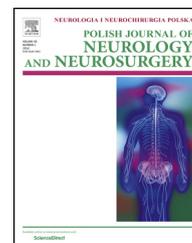


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## Original research article

# Dopa-responsive dystonia or early-onset Parkinson disease – Genotype–phenotype correlation



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## ABSTRACT

**Objective:** Dopa-responsive dystonia (DRD) is a rare form of hereditary movement disorder with onset in childhood, characterized by gait difficulties due to postural dystonia with marked improvement after low doses of levodopa. Mutations in the GCH1 gene are the most common cause of DRD, however, in some cases when the disease is associated with parkinsonism mutations in the PARK2 gene may be identified. The aim of this study was to analyze and compare genotype–phenotype correlation.

**Material/participants:** Four families with inter- and intrafamilial variability of progressive gait dysfunction due to lower limb dystonia occurring in childhood or adolescence were included in the analysis.

**Methods:** General and neurological examination was performed for all affected family members and asymptomatic mutation carriers. The molecular analysis encompassed GCH1 and PARK2 genes.

**Results:** All probands were clinically diagnosed with DRD. The molecular analysis revealed, however, that the dopa-responsive dystonia phenotype was caused by a mutation in the GCH1 gene in three families and in the PARK2 gene in one family. Obtained results allowed to establish the final diagnosis for all families as DYT5a or early-onset Parkinson disease (EO-PD).

**Conclusions:** Reported cases confirm that the DRD phenotype may have heterogeneous genetic background and may be caused by point mutations or rearrangements in the GCH1 gene as well as in the PARK2 gene. Differential diagnosis and genetic tests covering the analysis of genes causative for DRD and EO-PD should be obligatory in both disorders diagnostics as DRD, mainly adolescent onset dystonia, may be associated with parkinsonism.

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## 1. Introduction

Generalized dystonia is a rare form of hereditary movement disorder with onset in childhood, characterized by postural dystonia with marked diurnal fluctuations. Dystonia may be difficult to diagnose correctly because of its many presentations. However, the excellent response to low doses of levodopa (L-dopa) suggests the clinical diagnosis of Segawa disease, known also as dopa-responsive dystonia (DRD) or DYT5 (MIM 128230) [1]. DRD usually starts as foot dystonia causing gait disorder with diurnal fluctuations, and subsequent overflow of dystonic movements to other muscles and parts of the body. Atypical symptoms such as delayed and awkward gait (walking on toes) have also been reported [2]. That is why DRD patients may be misdiagnosed as having spastic diplegic cerebral palsy, intractable epilepsy, hereditary spastic paraplegia or a neurodegenerative disorder [3].

The most frequent type of DRD, referred as DYT5a, is inherited as an autosomal dominant trait with reduced penetrance, caused by mutations in the *GCH1* gene (MIM 600225) coding for GTP cyclohydrolase I – GCH1 (MIM 600225), and distinguished from the recessive form DYT5b caused by mutations in the *TH* gene (MIM 191290) coding for tyrosine hydroxylase – TH (MIM 191290). Both enzymes are involved in L-dopa synthesis pathway [3]. Additionally homozygous and heterozygous mutations of the sepiapterine reductase coding gene – *SPR* (MIM 182125) were described in DRD cases with wide spectrum of severity course and early onset (MIM 612716) [4]. Generally in all those types of DRD the metabolism of

dopamine is markedly disturbed as a consequence of reduced synthesis and activity of TH.

