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**Case Report**

# A case report on gonadal dysgenesis caused by a rare NR5A1-associated contiguous gene deletion: a diagnostic challenge

**Shiny Nivya G., Vidhya Jayashree K.***

Department of Obstetrics and Gynaecology, Institute of Obstetrics and Gynaecology, Madras Medical College, Egmore, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Vidhya Jayashree K.,
E-mail: vidhyajayashree@yahoo.co.in



## ABSTRACT

Disorders of sexual development (DSD) encompass a diverse group of congenital conditions characterised by atypical development of chromosomal, gonadal, or anatomical sex. Among these, NR5A1 mutations represent an important and heterogeneous cause of 46, XY DSD, often exhibiting wide phenotypic variability with limited genotype–phenotype correlation. Early incorporation of genetic testing is therefore pivotal, particularly when gonadal dysgenesis is suspected. We present a 19-year-old individual, raised as female, who presented with primary amenorrhoea and underdeveloped secondary sexual characteristics. Endocrine testing showed hypergonadotropic hypogonadism, and karyotyping identified a genotype of 46, XY. Genetic testing revealed a contiguous deletion involving the NR5A1 gene, consistent with severe gonadal dysgenesis. Pelvic magnetic resonance imaging showed the presence of an infantile uterus, but, on diagnostic laparoscopy, complete Müllerian agenesis was discovered. Bilateral gonadectomy showed dysgenetic testes without signs of malignancy. This case highlights the diagnostic complexity of NR5A1-related DSD, the potential discordance between imaging and operative findings, and the importance of a multidisciplinary approach to ensure accurate diagnosis and appropriate management.

**Keywords:** Gonadal dysgenesis, NR5A1 mutation, Primary amenorrhoea, 46, XY disorder of sex development

## INTRODUCTION

Disorders of sexual development (DSD) comprise a heterogeneous group of congenital conditions characterized by atypical development of chromosomal, gonadal, or anatomical sex. The reported incidence of DSD is approximately 1 in 4,500-5,000 live births, with significant variability in clinical presentation and underlying aetiology.[1] In individuals with a 46, XY karyotype, testicular differentiation or functioning abnormalities are a significant cause of DSD and can present as devirilization, external genitalia abnormalities, or primary amenorrhea in individuals raised as females. Early and proper diagnosis is important to guide hormonal control, sex assignment, surgical planning, and long-term psychosocial care.[2] The NR5A1 gene is found on chromosome 9q33.3, and it encodes steroidogenic factor-1 (SF-1), a nuclear receptor that is a key regulator of genes that control gonadal and adrenal development, steroidogenesis, and reproductive axis activity. The NR5A1-pathogenic variants have become a significant cause of 46, XY DSD, with a wide range of phenotypes, from complete gonadal dysgenesis to partial phenotypes that include androgen insensitivity phenotypes, hypospadias, and infertility.[3,4] Clinical expressions of NR5A1-related DSD are highly heterogeneous, even within those patients with similar variants, and a strong genotype–phenotype correlation has not been established yet, making it difficult to predict the diagnosis and genetic counselling.[5] Although heterozygous point mutations and small deletions or insertions in NR5A1 are well reported, deletion of neighboring genomic regions, including

NR5A1, is extremely infrequent. These deletions can lead to increasingly complicated and unusual clinical phenotypes because of the dose effects of multiple genes, and this fact provides the rationale for the significance of sophisticated genomic testing modalities.[6,7] The recent cohort studies and systematic reviews indicate that a multidimensional diagnostic strategy that combines clinical examination, endocrine testing, imaging, and molecular genetic testing is required.[8,9] The use of genomic analysis, such as copy-number variation analysis, at an early stage is becoming a commonly prescribed intervention in patients with suspected gonadal dysgenesis in order to support proper diagnosis, better management planning, and better long-term outcomes. Herein, we report a rare case of 46, XY gonadal dysgenesis resulting from a heterozygous contiguous gene deletion at chromosome 9q33.1-q34.1 encompassing NR5A1 and adjacent genes, identified using whole-exome sequencing with copy-number variation analysis. This case highlights the diagnostic value of comprehensive genomic evaluation in DSD and contributes to the limited literature on NR5A1-associated contiguous gene deletions.

## CASE REPORT

A 19-year-old individual, raised as female, born to non-consanguineous parents, presented to our hospital with primary amenorrhoea and cyclical abdominal pain. The patient was born at term by caesarean section, following an uncomplicated pregnancy. She looked like a normal baby girl and did not have any physical abnormality at birth. Her external genitalia appeared normal. She was raised as a girl with no history of any behavioural concerns in childhood. She had good scholastic performance. She was the second child in a family of two and her elder brother did not report to have any genetic or somatic abnormality. There was no family history of amenorrhoea, infertility or any abnormal development of external genitalia.

