

## A mother and son with Noonan syndrome resulting from a PTPN11 mutation: first report of molecularly proven cases from Turkey

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**SUMMARY:** Demir K, Yntema HG, Altıncık A, Böber E. A mother and son with Noonan syndrome resulting from a PTPN11 mutation: first report of molecularly proven cases from Turkey. *Turk J Pediatr* 2010; 52: 321-324.

Noonan syndrome is an autosomal dominant disorder characterized by short stature, typical craniofacial features, and congenital heart defects. The underlying genetic defects were not clear until 2001. This report is the first to describe a molecular analysis and associated clinical features of a Turkish mother and son, who were clinically diagnosed as Noonan syndrome when the boy was referred to our department due to short stature. The analysis revealed an A→G transition at position 923 in exon 8 of the *PTPN11* gene, indicating an Asn308Ser substitution.

**Key words:** Noonan syndrome, PTPN11, molecular analysis.

Noonan syndrome (NS, OMIM 163950) is an autosomal genetic disorder resulting in characteristic features, namely typical facial dysmorphism [hypertelorism, epicanthic folds, downward-slanting palpebral fissures, low-set posteriorly rotated ears with a thick helix, a short neck with excess nuchal skin, triangular face often appearing coarse or myopathic, prominent eyes, and (unilateral or bilateral) ptosis], congenital heart defects (pulmonary valve stenosis, hypertrophic obstructive cardiomyopathy), short stature, chest deformities, undescended testicles, and mild motor and mental retardation<sup>1</sup>. This condition is reported to be relatively common, with an estimated incidence of 1:1,000–1:2,500 live births; however, the diagnosis is not straightforward owing to marked variability in expression and facial features becoming less noticeable with age<sup>1,2</sup>. Accordingly, there are only a number of reports regarding NS from Turkey in the national and international medical literature<sup>3-5</sup>.

It was not until 2001 that one of the underlying genetic 325 in NS was recognized. Tartaglia et al.<sup>6</sup> identified mutations in the *PTPN11* gene, which encodes the non-receptor type protein tyrosine phosphatase (SHP-2) involved in

cellular response to growth factors, hormones, cytokines, and cell adhesion molecules. However, *PTPN11* mutations account for nearly 60% of the familial and 40% of the sporadic NS cases<sup>1</sup>. Recently, mutations of molecules in the RAS/MAPK cascade, which is required in cell proliferation, differentiation, survival and cell death, were detected in patients with NS without *PTPN11* mutations<sup>7</sup>. Molecular diagnosis of NS is not only of importance for the confirmation of the clinical diagnosis or genetic counseling, but also helps us to predict the response to growth hormone (GH) treatment<sup>8, 9</sup>.

This report is the first to describe the molecular analysis and associated clinical features of a Turkish mother and son, who were clinically diagnosed as NS when the boy was referred to our department due to short stature.

### Case Report

This 12½-year-old boy was referred to our department due to short stature. He had been short compared to his peers since infancy, while birth length was 51 cm (SD 0.38). His nutrition had long been poor owing to diminished appetite. Balloon valvuloplasty had been performed for dysplastic pulmonary valve

stenosis when he was 7 months old. Since then, no periodic follow-up had been made. His past medical history revealed that he was born to a 35-year-old mother who had been operated for pulmonary valve stenosis at the age of 15 years. A delay in mental development was suggested since his school performance was low to moderate. The parents were not related. His mother's height was 160 cm (SDS -0.5) and his father's was 170 cm (SDS -0.92).

Physical examination revealed the following: weight 22.7 kg (below 3rd percentile, SD -4.2), height 132 cm (below 3rd percentile, SD -2.75; According to height centiles for boys in Noonan syndrome: 50th percentile), weight for height 82%, hypertelorism, downward-slanting palpebral fissures, low-set ears, triangular face, prominent eyes, ptosis, thick lips, high-arched palate, prominent ears, and broad chest. The left testis was palpable with a volume of 3 ml, but the right testis was not palpable. There was no axillary or pubic hair. The remainder of the systemic examination was normal. His mother had hypertelorism, downward-slanting palpebral fissures, triangular face, prominent eyes and nasolabial folds, ptosis, and thick lips (Fig. 1-Informed consent was obtained for use of the photograph). Neither the maternal or paternal grandparents nor the father had dysmorphic findings or cardiac disease; however, his only sibling (21 years old, M) reportedly had the similar but milder phenotype without any complaints. Nevertheless, this case did not accept to be examined or provide a blood sample for molecular study.



**Fig. 1.** Photograph of the patient and his mother demonstrating the changes in facial features with age, characteristic of Noonan syndrome: more prominent nasolabial folds, thick hooded eyelids, and less prominent eyes in the mother.

