Letter to the Editor

Phenotypic heterogeneity and full penetrance in a family with dopa-responsive dystonia

To the Editor:

Dopa-responsive dystonia (DRD) is a dystonia-plus syndrome characterized by a diurnal fluctuation and excellent sustained response to low-doses of levodopa. DRD usually presents with limb dystonia, most often in lower limbs, which progresses to generalized dystonia (1). Anxiety, depression, obsessive–compulsive disorders, and sleep disturbances are also seen in DRD (2). Classical autosomal dominant DRD is due to mutations within the GTP cyclohydrolase 1 (GCH1) gene while rare forms of recessive DRD are caused by either tyrosine hydroxylase (TH) or sepiapterin reductase mutations (2). We here reported on a large Iranian family of Kurdish ancestry with a dominant and phenotypically heterogeneous form of DRD (Fig. 1). The local ethics committee approved this study and informed consent was obtained from all participants. All patients’ clinical data are summarized in Table 1. Six patients presented with classic DRD, with early-onset foot and leg dystonia that rapidly progressed to generalized disabling dystonia. Some of these patients also reported retrocollis, writer’s cramp, oromandibular, and truncal dystonia. Two patients presented with postural hand tremor that progressed to cervical dystonia in one and leg dystonia in the other. Postural hand tremor was later seen in most patients while leg tremor was seen in just one. Due to pseudopyramidal signs, five patients were diagnosed as having hereditary spastic paraplegia (HSP) and treated with muscle relaxant for years. A severe pain in large joints, as seen in Parkinson’s disease, was reported in 50% of our patients during off state. This was completely ameliorated by levodopa as so were additional dystonic symptoms such as torticollis and writers’ cramp. Patients with an earlier disease-onset showed more severe disease progression.

After the exclusion of pathogenic mutations in the GCH1 exonic region encoding for the active GTPCH1 enzyme, high-throughput single nucleotide polymorphism (SNP) genotyping was performed in all available individuals using HumanOmniExpress beadchips and the HiScanSQ system. Large CNVs were examined and excluded through the CNVpartition v3.1.6 plug-in software while small exon rearrangements were inspected by a comprehensive visualization of all GCH1 genotypes within GenomeStudio (Illumina). Although no exon rearrangements were observed, a closer inspection of the GCH1 locus-associated genotypes identified a large disease-segregating haplotype of 9.44 Mb, which was flanked by rs1950706 and rs2031798 SNPs. Subsequently, relative quantification of all GCH1 coding exons, performed and analyzed through the Eco Real-Time PCR system following the 2^-ΔΔCt method (3), identified a heterozygous GCH1 exon 1 deletion in all affected individuals (Fig. 1). Interestingly, the GCH1 exon 1 deletion was previously reported in a Turkish DRD patient showing legs dystonia and fatigue (4). The identification of this mutation in both Turkish and Kurdish patients suggests that the GCH1 exon 1 deletion may have a founder effect in the Middle East, possibly of Iranian origin. Despite that DRD usually presents with reduced penetrance (2), the GCH1 exon 1 deletion was associated with complete penetrance in this kindred. The presence of this mutation in nine affected individuals points out the need to inspect more frequently the presence of deletions, insertions, and duplications in DRD-associated genes. In this report, five patients were misdiagnosed with HSP. The fact that DRD patients due to TH mutations have been reported mimicking HSP (5) and patients with Spatacsin mutations have been reported presenting with either L-dopa responsive parkinsonism or complex HSP (6) suggests that due to the clinical resemblance and the co-occurrence of these disorders, accurate and reliable diagnostic tests are necessary for providing appropriate treatments.

We conclude that DRD due to GCH1 mutations is associated with wide phenotypic heterogeneity, the GCH1 mutational penetrance may be higher than previously thought, and levodopa should be tried in patients with complex forms of HSP.

