



THE GENETIC PUZZLE: A CASE OF NOONAN SYNDROME WITH A NOVEL RAF1 MUTATION IN INDIA AND THE CHALLENGES OF DIAGNOSIS AND MANAGEMENT

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ABSTRACT

We present a 17-month-old toddler with failure to thrive, developmental delay, characteristic facial dysmorphism, and a cardiac murmur suggestive of Noonan Syndrome. Echocardiography revealed hypertrophic cardiomyopathy, and molecular genetic testing confirmed the diagnosis, identifying a previously unreported RAF1 gene mutation (p.Thr260Lys) in India. The child was initiated on beta-blockers and received feeding advice, resulting in modest growth improvement over two months. Genetic testing further emphasized the importance of cascade screening. The child continues to receive multidisciplinary follow-up care under Paediatric OPD, Indira Gandhi Hospital, Dwarka. This case highlights the clinical significance of molecular testing in confirming Noonan Syndrome, particularly in cases with atypical or novel mutations. It also reflects the practical challenges faced by paediatricians in resource-limited healthcare settings, where barriers such as lack of awareness, financial constraints, and limited availability of genetic testing persist. Despite these limitations, genetic confirmation not only refines diagnosis and management but also provides valuable insight into at-risk individuals through family screening. Early recognition and comprehensive management can substantially improve outcomes and quality of life in affected children. Furthermore, the emotional, financial, and social stress experienced by caregivers of children with rare genetic disorders must be acknowledged, with the establishment of support systems to help families navigate these challenges.

Keywords: Noonan Syndrome; dysmorphism, mutation; RAF1 gene; hypertrophic cardiomyopathy.

INTRODUCTION

Noonan Syndrome (NS) is a genetically heterogeneous developmental disorder characterized by distinctive facial features, congenital heart defects, short stature, and developmental delay. It results from mutations in genes that regulate the **RAS/MAPK signalling pathway**, which plays a crucial role in cell growth, differentiation, and apoptosis.[1] The clinical presentation of NS is highly variable

and may overlap with other syndromic conditions, leading to diagnostic delays or misdiagnosis.[2] In India, early recognition and management of NS remain particularly challenging. Limited awareness among healthcare providers, the high cost of molecular testing, and the scarcity of accredited genetic laboratories often contribute to under-diagnosis and delayed intervention.[3] Although the **Government of India's National Policy for Rare Diseases (2021)** aims to address the needs of patients with rare disorders, its focus primarily lies on one-time curative therapies such as enzyme replacement or gene therapy.[4] However, disorders like NS require lifelong multidisciplinary management, including cardiologic monitoring, developmental rehabilitation, nutritional support, and psychosocial counselling

— aspects not yet adequately covered under the existing framework.[4]

We report the case of a **19-month-old Indian child** with failure to thrive and developmental delay, ultimately diagnosed with NS through molecular genetic testing. Identification of a **novel RAF1 gene mutation (p. Thr260Lys)** — previously unreported in the Indian literature

— expands the genotypic spectrum of NS and emphasizes the importance of incorporating genetic diagnostics into routine pediatric evaluation.

This case highlights the need for **India-specific strategies** that strengthen clinical awareness, improve access to genomic testing, and provide sustained institutional and policy support for children with rare genetic disorders.

Case Presentation

A 19-month-old toddler boy presented to Paediatrics OPD at Indira Gandhi Hospital, Dwarka with failure to thrive and delayed milestones. He visited several Govt. Health centres and few Paediatricians for this without any positive outcome. He was first born and only child out of non-consanguineous marriage through Caesarean section. He was noted to have weak cry with cyanosis at birth and shifted to Neonatal ICU. The boy received Ventilator support for few days and was discharged after three weeks. Parents were normal and detailed family history did not reveal any inherited disease or early deaths. Mother did not report any feeding difficulties during the rearing of the child. There was global developmental delay in achieving milestones specifically fine motor, language, and social milestones. Apparent Development age appeared to be 11-12 months. She also complained of poor head hair growth and persistent dry and pruritic skin. Weight (6.5 Kg) and Height (67 cm.) appeared below 3 SD as per Normal children as well as growth chart for Children with Noonan Syndrome (Figure1). Weight for age (9 months) and Height for age(11months) suggested showed chronic stunting and malnutrition.

