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Case Report

Genotype–phenotype discordance in Noonan syndrome: prenatal diagnosis in an asymptomatic mother

Priyanka Gupta*, Rageshwari Sharma, Amita Suneja, Taru Gupta

Department of Obstetrics and Gynecology, ESI PGIMSR, Basaidarapur, Delhi, India

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***Correspondence:**
Dr. Priyanka Gupta,
E-mail: drpriyankagupta3@gmail.com

ABSTRACT

Noonan syndrome is a RASopathy with variable clinical expression. Prenatal suspicion is often based on ultrasound findings such as increased nuchal fold. Increased nuchal fold on prenatal ultrasound led to genetic evaluation and identification of a pathogenic MAPK1 variant in the foetus. Segregation analysis revealed the same mutation in the phenotypically normal mother also. The neonate after birth was clinically normal with no structural abnormalities. This case highlights the importance of prenatal markers and demonstrates that Noonan syndrome may be present without classical phenotypic features.

Keywords: Noonan syndrome, RASopathy, Prenatal diagnosis, Nuchal fold, MAPK1 mutation, Psoriasis

INTRODUCTION

Noonan syndrome is a genetic disorder belonging to the group of RASopathies caused by mutations affecting the RAS–MAPK signaling pathway. It shows autosomal dominant inheritance or may arise due to de novo mutations. The condition demonstrates marked phenotypic variability, ranging from classical dysmorphic features and congenital heart defects to completely asymptomatic individuals.[1] Prenatal suspicion often arises from ultrasound findings such as increased nuchal translucency or nuchal fold thickness.[2] With advances in molecular diagnostics, individuals without classical phenotypic manifestations are increasingly identified.

We report a case where prenatal ultrasound findings led to the diagnosis of Noonan syndrome in a phenotypically normal mother.

CASE REPORT

A 36-year-old woman, gravida 5 with four previous abortions, presented to the antenatal clinic at 20 weeks of gestation for routine prenatal evaluation. All her previous pregnancies had been medically terminated in view of ongoing treatment with methotrexate for psoriasis. She had a long-standing history of chronic plaque psoriasis, diagnosed approximately 11 years earlier, with initial lesions appearing over the lower limbs that gradually progressed to involve multiple areas of the body.

A routine level II anomaly scan was done at 21 weeks of gestation, demonstrated increased nuchal fold measuring 6.2 mm. In view of these findings, the patient was referred to a fetal medicine specialist for further evaluation and genetic counseling.

A repeat ultrasound examination performed at 23 weeks of gestation confirmed persistently increased nuchal fold. Fetal echocardiography revealed no structural congenital cardiac abnormalities.

Given the presence of advanced maternal age and persistently increased nuchal fold, amniocentesis was performed to evaluate for chromosomal abnormalities and potential genetic syndromes. Genetic analysis identified a pathogenic variant in the MAPK1 gene (c.490A>G; p.Lys164Glu), which is associated with Noonan syndrome

(Figure 1). Fetal karyotyping demonstrated a normal chromosomal complement, with no abnormalities involving chromosomes 13, 18, 21, or the sex chromosomes. Subsequent segregation analysis revealed that the identified variant was absent in the father but present in a heterozygous state in the asymptomatic mother as can be seen in the report attached, confirming maternal carriage of the mutation. Subsequently, maternal echo was also done which was normal despite the presence of Noonan syndrome.

