CASE REPORT

Noonan syndrome caused by a pathogenic SOS1 variant: expanding the phenotypic spectrum and molecular correlations

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ABSTRACT

Background: Noonan syndrome (NS) is an autosomal dominant condition characterized by facial dysmorphism, congenital heart disease, growth impairment, and ectodermal findings. Variants in SOS1 account for a large proportion of cases.

Case presentation: We report a male infant with nasal bone hypoplasia and shortening of long bones identified during the prenatal period. After birth, he presented with facial dysmorphism, pulmonary valve stenosis, axial hypotonia, and renal anomalies. The karyotype was normal. Whole-exome sequencing with CNV analysis focused on NS-related genes identified a heterozygous SOS1 variant, c.1656G>T (p.Arg552Ser), classified as pathogenic according to ACMG criteria and curated databases, supporting the diagnosis of SOS1-related Noonan syndrome type 4. The SOS1 p.Arg552Ser variant has been reported in individuals with typical NS features, supporting the genotype–phenotype correlation. In this patient, the combination of prenatal skeletal markers and postnatal renal involvement illustrates the wide phenotypic variability. Early molecular confirmation allowed multidisciplinary care and targeted surveillance (cardiac, endocrine, and oncologic), as well as genetic counseling.

Conclusion: This case highlights the diagnostic utility of early exome sequencing when NS is suspected, but the phenotype is incomplete, and emphasizes the value of integrating prenatal markers with postnatal findings to enable timely management guided by precision medicine.

Keywords: Noonan syndrome, SOS1 gene, RAS/MAPK, RASopathies, phenotypic variability, precision diagnosis, personalized treatment.

Introduction

Noonan syndrome (NS) is a relatively common autosomal dominant disorder characterized by distinctive facial features, congenital heart disease, short stature, and ectodermal findings (1). Prevalence estimates range from 1:1000 to 1:2500 live births, and clinical expressivity is variable. Approximately 50% of cases are attributed to missense variants in the *PTPN11* gene, located on chromosome 12; however, multiple genes in the RAS/MAPK signaling cascade are also implicated, including *SOS1*, *RAF1*, *RIT1*, *KRAS*, *BRAF*, *NRAS*, and *LZTR1*. In nearly 10% of cases, no genetic alteration is identified, suggesting the existence of other yet-undiscovered genes. This genetic heterogeneity underlies a broad phenotypic spectrum and frequent overlap with related conditions historically grouped as RASopathies (2,3).

The syndrome was first described in 1968 by Jacqueline Noonan (4). The most frequent clinical manifestations include craniofacial dysmorphisms such as a triangular face, broad forehead, hypertelorism, ptosis, and low-set, posteriorly rotated ears—findings commonly associated with *PTPN11* variants. Growth delay, usually evident after the first year of life, is also characteristic in patients with variants in this gene (3,5).

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NS displays multisystem involvement. Cardiac disease occurs in approximately 80% of patients, with pulmonary valve stenosis being the most frequent (60%-70%), followed by hypertrophic cardiomyopathy (20%-30%) and atrial septal defect (10%-30%) (5,6). Neurologically, about 80% of patients have a normal intelligence quotient, although various neuropsychiatric manifestations are common, including alexithymia, mood disorders, social and communication difficulties, ADHD, language disorders, and autistic traits (1,7). Genitourinary anomalies (renal pyelectasis, ectopia, duplication of the collecting system, cryptorchidism) and lymphatic involvement—ranging from lymphedema to chylothorax and ascites—are frequent (3,8). Hematologic abnormalities include bleeding tendencies, often with prolonged aPTT and coagulation factor deficiencies, as well as an increased susceptibility to neoplasms such as JMML, MDS, ALL, and neuroblastoma (9). Ocular and auditory defects have also been described. Cutaneous manifestations include follicular keratosis on extensor and facial surfaces, multiple lentigines, and other pigmentary changes; these are particularly notable in *SOS1*-related cases (3,10).

Variants in the *SOS1* gene are among the main molecular causes of NS, accounting for approximately 20% of cases. *SOS1* encodes a multidomain guanine nucleotide exchange factor (GEF) for RAS that promotes RAS activation through GDP–GTP exchange (Figure 1). The resulting persistent activation of the RAS–MAPK pathway contributes to the developmental abnormalities characteristic of NS. Clinically, *SOS1*-related NS presents a distinctive phenotype that often includes pulmonary valve stenosis and prominent ectodermal abnormalities (e.g., keratosis pilaris, follicular hyperkeratosis, and curly hair), while cognitive development tends to be preserved compared with other molecular subtypes. Recognizing this pattern has practical implications for anticipatory guidance and targeted surveillance (11).

