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A Rasopathy Phenotype With Severe Congenital Hypertrophic Obstructive Cardiomyopathy Associated With a *PTPN11* Mutation and a Novel Variant in *SOS1*

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Abstract

The RAS-MAPK pathway is critical for human growth and development. Abnormalities at different steps of this signaling cascade result in neuro-cardio-facial-cutaneous syndromes, or the RASopathies, a group of disorders with overlapping yet distinct phenotypes. RASopathy patients have variable degrees of intellectual disability, poor growth, relative macrocephaly, ectodermal abnormalities, dysmorphic features, and increased risk for certain malignancies. Congenital heart disease, particularly hypertrophic cardiomyopathy (HCM) and pulmonic stenosis, are prominent features in these disorders. Significant locus heterogeneity exists for many of the RASopathies. Traditionally, these diseases were thought to be inherited in an autosomal dominant manner. However, recently patients with defects in two components of this pathway and overlapping features of various forms of Noonan syndrome and neurofibromatosis 1 and have been reported. Here we present a patient with severe, progressive neonatal HCM, elevated urinary catecholamine metabolites, and dysmorphic features in whom we identified a known LEOPARD syndrome-associated *PTPN11* mutation (c.1403 C > T; p.T468M) and a novel, potentially pathogenic missense *SOS1* variant (c.1018 C > T; p.P340S) replacing a rigid nonpolar imino acid with a polar amino acid at a highly conserved position. We describe detailed clinical manifestations, cardiac histopathology, and the molecular genetic findings. Oligogenic models of inheritance with potential synergistic effects should be considered in the RASopathies.

Keywords

hypertrophic cardiomyopathy; RASopathy; *PTPN11*; *SOS1*; LEOPARD syndrome; Noonan syndrome; Noonan syndrome-multiple lentigines; myectomy; myotomy

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INTRODUCTION

The RASopathies are a group of genetic syndromes caused by mutations in different components of the RAS-MAPK pathway. The disorders exhibit overlapping phenotypes and include Noonan syndrome (NS), LEOPARD syndrome (currently known as Noonan syndrome-multiple lentigines; NS-ML), Costello syndrome (CS), cardiofaciocutaneous (CFC) syndrome, neurofibromatosis 1 (NF-1), neurofibromatosis-Noonan syndrome (NFNS), and Legius syndrome [reviewed in Tartaglia and Gelb, 2010 and in Tartaglia et al., 2011]. Individuals with RASopathies have variable degrees of intellectual disability, short stature, macrocephaly, hair and skin manifestations, and facial and other dysmorphic features [reviewed in Tartaglia and Gelb, 2010 and Tartaglia et al., 2011]. Most of these disorders are associated with an increased risk of malignancy, including leukemias, rhabdomyosarcoma, and neuroblastoma [reviewed in Hasle, 2009]. Cardiac defects such as pulmonic stenosis, as well as HCM, are well-described manifestations of the RASopathies. HCM is thought to occur in up to 80% of individuals with NS-ML who have cardiac defects [reviewed in Tartaglia et al., 2011] and in approximately 60% of individuals with NS-ML due to a *PTPN11* mutation [Faenza et al., 2009]. Furthermore, certain *PTPN11* mutations such as the p.Q510E mutation in exon 13 are associated with more severe forms of HCM [Takahashi et al., 2005; Digilio et al., 2006a; Faenza et al., 2009].

Significant locus and allelic heterogeneity exist for many of the RASopathies [reviewed in Tartaglia and Gelb, 2010 and in Tartaglia et al., 2011]. For example, NS-ML can result from mutations in *PTPN11*, *RAF1*, and *BRAF* [reviewed in Tartaglia and Gelb, 2010 and in Tartaglia et al., 2011], and mutations in nine genes (*PTPN11*, *SOS1*, *KRAS*, *NRAS*, *SHOC2*, *BRAF*, *RAF1*, *MEK1*, and *CBL*) are known to cause NS [reviewed in Tartaglia et al., 2011]. For some of the RASopathies, particularly NS, significant genotype-phenotype correlation exists. For example, gain-of-function mutations in *SOS1* cause a form of Noonan syndrome with increased ectodermal abnormalities but with preserved cognition and linear growth [Roberts et al., 2007; Tartaglia et al., 2007; Lepri et al., 2011].