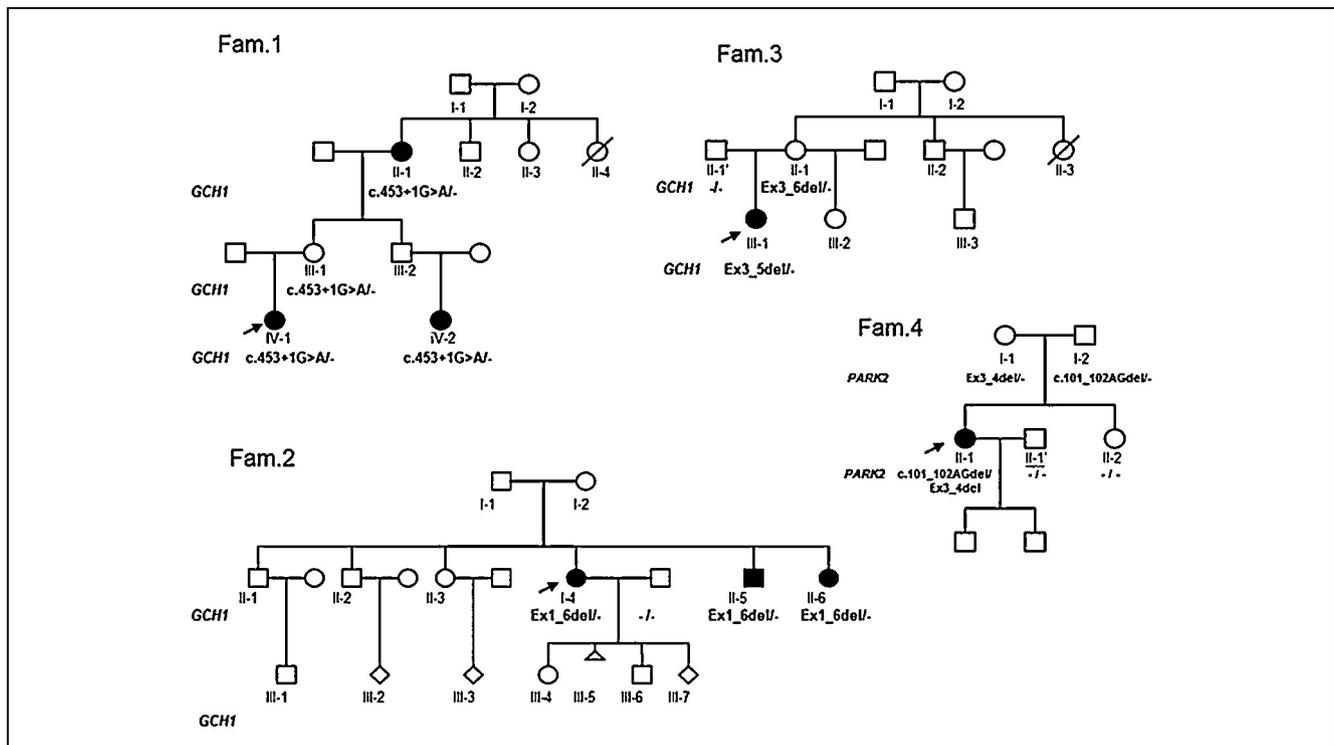
It is worth emphasizing that DRD, mainly of adolescent onset, may be associated with parkinsonism. In these cases differential diagnosis of early-onset Parkinson disease (EO-PD) (MIM 600116) due to the *PARK2* gene (MIM 600544) mutation should also be considered in a diagnostic algorithm.

Recent retrospective analysis of the published data on DRD (101 papers) [5] has indicated, that despite the well-known etiology of the disease and availability of genetic testing, there is still marked delay in its definitive diagnosis in many cases. In some patients lack of timely therapy may lead to residual motor or nonmotor signs (depression, anxiety, obsessive-compulsive disorder), and other complications, even if the proper treatment is finally introduced.

## 2. Materials and methods

### 2.1. Subjects

We present four families (Fig. 1) with progressive gait dysfunction due to lower limb dystonia occurring in childhood or adolescence with detailed clinical and neurological examination. One person, a specialist of movement disorders, in an academic high reference hospital, examined all patients. Additional diagnostic tests excluded secondary movement disorders including Wilson's disease (ceruloplasmine level), acanthocytosis and thyroid dysfunction in all of them. Their brain MR scans, EMG and basic laboratory measurements (biochemistry and morphology) were normal.



**Fig. 1 – Pedigree chart for the patients with dopa-responsive dystonia phenotype and their families with revealed mutations. □ indicates male, ○ represents female, ● or ■ denotes affected individuals, arrow indicates proband. A mutation beside □ or ○ denotes asymptomatic members.**

## 2.2. Methods (molecular analysis):

The molecular analysis of two genes, *GCH1* and *PARK2*, was performed for all probands, and an appropriate gene was analyzed in their relatives. Genomic DNA was extracted from venous blood using standard methods. Because sequence variants and exonic or whole gene deletion/duplications in both genes are known as pathogenic, two methods were used, the direct sequencing of all exons and exon/intron boundaries (intronic primers were used, sequence available on request) and Multiplex Ligation-dependent Probe Amplification (MLPA, SALSA MLPA Kit P051-B1/P052-C1 Parkinson; MRC Holland b.v.). Sequencing was the first step of the *GCH1* gene analysis, as sequence variants in this gene are identified in about 60% of DRD cases [6], while for the *PARK2* the frequency of both types of mutations is equal [7].

