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Clinical and Molecular Aspects of an Informative Family with Neurofibromatosis Type 1 and Noonan Phenotype

David A. Stevenson, David H. Viskochil, Alan F. Rope, and John C. Carey

Department of Pediatrics, Division of Medical Genetics, University of Utah, Salt Lake City, Utah

Abstract

NF-Noonan syndrome (NFNS) has been described as a unique phenotype, combining manifestations of neurofibromatosis type 1 (NF1) and Noonan syndromes, which are separate syndromes. Potential etiologies of NF-Noonan syndrome include a discrete syndrome of distinct etiology, co-segregation of two mutated common genes, variable clinical expressivity of NF1, and/or allelic heterogeneity. We present an informative family with an unusual *NF1* mutation with variable features of NF1 and Noonan syndrome. We hypothesize that an *NF1* mutant allele can lead to diagnostic manifestations of Noonan syndrome, supporting the hypothesis that *NF1* allelic heterogeneity causes NFNS.

Keywords

neurofibromatosis; noonan syndrome; *PTPN11*; pulmonic stenosis

INTRODUCTION

Neurofibromatosis type 1 (NF1) and Noonan syndrome are distinct genetic conditions. The criteria for the clinical diagnosis of NF1 are well established (1, 2) although there is a high degree of clinical variability (3). The *NF1* gene was mapped to the long arm of chromosome 17, cloned, and characterized as a Ras-GAP protein (4). Mutations in the *NF1* gene, encoding the protein product neurofibromin, result in loss of function leading to the NF1 phenotype.

Noonan syndrome is an autosomal dominant disorder affecting approximately 1 in 1000–2500 live births (5, 6). Common characteristics include short stature, skeletal anomalies, congenital heart defects (most commonly pulmonic stenosis and hypertrophic cardiomyopathy), learning disorders, and distinctive facial features (6–8). Missense mutations in the *PTPN11* gene have been found to cause Noonan syndrome in about 50% of cases examined in one study (9). The *PTPN11* gene encodes the non-receptor-type protein tyrosine phosphatase SHP-2, composed of two tandemly arranged amino-terminal src-homology 2 (SH2) domains (N-SH2 and C-SH2), a phosphotyrosine phosphatase, and a carboxy-terminal tail (6, 9, 10). The majority of reported mutations alter the amino N-SH2 and phosphotyrosine phosphatase domains switching the protein between the inactive and active conformation (10). The altered protein tyrosine phosphatase SHP-2 is thought to have a gain of function change, likely resulting in excessive SHP-2 activity.

Some manifestations of NF1 and Noonan syndrome overlap. Café-au-lait macules, pulmonic stenosis, short stature, and pectus abnormalities are reported in both conditions. In 1985, Allanson et al. described an association of the Noonan phenotype with NF1 in 4 cases (11). Subsequently, multiple cases of this association, sometimes referred to as the Neurofibromatosis-Noonan syndrome (NFNS), have been reported including multigenerational families (12). At the David W. Smith meetings in 1994, the reported cases of the Neurofibromatosis-Noonan syndrome were reviewed by 4 experts, and consensus of a convincing Noonan phenotype was reached on only 6/21 cases (13). Various explanations have been proposed including the coincidence of two common autosomal dominant disorders, phenotypic variability of either Noonan syndrome or NF1, and the presence of a genetically distinct disorder different from NF1 and Noonan syndrome (14, 15).

Two other disorders (Watson syndrome and LEOPARD syndrome) also have overlapping clinical manifestations with NF1 and Noonan syndrome. Watson syndrome is characterized by pulmonary stenosis, café au lait macules, and mild mental retardation (16), features variably seen in NF1. An in-frame tandem duplication of 42 bases in exon 28 of the *NF1* gene has been reported in a family with features of both Watson syndrome and Noonan syndrome (17), and an 80-kb deletion at the *NF1* locus has been documented in another patient with Watson syndrome (18). Recently, numerous patients with LEOPARD (multiple lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, sensorineural deafness) syndrome have been shown to have *PTPN11* mutations indicating that LEOPARD and Noonan syndromes are allelic. In the patients with LEOPARD syndrome, mutations of the *PTPN11* gene were found predominantly in exons 7, 12, and 13 with the large majority clustering in exons 7 and 12 (19–22). Mutations of the *PTPN11* gene in Noonan syndrome tend to cluster in exons 3 and 8 (10) suggesting possible site-specific genotype-phenotype correlations for LEOPARD syndrome and Noonan syndrome. Linkage analysis in a family with Noonan syndrome and café-au-lait macules and in a family with LEOPARD syndrome showed no linkage to the *NF1* locus (23). Subsequently, linkage to *PTPN11* was also excluded (21). However, a *de novo* missense mutation in exon 18 of the *NF1* gene (M1035R) in a single patient with LEOPARD syndrome has been reported (24). The presence and lack of clinical overlap in these syndromes may be helpful in understanding the underlying pathogenesis.

