

Supplemental table 1: All detected mutations in HSD17B3 gene in patients with 46,XY DSD

No.	Mutant Exon	Mutation	Mutation type/Effect	Ethnicity	Phenotype/Clinical presentation	References
1	Exon 1	p.Trp50Stop	Nonsense/Truncated protein	<i>Egyptian</i>	46,XY DSD; well-developed breasts (B5), pubic hair (P5) and axillary hair (A3), moderate hirsutism mainly affecting the lower limbs, failure to menstruate, and clitoris-like phallus with normal female external genitalia (Sinnecker type 5)	<i>Hassan et al., 2013</i>
2		p. Ala51Val	Missense (Found in compound heterozygosity with p.Gln176Pro)	<i>Egyptian</i>	46,XY DSD; ambiguous genitalia, bilateral palpable gonads, labioscrotal folds with single opening, and penis-like phallus	<i>The current study</i>
3	Exon 2	p.Ser65Leu	Missense/Inactivates enzyme	Iranian	46,XY DSD; evaluated for hirsutism, clitoromegaly and failure to menstruate.	

4		p.Thr54Ala	Missense	Egyptian	46,XY DSD; hirsutism in body and face, and well developed breasts (B5), pubic hair (P5) and axillary hair (A2). No palpable gonads, and penis like phallus	<i>The current study</i>
5		p.Ala56Thr	Missense/Severe impairment of enzyme	South Asian	46,XY DSD; female prepubertal external genitalia, pubertal virilization, severe hair growth, voice changes and clitoral enlargement (6 months, child diagnosed because of family history).	
6	Exon 3	p.Asn74Thr	Missense	Dutch	46,XY DSD; ambiguous genitalia, pubertal virilization.	
7		p.Arg80Gln	Missense/Impaired enzyme activity (NADPH binding site)	Palestinian, Dutch, Brazilian, Portuguese, Turkish	46,XY DSD; ambiguous genitalia at birth to mild clitoromegaly, pubertal virilization, male gender role, and many reassigned as males if raised as girls.	<i>Demir et al., 2015</i>

8		Duplication that spans exons 3-10 of the HSD17B3 gene and extends from intron 2 to intron 10	Duplication (Found in compound heterozygosity with p.R80Q)	<i>Cypriot</i>	46,XY DSD; ambiguous genitalia, small penis, perineal blind vaginal pouch and posterior labioscrotal fusion.	<i>Neocleous et al., 2012</i>
9		p.Arg80Trp	Missense/Complete loss of enzyme activity (NADPH binding site)	Spanish, Italian, <i>Lebanese, Iranian</i>	46,XY DSD; female external genitalia, palpable gonads, clitoral enlargement and virilization at puberty.	<i>George et al., 2011; Omrani et al., 2011</i>
10	Intron 3	c.325+2T>G	Splice junction/Disrupts splice donor site (found in compound heterozygosity with c.325+4A>T)	<i>Brazilian</i>	46,XY DSD; pubic hair was Tanner stage 4, the vagina ended in a 3-cm pouch, and no gonads were palpable, also presented with acne, hirsutism, voice deepening, phallus enlargement, and the skin of labioscrotal folds were pigmented and rugged.	<i>Castro et al., 2012</i>
11		c.325+4A>T	Splice junction/Disrupts splice acceptor site	Dutch, Brazilian, German, American, Italian	46,XY DSD; normal female to ambiguous genitalia, palpable inguinal gonads.	

12		c.326–1G>C	Splice junction	Dutch, Brazilian	46,XY DSD; inguinal hernia, failure of breast development, facial and body hair growth, voice changes, clitoral enlargement.	
13	Exon 5	p.Asn130Ser	Missense/Severe impairment of enzyme activity	English, German	46,XY DSD; pubertal virilization, mild clitoromegaly, voice changes.	
14	Exon 6	p.H155P	Missense	<i>Turkish</i>	46,XY DSD; normal clitoral size and vaginal and urethral openings, palpable gonads in the inguinal region	<i>Demir et al., 2015</i>
15	Intron 6	c.538–1G>A	Splice junction	Unknown	46,XY DSD.	
16	Exon 7	p.Met164Thr	Missense	<i>Egyptian</i>	46,XY DSD, ambiguous genitalia, two palpable gonads, single opening, and penis like phallus	<i>The current study</i>
17		c.585delG	Deletion/ Truncated protein	<i>Egyptian</i>	46,XY DSD, ambiguous genitalia, two palpable gonads, single opening, and clitoris like phallus	<i>The current study</i>

