The novel founder homozygous V225M mutation in the 17HSDB3 gene causes aberrant splicing and severe XY-DSD

Floris Levy-Khademi, Sharon Zeligson, Tehila Klopstock, Eran Lavi, Boris Chertin, Carmit Avnon- Ziv, Abdulsalam abulibdeh, Paul Renbaum, Tzvia Rozen, Shira Perlberg-Bengio, Fouad Zahadeh, Doron M Behar, Ephrat Levy-Lahad, David Zangen, Reeval Segel
Shaare Zedek Medical Center, Hadassah Hebrew University Medical Center, Jerusalem, Israel.

Background

- **Mutations in the gene HSD17B3 encoding the 17-ß hydroxysteroid dehydrogenase 3 enzyme cause testosterone insufficiency leading to XY-DSD.**
- **There are fourteen known isoenzymes of HSD17B in mammals with isoenzyme 3 being the major one expressed in the testes.**
- **Defects in the function of this enzyme may cause ambiguous or female external genitalia in a genotypically male at birth, or become overt only at puberty when an affected XY female presents with primary amenorrhea or progressive virilization.**
- **XX homozygous females appear to be asymptomatic.**

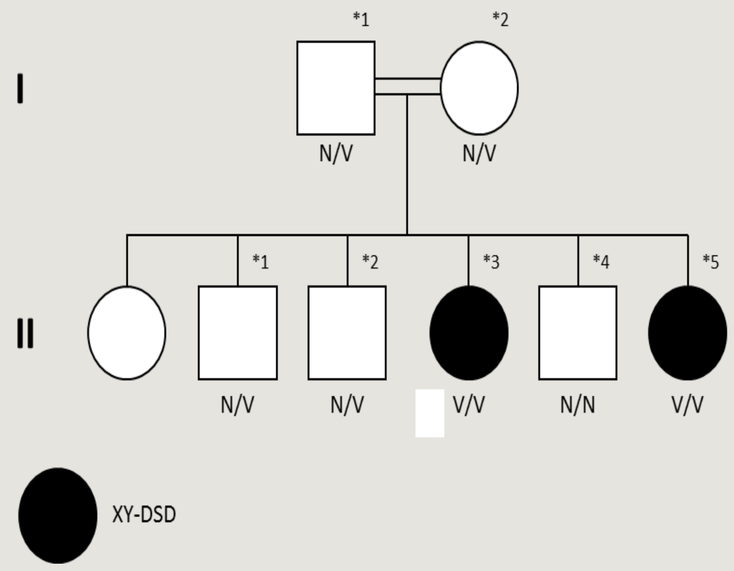
Patients

- **Patient II-5 is 8 years old female born with ambiguous genitalia, clitoris 0.7 mm and gonads in the inguinal canal.**
- **Karyotype was XY**
- **The results of ACTH stimulation test in this patient are shown below:**

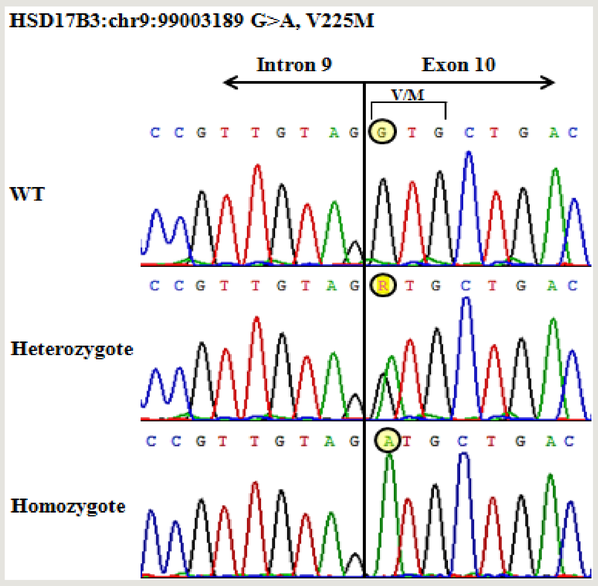
Time	Testosterone Nmol/l	Androstenedione Nmol/l	DHEAS Micromole/l	Cortisol Nmol/l	ACTH Pmol/l	17OHP Nmol/l	PRA Ng/ml/hr	Aldosterone Pmol/l	Testosterone/ Androstenedione ratio
0	0.96	4.48	<0.41	86.6	15.5	0.5	2.6	>2500	0.21
60	1.14	9.97	<0.41	1059		201			0.11

- **Her sister II-5 was diagnosed at age 8 years with the same phenotype**
- **A non related 8 months old patient was diagnosed with the same phenotype and genotype at 8 months**