The diagnosis of NS has traditionally been based on clinical criteria; however, given its wide phenotypic heterogeneity (Figure 2), this approach may be insufficient. Prenatal markers such as nasal bone hypoplasia and long bone shortening can raise early suspicion but are not specific. Postnatally, multisystem involvement—such as cardiac, neuromuscular, renal, lymphatic, or dermatologic manifestations—may appear in variable combinations, complicating a purely clinical diagnosis. In this context, next-generation sequencing (NGS) technologies such as targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS) have become key tools in clinical practice. These methods enable diagnostic confirmation and more precise classification; they inform genetic counseling, prognostic estimation, and personalized therapeutic decisions; and they facilitate the identification of new genes and variants, expanding the understanding of the genetic basis of NS and opening future research and therapeutic avenues. Early identification is essential to guide appropriate clinical follow-up and prevent complications (12,13).

Management of NS is multidisciplinary and requires lifelong follow-up to detect complications early and optimize quality of life. In the absence of a curative therapy, care is individualized according to clinical manifestations and depends on early diagnosis, which supports continuous cardiovascular surveillance given the risk of hypertrophic cardiomyopathy, arrhythmias, and sudden death, even in the absence of structural disease. Specific genetic variants inform oncologic risk and justify targeted monitoring strategies; early recognition also facilitates the detection of endocrine disorders such as growth hormone deficiency and helps avoid unnecessary investigations by distinguishing NS from other RASopathies (14,15) (Figure 2).

Cardiovascular abnormalities determine morbidity and mortality (50%-80% of cases). Hypertrophic cardiomyopathy is a major complication associated with a high risk of sudden death, and mortality correlates

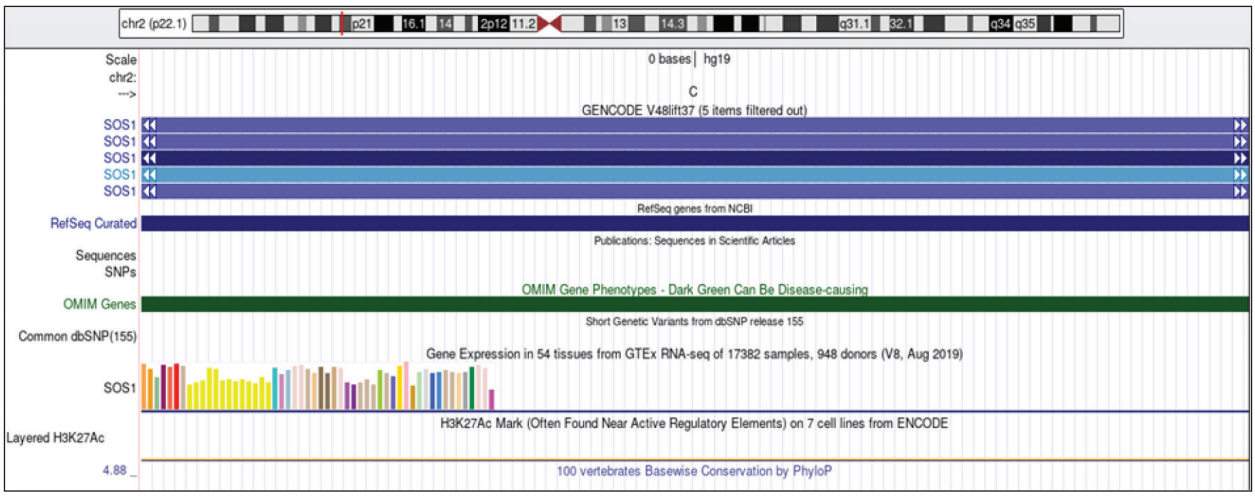

Figure 1. *Visualization, analysis, and exploration of the genomic information of the* SOS1 *gene.* This persistent activation of the RAS-MAPK pathway contributes to the developmental alterations observed in Noonan syndrome (NS). *Source: https://genome.ucsc.edu/*

with the severity of cardiac disease. A recent European cohort reported a 5.4% mortality rate (95% CI, 1.5%-10.1%) in the first year of life and an additional 2% by age five. Genotype–phenotype correlations, particularly those involving cardiac involvement, improve prognostic stratification and open opportunities for targeted and personalized strategies (16).

We report a case of Noonan syndrome caused by a pathogenic *SOS1* variant (c.1656G>T; p.Arg552Ser) to highlight its genotype–phenotype correlation and diagnostic implications.

Case Presentation

The patient was a male, the second child of a 24-year-old mother with a history of gestational diabetes and treated congenital syphilis. There was no parental consanguinity or family history of genetic or chromosomal disorders, and no exposure to teratogenic agents was reported during pregnancy. During prenatal care, an ultrasound revealed nasal bone hypoplasia and shortening of the long bones, findings suggestive of skeletal dysplasia. Karyotype analysis of amniotic fluid using G-banding was normal (46,XY).

