performed in some patients with FPD and those with early onset of disease (before age 50). However, according to recent studies, mutations affecting LRRK protein-2 (dardarin) and Parkin protein can also cause SPD. Genetic studies indicate that nearly 20% of patients with initial symptoms of PD before an age of 40 years may have a mutation of the *PRKN* gene encoding the Parkin protein. An increasing body of evidence points to the influence of mutations of this gene as a risk factor of PD at a later age (> 40 years). Moreover, it has been shown that, in some populations, as many as 40% of all PD patients have a mutation of the *LRRK2* gene [19]. Furthermore, there are newer reports in the literature of additional genes involved in the pathogenesis of PD and their possible interactions.

Genome-wide association studies (GWAS) indicate a strong association to the *SNCA* and *MAPT* gene [20-26]. The first meta-analysis of datasets from PD GWAS identified five novel risk loci for PD (*ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11* and *CCDC62/ HIP1R*) and six that had previously been identified (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK* and *LRRK2*) [27]. A recent meta-analysis revealed another five PD risk loci (*PARK16*, *STX1B*, *FGF20*, *STBD1* and *GPNMB*) [28].

Other genetic disorders may also be occasionally present with parkinsonism, including tau mutations, which may sometimes cause a progressive supranuclear palsy (PSP)-like presentation, *SCA3* mutations which may be present with parkinsonism as well as ataxia, the juvenile presentation of HD, and WD. Some genes related with PD may also be included in the pathogenesis of parkinsonism plus syndromes. Although parkinsonism plus syndromes have been classified based on phenomenology, the studies of the underlying pathology have changed our understanding of the relationship between these disorders. It is currently known that, in Pick disease and tau-positive frontotemporal dementia there is a predominance of 3-repeat isoform of tau protein, whereas corticobasal degeneration and progressive supranuclear palsy exhibit the 4-repeat tau isoform. It is also known that the presence of different protein isoforms is conditional, based on the presence of a particular genetic variant. On the other hand, in some cases of ubiquitin positive and tau negative frontotemporal dementias, mutations in the progranulin gene and in *TDP43* (a nuclear factor that functions in regulating transcription and splicing) were found [29-32]. *TDP43* has also been found to underlie familial cases of amyotrophic lateral sclerosis (ALS) and Guam-Parkinson dementia complex, suggesting a pathologic role [33]; while in Lewybodies dementia and multiple system atrophy (MSA), disturbances in α–synuclein (ASN) protein structure and the presence of Lewy bodies and fibrillary aggregates formed by this protein have been shown. Although MSA was previously widely considered to be a nongenetic disorder, recently several genes have been associated with an increased risk of MSA, including the *SNCA* gene encoding ASN first and foremost, but also other genes involved in oxidative stress, mitochondrial dysfunction, inflammatory processes, as well as parkin-

Table 1. Known Genes and Loci for Familial Parkinson Disease [18].

Locus	Chromosomal Location	Gene	Inheritance
PARK1, PARK4	4q21	*SNCA*	AD
PARK2	6q25.2-q27	*PRKN*	AR
PARK3	2p13	Unknown	AD
PARK5	4p14	*UCHL1*	AD
PARK6	1p35-p36	*PINK1*	AR
PARK7	1p36	*DJ1*	AR
PARK8	12p12	*LRRK2*	AD
PARK9	1p36	*ATP13A2*	AR
PARK10	1p32	Unknown	AD
PARK11	2q37.1	*GIGYF2*	AD
PARK12	Xq21-q25	Unknown	?
PARK13	2p13	*HTRA2*	?
PARK14	22q13.1	*PLA2G6*	AR
PARK15	22q12-q13	*FBXO7*	AR
PARK16	1q32	*SLC41A1*	?

AD- autosomal dominant; AR- autosomal recessive; ? –unknown.

sonism- and ataxia-related genes have been implicated as susceptibility factors. It has been demonstrated that clinical symptoms of *SNCA* multiplication in patients sometimes resemble symptoms usually seen in MSA, suggesting that the clinical phenotype can be more variable and does not necessarily resemble that of PD [34]. Moreover, sequencing studies, gene dosage measurements, and microsatellite testing have demonstrated a significant association of *SNCA* variants with MSA [35-38].

