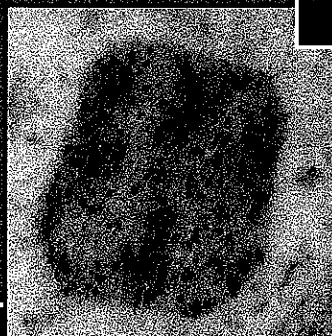
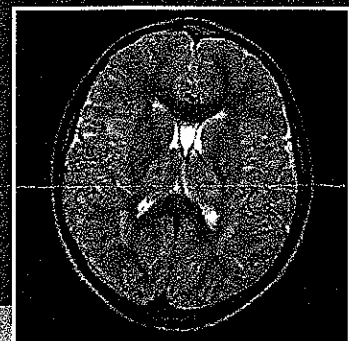


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Phenotype of five patients with dopa-responsive dystonia and mutations in *GCHI*

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Abstract. Autosomal dominant dystonia with diurnal variation, also known as DOPA-responsive dystonia (DRD, Segawa syndrome; MIM#128230), can be caused by mutations in the GTP cyclohydrolase I gene *GCHI* on chromosome 14q22.1-q22.2. Reports on patients with thoroughly characterized DRD phenotypes and *GCHI* mutations have disclosed marked phenotypic variability. Here, we report on five patients of two unrelated families with DRD and heterozygous nonsense (c.181G > T) or heterozygous splice site mutations (IVS5 + 3insT) of *GCHI*. Symptoms reported by these patients include gait abnormality, foot deformity, torticollis, muscle weakness, muscle cramps, myalgia, tremor, depression, and attention deficit. The severity of symptoms varied from mild involvement with good response to levodopa to severe dystonia with marked gait disturbances and only incomplete amelioration of symptoms upon levodopa treatment. The affected parent of each index patient had been misdiagnosed with a psychiatric and/or neurological disorder; the correct diagnosis was assigned only after the diagnosis of DRD had been established in their children. Our report adds further features to the phenotype of DRD caused by *GCHI* gene mutations.

Keywords: Dopa-responsive dystonia, Segawa syndrome, levodopa

1. Introduction

Dopa-responsive dystonia (DRD), also known as Segawa syndrome, is an autosomal dominant (MIM#

128230) or autosomal recessive (MIM#605407) inherited disorder with typical onset in the first decade of life [1–3]. Autosomal dominant DRD is caused by mutations of the GTP cyclohydrolase I gene *GCHI* on chromosome 14q22.1-q22.2 in about half of the patients [3,4]. A decrease in GCH activity causes a decrease in tetrahydrobiopterin (BH₄) levels, a subsequent decreased tyrosin hydroxylase (TH) activity, and eventually a selective nigrostriatal dopamine deficiency

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without neuronal loss [5,6].

Even though DRD is characterized by a significant phenotypic variation [7,8], dystonia typically starts in the lower limbs and then spreads to other regions of the body within several years [9]. The most common presenting symptom is therefore a gait disturbance due to a dystonic foot posture [9]. Typically, the muscle tone is increased, deep tendon reflexes are exaggerated, and plantar reflex is flexor, although striatal toe is common [1,4,9–11]. Parallel with the physiological change in TH activity, symptoms classically show a marked diurnal fluctuation with aggravation towards the evening in the early phase of the disease. Later, symptoms progress markedly until the disease becomes almost stationary at an age of about 30 to 40 years [9]. In older patients postural tremor and bradykinesia may develop. Also, sustained abnormal postures may result in contractures. Laboratory diagnosis is established by measurement of cerebrospinal fluid (CSF) neurotransmitter metabolites, pterins, and enzyme activity in cultured fibroblasts [12]. Moreover, an analysis of *GCHI* may confirm the clinical diagnosis of autosomal dominant DRD [13].

Here, we report on five patients of two unrelated families with DRD and thereby add further features to the phenotype of DRD caused by *GCHI* mutations demonstrating the remarkable phenotypic variation of this disease.

2. Case reports

We studied five patients of two unrelated non-consanguineous families of German descent after written informed consent (Fig. 1). The patients reported a clinical onset of dystonia in the first decade of life, and the diagnosis of DRD was established on the basis of clinical, biochemical, and genetic criteria. All pediatric patients were successfully treated with levodopa 2–4 mg/kg/day, and their symptomatic adult relatives received a dosage of 200–300 mg/day. Prior to the beginning of carbidopa-levodopa therapy, neurophysiological studies, cranial and spinal magnetic resonance imaging, catecholamine and catecholamine metabolite measurement in urine, serum, and cerebrospinal fluid specimen were performed.