At four months of age, the patient was admitted to the pediatric intensive care unit for viral bronchiolitis with bacterial superinfection requiring mechanical ventilation. During hospitalization, echocardiography revealed asymmetric septal hypertrophy without obstructive gradient, moderate supravalvular pulmonary stenosis, and a persistent ductus arteriosus.

Physical examination showed facial dysmorphism characterized by a prominent forehead, broad nasal bridge with bulbous tip, triangular chin, low-set auricles, and mild exophthalmos. Additional findings included a grade III–IV/VI systolic ejection murmur at the pulmonary focus, mild pectus excavatum, short neck, symmetric shortening of the limbs, and axial hypotonia.

Complementary studies revealed mild pulmonary valve stenosis (peak gradient 31 mmHg, mean 14 mmHg), preserved left ventricular systolic and diastolic function (LVEF 71%), and an electrocardiogram showing sinus rhythm with an rSR pattern in aVR. Abdominal ultrasound demonstrated splenomegaly, and renal ultrasound revealed bilateral dilation of the renal pelvis. Skeletal radiographs showed bilateral genu varum, with a normal spine.

Given the multisystem involvement, dysmorphic features, and normal karyotype, molecular testing was indicated. Whole-exome sequencing with copy-number variant (CNV) analysis targeting RASopathy-related genes identified a heterozygous *SOS1* variant, c.1656G>T (p.Arg552Ser), classified as pathogenic in major databases (ClinVar, HGMD, LOVD) according to ACMG criteria. These findings confirmed the diagnosis of *SOS1*-related Noonan syndrome type 4. Following molecular confirmation, multidisciplinary follow-up was initiated, including cardiology, endocrinology, and genetics surveillance. At the most recent evaluation, the patient remained clinically stable, with growth and neurodevelopment appropriate for age.

Genetic and family counseling were provided to support an accurate diagnosis that would guide therapeutic management, follow-up, and prognosis within the framework of precision and personalized medicine.

Results

Whole-exome sequencing (WES) with copy-number variant (CNV) analysis targeting RASopathy-related genes (LZTR1, PTPN11, RAF1, RIT1, and SOS1) was performed using next-generation sequencing technology, achieving >98% coverage with a minimum depth of 20×. Data processing included standard quality control, alignment, and variant annotation according to the reference genome (hg19).

A heterozygous variant in SOS1 was identified: c.1656G>T in exon 10, resulting in the substitution p.Arg552Ser (Figure 3). This missense variant affects a moderately conserved residue within a functional domain where other deleterious substitutions have been described.

The variant is reported as pathogenic in multiple curated databases, including ClinVar (ID 40684; 12 records), LOVD (3 records), and HGMD (CM070274), and has been previously described in patients with Noonan syndrome (PMID: 17586837, 18854871, 18651097, 22848035, 22488759, 28378436). It is absent from large population databases (gnomAD v4.1.0, TOPMed Bravo, 4.7KJPN, GenomeAsia, GME Variome, Iranome). In silico predictors (REVEL, MetaLR, among others) classify it as deleterious (Figure 4).

According to ACMG criteria (PM1, PM2, PM5, PP3, PP5, PS1, PS2, PS4), the SOS1 c.1656G>T (p.Arg552Ser) variant was classified as pathogenic. Pathogenic variants in SOS1 are associated with Noonan syndrome type 4 (Table 1).

Discussion

Noonan syndrome (NS) is a genetic disease with multisystem involvement and a variable clinical spectrum, and its diagnosis can be challenging in the absence of typical manifestations. This case describes a male infant with prenatal findings of nasal bone hypoplasia and long bone shortening, postnatal dysmorphic features, pulmonary stenosis, and renal anomalies. Molecular analysis identified a pathogenic SOS1 variant, c.1656G>T (p.Arg552Ser), confirming the diagnosis of SOS1-related Noonan syndrome type 4. This variant correlates with the patient's clinical phenotype and reinforces the diagnostic value of early exome sequencing in atypical or incomplete presentations.

Variants in SOS1 account for approximately 20% of NS cases and are typically associated with pulmonary stenosis, distinctive ectodermal findings, and generally preserved cognitive development. The p.Arg552Ser variant observed in our patient shows a genotype–phenotype correlation consistent with previous reports. Celik et al. (17)described patients with SOS1 variants who

shared similar craniofacial and cardiac features, while Najera et al. (2021) reported an infant with comparable characteristics, including lymphatic abnormalities. These findings underscore the phenotypic heterogeneity of SOS1-related NS and consolidate the role of this gene in the RAS/MAPK signaling pathway (17,18).