Furthermore, it is currently suggested that additional candidate genes for MSA may be among others: *PRKN*, PTEN-induced putative kinase 1 (*PINK1*) [39, 40], *MAPT* [41, 42], *SLC1A4*, *SQSTM1*, *EIF4EBPI* [43]. In addition, polymorphisms in *IL-1α*, *IL-1β*, *IL-8*, and *ICAM-1* have been reported to be associated with an increased risk of MSA [44-46]. The *ADHC1* G78X mutation has also been shown to be associated with MSA in the British, but not in the German population, whereas no significant associations were detected on *ADH7* gene in these populations [47, 48].

CHOREA

Chorea is a term for involuntary movements with a dancing, smooth character. The severity of chorea movement can vary greatly: from discrete to such that it prevents normal function. Chorea may occur as a result of various factors, which include the history of both the autosomal dominant (including HD, neuroacanthocytosis, benign familial chorea) and the autosomal recessive (such as WD) hereditary diseases [49].

HUNTINGTON'S DISEASE

Huntington's disease is a progressive neurodegenerative disease inherited in an autosomal dominant manner. It is caused by a mutation in the gene encoding the Huntingtin protein, and is located on the short arm of chromosome 4 (4p16.3.); it consists of a pathological increase in the quantity of CAG triplets [50]. The CAG tract is on exon 1 of the gene. The wild-type contains a CAG repeat, coding for a polyglutamine stretch in the protein at that site in the range between 6 and 26 copies. The number of trinucleotide repeats varies between generations due to the existence of meiotic instability, which in normal alleles is rare (<1%). Huntington's disease is associated with 36 repeats or more. Definite clinical manifestation will occur if the number of repeats exceeds 40. The range 36-39 leads to an incomplete penetrance of the disease or to a very late onset. The range between 29 and 35, the so-called intermediate alleles, is unstable, which means that these alleles are prone to changes during reproduction [51-54]. As a result of gene mutation, an excessive increase of the aberrant protein in a cell occurs, which leads to death of the cell. The normal wild-type Huntingtin protein plays a role in synaptic function, is necessary in the post-embryonic period, possibly has an anti-apoptotic function and is possibly protective against the toxic mutant Huntingtin [51]. There is evidence that the mutant form of Huntingtin leads to a gain of function as well as to a loss of function.

Huntington's disease incidence is 4-8 per 100 thousand of Europeans. The disease usually begins in the fourth decade of life, although there have been cases of early (5 years

old) and late (after 70 years) onset [55]. Due to the location of the neurodegenerative process, the most common symptoms of HD include chorea, progressive dementia, and depression. The juvenile form (Westphal) may result in an image resembling PD with rigidity and bradykinesia. Molecular diagnosis of HD in the families of patients provides an opportunity for the early detection of carriers and possible early therapeutic intervention [55]. It is also suggested that an increasing number of CAG trinucleotide repeats is associated with an earlier onset of the disease. The strongest correlation has been found in cases with a much greater number of repetitions (> 60), where the juvenile form of HD was observed [52-54].

The age at which the disease becomes apparent, may also be determined by other genetic factors, such as genetic polymorphisms of the *GluR6* gene, located on chromosome 6, or the apolipoprotein E4 gene. Moreover, since a Huntingtin-associated protein (HAP 1) is enriched in the brain, this may represent a possible basis for the selective brain pathology in HD [56]. It is likely that environmental factors can contribute in the presence of these changes.

The diagnosis of HD is based on clinical criteria, family history and genetic testing. When chorea is the first and most prominent sign of the disease, analyzing the history would be the initial and most valuable step. In many cases the underlying cause is another general internal disorder or an iatrogenic disorder. Only very few genetically determined disorders are responsible for choreatic syndromes. In about 1% of the cases clinically diagnosed as HD by the clinician, the genetic test does not confirm the diagnosis. These cases are called phenocopies and are defined by a clinical diagnosis of HD with chorea, psychiatric and or cognitive signs, and an autosomal dominant pattern of inheritance or family history (Table **2**) [57].

