Case Report
DOI: 10.4274/jcrpe.galenos.2026.2025-12-21

An Unexpected Result in a Case of Gonadal Dysgenesis: Noonan Syndrome Caused by *RIT1* Mutation

Şafak Demirtaş, Elif Özsu, Zeynep Şıklar, Zehra Aycan, Sirmen Kızılcan Çetin, Sema Nilay Abseyi, İlkyaz Türktan, Merih Berberoğlu
Ankara University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Türkiye

What is already known?
Noonan syndrome is a multisystemic rasopathy characterized by facial dysmorphism, short stature, and congenital heart defects. Male gonadal involvement is typically restricted to cryptorchidism and impaired Sertoli cell function leading to subfertility. 46, XY gonadal dysgenesis and ambiguous genitalia have not been previously reported in patients with Noonan syndrome spectrum.

What this study adds?
This report documents the first case of Noonan syndrome presenting with 46,XY partial gonadal dysgenesis and ambiguous genitalia. It identifies the *RIT1* (c.136T>G) variant as a novel genetic etiology for Disorders of Sex Development (DSD). The study emphasizes screening for Noonan syndrome in unexplained DSD cases, especially when cardiac or lymphatic abnormalities are present.

Abstract
Noonan syndrome occurs in approximately 1/1,000-1/2,500 live births and is caused by defects in the Ras/mitogen-activated protein kinase pathway. Pubertal development includes syndrome-specific differences which may manifest as delayed puberty in both sexes, as well as cryptorchidism and impaired gonadal function, especially in the males. However gonadal dysgenesis and disorders of sex development have not been previously reported in the literature before. Our patient presented with ambiguous genitalia at two days of age. There was no consanguinity between the parents. On physical examination, the external masculinisation score was 4. Laboratory tests were compatible with gonadal dysgenesis. Echocardiography revealed pulmonary stenosis and a secundum atrial septal defect. Karyotype was 46 XY, SRY (+) and no pathogenic variant was detected in the targeted gene sequencing panel for disorders of sex development. A targeted next-generation seqeuencing (NGS) panel for Noonan syndrome was performed in the patient due to pulmonary stenosis and suggestive facial appearance, identifying a pathogenic c.136 T>G variant in the *RIT1* gene. Noonan syndrome may cause gonadal dysfunction leading to delayed puberty and infertility; however, gonadal dysgenesis and ambiguous genitalia have not been previously reported. Noonan syndrome should be investigated in every patient with suggested clinical findings and affected gonadal functions.
Keywords: Noonan syndrome, RIT1, gonadal dysgenesis, disorders of sex development

Şafak Demirtaş, Ankara University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Türkiye
sadem987@gmail.com
0009-0001-4243-4742

19.12.2025
20.05.2026

Epub: 16.06.2026

Introduction
Noonan syndrome is a relatively common genetic disorder characterized by multiple congenital anomalies with an estimated incidence of 1:1,000 to 1:2,500 live births (1).
Distinctive facial features include relative macrocephaly, hypertelorism, down-slanting palpebral fissures, ptosis, epicanthal folds, and low-set ears. The spectrum of congenital heart defects includes pulmonary valve stenosis (PS, 50–60%), hypertrophic cardiomyopathy (20%) and atrial septal defects (6–10%). Affected individuals may also exhibit short stature, cryptorchidism, bleeding diathesis, skeletal malformations, developmental delay, lymphatic dysplasia, and ocular abnormalities (2,**3**).
It is an autosomal dominant disorder with variable expressivity, but most cases are sporadic (*de novo*). To date, nearly 20 genes have been found to be implicated in Noonan syndrome. About 50% of patients with Noonan syndrome have a pathogenic variant in the protein tyrosine phosphatase non-receptor type 11 (*PTPN11*) gene. Other common genes include *SOS1* (10-20%), *RAF1* (3-17%), *RIT1* (9%), and a group of genes with a frequency of 1-5%, including *SHOC2*, *RASA2*, *LZTR1*, *SPRED2*, *SOS2*, *CBL*, *KRAS*, *NRAS*, *MRAS*, *RRAS*, *BRAF*, *PPP1CB*, *A2ML1*, *MAP2K1,* and *CDC42* (4).
There is limited published data on gonadal function and fertility in Noonan syndrome. Cryptorchidism, pubertal delay, and Sertoli cell dysfunction in males are well-established clinical features, but gonadal dysgenesis has not yet been reported in the literature. In this report, we describe a patient with partial gonadal dysgenesis, suggestive facial dysmorphism, who was diagnosed with Noonan syndrome associated with a pathogenic variant in the *RIT1* gene.

