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MDPI

## *Supplementary Materials*

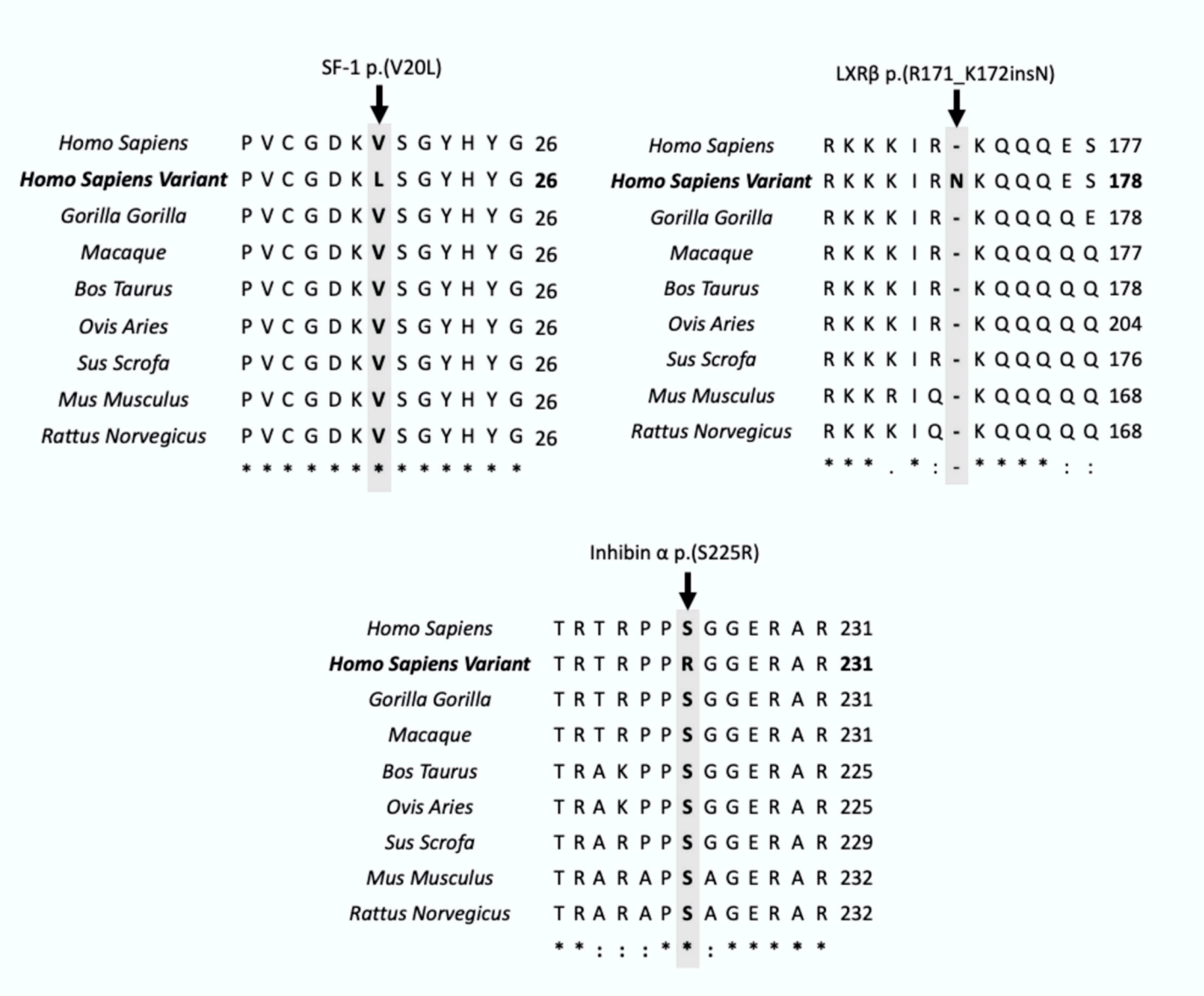



**Figure S1:** Protein localization and conservation across species of the three variants *NR5A1*/SF-1 p.(V20L), *NR1H2*/LXRβ p.(R171_K172insN) and *INHA*/inhibin α p.(S225R). The alignment of the various proteins across different species is shown. Localization of the identified human amino acid variants is indicated with arrows and seems highly conserved across species. *, conserved amino acid across species. :, different amino acid across species.

