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Letter to the Editor

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Secondary Amenorrhea Revealing XX/XY Chimerism in Dizygotic Twins with Discordant Sex Phenotype

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Letter to the Editor

To the Editor,

Sex-chromosome chimerism, characterized by the presence of both 46,XX and 46,XY cell lines within a single individual, represents a rare biological phenomenon most commonly associated with dizygotic twin pregnancies and placental vascular anastomoses. Since the first well-documented descriptions of XX/XY chimerism in opposite-sex dizygotic twins [1], a wide spectrum of phenotypic outcomes has been reported, ranging from typical male or female development to Disorders of Sex Development (DSD) [2]. Despite the presence of mixed sex-chromosome cell lines, phenotypic sex determination is often discordant with peripheral blood karyotype findings, highlighting the importance of tissue-specific distribution of chimeric cell populations [3]. Although most reported cases are identified during evaluation for ambiguous genitalia or primary amenorrhea, the clinical significance of XX/XY chimerism presenting with preserved early gonadal function

and subsequent reproductive axis disturbance remains poorly characterized. This underscores the relevance of reporting clinically atypical presentations that expand the recognized spectrum of chimerism-associated reproductive phenotypes [4].

A 15-year-old phenotypic female (Patient A) was referred for evaluation of secondary amenorrhea. Menarche had occurred at approximately 10 years of age, followed by regular menstrual cycles for 2–3 years, with cessation of menses since 2023. Clinical examination revealed normal female external genitalia and appropriate pubertal development. Pelvic ultrasonography demonstrated the presence of a uterus and ovaries at the lower limits of normal size. Cytogenetic analysis of peripheral blood lymphocytes revealed a mixed karyotype of 46,XY[37]/46,XX[13], while molecular analysis of the SRY gene did not identify pathogenic or likely pathogenic variants.

Given the presence of a dizygotic twin brother (Patient B), further evaluation was performed. Patient B exhibited a typical male phenotype and normal male pubertal development, with a medical history notable only for right inguinal hernia. Cytogenetic analysis similarly demonstrated a mixed karyotype of 46,XY[87]/46,XX[13], and molecular testing of SRY was likewise non-contributory. The principal clinical and cytogenetic findings of both siblings are summarized in **Table 1**.

Table 1: Clinical and cytogenetic findings in dizygotic twins with XX/XY chimerism.

Feature	Patient A (phenotypic female)	Patient B (phenotypic male)
Date of birth	02-Jan-09	02-Jan-09
Twin type	Dizygotic	Dizygotic
Reason for evaluation	Secondary amenorrhea	Family evaluation
Pubertal development	Appropriate for age	Appropriate for age
External genitalia	Typical female	Typical male
Menstrual history	Menarche at ~10 years; regular menses for 2–3 years; amenorrhea since 2023	Not applicable
Pelvic ultrasonography	Uterus and ovaries present, at lower limits of normal size	Not performed
Cytogenetic analysis (peripheral blood)	46,XY[37]/46,XX[13]	46,XY[87]/46,XX[13]

Molecular analysis of SRY	No pathogenic or likely pathogenic variants detected	No pathogenic or likely pathogenic variants detected
Relevant medical history	—	Right inguinal hernia

The present observation illustrates the substantial phenotypic heterogeneity that may accompany XX/XY chimerism, even among individuals with comparable cytogenetic findings in peripheral blood. Notably, despite the presence of a similar mixed sex-chromosome cell line distribution, both siblings exhibited clearly defined and non-ambiguous sex phenotypes, indicating that phenotypic divergence in this context does not necessarily involve external sexual differentiation. In this setting, the development of secondary rather than primary amenorrhea suggests preserved early gonadal function with subsequent disturbance of the reproductive axis, a pattern that remains under-represented in the literature on sex-chromosome chimerism. Recent genomic and clinical studies have demonstrated that XX/XY chimerism may be detected incidentally and can exhibit marked heterogeneity across tissues, with peripheral blood findings failing to capture the full biological and reproductive implications of chimerism [5-8]. Accumulating evidence further supports a critical role for tissue-specific and germ-cell lineage distribution in shaping reproductive outcomes, providing a biologically plausible framework for discordant clinical trajectories without implying a specific underlying mechanism [4,7,9]. From a clinical perspective, these findings underscore the importance of considering sex-chromosome chimerism in adolescents presenting with secondary amenorrhea, particularly in the context of twin or multiple pregnancies, and contribute to expanding the recognized spectrum of chimerism-associated reproductive phenotypes.

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