WILSON'S DISEASE

Wilson's disease or hepato-lenticular degeneration, is a rare disorder of the metabolism of copper [58-60]. The incidence of WD in most of the world's population is estimated to be approximately 1:30.000. This disease is more common in China, Japan (1:10.000), Sardinia (1:7000), Iceland and the Canary Islands (1:2600) [58-60].

Wilson's disease is caused by mutations in the gene encoding the P-type adenosine triphosphatase (*ATP7B*) located at chromosomal position 13q14-q21. The first symptoms usually appear between 10 and 40 years of age. Nearly half of the patients have impaired liver function: hepatitis (chronic or acute), cirrhosis and hyperacutehepatitis. Neuropsychiatric disorders are seen in the majority of patients, which may lead to an incorrect diagnosis, often schizophrenia or alcohol dependence [61].

Testing for mutations of the *ATP7B* gene is performed if the results of biochemical tests (including the concentration of copper in daily urine) or liver biopsy are inconclusive and do not allow for the diagnosis. Indications for genetic testing are WD in first-degree relatives of patients, if patients are not found to have a Keiser-Fleischer ring, and the concentration of ceruloplasmin is slightly reduced and patients have impaired liver function [62].

So far, more than 250 mutations have been described in the *ATP7B* gene [63]. The presence of missense and nonsense point mutations has been demonstrated, as have deletions, duplications and insertions. The individual mutations occur with different frequencies in different regions of the world. In Poland, the most common (72% of alleles) is believed to be mutation c.3207C>A, located in exon 14 of the *ATP7B* gene [64]. This mutation was also observed with high frequency in other European countries including Germany, Russia, Austria, Hungary, Greece, Sweden, Denmark, and England [65-72].

Table 2. Phenocopy of Huntington Disease [OMIM].

	Mutation	**Locus**
HDL1	Octapeptide repeat expansion *PRNP*	20pter.p12
HDL2	CTG/CAG-expansion *JPH3*	16q24.3
HDL3	Unknown	4p15.3
SCA17 (HDL4)	CAG/CAA-expansion *TBP*	6q27
SCA1/2/3	CAG-expansion *ATXN1/2/3*	6p23, 12q24, 14q24-q31
DRPLA	CAG-expansion *ATN1*	12p13
Chorea-acanthocytosis	mutation *VPS13A*	9q
McLeodsyndrome	mutation *XK*	Xp21.2-21.1
NBIA2	mutation *PLA2G6*	22q13.1
NBIA1/PKAN	mutation *PANK2*	20p13-12.3
FriedreichAtaxia	GAA-expansion *FXN*	9q13, 9p23-p11

HDL- Huntington Disease-Like; SCA- Spinocerebellar ataxia; DRPLA- Dentato-rubro-pallido-luysian atrophy; NBIA- Neurodegeneration with Brain Iron Accumulation; PKAN- Panthotenate Kinase Associated Neurodegeneration.

Because of the wide variety of mutations in the *ATP7B* gene, as well as a large variety of phenotypes of WD, a comparative analysis was performed to determine whether the genotype can be inferred by the phenotype of the disease. The comparative analysis of the phenotype of patients with the WD p.H1069Q mutation and patients with other mutations in *ATP7B* found that mutation p.H1069Q (as either homo-or heterozygous) is associated with significantly less severe disturbances in the metabolism of copper, and with later onset of the first clinical signs of WD in comparison with other mutations [73]. It is believed that the occurrence of WD in patients homozygous for the p.H1069Q mutation is caused by a defect in the treatment of ATP-ase7B and its accelerated degradation. Despite the observed genotype-phenotype relation, significant variations in the phenotype of the disease among people with the same type of mutation-have been found in all analyses. It is believed that the phenotypic variability in WD is largely due to the influence of other modifying factors, among which include the dietary intake of copper, the activity of antioxidant mechanisms, and the activity of other proteins involved in the metabolism of copper [60,74].

DYSTONIA

Dystonia is a group of symptoms involving persistent muscle spasms, often of a repetitive twisting movement, sometimes with the formation of fixed positions. Dystonia can affect the limbs, paraspinal muscles and muscles innervated by cranial nerves. Involuntary movements often increase with purposeful movement, which is sometimes called action dystonia. Sometimes muscle spasms are associated only with a specific function, such as writer's cramp, when symptoms occur only with attempting writing, and are not present in other activities. As the disease progresses, dystonic movements can be triggered by motor activity in the uninvolved areas of the body. With further progression of the disease, dystonic cramps appear also in the rest of the body. Finally, the disease leads to afixed body position [75].

