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Short Communication

D-2-hydroxyglutaric aciduria in a patient with speech delay due to a novel homozygous deletion in the *D2HGDH* gene

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ABSTRACT

D-2-hydroxyglutaric aciduria is a rare neurometabolic condition with a variable clinical spectrum. Here we report on a patient with speech delay, ascertained for an elevated urine 2-hydroxyglutaric acid levels, and found to have a novel pathogenic homozygous deletion in *D2HGDH* (NG_012012.1(NM_152783.4):c.(292 + 1_293–1)_(*847_?)del). This case expands on the reported phenotype, with speech delay being the prominent clinical finding and despite identifying a large deletion in the *D2HGDH* gene, the patient presents with the mild phenotype.

1. Introduction

D-2-hydroxyglutaric aciduria (D-2HGA) is a rare autosomal recessive neurometabolic disorder associated with elevated body fluid levels of D-2-hydroxyglutaric acid and a variable clinical spectrum. Since the first description by Chalmers in 1980 [1], two distinct phenotypes have emerged. The severe phenotype is characterized by infantile-onset epileptic encephalopathy with intractable seizures, significant hypotonia, cardiomyopathy, cortical blindness, apneas and stridor, severe global developmental delay, facial dysmorphisms, and early death. The characteristic brain MRI findings reported in the severe phenotype, include ventriculomegaly, subependymal cysts in the neonatal and early infantile period, and delayed cerebral maturation. The mild phenotype shares some features of the more severe presentation, though the features are present to a much milder degree. Features of the mild phenotype include medication-responsive epilepsy, hypotonia, lethargy, and developmental delay [2,3]. Similar brain MRI findings to those seen in the severe phenotype are reported in patients with the mild phenotype [3]. Additional features reported more recently in the mild phenotype, include spondyloenchondrodysplasia [4] and peripheral neuropathy [5].

Pathogenic variants in *D2HGDH* or *IDH2*, which encode the mitochondrial enzymes D-2-hydroxyglutarate dehydrogenase and isocitrate dehydrogenase respectively, result in accumulation of D-2-hydroxyglutaric acid [6,7] and follow an autosomal recessive or dominant mode of inheritance, respectively. In addition, pathogenic variants in *SLC25A1* encoding the mitochondrial citrate carrier can result in accumulation of both D-2-hydroxyglutaric acid and the enantiomer L-2-hydroxyglutaric acid [8].

The elevated D-2-hydroxyglutaric acid levels are found in the blood, urine, and CSF of patients with the severe and the mild phenotypes, and clinical severity does not appear to correlate with the absolute value of the metabolite.

Herein, we present the clinical and molecular findings of a patient with a novel homozygous deletion in the *D2HGDH* gene.

2. Case

A 5-year-old boy, born to consanguineous parents from Pakistan, was ascertained for developmental delay and an elevated urine 2-hydroxyglutaric acid on organic acid analysis. His prenatal and neonatal course were unremarkable, and apart from developmental delay, he was otherwise healthy. From an early age, his speech was delayed. His first words were spoken at 2 years, and he began to combine words at 3 years. Clinically, he was non-dysmorphic and mildly hypotonic. He was reported to be easily fatigued compared to his peers. Hearing and vision assessments were normal. On his initial evaluation at the age of 5 years, he was diagnosed with a moderate expressive speech delay, with preserved receptive language. He was also noted to have mild delay in his fine motor skills, including in self-care, feeding, and the use

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of a pencil. Gross motor skills were appropriate for age. Socially he was quite shy, but appropriate with familiar people and perceptive of others' emotions. There was no history of developmental regression. The speech and fine motor delays responded well to ongoing occupational and speech therapy.

Laboratory investigations were significant for an isolated elevation of urine 2-hydroxyglutaric acid on two occasions: 1348 mmol/mol Cr and 1497 mmol/mol Cr respectively (normal < 20 mmol/mol Cr). Conventional GC–MS analysis of organic acids does not differentiate between the L- and D-2-hydroxyglutaric acid enantiomers, each of which is associated with a distinct clinical phenotype. Therefore, molecular testing was done to differentiate between L-2-hydroxyglutaric aciduria and D-2-hydroxyglutaric aciduria. Brain MRI and *in vivo* 1H-magnetic resonance spectroscopy were normal.

3. Results

Molecular analysis of the four genes currently associated with elevated L- and D-hydroxyglutaric acid, *D2HGDH, IDH2, L2HGDH*, and *SLC25A1*, identified a novel pathogenic homozygous deletion of exons 3–10 in the *D2HGDH* gene (NG_012012.1(NM_152783.4):c.(292 + 1_293–1)_(*847_?)del). This gene contains 10 exons, and the deletion encompasses over 75% of the protein, predicted to result in a truncated protein.

Sequencing and deletion/duplication analysis was performed by next generation sequencing, with enrichment and analysis of coding regions and 10 bp of flanking intronic sequences. The 5′ breakpoint is located within intron 2, while the 3′ breakpoint extends beyond the terminal codon. This deletion overlaps the majority of variants previously reported in individuals with D-2-hydroxyglutaric aciduria (both the mild and severe phenotypes). This variant has not previously been reported in the literature and has been classified as pathogenic.

To further confirm the molecular diagnosis, enantiomer-specific 2-hydroxyglutaric acid measurement was performed using two different urine samples at the Academic Medical Center in Amsterdam and the results were as follows: In the first sample total 2-hydroxyglutaric acid was 1071.50 mmol/mol Cr (94% of which is D-2-hydroxyglutaric and 6% is L-2-hydroxyglutaric acid. In the second sample total 2-hydroxyglutaric acid was 1192.03 mmol/mol Cr 94% of which is D-2-hydroxyglutaric and 6% is L-2-hydroxyglutaric acid. This further confirms that the 2-hydroxyglutaric acid measured is predominantly of the D-form, consistent with the molecular diagnosis.

4. Discussion

This case expands on the reported clinical phenotype of D-2HGA due to *D2HGDH* variants, with speech delay being the most prominent clinical finding. A case series of 17 patients with D-2HGA identified one individual who presented similarly to our patient, with isolated speech delay [2]. Despite identifying a large deletion in *D2HGDH* predicted to severely impact protein function, our patient is on the milder end of the phenotypic spectrum of D-2HGA. This is consistent with the phenotypic heterogeneity previously reported in related individuals, including a report of monozygotic twins in which one was severely affected and the other was mildly affected [9]. This phenotypic variability highlights the role of as-of-yet-unknown genetic, epigenetic and environmental factor that influence the presentation of this rare neurometabolic condition.

Disclosure statement

All authors have no conflicts of interest to declare.

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