Classically, RASopathies are considered autosomal dominant disorders; in a given patient the phenotype results from a heterozygous mutation in a single gene encoding one of the proteins in the pathway. Recently, patients with mutations in two components of the RAS-MAPK pathway and overlapping features of NF1 and NS have been reported [Bertola et al., 2005; Thiel et al., 2009; Brasil et al., 2010; Longoni et al., 2010; Ekvall et al., 2011; Prada et al., 2011]. We describe a patient with congenital severe progressive hypertrophic cardiomyopathy, as well as elevated urinary catecholamine metabolites raising concerns for neuroblastoma, in whom we identified a known *PTPN11* mutation and a potentially pathogenic novel missense variant in the *SOS1* gene. We present the details of the clinical manifestations, the cardiac pathology, and the molecular genetic results and review the reported RASopathy patients with two mutations and their phenotypes.

CLINICAL REPORT

The proband is a full term female born to nonconsanguineous parents. The pregnancy was complicated by early polyhydramnios. Birth weight was 4.74 kg (99th centile). An echocardiogram prompted by a heart murmur noted at birth showed severe HCM. Initial peak instantaneous pressure gradient across the left ventricular outflow tract (LVOT) was 30 mm Hg estimated by Doppler.

At 7 weeks of age the proband was noted to be diaphoretic and irritable with poor oral intake and weight loss. Her EKG (Fig. 1A) showed left ventricular enlargement and possible right ventricular hypertrophy. Echocardiogram (Fig. 1B) showed worsening of the estimated LVOT gradient to a peak of 65–75 mm Hg, hyperdynamic left ventricular function with cavity obliteration, systolic anterior motion of the mitral valve, and trivial mitral regurgitation. The left ventricular end diastolic septal and posterior wall thicknesses were asymmetrically increased at 9 mm (z-score 6.9) and 6 mm (z-score 2.9), respectively. Oral propranolol of 6–8 mg/kg/day had only modest effect on heart rate and no effect on LVOT obstruction. LVOT gradient progressively worsened requiring verapamil in addition to propranolol. She ultimately required a surgical left ventricular septal myotomy and myectomy when Doppler estimated LVOT gradient peaked at 90–120 mm Hg and septal and posterior wall thickness increased to 17 mm (z-score 19.1) and 10 mm (z-score 9.8). The histology of the excised septum showed hypertrophy and vacuolization of cardiac myocytes (Fig. 1C), myocyte disarray and mild fibrosis (Fig. 1D), and endocardial thickening with a paucity of elastic fibers (Fig. 1E).

After myectomy the estimated gradient was initially reduced to 25 mm Hg but subsequently increased to 40–50 mm Hg at baseline. Clinically, the patient's irritability and oral intake improved; however, she continued to have poor weight gain. This was felt to be due initially to continuing cardiac failure. In addition, mild supravulvar pulmonic stenosis was noted on post-surgical echocardiogram.

She was evaluated by genetics consultants at 2, 6, and 11 months of age. Urine organic acid analysis performed as a part of the cardiomyopathy work up showed mild elevations of homovanillic acid (HVA) and vanillylmandelic acid (VMA) which raised concerns for neuroblastoma. However, imaging studies were negative, and on repeat testing quantitative urine HVA and VMA were normal. The possibility of neuroblastoma, along with severe progressive HCM, suggested a RASopathy.

Dysmorphic features included bilateral epicanthal folds with subjective hypertelorism, thick and droopy eyelids, wide and flat nasal bridge, deeply grooved philtrum with high peaks of the vermillion border of the upper lip, low-set and posteriorly rotated ears, fleshy and overfolded helices, and fleshy ear lobes. No hyperpigmented skin lesions were noted. She continued to have normal development without delays at 11 months of age. Though macrosomic at birth, she subsequently developed postnatal onset growth failure sparing her head (Fig. 2A,B). Family history was negative for cardiomyopathy. However, the patient's father, who was adopted, was reported to have "brown spots" on his back, and the maternal grandfather died at age 30 while swimming from an unknown cause.

