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Rare Mosaic Chromosomal Alterations with Unique Clinical Manifestations Among Swyer Syndrome Females

Swarnalatha Daram[1*]; Prashanth M.[2]; Keerthana Maram[3]; Pulipati Rojeesha[4]; Venkata Subramanian K.[5]; V. Anjali[6]; Annvia A.[7]; Vidyadhari M.[8]

[1,2,3,4,5,6,7,8]Department of Genetics and Molecular Medicine, Manipal TRUtest, Hyderabad, India.

Corresponding Author: Swarnalatha Daram[*]

ORCID ID: [1]0000-0002-58736892

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Abstract:

- ***Background***

Swyer syndrome is typically characterized by a 46,XY karyotype in females with complete gonadal dysgenesis. Mosaic chromosomal constitutions are associated with marked phenotypic variability, posing challenges in diagnosis and clinical management. Variable gonadal differentiation and the presence of Y chromosome significantly increase the risk of gonadal germ cell tumors, highlighting the importance of early cytogenetic diagnosis, molecular characterization.

- ***Methods***

A total of 4110 female samples were considered for the study during 2021 to 2026 and diagnosed Karyotyping at Department of Genetics and Molecular Medicine in Manipal TRUtest Diagnostics. Comprehensive clinical evaluation, including hormonal profiling and Ultrasonographic studies, was considered to assess gonadal morphology and uterine development. Conventional cytogenetic and FISH analysis was subsequently carried out to identify underlying chromosomal abnormalities and establish the genetic diagnosis.

- ***Results***

Out of 4110 females collected, 21 were diagnosed with Swyer syndrome. Three cases showed rare chromosomal variants, illustrating the cytogenetic and phenotypic heterogeneity of the disorder. These included mosaic karyotypes of 45,XO/46,X,idic(Y), 46,XY/47,XYY, and 45,XO/46,XY. The diverse clinical presentations highlight the diagnostic complexity of Swyer syndrome and underscore the importance of comprehensive cytogenetic evaluation for accurate diagnosis and risk assessment.

- ***Conclusion***

Comprehensive cytogenetic and molecular evaluation is essential for the accurate diagnosis of Swyer syndrome, particularly in patients with mosaic karyotypes. Early detection of Y chromosome is crucial for timely prophylactic gonadectomy due to the increased risk of gonadal malignancy. Further studies are needed to improve genotype–phenotype correlations and optimize diagnostic and therapeutic strategies.

Keywords: *Swyer Syndrome, Gonadal Dysgenesis, Mosaicism, Primary Amenorrhea, Cytogenetics.*

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I. INTRODUCTION

Swyer syndrome, also known as 46,XY gonadal dysgenesis, is a rare disorder of sex development (DSD) characterized by a female phenotype with a 46,XY karyotype. The condition results from complete failure of testicular differentiation during embryogenesis, leading to non-functional streak gonads despite the presence of a Y chromosome [1]. Affected individuals typically present with primary amenorrhea, delayed or absent secondary sexual characteristics, and normal female external genitalia. The dysgenetic gonads confer a substantially increased risk of germ cell malignancies, particularly gonadoblastoma and dysgerminoma, necessitating early diagnosis and clinical intervention [2].

Normal male sex determination is initiated by the sex-determining region Y (SRY) gene located on chromosome Yp11.32, which encodes the testis-determining factor (TDF). Activation of SRY initiates a cascade of downstream genes essential for Sertoli cell differentiation and testis development. Functional Sertoli cells secrete anti-Mullerian hormone (AMH), promoting regression of the Mullerian ducts, while Leydig cells produce testosterone, which facilitates the development of male internal and external genitalia [3]. In Swyer syndrome, pathogenic variants or deletions involving *SRY*, or defects in downstream genes regulating gonadal differentiation (including *SOX9, NR5A1, DHH, MAP3K1,* and *WT1*), disrupt testicular development. Consequently, AMH and testosterone production is absent or markedly reduced, resulting in persistence of Mullerian structures and development of female external genitalia despite the presence of a 46,XY karyotype [4].