**Table S1: Reported combined variants in *NR5A1* and associated genes**

The DSD phenotype, *NR5A1* and *NR5A1*-associated gene variants, zygosity and the genetic test used for the variants identification are presented.

| **Patient phenotype*** | ***NR5A1*/SF-1 variant** (NM_004959.5) | **Genetic test** | **Name of the additional gene variant/ (transcript)** | **Gene variant** | **References** |
|---|---|---|---|---|---|
| 46,XY DSD | c.1256T>A[1]; p.(L419Q) | Panel | *AR* (NM_000044.6) | c.2659A>G[2]; p.(M887V) | [1] |
| 46,XY DSD Hypospadias | c.251G>A[1] ; p.(R84H) | Panel | *ZFPM2* (NM_012082.4) | c.2107A>C[1]; p.(M703L) | [1] |
| 46,XY DSD CGD | c.630-636del[1]; p.(Y211Tfs*83) | WES | *TBX2* (NM_005994.4) | c.641A>G[1]; p.(N214S) | [2] |
| 46,XY GD | c.937C>T[1] ; p.(R313C) | Panel | *MAP3K1* (NM_005921.2) | c.710A>G[1]; p.(Q237R) | [3, 4] |
| 46,XY DSD Micropenis, hypospadias | c.104G>T[1] ; p.(G35V) | Panel | *BMP2* (NM_001200.4) | c.316G>A[1]; p.(A106T) | [4, 5] |
| 46,XY DSD Vulvar dysplasia, no inguinal gonad | c.634G>A[1]; p.(G212S) | Panel | *SRY* (NM_003140.3) | c.227G>T[2] ; p.(R76L) | [5] |
| | | | *FGF10* (NM_004465.2) | c.610A>G[1]; p.(M204V) | [5] |
| 46,XY DSD Micropenis, hypospadias, cryptorchidism | c.86C>A[1]; p.(T29K) | Panel | *AR* (NM_000044.6) | c.884T>C[1] ; p.(L295P) | [5] |
| | | | *MYH6* (NM_002471.4) | c.4231G>A[2] ; p.(A1411T) | [5] |
| 46,XY DSD, Micropenis, hypospadias, unilateral cryptorchidism | c.1109G>A[1] ; p.(C370Y) | Panel | *SOX3* (NM_005634.3) | c.157G>C[1]; p.(V53L) | [5] |
| 46,XY DSD Micropenis, hypospadias, cryptorchidism, gonadal dysplasia | c.1289G>T[1]; p.(S430I) | Panel | *HSD17B3* (NM_000197.2) | c.179T>C[1]; p.(I60T) | [5] |
| | | | *WT1* (NM_001198551.2) | c.19A>C[1]; p.(T7P) | [5] |
| 46,XY DSD Micropenis, hypospadias, cryptorchidism | c.849C>A[1]; p.(C283*) | Panel | *CST9* (NM_001008693.3) | c.259C>T[1]; p.(R87*) | [5] |

