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Case Study

# 46,XY,t(1;2;12;6;16)(q42;q23;q22;q13;q13) REPORT OF A CASE WITH SEX DIFFERENTIATION DISORDER (DSD) WITH COMPLEX CHROMOSOMAL REARRANGEMENT

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***Abstract:*** *In this study, we present a case of a 7-month-and-26-day-old patient with a novel karyotype associated with a 46,XY disorder of sexual development. This complex chromosomal rearrangements, described as 46,XY,t(1;2;12;6;16)(q42;q23;q22;q13;q13), was confirmed by FISH analysis and has not been previously reported in the literature. The patient exhibited ambiguous genitalia and faced urinary obstruction. No pathogenic variants were detected in genes associated with disorders of sex development in the Next-Generation Sequencing (panel, suggesting that structural rearrangements may disrupt genes critical for sexual and neurological development. Laparoscopic-assisted urogenital mobilisation successfully improved urinary function and genital appearance. This case demonstrates that the pathogenesis of disorders of sex development may involve structural chromosomal abnormalities in addition to gene-level mutations and highlights the importance of genomic rearrangements in disorders of sexual development. The findings emphasise the need for a multidisciplinary approach to the diagnosis and management of complex cases of disorders of sex development. Chromosomal abnormalities should be considered even in the presence of normal sex development genes. This rare karyotype provides new insights into the genetic basis of disorders of sex development, as similar cases have not been documented. We believe that reporting such unique cases will contribute to the understanding of the molecular mechanisms of disorders of sex development and the development of clinical strategies. In summary, we emphasize that structural chromosomal alterations can contribute to disorders of sex development independently of gene mutations and the value of genetic, clinical, and surgical collaboration in patient evaluation. This case expands knowledge of the etiology of disorders of sex development and supports further research on structural genomic alterations.*

***Key words:*** *DSD, ambiguous genitalia, complex chromosomal rearrangement.*

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## 1. Introduction

Ambiguous genitalia, a key feature of disorders of sex development (DSD), occurs in approximately 1 in 4,500 births and arises from disruptions in chromosomal, gonadal, or hormonal pathways governing sexual differentiation [1]. These disorders result from genetic mutations (e.g., in SRY and NR5A1), enzyme deficiencies (e.g., 21-hydroxylase), or complex chromosomal rearrangements that disrupt testicular or ovarian development [2]. During critical embryological stages (weeks 6-20 of gestation), abnormal androgen production, receptor dysfunction, or anti-Müllerian

hormone defects can lead to discordance between genetic sex and phenotypic genital development [3]. The resulting spectrum includes undervirilized males, masculinized females, or truly ambiguous anatomy, often requiring multidisciplinary diagnostic approaches.

Complex chromosomal rearrangements (CCRs), though rare, can disrupt multiple phases of sexual development by altering dosage-sensitive genes or regulatory elements. These structural anomalies may affect gonadal formation (weeks 6-8), steroidogenesis (weeks 8-12), or late genital maturation (weeks 12+), frequently presenting with ambiguous genitalia alongside other congenital anomalies [4]. Phenotypic variability depends on the affected genomic regions—for instance, rearrangements near SOX9 may cause 46,XY DSD, while DAX1 duplications can lead to 46,XY gonadal dysgenesis [5]. Given this complexity, advanced cytogenetics (karyotyping, FISH, microarray) and hormone profiling are essential for accurate classification and management.

## 2. Materials and Methods

Karyotype analysis was requested from a 7-month and 26-day-old patient admitted to Dicle University Faculty of Medicine Paediatric Endocrinology Clinic in March 2024 due to ambiguous genitalia. The study was approved by the Medical Ethics Committee. Dicle University Faculty of Medicine Ethics Committee (Ethics approval code:125).

