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CASE REPORT

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Hirschsprung Disease in an Infant with L1 syndrome: Report of a New Case and a novel *L1CAM* variant

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Abstract

L1syndrome is an X-linked disorder manifesting with congenital hydrocephalus, adducted thumbs and spasticity. There are rare cases of L1 syndrome and coincident Hirschsprung disease, with mutations in the *L1CAM* gene thought to underlie both. We present a novel pathogenic *L1CAM* variant in someone with L1 syndrome and Hirschsprung disease.

KEYWORDS

genetics, neurosurgery, paediatrics and adolescent medicine

1 | INTRODUCTION

The *L1CAM* gene encodes the membrane glycoprotein L1CAM, a calcium-independent cellular adhesion molecule involved in neuronal development. The L1CAM cell adhesion molecule is found on the X chromosome in humans (and other mammals) and has a 1253 amino acid protein sequence. The extracellular portion is comprised of six immunoglobulin domains followed by five fibronectin type III domains which are connected to a small intracellular domain by a transmembrane helix (Figure 1). Mutations in the *L1CAM* gene cause L1 syndrome, which encompasses a spectrum of disease that includes four major X-linked conditions: X-linked congenital hydrocephalus due to stenosis of the aqueduct of Sylvius (HSAS; OMIM #307000); mental retardation, aphasia, shuffling gait, and adducted thumbs syndrome (MASA; OMIM #303350); X-linked complicated hereditary spastic paraplegia type 1 (SPG1; OMIM#303350); and X-linked complicated agenesis of the corpus callosum (OMIM #304100).[1] More than 220 disease-causing variants

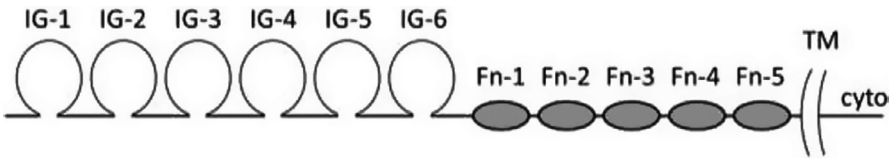

FIGURE 1 Schematic of the L1CAM protein with immunoglobulin domain (IG); fibronectin type III domain (Fn); transmembrane domain (TM); cytoplasm of cell (cyto)

in the *L1CAM* gene have been identified as causing the four major phenotypes of L1 syndrome.[2] Additionally, there are reports suggesting that additional mutations in *L1CAM* can cause mild behavioral and intellectual impairment.[3] The phenotypic manifestation of L1 syndrome is highly variable, even among patients who share the same pathogenic variant.

Hirschsprung disease (HD) is a congenital malformation of the enteric nervous system that has a prevalence of approximately 1 in 5000 live births in the United States.[4] Failure of neural crest cells to migrate the entire length of the developing gastrointestinal tract results in a segment of distal colon that lacks ganglion cells in the submucosal and myenteric plexuses, thus creating a functional obstruction. There are at least 12 genes in which known pathogenic mutations have been causatively associated with HD.[5] The incomplete penetrance and variable presentation of the disease, however, suggests a non-Mendelian model of inheritance.

Hirschsprung disease has previously been associated with L1 syndrome where children have been identified who had both verified *L1CAM* mutations and biopsy-proven HD.[1,2,6-10] Studies have suggested that *L1CAM* acts as a modifier gene for several HD-causative genetic mutations, such as *RET*, *SOX10,* and several genes that encode for proteins in the endothelin signaling pathway.[5,11] Evidence from a murine model suggests that interference of L1 protein function during embryogenesis impairs neural crest cell migration in

