Abnormal Growth in Noonan Syndrome: Genetic and Endocrine Features and Optimal Treatment

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Key Words

Noonan syndrome · Growth · Genetic defects · Growth hormone therapy

Abstract

Noonan syndrome (NS) is a phenotypically heterogeneous syndrome which is frequently associated with short stature. Recent genetic investigations have identified mutations in five genes, namely PTPN11, KRAS, SOS1, NF1 and RAF1 in patients with the NS phenotype. PTPN11 is the commonest, being present in approximately 50% of cases. The degree of short stature in children does not associate closely with the presence of mutations, however some PTPN11-positive patients have decreased GH-dependent growth factors consistent with mild GH insensitivity. GH therapy, using doses similar to those approved for Turner syndrome (TS), induced short-term increases in height velocity over 1–3 years, and may improve final adult height with longer-term treatment.

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Introduction

Noonan syndrome (NS; OMIM163950) is a developmental dysmorphic syndrome characterized by clinical and genetic heterogeneity. In 1930, Ullrich [1] described several male and female patients with short stature and webbed neck, and for a while the syndrome was known as Ullrich-Bonnevie phenotype. However, the definitive phenotype was described by Dr Jacqueline Noonan, a pediatric cardiologist, reporting patients with cardiac valvular stenosis, distinct dysmorphic facial features, webbed neck and chest deformities [2]. Short stature is a recognized feature of NS and its natural history from birth to adulthood was first described by Witt et al. [3].

Clinical Features

NS in childhood presents with wide phenotypic heterogeneity. Clinical features may vary between affected members of the same family and also change with age becoming more mild in adult life [4]. The clinical features may be so subtle that some patients without a known heart defect are considered to be normal during childhood. The characteristic facial features are hypertelorism, down-slanting, anti-mongoloid, palpebral fissures, ptosis, and low-set posteriorly rotated ears with a thickened

Table 1. Molecular genetic findings in Noonan syndrome

Mutation	First identified by	Chromosome loci	Mutation rate	Protein affected	Pathway involved	Testing method
PTPN11	Tartaglia et al. 2001 [22]	12q24.1	40–50%	Non-receptor tyrosine kinase SHP-2	RAS-MAPK	Sequence analysis
KRAS	Schubbert et al. 2006 [25]	12p12.1	3%	GTPase KRAS	RAS-MAPK	Sequence analysis
SOS1	Tartaglia et al. 2007 [27] Roberts et al. 2007 [26]	2p22-p21	10%	SOS1	RAS-MAPK	Sequence analysis
NF1	Hüffmeier et al. 2006 [30]	17q11.2	100% in phenotypic overlap subject	Neurofibromin	RAS	Sequence analysis
RAF1	Pandit et al. 2007 [31] Razzaque et al. 2007 [32]	3p25.2	3%	MEK1, MEK2	RAS-MAPK	Sequence analysis

helix. Pulmonary stenosis (50–62%) and hypertrophic cardiomyopathy (10–20%) are the most frequent heart defects. Feeding difficulties, bleeding diathesis (20%) and lymphatic dysplasias are also reported [5]. Other characteristics may include mild mental retardation, cryptorchidism, clotting disorders, hypogonadism, autoimmune thyroiditis, thoracic deformities, hearing difficulty, and juvenile myelomonocytic leukemia. Scoring systems based on phenotypic characteristics were devised to improve diagnostic sensitivity and specificity [6, 7] and have resulted in a higher percentage of genotype positivity [8].

Growth

Prenatal linear growth was initially reported to be normal [9], although edema may influence birth weight [10]. More recently, French and Japanese studies have reported mean birth weight and length SDS between 0 and –2 for the relevant populations [11, 12]. During childhood, mean height in both sexes approximates the third percentile until approximately 12 years in males and 10 years in females, after which mean height decreases below the normal range due to delayed puberty and decreased pubertal growth spurt [9]. Adult height has been reported by several groups [9]. Noonan et al. [13] described adult heights in 73 subjects aged over 21 years and reported 30% of males and females had heights above the 10th centile and 38% of males and 54.5% of females had heights below the 3rd centile. More recent British data reported mean adult height to be 167.4 cm in males ($n = 18$) and 152.7 cm in females ($n = 25$) [14]. Overall, mean adult height is approximately –2 SD.

