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PTPN11 Mutations Are Associated with Mild Growth Hormone Resistance in Individuals with Noonan Syndrome

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Context: Noonan syndrome is frequently associated with an unclear disturbance of GH secretion. Half the individuals with Noonan syndrome carry a heterozygous mutation of the nonreceptor-type protein tyrosine phosphatase, Src homology region 2-domain phosphatase-2 (SHP-2), encoded by *PTPN11*, which has a role in GH receptor signaling.

Objective: The objective of this study was to compare GH secretion and IGF-I/IGF-binding protein-3 (IGFBP-3) levels of the SHP-2 mutation-positive (mut$^+$ group) *vs.* mutation-negative individuals (mut$^-$ group).

Design, Setting, and Patients: All children presenting to us with short stature plus at least three typical anomalies of Noonan syndrome or pulmonic stenosis during the last 5 yr (n = 29; 10 females and 19 males) were recruited. Auxological data, dysmorphic features, and cardiac morphology were documented. Hormone levels were measured by RIA. All coding exons of *PTPN11* were sequenced after PCR amplification.

Intervention: A prepubertal subgroup (n = 11) was treated with recombinant human GH (rhGH) to promote growth.

Results: Sequencing yielded 11 different *PTPN11* missense mutations in 16 of the 29 patients (55% mut$^+$). Pulmonic stenosis (81 *vs.* 15%; $P = 0.0007$) and septal defects (63 *vs.* 15%; $P = 0.02$) were more frequently found in the mut$^+$ group, whereas minor anomalies, cryptorchidism, and learning disabilities were as frequent in the mut$^+$ group as in the mut$^-$ group. The mut$^+$ group was younger at presentation (mean ± SD, 5.1 ± 2.7 *vs.* 10.3 ± 5.2 yr; $P = 0.002$), but not significantly shorter [−3.15 ± 0.92 *vs.* −3.01 ± 1.35 height SD score (SDS)]. IGF-I levels (−2.03 ± 0.69 *vs.* −1.13 ± 0.89 SDS; $P = 0.005$) and IGFBP-3 levels (−0.92 ± 1.26 *vs.* 0.40 ± 1.08 SDS; $P = 0.006$) were significantly lower in the mut$^+$ group. In contrast, GH levels showed a tendency to be higher in the mut$^+$ group during spontaneous secretion at night and arginine stimulation ($P \geq 0.075$, not significant). The mean change in height SDS after 1 yr of rhGH therapy (0.043 mg/kg·d) was +0.66 ± 0.21 in the mut$^+$ group (n = 8), but +1.26 ± 0.36 in the mut$^-$ group (n = 3; $P = 0.007$).

Conclusions: Our data suggest that SHP-2 mutations in Noonan syndrome cause mild GH resistance by a postreceptor signaling defect, which seems to be partially compensated for by elevated GH secretion. This defect may contribute to the short stature phenotype in children with SHP-2 mutations and their relatively poor response to rhGH. **(*J Clin Endocrinol Metab* 90: 5377–5381, 2005)**

NOONAN SYNDROME (OMIM 163950) is a disorder characterized by facial dysmorphic features, heart defects, and short stature (1). The minor facial anomalies comprise hypertelorism; low-set, posteriorly rotated ears; broad forehead; inverse nuchal hair line; down-slanting palpebral fissures; ptosis; and high-arched palate (2). Many of these features are also present in girls with Turner syndrome (1). The typical heart defects in Noonan syndrome are pulmonic stenosis and hyperthropic cardiomyopathy (3). Short stature is found in 50% of the children with Noonan syndrome, with a mean final height of −1.9 height SD score (SDS) (4). GH secretion has been shown to be frequently abnormal, but classical GH deficiency is rare in Noonan syndrome (5, 6). Additional features of the Noonan syndrome are cryptorchidism, mild mental retardation, bleeding diathesis of diverse origin, webbed neck, and chest deformities (7).