METHODS

Informed consent was obtained from the patient's parents. The patient was followed up at the Pediatric Genetics and Cardiology clinics at Johns Hopkins Hospital. Echocardiography was performed using an iE33 (Philips Medical Systems, Andover, MA).

DNA Analysis

Extraction of genomic DNA and mutation analysis were performed by GeneDx (Gaithersburg, MD). Briefly, genomic DNA was amplified by PCR and sequenced using GeneDx custom-designed Affymetrix resequencing array and Sanger sequencing. The analysis included the complete coding regions and splice junctions of the following genes in the RAS-MAPK pathway: *BRAF*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *PTPN11*, *RAF1*, and *SOS1*, as well as exon 2 of *SHOC2*. The DNA sequence was analyzed and compared to published genomic reference sequences. The result was confirmed by repeat sequence analysis on a newly prepared DNA sample. Multiple databases were queried to determine the novelty of the identified *SOS1* variant, including a proprietary GeneDx database of previously tested patients, Human Gene Mutation Database, dbSNP, and NCBI/Pubmed. Also, the variant was analyzed using the missense variant pathogenicity prediction software SIFT (Sorting Intolerant From Tolerant; <http://sift.bii.a-star.edu.sg/>) [Ng and Henikoff, 2001] and POLYPHEN (Polymorphism Phenotyping; <http://genetics.bwh.harvard.edu/pph/>) [Sunyaev et al., 2000].

RESULTS

Molecular genetic testing of the RAS/MAPK pathway revealed a known pathologic heterozygous mutation in exon 12 of *PTPN11* (p.T468M) and a novel missense variant in *SOS1* (p.P340S; Fig. 3). The patient's mother's echocardiogram was normal, but she has repeatedly declined parental targeted mutation analysis. The father has declined repeated requests for echocardiography and molecular genetic testing. The parents declined requests for photographs; examination did not suggest a RASopathy.

DISCUSSION

Our patient has overlapping clinical features of *PTPN11*-related NS-ML and *SOS1*-related NS (Table I). This is reminiscent of recent reports of patients with features of NF1 and NS and mutations in two components of the RAS-MAPK pathway, who like our patient, exhibit hybrid phenotypes that would be expected to result from the individual mutations (Table II) [Bertola et al., 2005; Thiel et al., 2009; Brasil et al., 2010; Longoni et al., 2010; Ekvall et al., 2011; Prada et al., 2011]. Our patient is the first description of a NS-ML-associated mutation seen in combination with *SOS1*-related NS.

The *PTPN11* mutation identified in this patient is a well-described NS-ML-associated mutation at a conserved residue in the protein tyrosine phosphatase domain of SHP2, and it is predicted to disrupt the catalytic site [Digilio et al., 2002; reviewed in Sarkozy et al., 2008]. The novel missense variant c.1018 C > T (p.P340S) in *SOS1* is probably pathogenic because it involves a highly conserved position in the Dbl homology (DH) domain (Fig. 3A),

and it results in significant physicochemical consequences, with replacement of a rigid nonpolar imino acid by a polar amino acid at a highly conserved position across species (Fig. 3B). The DH domain plays a key role in autoinhibition of SOS1 by preventing RAS binding and stabilizing SOS1 in its inactive conformation [Tartaglia et al., 2007 and reviewed in Tartaglia and Gelb, 2010]. The missense variant pathogenicity prediction software SIFT [Ng and Henikoff, 2001] and POLYPHEN [Sunyaev et al., 2000] predicted the p.P340S amino acid change to be pathogenic.

Cardiomyopathy is common in NS-ML [Digilio et al., 2002, 2006b; Sarkozy et al., 2003, 2004; Keren et al., 2004], especially in association with mutations in exons 7 and 12 of *PTPN11* [Sarkozy et al., 2003] (Table I). Notably, our patient's mutation is located in exon 12. Interestingly, a rapidly progressive form of HCM is described in patients with NS-ML/NS phenotypes in association with the p.Q510E mutation in exon 13 of *PTPN11* [Digilio et al., 2006a; Faienza et al., 2009; Takahashi et al., 2005]. Hypertrophic cardiomyopathy, however, occurs in only about 10% of individuals with *SOS1*-associated NS (Table I) [Roberts et al., 2007; Tartaglia et al., 2007; Lepri et al., 2011]. Thus, the *PTPN11* mutation might be the major contributor to our patient's HCM, and the *SOS1* variant might be a modifier increasing the severity.