Genetic Features (table 1)

The incidence of NS is unknown, but is suggested to be in the region of 1:1,000 to 1:2,500 [15]. The syndrome may be familial, being inherited more commonly as an autosomal dominant [16] rather than a recessive [17] disorder; at least 50% of cases appear to be sporadic [4, 5]. Progress in the identification of a genetic cause of the syndrome came from the demonstration, from a genome-wide linkage analysis of a large Dutch kindred with autosomal dominant NS, of a probable gene locus on chromosome 12q [18]. Analysis of a four-generation Bulgarian family and a three-generation Dutch family further delineated and refined the critical locus to the N-SH2 component on chromosome 12q24.1 [19, 20]. Chen et al. [21], working in a mouse mutant model, independently reported genetic interaction between the epidermal growth factor receptor (EGFR) and protein tyrosine phosphatase, nonreceptor type 11 (PTPN11), which encodes a ubiquitously expressed cytoplasmic protein containing two Src homology 2 domains, SHP-2. EGFR was required for semilunar valve development [21]. In 2001, Tartaglia et al. [22] reported that missense mutations in the PTPN11 gene caused NS. The same group reported PTPN11 mutations in 59% of individuals with familial NS and 37% of sporadic cases ($p < 0.02$), suggesting that unidentified genes also contributed to NS and phenotypically related disorders such as LEOPARD, cardio-facial-cutaneous and Costello syndromes [23, 24].

Most PTPN-11 mutations in NS were missense involving a single amino acid in exons 3, 7, or 8 of the gene. Mutations involved either the N-SH2 or PTP domain leading to gain in function of the SHP-2 protein inducing increased phosphatase activity. It is not known with preci-

sion how expression of mutant SHP-2 translates into the specific NS phenotype [24]. SHP-2 plays a positive regulatory role in signal transmission via the receptor tyrosine kinase (RTK)-mediated RAS/ERK pathway. Through downstream signal transfer, SHP-2 phosphatase relays signals from activated RTK to effectors of the K-RAS protein leading to RAS-ERK cascade activation.

Twenty-five percent of cases of juvenile myelomonocytic leukemia (JMML) demonstrate a mutation in the KRAS or NRAS gene. Using sequence analyses, Schubert et al. [25] found a KRAS gene mutation in a PTPN11-negative female infant with the severe NS phenotype and associated JMML. Subsequent analyses of 174 NS subjects negative for a PTPN11 mutation and not suffering from JMML revealed KRAS gene mutations in 5 subjects [25]. The KRAS gene encodes for K-Ras protein, a GTPase that converts GTP to GDP, which transmits signals downstream and leads to activation of ERK. The KRAS gene mutation leads to a gain in function of the K-Ras protein causing it to be permanently active. During embryonic development, the overactive K-Ras protein and ERK disrupt the growth and maturation of normal tissue leading to signs and symptoms of NS.

More recently, Roberts et al. [26] and Tartaglia et al. [27, 28] reported an SOS1 gene mutation located on chromosome 2p22.1 which was present in 20% of NS cases. The SOS1 gene encodes for Ras-specific guanine nucleotide exchange factor (RAS-GEF) which is an important component in the receptor tyrosine kinase-mediated RAS-ERK cascade activation. A diagram of identified genes in NS and their proposed interaction with the GH-IGF-I axis is shown in figure 1.

Mutations in two further genes have been reported in association with NS. The first of these is NF1 [29]. Heterozygous mutations of NF1 were reported in all of 7 patients who had some of the combined features of NS and neurofibromatosis type-1 (NF1) [30]. None of the patients had PTPN11 mutations. It has been suggested that most variable phenotypes of the NF1-NS spectrum are variants of NF1. The fifth gene is RAF1, a downstream effector of RAS signaling in the MAPKinase pathway. Missense RAF1 mutations were reported in 18/231 individuals with NS and 2/6 patients with Leopard syndrome and were closely linked to hypertrophic cardiomyopathy [31]. Gain of function RAF1 mutations have been proposed as causative for NS and represent a new mechanism for the activation of the MAPKinase pathway [32].

To summarize, mutations in five known genes have been demonstrated in NS patients. PTPN11, KRAS, SOS1, NF1 and RAF1, accounting for 60–80% of cases. How

Fig. 1. Interaction between genes identified in Noonan syndrome and the pathways of GH action.

these mutations cause phenotypic changes is still unclear. However it must be remembered by the clinician that it is still possible to diagnose NS clinically in the absence of positive genetic findings.

Genotype and Phenotype Relationships

The causative influences of genetic mutations on the NS phenotype are not currently known. Numerous studies have tried to correlate the presence of genetic mutations with observed phenotypes. Mutations in PTPN11 lead to gain in function of SHP-2 which affects the morphogenesis of the semilunar valve in mice and may be responsible for pulmonary stenosis observed in some NS patients. Tartaglia et al. [23] studied 119 subjects of whom 54 were positive for PTPN11 mutations and found a significantly increased incidence of pulmonary stenosis in the PTPN11-positive (70.6%) compared to mutation-negative (46.2%) subjects. Hypertrophic cardiomyopathy was also more common in PTPN11 mutation-negative subjects and has now also been reported to have a strong association with RAF1 mutations [31, 32]. The NF1 gene mutations occur in patients with the overlap of NS and NF1 phenotypes [30].