### 2.1. Pedigree Analysis

The pedigree analysis revealed no consanguineous relationship between the progenitor's presentation, the infant's growth parameters (69 cm length, 7.65 kg weight) were appropriate for chronological age, with both measurements plotting within normal percentile ranges. On physical examination, a bilateral labial mass could not be palpated. In the pelvic ultrasonography examination, the left testicle was observed in the middle part of the inguinal canal, and its dimensions were measured as 10x6.5x14 mm. The right testicle could not be visualised along the inguinal canal. Cerebral ultrasonography showed that the ventricular system of the brain was symmetrical and aligned. Ventricular width was found to be within normal limits. The corpus callosum was visualised in sagittal sections, and its structural integrity was preserved. Echocardiography showed normal anatomical structures of the heart. The dimensions of the cardiac cavities, wall thickness of the ventricles and atria, valvular structures, and positions of the great vessels were within normal limits. Cardiac functions (ejection fraction, cardiac output) were measured normally.

According to the hearing test results, the baby's bilateral hearing was found to be within normal limits. Audiological evaluation showed that both ears responded to normal auditory stimuli. Hearing loss or pathological findings in auditory pathways were not detected.

### 2.2. Biochemical analyses

Biochemical analyses revealed normal thyroid function (TSH: 2.186 mIU/L, reference: 0.79-5.85; FT4: 1.06 ng/dL, reference: 0.64-1.71) and adequate cortisol levels (12.9 µg/dL, reference: 6.7-22.6). Gonadotropin levels were at the lower reference limit (FSH: 1.82 IU/L, reference: 1.27-19.26; LH: 0.75 IU/L, reference: 1.24-8.62), with markedly suppressed androgen production evidenced by undetectable testosterone (<0.01 ng/dL, reference: 1.75-7.81) and subnormal DHEA levels (<15 µg/L, reference: 80-160). Additional markers showed serum AFP (75 ng/mL) within the expected range for gestational age and undetectable hCG (0.38 mIU/mL, reference: <5).

### 2.3. Cytogenetic analysis

Cytogenetic analysis was performed using the standard lymphocyte culture technique, and a complex chromosomal rearrangement was detected: The specific chromosomal configuration is defined as 46,XY,t(1;2;12;6;16)(q42;q23;q22;q13;q13). A total of 50 metaphase cells were examined, and the results were confirmed. This novel karyotype demonstrates a unique pattern of balanced translocations involving five distinct chromosomal regions (Figure 1), representing an exceptionally rare cytogenetic finding in disorders of sex development.