Cardiac histopathologic findings of our patient are nonspecific but similar to those described in post-mortem examinations of the hearts of three children with CS and severe HCM [Hinek et al., 2005]. Myocardial disarray, in particular, has been well described not only in CS but also in other RASopathies [Lin et al., 2011]. Transiently elevated catecholamine metabolites without evidence of neuroblastoma, as seen here, have also been described in the RASopathies, namely in patients with CS [Gripp et al., 2004; Bowron et al., 2005].

Growth failure is a feature of the RASopathies in general and particularly of NS-ML and more traditional forms of NS, although it is less common in individuals with the p.T468M mutation in *PTPN11* and in patients with mutations in *SOS1* (Table I) [Roberts et al., 2007; Tartaglia et al., 2007; Lepri et al., 2011]. Our patient's severe cardiomyopathy is likely to have contributed to her failure to thrive early on. We suspect, however, a more significant ongoing contribution may come from her underlying RASopathy; it is certainly possible that the combination of her two mutations may act synergistically, leading to a more severe effect on weight gain and on linear growth. Macrocephaly is a frequent feature in individuals with both the *PTPN11* p.T468M mutation and mutations in *SOS1*, though it is more characteristic of individuals with *SOS1* mutations (Table I). *SOS1* mutations resulting in NS, particularly those affecting the interaction between the histone folds, DH, and PH domains (designated as class IB mutations by Lepri et al. [2011]), have been associated with macrosomia at birth (Table I). Notably, our patient's *SOS1* variant, p.P340S, is three amino acids away from a well-documented class IB mutation p.Y337C [Lepri et al., 2011], supporting the hypothesis that this novel *SOS1* variant is contributing to her phenotype. The p.T468M mutation in *PTPN11* has been associated with fetal macrosomia in one individual (Table I) [Digilio et al., 2006b].

Our patient has typical NS/NS-ML craniofacial dysmorphic features, including bilateral epicanthal folds with subjective hypertelorism, thick and droopy eyelids, low-set and

posteriorly rotated ears, fleshy and overfolded helices, and fleshy ear lobes [Allanson et al., 2010]. A post-surgical echocardiogram also revealed mild supralvalvar pulmonic stenosis, which is common in NS and NS-ML. She also exhibits some of the ectodermal abnormalities, which are consistent with *SOS1* mutations, including sparse eyebrows and sparse/thin hair. However, we did not note keratosis pilaris, nor does she exhibit other typical features of NS-ML, including abnormal genitalia, deafness, lentigines, or café au lait macules. Many of these features could still develop over time, particularly lentigines, which typically do not manifest until approximately age 4–5 years. A modifier effect of the *SOS1* variant is an alternative explanation.

Oligogenic inheritance with significant modifier effects from other components of the RAS-MAPK pathway could explain the well-known phenotypic variation among individuals with RASopathies in general. These components may have synergistic or opposing effects. For example, the p.T468M mutation in *PTPN11* is an inactivating mutation that impairs the function of the protein tyrosine phosphatase domain of SHP2 [Tartaglia et al., 2006]. However, the NS-associated *SOS1* mutations described to date, seem to be gain of function mutations [Roberts et al., 2007; Tartaglia et al., 2007; Lepri et al., 2011]. This presents a conundrum and might lead one to postulate that rather than worsening the phenotype, the two mutations might actually oppose one another and lead to a less severe phenotype. And, this could differ among tissues depending on the expression levels of the two RAS-MAPK pathway components, as well as the tissue-specific downstream effectors. This is consistent with our patient's clinical presentation in that her cardiac phenotype and short stature are certainly at the severe end of the spectrum, but her development and skin manifestations seem to be mild at this point. However, the latter would be expected to become more penetrant over time. Parental testing and comparison of the parental phenotypes with that of the proband could help us better understand the phenotypic contributions of these mutations. In all cases with two abnormalities in the RAS-MAPK pathway reported to date when parental testing was performed, one mutation was inherited from an affected parent and the other occurred de novo (Table II). Most RASopathy phenotypes described in these probands with two mutations consist of overlapping features of the two disorders expected to result from the individual mutations with no clear increase in severity (Table II). However, the most recent report described a significantly more severe, lethal phenotype in an infant with both *PTPN11* and *NF1* mutations [Prada et al., 2011]. Three out of the six reports of individuals with mutations in two components of the RAS-MAPK pathway involved mutations in *PTPN11* and *NF1* [Bertola et al., 2005; Thiel et al., 2009; Prada et al., 2011]. Studies of these patients suggest that an *NF1* mutation is sufficient to cause the NFNS phenotype in most cases but that in some cases there is a significant modifier effect to the phenotype from the *PTPN11* mutation [Bertola et al., 2005; Thiel et al., 2009; Prada et al., 2011].