Sequence was analyzed using Mutation Surveyor® v.3.24 software (Softgenetics LLC) in comparison to the CGH1 and *PARK2* reference sequences NM\_018105 and NM\_004562.2 (NCBIRefSeq; <http://www.ncbi.nlm.nih.gov/nuccore>). The Gene Marker v.1.51 software (SoftGenetics LLC) was used to MLPA dosage ratio analysis (standard parameters, dosage ratio boundaries <0.75 and >1.25 for deletion and duplication respectively). The whole *GCH1* gene deletion and exonic deletion in the *PARK2* gene were confirmed by the array-comparative genomic hybridization (aCGH) using the chromosome 6 and 14 NimbleGen 385 Tiling Array HG18, NCBI 36 (Roche NimbleGen Inc.) respectively. Genome positions of the rearrangements were specified according to Human Mar.2006 (NCBI36/hg18) assembly [University of California, Santa Cruz Genome Browser, <http://genome.ucsc.edu>].

Mutations identified for probands were analyzed in their family members (Fig. 1): Fam.1 *GCH1* exon 2 sequencing (3 persons), Fam.2 MLPA P052 (5 persons), Fam.3 MLPA P052 (3 persons), Fam.4 *PARK2* exon 2 sequencing and MLPA P051/P052 (4 persons) and the whole gene analysis for the proband's partner.

All subjects signed the informed consent to perform appropriate molecular tests.

## 3. Results

### 3.1. Clinical characterization

Results of clinical and neurological testing and response to L-dopa treatment are presented in Table 1.

### 3.2. Molecular characterization

Molecular background of the DRD phenotype was confirmed in all families. In three probands the heterozygous mutations in the *GCH1* gene and in one the biallelic mutation in the *PARK2* gene were identified. Obtained results allowed to establish final diagnosis for all those families, as DYT5a in the cases of Fam.1, 2, 3 and EO-PD in Fam.4.

Family 1 (Fig. 1 and Table 1; Fam.1): The diagnosis of the DYT5a was established according to the *GCH1* gene sequencing results, which revealed the heterozygous substitution in position c.453+1G>A; proband's genotype c.[453+1G>A];[=],

p[?];[=]. This mutation has already been reported in DRD [8]. Identified substitution is located in the conservative donor splice site of intron 2 and is likely to result in the exon 2 skipping and frame shift mutation, followed by premature STOP codon generation, as suggested previously [9]. Proband's mother and maternal grandmother were also carriers of this mutation. However, their medical history and neurological examination data demonstrate incomplete penetrance of the mutation resulting in the intrafamilial variability of the disorder's clinical picture (Table 1).

Family 2 (Fig. 1 and Table 1; Fam.2): This family was also diagnosed as DYT5a but due to a partial deletion of the *GCH1* gene. The MLPA analysis performed for proband identified the deletion of exons 1, 2, 3, 5 and 6 (there is no probe for exon 4 in the P052 kit); proband's genotype c.[-360-?\_668+?del];[=], p[?];[=]. The aCGH analysis confirmed the deletion of 156 kb on one chromosome in locus 14q22, covering the whole *GCH1* and the part of the *WDHD1* gene (array14(54,376,281-54,532,230) × 1). The MLPA analysis revealed the same mutation in the proband's siblings.

Family 3 (Fig. 1 and Table 1; Fam.3): Sequencing of the proband's *GCH1* gene revealed no point mutations, but the deletion of exons 3 and 5 were identified with MLPA method suggesting loss in one allele of the gene minimal region of 14 kb covering exons 3, 4 and 5 – proband's genotype c.[454-?\_c.626+?del];[=], p.[?];[=]. MLPA performed in the proband's parents confirmed maternal inheritance of the mutation.

Family 4 (Fig. 1 and Table 1; Fam.4): The molecular analysis showed no mutation in the *GCH1* gene in this family excluding the DYT5a diagnosis. Two heterozygous, biallelic mutations were found in the *PARK2* gene, the dinucleotide AG deletion in the exon 2 and the deletion of exons 3–4 (c.172-?\_534+?del), what allowed diagnosing EO-PD in the proband. The deletion c.101\_102del creates a frameshift starting at codon Gln34 and STOP codon four positions downstream p.Gln34Argfs\*5; proband's genotype c.[101\_102del];[172-?\_534+?del], p.[Gln34Argfs\*5];[?]. Exons deletion identified by MLPA was confirmed by the aCGH analysis showing the deletion in one allele of 176 kb fragment covering whole exons 3 and 4 (array6(162,514,594-162,691,028) × 1). The *PARK2* gene analysis performed in the proband's parents confirmed biallelic character of mutations, other tested family members were not carriers of identified mutations.