Patient Description
A 2-day-old neonate presented with ambiguous genitalia, including a micropenis and penoscrotal hypospadias. The gonads were non-palpable bilaterally and the External Masculinization Score (EMS) was 4. The stretched penile length was 0.8 cm (Figure 1A). Pelvic ultrasonography (US) revealed bilateral, abdominally-located, nodular, fusiform, hypoechoic structures measuring 8x6 mm on the right and 9x5 mm on the left; no Müllerian structures were detected. Echocardiography performed due to a systolic murmur in the pulmonary area revealed pulmonary vascular stenosis, multiple secundum atrial septal defects (ASD) and a mitral chordal anomaly.
At one month of age, laboratory tests revealed the following results: an FSH level of 22.4 mIU/mL, an LH level of 1.35 mIU/mL, and a total testosterone level of 23.32 ng/dL. Karyotype analysis resulted in 46,XY. At 8 months of age, a human chorionic gonadotropin (hCG) stimulation test resulted in a peak testosterone level of 104 ng/dL. The serum anti-Müllerian hormone (AMH) level was low (1.3 ng/mL: reference range: 28.0-142.0). No pathogenic variants were identified in the androgen receptor (*AR*), *NR5A1* or the sex determining region Y (SRY) genes.
The patient was discussed by a multidisciplinary team consisting of the pediatric endocrinology, pediatric surgery, pediatric urology, child and adolescent psychiatry, medical genetics, and medical ethics divisions at our institution. Consequently, it was decided to assign the male gender and proceed bilateral orchidopexy and hypospadias repair. Topical dihydrotestosterone gel was initiated and administered for six months. The stretched penile length increased from 0.8 cm to 4.0 cm.

Uncorrected Proof

At 8 years of age, physical examination revealed down-slanting palpebral fissures, and low-set ears. The patient's height and the growth velocity were within normal limits; however, genetic testing for Noonan syndrome was planned due to cryptorchidism, pulmonary stenosis, and suggestive facial features. Since a comprehensive multigene sequencing panel could not be performed at that time, only *PTPN11* analysis was conducted, and no pathogenic variant was identified. On follow-up US examination, the left testicular volume was 0.165 mL, and microlithiasis was observed in the suprascrotal location with an atrophic appearance. The right testis was not observed in the inguinoscrotal region, however a suspicious structure containing an echogenic focus measuring 5.5 x 3.6 x 2.5 mm was observed in the vicinity of the abdominal wall near the internal inguinal canal inner ring. Following reevaluation, a right orchiectomy was planned due to the potential risk of malignancy in the atrophic gonad. It was decided to preserve the left gonad under close follow-up, given its partially functional capacity. A right orchiectomy was subsequently performed; however, histopathological examination revealed an absence of testicular tissue.

At 10 years of age, the left testicular volume was 4 mL, the right testicle was non-palpable and the stretched penile length was 4.5 cm. Laboratory tests revealed an FSH level of 59 mIU/mL, an LH level of 7.5 mIU/mL, a total testosterone level of 58.8 ng/dL, an AMH level of 2.07 pmol/L (reference range: 78-781).

At 12 years of age, the patient developed bilateral lower extremity swelling, and lymphedema was confirmed by US. These findings regressed spontaneously after six months. Following the increased availability of advanced molecular diagnostics, a comprehensive multigene sequencing panel for Noonan syndrome was performed, which identified a pathogenic c.136T>G (p.Phe46Val) variant in the *RIT1* (Ras-like without CAAX1) gene (NM_001256820.2).

At the final follow-up visit at 15 years of age, the patient's body weight was 47.5 kg, height was 161 cm (-0.49 SDS), and body mass index (BMI) was 18.3 kg/m^2 (-0.78 SDS) (Figure 1B). The left testicular volume was 12-15 mL, and pubarche was Tanner stage 4. The stretched penile length was measured at 5.5 cm. Notably, while the left testis exhibited pubertal growth, the final volume of 12–15 mL remained significantly below the expected adult volume. This suboptimal enlargement, coupled with extremely low AMH and markedly elevated FSH levels, is consistent with partial gonadal dysgenesis and reflects restricted Sertoli cell mass and function.

