# Novel heterozygous mutation in Wilms tumor 1 gene in patient with mixed gonadal dysgenesis (MGD)

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## Introduction and Aim

Wilms tumor 1(WT1) gene mutations have been described in 46,XY patients with ambiguous genitalia or complete gonadal dysgenesis with or without Wilms tumor, nephropathy, gonadoblastoma and other defects e.g. cryptorchidism, hypospadias. Sex chromosome mosaicism is a major cause of DSD with a wide phenotypic variability. The phenotype is primarily dependent on the proportion of each cell line in the developing gonads. This study reports one year old infant, reared as a male, presented with ambiguous genitalia.

## Patient and Methods

Infant with ambiguous genitalia and a male sex of rearing was referred at the age of one year to the Endocrinology Clinic, Medical Centre for Scientific excellence, National Research Centre, Egypt.

Clinical investigations of the gonadal phenotype, gonadal histopathology, karyotype and FISH analysis on fresh tissue after gonadal cell culture using CEP X /CEP Y and SRY/ CEP X probes were performed. Additionally, Sequencing analysis of WT1 gene was considered.

## Results

1. **External genital examination** showed left undescended testis felt in the inguinal canal and right gonad in right scrotal sac (Quigley score is 3), micropenis phallus (2.5cm), labioscrotal fold with single penoscrotal opening.

2. **Hormonal investigations:** 17OH Progesterone= 10.5ng/dl (normal), Testosterone= 2.9ng/ml (Tanner III), DHT= 22ng/dl ( Tanner III).

3. **Pelvic Ultrasonography:** normal right kidney and the left kidney with moderate pelvicalyceal dilatation. No uterus was visualized, the left gonad was in medial end of inguinal canal, and the right testis was scrotal.

   **Histopathological examination** of the left gonad showed fibrous streak tissue

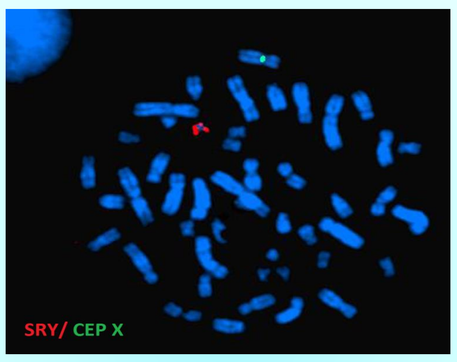
4. **Karyotype analysis** of blood lymphocytes, two cell lines were detected: **mos 45,X[90]/46,X,idic(Y)(q11.2)[10]**.

   **FISH analysis on gonadal cells** showed the same type of mosaicism:

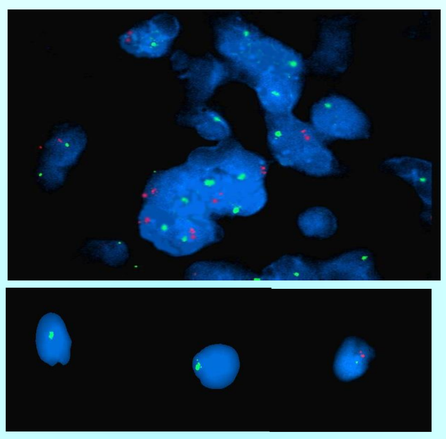
   **nuc ish X/Ycen(DXZ1 × 1)[75]/(DXZ1 × 1,DYZ3 × 2)[25], Yp11(SRY×2)**.

5. **Sequencing analysis of WT1 gene** showed a novel heterozygous missense mutation in exon 9, NM_001198552: c.689A>G; NP_077744.3: p.K459R. The mutation was not detected in both parents.

### FISH analysis of blood metaphases and gonadal interphase cells

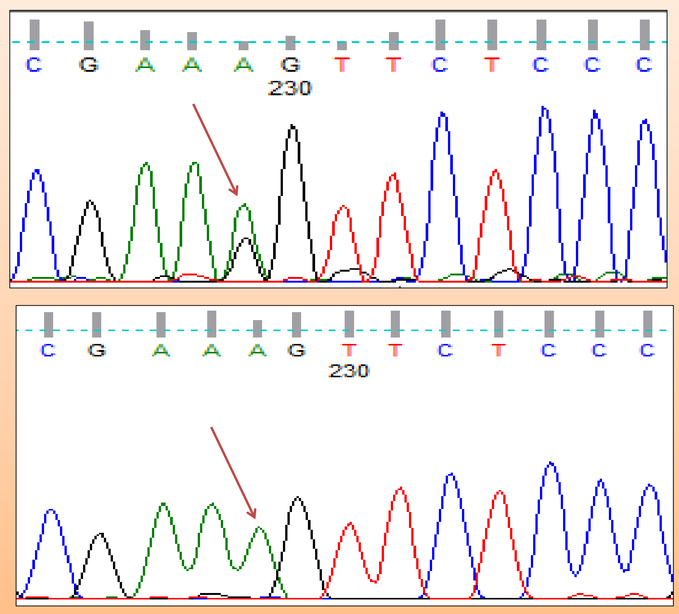



FISH on a blood metaphase showing 2 hybridization signals for the SRY gene seen on the abnormal Y and 1 signal for the X centromere (DXZ1).



FISH on gonadal tissue cells showing an X centromeric signal and a double hybridization signal for the Y centromere and for the SRY gene, respectively, with another cell line having one hybridization signal for the X centromere (45,X).

### Sequencing chromatogram showing the heterozygous mutation in WT! gene in the patient and the wild type sequence in the parent




## Conclusion

This is the first study to report a mutation in WT1 in MGD patient. This study demonstrates the importance of WT1 in male sexual differentiation and kidney development.

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Sex differentiation, gonads and gynaecology or sex endocrinology

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