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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.

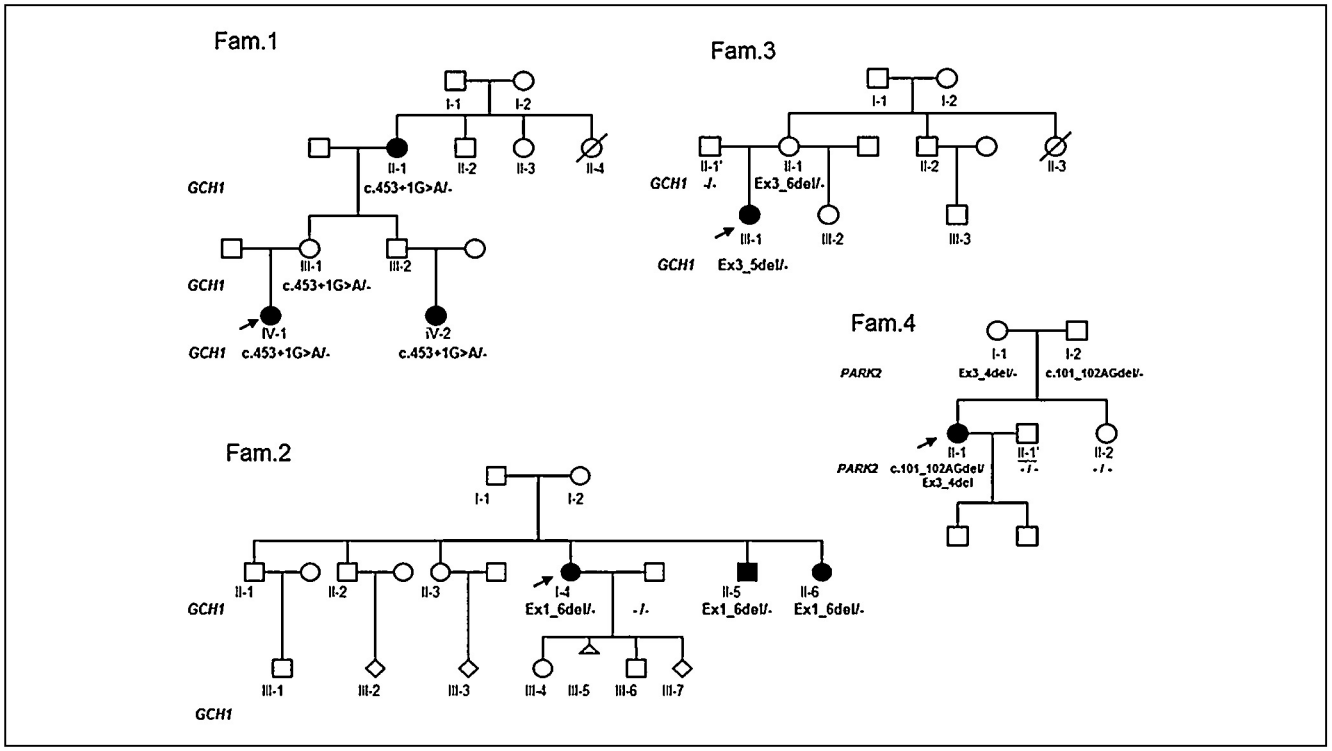

Fig. 1 – Pedigree chart for the patients with dopa-responsive dystonia phenotype and their families with revealed mutations. □ indicates male, ○ represents female, ● or ■ denotes affected individuals, arrow indicates proband. A mutation beside □ or ○ denotes symptomatic members.

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