MATERIALS AND METHODS

Blood samples were obtained with informed consent of each individual and cDNA and genomic DNA specimens were prepared by standard procedures. PCR with specific primer sets, sequencing of the *NF1* gene, and confirmatory high-throughput cDNA sequencing were performed under a protocol to be published separately.

Fragment analysis was performed at the Genomics Core Facility of the University of Utah. DNA samples were diluted to 20 ng per μ L. Three microliters (60 ng) of DNA were used per PCR reaction. Four polymorphic short tandem repeat microsatellite markers were selected from the Utah Index Set (D12S829, D12S800, and D12S811) from the Genomics Core Facility at the University of Utah, www.cores.utah.edu/genomics. D12S829 is located approximately 18 Mb proximal to the *PTPN11* gene respectively. D12S800 and D12S811 flank the *PTPN11* gene with D12S811 located approximately 1 Mb distal and D12S800 located approximately 8 Mb proximal to the *PTPN11* gene. These markers, specific for the long arm of chromosome 12 flanking the *PTPN11* gene, were analyzed on all family members. The markers were fluorescently tagged and incorporated in the PCR product. Reactions were performed in 96 well PCR plates. PCR reagents were combined (200 μ M dATP, 200 μ M dCTP, 200 μ M dTTP, 200 μ M dGTP, 10 mM Tris-HCl pH 8.3, 40 mM NaCl, 1.5 mM MgCl₂, 0.25 Units Taq Platinum [Invitrogen], 0.6 μ M forward and reverse

Primer) to a total reaction volume of 20uL. Thermocycling comprised: 94°C for 5 minutes followed by 8 cycles of 94°C for 20 seconds, 60°C for 20 seconds (–1.0 degree C per cycle), and 72°C for 40 seconds, followed by 35 cycles of 94°C for 20 seconds, 52°C for 20 seconds, and 72°C for 40 seconds, with a final extension of 72°C for 10 minutes then remain at 20°C.

Following PCR, the samples were diluted with 140 uL of water and 1 to 3 uL of the diluted PCR product was pulled into a new tray for use with the ABI 3100 Genetic Analyzer instrument. The samples were loaded onto the 36cm capillary of the 3100 Genetic Analyzer with Applied Biosystems HI-DI Formamide. Results were analyzed with Applied Biosystems GeneScan and Applied Biosystems Genotyper software.

Family Report

We report on a family with 2 affected generations with variable clinical findings of both NF1 and Noonan syndrome (see pedigree, Fig. 1). The index case (II-5) was referred to our genetics clinic for evaluation of café-au-lait macules, growth delay, and pulmonic stenosis (Fig. 2 and Fig. 3). A family history revealed other family members with similar findings. The parents (I-1 and I-2) and four of their children (II-2, II-3, II-4, and II-5) were subsequently evaluated by two of the authors.

Physical examination in this 2-generation family revealed multiple café-au-lait macules (>6) in 5 individuals (I-2, II-2, II-3, II-4, and II-5), with variable clinical features of Noonan syndrome. The father (I-1) and the oldest child (II-1) did not have clinical findings of either NF1 or Noonan syndrome. The clinical findings are summarized in Table I. The affected individuals are described individually.

The mother of the index case (I-2) had multiple café-au-lait macules (>6) with axillary freckling thus fulfilling the diagnostic criteria for NF1. Stature was 159 cm (25thcentile). She had relative macrocephaly with a head circumference of 57 cm (90thcentile). Craniofacial findings included ptosis and posteriorly angulated ears. She had a slightly broad neck. Heart abnormalities were not present. No additional features of either NF1 or Noonan syndrome were noted.