The presence of Y chromosome within dysgenetic gonads markedly increases the risk of malignant transformation, underscoring the importance of cytogenetic characterization. Swyer syndrome is estimated to occur approximately 1 in 80,000 live female births, highlighting its rarity and the need for comprehensive genetic evaluation [5]. Individuals with Swyer syndrome have an estimated lifetime risk of gonadal malignancy ranging from 30% to 45%, predominantly due to gonadoblastoma and dysgerminoma arising from dysgenetic gonadal tissue [6]. Consequently, early diagnosis through conventional cytogenetic analysis supplemented by advanced fluorescence in situ hybridization (FISH) is essential for detecting cryptic mosaicism and Y chromosome abnormalities. Prompt prophylactic bilateral gonadectomy is recommended following diagnosis to prevent malignant transformation. Long-term management includes hormone replacement therapy (HRT) to induce secondary sexual characteristics, preserve bone mineral density, and improve quality of life. Furthermore, comprehensive genetic counselling is indispensable for discussing diagnosis, fertility options, psychosocial support, and long-term health surveillance [7, 8].

Swyer syndrome is a rare disorder of sex development that highlights the importance of integrated cytogenetic and molecular analyses for accurate diagnosis. In this retrospective study, 21 clinically diagnosed cases referred to the Department of Genetics and Molecular Medicine, Manipal TRUtest Diagnostics, Hyderabad, India, between 2021 and 2026, were evaluated to characterize chromosomal mosaicism and rare cytogenetic variants. The findings expand the cytogenetic spectrum of Swyer syndrome and emphasize their significance in improving genotype–phenotype correlations, diagnosis and genetic counselling.

II. METHODOLOGY

➢ *Study Design*

A total of 4,110 females referred for diagnostic evaluation between 2021 and 2026 at the Department of Genetics and Molecular Medicine, Manipal TRUtest Diagnostics, Hyderabad, were included in this retrospective study. Cytogenetic analyses were performed to identify cases of Swyer syndrome. The study was conducted in accordance with institutional ethical guidelines, and informed consent was obtained from all participants or their legal guardians.

➢ *Cytogenetic Analysis*

Peripheral blood (0.5 mL) was collected in Sodium heparinized vacutainers and cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) and phytohaemagglutinin (PHA). Cultures were incubated at 37°C for 72 hours. Metaphase arrest was achieved by the addition of colchicine at the 70th hour, followed by hypotonic treatment with 0.075 M potassium chloride (KCl) and fixation using Carnoy's fixative (methanol:acetic acid, 3:1). Metaphase chromosome spreads were prepared, air-dried, and subjected to GTG-banding using trypsin and Giemsa staining. The metaphases were analyzed and karyotypes were interpreted according to the International System for Human Cytogenomic Nomenclature (ISCN) guidelines [9].

➢ *Fluorescence in Situ Hybridization (FISH) Analysis*

Fluorescence in situ hybridization (FISH) was performed to confirm chromosomal abnormalities and assess the presence of the *SRY* gene. Briefly, 700 µL of peripheral blood was subjected to hypotonic treatment, followed by fixation. Fixed cell suspensions were dropped onto clean glass slides and air-dried. Hybridization was carried out using the Vysis *SRY* locus-specific DNA probe according to the manufacturer's protocol. Slides were denatured at 98°C for 5 minutes and hybridized overnight at 37°C using a ThermoBrite hybridization system. Post-hybridization washes were performed in 2× SSC/0.1% Tween-20 and 0.5× SSC/0.1% Tween-20 at 45°C. After DAPI counterstaining, fluorescent signals were analyzed using a fluorescence microscope [10].

III. RESULTS

A total of 4,110 female patients presenting with primary or secondary amenorrhea underwent cytogenetic evaluation between 2021 and 2026. Among them, 21 cases were diagnosed with Swyer syndrome, exhibiting variable phenotypic features and gonadal characteristics. These

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findings highlight the clinical and cytogenetic heterogeneity of Swyer syndrome and underscore the importance of early diagnosis.

➢ *Cytogenetic Findings*

A total of 21 females diagnosed with Swyer syndrome were included in the study. The ages ranged from 10 to 35 years, with most of them during adolescence with primary amenorrhea and failure to attain puberty. Primary amenorrhea was the most common clinical presentation, observed in 18 of 21 cases (85.7%), while the remaining individuals were with ambiguous genitalia, disorders of sexual development, and atypical reproductive anatomy**.**

Cytogenetic analysis revealed a 46,XY karyotype in 18 of the 21 patients (85.7%)**,** consistent with the typical diagnosis of 46,XY karyotype and complete gonadal dysgenesis (Swyer syndrome). The remaining three females (14.3%) exhibited rare mosaic chromosomal abnormalities involving the Y chromosome, highlighting the cytogenetic heterogeneity of the disorder. These included 45,XO/46,X,idic(Y)(p11.2) mosaicism (Figure 1)**,** 46,XY/47,XYY mosaicism (Figure 2)**,** and 45,XO/46,XY mosaicism (Figure 3)**.** Additionally, one female is detected with a 46,XY,21pstk+ heteromorphic variant, which is considered a benign chromosomal polymorphism.