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| 46,XY DSD, Micropenis, hypospadias, unilateral cryptorchidism | c.1100A>G[1]; p.(E367G) | Panel | *CST9* (NM_001008693.3) | c.259C>T[1]; p.(R87*) | [5] |
| 46,XY DSD Micropenis, hypospadias | c.265del[1]; p.(R89fs*105) | Panel | *EGF* (NM_001178131.3) | c.2995G>A[1]; p.(V999M) | [5] |
| 46,XY DSD | c.1171A>T[1]; p.(K391*) | Panel | *ATRX* (NM_000489.6) | c.2595C>G[1]; p.(H865Q) | [6] |
| | | | *AMH* (NM_000479.5) | c.-2C>T[1] | [6] |
| 46,XY DSD GD | c.251G>A[1]; p.(R84H) | Panel | *ZFPM2* (NM_012082.4) | c.2107A>C[1]; p.(M703L) | [7, 8] |
| 46,XY DSD Hypospadias | c.1114_1116del[1]; p.(K372del) | Panel | *SRD5A2* (NM_000348.4) | c.680G>A[1]; p.(R227Q) | [7, 9] |
| 46,XY DSD, Ambiguous genitalia | c.70C>T[1]; p.(H24Y) | WES | *AKR1C3* (NM_003739.6) | c.548A>G[1]; p.(L183R) | [10] |
| | | | *DOCK8* (NM_203447.4) | c.1139T>C[1]; p.(l380T) | [10] |
| | | | *FSHR* (NM_000145.4) | c.1532A>G[1]; p.(Y511C) | [10] |
| | | | *NCOR1* (NM_006311.3) | c.6754C>T[1]; p.(H2252Y) & c.6544G>A[1]; p.(A2182T) | [10] |
| | | | *POR* (NM_001382662.3) | c.1264T>G[1]; p.(W422G) | [10] |
| 46,XY DSD Bilateral inguinal hernia | c.70delC[1]; p.(H24Tfs*51) | WES | *CACNG4* (NM_014405.4) | c.715C>T[1]; p.(R239W) | [10, 11] |
| | | | *FBLN2* (NM_001004019.2) | c.385G>A[1]; p.(D129N) | [10] |
| | | | *NAV1* (NM_020443.5) | c.2947C>A[1]; p.(P983T) | [10] |
| | | | *SMAD6* (NM_005585.5) | c.1455dupC[1]; p.(C486Lfs*79) | [10] |
| | | | *SRA1* (NM_001035235.3) | c.94C>G[1]; p.(Q32E) | [10] |
| | | | *ZDHHC11* (NM_024786.3) | c.676G>A[1]; p.(V226M) | [10] |
| | | | *ZFPM2* (NM_012082.4) | c.302G>A[1]; p.(G101E) | [10] |
| 46,XY DSD | c.614_615insC[1]; p.(Q206Tfs*20) | WES | *CHD7* (NM_017780.4) | c.7579A>C[1]; p.(M2527L) | [10, 11] |

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| Female external genitalia | | | *DENND1A* (NM_020946.2) | c.2351C>A[1]; p.(A784D) | [10] |
| | | | *GDNF* (NM_001190468.1) | c.328C>T[1]; p.(R110W) | [10] |
| | | | *GLI2* (NM_001371271.1) | c.4333C>T[1]; p.(L1445F) | [10] |
| | | | *SOX30* (NM_178424.2) | c.455C>T[1] ; p.(Pro152Leu) | [10] |
| 46,XY DSD Hypospadias, cryptorchidism | c.58G>C[1]; p.(V20L) | WES | *INHA* (NM_002191.4) | c.675T>G[1]; p.(S225R) | [10, 11] |
| 46,XY DSD | c.88T>A[1]; p.(C30S) | WES | *STAR* (NM_000349.3) | c.361C>T[1]; p.(R121W) | [12] |
| 46,XY DSD | c.614_615insC[1]; p.(Q206Tfs*20) | WES | *AMH* (NM_000479.5) | c.428C>T[1]; p.(T143l) | [11, 12] |
| 46,XY DSD | c.1183_1185delGAG[1]; p.(E395del) | WES | *ZFPM2* (NM_012082.4) | c.1632G>A[1]; p.(M544l) | [12, 13] |
| 46,XY DSD PGD | c.288_304del[1]; p.(M98Gfs*45) | WES | *DHX37* (NM_032656.4) | c.1399C>G[1]; p.(L467V) | [14] |
| 46,XY DSD PGD | c.11C>A[1]; p.(S4*) | WES | *DHX37* (NM_032656.4) | c.2995G>A[1]; p.(V999M) | [14] |
| 46,XY DSD (CAIS) | Deletion of exon 7. (~32 kb affecting chr9:127213317-127245328)[1]. | CNV Analysis | *AR* | Duplication of exon 2 of the X-linked *AR* gene | [15] |
| | | CNV analysis | *FSHR* | Deletion of exons 2–10. (~105 kb region affecting chr2:49189845-49295452)[3] | [15] |
| 46,XY DSD Micropenis | c.-762C>T[1] | WES | *SRA1* (NM_001035235.4) | c.478C>T[1]; p.(R160W) | [16] |
| 46,XY PGD | c.-413G>A[1] and c.-207C>A[1] | WES | *WDR11* (NM_018117.12) | c.3033_3036del[1]; p.(D1011Efs*21) | [16] |
| | | | *WWOX* (NM_016373.4) | c.1088C>A[1]; p.(A363D) | [16] |
| 46,XY DSD Ambiguous genitalia, GD | c.937C>T[1]; p.(R313C) | WES | *MAP3K1* (NM_005921.2) | c.710A>G[1]; p.(E237R) | [17] |
| 46,XY DSD Hypospadias | c.929A>C[1]; p.(H310P) | WES | *MAP3K1* (NM_005921.2) | c.2282T>C[1]; p. (I761T) | [18] |
| 46,XY DSD Hypospadias | c.991-1G>C[1]; p.(G330_S331del) | WES | *OTX2* (NM_021728.4) | c.425C>G[1]; p.(P134R)/p.(P142R) | [19] |