The oldest daughter (II-2) was a 14-year-old girl with multiple café-au-lait macules, short stature with a height of 148 cm (<5thcentile), and relative macrocephaly with a head circumference of 55 cm (75thcentile). She had a frontal upsweep to the hair, low nasal root, mild right ptosis, telecanthus, down-slanting palpebral fissures, malar hypoplasia, and slightly posteriorly rotated ears. She had a mildly broad neck with slight webbing contour. She also has a mild pectus deformity of her chest that includes both a carinatum superiorly and an excavatum inferiorly. Cardiac evaluation by a cardiologist did not show evidence of cardiovascular malformations. An MRI of the brain was performed at 2 years and was normal. She had normal development. No additional features of either NF1 or Noonan syndrome were noted.

The third oldest sib (II-3) is a 13-year-old boy with multiple café-au-lait macules (>8), unilateral axillary freckling, short stature with a height of 143 cm (<5thcentile), and relative macrocephaly with a head circumference of 54.5 cm (>50thcentile). He has a frontal upsweep to the hair, bilateral ptosis, telecanthus, down-slanting palpebral fissures, and a low nasal root (Fig. 4). He has a mild webbing contour to his neck with a pectus excavatum. An MRI of the brain at 18 months of age was normal. An echocardiogram showed pulmonic stenosis. Speech therapy was required for articulation defects. No additional features of either NF1 or Noonan syndrome were noted.

Patient II-4 is a 10-year-old boy with multiple café-au-lait macules (>6), normal height at 133 cm (10thcentile), and relative macrocephaly with a head circumference of 54.5 cm (75thcentile). He has a low nasal root and mild ptosis. He had a marked pectus excavatum that was surgically repaired (Fig. 5). A fetal echocardiogram documented pulmonic stenosis but an echocardiogram at almost 2 years of age was normal. He had mild developmental delay and received speech therapy. No additional features of NF1 or Noonan syndrome were noted.

The index case (II-5) is an 8-year-old girl with multiple café-au-lait macules (>6), short stature with a height of 113 cm (<5thcentile), and relative macrocephaly with a head circumference of 52.5 cm (75thcentile). Of all the family members, her phenotype is the most similar to Noonan syndrome (Fig. 2 and Fig. 3). She has a triangular face, low nasal root, epicanthal folds, telecanthus, ptosis, malar hypoplasia, and posteriorly rotated ears that are small and over-folded. She has moderate neck webbing and sloped shoulders with a mild pectus excavatum inferiorly and a mild pectus carinatum superiorly. Her severe ptosis interfered with vision, and she had an external levator resection at 7 years of age. An echocardiogram documented a secundum atrial septal defect with valvar and supra-valvar pulmonic stenosis. She required a balloon valvuloplasty at 7 months. She had mild developmental delay with speech delay most prominent. No additional features of either NF1 or Noonan syndrome were noted.

RESULTS

Mutation analysis of the *NF1* gene showed a 3-basepair deletion of exon 17 (2971delAAT) in all affected individuals (I-2, II-2, II-3, II-4, II-5). High-throughput *NF1* cDNA sequencing confirmed the 3-basepair deletion, and did not identify other sequence variants. This out-of-frame AAT deletion removes a methionine from the *NF1*-encoded peptide, neurofibromin. The unaffected sibling did not have the deletion.

Haplotype analysis, using the described markers specific for the long arm of chromosome 12 flanking the *PTPN11* gene (D12S829, D12S800, and D12S811), failed to show segregation of the *PTPN11* locus with the Noonan clinical features in this family (Fig. 1).

The mother (I-2) and four of her children (II-2, II-3, II-4, and II-5) fulfilled the clinical diagnostic criteria for NF1. The predominant NF1 findings were pigmentary changes with all affected individuals having >6 café-au-lait macules and the mother and one son (II-3) having axillary freckling. No neurofibromas were noted. Relative macrocephaly was present in all affected individuals but no individual had absolute macrocephaly. The affected individuals also had variable features of Noonan syndrome and overlapping features of Noonan syndrome and NF1 (Table I).