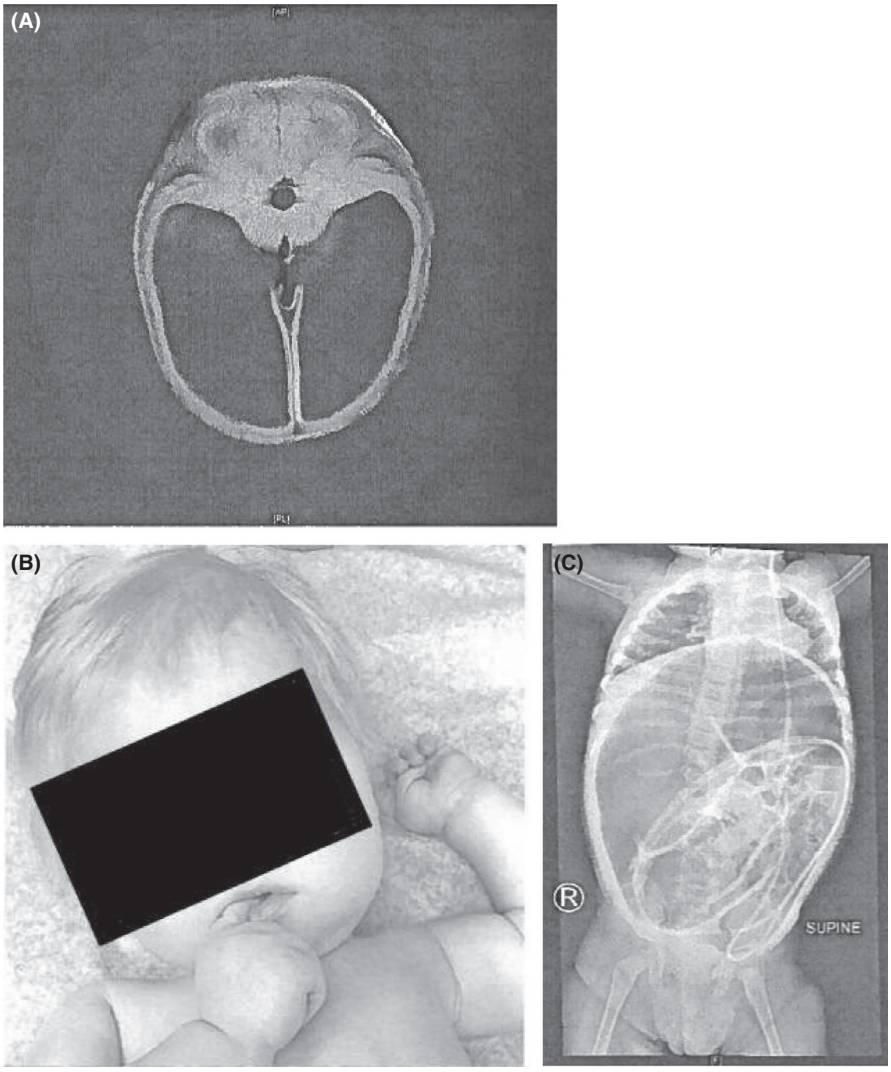

FIGURE 2 Clinical and diagnostic imaging characteristics of L1 Syndrome. A, Magnetic resonance imaging of head with ventriculomegaly and absent corpus callosum. B, Bilaterally adducted thumbs. C, Abdominal radiograph with dilated loops, characteristic of HD

the developing gut.[12] Resected sigmoid colon from infants with HD has been shown to lack expression of L1 protein via immunohistochemical staining.[13] Nevertheless, in humans, a pathogenic variant in *L1CAM* has not been identified whose causative presence always leads to HD. Therefore, a biopsy is always required to diagnose HD, even in patients with genetically diagnosed L1 syndrome.

Here we present a rare case of an infant with clinically diagnosed L1 syndrome who was found to have biopsy-proven Hirschsprung disease during admission for a ventriculoperitoneal shunt infection. Subsequent genetic confirmation of L1 syndrome by targeted sequencing of the *L1CAM* gene revealed a novel pathogenic variant (c.934T > C; p.Cys312Arg). We discuss the possible role of pathogenic *L1CAM* mutations in the pathogenesis of HD. We also emphasize that clinicians should have a high index of suspicion for HD when caring for patients with any form of L1 syndrome.

