Gastrointestinal Dysmotility Is a Significant Feature in 2 Siblings With a Novel Inositol 1,4,5-Triphosphate Receptor 1 (ITPR1) Missense Variant

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ABSTRACT

We present 2 siblings with a novel type 1 inositol 1,4,5-triphosphate receptor (ITPR1) missense variant who exhibit gastrointestinal dysmotility (chronic constipation and gastroparesis). ITPR1 is expressed in the cerebellum and interstitial cells of Cajal. Periodic release of calcium by ITPR1 initiates pacemaker currents, resulting in smooth muscle contraction. ITPR1 mutations are known to be associated with neurologic syndromes, and these variants have not previously been associated with significant gastrointestinal manifestations in humans. Using whole-genome sequencing, in silico prediction software, biopsy samples, and manometry, the identified novel ITPR1 variant is likely pathogenic and may have neurogastroenterology implications.

INTRODUCTION

Inositol 1,4,5-triphosphate (IP₃) receptor 1 (ITPR1) is an intracellular IP₃-gated channel that modulates calcium signaling through endoplasmic reticulum calcium release. ITPR1 is found in neuronal and non-neuronal tissues, including the cerebellum, enteroneudocrine cells, and interstitial cells of Cajal (ICC). ITPR1 gene variants have been associated with neurologic disorders such as spinocerebellar ataxia 15 (SCA15) (OMIM: 606658), congenital nonprogressive spinocerebellar ataxia 29 (SCA29) (OMIM: 117360), and Gillespie syndrome (OMIM: 206700). However, mutations in ITPR1 have not previously been reported in patients with gastrointestinal dysmotility. The siblings reported here suggest that, with further functional validation, a new likely pathogenic variant of ITPR1 may represent a novel mutation that expands the phenotype of ITPR1 syndromes already described or may expand the ITPR1 disorders in the form of a new neurogastroenterology syndrome.

CASE REPORT

Patient 1: An Asian-American boy presented at 12 months of age with hypotonia and severe constipation. He required aggressive bowel regimens and underwent multiple hospitalizations for recurrent fecal impactions. He was diagnosed with gastroparesis with a liquid gastric emptying scintigraphy study (T 1/2: 630 min). Gastroduodenal and high-resolution anorectal manometry studies identified normal gastroduodenal and anorectal function with an intact rectoanal inhibitory reflex (Figure 1). Colonic manometry demonstrated lack of high-amplitude propagating contractions. He had extremely prolonged colonic sitz marker retention. Sibling 1’s severe constipation is successfully managed with antegrade enema therapy through cecostomy tube.
Additional diagnostic testing for sibling 1 included a normal muscle biopsy, chromosomal microarray, and global Metabolomic Assisted Pathway Screen. Histology from rectal suction biopsy identified normal ganglion cells, neurofibrils, and the presence of ICC (Figure 2).

From a neurological perspective, gross motor delays were identified at 6 months of age. Brain magnetic resonance imaging at 2 years identified asymmetric white matter changes in the left frontal lobe and mildly prominent ventricles and extra-axial spaces. At age 4 years, he developed absence and generalized seizures that responded to antiepileptic medications. Despite persistent symptoms of gastrointestinal dysmotility, a repeat neurologic evaluation performed at age 5 years demonstrated clinical improvements in speech and gross motor skills and a normal repeat brain magnetic resonance imaging.

Whole-exome sequencing (WES) identified a heterozygous variant p.Ser1762Cys (AGT>TGT): c.5284A>T in exon 40 of the ITPR1 gene (NM_002,222.5) in both siblings, but not in the biologic mother and was confirmed with Sanger sequencing (Figure 3A). Paternal genetic testing was unavailable (sperm bank donation, same donor). No other potentially deleterious WES polymorphisms or mutations associated with mitochondrial metabolism were identified. The identified variant is in the ITPR1 coupling/regulatory domain (Figure 3B), and the resulting amino acid substitution occurs in a position conserved across several species, including rats and humans. Numerous in silico predictions (PolyPhen-2, Mutation t@ster, Provean, and Align GVGD) indicated that the variant is deleterious (significant...
The frequency for this mutation in the 1000 Genomes Project is 0.0002 (1/5008).11

DISCUSSION

We describe for the first time 2 siblings with a novel ITPRI variant in which neurogastrointestinal manifestations are a significant clinical feature. Heterozygous mutations in ITPRI have been implicated in 3 distinct human disorders, all of which are ataxia syndromes: SCA15, SCA29, and Gillespie syndrome. In humans, many gastrointestinal diagnoses occur before, or concomitantly with, the diagnosis of neurological disorders,12 likely because of the similarities in neuroanatomy and neurochemistry of the brain and enteric nervous system where common pathogenic mechanisms may lead to both central nervous system and gastrointestinal dysfunction.13

Both siblings (particularly sibling 1) had clinical features and characteristics present in other syndromes associated with heterozygous ITPRI mutations such as epilepsy, delayed motor development, hypotonia, and mild intellectual disability. Although the siblings are not ataxic, it is possible that the neurologic symptoms identified in sibling 1 may be part of a spectrum of neurologic disorders associated with this gene mutation. Variable expression is seen with other genetic neurologic disorders including those associated with SCN8a genetic mutations.

ICC currents generate electrical slow waves, facilitating phasic contractions, and are initiated by mitochondrial uptake of periodic release of calcium by Iltpr1.14,15 ICC abnormalities may lead to gastrointestinal motility disorders such as slow transit constipation and gastroparesis.14,16 Previous work in Itpri knockout mutant mice indicated that ITPRI affects gastric slow-wave generation. Although these mice had normal ICC and enteric neuronal development, they lacked gastric slow waves, suggesting that gastric slow waves require ICC calcium release.17 Consistent with the animal model, histopathology in sibling 1 identified typical c-Kit expression (indicating normal presence of ICCs) and normal enteric nervous system histology (Figure 2). The siblings’ presentations of constipation parallel the phenotype of a conditional ITPRI knockout model with impaired colonic motility (delayed transit time, abdominal distension, and reduced colonic spontaneous contractions).18 These animal model findings related to ITPRI increase the likelihood that the identified mutation in the siblings is clinically relevant to gastroenterology.

It should be noted that our findings meet Academy of Medical Genetics and Genomics and the Association for Molecular Physiology joint consensus guidelines,19 suggesting that the amino acid change resulting from the identified ITPRI variant is “likely pathogenic.” The lack of clinical and sequencing information from the biological father leaves unanswered questions regarding the nature of the variant such as if the variant occurred de novo, if there is variable penetrance or expressivity, if there is gonadal mosaicism, or if genetic anticipation may be involved. In addition, this report illustrates that WES may provide a tool to discover and diagnose genetic disorders affecting both the brain and gut enteric nervous system.20
In summary, we report 2 siblings with novel ITPR1 variants with gastrointestinal dysmotility as a significant clinical feature. Although the variant is likely pathogenic, further investigation is required to fully elucidate the physiologic implications of the identified ITPR1 variant.

DISCLOSURE

Author contributions: N.E.B. Tjaden wrote the manuscript and is the article guarantor. E. Chiou and B.P. Chumpitazi edited the manuscript. D.A. Schady provided the histopathology images. N.R. Pillai helped with genetic analysis. All authors critically read and approved the final manuscript.

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