DISCUSSION

This family has variable features of both NF1 and Noonan syndrome. Explanations for this association include the coincidence of two common autosomal dominant disorders, variable expressivity of either Noonan syndrome or NF1, and allelic heterogeneity (14, 15). This family demonstrates allelic heterogeneity, whereby an *NF1* mutation produces a discrete phenotype, separate from classical NF1 (no neurofibromas and restricted to pigmentary findings), and overlapping with Noonan syndrome (pulmonic stenosis, severe pectus deformities, webbed neck, and facial gestalt).

It is unlikely that there is a chance association of two autosomal dominant conditions (NF1 and Noonan syndrome) in this family, even though other families have been reported (25, 26). Bahuaui et al. showed exclusion of allelism of Noonan syndrome and NF1 in a large

family and subsequently found a nonsense mutation (C2446T→R816X) of the *NF1* gene, which was absent in 2 individuals with Noonan syndrome only (12, 27). Buehning and Curry described a man with full expression of both NF1 and Noonan syndrome phenotype with autosomal dominant transmission of the Noonan syndrome in family members, suggesting either extreme expression of the Noonan syndrome phenotype or a new *NF1* mutation in the index case (28).

Missense mutations in the *PTPN11* gene have been found to cause Noonan syndrome in 50% of cases (9) and LEOPARD syndrome in a number of cases (19–22). Haplotype analysis using informative markers from the long arm of chromosome 12 failed to show segregation of the *PTPN11* locus with the Noonan clinical features in our family, which indicates their Neurofibromatosis-Noonan syndrome phenotype is not allelic to cases of Noonan syndrome with *PTPN11* mutations. As previously noted (9), not all cases with Noonan syndrome have mutations in the *PTPN11* gene. It is possible that the features of Noonan syndrome in our family are due to abnormalities at another locus outside the haplotype interval screened in this study.

NF1 is a highly variable disorder and some families have been reported with interfamilial variability of the Noonan phenotype in families with NF1. NF1 and Noonan syndrome have overlapping features, raising the question of whether or not the Noonan features in NFNS are simply just part of the phenotypic variability of NF1. One study examined 94 individuals and documented that 9.5% had evidence of Noonan syndrome occurring as part of NF1 with a clustering of Noonan syndrome features in four families (29). Multigenerational families with discordance of the Noonan phenotype in individuals with NF1 are known (29, 30). In another report, a father and son with NF1 were described in which the son had classic Noonan syndrome and the father had variable features of the Noonan phenotype (31). Our family also exhibited phenotypic variability, but all affected family members had some features of Noonan syndrome. No one in the family had an absolutely classic phenotype of Noonan syndrome, and in isolation only the index case would have been characteristic for Noonan syndrome.

In the herein reported family the phenotype segregated with a mutation in the *NF1* gene, a 3-basepair deletion of exon 17 (2971delAAT), as all affected individuals (I-2, II-2, II-3, II-4, II-5) had the mutation and the unaffected sibling (II-1) did not have the mutation. This mutation removes a methionine residue just upstream of the Gap-related domain (exons 21 to 27a) of neurofibromin (32). We conclude that this is a disease-causing mutation. The out-of-frame 3-basepair deletion leading to an isolated loss of one methionine may provide a more proper peptide function producing a variant NF1 phenotype (eg. lack of neurofibromas). However, this mutation has not been observed in other individuals with the Neurofibromatosis-Noonan syndrome phenotype, and Baralle et al. mentioned unpublished data that they have observed the mutation described here in other patients with classical NF1 (33). Two individuals with NF1 and Noonan syndrome features also had deletions encompassing the *NF1* gene (34). Colley et al. stated that they found a large deletion encompassing the entire *NF1* gene in a mother and son with NF1 and Noonan syndrome features (29). Baralle et al. screened 6 patients with Neurofibromatosis-Noonan syndrome and mutations of the *NF1* gene (exons 23-2 and 25) were found in 2 individuals and whole gene deletions were excluded in the other individuals (33). Other genes, polymorphisms, or modifiers most likely interact with the mutant *NF1* gene and/or gene product to produce a modified NF1 phenotype.