## 4. Discussion

The presented four families, with progressive gait dysfunction due to lower limb dystonia occurring in childhood or adolescence and a good response to low doses of L-dopa, were clinically diagnosed with DRD. Results of the molecular analysis, however, brought on verification of this diagnosis. We identified among the probands mutations in the *GCH1* gene, what confirmed the DRD diagnosis – DYT5a, but also the mutations in the *PARK2* gene, what changed the diagnosis to EO-PD. The problem in distinguishing between those two forms of dopa-responsive disorders is not a new one and has already been raised and reported [1,10–12]. The question is, what kind of symptoms and signs might be important and helpful in better qualifications of the DRD

**Table 1 – Clinical characterization of the probands and their relatives from the presented families with DRD due to mutations in the GCH1 and PARK2 genes.**

Patients	Motor development	Age of onset [years]	Presenting symptom and main features	Neurological examination	Treatment	Other characteristic findings
<i>Fam.1 – CGH1 c.[453+1G&gt;A];[=], p.[?];[=]</i>						
IV-1	Normal, but never crawled	7	Gait difficulties, diurnal fluctuation with aggravation of symptoms toward the evening, she was not able to walk unsupported	Dystonic rotation of her left feet and abnormal posture of her trunk	Marked clinical improvement after 50 mg L-dopa + benzeraside	Dyskinesia after 100 mg L-dopa
II-1	Normal	Unknown-adolescence?	Fatigue, limb stiffness and gait difficulties	Bradykinesia with amimic face, forward bending of the trunk and hypokinesia observed during alternating movements of the both hands	Improvement after 100 mg L-dopa + benzeraside	No dyskinesia
IV-2	Normal	6	Gait difficulties	Dystonic rotation of her left feet	Symptoms withdraw after 50 mg L-dopa/day	Not seen
<i>Fam.2 – CGH1 c.[-360-?_668+?del];[=], p.[?];[=]</i>						
II-4	Normal	5	Gait difficulties – she was not able to walk unsupported and complained of fatigue	Not available at the onset, at the age of 19: dystonic rotation of her both feet and abnormal posture of her trunk, dystonic movements of the both upper limbs	Symptoms withdraw after 100 mg L-dopa	Not seen
II-5	ND	7	Gait difficulties	Not available at the onset	Symptoms withdraw after 100 mg L-dopa	Not seen
II-6	ND	7	Gait difficulties	Not available at the onset	Occasionally 100 mg L-dopa	Not seen
<i>Fam.3 CGH1 – c.[454-?_626+?del];[=], p.[?];[=]</i>						
III-1	Normal	5	Gait difficulties and fatigue	During neurological examination at the age of 10 she presented with left feet dystonic posture aggravated by the gait and dystonic rotation of her left hand	Marked improvement after 50 mg L-dopa + 12.5 mg benzeraside 3times daily	Not seen
<i>Fam.4 PARK2 – c.[102-102del];[172-?_534+?del], p.[Gln34Argfs*5];[?]</i>						
II-1	Normal	15	Gait difficulties and pain in lower limb, at the age of 22 she noticed progression of the symptoms and she started to fall down after long walk	During neurological examination at the age of 28 she presented with left feet dystonic posture aggravated by the gait	Improvement (with residual slight gait abnormalities) after 100 mg L-dopa + 25 mg benzeraside 3times daily	Not seen
ND – no data						

patients on the clinical level, and this is a subject we would like to discuss here.

In Fam.2 and 3, where partial and whole GCH1 gene deletions were identified, probands present with typical symptoms of DRD alleviated by low doses of L-dopa. Deletions in the GCH1 gene were previously identified as causative of a very similar phenotype as described in probands here [13]. However, among the mutation carriers, we observe the intrafamilial heterogeneity of the clinical picture, indicating its reduced penetrance, as it was previously described for DYT5a [10]. In Fam.3 the probands' mother being a carrier of

the mutation has been asymptomatic to date. In Fam.1, before molecular confirmation of DRD, a diagnosis of EO-PD was also considered as dyskinesias were observed after the initiation of the proband's treatment with L-dopa. Additionally the proband's grandmother (Fam.1 II-1) showed typical for PD motor symptoms such as bradykinesia, hypokinesia, amimic face and camptocormia.