These findings emphasize the importance of testing potential RASopathy patients for mutations in all components of the RAS-MAPK pathway. Oligogenic inheritance with potential synergistic effect may help explain the overlapping phenotypes observed in RASopathies, as well as variation in severity within a specific disorder.

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FIG. 1.

Patient's cardiac findings. A: Twelve-lead electrocardiogram at 7 weeks of age illustrating left ventricular hypertrophy and possible right ventricular hypertrophy. B: Echocardiogram illustrating the patient's hypertrophic obstructive cardiomyopathy. Parasternal long axis view of the heart with thin arrows indicating cardiac anatomic landmarks (LA, left atrium; LV, left ventricle; Ao, aorta). Thick arrows indicate severe ventricular septal hypertrophy. C–E: Histopathologic findings of the excised myocardium. C: Hematoxylin and eosin staining showing hypertrophy and vacuolization of cardiac myocytes. D: Masson's trichrome stain showing myocyte disarray and mild fibrosis (blue). E: Movat pentachrome stain reveals endocardial thickening with excess collagen (yellow), a paucity of elastic fibers, and greenish deposits of glycosaminoglycans.

FIG. 2.

Patient's growth charts (3rd to 97th percentiles) showing macrosomia at birth and postnatal onset growth retardation sparing her head. A: Length-for-age (top) and weight-for-age (bottom). B: Head circumference plotted against age.

FIG. 3. A: Schematic of human SOS1 protein with our patient's variant indicated in red bold type along with previously identified mutations. Variants of uncertain significance are in italics. Abbreviations: DH, Dbl homology domain; PH, pleckstrin homology domain; HL, helical linker; Rem, Ras exchanger motif; Pxxp, proline-rich region. Amino acid positions are indicated below the schematic. B: Multispecies alignment of SOS1 orthologues in the region of p.P340S showing conservation of proline at position 340 and surrounding residues from worms to humans. Proline at position 340 is indicated by a box. Amino acid residues are color coded according to their physiochemical properties. An * (asterisk) indicates positions which have a single, fully conserved amino acid residue. A: (colon) indicates conservation between groups of amino acids with strongly similar properties. A. (period) indicates conservation between groups of amino acids with weakly similar properties [Larkin et al., 2007; Goujon et al., 2010].

TABLE I

Phenotype of the Present Case in Comparison to Reported Individuals with the p.T468M mutation in *PTPN11* and Mutations in *SOS1*