The three mosaic cases represent uncommon cytogenetic variants associated with Swyer syndrome and demonstrate the influence of Y chromosome abnormalities on gonadal development and phenotypic variability. The 45,XO/46,X,idic(Y)(p11.2) mosaicism (45,XO in 18 cells and 46,X,idic(Y)(p11.2) in 62 cells) is indicative of structural instability of the Y chromosome frequently associated with gonadal dysgenesis and an increased risk of gonadal malignancy. The 46,XY/47,XYY mosaicism (46,XY in 29 cells and 47,XYY in 21 cells) represents a rare chromosomal constitution in a phenotypic female with Swyer syndrome, emphasizing that additional Y chromosome material does not necessarily result in normal testicular differentiation. Similarly, the 45,XO/46,XY mosaicism (45,XO in 39 cells and 46,XY in 61 cells) illustrates the phenotypic variability associated with Turner–Swyer mosaicism.

Advanced FISH analysis further supported these findings and confirmed the presence of the SRY gene in two females with mos 45, XO/46, X, idic(Y)(p11.2) and mos 46, XY/47, XYY karyotype, while SRY duplication was identified in the individual with 45,XO/46,XY mosaicism. In all the Swyer syndrome detected females, FISH analysis confirmed the presence of the Y chromosome, and complete SRY gene analysis was recommended for further molecular characterization. These findings highlight the complementary role of conventional karyotyping and advanced cytogenetic techniques, particularly in patients with mosaicism, for accurate diagnosis.

➢ *Clinical Investigations*

Clinical evaluation revealed that most females presented with absent or delayed secondary sexual characteristics**,** including primary amenorrhea, Tanner stage I development, and sparse or absent pubic and axillary hair**.** Ultrasonographic findings demonstrated hypoplastic or absent uterus, small or non-visualized ovaries, and Mullerian dysgenesis**,** consistent with gonadal dysgenesis, although a normal-sized uterus and ovaries was observed despite a 46,XY karyotype, reflecting phenotypic variability. Additional clinical features included short stature, webbed neck, ambiguous genitalia, bilateral non-palpable gonads, short phallus, hypotrichosis, low growth hormone levels, and absent reproductive organ development**.** Elevated FSH and LH levels were noticed along with hypergonadotropic hypogonadism, which confirmed the characteristic endocrine feature of Swyer syndrome.

Overall, this study demonstrates that although the 46,XY karyotype is the predominant cytogenetic finding in Swyer syndrome, mosaic chromosomal constitutions and structural abnormalities of the Y chromosome contribute to the genetic heterogeneity of the disorder. The wide spectrum of clinical manifestations, ranging from primary amenorrhea, delayed puberty, ambiguous genitalia to variable Mullerian development along with their respective karyotypes are listed as in Table 1. Thus this study highlights the importance of Clinical manifestations along with comprehensive cytogenetic and molecular evaluation for accurate diagnosis and further awareness through genetic counseling.

Table 1 The Clinical and Cytogenetic Characteristics of 21 Patients Diagnosed with Swyer Syndrome, Highlighting the Heterogeneity in Age, Karyotypic Findings, and Clinical Manifestations.

S.No:	Age (years)	Cytogenetic Result	Clinical History	Remarks
1	21	46, XY	Primary Amenorrhea	Swyer Syndrome
2	16	46, XY	Primary Amenorrhea	Swyer Syndrome
3	15	mos 46, XY[29]/47, XYY[21]	Primary Amenorrhea, tanner-I, small uterus & ovaries, short stature, webbed neck, absence of pubic hair	Swyer Syndrome, SRY +ve
4	15	46, XY	Primary Amenorrhea	Swyer Syndrome
5	16	46, XY	Primary Amenorrhea, not attained Menarche, Tanner Stage-I,	Swyer Syndrome
6	16	46, XY	Very short stature, absence of uterus & ovaries, low growth hormone, no secondary sexual features, looks like a 6 yrs old girl	Swyer Syndrome
7	22	46, XY	Suspected case of Primary Amenorrhea, no secondary sexual features, small uterus, small ovaries	Swyer Syndrome

