A Novel Heterozygous Missense Variant in the LZTR1 Gene as a Cause of Noonan Syndrome

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Disclosure statement
The authors declare no conflict of interest.

Introduction

- Noonan syndrome (NS) (OMIM# 163950) is an autosomal dominant disorder characterized by short stature, congenital heart defects, and characteristic facial features.
- Gain-of-function mutations of genes involved in the Ras/mitogen activated protein kinase (MAPK) pathway have been identified in 70–80% of patients with NS.
- Recently, leucine zipper-like transcription regulator 1 (LZTR1), which has not been associated with the pathway, was reported as a new causative gene for NS phenotype.

Case report

A Japanese male patient was born at 40 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, his length was 49.0 cm (+0 SD), weight 3.42 kg (+0.9 SD), and OFC 34 cm (+2.2 SD).

He had characteristic facial features consisting of ptosis, hypertelorism, downsizing palpebral fissures, and low set ears. He also had mild motor developmental delay. He held up his head at 5 months, rolled over at 7 months, and walked alone at 1 year 9 months of age.

At 5 years and 8 months of age, the patient was referred to us because of a short stature (~2.5 SD). A brain MRI examination, echocardiography and skeletal survey revealed no abnormalities.

Endocrine studies indicated GH deficiency (peak serum GH values: 3.42 ng/mL at insulin stimulation test, and 2.49 ng/mL at L-dopa stimulation test [cut off values: <6 ng/mL]).

He had severe intellectual disability (IQ56) and has attended to a special-needs school.

The non-consanguineous parents had well-proportioned figures without any dysmorphic features.

Clinical assessment alone was unable to lead to a conclusive diagnosis.

Discussion

Clinical and genetic features of NS patients with a heterozygous LZTR1 mutation

<table>
<thead>
<tr>
<th>Gene</th>
<th>cDNA</th>
<th>Protein</th>
<th>Phenotypic phenotype</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LZTR1</td>
<td>c.1234C&gt;T</td>
<td>p.Arg412Cys</td>
<td>Haploinsufficiency</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Patients with a heterozygous LZTR1 missense mutation show a typical phenotype of NS.

The structure of LZTR1 cDNA and the position of mutations associated with NS

LZTR1 cDNA

- All of them are missense mutations in the highly conserved kelch domains.
- Haploinsufficiency of LZTR1 (22q11.2 deletion syndrome) does not cause the phenotype of NS.
- Germline loss-of-function mutations of LZTR1 have been associated with multiple schwannomatosis.

The mechanism of the LZTR1 mutations for a NS phenotype remains obscure.

Conclusion

- The present report has provided further evidence that a heterozygous germline missense mutation in LZTR1 can cause a typical phenotype of NS.
- Further studies are needed to clarify the underlying pathogenic mechanism of the LZTR1 mutations for the phenotype of NS.
- Clinical diagnosis is sometimes difficult even in case of well-known syndromes (such as NS), because of their phenotypic complexity and lack of experience of their primary physicians.
- Whole exome sequencing can be highly advantageous for the diagnosis of such monogenic syndromes, and feedback from the genetic diagnosis will help improve our clinical skills.

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