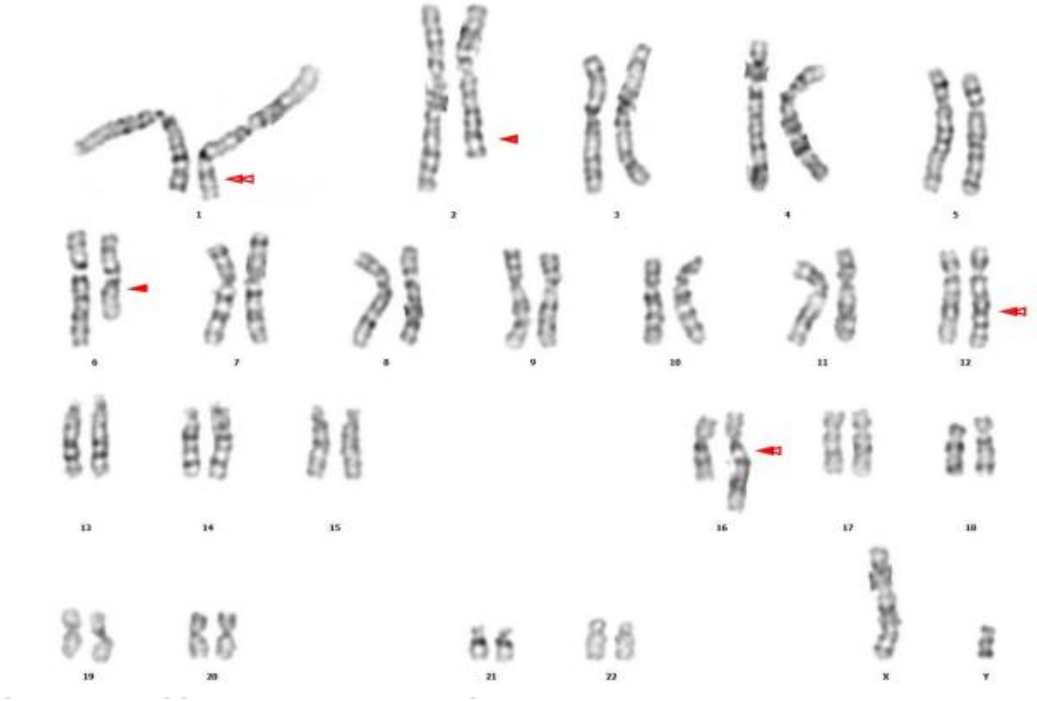

**Figure 1.** The karyotype of the patient was 46, XY, t(1;2;12;6;16)(q42;q23;q22;q13;q13). In detail, the chromosome 1 segment distal to 1q42 was assigned to the 2q23 region on chromosome 2; the chromosome 2 segment distal to 2q23 was assigned to the 12q22 region on chromosome 12; the chromosome 12 segment distal to 12q22 was assigned to the 6q13 region on chromosome 6; The chromosome 6 segment distal to 6q13 translocated to the 16q13 region on chromosome 16; and the chromosome 16 segment distal to 16q13 translocated to the 1q42 region on chromosome 1.

To confirm these complex chromosomal rearrangements, fluorescence in situ hybridisation (FISH) analysis was performed on metaphase plates obtained from cells cultured from the patient's peripheral blood sample using the CytoCell® TeloMark kit. A total of 50 different probes, including 41 subtelomeric-specific probes, three centromeric probes, and six locus-specific probes, were used in this analysis, and the presence of translocations was confirmed (Figure 2).

