Gillespie’s Syndrome with Minor Cerebellar Involvement and No Intellectual Disability Associated with a Novel ITPR1 Mutation: Report of a Case and Literature Review

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Abstract

Variants in the inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) gene have been recently identified as a cause of Gillespie’s syndrome, a rare inherited condition characterized by bilateral iris hypoplasia, congenital muscle hypotonia, nonprogressive cerebellar ataxia, and intellectual disability. Here, we describe the clinical and genetic findings in a patient who presented with iris hypoplasia, mild gait ataxia, atrophy of the anterior cerebellar vermis but no cognitive deficits. Whole-exome sequencing (WES) uncovered a heterozygous ITPR1 p.Glu2094Lys missense variant, affecting a highly conserved glutamic acid residue for which other amino acid substitutions have already been reported in Gillespie’s syndrome patients. Our data expand both the phenotypic and genetic spectrum associated with Gillespie’s syndrome and suggest a mutation hotspot on Glu2094.

Keywords

► ITPR1
► Gillespie’s syndrome
► ataxia
► cerebellar atrophy
► aniridia
► intellectual disability

Introduction

Gillespie’s syndrome (MIM 206700) is a rare inherited condition characterized by bilateral iris hypoplasia, congenital muscle hypotonia, nonprogressive cerebellar ataxia, and variable intellectual disability. Since the first description in 1965, less than 50 affected families have been reported worldwide. Clinical diagnosis is usually made shortly after birth due to a combination of fixed dilated pupils due to iris hypoplasia and muscular hypotonia. In 2016, the genetic basis of Gillespie’s syndrome was unraveled when recessive and dominant (de novo) variants in the inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) gene were identified. ITPR1 encodes one of the three members of the inositol triphosphate receptor (InsP3R) family that form large homo- and heterotetrameric calcium release channels localized predominantly in membranes of endoplasmic reticulum calcium stores. Variants in ITPR1 have been linked to several forms of nonsyndromic spinocerebellar ataxia and atrophy.

Here, we report a patient with an unusually mild phenotype, caused by a novel heterozygous ITPR1 mutation and review the genetic and clinical spectrum in genetically confirmed Gillespie’s patients that were published in the literature to date.
Case Report

The patient is the second child of healthy, nonconsanguineous parents with no family history of neurological or ocular disease. At birth, he presented with fixed dilated pupils due to iris hypoplasia. There was no perinatal hypotonia (Apgar’s score 10/10/10 at 1/5/10 minutes, respectively). Motor milestones were mildly delayed with independent walking at 2.5 years of age. At age 1.5 years, mild intention tremor of both hands was noted. Cognitive development was normal; he attended a school for visually impaired children and graduated from secondary modern school. As he experienced no disabling neurological deficits in daily life, he was not seen by a neurologist until age 22 years. Neurologic examination at age 22 years revealed bilateral ptosis and dilated pupils with no reaction to light. Visual impairment was mild (visual acuity both eyes 0.8) and he did not wear glasses in daily life. He had mild scoliosis and thoracic kyphosis. There was no muscle wasting or weakness. Muscle tone in the lower extremities was increased with brisk deep tendon reflexes though plantar responses were normal. He had mild ataxia on gait tests and was still able to run. He also showed moderate intention tremor of both hands. Total score for the assessment and rating of ataxia (SARA) score was 6.5/40. He had normal cognition and was trained in office communication. Montreal Cognitive Assessment (MoCA) score at age 26 years was normal (28/30). Brain magnetic resonance imaging (MRI) scan at age 22 years was reported to be normal; however, no mid sagittal sections were acquired hampering evaluation of the cerebellar vermis. Follow-up brain MRI at age 26 years confirmed normal volume of the cerebellar hemispheres but revealed atrophy of the anterior cerebellar vermis. There were no periventricular increased T2 white matter signals. Anterior segment optical coherence tomography (AS-OCT) revealed symmetrically incomplete aniridia in the entire circumference. Configuration of the cornea and anterior chamber was normal. Funduscopy was without any pathology (pink optic disc, cup-to-disc ratio: 0.1). Based on neurological and ophthalmological findings, the tentative diagnosis of Gillespie’s syndrome was made and genetic testing was performed in 2015. Since ITPR1 mutations had not yet been assigned to Gillespie’s syndrome at that time, we used whole-exome sequencing (WES) to search for the genetic defect.

Methods

Written informed consent was obtained from the patient for genetic testing and publication of genetic and clinical data. WES of the DNA sample of the patient was performed using a SureSelect Human All Exon 60 Mb V6 Kit (Agilent, Santa Clara, California, United States) for enrichment and sequencing was done on a HiSeq 4,000 engine (Illumina, San Diego, California, United States). WES yielded 10.990 Gb of sequence with 97.72% of the targeted region covered at least 20x. Variant prioritization was performed based on an autosomal recessive pattern of inheritance (homozygous or putative compound heterozygous variants with minor allele frequency < 1%), as well as on an autosomal dominant pattern of inheritance (heterozygous variants with a minor allele frequency < 0.01%).

