

Mutations in *PTPN11* and Pulmonic Stenosis – an Overview

Introduction

Congenital heart defects occur in about 1 in 160 newborns (1). These cardiac abnormalities are mostly idiopathic and isolated, but can also be part of hereditary syndromes such as Down syndrome, Marfan syndrome, Ellis-van Creveld syndrome, Turner syndrome, or Noonan syndrome. Noonan syndrome has an estimated incidence of about 1:1000 – 1:2,500 live births and leads to congenital heart defects in about 50% of affected individuals, or in about 1:2000 – 1:5000 newborns (2-4). The cardiac abnormalities most often associated with Noonan syndrome are pulmonary valve stenosis and hypertrophic cardiomyopathy, but atrial and ventricular septal defects, branch pulmonary artery stenosis, tetralogy of Fallot, coarctation of aorta, and coronary aneurysms have also been reported (4). Noonan syndrome is genetically heterogeneous, showing both autosomal dominant and, more rarely, autosomal recessive inheritance, and so far has been linked to mutations in either of two genes, *PTPN11* or *KRAS* (5-8). Autosomal dominant gain-of-function mutations in the gene *PTPN11* account for about 50% of all cases of Noonan syndrome and most of the cases associated with pulmonary valve stenosis (9-12). It is important to identify mutations in *PTPN11* as the cause of congenital cardiac abnormalities, since *PTPN11*-related Noonan syndrome may be associated with a host of other manifestations, including bleeding diathesis and juvenile myelomonocytic leukemia (JMML) (13), and because the condition shows a dominant mode of inheritance.

Molecular Pathophysiology

PTPN11 codes for a non-receptor associated protein-tyrosine phosphatase (SHP-2), which plays a key role in a number of different signaling cascades controlling developmental processes such as mesodermal patterning, limb development, hematopoietic cell differen-

tiation, and cardiac semilunar valvulogenesis (9). SHP-2 activation is triggered by binding of various growth factors, cytokines, or hormones to their respective cell-surface receptors. In most cases, SHP-2 activity stimulates downstream signaling (e.g., the Ras/MAPK cascade induced by epidermal growth factor), but it can also exert a negative control (e.g., on interferon-stimulated JAK/STAT signaling). In addition to the enzymatic phosphatase domain (PTP), SHP-2 contains two regulatory src-homology (SH2) domains. In the basal state, the PTP domain is inactive because it is blocked by the N-terminal SH2 domain (14). Binding of a specific phosphopeptide to the SH2 domains releases this block by inducing a conformational shift in SHP-2 that renders the PTP domain accessible to its substrate. The triggering phosphopeptide may be part of a cell-surface receptor or of a separate adapter molecule (15).

About half of all cases of Noonan syndrome are associated with germline gain-of-function mutations in *PTPN11* (7). These gain-of-function mutations disrupt the interaction between the N-terminal SH2 domain and the phosphatase domain, destabilizing the inactive conformation of SHP-2 and allowing SHP-2 to activate or inhibit a downstream signaling cascade in the absence of the appropriate upstream triggering event. Noonan-syndrome associated germline mutations are typically missense mutations (7,9,10,16), although small in-frame deletions have also been reported (17). Somatic rather than germline mutations in *PTPN11* have been identified in 34% of non-syndromic juvenile myelomonocytic leukemia (JMML), 10% of childhood myelodysplastic syndrome (MDS), and 4% of childhood acute myeloid leukemia (AML) (13) and also play a less prominent role in various other cancers (18). It has been suggested that mutations in *PTPN11* cause JMML by overstimulating the Ras signal transduction pathway, and that somatic mutations lead to a more pronounced destabilization of the SHP-2 inactive conformation than germline mutations (13).