Both the patient and his mother were diagnosed with NS using the scoring system described by van der Burgt (Table I)<sup>1</sup>. Complete blood count and kidney, liver and thyroid function tests of our patient were within normal ranges, as were the abdominal ultrasonography and audiological evaluation. Serum insulin-like growth factor (IGF)-I level was 54.5 ng/ml (SD -3.33) and IGF binding protein (IGFBP)-3 level was 3480 ng/ml (SD -0.7). Serum follicle-stimulating hormone (FSH) level was 6.47 mIU/ml, luteinizing hormone (LH) 0.798 mIU/ml, and total testosterone 25.2 ng/dl. Bone age was consistent with 10 years of age. Ultrasonography and magnetic resonance imaging showed that the right testis (2.6 ml) was located intra-abdominally and adjacent to the external iliac vascular structures. Ophthalmologic examination disclosed myopia and astigmatism. Peak levels of GH following stimulation with insulin and L-dopa without priming were 8.34 ng/ml and 6.5 ng/ml (normal, >10 ng/ml), respectively. A bone mineral density test revealed a normal Z-score (0.85). Radiologic examination of the skeletal system revealed normal findings. His Wechsler Intelligence Scale for Children (WISC-R) test scores were as follows: verbal IQ 77, performance IQ 88 and total IQ 80.

In the DNA diagnostics laboratory of the Radboud University Nijmegen Medical Centre (The Netherlands), mutation analysis of the *PTPN11* gene was performed. DNA was extracted from blood lymphocytes using standard procedures. Nine of the 15 coding exons (exons 1, 2, 3, 4, 5, 7, 8, 12, 13, and 14) of the *PTPN11* gene (NCBI accession number NM\_002834.3) and their flanking sequences were amplified by polymerase chain reaction (PCR). Subsequently, sequence analysis was performed using a 3730 automated sequencer (Applied Biosystems, Foster City, CA). Primer sequences and conditions for PCR amplification are available upon request. In the DNA of the index patient, a pathogenic mutation in exon 8 of the *PTPN11* gene was identified: c.923A>G (p.Asn308Ser). The same mutation was found to be present in the DNA of his mother.

His target height was 171.5 cm (SD -0.75) and predicted adult height was 162.5 cm (SD -2.0). GH therapy was started at a dose of 0.25 mg/kg/week (35 µg/kg/d), which provided a

**Table I.** Diagnostic Criteria for Noonan Syndrome<sup>1</sup>

Feature	Major	Minor
1. Facial	Typical face dysmorphology <sup>α, β</sup> Pulmonary valve stenosis, hypertrophic obstructive cardiomyopathy and/or ECG typical of NS <sup>α, β</sup>	Suggestive face dysmorphology
2. Cardiac		Other defect
3. Height	<3 <sup>rd</sup> percentile <sup>α</sup>	<10 <sup>th</sup> percentile
4. Chest wall	Pectus carinatum/excavatum <sup>α</sup>	Broad thorax
5. Family history	First-degree relative with definitive NS <sup>α, β</sup> Mental retardation, cryptorchidism and lymphatic dysplasia	First-degree relative with suggestive NS One of mental retardation, cryptorchidism, lymphatic dysplasia <sup>α</sup>
6. Other		

Definitive NS: Typical face dysmorphology plus one other major sign or two minor signs OR suggestive face dysmorphology plus two major signs or three other minor signs. <sup>α</sup> The criteria met by the son; <sup>β</sup> The criteria met by the mother.

height velocity of 7.2 cm/year. Staged Stephen-Fowler laparoscopic orchiopexy was performed for the right testicle. Educational support was planned.

### Discussion

The identified mutation in our patient has also been detected in numerous studies on NS around the world<sup>10-12</sup>. Lopez-Canti et al.<sup>10</sup> found that the most common *PTPN11* mutation was the same as ours; however, neither the exact frequency and associated clinical features nor whether this mutation was detected from the related patients was delineated. However, there was a single case with *Asn308Ser* mutation in the study of Ferrero et al.<sup>11</sup> and the only data available regarding this case were short stature and minor facial features. Our case (typical face dysmorphology plus 4 major and 1 minor criteria) and his mother (typical face dysmorphology plus 2 major criteria) fulfilled the clinical diagnostic criteria for NS.

Interestingly, the mutation found in our patient was also demonstrated in a family including siblings with giant cell lesions in various bones in addition to NS phenotype and their mother with only NS phenotype without bone lesions, consistent with Noonan-like syndrome and multiple giant cell lesions (NL/MGCLS, OMIM 163955)<sup>13,14</sup>. However, as in our cases, the same *Asn308Ser* mutation was observed in another family with NS that had no known bony involvement<sup>6</sup>. Furthermore, two other known NS mutations were detected in two of three patients with NL/MGCLS<sup>15</sup>. As a result, it was suggested that NL/MGCLS should be considered as part of the NS phenotypic spectrum<sup>13</sup>.