Several studies have attempted to correlate genotype with parameters of linear growth. Birth weight and length were reported to be similar in PTPN11-positive (n = 18)

Table 2. Studies of GH therapy in Noonan syndrome

Reference	Patients n, sex	Study duration years	Age at start of GH, years	GH dose	Height SDS			
					pretreatment	1 year	2 years	3 years
Ogawa et al. [48]	15	2	7.5 ± 2.5	0.5 U/kg/week	-2.8 ± 0.7	-2.4 ± 0.7	-2.2 ± 0.5	NA
Osio et al. [51]	11, female	2–10	7.7 ± 2.2	33 (n = 6) and 66 (n = 7) µg/kg/day	-3.1 ± 0.5	ND	ND	ND
	7, male	2–10	8.6 ± 3.4	33 (n = 4) and 66 (n = 8) µg/kg/day	-2.7 ± 0.4	ND	ND	ND
				0.3 ± 0.06 mg/kg/week	-3.3 ± 0.9	-2.8 ± 1.1	-2.6 ± 1.1	-2.4 ± 1.1
Romano et al. [40]	42	4	10.6 ± 3.8	0.33 mg/kg/week	-2.7 ± 0.4	-2.2 ± 0.6	-2.1 ± 0.9	-1.9 ± 0.9
Macfarlane et al. [50]	23	3	9.3 ± 2.6	0.33 mg/kg/week	-3.0 ± 0.1	-2.4 ± 0.1	NA	NA
Cotterill et al. [41]	27	1	8.9 ± 0.5	0.8 ± 0.24 U/kg/week	-2.9 ± 0.7	-2.6 ± 0.8	ND	ND
Kirk et al. [46]	66	1–6	10.2 ± 3.3	ND	-3.4	ND	ND	ND
Shaw et al. [14]	10	12	ND	0.15 U/kg/day	-3.2 ± 0.8	ND	ND	ND
Noordam et al. [52]	Group A, n = 7	4	9.5 ± 2.9	0.15 U/kg/day	-3.4 ± 0.5	ND	ND	ND
	Group B, n = 10	4	8.3 ± 3.2	0.15 U/kg/day	-2.9 ± 0.7	ND	ND	ND
	Group C, n = 6	3	10.1 ± 3.7	0.15 U/kg/day	-2.3	-1.8	ND	ND
De Schepper et al. [47]	23	1	10.3	1.1 U/kg/week				

NA = Not applicable; ND = not described; BA = bone age, HA = Height age.

Noordam Study; Group A- GH for 2 years, discontinued for 3rd year, reinstituted for 4th year; Group B 1st year served as controls, GH administered for 2nd, 3rd & 4th year; Group C GH administered for the first three years, 4th year served as control.

and negative subjects (n = 27) [12]. A recent French study evaluated 35 individuals with NS of whom 20 were positive for the PTPN11 mutation [11]. There was a trend of decreased birth length in mutated (-1.4 ± 1.2 SD) compared with non-mutated (-0.9 ± 1.0 SD) newborns but the difference was not significant ($p = 0.24$), although 6 mutated and 2 non-mutated subjects were small for gestational age.

Studies of postnatal growth provide conflicting data on the severity of short stature between mutation-positive and mutation-negative groups. Kosaki et al. [33] reported severe growth restriction in 6 of 7 PTPN11-positive cases. Growth in a study of 45 subjects was comparable in mutation-positive and mutation-negative males, whereas height SDS was lower in mutation-positive females [12]. In other studies, there were no differences in growth parameters between 51 mutation-positive and 64 mutation-negative subjects [23] nor in the analysis of growth to final height in 56 cases by Shaw et al. [14]. However, in other studies of NS, patients with PTPN11 mutations were significantly shorter than those without the mutation [34, 35]. Zenker et al. [34] reported that 82% of 34 mutation-positive cases had heights less than -2 (mean -3.1) SDS compared with 57% of the 23 mutation-negative subjects (mean -2.4 SDS). Similarly, Sarkozy et al. [35] found that 86% of mutation-positive cases compared with 40% of mutation-negative cases had short stature.

Limal et al. [11] also reported more pronounced growth disturbance in mutation-positive subjects at the age of 6 years. To date only one study has described the phenotype in cases with KRAS germline mutations, which showed that 8 such patients had heights below the 10th centile [36].