	Present patient (<i>PTPN11</i> p.T468M; <i>SOS1</i> p.P340S)	Reported patients with <i>PTPN11</i> p.T468M ^a	Reported patients with <i>SOS1</i> mutations ^b
Cardiac defects			
HCM	+	11/25 (44%)	8/70 (11%)
PS	+	3/25 (12%)	48/70 (69%)
Other	–	8/25 (32%)	28/70 (40%)
Growth/development			
Fetal macrosomia	+	1/1 (100%)	23/53 (43%)
Short stature	+	1/17 (5.8%)	17/67 (25%)
Failure to thrive	+	0/1 (0%)	NR
Macrocephaly (rel/true)	+	5/13 (38%)	33/55 (60%)
DD/ID	–	6/18 (33%)	10/66 (15%)
Dysmorphic features			
Craniofacial	+	18/18 (100%)	70/70 (100%)
Hand	+	NR	7/38 (18%)
Sternal deformity	–	11/15 (73%)	48/55 (87%)
Short or webbed neck	–	2/8 (25%)	46/55 (84%)
Skin lesions			
Lentigines	– *	19/25 (76%)	1/39 (2.6%)
Café au lait macules	– *	18/25 (72%)	NR
Other ectodermal abnormalities			
Sparse eyebrows	+	NR	30/39 (77%)
Thin hair	+	NR	12/39 (31%)
Curly hair	+ **	1/1 (100%)	41/55 (74%)
Keratosis pilaris	–	NR	21/55 (38%)
Other			
Deafness	–	0/25 (0%)	NR
Polyhydramnios	+	NR	26/52 (50%)

+, Present; – absent;

* not expected to be present at current age;

** curly hair may be due to ethnicity rather than *SOS1* mutation; DD, developmental delay; ID, intellectual disability; NR, not reported; rel, relative.

^a p.T468M data from Digilio et al. [2002, 2006b], Keren et al. [2004], Sarkozy et al. [2004].

^b *SOS1* mutation data from Lepri et al. [2011], Roberts et al. [2007], Tartaglia et al. [2007].

TABLE II
Comparison of RASopathy Patients With Mutations in 2 Genes in the RAS-MAPK Pathway

	Gene	Mutation (inheritance)	Diagnosis	Phenotype of proband	Phenotype of affected parent
Present patient	<i>PTPN11</i> <i>SOS1</i>	p.T468M (NR) p.P340S* (NR)	NS-ML NS	Macrosomia at birth, SS, FTT, relative macrocephaly, NS facies, HCM, PS	NR
Bertola et al.	<i>PTPN11</i> <i>NF1</i>	p.Q510R* (Fam) p.L844R(<i>de novo</i>)	NS NF1	SS, FTT, relative macrocephaly, NS facies, SN/LPH, SD, PS, CAL, axillary/inguinal freckling, Lisch nodules, astrocytoma	SS, NS facies, SD
Thiel et al.	<i>PTPN11</i> <i>NF1</i>	p.T21 (<i>de novo</i>) c.4661 + 1G > C* (Fam)	NS NF1	Macrosomia at birth, SS, FTT, NS facies, PS, CAL, bilat optic gliomas	CAL, axillary freckling, SS, DSPFs
Longoni et al.	<i>RAF1</i> <i>SOS1</i>	p.P261S(<i>de novo</i>) p.R497Q* (Fam)	NS NS	NS facies, PS, HCM, CAL, EA (KP, xerosis)	NS facies, EA, normal stature/ development
Brasil et al.	<i>PTPN11</i> <i>SOS1</i>	p.N308D (NR) p.R552G (NR)	NS NS	SS, NS facies, PS	NR
Ekvall et al.	<i>SHOC2</i> <i>PTPN11</i>	p.S2G(<i>de novo</i>) p.G409A (Fam)	NS-LAH NS	SS, macrocephaly, ID, NS facies, SN/LPH, KP, sparse/LAH, SD, CAL, neuroblastoma	Delayed puberty, cryptorchidism, KP, CAL
Prada et al.	<i>NF1</i> <i>PTPN11</i>	p.N1430D** (Fam) p.N308D (NR)	NF1/NFNS NS	CAL, cutaneous/plexiform neurofibromas, SS, PS, HCM, VSD, NS facies, SN/LPH, SD, cryptorchidism	ID, CAL, axillary freckling, cutaneous neurofibromas

* Novel;

** nonidentical alteration of a residue previously reported [De Luca et al., 2005];

CAL, café au lait macules; DSPFs, downsloping palpebral fissures; EA, ectodermal abnormalities; fam, familial; FTT, failure to thrive; HCM, hypertrophic cardiomyopathy; ID, intellectual disability; KP, keratosis pilaris; NR, not reported; NS-LAH, Noonan syndrome with loose anagen hair; PS, pulmonary stenosis; SD, sternal deformity; SN/LPH, short neck/low posterior hairline; SS, short stature; VSD, ventricular septal defects.