Dystonia may be a separate disease, but it can also be a symptom of the course of other diseases. According to the symptomatic classification of dystonia, it may be generalized, focal, multifocal, segmental, or unilateral (hemidystonia). Hemidystonia is often secondary to organic brain damage, such as perinatal injury [76]. According to classification based on age of onset, dystonia is divided into dystonia onset in childhood (under 12 years), beginning at a young age (between 13 and 20 years old) and dystonia onset in adulthood (after age 20) [77].

According to recently published epidemiological studies, the prevalence of primary dystonia in Europe is approximately 0.05 per 1000. Dystonia is particularly frequent in the population of Ashkenazi Jews, in which the rate is about 1 per 6000 [78]. Genetic studies have allowed the identification of 15 types of familial dystonia, which are listed chronologically according to their description, from DYT1 to DYT15, although there is currently even a DYT25 form (Table **3**). The genetically determined generalized dystonias include: the earliest described generalized dystonia DYT1, idiopathic torsion dystonia DYT2, X-linked dystonia, which can be both generalized and segmental (DYT3), and 2 forms of dystonia responsive to levodopa (DYT5 and DYT14) [79].

The most well-known, idiopathic torsion dystonia DYT 1, described at the beginning of the last century, is dystonia associated with an autosomal dominant mutation located on chromosome 9 (9q34) [80-83]. This gene encodes the Torsin protein, whose role under normal conditions is connected totransmembrane transport in the dopaminergic system, involving a cell's response to stress and the process of intracellular protein metabolism. The mutation (a 3-bp deletion in the coding sequence of the *TOR1A* gene) leads to the loss of the ability of Torsin to bind to a target protein. This mutation is found in diverse ethnicities, either inherited as a founder mutation or – *de novo* [84], and only two additional mutations of unclear pathogenicity (p.R288Q and p.F205I) have been described in isolated a typical cases [85, 86]. What is interesting is that the penetrance of the mutated gene is only about 40%, which means that not all carriers of these mutations have symptoms of the disease [80-83].

Hereditary focal and segmental dystonia are DYT 4, 6, 7 and 13. DYT 4 is described in several families and is called whispering dysphonia. For DYT 4, the p.R2G mutation in the *TUBB4a* gene (DYT4, encoding isoform 'a' of β-Tubulin) has been identified by sequencing [87]. It is known that this form of dystonia is inherited in anautosomal dominant manner, while DYT 6 is related with an autosomal dominant mutation in gene *THAP1* (thanatos associated protein-1) for which the genetic location is not yet fully known (chromosome 8 p21-q22), with onset of symptoms in adulthood [88]. DYT 7 is associated with an autosomal dominant mutation on chromosome 18p11.3, where an unknown gene product leads to focal dystonia with onset in adulthood [89]. Furthermore, it is known that dystonia DYT 13 is related with an autosomal dominant mutation on chromosome 1p36 with an unknown gene product, leading to focal or segmental, usually mild, dystonia.

Paroxysmal dystonias are the three successively described DYT 8, 9 and 10, while among DYT 11 and DYT 12 belong to the genetically determined form of dystonia with specific symptomatology. DYT 11 is an autosomal dominant myoclonic dystonia associated with the mutation located on chromosome 7q21-Q31 and chromosome 11q23. The gene product, which is subject to mutation, in the first case is the gene for the protein ε-sarcoglycan, and in the second case is the gene for the dopamine D2 receptor protein. Clinically, DYT 11 manifest smyoclonic muscle break up mainly of the shoulder and neck, accompanied by dystonia [90]. DYT 12 is a dystonia with parkinsonism with the rapid development of symptoms. Inheritance is autosomal dominant and the mutation is located on chromosome 19q13 in the gene for ATPase associated with the sodium-potassium pump. DYT 15 is a recently identified myoclonic dystonia genetically different from DYT 11 [79, 90].