Index patient III: 4 of family 1 presented at the age of 14 years with progressive painful muscle cramps in his calves and intermittent spontaneous dorsal extension of his right great toe (Figs 1a and 2a). He exhibited a striatal toe and slightly decreased muscle strength in com-

ination with hyperreflexia of his lower extremities. His 38-year old father (patient II: 5; Fig. 1a) suffered from a gait disturbance with frequent tripping since the age of 8 years, muscle cramps, and an increased muscle tone predominantly of his lower extremities. He also reported a continuous tremor of his hands and a short attention span. Due to the nature of his symptoms, he had been treated with psychotherapy and regular oral anti-depressant medication. On examination, he showed a striatal toe and hyperreflexia of his lower extremities. Electromyography (EMG) at the age of 14 years was normal without spontaneous activity or myotonic runs. The paternal aunt of the index patient (patient II: 8, Fig. 1a) suffered from muscle stiffening, most prominently of her neck muscles, intermittent abnormal postures and movements of the head (torticollis), difficulties walking, and tremor of her hands. In all three patients, symptoms worsened upon exertion and during the course of the day.

The diagnosis of DRD was established in the index patient on account of his symptoms, physical examination, biochemical analyses, and good response to levodopa therapy. 5-hydroxyindole acetic acid (5-HIAA), homovanillic acid (HVA), neopterin, and biopterin were significantly reduced in a single CSF sample (Table 1), while the urine excretion of 5-HIAA and HVA as well as the phenylalanine provocation test were normal (data not shown). A study of *GCHI* activity in fibroblasts of affected family members showed a decreased activity to 8–13% of controls. In all three patients a nonsense mutation at position 181 of exon 1 of the *GCHI* gene (c.181G > T) was identified. This mutation introduces a stop codon at position 61 of the amino acid sequence (E61X) and thereby causes a truncated *GCHI* protein with a decreased activity.

The administration of levodopa/carbidopa resulted in a prompt alleviation of muscle cramps and dorsal extension of the great toe in the index patient; his father became asymptomatic after a period of 6 months of treatment. However, the latter developed a severe depression 12 months following the initiation of therapy, potentially a side effect of this therapy, albeit depression has been reported as a symptom of DRD. Minor cervical dystonia and torticollis persisted in the paternal aunt despite the application of levodopa/carbidopa.

Index patient III: 5 of family 2 presented at the age of 10 years (Figs 1b and 2b) with a movement disorder that had started at the age of 4 years with tiptoe walking. Since the age of 7 years, her parents noticed a rapid deterioration of her gait with a progressive painful foot deformity and decreased strength of her

Table 1
Neurotransmitter metabolites in the initial diagnostic cerebrospinal fluid (CSF) analysis of two index patients with GCHI DRD

	5-HIAA (N: 101–237 nmol/L)	HVA (N: 285–560 nmol/L)	Neopterin (N: 9–20 nmol/L)	Biopterine (N: 10–30 nmol/L)	BH ₄ (N: 20–49 nmol/L)
Family 1					
Patient II: 8	52 ↓	138 ↓	4 ↓	6 ↓	16 ↓
Family 2					
Patient III: 5	144	308	5 ↓	1 ↓	18 ↓

5-HIAA: 5-hydroxyindole acetic acid; HVA: Homovanillic acid; BH₄: Tetrahydrobiopterine.

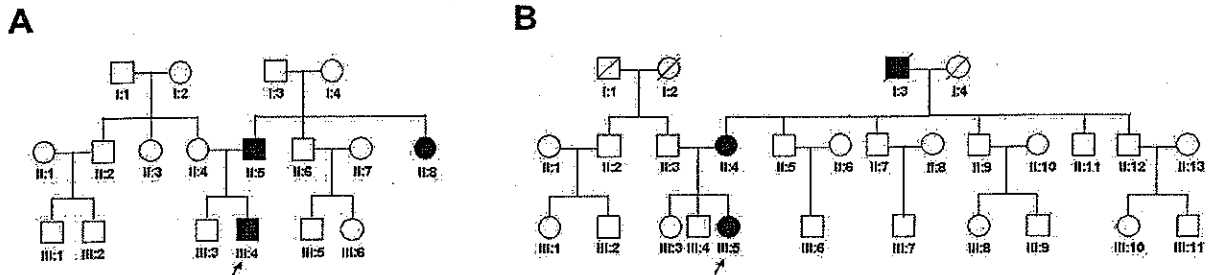


Fig. 1. Pedigrees of two families with autosomal dominant dopa-responsive dystonia and mutations of GCHI. Arrows indicate the index patient of family 1 (a) and family 2 (b).

lower extremities. She could no longer ride her bicycle, showed marked exhaustion upon walking merely short distances of about 100 feet on even ground or climbing stairs with support. At the end of a day, she walked backwards for relief. On examination, the patient exhibited an unsteady gait on account of severe bilateral pes adductus (Figs 1b and 2b) and contractures of both ankle joints. Muscle tone was slightly and reflexes significantly increased in her lower extremities, while the muscle strength of her dorsal extensors was decreased. Her 44-year-old mother (patient II: 4; Fig. 1b) had been diagnosed with cerebral palsy early in childhood and treated with baclofen for many years. She experienced a progression of symptoms with age and during the course of the day. Walking on even ground for more than 1–2 miles lead to increased muscle stiffness of her lower extremities. On examination, she showed a rigid gait easily confused with spasticity [1,11], increased muscle tone, and hyperreflexia especially of her lower extremities. Plantar reflex was flexor, without striatal toe.