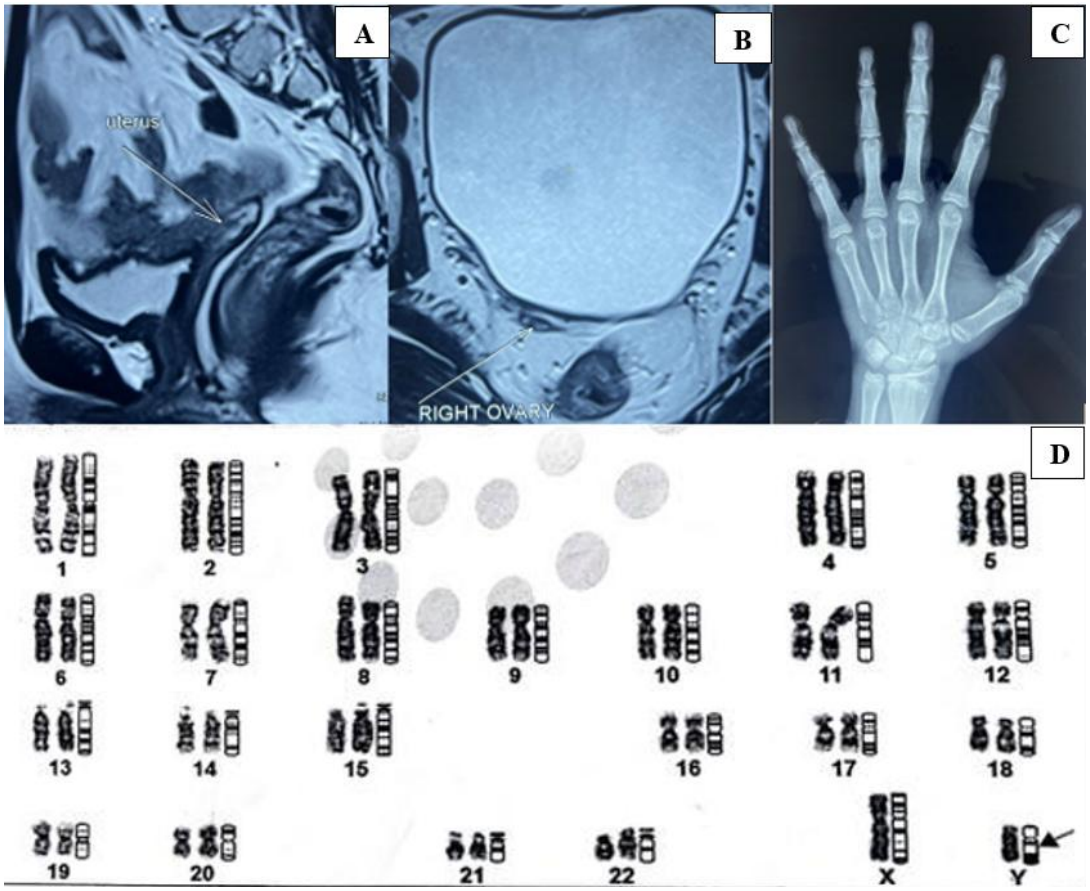


**Figure 1: Radiological and cytogenetic evaluation showing (A) pelvic MRI sagittal section demonstrating an infantile uterus, (B) pelvic MRI axial section showing the right ovary, (C) hand radiograph with normal skeletal anatomy and (d) karyotype analysis revealing a 46, XY chromosomal pattern.**

At presentation, at 19 years of age, clinical examination revealed vitals within normal limits with a weight of 60 kg, height of 164 cm and BMI 22.3. Her blood pressure was normal at 100/60 mmHg. Clinical examination revealed Tanner stage I breasts, Tanner stage II pubic hair. Hair distribution was normal with no facial, chest or abdominal hair with sparse axillary hair. Genital examination revealed mild clitoromegaly, normal urethral and vaginal orifices, a blind ending vagina of length 4 cm, normal labia majora and underdeveloped labia minora. There were no palpable masses in the abdomen. Laboratory workup showed creatinine 54 µ