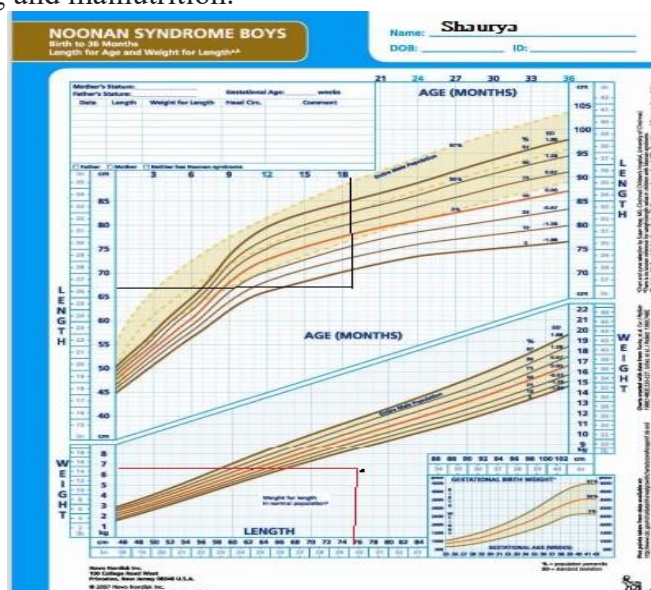


Figure 1: Growth chart for boys with Noonan Syndrome showing patient's anthropometric data (weight and length) at 19 months; both below the 3rd percentile.



Figure 2: Facial dysmorphism and Prominent sternum

He was alert, Pulse-108/minute, good volume, Respiratory rate 50/minute, tachypnoeic but no respiratory distress, Saturation in Room Air-95%; no cyanosis, no icterus/oedema; BP-RA 86/50; RL 97/55.

He had facial dysmorphism with broad forehead, open anterior fontanelle, hypertelorism, hooded eyelids, antimongoloid slant and short palpebral fissures, sparse eyebrows, epicanthal folds, short, fuzzy scalp hair, depressed bridge of nose, inverted V-shaped upper lip, anteverted anterior nares, short neck and low set, posterior rotated big ears (Figure 2). He also exhibited small hands, pectus carinatum, generalized hypotonia and cryptorchidism. Skin: He had generalized dryness, itchy, rough skin with skin-coloured papules in perineal region and thighs. The child was noted to have grade 4/6 ejection systolic murmur, localized at left midsternal border with wide, variable split-second heart sound. Respiratory System: Pectus carinatum, Tachypnoic-50/minute, no distress, bilateral vesicular breathing. Abdominal assessment showed Liver just palpable; spleen not palpable; bilateral cryptorchidism with hypoplastic scrotum. His Complete blood count showed mild anaemia (Hb11gm%); normal blood and platelets. His Liver and Renal function tests, Coagulation and Thyroid profile was normal. ECG findings are suggestive of sinus tachycardia with right atrial enlargement along with left and right ventricular hypertrophy with characteristic superior Northwest axis (Figure 3).