Laboratory examination showed an FSH level of 99.3 mIU/mL, an LH level of 57.1 mIU/mL, a testosterone level of 165 ng/dL, an AMH level of 0.1 (reference range: 4-22) ng/mL. The patient is currently followed by the pediatric cardiology department due to pulmonary stenosis and presents with no additional problems.

Matherials and Methods

Variant Classification and Bioinformatic Analysis

Targeted next-generation sequencing (NGS) was performed on genomic DNA isolated from peripheral blood samples. Target regions were amplified using the QIAseq Targeted DNA Custom Panel (QIAGEN, Hilden, Germany), and the sequencing reaction was conducted on the Illumina MiSeq system using compatible reagent kits. Bioinformatic analysis was conducted via the QIAGEN CLC Genomics Workbench and QIAGEN Clinical Insight (QCI) Interpret (version 5.6.20200129) interfaces. The GRCh37/hg19 assembly served as the human reference genome. Variant annotation and interpretation were supported by the Ingenuity Knowledge Base, CADD (v1.4), and the Allele Frequency Community database. Variant classification was performed in accordance with the standards and guidelines established by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).

Results

Molecular analysis identified a heterozygous missense variant, c.136T>G (p.Phe46Val), in the *RIT1* gene (NM_001256820.2). The variant was identified with high confidence, exhibiting a sequencing depth of 700x and an allele frequency of 47.71%. According to American College of Medical Genetics and Genomics (ACMG) guidelines, the variant was classified as 'pathogenic' based on the following criteria:

Evidence of Pathogenicity: The variant is recognized as a mutational hotspot and has been established in the literature as a recurrent cause of Noonan syndrome (PS4). It is situated within a critical functional domain where a high density of other pathogenic variants has been identified (PM1, PM5).

Population and Functional Data: The variant is entirely absent from large population databases, including gnomAD (PM2). Multiple *in silico* computational tools, including CADD v1.4, predict a deleterious impact on the protein product (PP3).

Literature and Clinical Correlation: The variant has been documented as occurring *de novo* in affected individuals (PS2, PM6) and is supported by functional studies demonstrating its disruptive effect on the Ras/MAPK pathway (PS3). Furthermore, the variant is registered as pathogenic in the ClinVar database (PP5).

Ethical considerations and informed consent

Written informed consent was obtained from both parents for the publication of this case report and any accompanying images. All clinical investigations and genetic testing were performed in accordance with the principles of the Declaration of Helsinki guidelines.

Discussion

Our patient was presented to our department with disorders of sex development (DSD) and was diagnosed with gonadal dysgenesis. The clinical features of Noonan syndrome had become more prominent with age. Partial gonadal dysgenesis is characterized by incomplete testicular development and a variable degree of virilization of the external genitalia, ranging from a micropenis to female-appearing genitalia, frequently presenting with a combination of Wolffian and Müllerian structures (5). Along with *SRY*, pathogenic variants in *NR5A1* and *MAP3K1* genes are the most common causes of 46,XY gonadal dysgenesis; however together they account for less than 40% of all non-syndromic forms. Although the diagnostic rate has increased with modern genetic testing, the etiology remains unexplained in approximately 50% of cases (6,7).

RASopathies represent a group of disorders characterized by pathogenic variants in genes encoding components of the Ras/mitogen-activated protein kinase (Ras/MAPK) pathway, with Noonan syndrome is the most prevalent. Noonan syndrome is a complex, multisystem disorder exhibiting variable clinical severity. Gonadal dysfunction and subfertility are rarely investigated in these patients, and the underlying mechanisms remain incompletely elucidated. Although the Ras/MAPK pathway plays a role in folliculogenesis in females, it is generally accepted that female gonadal function and fertility are largely preserved (8). In males, cryptoorchidism is very common and has been suggested as the primary cause of gonadal dysfunction (9). However, recent studies suggest that gonadal dysfunction may develop independently of cryptoorchidism, indicating an intrinsic gonadal defect (10-12).

