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Mutation in 5'upstream region of *GCH*I gene causes familial dopa-responsive dystonia

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Dopa-responsive dystonia (DRD) is commonly caused by heterozygous mutations in the guanosine triphosphate (GTP) cyclohydrolase I gene (*GCH*1) [1]. In the 5' upstream region, 3 different mutations have been identified in 2 subjects with DRD [2,3]. One subject had 2 mutations, -39C>T and -132C>T and another had a single mutation, -22 C>T, with no data available on first-degree relatives [2, 3]. We report on multiple generations of one family with DRD, in whom the -22 C>T mutation segregates with affected status.

One family of Irish/French-Canadian ethnicity was studied. Ten family members, spanning 3 generations, underwent a neurologic exam and provided blood samples. The local institutional review board approved the study. All participants gave informed consent.

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The criterion for definite DRD was definite dystonia and a marked, sustained response to levodopa or dopamine agonist [4]. The criterion for probable DRD was definite dystonia in a subject who declined a trial of medication. A movement disorders neurologist (NS) determined the diagnosis and affected sites as described [5]. Establishment of dystonia status was made prior to genetic testing, which was done blind to clinical designation.

The full *GCH*I gene (exons 1 -6) was analyzed by bi-directional sequencing from genomic DNA from every subject. Control samples, consisting of 46 European Caucasian samples from the CEPH collection and 7 from the discarded sample collection of the Massachusetts General Hospital Neurogenetics DNA Diagnostic Lab, were utilized.

Six subjects had dystonia (III-2, III-4, IV-2, IV-5, V-2 and V-3). Four were receiving medical treatment (III-2, III-4, IV-5 and V-2). All six affected subjects experienced onset in a foot or leg during childhood. Two displayed involvement of a non-contiguous body region; the neck and right leg in subject III-2 and the neck, right leg and left hand in subject V-2. Duration of disease varied, from one year (V-3) to fifty-four years (III-2). Subject V-2, with the greatest spread in symptoms, had DRD for twelve years. Subject III-4 did not display any progression, with dystonia remaining in the right foot, and had DRD for fifty-three years. Of the affected subjects, three demonstrated a good response to relatively low therapeutic doses of carbidopa/levodopa (III-2, III-4, V-2). IV-5 became nauseous on carbidopa/levodopa but displayed a good response to a relatively low therapeutic dose of ropinirole. Subject IV-2 had taken carbidopa/levodopa in the past and saw improvement, but discontinued medication based on personal preference. Subject V-3 had relatively mild symptoms and declined medical treatment. Thus, V-3 was classified as probable DRD and the other affected subjects (III-2, III-4, IV-2, IV-5, V-2) were classified as definite DRD.

We demonstrate that the -22 C>T mutation in the *GCH*1 gene segregates with affected status in multiple generations of a single DRD family. This mutation was not found in 53 control samples (106 normal alleles), nor in 214 clinical samples (428 alleles), about which we have no phenotypic information, that have been sequenced in the MGH Neurogenetics DNA Diagnostic Laboratory. This makes it likely that the -22 C>T mutation is pathogenic and results in DRD.

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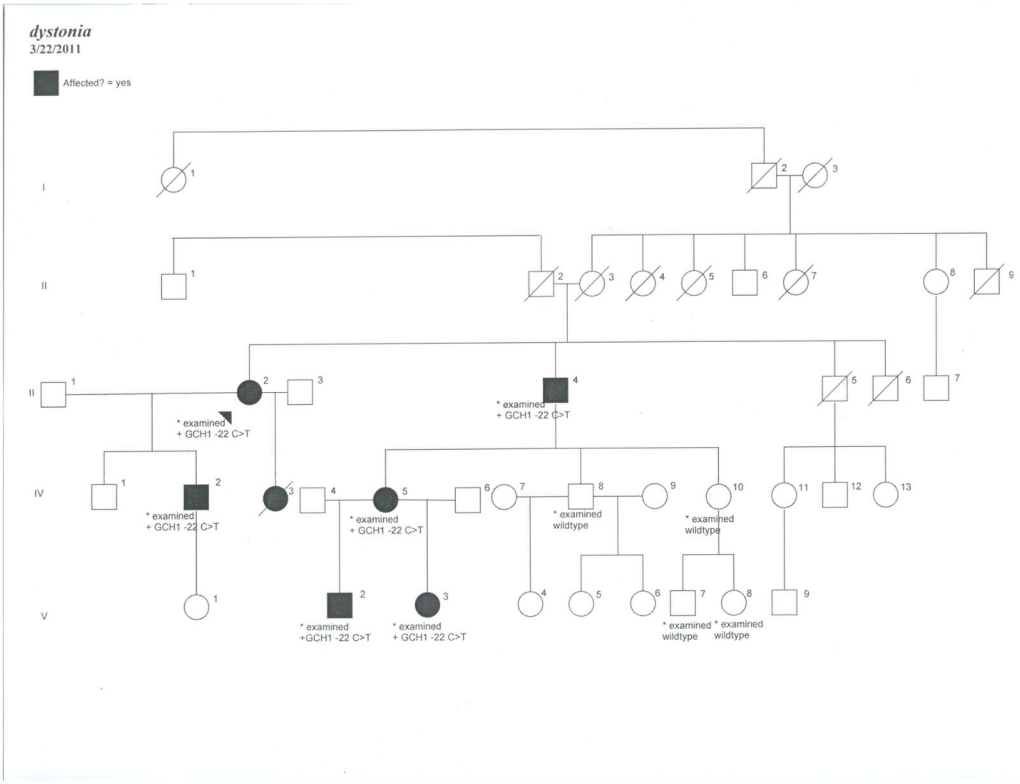

Figure 1. Pedigree

Arrow identifies proband. Shaded symbols represent those with dopa-responsive dystonia. Clear symbols indicate unaffected individuals. Asterisk (*) identifies those who underwent an exam and provided DNA. The (+) are those with the mutation and‘wildtype’ are those without the mutation.