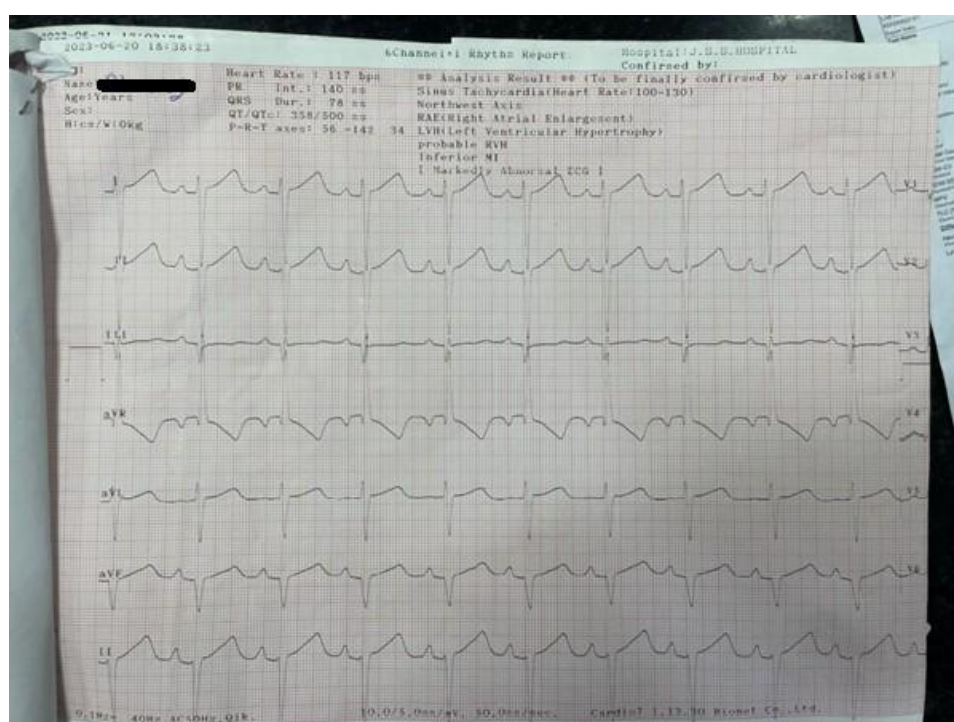


Figure 3: ECG Sinus tachycardia with biventricular hypertrophy and superior northwest axis.

ECHO showed biventricular hypertrophy; Right Ventricular infundibular outflow obstruction (50mm Hg); Left Ventricular outflow tract obstruction(60mmHg); Small ASD with left to right shunt (Figure 4)

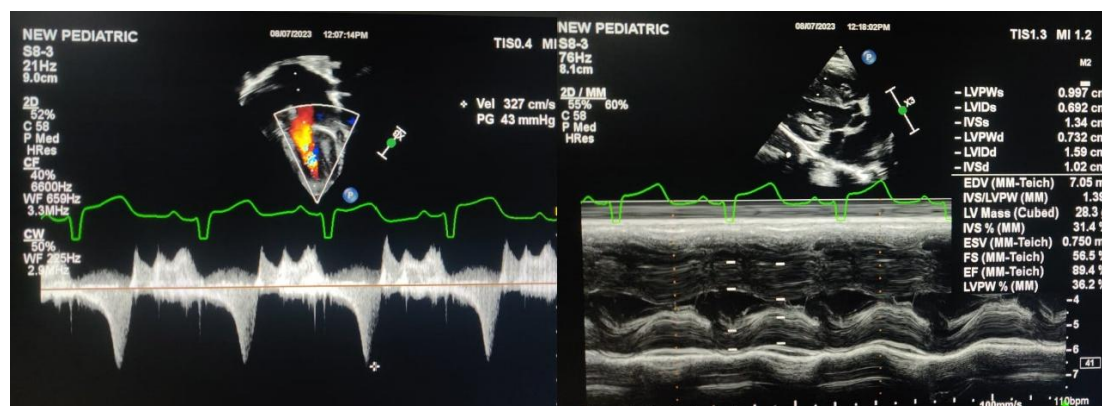


Figure 4: Echocardiogram Biventricular hypertrophy with RV and LV outflow obstruction and small ASD.

Holter Monitoring was done in coordination with Department of Cardiology and did not reveal any sustained arrhythmia.

Table 1: Molecular DNA Report

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
RAF1 (-) (ENST00000442415.7)	Exon 7	c.779C>A (p. Thr260Lys)	Heterozygous	Noonan syndrome-5 (OMIM#611553) ; LEOPARD syndrome-2	Autosomal dominant	Likely Pathogenic (PM1, PM2, PM5, PP3, PP5)