It is now possible to allow genetic testing to confirm DYT 1 dystonia. It is believed that genetic testing in DYT 1 is justified in patients with primary dystonia with onset of symptoms before 26 years of age and in patients with primary dystonia with alater start but with a family in which early-onset dystonia has occurred. Some centers worldwide are also able to provide genetic tests for DYT 11 and DYT 5.

Table 3. Molecular Classification of Dystonia Syndromes.

Disease	Gene	Locus	Phenotype	Inheritance
Pure Primary Torsion Dystonia				
DYT1	*TOR1A*	9q34	Early-onset generalized limb onset dystonia	AD
DYT2	–	–	Early-onset generalized dystonia with prominent cranio-cervical involvement	AR
DYT4	*TUBB4a*	19p13.12–13	Whispering dysphonia	AD
DYT6	*THAP1*	8p11.21	Generalized cervical and upper-limb-onset dystonia	AD
DYT7	–	18p	Adult-onsetcervical dystonia	AD
DYT13	–	1p36.32–p36.13	Cervical and upper-limb dystonia	AD
DYT17	–	20p11.2–q13.12	Segmental or generalized dystonia with prominent dysphonia	AR
DYT21	–	2q14.3–q21.3	Adult-onset generalized or multifocal dystonia, often starting with blepharospasm	AD
DYT23	*CIZ1*	9q34	Adult-onsetcervical dystonia	AD
DYT24	*ANO3*	11p14.2	Cranio-cervical dystonia with laryngeal and upper-limb involvement	AD
DYT25	*GNAL*	18p11	Adult-on setcervical dystonia	AD
Primary Dystonia-Plus Syndrome				
DYT5	*GCH1*	14q22.2	Dopa-responsive dystonia	AD
THD	*TH*	11p15.5	Dopa-responsive dystonia	AR
DYT11	*SGCE*	7q21.3	Myoclonus-dystonia	AD
DYT12	*ATP1A3*	19q13.2	Rapid-onset dystonia parkinsonism	AD
DYT15	–	18p11	Myoclonus-dystonia	AD
DYT16	*PRKRA*	2q31.2	Early-onset dystonia parkinsonism	AR
Paroxysmal Syndrome				
DYT8	*MR1*	2q35	Paroxysmal non-kinesigenic dyskinesia (PNKD)	AD
DYT9/ DYT18	*SLC2A1*	1p34.2	Paroxysmal dyskinesias with episodic ataxia and spasticity/paroxysmal exercise-induced dystonia (PED)	AD
DYT10	*PRRT2*	16p11.2	Paroxysmal kinesigenic dyskinesia (PKD)	AD
DYT19	–	16q13–q22.1	Paroxysmal kinesigenic dyskinesia 2 (PKD2)	AD
DYT20	–	2q31	Paroxysmal non-kinesigenic dyskinesia 2 (PNKD2)	AD
Heredodegenerative Dystonia Syndrome				
DYT3	TAF1	Xq13.1	Dystonia parkinsonism	X-R

AD -autosomal dominant; AR -autosomal recessive; X-R -x-linked recessive.

SPINOCEREBELLAR ATAXIAS

Spinocerebellar ataxias (SCA) are an autosomal dominant clinically and genetically heterogeneous group of disorders. To date, 27 loci and genetic mutations have been identified in different types of spinal cerebellar ataxia (SCA1-SCA27, Table **4**). The disease usually begins in adulthood, most often between 30 and 45 years old, and has a progressive course usually leading to severe disability. Spinocerebellar ataxias show a wide variation in incidence in different regions of the world [91].

It is assumed that the most common type of the disease is SCA3, which appears to be very rare in Poland (not a single case found to date), while the most common types seen in Poland are SCA1 (the most) and SCA2. A characteristic feature of most forms of SCA is the phenomenon of genetic anticipation, caused by trinucleotide repeat instability. This phenomenon depends on the earlier onset of symptoms in subsequent generations, as well as increasingly more severe course. In all types of SCA the cerebellar syndrome is similar, dominating increasingly problematic balance and gait abnormalities accompanied by dysarthria and ataxia of the upper limbs [92-94].

Table 4. Spinocerebellar Ataxias in Which Genetic Testing is Performed [90, 91].