Growth Hormone-IGF-I Axis

Qualitatively abnormal spontaneous GH secretion with high trough GH levels consistent with neurosecretory dysfunction has been reported [37–39]. In a large study of 150 NS subjects from the National Cooperative Growth Study (NCGS), Romano et al. [40] reported that 45% had peak GH responses to provocation with <10 µg/l. Cotterill et al. [41] reported similar data with 10 of 27 children having peak GH levels of <12.5 µg/l. Other studies have reported normal GH secretion [11, 42]. Several investigators have reported low IGF-I levels [11, 41–43], whereas IGFBP-3 is usually normal [11, 41]; amyotrophic lateral sclerosis may be decreased.

There are theoretical reasons why PTPN11, RAS, SOS1 and RAF1 mutations may affect the function of the GH axis, leading to some deficiency of IGF-I (fig. 1). GH secretion and GH-dependent peptides have been compared in PTPN11 mutation-positive and mutation-negative

Δ Height SDS after treatment	Final height SDS	Height velocity, cm/years				Bone age		Δ BA/ Δ HA
		basal	1 year	2 years	3 years	pretreatment	after treatment	
ND	NA	4.8 ± 1	7.0 ± 1.2	5.5 ± 0.6		5.8 ± 2.1		1.1 ± 0.5
1.5 ± 0.8	-1.6 ± 0.8	ND	ND	ND	ND	ND	ND	ND
1.8 ± 1.0	-0.9 ± 1.2	ND	ND	ND	ND	ND	ND	ND
ND	ND	4.3 ± 2.3	8.0 ± 2.0	6.9 ± 1.7	6.0 ± 1.5	-2.9 ± 1.7		1.12
ND	ND	4.4 ± 1.7	8.4 ± 1.7	6.2 ± 1.7	5.8 ± 1.8	ND	ND	ND
0.65 ± 0.1	NA	4.9 ± 0.2	8.1 ± 0.4	NA	NA	7.6 ± 0.4	9.3 ± 0.5	ND
ND	ND	4.8 ± 1.1	7.2 ± 1.7	ND	ND	ND	ND	1.0
ND	-2.7	ND	ND	ND	ND	ND	ND	ND
0.8 ± 0.7	ND	ND	ND	ND	ND	7.8 ± 2.8	ND	1.1 ± 0.1
0.8 ± 0.5	ND	ND	ND	ND	ND	6.7 ± 3.6	ND	1.1 ± 0.3
0.9 ± 0.9	ND	ND	ND	ND	ND	8.4 ± 3.3	ND	1.2 ± 0.4
0.5 ± 0.5	ND	4.5	8.5	ND	ND	ND	ND	ND

subjects [11, 42]. Binder et al. [43] reported spontaneous and stimulated GH secretion to be significantly higher and IGF-I levels significantly lower in mutation-positive subjects suggesting mild GH resistance. Since tyrosine phosphorylation is a critical component of GH receptor signaling, it is thought that the abnormally enhanced phosphatase activity of SHP-2 leads to increased tyrosine dephosphorylation and may disturb GH receptor and JAK2 interaction thus interrupting GH-stimulated pathways [44, 45].

Growth Hormone Therapy

The efficacy of GH therapy in other non-GH-deficient disorders such as Turner syndrome, together with the demonstration of possible GH-IGF1 axis abnormalities has led to research into the use of GH in NS. Most reports are of observational studies involving small numbers of subjects and lacking randomization or control groups. The dosage used has varied from standard replacement doses to higher doses such as those used in Turner syndrome (table 2). Most studies have reported fair short-term responses to GH therapy by demonstrating an increase in height velocity [37, 40, 41, 46–48]. Short-term growth acceleration comparable to that seen in Turner syndrome has been reported [40, 49]. However over a pe-

riod of time waning of the response has been reported [44, 48, 50]. Some longer-term studies have reported no sustained catch-up growth, although height gain was maintained until the onset of puberty [51]. An acceleration in bone maturation has been demonstrated which could compromise the GH response to adult height [52]. In May 2007, NovoNordisk obtained FDA approval for treatment of NS with their GH preparation nortitropin using a dose of 0.066 mg/kg/day.

Adult Height

Only a small number of studies have reported adult heights achieved with prolonged GH treatment. Kirk et al. [46] reported a disappointing gain in adult height of +0.8 SDS (3 cm) after a mean of 5.3 years treatment in 10 patients. Only 1 child reached final height above the 3rd centile.

An uncontrolled study of 18 children who reached adult height after a mean duration of treatment of 7.5 years reported an increase in height SDS from -2.9 ± 0.4 before GH therapy to -1.2 ± 1.0 . This was equivalent to a gain of 10.3 cm compared to pretreatment predicted adult height [51]. The initial rhGH dose in this study was either 0.033 or 0.066 mg/kg/day. FDA approval has recently been given to rhGH treatment of short children with NS in the US, using doses up to 0.066 mg/kg day.

