

Noonan syndrome associated with growth hormone deficiency with biallelic *LZTR1* variants

We read with great interest the paper by Johnston et al. about Noonan syndrome (NS) associated with *LTZR1*, the first with biallelic variants.¹ Here we report a patient with growth hormone (GH) deficiency and Noonan syndrome also with biallelic *LTZR1* variants. One of the patients reported by Johnston et al. (proband of family 3, individual II-4) also had GH deficiency. Although short stature is a frequent finding in Noonan syndrome (NS), its pathophysiology remains unknown.

Our patient was born at 3330 g and 50 cm to nonconsanguineous parents. Postnatal echocardiography demonstrated transposition of the great vessels, pulmonary stenosis, interventricular and interatrial communication, and he underwent Senning correction surgery at the age of 8 months. He also had typical facial features of NS including ptosis, triangular face, high-arched palate, low-set ears, and micrognathia, in addition to pectus excavatum.

At the age of 12.5 years, he was diagnosed with GH deficiency. His height was 123.6 cm (SDS -3.5), insulin-like growth factor 1 concentration 46 µg/L (reference for sex and age 63 to 761 µg/L) and GH peak after clonidine and glucagon stimulation tests was only 1.4 µg/L (normal >5 µg/L). At the chronological age of 14 years he had a bone age of 7 years. He was treated with human recombinant GH (rhGH, Somatropin) from 12.5 to 22 years reaching a final adult height of 157.5 cm. Retesting during the transition phase confirmed GH deficiency. Pituitary magnetic resonance imaging (MRI) revealed thickening of the left side of the optic chiasm suggestive of glioma and no other abnormalities. There was no characteristics of schwannomatosis.

The patient's DNA was submitted to a targeted gene panel containing 64 genes associated with short stature including 17 genes associated with NS (*PTPN11*, *SOS1*, *SOS2*, *NF1*, *NRAS*, *HRAS*, *KRAS*, *SHOC2*, *BRAF*, *RAF1*, *MAP2K1*, *MAP2K2*, *CBL*, *SPRED1*, *RASA2*, *RIT1*, *LZTR1*) and 24 genes for GH deficiency (capture and sequencing with Agilent and Illumina

technologies, respectively). The analysis revealed compound heterozygosity for *LZTR1* variants and was negative for the other panel genes. The patient has a missense pathogenic variant c.881G>T:p.Arg294Leu NM_006767.3 (gnomAD 0, CADD 36) inherited from his mother and a stop-gain variant c.2212C>T:p.Gln738* (ExAC 0.00001657, gnomAD 0.00001805, CADD 43) inherited from his father and also present in both of his brothers, all of whom have normal phenotype and height. The missense variant is in the Kelch_5 motif of the epithiospecifier domain and the stop-codon in the BTB domain of *LTZR1*.

The molecular mechanisms relating *LTZR1* alterations to NS or GH deficiency remain to be elucidated. Association of NS and GH deficiency is not frequent but the present patient and one patient reported by Johnston et al. suggest that this occurrence may be more frequent when associated to *LZTR1* variants.

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DISCLOSURE

The authors declare no conflicts of interest

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