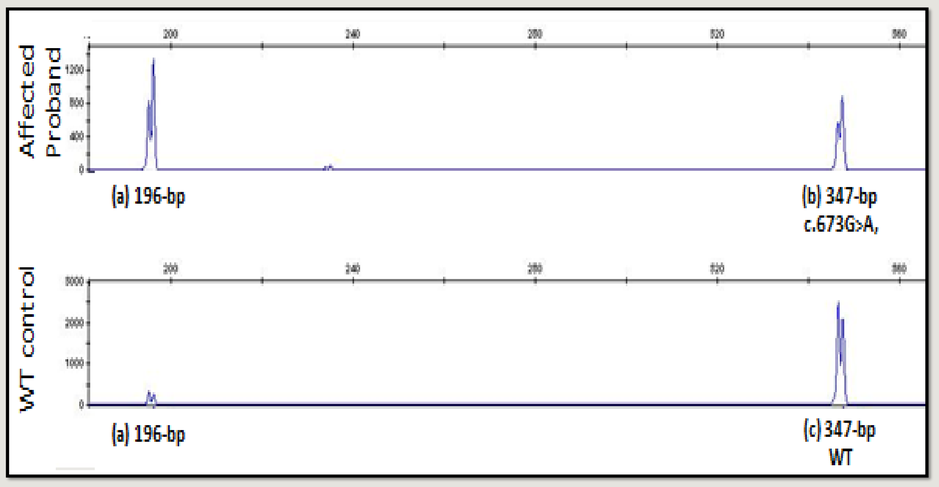
Molecular Analysis



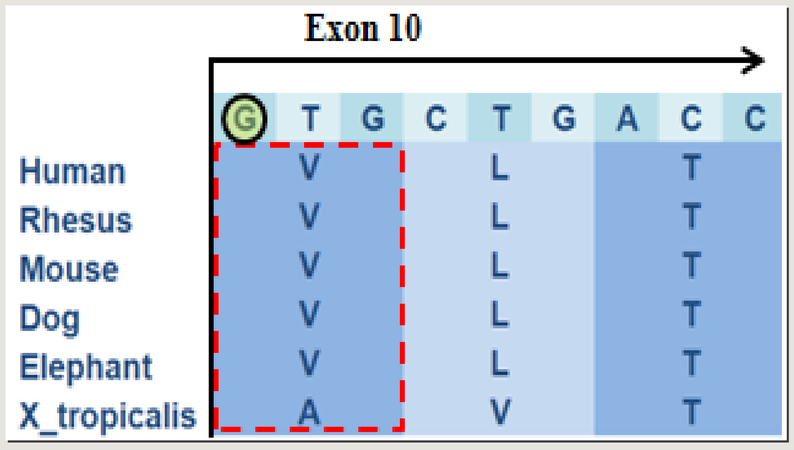
Family 1 pedigree. Affected sisters, II-3 and II-5, are homozygous for HSD17B3 c.673G>A mutation. N – normal, V – variant



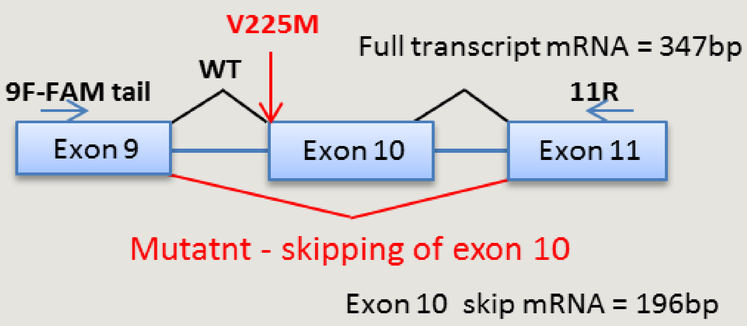
HSD17B3 genomic chormatogram sequence. The mutation in the first nucleotide of exon 10 is indicated with circle



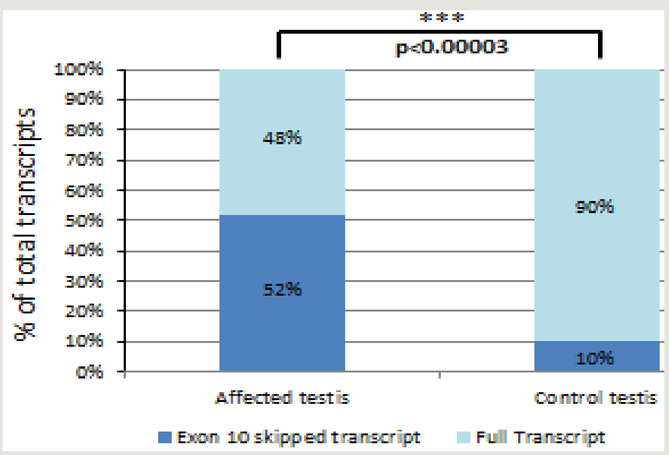
Electropherogram of fluorescently tagged RT-PCR products of HSD17B3, in two samples: Affected homozygote (upper lane) and a control testes sample



Cross-species conservation of the residues adjacent to V225 bordered by vertical dashed lines (adapted from *http://genome.ucsc.edu*). The mutation in the first nucleotide of exon 10 is indicated with circle



Schematic representation of WT and alternative splicing of exon 10



A bar chart demonstrating the relative proportions of WT and aberrant transcripts in the affected homozygotes and the WT control testis samples. For each individual, the proportion shown represents the mean of 3 repeated experiments. The range of SDs for all samples: 0.66%-3.24%.

Conclusions

- **Here we describe a novel homozygote founder mutation c.673G>A p.V225M in 2 unrelated families**
- **Functional studies using normal human testes show that this mutation leads to skipping of Exon 10 and changes in the transcription of the gene**
- **While some of the patients undergo profound virilization during puberty, the issue of gender assignment in these patients may be challenging**

58ESPE P1-128
Sex differentiation, gonads and gynaecology or sex endocrinology
Floris Levy-Khademi
Poster presented at: ESPE 2019 VIENNA
PosterSessionOnline.com