Disease	Gene	Locus	Onset
SCA1	*ATXN1*	6p23	30 y.o.
SCA2	*ATXN2*	12q24	20–30 y.o.
SCA3	*ATXN3*	14q24.3-q31	10–70 y.o.
SCA6	*CACNA1A*	19p13	>25 y.o.
SCA7	*ATXN7*	3p21.1-p12	0–60 y.o.
SCA8	13q	13q21	18–65 y.o.
SCA10	*ATTCT*	22q13	36 y.o.
SCA12	*PPP2R2B*	5q31-q.33	8–55 y.o.
SCA14	*PRKCG*	19q13.4	12–42 y.o.
SCA17	*TBP*	6q27	6–34 y.o.
DRPLA	atrophin-1 or DRPLA protein	12p13.31	3–36 y.o.

Extrapyramidal symptoms are sometimes observed (chorea, PD), as well as abnormal eye movements, symptoms of upper motor neuron damage, dementia, and peripheral neuropathy. The genetic basis of the majority of SCA cases is associated with instability of CAG trinucleotide repeats found in the coding regions of the various genes *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7* and *SCA17* [95, 96]. However, two genes have been identified in which the unstable sequences are in the untranslated ends of genes, and their expansion underlies two types of the disease - SCA8 and SCA12. In SCA10 the repeat instability has been shown in fivenucleotide sequences located in an intron [93, 94].

Except for SCA6, wherein said defect in the gene encoding the subunit calcium channel CACNA1A, and for SCA17 with a *TBP*-defective gene, other genes associated with particular types of SCA encode proteins of unknown function and lack homology to other known proteins present. It was also found that the multiplication of the number of CAG repeats in the *CACNA1A* gene leads to the onset of symptoms characteristic of SCA6 and point mutations in the same gene are associated with the presence of other diseases: episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM) [91].

DRPLA is often included in the group of SCA, as there is also a reported effect in the number of CAG trinucleotide repeats and ataxia is the predominant clinical symptom. The most common form of cerebellar ataxia is inherited in therecessive Friedreich disease (FD). An increased number of GAA trinucleotide repeats and point mutations have been detected in the locus encoding the protein Frataxin on chromosome 9q13-21.1. In the gene encoding Frataxin, the correct number of repetitions is 6-28, while number ranging from 66 to 1700 has been reported in patients. It is believed that Frataxin is involved in iron transport, and in the course of FD there is a significant accumulation of iron in the mitochondria [97].

Two types of ataxia with oculomotor apraxia have been identified to date. In type I, missense mutations were detected in the *APTX* gene located on chromosome 9q13, encoding the Aprataxin protein, which belong to the histidine triad family. Early symptoms (typically at 20 years of age) and a rapid development of the disease have been observed. Early in the onset, there is a cerebellar syndrome and oculomotor apraxia present, and later peripheral neuropathy, chorea and dementia are seen. Hypercholesterolemia and hypoalbuminemia have also been observed [98, 99]. Ataxia with oculomotor apraxia type II is a recently described ataxia in which mutations were located on chromosome 9q34. Clinical symptoms occur later in life, the disease progression is slower, and increased levels of serum α-fetoprotein (AFP) have been detected [100].

In the genes associated with the occurrence of SCA, the normal range of microsatellite repeats is characterized by a high degree of polymorphism. A specific CAG range that is stable and does not tend to expand was found in each of the *SCA* genes. The number of CAG repeats usually does not exceed 40. However, the presence of intermediate alleles (IA) has been shown to not to cause symptoms of the disease, but is characterized by reduced stability and an increased risk of the emergence of new pathogenic mutations in the number of CAG repeats [91].

Molecular diagnosis of SCA is based on DNA analysis to determine the number of CAG repeats in the genes associated with the occurrence of various types of SCA. It is possible to confirm the clinical diagnosis and to determine the type of ataxia, if it is shown that the number of CAG repeats in one of the studied genes exceeded the normal range. The diagnosis of six autosomal dominant forms of spinal cerebellar ataxia is possible using DNA testing: SCA1, SCA2, SCA3, SCA6, SCA7 and DRPLA. Genetic studies help us detect the cause of about 50% of all dominant ataxias [101].

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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