2 | CASE REPORT

The proband, who was the first child born to non-consanguineous Caucasian parents, was diagnosed with hydrocephalus in utero. On DOL 1, magnetic resonance imaging of the brain demonstrated profound ventriculomegaly and the corpus callosum was not able to be visualized (Figure 2A). A ventriculoperitoneal (VP) shunt was placed on DOL 2 to manage hydrocephalus. The child was also diagnosed with bilaterally adducted thumbs (Figure 2B). Notably, the patient's maternal uncle was also born with hydrocephalus and bilaterally adducted thumbs and remains wheelchair-bound with severe intellectual disability. During his fifth week of life, the patient was admitted to hospital with concern for VP shunt malfunction and infection. The VP shunt was removed and an external ventricular drain was placed. He remained in hospital for full treatment of *Staphylococcus epidermidis* ventriculitis/meningitis. The patient had a prolonged hospital course typified by the need for mechanical ventilation and sedation. The external ventricular drain was removed prior to discharge, followed by a "shunt holiday" until a new VP shunt was placed at 11.5 weeks of age.

During the patient's admission for ventriculitis/meningitis, he developed a distended abdomen and failure to pass stool. Abdominal radiographs demonstrated profoundly dilated loops of colon (Figure 2C). A diagnosis of HD was considered but was initially deemed unlikely given the patient's late presentation. In parental retrospect and on chart review of his NICU stay, it was determined that the patient had suffered from intermittent constipation with abdominal distension during his first month of life. Due to concern for L1 syndrome with coincident HD, a rectal biopsy was ultimately performed at 6.5 weeks of age. The rectal biopsy was significant for the absence of ganglion cells on 76 consecutive sections of rectal biopsy and for the absence of typical neurotic fibers in lamina propria. The calretinin and acetylcholine esterase immunohistochemical staining were both negative and prominent hypertrophic nerve trunks were seen in the muscularis mucosa (Figure 3). These findings were pathognomonic for Hirschsprung disease. Subsequent targeted sequencing of the patient's *L1CAM* gene demonstrated a previously-unreported variant in exon 8 of the *L1CAM* gene (NM_000425.3): c.934T > C; p.Cys312Arg (C312R).

3 | DISCUSSION

There are 13 previously described cases of pathogenic *L1CAM* mutations in patients with both L1 syndrome and Hirschsprung disease (Table 1).[1,2,6-8,14-19] Here, we describe

