A novel mutation in L1CAM causes a mild form of L1 syndrome: a case report

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Key Clinical Message
Clinical geneticists, neurologists, psychiatrists, and other healthcare providers can learn from this case report that patients with a behavioral phenotype that includes a mild learning disability may also require a thorough examination, including brain MRI and whole-exome sequencing.

Keywords
Behavioral phenotype of genetic syndromes, corpus callosum hypogenesis, L1CAM mutation, X-linked mental retardation.

Introduction
Mutations in the gene encoding L1 cell adhesion molecule (L1CAM) are phenotypically characterized by X-linked hydrocephalus (OMIM #307000) or—in milder cases—corpus callosum agenesis or hypogenesis (OMIM #304100) [1]. The variability in clinical presentation reflects different functions of L1CAM. Hydrocephalus is a very complex disorder. Mutations in L1 as a cell adhesion molecule play a role in the pathogenesis of hydrocephalus. The corpus callosum hypogenesis reflects dysfunction as a neural recognition molecule through disorders in axonal growth and guidance [2].

The L1CAM gene is located on the X chromosome at Xq28 and is expressed primarily in the nervous system, where it plays important roles in neuronal development, including the guidance of neurite outgrowth, neuronal cell migration, axon bundling, synaptogenesis, myelination, neuronal cell survival, and long-term potentiation [3].

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The patients with hydrocephalus have a worse prognosis [4]. This is in agreement with recent evidence that some forms of hydrocephalus and the inborn neurological impairment are inseparable phenomena. This is because both fetal onset hydrocephalus and abnormal neurogene-
sis have a common origin: a primary pathology of the embryonic ventricular zone, involving neural stem cells and multiciliated ependymal cells. Junctional failure and loss of neural stem cells underpin the etiology of neuronal migration defects at specific regions of brain. Thus, neo-
nates are born with a neurodevelopmental deficit that derivative surgery cannot solve [5, 6].

Here, we report a patient with a generally mild physical presentation but with a more distinct behavioral phenotype.

Clinical Description

The proband (referred to here as “Patient A”) is a 56-
year-old man born in a family with two brothers from
nonconsanguineous healthy parents. One of his two
brothers has a learning disability of unknown severity; the other does not. Their mother had 14 siblings; three of her
brothers had a learning disability. Patient A’s parents died
around the age of 75. Patient A’s daughter developed epi-
lepsy at the age of 6; she initially experienced absence sei-
zuers, and later developed grand mal seizures. For the
past 2 years, she has taken valproate and has been sei-
zure-free. Patient A’s son is healthy.

The proband sought help from professional caregivers
due to anxiety and depression following several major life
events. He was fired 10 years ago and was unable to find
a new job until he found employment at a sheltered
workplace as a postal employee. In addition, he experi-
enced the deaths of his parents and his parents-in-law.
Patient A also experienced difficulty remembering essen-
tial information during work and at home. He lives with
his wife and two adult children in the center of a large
city in the Netherlands, where he was born. The patient
requested a psychological and neurological evaluation
because he experienced a subdural hematoma with cere-
bral contusion following an unexpected fall when he was
28 years of age. Although the subdural hematoma was
caused by an epileptic seizure, as he fre-
quently experienced unexpected falls.

The results of a psychological examination revealed
overall difficulties with cognitive functioning, including
impaired memory, attention, and executive functions. The
patient’s clinical history and test results revealed that psy-
chological problems appeared at an early age, leading to
social, emotional, and behavioral problems. Therefore,
combined with his intellectual challenges, the patient
lacked sufficient opportunities to learn the appropriate
skills needed to cope during complex, stressful situations.
These developmental issues, limited coping skills, and
limited opportunities to express himself emotionally likely
predispersed the patient to develop depression, particularly
when experiencing stress due to a lack of structure in his
daily life, thereby having a strongly disrupting effect on
daily functioning and activities (Table 1).