18	Intron 7	c.572+2T>A	Splice junction	<i>Sudanese</i>	46,XY DSD, primary amenorrhea, undeveloped breasts, male pattern secondary characteristics, and external genitalia showed type IV genital circumcision.	<i>Ellaithi et al., 2014</i>
19	Exon 8	p.Gln176Pro	Missense	American (Italian, German-Irish), <i>Egyptian</i>	46,XY DSD; clitoromegaly and coarsening of voice, scrotalization of labia majora and inguinal masses. 46,XY DSD; ambiguous genitalia, Quigley score was 3	<i>The current study</i>
20		c.608delT	Deletion/Downstream premature Stop codon	German	46,XY DSD; female prepubertal development, clitoral enlargement at 12 years of age, testes in inguinal canal.	
21		p.Ala188Val	Missense/Inactivates enzyme	Turkish	46,XY DSD; prepubertal female external genitalia, inguinal mass.	
22		p.Trp192Stop	Nonsense/Truncated protein	<i>Omani</i>	46,XY DSD; ambiguous genitalia	<i>Al-Sinani et al., 2015</i>

23		p.Leu194Pro	Missense (Found in compound heterozygosity with silent mutation c.588C>T)	<i>Egyptian</i>	46,XY DSD; virilization after puberty and chest hair, two openings, and penis like phallus	<i>The current study</i>
24		p.Met197Lys	Missense/Alters secondary protein structure	Afghan	46,XY DSD; pubertal virilization, facial hair, 4–8 cm phallus and labioscrotal folds.	
25	Intron 8	c.655–1G>A	Splice junction/Disrupts splice acceptance site	Syrian, Turkish, Dutch, Greek-American	46,XY DSD; prepubertal female external genitalia, pubertal virilization, male gender role.	
26	Exon 9	p.Ala203Val	Missense/Inactivates enzyme	African-Brazilian, Italian	46,XY DSD; absence of menses, failure of breast development, facial and chest hair and clitoral enlargement, male and female gender identity in siblings.	
27		p.Ala203Glu	Missense	Southern Italian	46,XY DSD; pubertal virilization.	
28		p.Val205Glu	Missense/Inactivates enzyme	White American, English	46,XY DSD; prepubertal female external genitalia to perineoscrotal hypospadias, primary amenorrhea, mild clitoromegaly.	

29		p.Phe208Ile	Missense/Inactivates enzyme	German	46,XY DSD; born with ambiguous genitalia, clitoromegaly (1.5 cm) and posterior fusion and scrotalization of the labia majora which contained palpable masses.	
30		p.Leu212Gln	Missense/Inactivates enzyme	Italian	46,XY DSD; inguinal mass, mild clitoromegaly compound hetrozygous with M235V.	
31		c.461_467delGCACCCG	Deletion (Found in compound heterozygosity with c.761_762delAG)	<i>Turkish</i>	46,XY DSD; female external genitalia, 2 palpable gonads	<i>Sagsak et al., 2015</i>
32		p.Glu215Asp	Missense/Inactivates enzyme	White Brazilian, English	46,XY DSD; female or ambiguous genitalia at birth, male behaviors in childhood, pubertal virilization, absence of menses, male gender role.	
33		p.Cys206Stop	Nonsense/Truncated protein	<i>Tunisian</i>	46,XY DSD; female Prader IV.	<i>Ben Rhouma et al., 2012</i>
34	Exon 10	p.Ser232Leu	Missense/Inactivates enzyme	African-American, South Asian	46,XY DSD; clitoromegaly, primary amenorrhea, absent labia minora, severe hypospadias with undermasculinization – raised as males and females.	

35		p.Met235Val	Missense/Inactivates enzyme	African-American, Italian	46,XY DSD; clitoromegaly, primary amenorrhea, inguinal masses.	
36		c.777–783delGATAACC	Deletion/Frame shift truncates protein	Polish, <i>Turkish, Egyptian</i>	46,XY DSD; testis in herniorrhaphy sac, failure to menstruate. 46,XY DSD; ambiguous genitalia with two openings, and clitoromegaly	<i>Alikasifoglu et al., 2012; The current study</i>
37		c.761_762delAG	Deletion (Found in compound heterozygosity with c.461_467delGCACCCG)	<i>Turkish</i>	46,XY DSD; female external genitalia, 2 palpable gonads	<i>Sagsak et al., 2015</i>
38		p.Cys268Tyr	Missense/Inactivates enzyme	Pakistani	46,XY DSD; prominent clitoris, palpable inguinal gonads.	
39		p.His271Arg	Missense/Inactivates enzyme	French	46,XY DSD	
40	Exon 11	p.Pro282Leu	Missense/Inactivates enzyme	White American, Dutch	46,XY DSD; clitoromegaly, failure of breast development and deepening of voice.	
41		p.Tyr287Stop	Nonsense/Truncated protein	<i>Turkish</i>	Tanner stage 5. The patient had hirsutism and deepening voice change with normal female external genitalia except for a cliteromegaly (sinnecker type 5).	<i>Tuhan et al., 2015</i>

42		p.Gly289Ser	Polymorphism/Unknown	Italian, West Indian, <i>Brazilian, Egyptians</i>	46,XY DSD; normal female prepubertal genitalia, bilateral inguinal hernia at sonography. 46,XY DSD; ambiguous genitalia, single opening and penis-like phallus	<i>Castro et al., 2012; The current study</i>
* A modified table of <i>George et al., 2010</i> with the references of the added cases in <i>Bold Italic</i> style.						