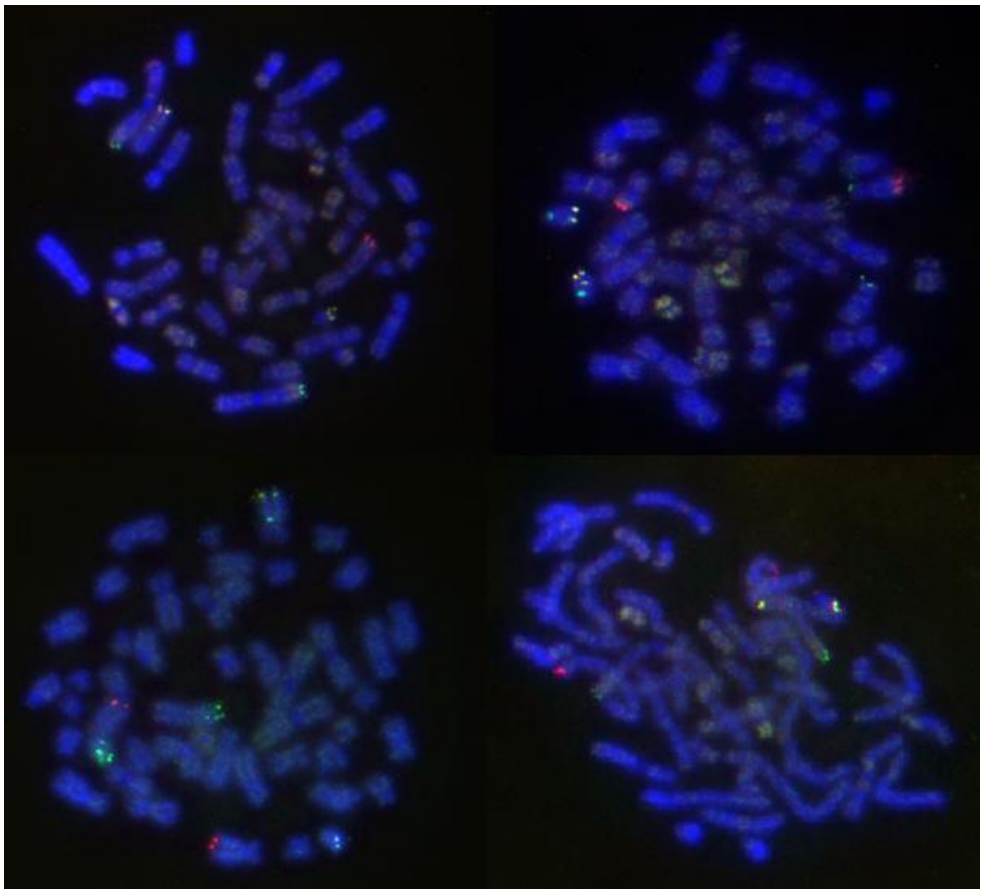

**Figure 2.** Patient's 46,XY,t(1;2;12;6;16)(q42;q23;q22;q13;q13) karyotype confirmed by FISH.

### 2.4. Genomic DNA Extraction and Quantification

Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Blood Kit (QIAGEN, Hilden, Germany) on an automated QIAcube HT platform, according to the manufacturer's protocol. DNA concentration and purity were assessed fluorometrically using the Qubit™ 4.0 system with the dsDNA High Sensitivity Assay Kit (Invitrogen, Waltham, MA, USA), ensuring optimal quality for downstream sequencing applications.

### 2.5. Next-Generation Sequencing and Variant Analysis

A targeted next-generation sequencing panel encompassing all known DSD-associated genes was performed, with comprehensive coverage of exonic regions and flanking ±10 bp intronic sequences. Sequencing was aligned to the GRCh37/hg19 reference genome, achieving a mean read depth of 20× and 99.65% coverage of the target regions. The list of 65 DSD genes was compiled from online databases such as OMIM (http://www.omim.org) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed), as well as a comprehensive review of the current literature. The genes included in the panel are as follows: *ANOS1, AMH, AMHR2, AR, ARX, ATP6V0A4, ATRX, BCOR, CDKN1C, CHD7, CTU2, CUL4B, CYB5A, CYP11A1, CYP11B1, CYP17A1, CYP19A1, DHCR7, DHH, FEZF1, FGF8, FRAS1, FSHB, GATA4, GLI2, HOXA13, HSD17B3, HSD3B2, INPP5E, LHCGR, MAMLD1, MAP3K1, MYRF, NR0B1, NR2F2, NR3C1, NR5A1, NSMF, PAX6, PAX8, PBX1, POR, RPL10, RSPO1, SAMD9, SEMA3E, SGPL1, SOX10, SOX9, SRY, STAR, TCF12, TOE1, TWIST2, WT1, TTC21B, TTC8, UBR1, WDPCP, WDR11, WDR35, ZMYND10, AAAS, POMC, MCM4.*

### 2.6. Genetic Analysis Findings

Comprehensive genomic evaluation revealed no pathogenic or likely pathogenic variants in known DSD-associated genes that could explain the patient's phenotype. To investigate the origin of the observed complex translocation, we performed conventional karyotyping of first-degree relatives. Parental analysis demonstrated normal chromosomal constitutions in both progenitors (mother: 46,XX; father: 46,XY), while the sibling (46,XY) similarly showed no evidence of the translocation (Figures 3-5). This familial cytogenetic pattern confirms the de novo occurrence of the complex chromosomal rearrangement in the proband.