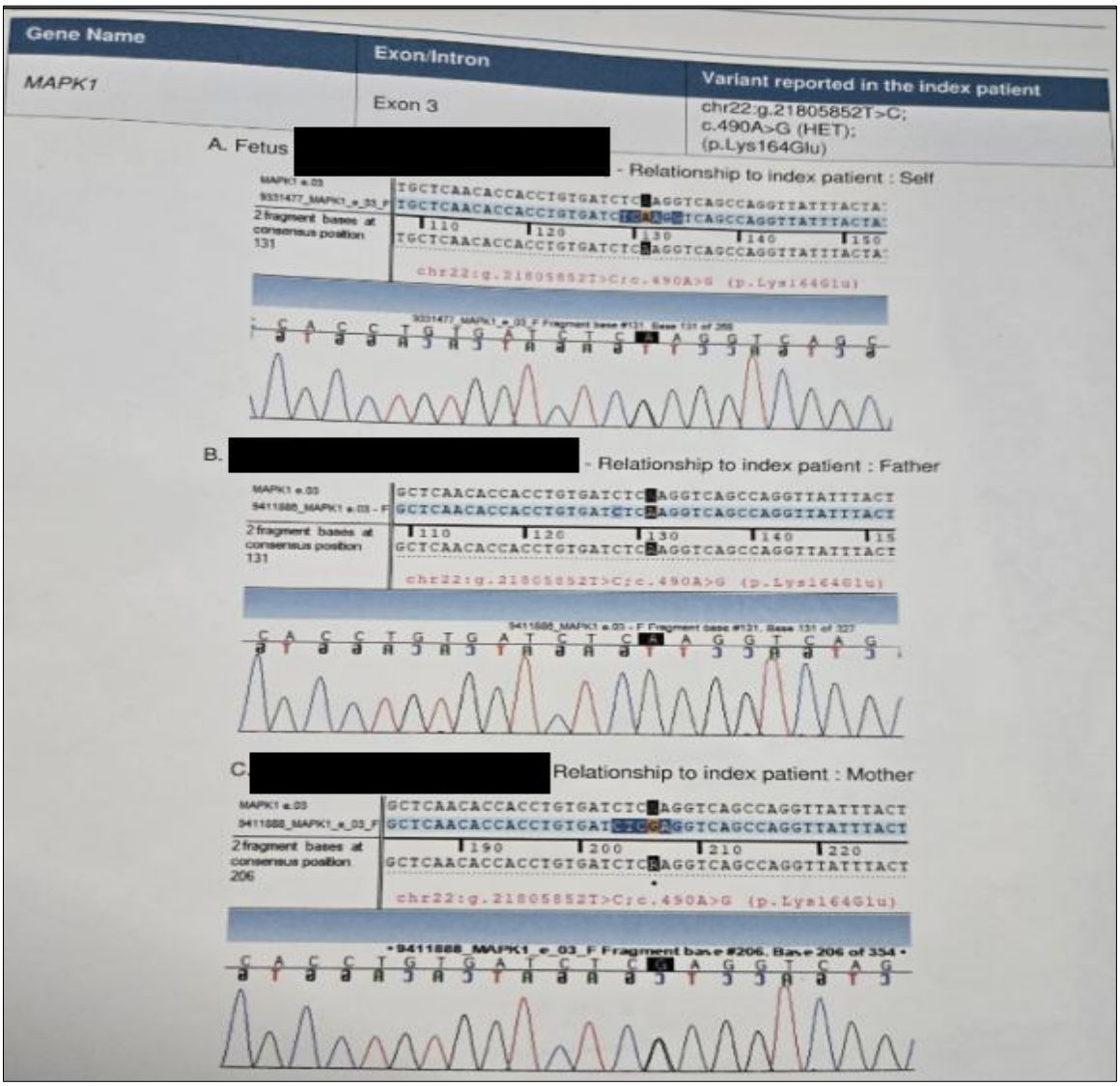

Figure 1: Genetic analysis.

The pregnancy was subsequently monitored with regular antenatal follow-up. During the third trimester, the patient experienced an exacerbation of her psoriatic lesions. Her psoriasis had previously been managed with oral methotrexate, initially at a dose of 2.5 mg weekly and gradually escalated to 20 mg weekly until 2018. Due to persistent disease activity, therapy was subsequently modified to include cyclosporine and later with an immunomodulator, etanercept. All systemic medications were discontinued at approximately six months of gestation in view of the ongoing pregnancy.

At 36 weeks and 6 days of gestation, the patient presented with complaints of leaking per vaginum and lower abdominal pain, suggestive of preterm premature rupture of membranes. She subsequently delivered a healthy male neonate weighing 3.27 kg.

The newborn was phenotypically normal, with no dysmorphic facial features or clinical findings suggestive of Noonan syndrome. Postnatal evaluation, including chest radiography, abdominal ultrasonography, and hearing screening, was unremarkable. Follow-up echocardiography performed at three months of age also demonstrated no structural cardiac abnormalities.

Notably, during postnatal follow-up, the patient reported a significant improvement in her psoriatic lesions.

DISCUSSION

Noonan syndrome is a genetically heterogeneous disorder caused by mutations affecting the RAS–MAPK signaling pathway, which plays an important role in cellular growth, differentiation, and immune regulation.[1] These disorders are collectively referred to as RASopathies and share overlapping genetic mechanisms and clinical features.[2] Although Noonan syndrome is classically associated with characteristic facial features, congenital heart defects, and short stature, the clinical presentation can be highly variable, and some individuals may remain undiagnosed due to minimal or absent phenotypic findings.[3]

The present case highlights an unusual diagnostic pathway in which a phenotypically normal adult woman was identified as having genetically confirmed Noonan syndrome following abnormal prenatal ultrasound findings. During routine antenatal evaluation, increased nuchal thickness detected on fetal ultrasound prompted further genetic testing.

