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SHORT COMMUNICATION

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Hydrocephalus and Hirschsprung's disease with a mutation of L1CAM

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Abstract Abnormalities of the L1CAM gene, a member of the immunoglobulin gene superfamily of neural-cell adhesion molecules, are associated with X-linked hydrocephalus and some allelic disorders. Hirschsprung's disease (HSCR) is characterized by the absence of ganglion cells and the presence of hypertrophic nerve trunks in the distal bowel. There have been three reports of patients with X-linked hydrocephalus and HSCR with a mutation in the L1CAM gene. We report three more patients with similar conditions. We suspect that decreased L1CAM may be a modifying factor in the development of HSCR.

Keywords X-linked hydrocephalus · L1CAM · Hirschsprung's disease · Cell adhesion molecule

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Introduction

X-linked hydrocephalus (XLH), or HSAS (hydrocephalus due to congenital stenosis of the aqueduct of Sylvius; McKusick 307000) syndrome, is characterized by severe mental retardation, spastic tetraplegia, and bilateral adducted thumbs. Abnormalities in the L1CAM gene, a member of the immunoglobulin gene superfamily of neural-cell adhesion molecules, underlie this syndrome (Rosenthal et al. 1992). L1CAM plays an important role in neuronal migration, adhesion, neurite outgrowth, fasciculation, and myelination. Over 150 mutations in the L1CAM gene have been reported (http://dnalab-www.uia.ac.be/dnalab/l1/).

Hirschsprung's disease (HSCR) is characterized by the absence of ganglion cells and the presence of hypertrophic nerve trunks in the distal bowel. It has been suggested that failure of migration of the neural crest cells underlies aganglionosis. Puri et al. (1998) suggested that aganglionosis may be caused by failure of differentiation of nerve cells due to microenvironmental changes after neuronal migration has occurred. Although molecular investigations on HSCR have led to dramatic developments, the basic mechanism of migration failure is not clearly understood.

We reported a patient with XLH due to a 2-bp deletion in exon 18 (2421delTG) who had cleft palate and HSCR (Okamoto et al. 1997). Vits et al. (1998) and Parisi et al. (2002) reported similar conditions. We report three novel patients with XLH and HSCR due to L1CAM mutation. We discuss the L1CAM abnormalities and HSCR.

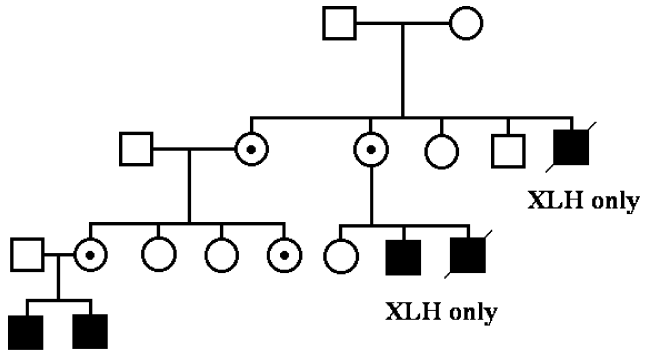

Fig. 1 Pedigree of X-linked hydrocephalus (XLH_ family including Cases 1 and 2)

Materials and methods

Case 1

The patient was the first child of nonconsanguineous, healthy Canadian parents (Fig. 1). His maternal grandmother's sister had two sons with congenital hydrocephalus. One of them was stillborn and the other did not have HSCR. The maternal grandmother also had a younger brother with congenital hydrocephalus who died in the infantile period. This family history is consistent with the X-linked recessive pattern of inheritance. Shortly after birth, the patient had feeding difficulty and was diagnosed with HSCR. A colostomy was performed. The patient was seen at the age of 3 months of age because of macrocephaly. The CT and MR scan demonstrated marked dilatation of the lateral and third ventricles, evidence of cerebellar hypoplasia and corpus callosal dysgenesis. Bilateral adducted thumbs and flexion contracture of the fingers were noted.

Case 2

The patient was the younger brother of Case 1. Amniocentesis demonstrated that he was a male infant, and intrauterine hydrocephalus was diagnosed at 17 weeks gestational age. A maternal MR of the fetus was carried out at 28 weeks of gestational age that demonstrated hydrocephalus secondary to aqueduct stenosis, a hypoplastic cerebellum, and corpus callosal dysgenesis. He was delivered electively at 36 weeks of gestational age by C-section because of a rapidly increasing ventriculomegaly. He had bilaterally adducted thumbs and had flexion contractures of his index fingers. A shunt was inserted at 3 days after birth. Within a week of birth he showed abdominal distention, and a rectal biopsy confirmed HSCR. A colostomy was performed at 6 months of age.

Case 3

The patient is 14 years old. He is the first child of nonconsanguineous Spanish parents. A second gestation was stopped because of fetal malformation similar to that of the patient. The third child is healthy. The patient has mental retardation and aphasia with spastic paraparesis and bilateral adducted thumbs. Brain MRI showed hydrocephalus, corpus callosum agenesis, thalami fusion, irregular ventricular wall, and decreased white matter volume. He also had HSCR, which was surgically treated.