In a longitudinal study by Ankarberg-Lindgren et al. (10) involving males with Noonan syndrome, it was observed that although testicular volumes often reached normal range by adulthood, hormonal profiles remained atypical. Specifically, patients exhibited elevated levels of FSH, LH, testosterone, and estradiol along with decreased AMH and inhibin B levels, compared to the reference population. Notably, no significant hormonal differences were found between patients with and without cryptorchidism. These findings suggest that both Sertoli and Leydig cell functions are impaired in Noonan syndrome, indicating that cryptorchidism is not the sole contributing factor to gonadal dysfunction (10). While this study suggests a combined cell-type impairment, other authors argue that Sertoli cell function is predominantly affected (9, 10). Consistent with this findings, our patient's left testis reached a volume of 12–15 mL; however, the markedly elevated FSH and low AMH levels confirmed that this enlargement did not reflect adequate Sertoli cell function.

Similarly, Marcus et al. (11) evaluated patients with Noonan syndrome primarily harboring *PTPN11* or *BRAF* variants. While LH and testosterone levels were generally within the normal range during puberty, an elevation in FSH levels and a reduction in inhibin B levels were frequently observed. These findings suggest that in males with Noonan syndrome, gonadal dysfunction is specifically associated with Sertoli cell impairment, whereas Leydig cell function is typically preserved (11). Furthermore, the authors suggested that any transiently

Incorrect proof

subnormal testosterone levels observed were likely attributable to delayed puberty rather than primary Leydig cell failure.
In another study, Moniez et al. (12) evaluated 37 patients with genetically confirmed Noonan syndrome. Their findings indicated that while testosterone levels remained normal during the pubertal period—suggesting preserved Leydig cell function— the levels of AMH and inhibin B were significantly lower than those in the general population. This led to the conclusion that Noonan syndrome is associated with Sertoli-cell-specific primary testicular insufficiency. Furthermore, consistent with previous reports, no significant differences in AMH and inhibin B levels were observed between cryptorchid and non-cryptorchid patients, reinforcing the theory that the underlying pathology is intrinsic to the syndrome rather than secondary to testicular maldescent (12).
Overall, studies addressing gonadal function in Noonan syndrome remain limited, and the reported data exhibit notable inconsistencies. Furthermore, the significant genetic heterogeneity of the syndrome results in distinct clinical phenotypes associated with different genotypes. Pathogenic variants in less common genes, such as *RIT1*, may manifest with novel clinical findings that have yet to be fully characterized. *RIT1*, located on chromosome 1q22 and comprising of six exons, was first identified as a causative gene for Noonan syndrome in 2013 by Aoki et al. (13). As a member of the RAS subfamily of GTPases, RIT1 protein shares over 50% sequence identity with RAS proteins. Pathogenic variants in this gene lead to the aberrant activation of the ETS transcription factor ELK1, which regulates critical cellular processes such as cell growth, proliferation, apoptosis, and tissue remodeling (14). Furthermore, the RIT1 protein is involved in neuronal differentiation and morphogenesis (15).
Functional studies using zebrafish embryos demonstrated that the introduction of mutant *RIT1* mRNAs results in craniofacial abnormalities, cardiac defects—such as incomplete cardiac looping and hypoplastic chambers—and elongated yolk sacs, recapitulating the biological effects seen with variants in other RASopathy-associated genes (13). *RIT1* variants account for approximately 5% of Noonan syndrome cases (14). Phenotypically, these patients are characterized by a high incidence of congenital heart disease (94%), particularly hypertrophic cardiomyopathy (71%) and pulmonary stenosis (65%), as well as lymphedema (15%) (16-18).
It has been reported that short stature is less common in individuals with *RIT1* variants compared to other genetic causes of Noonan syndrome (19). Consistent with the literature, our patient exhibited pulmonary stenosis and maintained a height within the normal range. While pulmonary stenosis was detected in the neonatal period, lymphedema—a known feature of the *RIT1* phenotype—developed at 12 years of age. Extremity and genital lymphedema are the most frequently reported types of postnatal lymphedema in Noonan syndrome; limb lymphedema typically manifests between 3 and 55 years of age, with a median onset of 10 years (18). Although the patient did not initially meet the full Van der Burgt diagnostic criteria, the subsequent development of lymphedema strengthened the clinical diagnosis of Noonan syndrome. Interestingly, hypertrophic cardiomyopathy which is frequently associated with *RIT1* pathogenic variants was not observed in our case.
RIT1 gene is expressed in both the testes and ovaries (20). However, as with other genotypes of Noonan syndrome, a case presenting with gonadal dysgenesis associated with a *RIT1* variant has not been previously reported in the literature. This novel association suggests that the phenotypic spectrum of *RIT1* may be broader than previously recognized, potentially encompassing early defects in gonadal morphogenesis. Our patient presented with ambiguous genitalia at two days of age and was diagnosed with 46,XY partial gonadal dysgenesis. Notably, the initial targeted gene sequencing panel for DSD did not identify a causative pathogenic variant. However, the subsequent identification of a *RIT1* variant—guided by suggestive facial features, pulmonary stenosis, and lymphedema—confirmed the diagnosis of Noonan syndrome. The diagnosis of Noonan syndrome was likely delayed due to the absence of short stature and the predominance of DSD findings, which initially overshadowed the syndromic presentation. Furthermore, the limited availability of comprehensive genetic testing at the time of initial presentation contributed to this delay. While gonadal dysfunction, particularly involving Sertoli cells, is a recognized feature of Noonan syndrome, true 46,XY gonadal dysgenesis as observed in our case has not been previously reported.
The *RIT1* variant may represent a novel genetic etiology for gonadal dysgenesis. The lack of prior reports is likely due to the relatively recent identification of the *RIT1* gene and the limited number of characterized cases. Given the clinical heterogeneity of Noonan syndrome, this case highlights the importance of considering RASopathies in the differential diagnosis of unexplained 46,XY DSD, especially when associated with cardiac or lymphatic abnormalities.