Results

No pathogenic mutation was identified in the PAX6, FOXC1, and PITX2 genes, which are associated with more than 90% of cases of isolated aniridia. After publication of ITPR1 variants in individuals with Gillespie’s syndrome, we reevaluated WES results and observed a heterozygous ITPR1 missense mutation, c.6280G > A (p.Glu2094Lys). The mutation was not present in the unaffected mother. The father’s DNA sample was not available for analysis. Based on molecular data, the clinical diagnosis of autosomal dominant Gillespie’s syndrome was confirmed.

Discussion

So far, 25 genetically confirmed patients with Gillespie’s syndrome have been reported. In total, 12 mutations have been identified, including dominant and recessive variants. The mutations found in Gillespie’s syndrome are, with one exception, localized either in the regulatory domain or in the C-terminal transmembrane domain of ITPR1. They act either through a dominant-negative mechanism preventing the assembly of functional homotetrameric structures or a loss-of-function mechanism, generating prematurely truncated proteins. All reported patients show partial aniridia, cerebellar ataxia, variable cognitive impairment (usually mild to moderate), and a motor delay, as none of them walked before the age of 6 years (range: 6–16 years; Table 1). Nearby all show additionally a cerebellar atrophy on brain scans (Table 1).

The patient, we reported here, exhibited the typical ocular characteristics (partial aniridia with iridolenticular strands) that are an invariant feature of Gillespie’s syndrome. He showed a normal intelligence and mild cerebellar involvement. Although ITPR1 mutations have been initially found in cases with spinocerebellar ataxia, our observations suggest that neurological and neuroradiological manifestations can be minor. We speculate that extending ITPR1 mutation screening to isolated iris hypoplasia cases without mutations in the PAX6, FOXC1, and PITX2 will increase the diagnostic yield in these cohorts.

The ITPR1 variant in our case most likely occurred de novo, either in one of the parental gametes or postzygotically in the patient. However, we cannot provide formal evidence as no DNA sample could be obtained from the reportedly healthy father. The pathogenic relevance of the identified variant is supported by the observation that it leads to a nonconservative exchange of a highly evolutionarily conserved amino acid residue that has already been targeted by different dominant mutations in other cases with Gillespie’s syndrome. Indeed, the p.Glu2094Lys mutation reported here increases the number of different variants affecting this residue to three, confirming a mutation hot-spot and a critical role of Glu2094 in protein function.
Fig. 1  
Brain MRI images, schematic representation of Gillespie’s variants in human ITPR1 and multiple sequence alignment. MRI, magnetic resonance imaging.  
(A) Atrophy of the anterior cerebellar vermis (T1-weighted image).  
(B) Volume of the cerebellar hemispheres was normal (T2-weighted image).  
(C) No increase of periventricular white matter signals were observed (T1-weighted image).  
(D, E) Anterior segment optical coherence tomography revealed incomplete aniridia in the entire circumference of the left (D) and right (E) eye.  
Configuration of the cornea and the anterior chamber appeared normal.  
(F) Schematic representation of human ITPR1 and its functional domains showing the position of the mutations associated with Gillespie’s syndrome. The newly identified p.E2094K mutation and two other mutations affecting residue 2094 are marked red. Amino acid numbering and domain positions are based on the 2743-amino acid isoform 2: Q14643 –2, encoded by the canonical transcript GenBank NM_001168272.1; ENST00000302640.  
(G) Multiple sequence alignment of ITPR1 protein regions surrounding the p.E2094Q residue (red) in various species.
In conclusion, we describe a rare case of a patient with genetically confirmed Gillespie's syndrome without cognitive impairment and minor cerebellar involvement harboring a novel ITTP1 mutation, expanding both, the phenotypic and genotypic spectrum of ITTP1-associated diseases.

Conflict of Interest
The authors declare no conflict of interest.

References

Table 1: Clinical and genetic features of patients with genetically confirmed Gillespie's syndrome

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Sex</th>
<th>Variant</th>
<th>Bilateral iris hypoplasia</th>
<th>Ataxia</th>
<th>Hypotonia</th>
<th>Age at walking</th>
<th>Intellectual disability</th>
<th>Cerebellar atrophy on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentici et al, 2017</td>
<td>F</td>
<td>c.7786_7788delAAAG, p.K2596del</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>&gt;10 y</td>
<td>Y (severe)</td>
<td>Y</td>
</tr>
<tr>
<td>Carvalho et al, 2018</td>
<td>M</td>
<td>c.2952_2953insTATA; p.N984fs, homozygous</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>16 y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Paganini et al, 2018</td>
<td>M</td>
<td>c.278_279 +2delACGT; p.H93fs, homozygous</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>9 y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>De Silva et al, 2018</td>
<td>F</td>
<td>c.7786_7788delAAAG, p.K2596del</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>6 y</td>
<td>Y (mild)</td>
<td>Y</td>
</tr>
<tr>
<td>Present study</td>
<td>M</td>
<td>c.6280G&gt;A, p.E2094L</td>
<td>Y</td>
<td>Y (mild)</td>
<td>N</td>
<td>2.5 y</td>
<td>N</td>
<td>N (22 y)</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; MRI, magnetic resonance imaging; N, no; NA, not achieved; NR, not reported; Y, yes.
14 Hall HN, Williamson KA, FitzPatrick DR. The genetic architecture of aniridia and Gillespie syndrome. Hum Genet 2018; (e-pub ahead of print). Doi: 10.1007/s00439-018-1934-8
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