Table 3. Response to growth hormone treatment in Noonan syndrome patients with and without *PTPN11* mutations

Reference	Parameter	Number of patients (mut+/mut-)	<i>PTPN11</i> mutation+	<i>PTPN11</i> mutation-	p value
<i>Height SDS</i>					
Limal et al. 2006 [11]	Pre-Tx Ht SDS	15/10	-3.5 ± 0.9	-3.0 ± 0.8	0.18
	Year 1 Ht SDS	15/10	-3.1 ± 1.2	-2.4 ± 0.7	0.08
	Year 2 Ht SDS	15/10	-3.1 ± 1.4	-2.0 ± 0.9	0.03
Binder et al. 2005 [43]	Pre-Tx Ht SDS	8/3	-3.46 ± 0.71	-3.80 ± 0.13	0.44
	Year 1 Δ Ht SDS	8/3	+0.66 ± 0.21	+1.26 ± 0.36	0.007
Ferreira et al. 2005 [42]	Pre-Tx Ht SDS	7/7	-3.6 ± 1	-3.4 ± 1	NS
	Year 1 ΔHt SDS	7/7	+0.30 ± 0.41	+0.42 ± 0.43	NS
	Years 1-2 ΔHt SDS	6/6	+0.69 ± 0.45	+0.82 ± 0.70	NS
	Years 1-3 ΔHt SDS	4/4	+0.76 ± 0.41	+1.74 ± 0.10	<0.01
<i>Height velocity, cm/years</i>					
Limal et al. 2006 [11]	Pre-Tx HV	15/10	4.3 ± 0.9	5.2 ± 1.4	0.09
	Year 1 HV	15/10	7.4 ± 1.6	8.5 ± 1.7	0.09
	Year 2 HV	15/10	5.8 ± 1.4	6.9 ± 1.6	0.13
Ferreira et al. 2005 [42]	Pre-Tx HV	7/7	4.3 ± 1.0	3.9 ± 1.4	NS
	Year 1 HV	7/7	6.8 ± 1.5	7.6 ± 1.9	NS
	Year 2 HV	6/6	5.4 ± 1.5	7.1 ± 2.3	NS
	Year 3 HV	4/5	5.7 ± 1.5	7.0 ± 3.8	NS

HT = Height; HV = height velocity; NS = not significant; Tx = GH therapy.

Genetics and Response to Growth Hormone (table 3)

Results of GH therapy related to *PTPN11* mutation status have been reported in three studies. Growth responses to GH were significantly greater in mutation-negative subjects, consistent with the hypothesis of GH resistance in the mutation-positive patients [11, 42, 43]. However the growth response to GH therapy is difficult to predict. We have recently seen an excellent response to GH therapy in a young NS child who had biochemical features of GH resistance but was negative for the *PTPN11* mutation [53]. GH-dependent growth factors all normalized on GH treatment.

Cardiac Status

GH therapy in NS children with congenital heart diseases may pose potential risks of aggravation of the heart condition. Most of the studies have excluded subjects with hypertrophic cardiomyopathy. However no adverse effects on cardiac muscle mass has been reported and no patients have developed features of hypertrophic cardiomyopathy during treatment with GH [41, 54]. Although GH therapy may be best avoided in children with active cardiac decompensation, in the child without detectable cardiac dysfunction GH treatment does not appear to be contraindicated.

Possible Rationale for rhIGF-I Therapy

The theoretical disturbance of the GH-IGF-I axis in NS, particularly that of impaired IGF-I production in mutation-positive patients, has been discussed above. There may be a rationale for a clinical trial of rhIGF-I therapy in patients with severely abnormal growth who have biochemical features of GH resistance. The indication for rhIGF-I therapy may be strengthened by a lack of response to GH therapy. As discussed previously, growth in NS is variable and the response to GH therapy is difficult to predict with confidence. Nonetheless, we feel that in the NS patient with severe growth failure, some benefit can be expected with GH as first-line therapy. rhIGF-I may in the future be considered a second-line option, particularly for mutation-positive patients, however no data have been reported to support a recommendation at this time.

Conclusions

NS is a phenotypically heterogeneous clinical disorder characterized by certain recognizable physical abnormalities. In childhood, impaired linear growth is one of

the more concerning features of NS, which may be accompanied by pubertal delay. Genetic defects have been demonstrated which may affect the function of the GH-IGF-I axis, and have been reported to affect over 60% of cases. However, there are likely other, as yet unidentified, genetic defects causing the NS phenotype, since classical familial NS can occur in the absence of the known mutations.