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8	35	46, XY	B/L non-palpable gonad, short phallus, single opening, scrotal fold +	Swyer Syndrome
9	10	46, XY	Non visualized uterus & upper 2/3rd vagina, hypoplastic ovaries	Swyer Syndrome
10	16	46, XY	Ambiguous Genitalia	Swyer Syndrome
11	34	46, XY	Primary Amenorrhea, raised hormones of FSH & LH, Tanner Stage-III	Swyer Syndrome
12	21	46, XY 21 pstk+	Primary Amenorrhea	Swyer Syndrome
13	25	mos 45, XO[39]/46, XY [61]	Primary Amenorrhea, Mullerian dysgenesis, hypoplastic uterus	Mosaic Turner - Swyer Syndrome, SRY Duplication
14	16	46, XY	Primary Amenorrhea	Swyer Syndrome
15	13	mos 45, XO[39]/46, X, idic(Y)(p11.2)[62]	Primary Amenorrhea	Swyer Syndrome, SRY +ve
16	20	46, XY	Primary Amenorrhea	Swyer Syndrome
17	16	46, XY	Primary Amenorrhea, Tanner Stage-I, right ovary not visualized, small left ovary	Swyer Syndrome
18	29	46, XY	Primary Amenorrhea	Swyer Syndrome
19	15	46, XY	Primary Amenorrhea, uterus not visualized, sparse axillary and pubic hair (hypotrichosis), no external genetilia, vaginal orifice normal, small ovaries	Swyer Syndrome
20	16	46, XY	Primary Amenorrhea, menarche not attained, Tanner stage 1, no development of reproductive organs	Swyer Syndrome
21	31	46, XY	Uterus and ovaries are normal in size, shape & echotexture, AMH is low	Swyer Syndrome