Analysis of pedigrees in familial cases of Noonan syndrome suggested an autosomal dominant inheritance (7). Recently, *PTPN11* (OMIM 176876), which encodes the nonreceptor-type protein tyrosine phosphatase, Src homology region 2-domain phosphatase-2 (SHP-2), has been identified as the major Noonan syndrome disease gene using a positional candidacy approach (8). Screening for mutations revealed the existence of missense mutations of *PTPN11* in 40–50% of individuals with Noonan syndrome (3, 9–12). SHP-2 is a protein tyrosine phosphatase that is ubiquitously expressed and implicated in postreceptor signaling of developmental processes such as mesodermal patterning, limb development, hemopoietic cell differentiation, and valvulogenesis (13). In SHP-2, the N-SH2 domain interacts with the PTP domain blocking the catalytic site, which becomes active when N-SH2 binds a phosphotyrosyl residue (14). To date, all detected missense mutations in Noonan syndrome affect amino acids involved in the interaction of the N-SH2 domain and the PTP domain, which are very likely to result in a chronic stabilization of the active conformation and, therefore, a gain of function (8). Activated SHP-2 has been shown to be involved in the GH receptor (GHR) signaling pathway

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Abbreviations: GHR, GH receptor; IGFBP, IGF binding protein; JAK-2, Janus kinase-2; mut$^+$, positive for mutations of Src homology region 2-domain phosphatase-2; mut$^-$, negative for mutations of Src homology region 2-domain phosphatase-2; rhGH, recombinant human GH; SDS, SD score; SHP-2, Src homology region 2-domain phosphatase-2; STAT5, signal transducer and activator of transcription-5.

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as a negative regulator (15). In this study we compared the auxological data, the GH-IGF-I axis, as well as the clinical phenotype of short children with Noonan syndrome who were positive for mutations of SHP-2 (mut^+) to those of children who were negative for mutations of SHP-2 (mut^-).

Subjects and Methods

We recruited all children presenting to us with short stature plus at least three typical anomalies of Noonan syndrome or pulmonic stenosis during the past 5 yr (n = 29; 10 females and 19 males) (2, 7). Two pairs of siblings were included. All anomalies were systematically observed and recorded (2). The heart was examined by electrocardiogram and echocardiography. Height was measured using an electronic stadiometer and was expressed as the height SDS according to Prader *et al.* (16). Birth length and weight were expressed as SDS according to Niklasson *et al.* (17).

By chance, four individuals had been independently studied by Zenker and colleagues and incorporated into their publication (3). The parents' heights were measured in all but one patient, who was adopted. The DNA and syndromatology of the parents were not systematically studied. Informed consent was obtained from the parents and caregivers of all patients studied.

Materials

Genomic DNA was extracted from blood lymphocytes using NucleoSpin Blood XL (Macherey-Nagel, Duren, Germany). For the PCR amplification and direct sequencing of all coding exons and their flanking regions, primers previously reported by Tartaglia *et al.* (8) and the following additional primers were used: 5′-TCTACTCTGCTCATAATGCGTCT-3′ (exon 2); 5′-GGTAAATTCGTTCCTTGGG-3′, 5′-ATAACTGGTCGAGAGCCACC-3′, and 5′-CAGTCACAAGCCTTTGGAGTCAG-3′ (exon 3); 5′-GTCATTCTTACCATCTTTGTG-3′ and 5′-CTTTGAATGTAATGGTGTTTG-3′ (exon 4); 5′-CAAGAGCACACGACCCTGAG-3′ (exon 7); 5′-GAATTTTCTTGTACCTTCTCTGAG-3′ and 5′-GGGCTTTGAATTGTTGCAC-3′ (exon 8); and 5′-CTGCCACTTCGTTATTTATG-3′ and 5′-CAGTTGTCTATCAGAGCCT-3′ (exon 13). Both strands of the PCR products were automatically sequenced using the ABI BigDye Terminator Sequencing Kit and an ABI 3100 capillary sequencer (Applied Biosystems, Foster City, CA). Sequence analysis was performed using the support of Sequencher 4.1 software (Gene Codes Corp., Ann Arbor, MI).