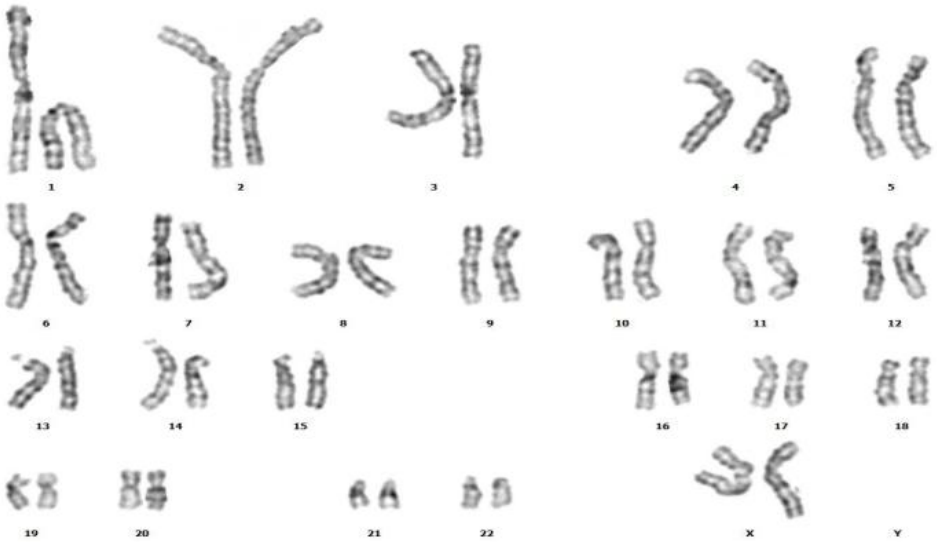

**Figure 3.** Karyotype analysis of the patient's mother was performed using the standard GTG banding (Giemsa-Trypsin-Giemsa) method. As a result of the analysis, a normal female karyotype with a chromosomal structure of 46,XX was detected.

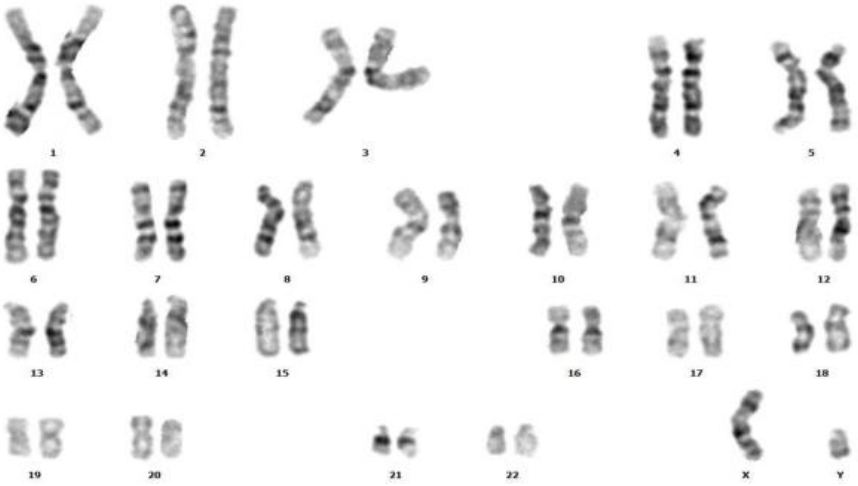

**Figure 4.** Karyotype analysis of the patient's father was performed using the standard GTG banding (Giemsa-Trypsin-Giemsa) method. As a result of the analysis, a normal male karyotype with 46,XY chromosomal structure was detected.

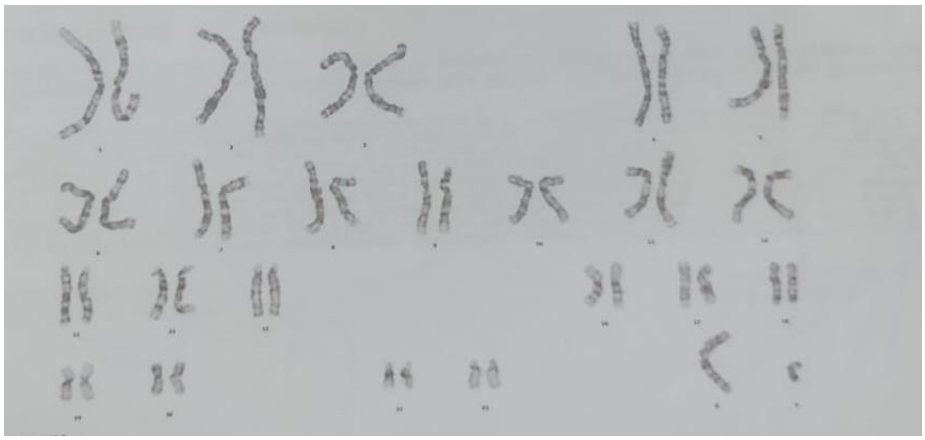

**Figure 5.** Karyotype analysis of the patient's brother was performed using the standard GTG banding (Giemsa-Trypsin-Giemsa) method. The analysis revealed a normal male karyotype with a 46,XY chromosomal structure.

The patient underwent laparoscopic-assisted total urogenital mobilisation to correct ambiguous genitalia and improve urinary function. After this procedure, both urinary functions and cosmetic results were significantly improved (Figure 6).

