

Dopa-Responsive Dystonia and Tourette Syndrome in a Large Danish Family

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Background: Guanosine triphosphate cyclohydrolase I (GTPCH) catalyzes the first step in the synthesis of tetrahydrobiopterin (BH₄). Autosomal dominantly inherited defects in the GTPCH gene (*GCHI*) cause a form of dystonia that is responsive to treatment with levodopa (dopa-responsive dystonia [DRD]).

Objective: To investigate molecular and clinical aspects of DRD in a large Danish family.

Methods: For analysis of the *GCHI* gene, a mutation-scanning method based on denaturing gradient gel electrophoresis (DGGE) was used. A novel mutation, X251R, was identified in the *GCHI* gene of 2 distantly related Danish patients with DRD, one of whom also had Tourette syndrome (TS). Thirty-five additional family members were investigated for this mutation, and 16 of them underwent clinical neurological examination.

Results: A total of 18 patients were heterozygous for the X251R allele, 16 of whom had neurological complaints spanning from very mild parkinsonism to severe invalidism due to dystonia. Of 13 symptomatic heterozygotes who had been neurologically examined, 10 had signs of dystonia or parkinsonism. Sixteen of the heterozygotes were treated with levodopa, and 13 reported a treatment benefit. Three of the symptomatic heterozygotes had signs of TS.

Conclusions: This study confirms the large variability in DRD symptoms and emphasizes the usefulness of molecular analysis for diagnosis and treatment of DRD. The presence of TS is suggested to be coincidental, though the development of TS-like symptoms due to mutations in *GCHI* cannot be excluded.

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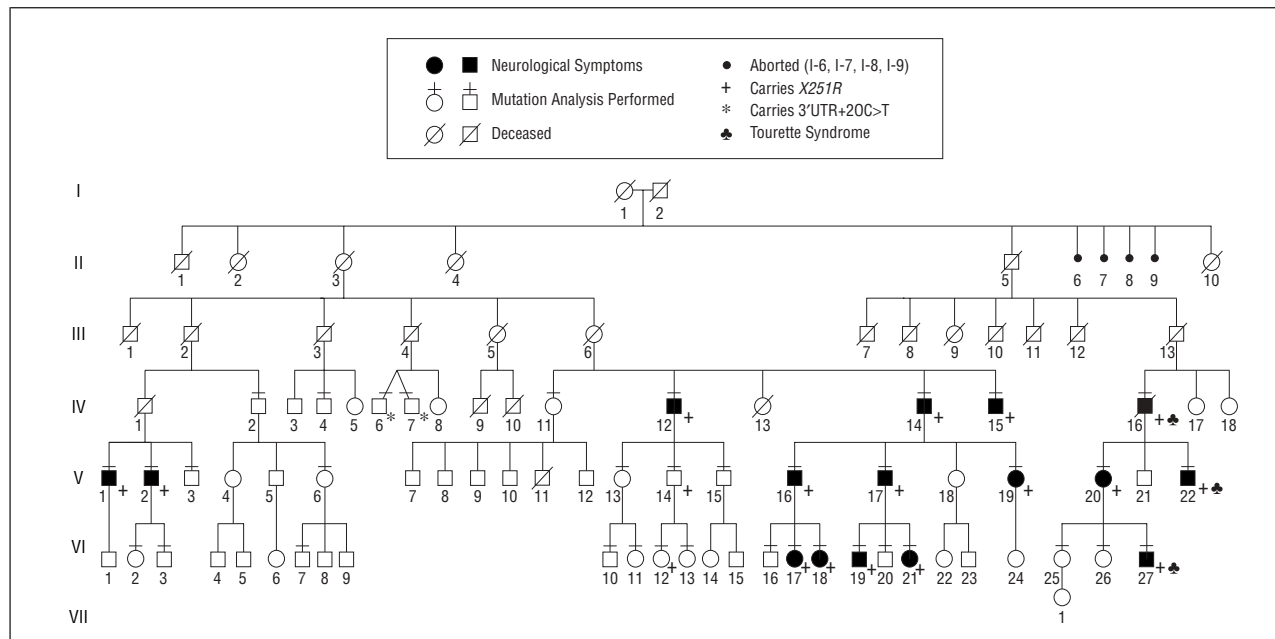
GUANOSINE TRIPHOSPHATE (GTP) cyclohydrolase I (GTPCH; E,C,3,5,4,16) catalyzes the conversion of GTP to 7,8-dihydroneopterin triphosphate (H₂NTP). This is the first step in the synthesis of tetrahydrobiopterin (BH₄), which is the cofactor of the 3 aromatic amino acid hydroxylases (phenylalanine hydroxylase, tyrosine hydroxylase [TH], and tryptophan hydroxylase) as well as glycerol ether monooxygenase and nitric oxide synthase.¹

