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

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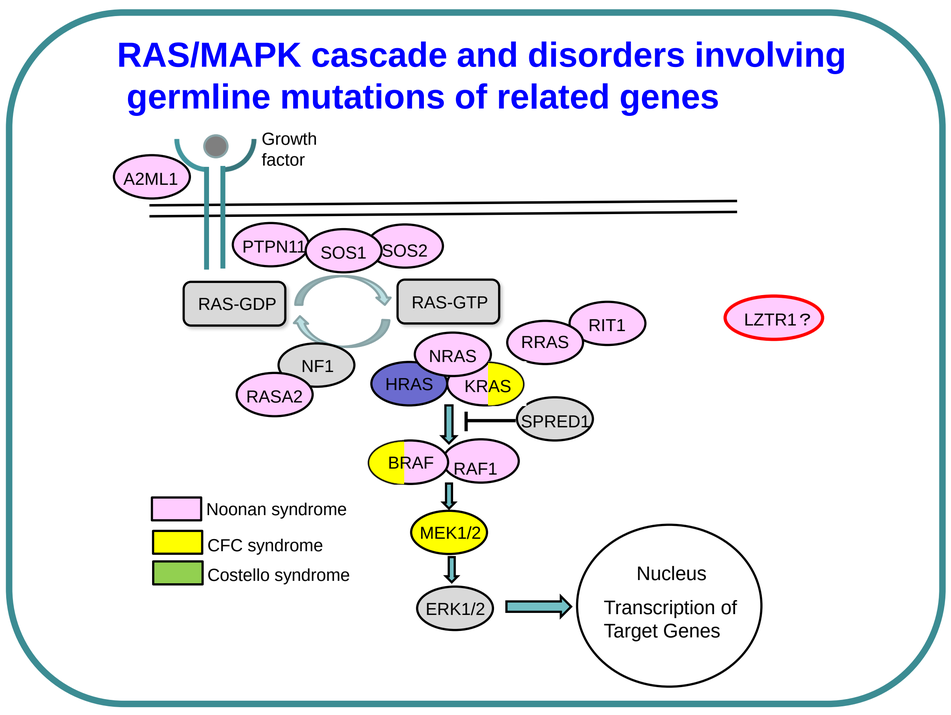
Disclosure statement
The authors declare no conflict of interest.

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.

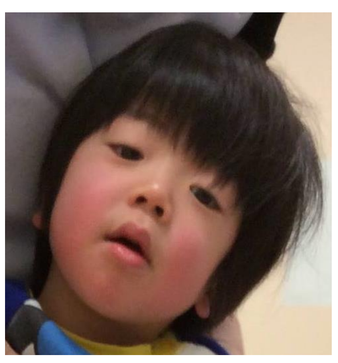
☑ Recently, **leucine-zipper-like transcription regulator 1 (*LZTR1*)**, which has not been associated with the pathway, was reported as a new causative gene for NS phenotype.



Case report

A Japanese male patient was born at 40 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, her 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, downslanting palpebral fissures, and low set ears. He also had mild motor developmental delay. He held up her head at 5 months, rolled over at 7 months, and walked alone at 1 year 9 months of age.

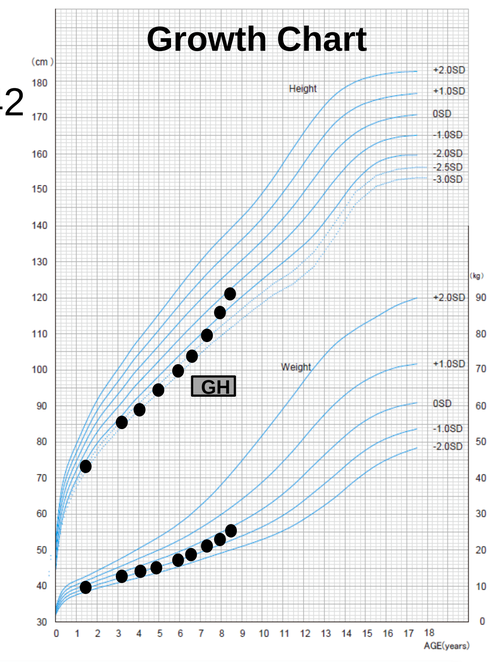


At 5 years and 8 months of age, the patient was referred to us because of a short stature (–2.5 SD). A brain MRI examination, echocardiography and skeletal survey revealed no abnormalities.

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.