mol/L (46-96), Na 142 m mol/L (135-145), K 4.2 mmol/L (3.5-5.0), follicle-stimulating hormone (FSH) 66.7 IU/L (1.5-12.4), luteinizing hormone (LH) 19.6 IU/L (1.7-8.6), testosterone 3.55 nmol/L (0.2-2.9), estradiol 5 pmol/L (28-156), progesterone 0.04 nmol/L (follicular phase levels, 0.6-4.7), AMH 0.12 ng/ml (2-6.8 ng/ml) and prolactin 7.5 ng/ml (<25 ng/ml). Pelvis ultrasound examination showed no visualisation of uterus except for a linear line of 5 mm thickness suggestive of rudimentary tissue. Both ovaries were not visualised. Left ectopic kidney was present. Pelvic magnetic resonance imaging showed an infantile uterus measuring about 2.4×0.7×0.2 cm in craniocaudal and transverse diameter with small, thin endometrial stripe. Right ovary identified with tiny follicles 9x4 mm in size. Left ovary was not visualised. Cervix-corpus ratio 1:1. Vagina traced from introitus to cervix. CT imaging of abdomen and pelvis showed an infantile uterus with no evidence of ovary. Testes-like structure was visualised in abdomen and pelvis.

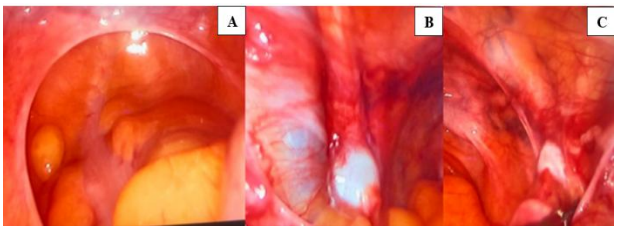


**Figure 2: Intra-operative laparoscopic images showing (A) overview of the pelvic cavity, (B) gonadal tissue identified along the pelvic sidewall- right side and (c) gonadal tissue identified along the pelvic sidewall, left side.**

Comprehensive genetic evaluation was done. Peripheral blood karyotyping revealed 46, XY disorder of sexual development. Whole-exome sequencing (WES) with copy-number variation (CNV) analysis was performed on genomic DNA extracted from peripheral blood. The analysis identified a heterozygous contiguous gene deletion involving chromosome 9q33.1-q34.1, encompassing the NR5A1 gene along with adjacent genes. The CNV was classified as likely pathogenic and was consistent with the patient's clinical phenotype. The copy number for the affected region was reduced to one, confirming a deletion. No additional pathogenic single-nucleotide variants relevant to the phenotype were detected. Psychosocial evaluation repeatedly confirmed that she has a female gender identity. After counselling regarding malignancy risk and after getting consent, diagnostic laparoscopy was done. Intraoperatively there was complete absence of uterus, tubes, with no identifiable Müllerian remnants. Bilateral streak testis like gonads were present along the lateral pelvic walls which was further removed.

***Postoperative outcome and follow-up***

The patient had an uneventful postoperative recovery following laparoscopic bilateral gonadectomy. Histopathological examination revealed seminiferous tubules lined by sertoli cells without identifiable spermatogonia, along with epididymal tissue, consistent with dysgenetic testes and without evidence of malignancy. Complete excision of dysgenetic gonadal tissue effectively eliminated the risk of gonadal germ cell malignancy, and no further tumour-specific surveillance was required, in accordance with established recommendations for individuals with 46, XY gonadal dysgenesis.

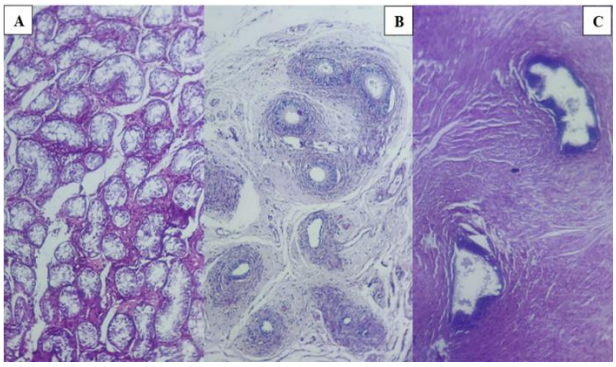


**Figure 3: Histopathological examination of excised gonadal structures showing (A) dysgenetic testicular tissue with seminiferous tubules, (B) epididymal tissue with multiple ductal profiles and (C) VAS deferens characterised by a thick muscular wall and narrow lumen (hematoxylin and eosin stain×10).**