Methods

Genomic DNA was extracted from peripheral leukocytes according to standard protocols. Amplification of the exons and the exon–intron boundaries of the L1CAM gene was performed by the polymerase chain reaction (PCR) using the oligonucleotide primers as described previously (Jouet et al. 1994; Kanemura et al. in preparation). Purified PCR amplification products were directly sequenced using ABI BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems) and analyzed with a capillary DNA sequencer (ABI PRISM 310 Genetic Analyzer, Applied Biosystems).

Results

Cases 1 and 2 had a splice donor-site mutation of intron 15 (IVS15 + 5 G to A). Their mother was heterozygous for the mutation, and one of her sisters and relatives, represented by dotted circles in Fig. 1, are carrying the genetic defect by linkage studies (data not shown). Case 3 had a nonsense mutation in exon 22 (C2974T, Gln992Stop). These mutations were not found in general population and patients with hydrocephalus so far studied.

Discussion

We report two novel L1CAM mutations with XLH and HSCR. There have been three reports on the combination of the two disorders with L1CAM mutations (Table 1). These results further support the idea that the combination of the two disorders is not incidental. Making a rough estimate, the incidence of HSCR among XLH is about 3%. However, in many cases, the patients with XLH die in the newborn period and the appropriate postmortem examination for aganglionosis may not be complete. Some patients may be diagnosed with chronic constipation, which is a frequent problem in severely handicapped children.

Table 1 Reports on X-linked hydrocephalus (XLH) and Hirschsprung's disease (HSCR) with a mutation of L1CAM

References	Mutations	
Okamoto et al. (1997)	2421delTG	Exon 18
Vits et al. (1998)	Arg632Pro	Exon 15
Parisi et al. (2002)	Val752Met	Exon 18
Case 1 and 2	IVS15 + 5 G → A	Intron 15
Case 3	Gln992Stop	Exon 22
Hofstra et al. (2002)	IVS5 + 6 T → > G[a]	Intron 5

[a]Not pathogenic

L1CAM mutations have intrafamilial and interfamilial heterogeneity. Kaplan (1983) reported a 2-year-old boy with psychomotor retardation, bilateral adducted thumbs, and HSCR, with enlarged ventricles, complete agenesis of the corpus callosum, and hypoplasia of the inferior vermis and cerebellum. The maternal uncle of the proband also had marked psychomotor retardation and agenesis of the corpus callosum but no adducted thumbs or HSCR. A maternal third cousin had HSCR. Later, Vits et al. (1998) found an Arg632Pro missense mutation in the boy and his maternal uncle. Recently, Parisi et al. (2002) found a Val752Met mutation in a patient with XLH and HSCR. Interestingly, the Val752Met mutation has been reported by Gu et al. (1997) in a male XLH patient without HSCR. Cases 1 and 2 in our report had XLH and HSCR, but their male relatives had XLH without HSCR. As a result, L1CAM mutation alone cannot explain the pathogenesis of HSCR accompanied by XLH. Disruption of the mouse L1CAM gene leads to malformations of the nervous system but not intestinal abnormalities (Dahme et al. 1997).

HSCR is a neurocristopathy characterized by the absence of parasympathetic ganglion cells of the terminal hindgut. It is associated with various syndromes and shows complex patterns of inheritance (Amiel and Lyonnet 2001). To date, mutations in the RET proto-oncogene, endothelin-receptor B (EDNRB) and endothelin-3 (EDN3), GDNF, Neurturin, ECE, SOX10, and SIP1 have been reported in HSCR cases. However, it is not clear why these mutations are related to neural-cell migration failure.

Because genes related to HSCR are on the autosomal chromosomes, it might be speculated that L1CAM on Xq28 could contribute to the unexplained unequal distribution of HSCR over males and females (approx. 3:1 to 5:1). Hofstra et al. (2002) screened 28 patients with HSCR and two patients with HSCR and hydrocephalus for L1CAM mutations. They did not find pathogenic mutations and concluded that a substantial role of L1CAM in explaining the excess of affected males was very unlikely.

Parisi et al. (2002) hypothesized that either RET or another HSCR gene contributes to aganglionosis under the influence of defective L1CAM, and L1CAM may act as an X-linked modifier gene for the development of HSCR. Evidence is accumulating that L1CAM is an important component of a complex network of cell-adhesion molecules (CAM), cytoskeletal elements, and signaling molecules involved in intestinal neuroblast migration. Ikawa et al. (1997) demonstrated that expression of L1CAM was impaired in the extrinsic nerve fibers in the aganglionic colon. Yoneda et al. (2001) investigated the expression of FGF, cell-adhesion molecules, and FGFR in HSCR. The neural-cell adhesion molecule (NCAM), L1CAM, and N-cadherin were included in their study. They found a markedly decreased number of CAM-positive nerve fibers in the aganglionic bowel compared to that in the normal bowel. They suggested that CAM–FGF signaling is altered in HSCR and may be responsible for the failure of neural-cell migration in the intestinal tract.

The mutation of L1CAM has an important role in the pathogenesis of HSCR in some patients. However, L1CAM mutation alone is not sufficient for the development of HSCR. Complex associations of other genetic or environmental factors may alter CAM–FGF signaling and result in HSCR. Decreased expression of L1CAM may be caused by a primary genetic defect of the L1CAM gene or a secondary effect of other genetic or environmental factors. Further studies are necessary to elucidate the interaction of L1CAM with other genes.

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