Variant description: A heterozygous missense variant in exon 7 of the RAF1 gene (chr3: g.12604191G>T; Depth: 124x) that results in the amino acid substitution of Lysine for Threonine at codon 260 (p. Thr260Lys; ENST00000442415.7) was detected (Table 1). An alternative allele has previously been reported (as p. Thr260Arg) in patients affected with Noonan and LEOPARD syndromes [PMID: 17603483]. The observed variant is classified as Pathogenic/ Likely pathogenic by the CLIN Var database [VCV000639302.4]. The p. Thr260Lys variant has not been reported in the 1000 genomes, *gnomAD*(v3.1), The p. Thr260Lys variant has not been reported in the 1000 Genomes, *gnomAD*(v3.1), *gnomAD*(v2), TOP Med, or our internal databases. The in-silico prediction tools classify this variant as *possibly damaging* by PolyPhen-2 (Hum Div) and *damaging* by SIFT, LRT, and MutationTaster2. The reference codon at position 260 in the *RAF1* gene, coding for threonine, is highly conserved across different species. The normal function of RAF1 is crucial for proper heart formation during embryonic development. Variants that alter protein function may lead to structural abnormalities of the heart. OMIM phenotype: Noonan syndrome-5 (OMIM#611553) and LEOPARD syndrome-2 (OMIM#611554) are caused by heterozygous mutations in the RAF1 gene (OMIM*164760). [1] Based on the above evidence, this RAF1 variation is classified as a likely pathogenic variant and has to be carefully correlated with the clinical symptoms.

Management and Outcome

Noonan Syndrome was confirmed through genetic testing that identified a mutation in the RAF1 gene, representing a previously unreported variant in India. This underscores the importance of expanding our understanding of this rare genetic disorder within diverse populations. While the global incidence of Noonan Syndrome is estimated at approximately 1 in 2,500 live births [2], there is a

notable paucity of epidemiological data specific to India, making this case both diagnostically and clinically significant.[3] The diagnosis initially caused shock and grief among the parents, who were counselled regarding the cardiac and developmental aspects of the condition and the need for lifelong multidisciplinary support. Coordination of care was ensured across multiple departments.

As the child had significant biventricular obstructive cardiomyopathy with a risk for sudden cardiac death, oral propranolol was initiated at 2 mg/kg/day with electrocardiographic monitoring. The dose was gradually increased to 3 mg/kg/day, resulting in a reduction in heart rate from 110/min to 90/min and respiratory rate from 50/min to 44/min. Physical, occupational, and speech therapy were instituted under the Department of Physical Rehabilitation, leading to noticeable improvement in developmental milestones—the child began articulating bi syllables within weeks.

Parents were advised on skincare management; regular use of emollients led to modest improvement in xerosis, pruritus, and recurrent skin infections.

In consultation with the Department of Dietetics, the child was prescribed a high-calorie, high-protein diet providing approximately 100 kcal/kg/day and 70 g protein daily. Over three months, the child's weight increased from 6.5 kg to 7 kg, and height from 67 cm to 68 cm, reflecting gradual improvement in growth parameters. The child continues to have follow up with the Department of Pediatric Surgery for evaluation and management of bilateral cryptorchidism, with orchiopexy planned at an appropriate age.

Discussion

Noonan syndrome (NS) shows marked genetic heterogeneity with pathogenic variants across multiple genes. The PTPN11 gene accounts for roughly half of NS cases and has been repeatedly demonstrated across cohorts and mutation-spectrum studies.[5,6,7] In contrast, RAF1 variants—classically linked to hypertrophic cardiomyopathy (HCM)—drive a distinct genotype–phenotype pattern wherein myocardial hypertrophy and early/severe cardiac involvement are more common than in PTPN11-positive NS.[1] Our case with a novel RAF1 p.Thr260Lys variant fits this correlation and aligns with prior evidence implicating RAF1 gain- of-function in HCM-predominant NS.[1] Mechanistically, dysregulation of the RAS/MAPK pathway underlies developmental abnormalities in NS.(Figure 1) Hyperactivation of “RAS–MAPK signalling pathway” perturbing cellular differentiation, and apoptosis, providing a biologic basis for syndromic cardiac remodeling and hypertrophy.[8,9]