The growth pattern in NS is variable and approximately half of the affected individuals attain adult heights below the normal range without treatment. The response to rhGH therapy has likewise been variable, with modest

increases in height velocity on standard doses. The PTPN11 mutation appears to be a pharmacogenetic predictor of GH responsiveness. rhGH therapy using higher doses similar to those licensed for Turner syndrome have been shown to give substantial short-term increases in height velocity. Longer-term benefit has been reported in a small number of patients treated to adult height. Marketing approval has been granted in the US, but not currently in Europe. Due to the possibility of impaired IGF-I generation in NS, treatment with rhIGF-I should be explored in future studies.

References

- Ullrich O: Ueber typische Kombinationsbilder multipler Abarten. *Z Kinderheilk* 1930;49:271–276.
- Noonan JA: Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. *Am J Dis Child* 1968;116:373–380.
- Witt DR, Keena BA, Hall JG, Allanson JE: Growth curves for height in Noonan syndrome. *Clin Genet* 1986;30:150–153.
- Allanson JE, Hall JG, Hughes HE, Preus M, Witt DR: Noonan syndrome: the changing phenotype. *Am J Med Genet* 1985;21:507–514.
- Sharland M, Burch M, McKenna WM, Patton MA: A clinical study of Noonan syndrome. *Arch Dis Child* 1992;67:178–183.
- Duncan WJ, Fowler RS, Farkas LG, Ross RB, Wright AW, Bloom KR, Huot DJ, Sondheimer HM, Rowe RD: A comprehensive scoring system for evaluating Noonan syndrome. *Am J Med Genet* 1981;10:37–50.
- van der Burgt I, Berends E, Lommen E, van BS, Hamel B, Mariman E: Clinical and molecular studies in a large Dutch family with Noonan syndrome. *Am J Med Genet* 1994;53:187–191.
- Jongmans M, Sistermans EA, Rikken A, Nillesen WM, Tamminga R, Patton M, Mair EM, Tartaglia M, Noordam K, van der Burgt I: Genotypic and phenotypic characterization of Noonan syndrome: new data and review of the literature. *Am J Med Genet A* 2005;134:165–170.
- Ranke MB, Heidemann P, Knupfer C, Enders H, Schmaltz AA, Bierich JR: Noonan syndrome: growth and clinical manifestations in 144 cases. *Eur J Pediatr* 1988;148:220–227.
- Allanson JE: Noonan syndrome. *J Med Genet* 1987;24:9–13.
- Limal JM, Parfait B, Cabrol S, Bonnet D, Leheup B, Lyonnet S, Vidaud M, Le BY: Noonan syndrome: relationships between genotype, growth, and growth factors. *J Clin Endocrinol Metab* 2006;91:300–306.
- Yoshida R, Hasegawa T, Hasegawa Y, Nagai T, Kinoshita E, Tanaka Y, Kanegane H, Ohyama K, Onishi T, Hanew K, Okuyama T, Horikawa R, Tanaka T, Ogata T: Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. *J Clin Endocrinol Metab* 2004;89:3359–3364.
- Noonan JA, Raaijmakers R, Hall BD: Adult height in Noonan syndrome. *Am J Med Genet* 2003;123:68–71.
- Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA: The natural history of Noonan syndrome: a long-term follow-up study. *Arch Dis Child* 2007;92:128–132.
- Mendez HM, Opitz JM: Noonan syndrome: a review. *Am J Med Genet* 1985;21:493–506.
- Jongmans M, Otten B, Noordam K, van der Burgt I: Genetics and variation in phenotype in Noonan syndrome. *Horm Res* 2004;62(suppl 3):56–59.
- van der Burgt I, Brunner H: Genetic heterogeneity in Noonan syndrome: evidence for an autosomal recessive form. *Am J Med Genet* 2000;94:46–51.
- Jamieson CR, van der Burgt I, Brady AF, Van Reen M, Elsayi MM, Hol F, Jeffery S, Patton MA, Mariman E: Mapping a gene for Noonan syndrome to the long arm of chromosome 12. *Nat Genet* 1994;8:357–360.
- Brady AF, Jamieson CR, van der Burgt I, Crosby A, Van Reen M, Kremer H, Mariman E, Patton MA, Jeffery S: Further delineation of the critical region for Noonan syndrome on the long arm of chromosome 12. *Eur J Hum Genet* 1997;5:336–337.
- Legius E, Schollen E, Matthijs G, Fryns JP: Fine mapping of Noonan/cardio-facio cutaneous syndrome in a large family. *Eur J Hum Genet* 1998;6:32–37.
- Chen B, Bronson RT, Klamann LD, Hampton TG, Wang JF, Green PT, Magnuson T, Douglas PS, Morgan JP, Neel BG: Mice mutant for *Egfr* and *Shp2* have defective cardiac semilunar valvulogenesis. *Nat Genet* 2000;24:296–299.
- Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD: Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001;29:465–468.
- Tartaglia M, Kalidas K, Shaw A, Song X, Musat DL, van der Burgt I, Brunner HG, Bertola DR, Crosby A, Ion A, Kucherlapati RS, Jeffery S, Patton MA, Gelb BD: PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet* 2002;70:1555–1563.
- Tartaglia M, Gelb BD: Noonan syndrome and related disorders: genetics and pathogenesis. *Annu Rev Genomics Hum Genet* 2005;6:45–68.
- Schubbert S, Zenker M, Rowe SL, Boll S, Klein C, Bollag G, van der Burgt I, Musante L, Kalscheuer V, Wehner LE, Nguyen H, West B, Zhang KY, Sistermans E, Rauch A, Niemeyer CM, Shannon K, Kratz CP: Germline KRAS mutations cause Noonan syndrome. *Nat Genet* 2006;38:331–336.
- Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Kucherlapati RS: Germline gain-of-function mutations in *SOS1* cause Noonan syndrome. *Nat Genet* 2007;39:70–74.