Defects in the GTPCH enzyme can cause dopa-responsive dystonia (DRD), also called hereditary progressive dystonia with marked diurnal fluctuation (HPD) or Segawa syndrome (OMIM 128230).^{2,3} Dystonia is a movement disorder characterized by sustained muscle contractions, frequently causing involuntary, repetitive twisting movements that can be focal, multifocal, segmental, or generalized.⁴ Dystonia may be primary, as in DRD,

or secondary when it is part of a neurological syndrome or caused by external factors. Dopa-responsive dystonia is characterized by the onset of dystonia in early childhood or adolescence, and by the concurrent or subsequent development of parkinsonian signs and an excellent response to small doses of levodopa.³ The disease is characterized by a greater presence in female patients than in males (4.3:1).⁵ The increasing number of reported DRD cases has broadened the classic clinical description to include cases presenting as cerebral palsy, focal dystonia, parkinsonism, and hypotonia.⁶⁻⁹

Dopa-responsive dystonia is mainly inherited in an autosomal dominant fashion, but reports of recessively inherited DRD have also appeared.^{10,11} At present, more than 70 different disease-causing mutations in the *GCHI* gene have been described and are listed in the database of mutations causing BH₄ deficiencies (BIOMDB).¹² This study describes *GCHI* mutation findings and clinical manifesta-

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Pedigree of a Danish family with dopa-responsive dystonia and Tourette syndrome.

tions in a large Danish family with DRD and Tourette syndrome (TS).

METHODS

PATIENTS

DNA was extracted from 10 mL of EDTA-anticoagulated blood from a total of 37 subjects belonging to a family with DRD. The **Figure** presents a pedigree of this family. The procedures used were in accordance with the current revision of the Helsinki Declaration of 1975. Two patients, VI-17 and VI-27, were referred independently for molecular analysis of the *GCHI* gene on the basis of a classic DRD picture; dystonia in the legs (onset before 10 years of age); and almost total resolution of symptoms in response to treatment with levodopa. The novel mutation, X251R, in exon 6 of the *GCHI* gene (c.899T>C; NCBI GenBank accession No. NM_000161) was identified in both subjects. Subsequently, the X251R mutation was tested in 35 additional family members. All of these were interviewed, and 18 underwent careful neurological examination.

Tourette syndrome was diagnosed in VI-27 and his uncle (V-22) and was anecdotally suspected in his grandfather (IV-16). These 3 patients were also clinically diagnosed with DRD before genetic analysis.

MUTATION ANALYSIS

The mutation scanning method used in this study used the polymerase chain reaction method in combination with denaturing gradient gel electrophoresis (DGGE) for scanning of the 6 coding regions of the *GCHI* gene, followed by direct sequencing to identify the mutation. This method is described in detail elsewhere (A. Romstad, S. Kalkanoglu, J. vanHove, et al, unpublished data, 2002 [in preparation]). For analysis of the 35 additional family members, DGGE analysis or direct sequencing of *GCHI* exon 6 was performed.