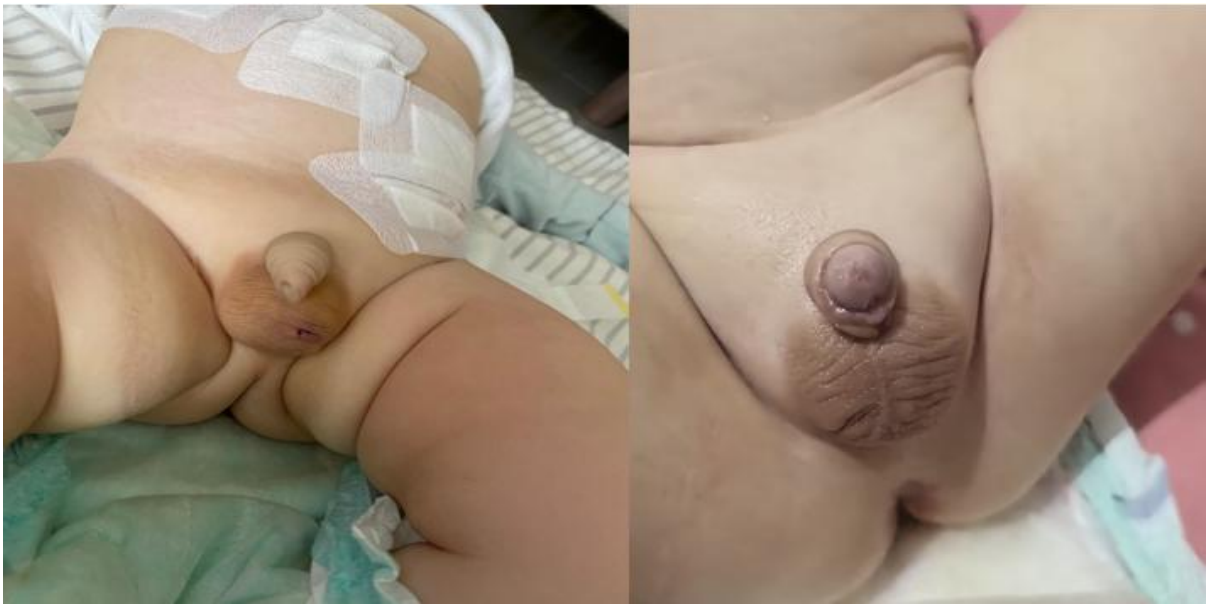

**Figure 6.** The patient underwent laparoscopic-assisted total urogenital mobilisation surgery at 8 months of age. This surgery involves repositioning and mobilisation of the urogenital system (urinary and reproductive organs). The images taken 1 year after the surgery showed that the healing process of the genital organs was successfully completed, and the normal anatomical structure was restored. This indicates that the surgical intervention was successful and the patient's recovery process is progressing favourably.

## 3. Results and Discussion

Our 7 months and 26 days old patient with chromosome 46,XY presented with complaints of ambiguous genitals and difficulty urinating. Investigation and management of a child with 46,XY genetic male sex and ambiguous genitalia is quite difficult. History and clinical examination stand out as the most basic and effective methods of diagnosing DSD cases [**6**]**.** The patient's history, physical

findings, and clinical symptoms should be carefully assessed. However, additional diagnostic methods may be required to make a definitive diagnosis. At this point, karyotype analysis is of great importance as it clearly shows the chromosomal structure and identifies abnormalities in the sex chromosomes (e.g., 46,XX; 46,XY or mosaic structures) [**6**]**.** Although translocations are rare in DSBs, the dosage of affected genes in the translocated chromosome influences the phenotype of the translocation. Karyotype analysis showed that the karyotype of our patient with DSB was 46,XY,t(1;2;12;6;16)(q42;q23;q22;q22;q13;q13). The diagnosis was confirmed by FISH. Such CCRs are structural chromosomal abnormalities that are extremely rare in the population and are usually characterised by the involvement of two or more chromosomes containing at least two breakpoints; in their simplest form, such rearrangements involve three breakpoints, while more complex cases may involve eight or more breakpoints. This wide variation results in CCRs showing a great genetic and clinical diversity [**7**]**.** The substantial prevalence of CCRs (approximately 23%) among individuals with multiple congenital anomalies and/or intellectual disability underscores their diagnostic relevance in clinical genetics. Notably, the observation that >50% of de novo CCRs are associated with abnormal phenotypes strongly implicates unbalanced chromosomal rearrangements as a frequent contributor to developmental pathology [**7-10**]**.** In our case, de novo CCRs were reflected in the phenotype as an undetermined sex anomaly.