Increased nuchal translucency or nuchal fold thickness is a recognized prenatal marker associated not only with chromosomal abnormalities but also with RASopathies such as Noonan syndrome.[4] These findings are thought to result from abnormal lymphatic development caused by dysregulation of the RAS–MAPK pathway, leading to transient fluid accumulation in the fetal neck region.[5]

In our patient, the prenatal ultrasound abnormality led to detailed genetic evaluation, which unexpectedly revealed a pathogenic variant associated with Noonan syndrome in the foetus and also in the mother despite the absence of classical clinical features. This finding illustrates the concepts of variable expressivity and incomplete penetrance that are well described in Noonan syndrome.[1,2] With increasing use of prenatal genetic testing, individuals carrying pathogenic variants may be identified incidentally during fetal assessment, thereby expanding the recognized clinical spectrum of the disorder.

Cardiac involvement remains the most important clinical concern in Noonan syndrome, with pulmonary valve stenosis and hypertrophic cardiomyopathy being the most frequently reported abnormalities.[6] Importantly, cardiac manifestations may not be evident at birth and can develop later in childhood. In the present case, fetal echocardiography, postnatal cardiac evaluation of the neonate, and maternal echocardiography were all normal, suggesting a mild phenotypic expression. However, continued clinical and echocardiographic follow-up is recommended, as cardiac abnormalities may appear later in life.[6]

An additional noteworthy feature of this case is the coexistence of long-standing psoriasis in the mother. Psoriasis is a chronic immune-mediated inflammatory disorder characterized by dysregulated immune pathways and increased keratinocyte proliferation involving cytokines such as interleukin-17 and interleukin-23.[7,8] Emerging evidence suggests that signaling pathways regulating cellular proliferation and immune responses, including the RAS–MAPK cascade, may also play a role in inflammatory skin disease.[7] Although a direct association cannot be established from a single case, this coexistence raises the possibility of shared molecular mechanisms contributing to immune dysregulation.

Pregnancy induces significant hormonal and immunological changes that may influence autoimmune and inflammatory diseases. A relative shift toward a T-helper-2 predominant immune state during pregnancy can modify psoriasis activity.[7,8] In this patient, worsening of psoriatic lesions during late pregnancy followed by postpartum improvement was observed, a pattern that has been described in previous studies evaluating psoriasis during pregnancy.[9]

This case emphasizes the importance of careful evaluation of prenatal ultrasound soft markers. Increased nuchal thickness may serve as an early indicator of underlying genetic disorders even when structural anomalies are absent.

The diagnosis of Noonan syndrome in a clinically asymptomatic mother highlights the limitations of relying solely on phenotypic appearance and underscores the value of integrating prenatal imaging with molecular genetic testing.

Overall, our case demonstrates how prenatal suspicion based on increased nuchal thickness led to the diagnosis of Noonan syndrome in an otherwise phenotypically normal mother and allowed appropriate counselling and follow-up. Such cases broaden the known clinical spectrum of Noonan syndrome and reinforce the role of multidisciplinary prenatal assessment in identifying subtle presentations of RASopathies.

Key learning points

Noonan syndrome shows considerable phenotypic variability, and genetically confirmed cases may occur in individuals without classical clinical features. Increased nuchal fold on prenatal ultrasound should prompt evaluation for RASopathies such as Noonan syndrome. Serial cardiac surveillance is recommended in individuals with suspected or confirmed Noonan syndrome, although structural abnormalities may be absent. Although MAPK1 mutations are less frequently reported in Noonan syndrome, variants affecting the RAS-MAPK pathway may produce RASopathy phenotypes.

The coexistence of psoriasis and Noonan syndrome raises the possibility of shared molecular pathways involving dysregulation of the RAS-MAPK signaling cascade. Pregnancy related immunological changes may influence the course of psoriasis.

CONCLUSION

This case highlights the broad phenotypic spectrum of Noonan syndrome and demonstrates that genetically confirmed disease may occur in individuals without classical phenotypic manifestations. Increased nuchal fold remains an important prenatal marker prompting further genetic evaluation. The coexistence of psoriasis in this patient suggests a potential interaction between RAS-MAPK signaling abnormalities and inflammatory dermatologic disease, warranting further investigation.

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