A genetic examination was also performed. SNP array
analysis revealed a normal male karyotype. Whole-exome
sequencing (WES) was performed essentially as reported
previously [7]. Exome capture was performed using the
Agilent SureSelect Human All Exon v4 enrichment kit
(Agilent Technologies, Santa Clara, CA), and WES was
performed using the Illumina HiSeq platform (BGI,
Copenhagen, Denmark). Data were analyzed using the
BWA (read alignment) and GATK (variant calling)
software packages. Variants were annotated using an in-
house-developed pipeline and prioritized using an in-
house-designed “variant interface” with manual curation.
Putative causative variants were confirmed by Sanger
sequencing. WES revealed the missense mutation
c.998C>T (p.Pro333Leu) in the proband’s L1CAM gene
(NM_000425.3). Segregation analysis revealed that the
same mutation was present in the proband’s brother with
a learning disability; in contrast, the proband’s other
brother—who did not have developmental abnormalities
—did not carry this variant. It was not possible to obtain

\[ L_1 \text{ variant & mild behavioral phenotype} \]

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genetic material for testing the proband’s deceased mother—who would have been an obligate carrier of the variant—or her brothers with mental disability.

This missense variant causes the substitution of a highly conserved nucleotide (phyloP: 5.29) and amino acid residue in the immunoglobulin-like domain of the L1CAM gene and protein, respectively. This mutation has not been described previously in any SNP database, including dbSNP and the EXAC database (http://exac.broadinstitute.org/); moreover, several mutation prediction tools predict that this variant is likely to be pathogenic.

Discussion

In this clinical report, we present a male patient with a novel, putative pathogenic variant in the L1CAM gene. This variant affects the structure of the fourth immunoglobulin-like domain in the protein, as Pro333 is believed to be one of the key residues required for proper folding of this domain [8]. Therefore, this variant likely disrupts interactions between both L1-L1 proteins and L1-non-L1 proteins, interactions that are important for protein function. Interestingly, a different variant in the same amino acid (p.Pro333Arg) was described in a patient with X-linked hydrocephalus; this patient died before the age of 1 [4]. As we mentioned before, some forms of hydrocephalus are not just ventriculomegaly, but the tip of the iceberg of a complex neurodevelopmental disorder [5, 6].

In the family reported here, the c.998C>T variant was present in both the proband and his affected brother, but
not in the proband’s unaffected brother. Both the patient and his affected brother presented with a rather mild clinical course. In most families with L1 syndrome, the affected boys die before, during, or soon after birth; however, both interfamilial variability and intrafamilial variability have been reported [9]. Basel-Vanagaite et al. described two half-brothers who had a mutation in the L1CAM gene and a hypoplastic corpus callosum, but no other characteristics of L1 syndrome [1]. Epilepsy has also been reported in a minority of patients with L1 syndrome [10].

In our study, the proband presented with a hypoplastic corpus callosum and some minor clinical features of L1 syndrome. In this case, the patient’s behavioral phenotype appeared to be more severe and distinct than his physical phenotype. Because social delays and behavioral abnormalities have been described in patients with corpus callosum abnormalities, an integrative examination of these functions should be included in the diagnostic protocol [11].

The value to this family from obtaining this diagnosis should not be underestimated. For example, several family members—particularly the proband’s adolescent daughter—now have the opportunity to seek clinical genetic advice when deciding whether to have children. Moreover, this family has learned that they should not expect the proband to achieve a higher level of functioning, and they have learned not to overestimate his abilities as either a husband or a father. After receiving this genetic diagnosis, his primary clinical goal—namely to help resolve his depressive symptoms—has waned.

Based on these findings, clinicians should be aware of the value of performing neuroimaging in persons with developmental disabilities, and they should offer their patients the opportunity to seek an etiological diagnosis, including genetic testing. Psychiatrists—particularly those who work in the field of intellectual disabilities/learning disabilities—should be made aware of the options available regarding diagnostic procedures based on clinical genetics and neuroimaging. These procedures can provide evidence-based assistance to patients and their families, including preventive management, thereby improving quality of life.

**Authorship**

MO: main author, was responsible for writing and reviewing the manuscript, literature review, and provided direct neuropsychiatric care to the patient. MW: participated in study design, coordination, and data analysis, especially concerning clinical genetic aspects, and provided direct clinical genetic care to the patient and his family. MP: performed the psychological assessment and wrote Table 1. RP: performed the WES and analyzed the molecular data and co-authored the description of the molecular details in the manuscript. YV: analyzed the molecular data and co-authored the description of the molecular details in the manuscript. RJN: reviewed the MRI of the brain and provided the figures. CS: involved in overall supervision of the writing of the manuscript.

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**Conflict of Interest**

The authors declare to have no conflict of interest.
References