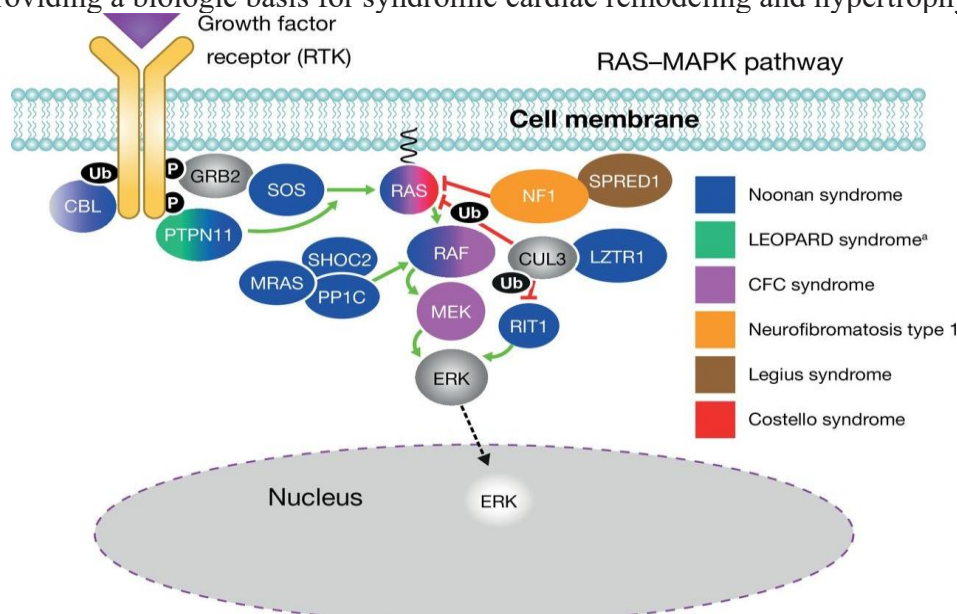


Figure 5: RAS MAPK Pathway Schematic representation of the pathway showing RAF1 activation leading to downstream MAPK signalling dysregulation.

summarized in classic and longitudinal descriptions [10,11,12]. Compared with PTPN11-positive patients, who more often exhibit pulmonary valve stenosis and less frequent HCM [6,7], RAF1-positive patients tend to have earlier and more severe HCM with greater risk of arrhythmia and sudden cardiac death [1]—supporting vigilant rhythm surveillance in management.

From a systems perspective, our case also illustrates contextual challenges in India: limited clinician awareness and constrained access to accredited genetic testing lead to delayed diagnoses and missed opportunities for anticipatory guidance and cascade screening [3]. The National Policy for Rare Diseases (2021) acknowledges rare-disease needs but is oriented toward one-time curative modalities; conditions like NS require lifelong, multidisciplinary care (cardiology, development/rehabilitation, nutrition, psychosocial support), which remains under-resourced within public frameworks [4]. Broader perspectives on India's genomic medicine ecosystem similarly highlight the need to expand infrastructure, workforce capacity, and equitable access to molecular services [13]. Against this backdrop, our identification of a previously unreported RAF1 variant in India adds to the regional mutational landscape and underscores the value of molecular confirmation for prognosis, surveillance (especially for HCM/arrhythmia), and family cascade testing.

In summary, this case reinforces prior genotype–phenotype observations (RAF1 ↔ HCM) [1] while contrasting them with PTPN11-dominant patterns [5–7]; it also emphasizes pathway biology [8,9] and the breadth of cardiac associations described historically.[10–12] Within India's current ecosystem [3,4,13], strengthening early genetic diagnosis, structured cardiac follow-up, and integrated multidisciplinary support can meaningfully improve outcomes.

Conclusion

This case serves as a poignant reminder of the pivotal role that **molecular genetic testing** plays in confirming the diagnosis of **Noonan Syndrome**, particularly in the presence of atypical or novel mutations. The identification of a previously unreported **RAF1 gene variant** not only expands the mutational spectrum of NS in India but also reinforces the importance of genotype–phenotype correlation in clinical practice.

Beyond diagnostic confirmation, this report underscores the urgent need for **comprehensive and sustained support systems** for families of children with rare genetic disorders. The emotional, financial, and social stressors associated with such conditions remain formidable challenges, particularly in resource-limited settings. Strengthening **multidisciplinary care**, improving **access to genetic testing**, and expanding the scope of India's **National Policy for Rare Diseases** to include lifelong management and psychosocial support are critical next steps.

By strengthening early recognition, counselling, and coordinated care, clinicians can improve quality of life and outcomes for children with Noonan Syndrome while contributing to global understanding of this multifaceted disorder

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