The patient with a 46,XY karyotype shows a complex multiple translocation in the form of t(1;2;12;6;16)(q42;q23;q22;q13;q13). When the clinical significance of these translocations is compared with the data in the literature, it is seen that they are particularly associated with neurological, psychiatric, and developmental disorders. Cytogenetic disruptions at 1q42 represent a recognized genetic risk architecture for neuropsychiatric disorders, with balanced translocations in this locus demonstrating phenotypic penetrance across cognitive and behavioral domains [**11-15**]**.** Clinical findings of Robinow syndrome were found in two patients with a 1q42 deletion. These findings include phenotypic features, including short stature, hypertelorism, short limbs, and hypoplastic genital organs [1**6**]**.** The 2q23.1 microdeletion syndrome has been documented in 18 reported cases, with a consistent phenotypic spectrum encompassing intellectual disability, severe speech impairment, epilepsy, and behavioral abnormalities. Additional clinical hallmarks include microcephaly, subtle craniofacial dysmorphism, brachydactyly, postnatal growth restriction, and a wide-based ataxic gait, suggesting a distinct neurodevelopmental disorder associated with this genomic region [**17**]**.** Balanced translocations of chromosome 6 have been reported to be associated with reproductive failure [**18**]**.** This indicates that the translocation may lead to problems in meiotic segregation as a consequence of the rearrangement of genetic material. Chromosome 16q translocations have been linked to various physical and developmental disorders, including postnatal growth retardation, marked psychomotor retardation, dysmorphic facial features, flexion contractions of joints, foot deformities, congenital heart defects, ambiguous genitalia, hypospadias, small penis, bifid scrotum, undescended testes, intestinal malformations, and anorectal abnormalities [**19-20**]**.** Such findings suggest that the translocations observed in our patient may have clinical significance in terms of neurological, psychiatric, and developmental disorders. Additional clinical correlation studies and functional genomic analyses are needed to determine the exact phenotypic consequences of these complex translocations.

Sexual development in 46,XY individuals is controlled by a critical network of regulatory genes that orchestrate gonadal differentiation and genital morphogenesis. Disruption of these genes, through deletions, pathogenic variants, or dysregulation, can result in a wide range of phenotypes, from isolated hypospadias to complete sex reversal. Because of this genetic complexity, we used next-generation sequencing (NGS) to analyze a comprehensive panel of DSD genes, including the central SRY locus, to elucidate potential molecular etiologies in this case. The analysis revealed no pathogenic or significant mutations in the genes included in the panel. This finding suggests that the genetic causes of the patient's abnormalities of sex development should be further investigated.

## 4. Conclusion

Taken together, these findings suggest that 46,XY DSD is a phenotypically and genetically heterogeneous disorder that requires systematic genomic characterization combined with long- term multidisciplinary follow-up to improve prognostic accuracy and personalized interventions. While radiologic imaging, hormonal analysis and genetic testing are indispensable tools in the diagnosis of DSD, providing critical information about the underlying pathology, the phenotypic variability associated with chromosomal rearrangements further emphasizes the importance of comprehensive clinical and genetic evaluation. By integrating these diagnostic modalities, clinicians can optimize patient care and provide informed guidance to families, ultimately improving outcomes for individuals with this complex disorder.

**Ethical statement:**

The study was approved by the Medical Ethics Committee. Dicle University Faculty of Medicine Ethics Committee. (Ethics approval code: 125 / Date: 06.02.2020)

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No acknowledgements were declared.

**Conflict of interest:**

The authors declare no conflicts of interest.

**Authors' Contributions:**

All authors collaboratively reviewed and analyzed the clinical findings and karyotype results of the case.

**Generative AI statement**

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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