In view of definitive gonadal failure, long-term management focused on endocrine replacement and prevention of complications related to prolonged hypogonadism. Oestrogen replacement therapy was initiated using oral oestradiol valerate, with gradual dose escalation to achieve physiological pubertal induction. Follow-up assessments demonstrated progressive development of secondary sexual characteristics and improvement in overall wellbeing. Serial monitoring of serum oestradiol, follicle-stimulating hormone, and luteinising hormone levels was planned to ensure adequate hormonal replacement and long-term endocrine stability. Given the prolonged duration of untreated hypogonadism prior to diagnosis, surveillance of skeletal health was prioritised. The evaluation of baseline bone mineral density was scheduled with the utilisation of dual-energy X-ray absorptiometry and the repetition of the measurements at the specified intervals, depending on the initial results and compliance with hormone treatment. In accordance with the international recommendations, adequate dietary calcium and vitamin D intake, as well as regular weight-bearing exercise, were recommended to lower the risk of future fractures.

Metabolic surveillance became a part of regular follow-up, with regular measurement of body mass index, blood pressure, lipid profile, and glucose metabolism, as per the guidelines of subjects under long-term sex steroid replacement therapy. Even though adrenal insufficiency is

not prevalent in patients with isolated NR5A1 variants, an initial assessment of adrenal function was conducted and reported normal. Clinical observation was recommended to continue, and repeat assessment was to be considered when symptoms of adrenal malfunction appeared. Psychological follow-up remains an integral component of care. Recurrent psychosocial evaluation revealed a consistent female gender identity. Continued counselling was offered to assist in the adaptation to the diagnosis, hormone dependence throughout life, and fertility issues. Fertility counselling was done in a sensitive way, and reproductive options available were discussed depending on the preference of the patient. The patient remains under follow-up by a multidisciplinary team comprising endocrinology, gynaecology, genetics, and mental health services, with plans for lifelong surveillance tailored to evolving clinical needs.

### *Differential diagnosis*

A systematic assessment of DSD should be undertaken in a phenotypic female with primary amenorrhoea and variable secondary sexual characteristics, especially after the detection of a 46, XY karyotype. Several conditions were considered in this case. Complete gonadal dysgenesis (46, XY DSD) was a primary diagnostic consideration. Individuals typically have female external genitalia, non-functional or streak gonads, hypergonadotropic hypogonadism, and absent pubertal development. While Müllerian structures are generally present due to insufficient anti-Müllerian hormone secretion, variability in internal reproductive anatomy has been reported in genetically heterogeneous forms of gonadal dysgenesis. The endocrine profile and dysgenetic testes identified on histopathological examination were consistent with this diagnosis. Complete androgen insensitivity syndrome was also considered. This condition is characterised by a female phenotype with absent Müllerian structures due to normal sertoli cell function and anti-Müllerian hormone production. However, affected individuals usually develop normal breast tissue at puberty as a result of peripheral aromatisation of androgens. The absence of secondary sexual development and the presence of elevated gonadotropin levels in this patient made androgen insensitivity unlikely. Defects in androgen biosynthesis, including 17β-hydroxysteroid dehydrogenase deficiency and 5α reductase deficiency, were less likely. These conditions commonly present with ambiguous genitalia and may demonstrate virilisation at puberty, features that were not observed in this case. Additionally, preserved testicular tissue and more normal androgen production are typically seen, in contrast to the dysgenetic gonads identified here. Müllerian agenesis was initially suggested by pelvic imaging; however, this diagnosis is associated with a 46, XX karyotype, normal ovarian function, and normal secondary sexual characteristics. The absence of pubertal development, hypergonadotropic hypogonadism, and confirmation of a 46, XY karyotype effectively excluded this condition. The combination of clinical findings, hormonal profile, operative findings, and genetic analysis identifying a pathogenic NR5A1 variant supported the final diagnosis of NR5A1-related 46, XY disorder of sexual development with severe gonadal dysgenesis. This case underscores multidisciplinary assessment and early genetic testing in the distinction of the clinically overlapping DSD conditions.

## DISCUSSION

Disorders of sexual development with a 46, XY karyotype represent a challenging group of disorders to diagnose because of the overlapping of clinical, hormonal, and anatomical features. The case demonstrates the intricacy of late-presenting 46, XY DSD and the need to consider the inclusion of genetic analysis at the initial stages of the diagnostic process in the case where gonadal dysgenesis is suspected. Recent developments in genomic diagnostics, especially WES followed by CNV analysis, have greatly enhanced the diagnostic output in patients with unexplained DSD by facilitating both sequence and structural genomic changes.[7-9]