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Table 1. Clinical data of patients with DRD and GCH1 exon 1 deletion

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex/Age</th>
<th>Age at onset</th>
<th>Site of onset</th>
<th>Sites affected</th>
<th>Levodopa doses (mg/day)</th>
<th>Additional clinical features</th>
<th>Exacerbating factors</th>
<th>Sleep benefit</th>
<th>First diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>M/45</td>
<td>37</td>
<td>Arms and legs</td>
<td>Arms and legs</td>
<td>200</td>
<td>Postural tremor and pain</td>
<td>Fatigue and emotional stress</td>
<td>+++</td>
<td>DRD</td>
</tr>
<tr>
<td>A2</td>
<td>M/40</td>
<td>30</td>
<td>Legs</td>
<td>Arms and legs</td>
<td>NA</td>
<td>Not examined</td>
<td>NA</td>
<td>NA</td>
<td>DRD</td>
</tr>
<tr>
<td>A3</td>
<td>M/20</td>
<td>7</td>
<td>Legs</td>
<td>Arms, legs, trunk, and jaw</td>
<td>400</td>
<td>Muscle jerks, pain, postural tremor, oromandibular dystonia, and postural tremor</td>
<td>Physical and emotional stress</td>
<td>NA</td>
<td>HSP</td>
</tr>
<tr>
<td>A4</td>
<td>M/42</td>
<td>35</td>
<td>Arms</td>
<td>Arms and neck</td>
<td>375</td>
<td>Postural tremor and cervical dystonia</td>
<td>Prolonged physical activity</td>
<td>+</td>
<td>HSP</td>
</tr>
<tr>
<td>A5</td>
<td>M/32</td>
<td>6</td>
<td>Legs</td>
<td>Arms and legs</td>
<td>150</td>
<td>Writer's cramp and postural tremor</td>
<td>Prolonged walking</td>
<td>++</td>
<td>NK</td>
</tr>
<tr>
<td>A6</td>
<td>F/34</td>
<td>5</td>
<td>Legs</td>
<td>Arms, legs, and trunk</td>
<td>125</td>
<td>Postural tremor and leg and arm dystonia</td>
<td>Fatigue and emotional stress</td>
<td>++</td>
<td>HSP</td>
</tr>
<tr>
<td>A7</td>
<td>M/29</td>
<td>6</td>
<td>Legs</td>
<td>Arms, legs, trunk, and neck</td>
<td>250</td>
<td>Muscle jerks, scoliosis, retrocollis, and joint pain</td>
<td>Lack of sleep and physical and emotional stress</td>
<td>+</td>
<td>HSP</td>
</tr>
<tr>
<td>A8</td>
<td>M/21</td>
<td>5</td>
<td>Legs</td>
<td>Arms, legs, and trunk</td>
<td>6 mg*</td>
<td>Postural tremor, writer's cramp, muscle jerks, and postural instability, oromandibular dystonia</td>
<td>Fatigue</td>
<td>++</td>
<td>HSP</td>
</tr>
<tr>
<td>A9</td>
<td>F/14</td>
<td>4</td>
<td>Legs</td>
<td>Arms, legs, trunk, and jaw</td>
<td>200</td>
<td>Muscle jerks, writer's cramp, joint pain, oromandibular dystonia, and postural tremor</td>
<td>Lack of sleep</td>
<td>++</td>
<td>DRD</td>
</tr>
</tbody>
</table>

NK, Not known; DRD, dopa-responsive dystonia; HSP, hereditary spastic paraplegia; M, male; F, female; *, A8 takes Biperidin instead of Levodopa; +, <1 h; ++, 1–2 h; ++++, >2 h.

aThe muscle jerks described here are most probably dystonic jerks; however, electrophysiological tests were not available.
Fig. 1. Upper panel: Pedigree structure of the Iranian DRD Family. The pedigree consisted of nine patients and one healthy sibling. Affected individuals are represented with filled circles (females) and squares (Males). Based on patients’ reports and available clinical files, several deceased individuals are labeled as being affected in the current pedigree structure. All members with DNA available are also labeled: A, affected; NA, non-affected. Lower Panel: GCH1 gene dosage analysis. Each DNA sample was run in quadruplicate, an equimolar mix of DNA samples of 10 healthy individuals (6 males and 4 females) with an average of age of 66.7 years was used as reference sample, and the GPR15 gene was used as reference gene (7). Individuals are shown in different colors. Y-axis: GCH1/GPR15 ratios for each exon; X-axis: GCH1 coding exons. All affected individuals (A) show only one copy of the GCH1 exon 1 (Ratio: 0.4–0.6), but two copies of the remaining exons (Ratio: 0.8–1.2). The unaffected member (NA) shows two copies of each GCH1 exon.

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References