In the second index patient, muscle ultrasound revealed a diffuse increase in echogenicity and fasciculations. A single CSF examination demonstrated a significant reduction of 5-HIAA, HVA, neopterin, and biopterin, while BH₄ was only slightly decreased in the CSF (Table 1). The urine excretion of neopterin and biopterin was decreased, her serum dihydropteridine reductase activity was normal (data not shown). Genetic analysis revealed an insertion of thymine at

position +3 of intron 5 (IVS5 + 3insT) of *GCHI* of both patients but not in controls. This mutation affects a splice site and can thereby cause exon skipping and thus a shift of the reading frame that result in a truncated protein [10].

Both the index patient and her mother showed a rapid improvement of their symptoms following the initiation of levodopa/carbidopa therapy. The index patient was able to go on an extended walk after her first dose of levodopa/carbidopa; her foot deformity had almost diminished six months later, and she had taken up regular physical exercise again. By that time, her mother showed a marked decrease of rigidity. Both patients were able to walk on even ground without any restrictions and have been asymptomatic on regular levodopa medication over a period of 1 year.

3. Discussion

We report on the phenotype of five patients of two unrelated families with DRD and two different heterozygous mutations within the *GCHI* gene. Among patients sharing the same heterozygous mutation, there was considerable variability of presenting symptoms, pattern of dystonia, disease progression, and response to therapy; asymptomatic family members were not screened for the mutation. Although the range of symptoms and severity even within one family was broad, all affected individuals exhibited a childhood onset of

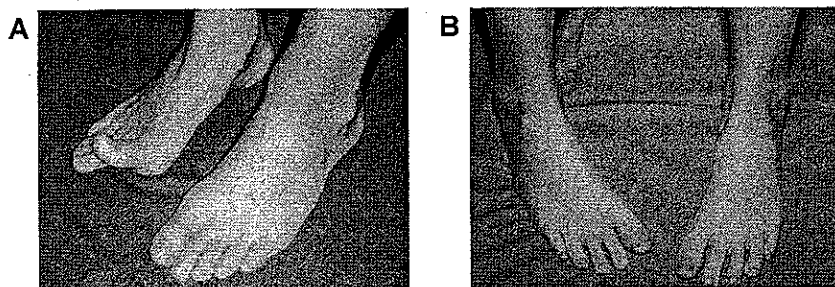


Fig. 2. Patients with *GCHI* dopa-responsive dystonia. (a) Index patient III: 4 of family 1 exhibited a striatal toe prior to therapy with levodopa/carbidopa. Note the prominent tibialis anterior tendon. (b) Index patient III:5 of family 2 had bilateral pes adductus prior to therapy with levodopa/carbidopa.

symptoms. In DRD, symptoms typically commence in the first decade of life, though late-onset has been reported [14–16]. The slightly earlier onset of symptoms progression, in particular in index patient III: 5, who nearly lost ambulation within a few years following the onset of symptoms. In family 1, the residual *GCHI* activity in fibroblasts was especially low in the paternal aunt who also exhibited the most severe phenotype and the least improvement of symptoms upon therapy with levodopa. This finding corresponds to that of previous studies that demonstrated a lower *GCHI* base level in females compared to men [3]. Whether the onset of symptoms at the beginning of the second decade in the male index patient of family 1 correlates with a higher *GCHI*-base level remains elusive. In general, there is a predominance of affected female DRD-patients with a penetrance of *GCHI* gene mutations that is 2.3 times higher than in men [17]. Sex-influenced differences in dopamine uptake or in components of the BH4 pathway have been accused to influence symptom manifestation [18,19], but the exact pathomechanism remains to be deciphered.

Correlations between heterozygous mutations of the *GCHI* gene and the highly variable phenotypes cannot be established. Moreover, the inter- and intrafamilial phenotypic variability explains the assignment of DRD symptoms to false diagnoses. The affected parent of each index patient had been diagnosed with an incorrect psychiatric and/or neurological disorder, a misdiagnosis with far-reaching consequences, including physical handicap, pain, psychological impact, and long-term therapies including physical therapy, psychiatric therapy, and medication with an antidepressant or baclofen.

In conclusion, neuropaediatricians should be encouraged to include DRD into their work-up of a patient with unclear neurological symptoms particularly with regard to gait abnormalities, foot deformities, and myalgia.

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