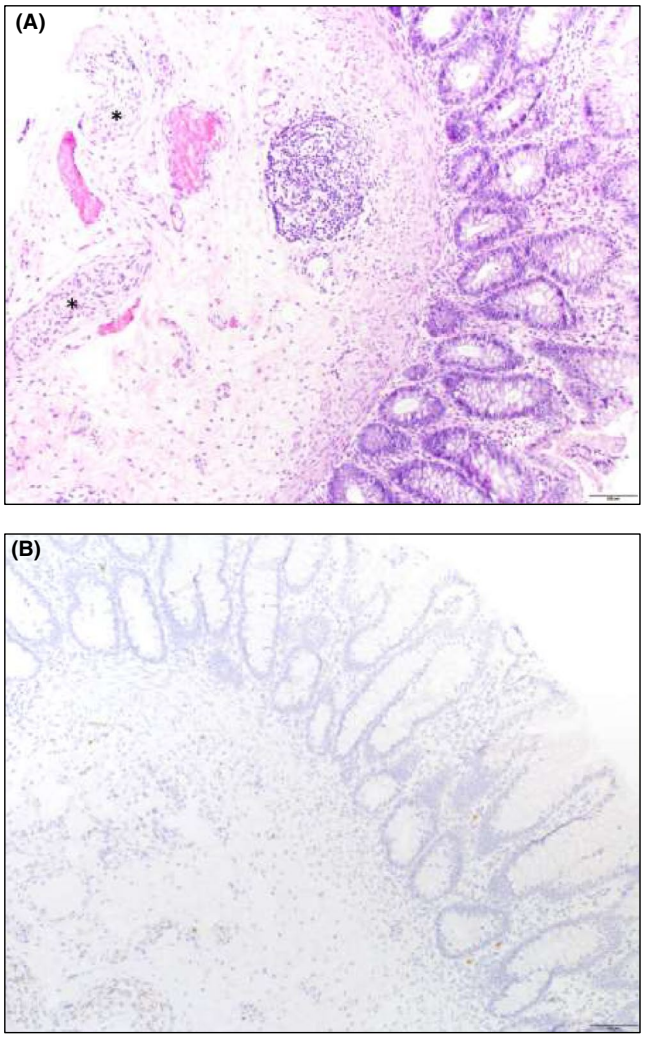

FIGURE 3 Histopathology of colon biopsy at 10× magnification. A, Hematoxylin and eosin stain demonstrating rectal mucosa with absence of ganglion cells in the submucosal plexus and hypertrophic nerve bundles (*). B, Calretinin immunohistochemical stain revealing absence of neurofibrils within the lamina propria or submucosal ganglion cells, a staining pattern consistent with Hirschsprung disease

TABLE 1 Reports of *L1CAM* Mutations in Patients with L1 Syndrome and Hirschsprung Disease

Reference	Mutation	Intron/Exon	Protein change	Domain	CADD Score
Okamoto et al, 1997	c.2421_2422delTG	Exon 18	p.Gly808ArgfsX9	Fn-2	-
Vits et al, 1998	c.1895G > C	Exon 15	p.Arg632Pro	Fn-1	23.2
Parisi et al, 2002	c.2254G > A	Exon 18	p.Val752Met	Fn-2	26.1
Okamoto et al, 2004 (case 1)	c.1939 + 5G>A	Intron 15	Unknown	N/A	23.7
Okamoto et al, 2004 (case 2)	c.1939 + 5G>A	Intron 15	Unknown	N/A	23.7
Okamoto et al, 2004 (case 3)	c.2974C > T	Exon 22	p.Gln992X	Fn-4	21.5
Basel-Vanagaite et al, 2006 (case 1)	c.719C > T	Exon 7	p.Pro240Leu	Ig-3	25.8
Tegay et al, 2007	Xq28 microdeletion	-	deletion	-	-
Nakakimura et al, 2008	c.92T > C	Exon 3	p.Val31Ala	N-terminus	24.5
Jackson et al, 2009	c.1672C > T	Exon 13	p.Arg558X	Ig-6	10.0
Griseri et al, 2009	c.2265delC	Exon 18	p.Pro756Leufs95X	Fn-2	-
Fernandez et al, 2012	c.2092G > A	Exon 16	p.Gly698Arg	Fn-1	28.2
Takenouchi et al, 2012	c.61C > T	Exon 1	p.Gln21X	N-terminus	15.2
The propositus	c.934T > C	Exon 8	p.Cys312Arg	Ig-3	26.6

Note: CADD score was not calculated for deletions.

Abbreviations: Fn, fibronectin type III domain; Ig, immunoglobulin domain.

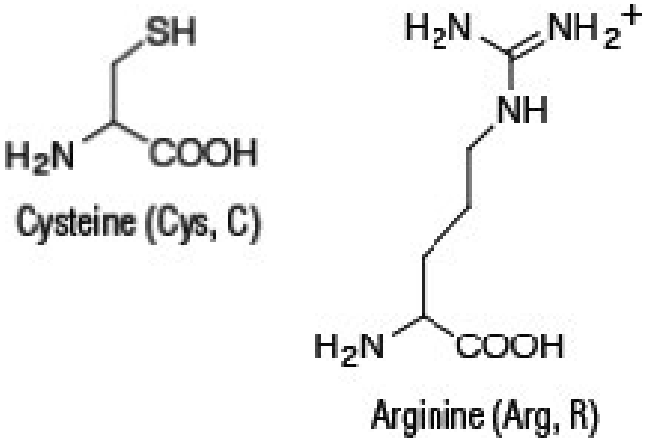

FIGURE 4 Amino acid structures of cysteine and arginine. Note charged vs. uncharged side groups