The NR5A1 gene encodes steroidogenic factor-1 (SF-1), a transcription factor required in testicular differentiation, sertoli and leydig cell activity, and steroidogenic enzyme regulation in gonadal and adrenal development.[5-10] NR5A1 pathogenic variants impair early gonadal growth, which causes a broad spectrum of phenotypes with either total gonadal dysgenesis to more mild undervirilisation and hypospadias in 46, XY individuals.[3,4,6] The high phenotypic diversity within even those who possess the same variants indicates the complexity of the sex determination pathways and the effect of modifying genetic and environmental factors, which makes the correlation of genotype–phenotype difficult. In the present case, genetic analysis using WES with CNV assessment identified a heterozygous contiguous gene deletion at chromosome 9q33.1-q341 encompassing NR5A1. Structural variants involving NR5A1 are rare but increasingly recognized as a cause of severe 46, XY DSD phenotypes. These deletions cause NR5A1 haploinsufficiency and loss of SF-1 function, which causes early testicular failure. This is in line with the histopathological observation of seminiferous tubules that are lined only by sertoli cells without the germ cells, indicating testicular differentiation during embryogenesis. Early developmental dysfunction of sertoli cells accounts for the lack of müllerian structures seen at laparoscopy despite preoperative imaging of an infantile uterus. Inconsistency between radiological appearance and operative anatomy has been observed in DSD, demonstrating the limitations of relying on imaging alone to establish internal reproductive structures.[7,8] The diagnostic pathway in the patient emphasizes various significant clinical principles. Initial evaluation of primary amenorrhea with absent secondary sexual characteristics appropriately included hormonal profiling, which demonstrated hypergonadotropic hypogonadism, indicative of primary gonadal failure. Identification of a 46, XY karyotype redirected evaluation toward DSD

rather than isolated gynecological causes. Current international guidelines recommend early incorporation of molecular genetic testing, including next-generation sequencing and CNV analysis, in individuals with suspected gonadal dysgenesis to improve diagnostic accuracy and guide counselling and long-term management.[7-9] Gonadal malignancy risk remains a significant concern in individuals with dysgenetic gonads. Although the precise tumour risk in NR5A1-related DSD remains uncertain, cases of germ cell neoplasia in situ have been reported.[9-11] Current consensus supports prophylactic gonadectomy in individuals with non-functional intra-abdominal gonads, particularly when raised female, following appropriate counselling.[9-11] The absence of malignancy in this patient is consistent with findings from recent case series involving NR5A1-associated gonadal dysgenesis.

Several comparable cases of 46, XY disorders of sex development due to NR5A1 variants have been described in recent literature. Published case reports and cohort studies have documented adolescents and young adults presenting with primary amenorrhea, hypergonadotropic hypogonadism, and dysgenetic testes, often in the absence of adrenal insufficiency, closely paralleling the clinical features observed in the present case.[7-12] Studies evaluating NR5A1 gene deletions and pathogenic variants have also demonstrated marked phenotypic heterogeneity, including variable development or absence of müllerian structures, underscoring the diagnostic uncertainty associated with this condition.[6] These reports, together with the present case, highlight that delayed presentation is not uncommon in NR5A1-related DSD and that reliance on imaging alone may be misleading, reinforcing the importance of comprehensive genetic and surgical evaluation.[6,7] Long-term outcomes following gonadectomy depend on appropriate hormone replacement therapy and multidisciplinary follow-up. Recent recommendations focus on lifelong sex steroid replacement, surveillance of bone and metabolic health, and systematic psychological interventions in relation to gender identity, fertility, and quality of life. Isolated NR5A1 mutations are rare, and adrenal insufficiency must be considered in case of suggestive symptoms. Altogether, this case contributes to the increasing body of evidence of the clinical heterogeneity related to NR5A1-associated 46, XY DSD and the significance of detailed genomic testing, including CNV analysis. There is a need to perform early genetic testing in conjunction with multidisciplinary assessment to facilitate proper diagnosis, counselling, and long-term management.

## CONCLUSION

DSD may present during late adolescence and be associated with primary amenorrhoea and the absence of secondary sexual characteristics, which requires close consideration outside the usual gynaecological causes. NR5A1 mutations are a significant and heterogeneous etiologic factor of 46, XY DSD, which should be considered in the suspicion of gonadal dysgenesis even in cases where there is no apparent genotype-phenotype correlation. Imaging can be inaccurate in patients with DSD, and when radiological and clinical evidence is discordant, surgical exploration can offer definitive anatomy. The timely introduction of genetic testing, especially next-generation sequencing and copy-number variation analysis, into a multidisciplinary approach is critical to proper diagnosis, proper counselling, and maximisation of long-term management and outcomes in patients with DSD.

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