Mean height of patients with NS is around the lowest range of the normal growth curve during childhood. With delay in puberty, short stature becomes more pronounced<sup>16</sup>. In 2003, Noonan et al.<sup>17</sup> reported that height of approximately two-thirds of the adult males was below the 10<sup>th</sup> centile, while in half of them, height was below the 3<sup>rd</sup> centile. Although the mother had a normal height (SD score 0.5), our patient was significantly short compared to his peers (SD score -2.75). GH stimulation tests without priming revealed subnormal results. Although there are conflicting results regarding the GH-IGF-1 axis in patients with NS, such as neurosecretory dysfunction, low peak GH responses to provocation, normal GH secretion, and mild GH resistance, in cases with *PTPN11* mutations, including ours, many children with NS have been treated with GH, resulting in significant increase in growth velocity especially in the first years, as observed in our case<sup>16,18</sup>. Recently, in a long-term observational study including a large number of patients, significant improvement was reported in near-final height SDS of patients with NS (+1.4), similar to that seen in Turner syndrome (+1.2), especially when the prepubertal treatment duration is long<sup>19</sup>.

In conclusion, we emphasize herein that patients with this relatively common syndrome, which has a favorable prognosis with treatment of cardiac problems and short stature, can now be genetically analyzed and counseled.

### REFERENCES

1. van der Burgt I. Noonan syndrome. *Orphanet J Rare Dis* 2007; 2: 4.
2. Zenker M, Voss E, Reis A. Mild variable Noonan syndrome in a family with a novel *PTPN11* mutation. *Eur J Med Genet* 2007; 50: 43-47.

3. Balcı S, Onat M, Say B, Halıcioğlu C, Hatiboğlu N, Atası M. Erkek Turner fenotipi (Male Turner) ve ailevi Akdeniz ateşi (FMF = Familial Periodik Ateş) - bir vaka münasebetiyle. Çocuk Sağlığı ve Hastalıkları Dergisi 1972; 15: 225-238. [Turkish]
4. Uçar B, Okten A, Mocan H, Erçin C. Noonan syndrome associated with central giant cell granuloma. Clin Genet 1998; 53: 411-414.
5. Alanay Y, Balcı S, Ozen S. Noonan syndrome and systemic lupus erythematosus: presentation in childhood. Clin Dysmorphol 2004; 13: 161-163.
6. Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet 2002; 70: 1555-1563.
7. Aoki Y, Niihori T, Narumi Y, Kure S, Matsubara Y. The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. Hum Mutat 2008; 29: 992-1006.
8. Binder G, Neuer K, Ranke MB, Wittekindt NE. PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. J Clin Endocrinol Metab 2005; 90: 5377-5381.
9. Ferreira LV, Souza SA, Arnhold IJ, Mendonca BB, Jorge AA. PTPN11 (protein tyrosine phosphatase, nonreceptor type 11) mutations and response to growth hormone therapy in children with Noonan syndrome. J Clin Endocrinol Metab 2005; 90: 5156-5160.
10. Lopez-Canti LF, Canete R, del Valle CR, et al. Study of the PTPN11 gene in a group of patients with Noonan syndrome. Horm Res 2006; 65: 1-213. [Abstract]
11. Ferrero GB, Baldassarre G, Delmonaco AG, et al. Clinical and molecular characterization of 40 patients with Noonan syndrome. Eur J Med Genet 2008; 51: 566-572.
12. Bertola DR, Pereira AC, Albano LM, De Oliveira PS, Kim CA, Krieger JE. PTPN11 gene analysis in 74 Brazilian patients with Noonan syndrome or Noonan-like phenotype. Genet Test 2006; 10: 186-191.
13. Tartaglia M, Gelb BD. Germ-line and somatic PTPN11 mutations in human disease. Eur J Med Genet 2005; 48: 81-96.
14. Bertola DR, Kim CA, Pereira AC, et al. Are Noonan syndrome and Noonan-like/multiple giant cell lesion syndrome distinct entities? Am J Med Genet 2001; 98: 230-234.
15. Lee JS, Tartaglia M, Gelb BD, et al. Phenotypic and genotypic characterization of Noonan-like/multiple giant cell lesion syndrome. J Med Genet 2005; 42: e11.
16. Padidela R, Camacho-Hübner C, Attie KM, Savage MO. Abnormal growth in Noonan syndrome: genetic and endocrine features and optimal treatment. Horm Res 2008; 70: 129-136.
17. Noonan JA, Raaijmakers R, Hall BD. Adult height in Noonan syndrome. Am J Med Genet A 2003; 123A: 68-71.
18. Noonan JA. Noonan syndrome and related disorders: alterations in growth and puberty. Rev Endocr Metab Disord 2006; 7: 251-255.
19. Romano AA, Dana K, Bakker B, et al. Growth response, near-adult height, and patterns of growth and puberty in patients with Noonan syndrome treated with growth hormone. J Clin Endocrinol Metab 2009; 94: 2338-2344.