RESULTS

Analysis of this large family with DRD and TS was initiated when the same novel *GCHI* mutation, X251R, was found in 2 patients (VI-17 and VI-27) who were originally thought to be unrelated. This mutation is predicted to elongate the GTPCH amino acid chain with 34 additional amino acids. Prior to the identification of X251R, the diagnosis of DRD was highly suspected in both patients on the basis of clinical signs and symptoms and a family history of dystonia. The identification of X251R in both patients and some of their close relatives suggested that they were related, which was confirmed by genealogical studies of the family across 7 generations (Figure). The pedigree presents all X251R heterozygotes and all neurologically affected family members. In total, the screening of 37 individuals revealed the presence of X251R in 18 of the cases. On the basis of genealogical data (Figure), II-3, II-5, III-2, III-6, III-13 and IV-1 could be assigned as obligate heterozygotes for X251R. Analysis of exon 6 and a part of the 3' untranslated region (3'UTR) of the *GCHI* gene revealed an additional sequence variant, 3'UTR+20C>T (c.921C>T; NCBI GenBank accession No. NM_000161), in 2 asymptomatic family members (IV-6 and IV-7; twins), who did not carry the X251R allele. The X251R and 3'UTR+20C>T variants were not identified among 100 control chromosomes.

The X251R allele cosegregated with neurological symptoms and signs in 16 of the 18 heterozygotes. **Table 1** and **Table 2** list the clinical manifestations. These 16 symptomatic heterozygotes (11 males and 5 females) had neurological difficulties varying from very mild symptoms (tired legs after gait) to severe invalidism, requiring the use of a wheelchair. They were all interviewed, and 13

Table 1. Clinical Manifestations in Heterozygotes for the X251R Allele in *GCH1*

Subject/Birth Year/Sex, M/F	Symptoms	Signs	Age at Onset of Symptoms, y	Treatment With Levodopa
IV-12/1924/M	Stiffness and pain in the legs after exercise and gait	Mild parkinsonism	65	Good response
IV-14/1928/M	Heavy and painful legs after gait	Mild parkinsonism	10	Good response
IV-15/1931/M	Stiffness and pain in the legs after gait and dance	Only interviewed	15	No response
IV-16/1932/M	Gait disturbances followed by dystonic movements of arms, neck, and shoulders; anecdotally Tourette syndrome in childhood; died 1999	Parkinsonism	6	Good response
V-1/1943/M	Easily tired muscles with pain after gait and bicycling uphill	Only interviewed	10	No response
V-2/1950/M	Muscular stiffness and pain in legs after handball playing and gait	Mild parkinsonism	41	Good response
V-14/1954/M	None	Only interviewed	NA	Treated for 2 months without any subjective changes
V-16/1955/M	Mild motor clumsiness in legs during childhood; very heavy legs after training	Mild parkinsonism and dystonia	6	Good response
V-17/1958/M	Mild gait disturbance for many years	Mild parkinsonism	15	Good response
V-19/1963/F	Was a slow runner in childhood; pain in leg muscles after exercise	Only interviewed	10	No due to pregnancy
V-20/1957/F	Pain in leg muscles after exercise	No signs	10	Good response
V-22/1962/M	Intermittent gait disturbances; symptoms worsening upon exercise; Tourette syndrome since age 6 years	Parkinsonism and dystonia	2.5	Good response
VI-12/1984/F	None	Only interviewed	NA	No
VI-17/1985/F	Initially dystonia in the legs causing walking difficulties; developing into severe walking difficulties	Dystonia	9	Good response
VI-18/1996/F	Stiffness of legs and tired in legs after walking	No signs	5	Good response
VI-19/1984/M	Has been a "slow runner" since childhood; some tendency to writing dystonia	Mild parkinsonism	6	Good response
VI-21/1990/F	Easily tired legs with dystonic tension after gait	No signs	8	Good response
VI-27/1992/M	Dystonia in the legs; walking difficulties; Tourette syndrome	Dystonia	3	Good response

Abbreviation: NA, not applicable.