- 27 Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, Pandit B, Oishi K, Martinelli S, Schackwitz W, Ustaszewska A, Martin J, Bristow J, Carta C, Lepri F, Neri C, Vasta I, Gibson K, Curry CJ, Siguero JP, Digilio MC, Zampino G, Dallapiccola B, Barsagi D, Gelb BD: Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. *Nat Genet* 2007;39:75–79.
- 28 Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, Pandit B, Oishi K, Martinelli S, Schackwitz W, Ustaszewska A, Martin J, Bristow J, Carta C, Lepri F, Neri C, Vasta I, Gibson K, Curry CJ, Siguero JP, Digilio MC, Zampino G, Dallapiccola B, Barsagi D, Gelb BD: Corrigendum: Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. *Nat Genet* 2007;39:276.
- 29 Noordam K: Expanding the genetic spectrum of Noonan syndrome. *Horm Res* 2007;68:24–27.
- 30 Hüffmeier U, Zenker M, Hoyer J, Fahsold R, Rauch A: A variable combination of features of Noonan syndrome and neurofibromatosis type 1 are caused by mutations of the NF1 gene. *Am J Med Genet A* 2006;140:2749–2756.
- 31 Pandit B, Sarkozy A, Pennacchio LA, Carta C, Oishi K, Martinelli S, Pogna EA, Schackwitz W, Ustaszewska A, Landstrom A, Bos JM, Ommen SR, Esposito G, Lepri F, Faul C, Mundel P, Lopez Siguero JP, Tenconi R, Selicorni A, Rossi C, Mazzanti L, Torrente I, Marino B, Digilio MC, Zampino G, Ackerman MJ, Dallapiccola B, Tartaglia M, Gelb BD: Gain-of-function RAF1 mutations cause Noonan and leopard syndromes with hypertrophic cardiomyopathy. *Nat Genet* 2007;39:1007–1012.
- 32 Razzaque MA, Nishizawa T, Komoike Y, Yagi H, Furutani M, Amo R, Kamisago M, Momma K, Katayama H, Nagakawa M, Fujiwara Y, Matsushima M, Mizuno K, Tokuyama M, Hiroto H, Muneuchi J, Higashinakagawa T, Matsuoka R: Germline gain-of-function mutations in RAF1 cause Noonan syndrome. *Nat Genet* 2007;39:1013–1017.
- 33 Kosaki K, Suzuki T, Muroya K, Hasegawa T, Sato S, Matsuo N, Kosaki R, Nagai T, Hasegawa Y, Ogata T: PTPN11 (protein-tyrosine phosphatase, nonreceptor-type 11) mutations in seven Japanese patients with Noonan syndrome. *J Clin Endocrinol Metab* 2002;87:3529–3533.
- 34 Zenker M, Buheitel G, Rauch R, Koenig R, Bosse K, Kress W, Tietze HU, Doerr HG, Hofbeck M, Singer H, Reis A, Rauch A: Genotype-phenotype correlations in Noonan syndrome. *J Pediatr* 2004;144:368–374.
- 35 Sarkozy A, Conti E, Seripa D, Digilio MC, Grifone N, Tandoi C, Fazio VM, Di C, V, Marino B, Pizzuti A, Dallapiccola B: Correlation between PTPN11 gene mutations and congenital heart defects in Noonan and LEOPARD syndromes. *J Med Genet* 2003;40:704–708.
- 36 Zenker M, Lehmann K, Schulz AL, Barth H, Hansmann D, Koenig R, Korinthenberg R, Kreiss-Nachtsheim M, Meinecke P, Morlot S, Mundlos S, Quante AS, Raskin S, Schnabel D, Wehner LE, Kratz CP, Horn D, Kutsche K: Expansion of the genotypic and phenotypic spectrum in patients with KRAS germline mutations. *J Med Genet* 2007;44:131–135.
- 37 Ahmed ML, Foot AB, Edge JA, Lamkin VA, Savage MO, Dunger DB: Noonan's syndrome: abnormalities of the growth hormone/IGF-I axis and the response to treatment with human biosynthetic growth hormone. *Acta Paediatr Scand* 1991;80:446–450.
- 38 Noordam C, van der Burgt I, Sweep CG, Delemarre-van de Waal HA, Sengers RC, Otten BJ: Growth hormone (GH) secretion in children with Noonan syndrome: frequently abnormal without consequences for growth or response to GH treatment. *Clin Endocrinol (Oxf)* 2001;54:53–59.