Clinical Presentation

Noonan syndrome typically presents in infancy or childhood, with heart defects (most often pulmonary valve stenosis and hypertrophic cardiomyopathy), dysmorphic facial features (hypertelorism with down-slanting palpebral fissures, ptosis, low-set posteriorly angulated ears with thickened helices), a webbed neck with excess nuchal skin, an unusual chest shape (superior pectus carinatum with inferior pectus excavatum), proportionate short stature, and, in males, cryptorchidism (4). Mild retardation, coagulation defects, and spinal deformities may also be present. Noonan patients are at an increased risk for developing JMML, but such syndromic JMML typically has a much better prognosis than isolated JMML (13,16,19,20). Germline gain-of-function mutations in *PTPN11* are also associated with LEOPARD syndrome (21,22) and Noonan-like/multiple giant-cell lesion syndrome (9,23), clinical variants of Noonan syndrome that are characterized by multiple lentiginos and cyst-like osteolytic lesions, respectively.

Diagnosis

Clinical diagnosis of Noonan syndrome in children with cardiac abnormalities is based on presence of characteristic symptoms such as

dysmorphic facial features and short stature (24). However, short stature may not be obvious in young children, and facial dysmorphies tend to become less prominent with age and may be subtle enough to be missed (25,26), complicating clinical diagnosis. A family history may not always be apparent, as an affected parent can be identified in only 30-75% of cases (3,9,16). Since published studies have established a causal relationship between certain variants of *PTPN11* and Noonan syndrome, a clinical diagnosis or suspicion of Noonan syndrome may be confirmed through genetic testing (7,9).

Treatment

Treatment of Noonan syndrome is symptomatic. Noonan-syndrome related heart defects and spine deformities may require surgery, which may be complicated by coagulation defects or malignant hyperthermia (27). Growth-hormone therapy has been shown to increase growth velocity in the first year of treatment, but its effect on adult height is not yet clear (28). In contrast to non-syndromic JMML, Noonan-syndrome related JMML typically has a relatively good prognosis, often showing spontaneous improvement (16,19,20,29).

References

1. Hoffman JIE, Kaplan S (2002) The incidence of congenital heart disease. *J Am Coll Cardiol* 39:1890-900.
2. Nora JJ, Nora AH, Sinha AK, Spangler RD, Lubs HA (1974) The Ullrich-Noonan syndrome (Turner phenotype). *Am J Dis Child* 127:48-55.
3. Allanson JE (1987) Noonan syndrome. *J Med Genet* 24:9-13.
4. Allanson JE. Noonan syndrome. GeneReviews. Available at: <http://genetests.org>. Accessed July 13, 2005.
5. Jamieson CR, van der Burgt I, Brady AF, van Reen M, Elswawi MM, Hol F, Jeffery S, Patton MA, Mariman E (1994) Mapping a gene for Noonan syndrome to the long arm of chromosome 12. *Nat Genet* 8:357-360.
6. Van der Burgt I, Brunner H (2000) Genetic heterogeneity in Noonan syndrome: evidence for an autosomal recessive form. *Am J Med Genet* 94:46-51.
7. Tartaglia M, Mehler EL, Goldberg R, Zampino G, et al (2001) Mutations in *PTPN11*, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 29:465-8.
8. Schubert S, Zenker M, Rowe SL, Boll S, et al (2006) Germline KRAS mutations cause Noonan syndrome. *Nat Genet* 38:331-6.
9. Tartaglia M, Kalidas K, Shaw A, Song X, et al (2002) *PTPN11* mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet* 70:1555-63.
10. Yoshida R, Hasegawa T, Hasegawa Y, Nagai T, Kinoshita E, et al (2004) Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. *J Clin Endocrinol Metab* 89:3359-64.