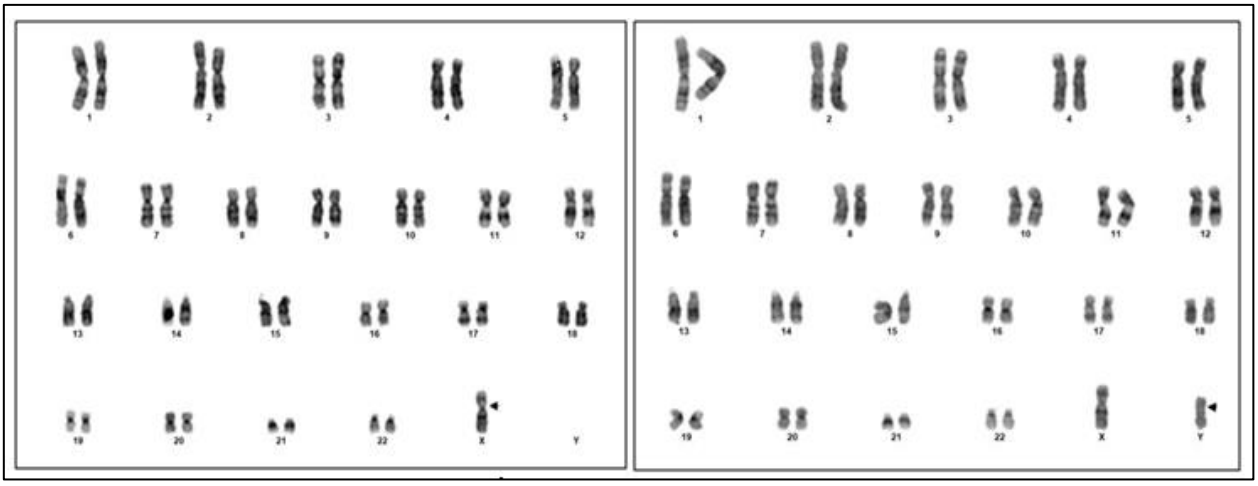

Fig 1 Mosaic 45,XO[18]/46,X,idic(Y)(p11.2)[62] Karyotype

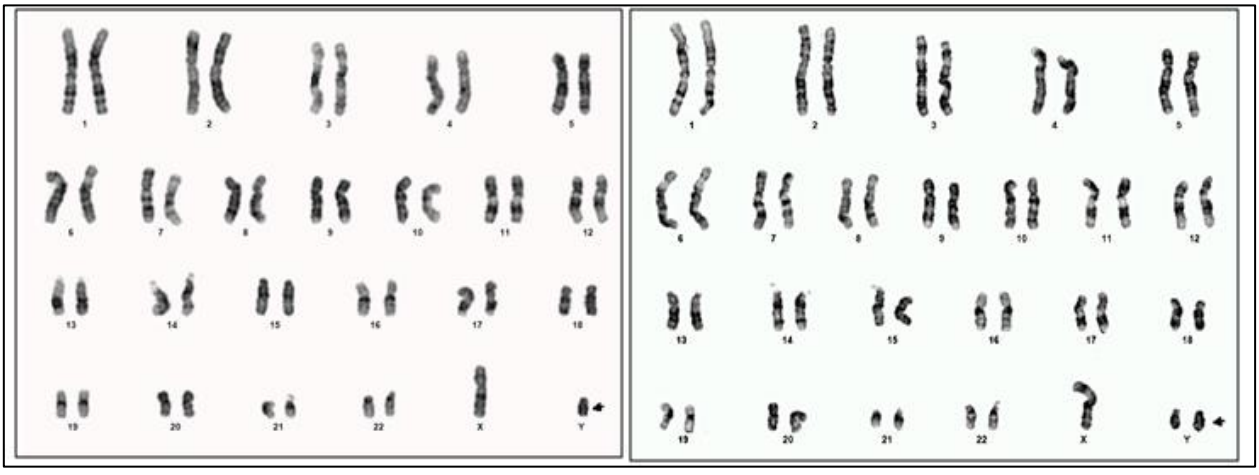

Fig 2 Mosaic 46,XY[29]/47,XYY[21] Karyotype

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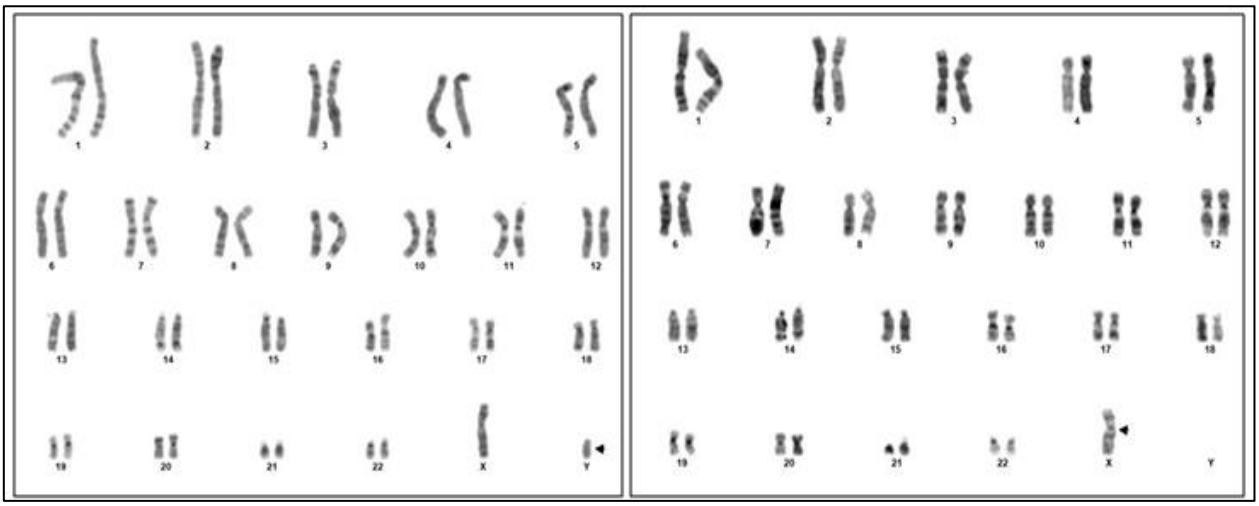

Fig 3 Mosaic 45,XY[61]/46,XO[39] Karyotype

IV. DISCUSSION

Swyer syndrome, results from failure of testicular differentiation during embryogenesis is a condition typically associated with a 46,XY karyotype, streak gonads, normal Mullerian structures, delayed puberty, and hypergonadotropic hypogonadism [11,12]. In the present study, the majority of patients exhibited the 46,XY karyotype, while three females showed rare mosaic chromosomal constitutions involving the Y chromosome, emphasizing the cytogenetic heterogeneity of Swyer syndrome.