Early molecular confirmation allowed optimization of clinical management and the implementation of individualized follow-up, including continuous cardiovascular surveillance due to the risk of progression to hypertrophic cardiomyopathy, as well as growth monitoring and endocrine evaluation to detect potential hormonal disturbances. In addition, genetic counseling was crucial to inform the family about the autosomal dominant inheritance pattern, recurrence risk, and future reproductive implications, providing anticipatory guidance.

This case emphasizes how early genetic diagnosis in prenatal contexts with suggestive skeletal findings can shorten the diagnostic process and facilitate a comprehensive clinical approach. The coexistence of prenatal skeletal markers and postnatal renal abnormalities—rarely described in SOS1-associated NS—broadens the known clinical spectrum of this subtype and provides additional evidence of its phenotypic variability.

Conclusion

Noonan syndrome (NS) is one of the most prevalent RASopathies, with a broad phenotypic spectrum that can make clinical diagnosis challenging, particularly in subtle or atypical presentations. In this case, the use of next-generation sequencing (NGS) technologies—specifically whole-exome sequencing (WES) with CNV analysis targeting LZTR1, PTPN11, RAF1, RIT1, and SOS1—enabled the identification of a heterozygous pathogenic SOS1 variant, c.1656G>T (p.Arg552Ser), which demonstrated a consistent clinical correlation with the observed phenotype, characterized by cardiovascular involvement and mild ectodermal findings.

The diagnostic accuracy achieved through WES underscores its essential role in distinguishing NS from overlapping RASopathies and optimizing clinical outcomes. Beyond confirming clinical suspicion, molecular diagnosis enables precise prognostic stratification, informs family counseling, and supports precision-based medical care. This case reinforces the integration of genomic and bioinformatic tools into clinical practice, highlighting the transformative value of precision medicine in hereditary disorders. Although no curative treatment currently exists, ongoing research into RAS/MAPK signaling continues to expand therapeutic possibilities aimed at improving prognosis and quality of life.

Figure 3. *SOS1 Gene SOS1 c.1656G>T Region Viewer Source:https://franklin.genoox.com/clinical-db/variant/snp/chr2-39249913-CA?app=assessment-tools*

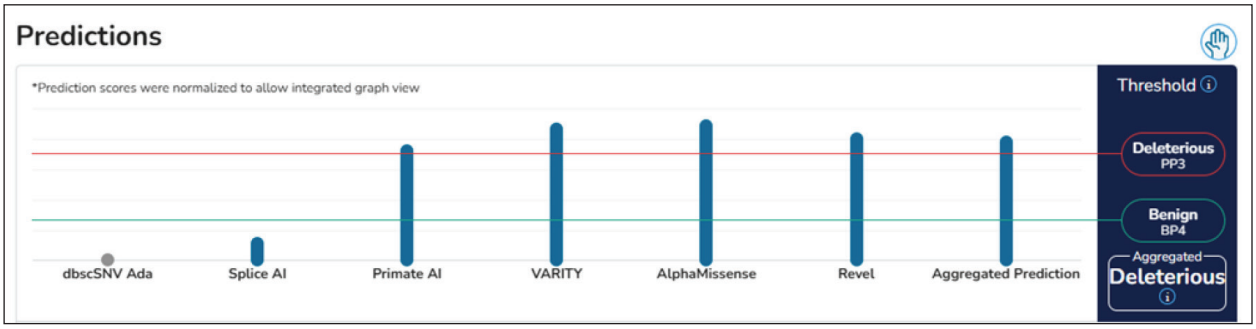

Figure 4. *Classification of clinical significance according to predictors.*

Table 1. *Disease associated with pathogenic variants in SOS1 (compiled by the authors using data from the Human Phenotype Ontology: https://hpo.jax.org/browse/gene/NCBIGene:6654).*

Gene	Disease (Identifier)	Inheritance	Main Clinical Features
SOS1	Noonan syndrome type 4 (OMIM #610733 / ORPHA #648)	Autosomal dominant	Distinctive facial features (broad forehead, triangular face, hypertelorism, ptosis, low-set ears), short neck, pectus excavatum, short stature, congenital heart defects (pulmonary stenosis, hypertrophic cardiomyopathy, septal defects), keratosis pilaris, curly hair, cryptorchidism, renal anomalies, mild intellectual disability, and a tendency toward abnormal bleeding.

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Conflict of interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for participate

Written informed consent was obtained from all the participants.

Ethical approval

This case report is based on a retrospective review of clinical data and did not involve any experimental intervention. Therefore, approval by a medical ethics committee was not required. Written informed consent was obtained from the patient's parents, and the report was conducted in accordance with ethical principles and institutional good clinical practice standards.

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