Dyskinesias may be present in patients with GCH1-deficient DRD at the initiation of L-dopa therapy, especially if doses are relatively high or increased rapidly, but they subside after reducing the dosage and do not reappear with

later slow increment in dose [14,15]. However, it is known, that some *GCH1* mutations like in frame deletion in exon 1 c.235\_240delCTGAGC/p.Leu79\_Ser80del cause persistent treatment limiting dyskinesias, which may develop after few years of continuous L-dopa therapy [16]. Some patients may also present with DRD showing atypical symptoms such as hand tremor, spastic paraplegia, rigidity [11,12,15]. In previously published studies the mutation in the *GCH1* gene causing DRD-plus syndrome, parkinsonism has also been reported [17,18]. The presence of gait difficulties in adolescence (probably due to dystonia) and parkinsonism in adulthood, as we observed in subject II-1 in Fam.1 (proband's grandmother) revise the question of non-treated DRD late symptomatology. In a recent study 4 patients presenting with adult-onset parkinsonism, positive family history of DRD and the *GCH1* mutations were described. They fully met the UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical criteria, had imaging evidence of nigrostriatal dopaminergic denervation and were diagnosed as neurodegenerative PD. This implies that the *GCH1* gene mutations may be associated not only with the parkinsonian phenotype but also with an increased risk of PD, by 7-fold on average according to Mencacci et al. [19] Analysis of 576 cases [5] indicates that DRD first symptoms start more frequently in the lower limbs than in the upper limbs and neck in early-onset cases (0–14 years old), as compared with the late-onset cases (over 15 years old) where parkinsonism is more common.

Our study shows that the mutation of the *GCH1* gene may cause dystonia with L-dopa induced dyskinesia (Fam.1 IV-1), while the *PARK2* mutation (Fam.4 II-1) may present with dystonia but no parkinsonism or treatment related dyskinesia. Mutations we identified in Fam.4 proband may cause the classical phenotype of EO-PD not the DRD phenotype [7,20,21]. EO-PD is generally characterized by a good response to L-dopa and a rather benign course. Dystonia, hyperreflexia, and psychiatric features may be present, however, isolated leg dystonia as a presenting symptom has not been reported to date [22]. Mutations of the *PARK2* gene have been reported as causative for some *GCH1* mutation-negative DRD cases [11].

There are some differences between DRD and EO-PD that can be pointed out comparing the presented cases of four families. First, the families with genetically confirmed DRD (*DYT5a*) had very similar age of the disease onset in contrast to the patient with the *PARK2* mutation (proband's age onset 5–7 vs 15 years old). Diurnal fluctuation with aggravation of the symptoms toward the evening, one of the most characteristic feature of DRD, was very significant in the patient IV-1 Fam.1 and also present but less demonstrated by other patients with DRD unlike the patient II-1 Fam.4. The degree of fluctuation may differ among patients and attenuates with the disease progression [6]. In DRD families symptoms disappeared almost completely after starting the L-dopa therapy, while in EO-PD significant clinical improvement was observed but the patient experienced mild residual gait difficulties.

The linkage between DRD and EO-PD is still debated and further studies of these two conditions are needed. DRD patients show normal 18-fluorodopa (18F-dopa) uptake in the positron emission tomography (PET) [23] and in most cases normal dopamine transporter (DAT) imaging nigrostriatal neurons in the single photon emission computed tomography

(SPECT) [24], however, distinct reduction of DAT has been reported and is associated with nigrostriatal dopaminergic denervation [19,25,26]. This implies that mild parkinsonian symptoms, with an excellent response to low dosages of L-dopa and a reduced uptake in the [<sup>123</sup>I] FP-CIT-SPECT (DaTSCAN) may be more commonly seen in the *GCH1* mutation carriers than previously supposed. Neuropathological data in DRD are limited, however, it appears that in the substantia nigra there is a reduction of melanin pigment more pronounced in the lateral compared to the medial aspect, in a pattern similar to the neuronal loss in PD [27]. The difference is that there is no evidence of Lewy bodies in the substantia nigra in DRD [28]. However, there is no atrophy of dopaminergic and noradrenergic neurons in the nigra and the locus coeruleus.

Our cases indicate that the DRD phenotype can be caused by a point mutation or rearrangements in both, the *GCH1* and the *PARK2*, genes. Therefore genetic tests should be obligatory in the diagnostics of both DRD and EO-PD. Moreover, patients with parkinsonism, especially EO-PD, if mutations in known causative genes – *PARK2*, *DJ-1* and *PINK1* – are excluded, should be also tested for a genetic mutation characteristic for dystonia.

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### Conflict of interest

None declared.

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None declared.

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### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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