The presence of mosaicism significantly contributes to the phenotypic variability along with Swyer syndrome. One female exhibited 45,XO/46,X,idic(Y)(p11.2) mosaicism, another showed 45,XO/46,XY mosaicism with SRY duplicatio**n**, and a third individual with 46,XY/47,XYY mosaicism. These uncommon chromosomal abnormalities illustrate the complexity of sex determination and suggest that variable proportions of abnormal cell lines influence gonadal differentiation. Similar observations have been reported in previous studies, where mosaicism involving the X and Y chromosomes resulted in a broad spectrum of phenotypes ranging from Turner syndrome to complete gonadal dysgenesis and mixed gonadal dysgenesis [13, 14, 15]. Structural abnormalities such as isodicentric Y chromosomes are particularly associated with instability during cell division, leading to mosaicism and variable clinical manifestations [16, 17].

The clinical findings in the study were highly heterogeneous despite similar cytogenetic anomalies. While primary amenorrhea and absence of pubertal development were the predominant findings, several females demonstrated atypical features, including ambiguous genitalia, short stature, webbed neck, hypoplastic or absent reproductive organs, Mullerian dysgenesis, and non-palpable gonads**.** Such variability reflects the complex interplay between chromosomal constitution, SRY expression, and downstream gene regulating gonadal differentiation. A notable finding in the present study was the identification of SRY positivity and SRY duplication in mosaic cases. Although approximately 10–20% of Swyer syndrome cases are attributed to pathogenic variants in the SRY gene, the majority remain genetically unexplained, suggesting involvement of additional genes regulating gonadal differentiation [18,19]. Therefore, comprehensive molecular evaluation using targeted gene panels or whole-exome sequencing may improve diagnostic yield, particularly in individuals with atypical karyotypes or unusual phenotypes.

One of the most important clinical considerations in Swyer syndrome is the high risk of gonadal germ cell tumors, particularly gonadoblastoma and dysgerminoma, associated with dysgenetic gonads containing Y chromosome. The reported lifetime risk ranges from 20% to 45%**,** with the risk being particularly high in females with structurally abnormal Y chromosomes or mosaic karyotypes [20]. Consequently, current international guidelines recommend prophylactic bilateral gonadectomy soon after diagnosis, regardless of age, to prevent malignant transformation while preserving the uterus for future fertility through assisted reproductive techniques [21].

Beyond medical management, Swyer syndrome has significant psychosocial implications. Diagnosis often occurs during adolescence following investigation for primary amenorrhea, a period associated with considerable psychological vulnerability. Issues related to gender identity, infertility, delayed puberty, and lifelong hormone replacement therapy require multidisciplinary care involving endocrinologists, gynecologists, geneticists, psychologists, and reproductive specialists. Early genetic counseling and individualized psychological support are therefore essential components of long-term management [22].

The present study further highlights the importance of integrating cytogenetic analysis, FISH, and Ultrasonographic findings for accurate diagnosis. Conventional karyotyping remains the cornerstone for detecting numerical and structural chromosomal abnormalities, while FISH facilitates identification of cryptic Y chromosome and SRY localization.

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V. CONCLUSION

This study expands the cytogenetic spectrum of Swyer syndrome by identifying rare mosaic chromosomal anomalies involving 45,XO/46,XY**,** 45,XO/46,X,idic(Y), and 46,XY/47,XYY. It thus demonstrates the marked phenotypic variability associated with Y chromosome mosaicism and emphasize the need for comprehensive genetic evaluation to facilitate early diagnosis, accurate risk assessment, timely prophylactic gonadectomy, and appropriate genetic counseling. Future studies employing whole-exome sequencing, whole-genome sequencing, and functional genomic approaches are warranted to elucidate the molecular mechanisms underlying unexplained cases and improve genotype-phenotype correlations.

- *Ethics Approval and Consent to Participate*

This study was conducted in accordance with the ethical standards of the institutional and national research committees.

- *Consent for Publication*

Written informed consent for publication of the clinical details and accompanying images were obtained from the patient's parents/legal guardians.

- *Availability of Data and Materials*

All data generated or analyzed during this study are included in this published article. Additional information is available from the corresponding author upon reasonable request.

- *Competing Interests*

The authors declare that they have no competing interests.

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- *Authors' Contributions*

All authors contributed equally to the conception and design of the study, data collection, cytogenetic analysis, interpretation of findings, literature review, manuscript preparation, and critical revision of the manuscript. All authors read and approved the final manuscript.

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