Table 2. Signs Observed in the Heterozygotes

Parkinsonian Signs	Subjects
Loss of facial expression	IV-12, IV-16
Muscle rigidity	IV-14, IV-16, V-16, V-22, VI-19
Glabella tap phenomenon	IV-12, IV-14, V-2, V-17
Bradykinesia	IV-16
Dystonia and others	
Wheelchair bound	IV-16, VI-17
Writing cramps/dystonia	V-2, V-17, VI-19
Clumsiness of fine motor function	V-20
Severe gait disturbances	IV-16, V-22, VI-17
Dystonic equinovarus	V-16, VI-17
Severe dystonic movements of upper trunk, left arm, neck, and shoulder	V-22

were clinically examined, either by the neurologist (E.D.) or the pediatrician (B.K.). Fifteen of the 16 symptomatic heterozygotes were treated with levodopa, either prior to or after the genetic diagnosis, and 13 reported a reduction in motor difficulties from this treatment. One of the 2 asymptomatic heterozygotes (V-14) also requested treatment with levodopa but did not report any neurological changes during a 2-month treatment period.

The X251R mutation was observed to cosegregate not only with DRD but also with TS in 3 generations of

the family (Figure). The grandfather (IV-16) died in 1999, prior to further confirmation of the TS diagnosis, which included a history of involuntary movements of the head and limbs. In VI-27, motor and vocal tics led to the diagnosis of TS at age 6 years and treatment with pimo- zide was initiated. This treatment decreased the number of tics but worsened the dystonic symptoms, which had been observed with diurnal variations from age 3 years. At the same time, a "zombie-like" or parkinsonian appearance was noticed. As a consequence, treatment with levodopa was initiated, and the symptoms of dystonia and/or bradykinesia improved. At age 8 years, treat- ment with pimo- zide was discontinued, which did not lead to a worsening of TS symptoms. In V-22, the TS symp- toms initiated at age 4 years and included tics of the neck and limbs, together with vocal tics and temper out- bursts. The patient was never treated for TS, but treat- ment with levodopa reduced the tics in neck and limbs to a certain degree, whereas stereotypies such as hand clapping were somewhat increased. The vocal tics and feelings of restlessness were unchanged.

COMMENT

The purpose of this study was to determine the pres- ence of a mutant *GCH1* allele in a family with DRD in order to suggest treatment with levodopa in neurologi- cally affected subjects. A total of 37 family members were

examined—18 were found to be heterozygous for the X251R mutation, and 16 of these were symptomatic. The pathogenicity of X251R with respect to DRD was strongly supported by the fact that it cosegregated with recognized dystonia in 16 of 18 heterozygotes and was not present among 100 control chromosomes. Fifteen of the 16 symptomatic heterozygotes underwent treatment with levodopa in daily doses of as much as 150 mg, which had a beneficial effect in all but 2 cases. Although a lack of effect from treatment with levodopa is not typical in DRD, these 2 cases showed a high degree of resemblance to a previously described patient.⁸ The lack of response is possibly explained by the subtle symptoms in combination with the subjective evaluation of both symptoms and response to treatment.