Study Limitations

A limitation of this study is that the identified *RIT1* variant has not been previously reported to present with such an expanded phenotype. Although the clinical features strongly suggest that the *RIT1* variant is the unifying cause of both Noonan syndrome and gonadal dysgenesis in our patient, causality cannot be definitively established in the absence of functional assays. Additionally, while the initial targeted gene sequencing panel for DSD was negative, the possibility of a "dual diagnosis" involving a second, cryptic genetic factor cannot be entirely excluded without Whole Exome Sequencing (WES). However, the known expression of *RIT1* in gonadal tissues and the specificity of the clinical findings strongly support our hypothesis.

Conclusion

In conclusion, we present a case of 46,XY partial gonadal dysgenesis and Noonan syndrome associated with a pathogenic *RIT1* variant. To our knowledge, this represent the first documented case in the literature where Noonan syndrome is associated with true gonadal dysgenesis. This finding suggests that the phenotypic spectrum of *RIT1* may be broader than previously recognized, potentially including defects in early gonadal morphogenesis. Clinicians should consider RASopathies in the differential diagnosis of unexplained DSD, particularly when associated with cardiac or lymphatic abnormalities. Further studies are warranted to elucidate the precise role of the Ras/MAPK pathway in human gonadal development.

Conflict of interests: The authors do not have any financial interests or relationships to disclose.