a new patient with genetically confirmed L1 syndrome and biopsy-proven HD. We also report a novel missense point mutation (c.934T > C) that results in a newly-described amino acid sequence change (p.Cys312Arg) in exon 8 of the *L1CAM* gene. This exon encodes for the Immunoglobulin (Ig) 3 domain of the L1CAM protein (Figure 1). Previous studies have linked this domain to homophilic interactions with L1CAM proteins on neighboring cells.[20] Of the previously reported *L1CAM* mutations in patients with L1 syndrome and HD, the majority affect the fibronectin type 3 domain, with only one mutation reported by Basel-Vanagaite et al 2006 affecting the Ig 3 domain (Table 1).[1] Notably, the mutation reported by Basel-Vanagaite et al 2006 was present in two half-siblings, but only one was diagnosed with HD. A different DNA mutation (c.935G > A) and amino acid substitution (p.Cys312Tyr) at the same locus of our patient's mutation was described by Kanemura et al 2006, but that case was reported as L1 syndrome without associated HD.[21] Thus, mutations that affect the Ig 3 domain of the L1 protein may cause L1 syndrome, but do not necessarily also result in HD. Our patient's C312R variant results in a non-conservative amino acid substitution of cysteine with arginine, resulting in the exchange of an amino acid with an uncharged side chain with one that has a positively charged side chain (Figure 4). This substitution could very likely affect L1CAM protein conformation or disrupt homophilic or heterophilic interactions of L1CAM protein with other proteins, thus altering L1CAM function. Analysis of the c.934T > C point mutation using the Combined Annotation-Dependent Depletion (CADD) tool—an in silico prediction algorithm that assesses genetic variants as benign or pathogenic—yields a CADD score of 26.6, which corresponds to a likely pathogenic variant.[22] The majority of mutations reported in Table 1 also have CADD scores > 15, strongly suggesting that *L1CAM* mutations are indeed pathogenic in each case. Therefore, our patient's novel missense point

mutation (c.934T > C) could be considered causative of his L1 syndrome. This mutation might also be implicated in this child's HD.

This case adds to a small number of reports of L1 syndrome with coincident HD, further supporting the hypothesis that *L1CAM* gene mutations may be involved in the pathogenesis of HD, most likely resulting in modified proteins that impact genetically susceptible individuals. Yet, there are hundreds of pathogenic *L1CAM* mutations described in cases of L1 syndrome without associated HD,[1,21,23] indicating that the presence of an *L1CAM* mutation alone is not diagnostic of HD in a child with phenotypic L1 syndrome. We conclude that Hirschsprung disease should be considered and rectal biopsy pursued in all children with intestinal obstructive dysfunction and suspected L1 syndrome. Conversely, diagnosis of L1 syndrome might be considered in children who are diagnosed with HD and exhibit features such as adducted thumbs, frontal bossing or developmental delay. Since L1 syndrome manifests across a wide phenotypic spectrum, clinicians—and pediatricians in particular—should be familiar with the major phenotypes of this disease.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

T. Gauntner, M. Karumuri, H. Pinz, S. Braddock and T. L. Andreone identified the case for this case report and contributed to management of the patient. T. Gauntner wrote the case report. T. L. Andreone revised the case report and facilitated the submission of the case report for publication. T. L. Andreone, S. Braddock, S. Besmer and H. Pinz critically reviewed and edited the case report. T. L. Andreone, M. Guzman, S. Starnes, S. Besmer provided diagnostic care and assisted with radiology and histopathology images. H. Pintz facilitated the genomic sequencing. H. Pinz and S. Braddock provided genetic counseling to the patient's parents.

ETHICAL STATEMENT

The parents were asked at the time that their child was being cared-for, whether they would consent to the reporting of their child's medical journey with the understanding that their child's identity would remain confidential. They consented for us to proceed with the preparation of a manuscript. The parents subsequently received a copy of the completed case report for their review. After their review, the parents then signed a release to allow publication of the case report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, TLA, upon reasonable request.

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