The Evolving Role of WES in the Diagnosis of Disorders of Sex Development (DSD)

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Introduction:

Disorders of sex development (DSD) are classified as a congenital discrepancy between external genitalia, gonadal and chromosomal sex. Despite extensive laboratory and imaging investigation, the etiology of DSD is unknown in more than 50% of patients.

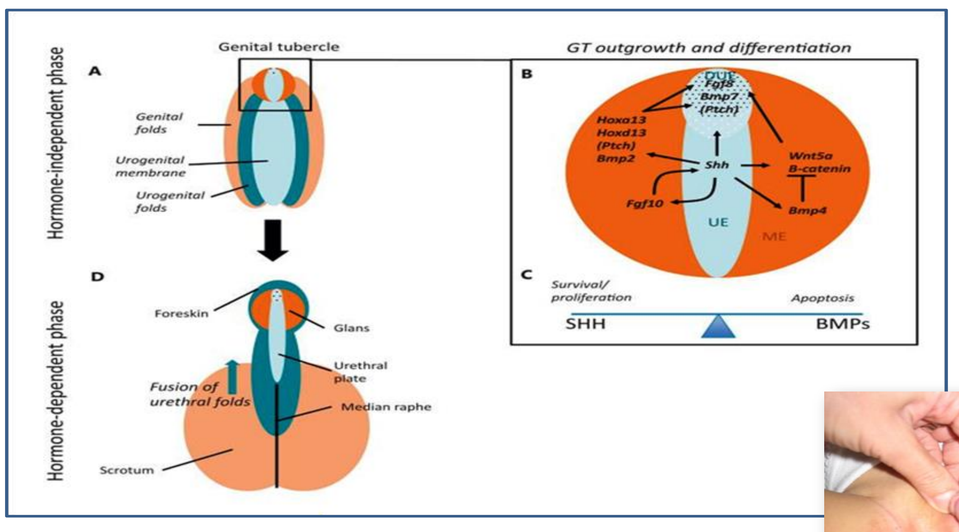
The aim of this study to report our experience in the era of WES in the diagnosis of DSD

Results:

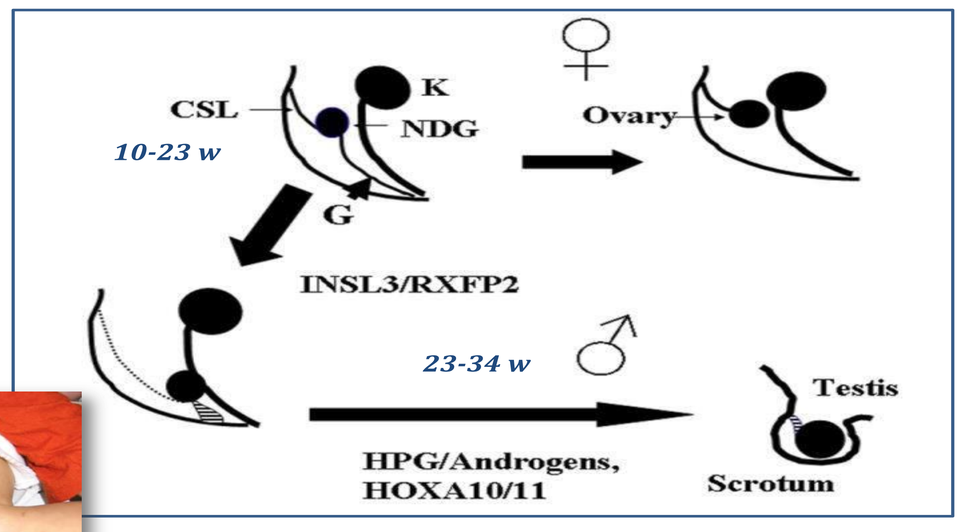
Molecular genetic findings

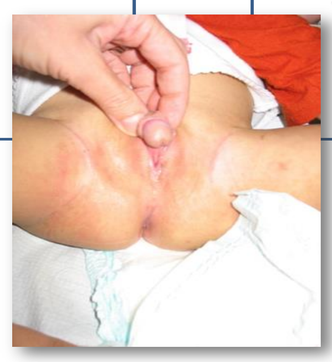
No.	Karyotype	Age at presentation (days)	Age at WES (years)	WES findings	Type of mutation
1	46,XY	10	12.8	*LGR8 (RFXP2)*	AD c.A664C, p.T222P
2	46,XY	90	8	*HSD17B3*	AR-novel c.673G>A, p.V225M
3	46,XY	7	12	*WT1*	Splice mutation-*de-novo* c.1433-3C>G
4	46,XY	12	11.3	*BMP4*	AD-*de novo* c.G209T, p.R70L
5	46,XX	30	11	*POR*	AR- previously described c.G1615A, p.G539R
6	46,XY	25	3.5	*CHDR7*	AD-*de novo* c. 1480C>T, p.R94T
7	46,XY	14	11	*No pathologic variants*	
8	46,XY	455	8	*Variants of unknown significance*	
9	46,XY	18	12.75	*No pathologic variants*	
		73 (7-455)	10 (3.5-12.8)	*67%*	

Bone morphogenetic protein 4 (BMP4) has a role in external genital development



Insulin-like factor 3 receptor (LGR8) has a role in testicular descent in mammals





Summary & Conclusions:

- **Based on our previous approach, specific diagnosis of the etiology of DSD is often delayed to the *second decade* of life, particularly in 46,XY DSD**
- ***Likely gender identity at adulthood* is the major consideration in determining sex of rearing**
- **The *specific etiology* of DSD is crucial for this decision**
- **Our findings indicate that WES identified the etiology of DSD in up to 70% of cases including the following: *LGR8, HSD17B3, WT1, BMP4, POR & CHD7* gene mutations**
- **The clinical significance of WES findings is not always known and this may cause difficulties in genetic counselling**
- **WES plays an important role in early molecular diagnosis of DSD with important implications for sex of rearing**