

A NORMAL 46 XX KARYOTYPE DOES NOT ALWAYS REPRESENT FEMALE PHENOTYPE

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[I] KARYOTYPE

A karyotype generally refers to the number and the appearance of metaphase chromosomes in a diploid cell. Generally, G-banding (Giemsa) is used to stain the chromosomes for karyotyping. A Karyotype analysis is done to investigate chromosomal aberrations to diagnose various blood cancers where in general translocation occurs and syndromes such as Down syndrome, Turner syndrome among others where the number of chromosome varies. Therefore, karyotype analysis has great importance in prenatal diagnosis and medical genetics. Another important aspect of karyotype analysis is underlying in sex determination. The normal human male karyotype shows 46 XY and female 46 XX. However, the genotype-phenotype does not match always and there are phenotypically males with 46 XX and females with 46 XY. Such instances are very rare. The G-banding generally fails to correlate such genotype-phenotype correlation.

1.1 46 XX males

Males with 46 XX karyotype are referred as XX male syndrome or de la Chapelle syndrome. These individual are phenotypically male but are genetically female and the phenotype is clinically termed as XX male syndrome. The incidences are very rare (4 in 1 lakh). Individuals exhibit feminine characteristics, develop small testes, develop gynecomastia, without Müllerian tissue (that develop fallopian tubes, uterus, cervix, vagina etc in female), and are sterile. The SRY (Sex determining Region Y)

on Y chromosome is responsible for male sex determination in an individual. In XX male syndrome, the X chromosome contains the SRY gene due to unequal crossing over between the X and Y chromosomes in the father during the meiosis. The abnormal X chromosome containing the SYR gene when transmitted to an individual with a normal X chromosome, it gives rise to 46, XX karyotype (female karyotype); however, due to presence of the SYR gene, the individual is phenotypically male [1].

1.2. 46 XY female

Similarly, an individual having 46 XY does not always represent male characters; instead it may represent XY complete gonadal dysgenesis (CGD) or Swyer syndrome. Although, in these genetically male fetuses, the Y chromosome is present; gonads do not differentiate into active testes due to loss of function mutation in SYR gene. In such case the gonads represent as streak gonads without having ovarian or testicular tissue. Testosterone or antimüllerian hormone (AMH) does not produce due to lack of testis and therefore male sexual organs do not develop. Instead it develops female sexual organs such as uterus, fallopian tubes, cervix, and vagina from Müllerian ducts. Such individuals are phenotypically female at infant stage and fail to develop secondary sex characteristics such as breast development and menstrual periods etc. in the later age. The diagnosis is difficult at early age; however a delay in puberty, 46 XY karyotype, presence of a

pubic hair and uterus but no ovaries, and absence of breasts along with female sexual organs confirm Swyer syndrome [2].

[II] TESTS

The conventional karyotyping using G-banding is not always helpful in diagnosing these disorders. Fluorescence in situ Hybridization (FISH) based karyotyping using SRY gene probes and additional gene tests are recommended. The following tests can be used to determine 46 XX male and 46 XY female genotypes.

2.1. Tests for 46 XX males

Clinical diagnosis: 46 XX karyotype, male external genitalia, two testicles, absence of germ cells in testis, azoospermia, no Müllerian structures.

Hormone tests: Elevation of serum LH and FSH, decreased or lack of serum testosterone. **Cytology:** Conventional karyotyping. However, sensitivities of these tests are low and may not conclude genotype-phenotype correlation. Therefore, **molecular genetic tests** are required. Such tests are- Karyotyping using FISH method: for presence of SRY gene in X chromosome. **Gene tests** for SRY gene (80% cases) using PCR amplification for presence of SYR gene are recommended [1].

2.2 Tests for 46 XY females

Clinical diagnosis: 46 XY karyotype, normal female external genitalia, streak gonads, no sperm production, presence of Müllerian structures.

Hormone tests: Elevation of serum LH and FSH, decreased or lack of serum testosterone. **Diagnostic imaging:** USG, MRI, laparoscopy etc. shows uterus but no ovaries. However, the sensitivities of these tests are low. Therefore, karyotyping using **FISH method** for deletion of SRY gene and additional genetic tests are advised. Such **gene tests** are- SRY gene (15% cases) -FISH or deletion /duplication analysis; **DNA Sequencing:** DHH gene (50% cases)-sequencing for heterozygous mutations; NR5A1 (SF1), NR0B1 (DAX1), and WNT4 (rare), FISH

analysis for deletion/duplication analysis of these genes [2].

[III] CONCLUSION

Conventional G-banding based karyotype sometimes failed to explain genotype-phenotype correlation in respect to 46 XX male and 46 XY female. Therefore, additional gene test are recommended to precisely characterize the sex of an individual while the phenotype of an individual varies from its karyotype.

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