References

1. Mendez HMM, Opitz JM. Noonan syndrome: A review. Am J Med Genet. (1985) 21:493–506. doi: 10.1002/ajmg.1320210312.
2. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet. 2013 Jan 26;381(9863):333-42. doi: 10.1016/S0140-6736(12)61023-X.
3. Demir K, Yüksek Acınıklı K. Noonan Syndrome, Cancer Risk, and Growth Hormone Treatment. J Clin Res Pediatr Endocrinol. 2025 Dec 11;17(4):370-378. doi: 10.4274/jcrpe.galenos.2025.2024-9-13. Epub 2025 Feb 20. PMID: 39974721; PMCID: PMC12699086.
4. Patti G, Scaglione M, Maiorano NG, Rosti G, Divizia MT, Camia T, De Rose EL, Zucconi A, Casalini E, Napoli F, Di Iorgi N, Maghnie M. Abnormalities of pubertal development and gonadal function in Noonan syndrome. Front Endocrinol (Lausanne). 2023 Jul 28;14:1213098. doi: 10.3389/fendo.2023.1213098.
5. Zidoune H, Martinerie L, Tan DS, Askari M, Rezgoune D, Ladjouze A, Boukri A, Benelmadani Y, Sifi K, Abadi N, Satta D, Rastari M, Seresht-Ahmadi M, Bignon-Topalovic J, Mazen I, Leger J, Simon D, Brauner R, Totonchi M, Jauch R, Bashamboo A, McElreavey K. Expanding DSD Phenotypes Associated with Variants in the DEAH-Box RNA Helicase DHX37. Sex Dev. 2021;15(4):244-252. doi: 10.1159/000515924.
6. Elzaiat M, McElreavey K, Bashamboo A. Genetics of 46,XY gonadal dysgenesis. Best Pract Res Clin Endocrinol Metab. 2022 Jan;36(1):101633. doi: 10.1016/j.beem.2022.101633.
7. Özalp Kızılay D, Özen S. Current Diagnostic Approaches in the Genetic Diagnosis of Disorders of Sex Development. J Clin Res Pediatr Endocrinol. 2024 Dec 4;16(4):401-410. doi: 10.4274/jcrpe.galenos.2024.2024-3-3. Epub 2024 Apr 29. PMID: 38683034; PMCID:

Uncorrected Proof

PMC11629718.
8. Edouard T, Cartault A. Gonadal function in Noonan syndrome. Ann Endocrinol (Paris). 2022 Jun;83(3):203-206. doi: 10.1016/j.ando.2022.04.008.
9. Elsawi MM, Pryor JP, Klufio G, Barnes C, Patton MA. Genital tract function in men with Noonan syndrome. J Med Genet. 1994 Jun;31(6):468-70. doi: 10.1136/jmg.31.6.468.
10. Ankarberg-Lindgren C, Westphal O, Dahlgren J. Testicular size development and reproductive hormones in boys and adult males with Noonan syndrome: a longitudinal study. Eur J Endocrinol. 2011 Jul;165(1):137-44. doi.org/10.1530/EJE-11-0092
11. Marcus KA, Sweep CG, van der Burgt I, Noordam C. Impaired Sertoli cell function in males diagnosed with Noonan syndrome. J Pediatr Endocrinol Metab. 2008 Nov;21(11):1079-84. doi: 10.1515/jpem.2008.21.11.1079.
12. Moniez S, Pienkowski C, Lepage B, Hamdi S, Daudin M, Oliver I, Jouret B, Cartault A, Diene G, Verloes A, Cavé H, Salles JP, Tauber M, Yart A, Edouard T. Noonan syndrome males display Sertoli cell-specific primary testicular insufficiency. . Eur J Endocrinol. 2018 Dec 1;179(6):409-418. doi: 10.1530/EJE-18-0582.
13. Aoki Y, Niihori T, Banjo T, Okamoto N, Mizuno S, Kurosawa K, Ogata T, Takada F, Yano M, Ando T, Hoshika T, Barnett C, Ohashi H, Kawame H, Hasegawa T, Okutani T, Nagashima T, Hasegawa S, Funayama R, Nagashima T, Nakayama K, Inoue S, Watanabe Y, Ogura T, . Matsubara Y. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. Am J Hum Genet. 2013 Jul 11;93(1):173-80. doi: 10.1016/j.ajhg.2013.05.021.
14. Zha P, Kong Y, Wang L, Wang Y, Qing Q, Dai L. Noonan syndrome caused by RIT1 gene mutation: A case report and literature review. Front Pediatr. 2022 Sep 7;10:934808. doi: 10.3389/fped.2022.934808.
15. Gos M, Fahiminiya S, Poznański J, Klapecki J, Obersztyn E, Piotrowicz M, Wierzba J, Posmyk R, Bal J, Majewski J. Contribution of RIT1 mutations to the pathogenesis of Noonan syndrome: four new cases and further evidence of heterogeneity. Am J Med Genet A. 2014 Sep;164A(9):2310-6. doi: 10.1002/ajmg.a.36646.
16. El Bouchikhi I, Belhassan K, Moufid FZ, Iraqui Houssaini M, Bouguenouch L, Samri I, Atmani S, Ouldim K. Noonan syndrome-causing genes: Molecular update and an assessment of the mutation rate. Int J Pediatr Adolesc Med. 2016 Dec;3(4):133-142. doi: 10.1016/j.ijpam.2016.06.003.
17. Kouz K, Lissewski C, Spranger S, Mitter D, Riess A, Lopez-Gonzalez V, Lüttgen S, Aydin H, von Deimling F, Evers C, Hahn A, Hempel M, Issa U, Kahlert AK, Lieb A, Villavicencio-Lorini P, Ballesta-Martinez MJ, Nampoothiri S, Ovens-Raeder A, Puchmajerová A,. Satanovskij R, Seidel H, Unkelbach S, Zabel B, Kutsche K, Zenker M. Genotype and phenotype in patients with Noonan syndrome and a RIT1 mutation. Genet Med. 2016 Dec;18(12):1226-1234. doi: 10.1038/gim.2016.32.
18. Sleutjes J, Kleimeier L, Leenders E, Klein W, Draaisma J. Lymphatic Abnormalities in Noonan Syndrome Spectrum Disorders: A Systematic Review. Mol Syndromol. 2022 Feb;13(1):1-11. doi: 10.1159/000517605.
19. Shoji Y, Hata A, Maeyama T, Wada T, Hasegawa Y, Nishi E, Ida S, Etani Y, Niihori T, Aoki Y, Okamoto N, Kawai M. Genetic backgrounds and genotype-phenotype relationships in anthropometric parameters of 116 Japanese individuals with Noonan syndrome. . Clin Pediatr Endocrinol. 2024;33(2):50-58. doi: 10.1297/cpe.2024-0005.
20. Franklin by Genoox. RIT1 Gene. [Internet]. 2026 [cited 2026 Feb 4]. Available from: https://franklin.genoox.com/clinical-db/gene/hg19/RIT1