Hormone measurements

Human GH (hGH) levels in serum were measured by a polyclonal in-house RIA and were calibrated against the World Health Organization International Reference Preparation 88/624 (1 mg = 3 IU). The lower detection limit was 0.1 μg/liter. The mean intraassay coefficient of variation was 6.9%, and the mean interassay coefficient was 9.5% (18). Serum levels of IGF-I and IGF-binding protein-3 (IGFBP-3) were measured by RIA, as described by Blum *et al.* (19). The mean intra- and interassay coefficients of the IGF-I assay were lower than 10%. For the IGFBP-3 assay, the intraassay coefficient of variation was 4.1%, and the interassay coefficient of variation was 9.7%. The age-, gender-, and maturity-dependent IGF-I and IGFBP-3 serum levels were expressed as the SDS for age and gender in females younger than 11 yr and in boys younger than 13 yr (20). The IGF-I levels of three children with delayed puberty were expressed as the SDS for bone age and gender (20).

Statistical analysis

Statistical analysis was performed using two-tailed Fisher's exact probability test for dichotomic and two-tailed Student's *t* test for continuous variables. $P < 0.05$ was considered to indicate significance.

Results

Mutational analysis

The sequencing analysis yielded 11 different missense mutations of the *PTPN11* in 16 patients with Noonan syndrome from 14 unrelated families (Table 1). All but two mutations have been described in previous reports on Noonan syndrome and were not found in controls (3, 8, 9). The majority of the mutations (11 of 14) resided in exons 3, 8, and 13. The two new mutations of this study (Q256K and P491L) were located at sites of SHP-2 where other missense mutations have been described previously (*i.e.* Q256R and P491S) (3).

Clinical characteristics

Table 2 compares the characteristics of the mut^+ group and the mut^- group. Parents with short stature were only found in the mut^+ group ($P = 0.01$). Patients with pulmonic stenosis and septal defects were significantly more frequent in the mut^+ group ($P = 0.0007$ and 0.02). The three mut^+ individuals without pulmonic stenosis (no heart defect, n = 2; coarctation of the aorta, n = 1) were the only ones with mutations located outside exons 3, 8, and 13. Minor anomalies, including the typical facial trias with dysplastic ears, ptosis, and hypertelorism, were as frequent in the mut^+ as in the mut^- group. The same was true for cryptorchidism, short stature of any degree, and learning disabilities (Table 2). One 9-yr-old boy with a giant cell granuloma of the mandible, a rare disorder associated with Noonan syndrome, was found to carry a Y62D mutation of SHP-2.

Growth failure

The children presenting to us because of their short stature underwent exact auxological measurements and tests of GH secretory capacity (Table 3). As expected, the growth failure of the studied children was more severe than that of the total population of children with Noonan syndrome, indicating a selection bias toward short stature (4). The mut^+ patients presented 5 yr earlier than the mut^- patients ($P = 0.002$). At presentation, growth failure was as severe in the mut^+ group as in the mut^- group ($P = 0.74$).

GH-IGF-I axis

Interestingly, IGF-I levels (−2.03 *vs.* −1.13 SDS; $P = 0.005$) and IGFBP-3 levels (−0.92 *vs.* +0.40 SDS; $P = 0.006$) at the time of GH testing or at first presentation (if GH testing was not performed) were significantly lower in the mut^+ group. In contrast, GH levels during spontaneous secretion at night showed a clear, albeit not significant, tendency to be higher

TABLE 1. *PTPN11* mutations in 16 patients with Noonan syndrome

Exon	Nucleotide substitution	Amino acid substitution	n	Ref.
2	124 A to G	T42A	1	9
3	179 G to C	G60A	1	9
3	181 G to A	D61N	1	3
3	184 T to G	Y62D	1	9
3	228 G to T	E76D	3[a]	9
7	766 C to A	Q256K	1	New
7	844 A to G	I282V	1	8
8	922 A to G	N308D	3	9
8	923 A to G	N308S	1	9
13	1472 C to T	P491L	2[a]	New
13	1510 A to G	M504V	1	9

[a] Includes one sibling pair.

