

# Revisiting The Diagnosis: Next Generation Sequencing (NGS) Identifies Concurrence Of PAIS In A Previously Reported Case Of Klinefelter Syndrome (47,XXY) With Hypospadias

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## Background

Klinefelter syndrome (KFS) is a sex chromosomal disorder characterised by hypogonadism, progressive testicular failure, gynaecomastia and learning difficulties. Genital anomalies are rarely observed in KFS. Androgen insensitivity has been previously postulated, but not proven to cause genital ambiguity in KFS. Androgen receptor (AR) gene defects are reported in AIS, but have not been reported in children with KFS with mild hypospadias.

## Aim

We describe a novel p.Phe795Tyr (c.2384T>A) mutation in the AR gene affecting two male siblings of which one had concurrent KFS.

## Case

**Case 1:** A term infant born to consanguineous parents of Asian origin presented with penoscrotal hypospadias, bifid scrotum and bilateral palpable testes at birth. Investigations showed normal electrolytes and androgen profile. Chromosome analysis revealed a 46,XY karyotype. Molecular analysis of the AR gene was performed using a NGS 32-gene DSD panel platform and DNA sequencing revealed a novel hemizygous mutation p.Phe795Tyr (c.2384T>A) in the AR gene.

**Case 2:** The older sibling presented with genital ambiguity (mild hypospadias and micropenis) at birth. Chromosome analysis diagnosed KFS (47,XXY) which was considered to account for the hypospadias, and he underwent surgical repair at 1 year of age. The gonadotropins were elevated. This case has been previously reported as association of genital anomalies in KFS. The finding of AR gene mutation in his brother (Case 1) triggered molecular genetic analysis. The same hemizygous missense variant p.Phe795Tyr (c.2384T>A) in the AR gene was identified as in his brother, confirming partial androgen insensitivity syndrome (PAIS).

## Discussion

This mutation has not been previously described in the literature. The PAIS phenotypes of these two siblings suggest that normal AR is partially functional. Furthermore, X-inactivation studies conducted showed a random X inactivation pattern with no evidence of skewed X-inactivation in case 2. The X-inactivation status is confirmed in lymphocytes only, which may not be representative of other tissues. Given that the variant was identified in both the index Case 1 and his affected brother (Case 2), this increases the likelihood that the variant is the cause of the clinical features of undervirilisation seen in this family. Despite the use of dihydrotestosterone gel to enhance penile growth, there was limited clinical response. He further received psychology input to support his emotional well-being.

## Conclusions

This report emphasizes the importance of considering concurrent finding of PAIS in KFS with ambiguous genitalia. It also highlights the significance of NGS panel in revisiting the diagnosis of DSD.

## References

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