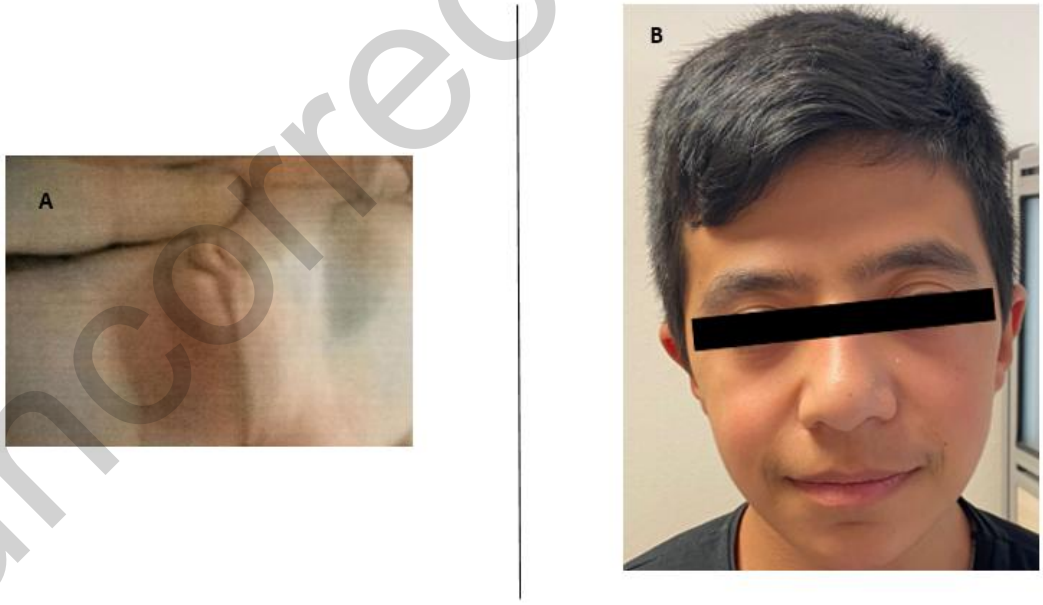

Figure 1. Clinical Phenotype of the Patient
Figure 1A: Appearance of the external genitalia at one month of age, showing ambiguous features consistent with 46,XY partial gonadal dysgenesis.
Figure 1B: Facial appearance at the final follow-up, demonstrating characteristic Noonan syndrome dysmorphism.

uncorrected proof