TABLE 2. Characteristics of the children with Noonan syndrome grouped into SHP-2 mutation positive (mut$^+$) and negative (mut$^-$) individuals

	mut$^+$ (n = 16)	mut$^-$ (n = 13)	*P*
Gender (male:female)	11:5	8:5	0.71
Parent with short stature [no./total (%)]	7/16 (44)	0/12 (0)	0.01[a]
Dysplastic ears and ptosis and hypertelorism	7/16 (44)	6/13 (46)	1.00
Pulmonic stenosis	13/16 (81)	2/13 (15)	0.0007[a]
Septal defect	10/16 (63)	2/13 (15)	0.02[a]
Hypertrophic cardiomyopathy	2/16 (13)	1/13 (8)	1.00
Coarctation	3/16 (19)	3/13 (23)	0.64
Heart surgery or balloon valvuloplasty	8/16 (50)	2/13 (15)	0.11
Cryptorchidism	6/10 (60)	5/8 (63)	1.00
Short stature	14/16 (88)	11/13 (85)	1.00
Learning disabilities	6/16 (38)	7/13 (54)	0.47
Pterygium colli	9/16 (56)	6/13 (46)	0.72
Inverse nuchal hairline	9/16 (56)	8/13 (62)	1.00
High-arched palate	3/16 (19)	5/13 (38)	0.41
Down-slanting palpebral fissures	8/16 (50)	6/13 (46)	1.00
Pectus deformity	10/16 (63)	9/13 (69)	1.00
Cubitus valgus	1/16 (6)	3/13 (23)	0.29

Data represent number of affected children/total number (%) unless described otherwise.
[a] Indicates a P value < 0.05.

in the mut$^+$ group than in the mut$^-$ group [maximum GH, 16.2 ± 10.2 *vs.* 7.4 ± 3.3 ng/ml ($P = 0.091$); mean GH, 4.5 ± 1.8 *vs.* 2.7 ± 0.9 ng/ml ($P = 0.075$)]. A similar tendency was observed during arginine stimulation (maximum GH, 11.8 ± 6.3 *vs.* 5.6 ± 1.6 ng/ml; $P = 0.14$).

Therapeutic trials with recombinant human GH (rhGH)

A subgroup of prepubertal patients was treated with rhGH (mean dose, 0.043 mg/kg · d; the dose used to promote growth in Turner syndrome) on the basis of individual therapeutic trials. The mean change in height SDS after 1 yr of rhGH therapy was significantly lower in the mut$^+$ group (n = 8) than in the mut$^-$ group (n = 3; +0.66 *vs.* +1.26; $P = 0.007$). The latter group was treated with a slightly higher GH dose (0.050 *vs.* 0.042 mg/kg · d).

Discussion

The biological basis of short stature in Noonan syndrome is not yet clear. The detection of SHP-2 mutations in approximately half of all individuals with Noonan syndrome has opened up a new perspective from the endocrine point of view, because SHP-2 is implicated in GHR signaling (15). Previous studies reported discordant results, with low and normal serum IGF-I levels (21, 22) as well as low, normal, and high spontaneous GH secretion (6, 22, 23) in children with Noonan syndrome. In this study, for the first time, the GH-IGF axis in Noonan syndrome was examined in relation to the presence or absence of an SHP-2 defect. Our data on the frequency of SHP-2 mutations (55% carried a missense mutation) and the genotype-phenotype correlation of distinct major and minor anomalies are in agreement with recent reports (3, 9, 12). It must be emphasized that our children

TABLE 3. Auxological data, hormone levels of the GH-IGF-I axis, and response to rhGH