Mutations in the *PTPN11* gene that cause the altered protein tyrosine phosphatase SHP-2 (composed of two tandemly arranged amino-terminal src-homology 2 domains, a phosphotyrosine phosphatase, and a carboxy-terminal tail) is thought to have a gain-of-

function change, resulting in excessive SHP-2 activity (6, 9, 10). However, we are unaware of reports of isolated *PTPN11* mutations in patients with the Neurofibromatosis-Noonan syndrome phenotype, although 2 patients with a “partial phenotype” of LEOPARD syndrome and *PTPN11* mutations have been reported (22). These 2 patients had café-au-lait spots without multiple lentigines representing some features observed in the NF-Noonan phenotype (22).

Mutations in the *NF1* gene generally result in haploinsufficiency of neurofibromin through a loss-of-function and lead to the NF1 phenotype. Neurofibromin interacts with ras protein by stimulating its intrinsic GTPase to inactivate the GTP-bound form of ras. This leads to decreased intracellular signaling (4, 35). Ras protein is a protooncogene product that cycles between an inactive and active state triggering various signaling pathways involved in proliferation and apoptosis (36). SHP-2 is a key component of several signal transduction pathways that control protean developmental processes including valvulogenesis (epidermal growth factor signaling) (9) and is involved in the signalling of the Ras/mitogen-activated protein kinase (MAPK) cascade (37, 38). SHP-2 has been shown to promote the undifferentiated epidermal cell state by facilitating Ras/MAPK signaling (39). SHP-2 also participates in the Gab1-organized complex and binds and dephosphorylates p90 leading to activation of the Ras-Raf-Mek-Erk cascade (40). Neuregulin-mediated activation of this cascade is enhanced in fibroblast cells that express a mutant SHP-2 (41). We postulate that the *PTPN11* gene product interacts either with neurofibromin directly or with shared biochemical components downstream of ras, and that certain *NF1* mutant alleles causing an altered neurofibromin peptide can disrupt this interaction, resulting in Noonan syndrome features in the context of NF1. We hypothesize that increased or decreased signaling through specific interacting pathways in different cell types causes variable phenotypes. It is likely that there are other genes or modifiers influencing these pathways, resulting in a modified NF1 phenotype. Further studies to identify, shared signaling pathways, involving both SHP2 and neurofibromin will be essential in understanding developmental processes and the pathogenesis of these disorders with overlapping features.

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Figure 1. Pedigree and chromosome 12q haplotypes of the affected family: The NF1 clinical features segregate with the 3-base pair deletion of the *NF1* gene (2971delAAT). Haplotype analysis does not show segregation of the *PTPN11* locus with the Noonan clinical features using polymorphic short tandem repeat microsatellite markers specific for chromosome 12q. D12S829 and D12S800 are located approximately 18 Mb and 8 Mb proximal to the *PTPN11* locus respectively. D12S811 is located approximately 1 Mb distal to the *PTPN11* locus. A cross-over event likely occurred between markers D12S829 and D12S800 in II-3. CH 12q = chromosome 12q; c = centromere; t = telomere; NF1 = neurofibromatosis type 1.

Figure 2.
Photograph of index case (II-5) at 8 months of age.

Figure 3.
Photograph of index case (II-5) at 2.5 years of age.

Figure 4.
Photograph of 13-year old boy (II-3).

Figure 5.
Photograph of chest of 10-year old boy (II-4) showing surgically corrected pectus excavatum and café-au-lait macules.

Table I

Variable Clinical Findings of NF1 and Noonan Syndrome in Family

Finding	I-1	I-2	II-1	II-2	II-3	II-4	II-5
>6 café au lait macules	-	+	-	+	+	+	+
axillary freckling	-	+	-	-	+	-	-
neurofibromas	-	-	-	-	-	-	-
relative macrocephaly	?	+	-	+	+	+	+
absolute macrocephaly	?	-	-	-	-	-	-
short stature	-	-	-	+	+	-	+
scoliosis	-	-	-	-	-	-	-
speech delay	-	-	-	-	+	+	+
ptosis	-	+	-	+	+	+	+
downslanting palpebral fissures	-	-	-	+	+	-	-
telecanthus	-	-	-	+	+	-	+
posteriorly angulated ears	-	+	-	+	+	-	+
malar hypoplasia	-	+	-	+	-	-	+
broad/webbed neck	-	+	-	+	+	-	+
pectus abnormality	-	-	-	+	+	+	+
pulmonic stenosis	-	-	-	-	+	+/-	+