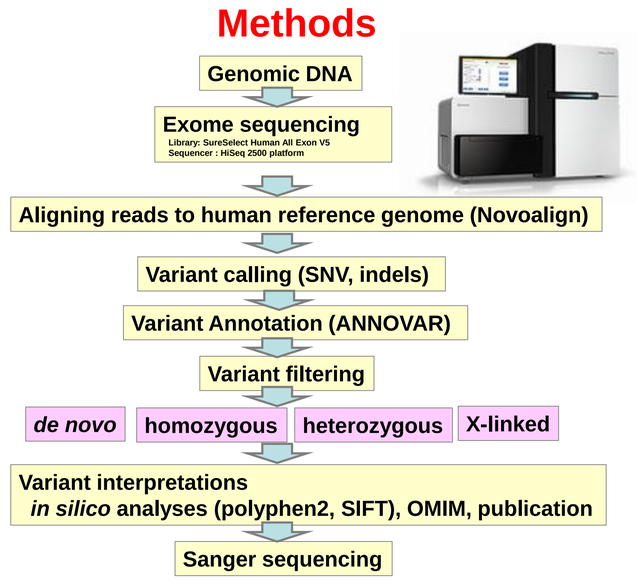
The non-consanguineous parents had well-proportioned figures without any dysmorphic features.



Clinical assessment alone was unable to lead to a conclusive diagnosis

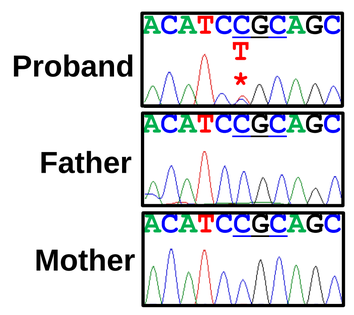
Trio whole-exome sequencing

Methods

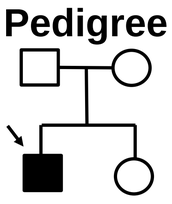


Results

LZTR1
c.1234C>T
p.Arg412Cys
(CGC→TGC)



Pedigree



Discussion

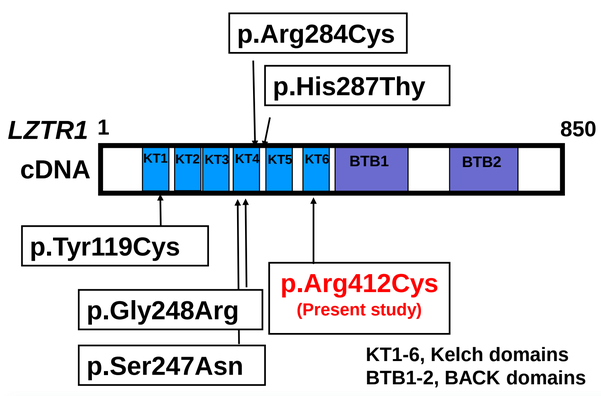
Clinical and genetic features of NS patients with a heterozygous *LZRT1* mutation

		Yamamoto et al J Med Gnet 2015													Present case
		Familiy 1			Family 2						Faily 3	Family 4	Family 5		
Age at the last examination (yrs)		11	45	69	14	38	16	15	12	3.5	16	30	18	53	5
Sex		Female	Female	Male	Female	Female	Female	Male	Female	Female	Male	Female	Male	Female	Male
LZTR1 mutations															
cDNA			c.742G>A					c.850C>T			c.859C>T	c.356A>G	c.740C>A		c.1234C>T
Protein			p.G248R					p.R284C			p.H287Y	p.Y119C	p.S247N		p.Arg412Cys
Present measurements															
Short Stature	36% (5/14)	+	+	+	-	-	-	-	-	+	-	-	-	-	+
Height (SD)		-2.1	-2.5	-2.9	-1.8	-1.9	-0.7	-1.8	-1.2	-3.8	0.3	0.1	1	-1.6	-2.5
Clinical features															
Typical facial features	100% (14/14)	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cariatic abnormaoitis	62% (8/13)	+	+	+	+	-	ND	-	-	-	+	+	+	+	-
		PVS/ASD	MVP	MVP	PVS						PVS/ASD	LVH	MVP	AoCo	
Short/webbed neck	50% (7/14)	+	+	+	-	-	-	-	+	-	-	-	+	+	+
Developmental delay	21% (3/14)	-	-	-	-	-	-	-	-	-	+	-	+	-	+
Learning disablility	23% (3/13)	-	-	-	-	-	-	-	-	NA	+	-	+	-	+
Cryptorchidism	20% (1/5)	NA	NA	-	NA	NA	NA	-	NA	NA	+	NA	-	NA	-
Coagulation defects	27% (3/11)	-	-	+	+	-	ND	-	ND	ND	+	-	-	-	-
Ectodermal findings	36% (5/14)	-	-	-	-	-	-	+	+	-	-	-	+	-	+
Tumors	7% (1/14)	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Pectus deformity	43% (6/14)	+	+	+	+	-	-	-	-	-	-	-	+	-	+
Other findings		Lacrimal duct obstruction				Nevi		Nevi	Hemangioma			Lymphedema			

SD, standard deviation; OFC, occipitofrontal circumference; +, Present; -, Absent; ND., not described; NA., not applicapable; PVS, pulmonary valve stenosis; ASD, atrial septal defect; MVP, mitral valve prolapse; LVH, left ventricular hypertrophy; AoCo, aorta coarctation

Patients with a heterozygous *LZRT1* missense mutation show a typical phenotype of NS.

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



- 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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