	n (mut$^+$/mut$^-$)	mut$^+$	mut$^-$	*P*
Age of gestation (wk)	16/12	38.7 (1.9)	37.1 (4.3)	0.19
Birth length (SDS)	16/11	−0.48 (1.59)	−0.25 (1.58)	0.72
Birth weight (SDS)	16/11	−0.70 (1.49)	−0.40 (1.17)	0.58
Mother's height (cm)	16/12	157.8 (8.4)	165.9 (7.4)	0.014[a]
Father's height (cm)	16/12	173.6 (8.2)	179.6 (5.8)	0.045[a]
Age at first visit (yr)	16/13	5.1 (2.7)	10.3 (5.2)	0.002[a]
Height at first visit (SDS)	16/13	−3.15 (0.92)	−3.01 (1.35)	0.74
Age at GH testing (yr)	11/9	7.7 (3.6)	7.6 (4.7)	0.93
IGF-I (SDS)	16/13	−2.03 (0.69)	−1.13 (0.89)	0.005[a]
IGFBP-3 (SDS)	16/13	−0.92 (1.26)	+0.40 (1.08)	0.006[a]
GH peak, arginine (ng/ml)	11/6	11.8 (6.3)	5.6 (1.6)	0.14
GH peak, spontaneous (ng/ml)	9/5	16.2 (10.2)	7.4 (3.3)	0.091
GH mean, spontaneous (ng/ml)	9/5	4.5 (1.8)	2.7 (0.9)	0.075
Age at GH start (yr)	8/3	7.4 (2.2)	6.3 (1.9)	0.35
Height at GH start (SDS)	8/3	−3.46 (0.71)	−3.80 (0.13)	0.44
GH dose (mg/kg·d)	8/3	0.042 (0.007)	0.050 (0.008)	0.17
Δ height SDS after 1 yr rhGH (SDS)	8/3	+0.66 (0.21)	+1.26 (0.36)	0.007[a]
Age at last visit (yr)	15/13	12.0 (4.0)	13.6 (4.2)	0.31
Height at last visit (SDS)	16/13	−2.37 (0.82)	−2.50 (1.63)	0.79

Data represent mean (SD).
[a] Indicates a P value < 0.05.

with Noonan syndrome were all short, approximately 1 SD in height below the mean for Noonan syndrome. Interestingly, IGF-I and IGFBP-3 levels, which are markers of the biological effect of GH (19), were significantly lower in those Noonan children who carried an SHP-2 mutation. Furthermore, spontaneous and stimulated GH secretion tended to be higher in the mut$^+$ group, excluding GH insufficiency as the cause of IGF-I insufficiency. Taken together, these observations suggest a mild form of GH resistance (24) in the presence of SHP-2 mutations in Noonan syndrome.

These data are in line with the *in vitro* findings of the role of SHP-2 in the GHR signaling pathway. After binding of its ligand, the GHR dimer initially activates Janus kinase-2 (JAK2), which includes autophosphorylation of the kinase domain of JAK2. Activated JAK2 then phosphorylates itself on additional tyrosines as well as thyrosines within the cytoplasmic domain of the GHR and many other signaling molecules, including signal transducer and activator of transcription-5 (STAT5) (25). These phosphorylated tyrosines establish binding sites for diverse phosphotyrosine-binding domain-containing signaling molecules, including SHP-2 (26), which has been shown to associate directly with GHR in response to GH *in vitro* (27). SHP-2 acts as a cytosolic phosphatase of STAT5 that down-regulates its activity (28, 29). Consequently, abolishing the SHP-2 binding site on GHR causes prolongation of tyrosyl phosphorylation of GHR, JAK2, and STAT5B in response to GH (15).

Therefore, the *in vitro* ability of SHP-2 to bind and dephosphorylate signaling molecules such as STATs and JAKs, which include positive regulators of the cellular response to GH, are in agreement with our *in vivo* findings that gain of function mutations of SHP-2 can negatively regulate the cellular response to GH in children with Noonan syndrome, as reflected by serum levels of IGF-I/IGFBP-3 and GH. It has to be emphasized, however, that experimental data for direct effects on gene expression exerted by activated SHP-2 are still missing (29).

Interestingly, the mut$^+$ group was not shorter than the mut$^-$ group and did not display any clinical characteristic of GH resistance besides short stature. Considering the enormous number of intracellular interactions of the ubiquitously expressed SHP-2, GHR signaling may only be one of 10 mechanisms affected and involved in the short stature phenotype of Noonan syndrome. However, this pathway is of major interest when rhGH is administered in high doses to short children to promote growth and final height (30). Our data from GH-treated individuals with Noonan syndrome are in line with the suggestion that the response to high-dose GH therapy is poorer in SHP-2 mut$^+$ individuals than in mut$^-$ individuals. These latter findings, however, need to be confirmed by additional studies, because the groups studied were small, and the GH doses used were not identical.

In conclusion, our data suggest that SHP-2 mutations cause mild GH resistance by a postreceptor signaling defect, which may contribute to growth failure and the relatively poor response to rhGH in Noonan syndrome.

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