A high variation in penetrance is characteristic of DRD and was also observed in this study, as some heterozygotes did not report any symptoms, some had slight parkinsonian symptoms and signs, while others were severely affected with dystonia. Studies have indicated a possible correlation between the severity of symptoms and the mutant-normal ratio of *GCHI* messenger RNA,¹³⁻¹⁵ although the factor(s) determining this ratio are unknown. Alternative suggestions may explain the variations in phenotype. First, the expression of GTPCH is stimulated by cytokines as interferon- γ and nerve growth factor, probably in a cyclic adenosine monophosphate-dependent manner.¹⁶⁻¹⁸ Nerve growth factor plays an important role in neural development and levels of it have been found to be elevated in certain patient groups (ie, patients with Down syndrome).¹⁹ Individual differences in the levels of cytokines, as with nerve growth factor, could possibly influence GTPCH expression and contribute to the variation in phenotype. However, such differences in expression may be subtle and localized, as bipterin concentrations in the cerebrospinal fluid of symptomatic and asymptomatic heterozygotes are not significantly different.²⁰ Second, BH₄ was recently found to be important for the stability of the TH protein in striatum and at the sympathetic nerve terminals.²¹ Interindividual variations in TH protein levels, as observed among normal controls,²² could possibly contribute to the differences in age of onset and possibly also to the severity of symptoms. Third, the influence of modifier genes may play an important role in the clinical outcome of DRD, as has been suggested in other inherited disorders such as cystic fibrosis.²³ Potential modifier-gene candidates may include the highly polymorphic dopamine receptors, which have been extensively studied, especially with regard to linkage to psychiatric disorders.²⁴ Notably, a missense mutation in dopamine receptor D2 (DRD2) was associated with myoclonus dystonia, supporting the possible role of DRD2 in dystonia.²⁵ Some studies of polymorphic variants in DRD3 and DRD4 have shown a significant association with the response to clozapine, a dopamine receptor antagonist, suggesting that DRD3 and DRD4 may also be involved in the variable phenotypes of DRD.^{26,27}

Dopa-responsive dystonia is normally characterized by a higher penetrance of symptoms in females as compared with males,⁵ which possibly relates to a higher activity of GTPCH in males as compared with females,²⁸ or to the hormonally influenced differences in vulner-

ability to decreased levels of dopamine.²⁹ In this family, 5 of 6 mutation-positive females and 11 of 12 mutation-positive males were affected, corresponding to a sex penetrance of 83% for females and 92% for males, which is not significantly different. Furthermore, female patients were not more severely affected than males. If unknown sex-influenced mechanisms affect the pathogenicity of mutations in the *GCHI* gene, this does not seem to be the case for X251R mutation.

Three members of the family (one of the index patients, his uncle, and his grandfather) had a diagnosis of TS that cosegregated with DRD and the *GCHI* X251R allele. Tourette syndrome is frequently associated with attention-deficit disorder, attention-deficit/hyperactivity disorder, obsessive-compulsive behaviors, anxiety disorders and panic attacks, learning disabilities, and drug abuse,³⁰ but it has not been associated with defects in the *GCHI* gene. In TS, treatment strategies, biochemical findings, and linkage studies have implicated the serotonergic, dopaminergic, and noradrenergic systems in the pathogenesis, indicating that TS is a polygenic disorder and is probably much more complex than DRD.^{30,31} Originally, TS was suggested to be associated with a hyperactivity of dopamine on the basis of the successful use of neuroleptics (DRD2 antagonists) for treatment, neuropathological studies showing an increased striatal dopamine transporter binding in patients with TS,³² and an increased and significant correlation between caudate DRD2 binding and TS severity.³³ However, the complex pathogenesis of TS was indicated by reports of a beneficial outcome of treatment with a dopamine agonist, pergolide,³⁴ and by the improvement of tics upon acute doses of levodopa.³⁵ These contradictory observations, with regard to dopamine, are in line with the findings in this study, where treatment with levodopa did not cause changes in tic frequency or type in subject VI-27, whereas a slight worsening of motor tics was observed in subject V-22. In addition, discontinuation of treatment with a DRD antagonist in subject VI-27 did not lead to a worsening of tics, which was probably owing to the continuous treatment with levodopa. The inconsistent response of TS to levodopa does not allow any conclusion regarding the possible role of *GCHI* mutations in the pathogenesis of TS. The fact that TS only occurred in one branch of the family may speak in favor of 2 different genetic components. Alternatively, and in agreement with a recent study showing bilineal transmission of TS,³⁶ a second genetic component may be segregating in this branch of the family, which is required for expression of the TS phenotype in *GCHI* heterozygotes.

In summary, we examined a large Danish family with DRD and TS. Our study further documents the wide range of neurological features in individuals with identical mutations in the *GCHI* gene.

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