- 39 Tanaka K, Sato A, Naito T, Kuramochi K, Itabashi H, Takemura Y: Noonan syndrome presenting growth hormone neurosecretory dysfunction. *Intern Med* 1992;31:908–911.
- 40 Romano AA, Blethen SL, Dana K, Noto RA: Growth hormone treatment in Noonan syndrome: the National Cooperative Growth Study experience. *J Pediatr* 1996;128:S18–S21.
- 41 Cotterill AM, McKenna WJ, Brady AF, Sharland M, Elswi M, Yamada M, Camacho-Hübner C, Kelnar CJ, Dunger DB, Patton MA, Savage MO: The short-term effects of growth hormone therapy on height velocity and cardiac ventricular wall thickness in children with Noonan's syndrome. *J Clin Endocrinol Metab* 1996;81:2291–2297.
- 42 Ferreira LV, Souza SA, Arnhold JJ, 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.
- 43 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.
- 44 Stofega MR, Herrington J, Billestrup N, Carter-Su C: Mutation of the SHP-2 binding site in growth hormone (GH) receptor prolongs GH-promoted tyrosyl phosphorylation of GH receptor, JAK2, and STAT5B. *Mol Endocrinol* 2000;14:1338–1350.
- 45 Maile LA, Clemmons DR: Regulation of insulin-like growth factor 1 receptor dephosphorylation by SHPS-1 and the tyrosine phosphatase SHP-2. *J Biol Chem* 2002;277:8955–8960.
- 46 Kirk JM, Betts PR, Butler GE, Donaldson MD, Dunger DB, Johnston DI, Kelnar CJ, Price DA, Wilton P, Group tU: Short stature in Noonan syndrome: response to growth hormone therapy. *Arch Dis Child* 2001;84:440–443.
- 47 De Schepper J, Otten BJ, Francois I, Bourguignon JP, Craen M, van der Burgt I, Massa GG: Growth hormone therapy in pre-pubertal children with Noonan syndrome: first year growth response and comparison with Turner syndrome. *Acta Paediatr* 1997;86:943–946.
- 48 Ogawa M, Moriya N, Ikeda H, Tanaka A, Tanaka T, Ohya K, Mori O, Yazawa T, Fujita K, Seino Y, Kubo T, Tanaka H, Nishi Y, Yoshimoto M: Clinical evaluation of recombinant human growth hormone in Noonan syndrome. *Endocr J* 2004;51:61–68.
- 49 De Schepper J, Otten BJ, Francois I, Bourguignon JP, Craen M, Van der Burgt I, Massa GG: Growth hormone therapy in pre-pubertal children with Noonan syndrome: first year growth response and comparison with Turner syndrome. *Acta Paediatr* 1997;86:943–946.
- 50 Macfarlane CE, Brown DC, Johnston LB, Patton MA, Dunger DB, Savage MO, McKenna WJ, Kelnar CJH: Growth hormone therapy and growth in children with Noonan's syndrome: results of 3 years' follow-up. *J Clin Endocrinol Metab* 2001;86:1953–1956.
- 51 Osio D, Dahlgren J, Wikland KA, Westphal O: Improved final height with long-term growth hormone treatment in Noonan syndrome. *Acta Paediatr* 2005;94:1232–1237.
- 52 Noordam C, van der Burgt I, Sengers RC, Delemarre-van de Waal HA, Otten BJ: Growth hormone treatment in children with Noonan's syndrome: four year results of a partly controlled trial. *Acta Paediatr* 2001;90:889–894.
- 53 Walton-Betancourth S, Martinelli CE, Thallange NKS, Dyke MP, Acerini CL, White S, Camacho-Hübner C, Savage MO: Excellent growth response to growth hormone therapy in a child with PTPN11-negative Noonan syndrome. *J Endocrinol Invest* 2007;30:439–441.
- 54 Noordam C, Draaisma JM, van den Nieuwenhof J, van der Burgt I, Otten BJ, Daniels O: Effects of growth hormone treatment on left ventricular dimensions in children with Noonan's syndrome. *Horm Res* 2001;56:110–113.