11. Musante L, Kehl HG, Majewski F, Meinecke P, Schweiger S, et al (2002) Spectrum of mutations in *PTPN11* and genotype-phenotype correlation in 96 patients with Noonan syndrome and five patients with cardio-facio-cutaneous syndrome. *Eur J Hum Genet* 11, 201-6.
12. Zenker M, Buheitel G, Rauch R, Koenig R, et al (2004) Genotype-phenotype correlations in Noonan syndrome. *J Pediatr* 144:368-74.
13. Tartaglia M, Niemeyer CM, Fragale A, Song X, et al (2003) Somatic mutations in *PTPN11* in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. *Nat Genet* 34:148-150.
14. Hof P, Pluskey S, Dhe-Paganon S, Eck MJ, Shoelson SE (1998) Crystal structure of the tyrosine phosphatase SHP-2. *Cell* 92:441-50.
15. Neel BG, Gu H, Pao L (2003) The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem Sci* 28:284-93.
16. Jongmans M, Sistermans EA, Rikken A, Nillesen WM, et al (2005) Genotypic and phenotypic characterization of Noonan syndrome: new data and review of the literature. *Am J Med Genet* 134A:165-170.
17. Lee WH, Raas-Rotschild A, Miteva MA, Bolasco G, Rein A, et al (2005) Noonan syndrome type I with *PTPN11* 3 bp deletion: structure-function implications. *Proteins* 58:7-13.
18. Bentires-Alj M, Guillermo Paez J, David FS, Keilhack H, et al (2004) Activating mutations of the Noonan syndrome-associated *SHP2/PTPN11* gene in human solid tumors and adult acute myelogenous leukemia. *Cancer Res* 64:8816-20.
19. [Bader-Meunier B](#), [Tchernia G](#), [Mielot F](#), [Fontaine JL](#), et al (1997) Occurrence of myeloproliferative disorder in patients with Noonan syndrome. *J Pediatr* 130:885-9.
20. [Choong K](#), [Freedman MH](#), [Chitayat D](#), [Kelly EN](#), et al (1999) Juvenile myelomonocytic leukemia and Noonan syndrome. *J Pediatr Hematol Oncol* 2:523-7.
21. Legius E, Schrandt-Stumpel C, Schollen E, Pulles-Heintzberger C, et al (2002) *PTPN11* mutations in LEOPARD syndrome. *J Med Genet* 39:571-574.
22. Digilio MC, Conti E, Sarkozy A, Mingarelli R, et al (2002) Grouping of multiple-lentiginos/LEOPARD and Noonan syndromes on the *PTPN11* genes. *Am J Hum Genet* 71:389-94.
23. Sarkozy A, Obregon MG, Conti E, Esposito G, et al (2004) A novel *PTPN11* gene mutation bridges Noonan syndrome, multiple lentiginos/LEOPARD syndrome and Noonan-like/multiple giant cell lesion syndrome. *Eur J Hum Genet* 12:1069-72.
24. van der Burgt I, Berends E, Lommen E, van Beersum S, et al (1994) Clinical and molecular studies in a large Dutch family with Noonan syndrome. *Am J Med Genet* 53:187-91.
25. Allanson JE, Hall JG, Hughes HE, Preus M, Witt RD (1985) Noonan syndrome: the changing phenotype. *Am J Med Genet* 21:507-14.
26. Bertola DR, Pereira AC, de Oliveira PAL, Kim CA, Krieger JE (2004) Clinical variability in a Noonan syndrome family with a new *PTPN11* gene mutation. *Am J Med Genet* 130A:378-383.
27. Lee CK, Chang BS, Hong YM, Yang SW, et al (2001) Spinal deformities in Noonan syndrome: a clinical review of sixty cases. *J Bone Surg Am* 83-A:1495-502.
28. Kirk JM, Betts PR, Butler GE, Donaldson MD, et al (2001) Short stature in Noonan syndrome: response to growth hormone therapy. *Arch Dis Child* 84:440-3.
29. Fukuda M, Horibe K, Miyajima Y, Matsumoto K, Nagashima M (1997) Spontaneous remission of juvenile chronic myelomonocytic leukemia in an infant with Noonan syndrome. *J Pediatr Hematol Oncol* 19:177-9