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| 46,XDY DSD Hypospadias | c.991-1G>C[1]; p.(G330_S331del) | WES | *PROP1* (NM_006261.5) | c.301_302delAG[1]; p.(L102CfsTer8) | [19] |
| 46,XY Mild DSD | c.437G>C[1]; p.(G146A) | WES | *FGFR3* (NM_000142.5) | c.1633_1634del[1]; p.(C545Hfs*17) | [20] |
| | | | *ADAMTS16* (NM_139056.4) | c.1822_1823del[1]; p.(H608*) | [20] |
| | | | *INSR* (NM_000208.4) | c.660_661del[1]; p.(P220Hfs*4) | [20] |
| 46,XY Severe DSD | c.437G>C[1]; p.(G146A) | WES | *GLI2* (NM_001371271.1) | c.3528G>T[1]; p.(Q1176H) | [20] |
| | | | *CHD7* (NM_017780.4) | c.1623C>A[1]; p.(H541Q) | [20] |
| | | | *MYO7A* (NM_000260.4) | c.2882G>A[1]; p.(G961A) | [20] |
| | | | *VDR* (NM_000376.3) | c.176C>T[1]; p.(T59I) | [20] |
| 46,XY Mild DSD | c.437G>C[1]; p.(G146A) | WES | *NRP1* (NM_003873.7) | c.182C>A[1]; p.(P61Q) | [20] |
| 46,XY Opposite sex DSD | c.437G>C[1]; p.(G146A) | WES | *LHCGR* (NM_000233.4) | c.757T>C[3]; p.(S253P) | [20] |
| 46,XX Opposite sex DSD | c.437G>C[3]; p.(G146A) | WES | *COL27A1* (NM_032888.4) | c.3715C>T[1]; p.(R1239W) | [20] |
| | | | *TYRO3* (NM_006293.4) | c.666_667insCACTGCCTGCAGCCCCCTTCAACATCACC[1]; p.(A223Hfs*21) | [20] |
| 46,XY Mild DSD | c.437G>C[1]; p.(G146A) | WES | *SOX8* (NM_014587.5) | c.676A>C[1]; p.(T226P) | [20] |
| 46,XY Severe DSD | c.437G>C[1]; p.(G146A) | WES | *POR* (NM_001395413.1) | c.1679C>T[1]; p.(T560M) | [20] |
| | | | *PKD1* (NM_001009944.3) | c.2624C>T[1]; p.(P875L) | [20] |
| | | | *SRCAP* (NM_006662.3) | c.7142G>A[1]; p.(R2381H) | [20] |
| | | | *SOX9* (NM_000346.4) | c.710dup[1]; p.(P238Tfs*14) | [20] |
| 46,XY Opposite sex DSD | c.437G>C[1]; p.(G146A) | WES | *AR* (NM_000044.6) | c.2323C>T[2]; p.(R775C) | [20] |

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| 46,XY Idiopathic oligozoospermia | c.1063G>A[1]; p.(V355M) | Panel | *USP9Y* (NM_004654.4) | c.3178G>A[2]; p.(A1060T) | [21] |
| 46,XX BPES and POI | c.578T>A[1]; p.(I193N) | Sanger sequencing | *LHX4* (NM_033343.4) | c.250C>T[1]; p.(R84C) | [22] |
| 46,XX DSD | c.486C>T[n/a]; p.(=) | Panel | *LHCGR* (NM_000233.4) | c.458+3A>G[n/a] | [6] |
| 46,XY DSD | c.77C>T[1]; p.(G26V) | Panel | *DHX37* (NM_032656.4) | c.1474G>C[1]; p.(A494P) | [23] |
| 46,XX POI | c.1233C>T[1]; p.(H410=) | Panel | *FSHR* (NM_000145.4) | c.1664C>T[1]; p.(T555I) | [24] |
| 46,XY DSD | c.634G>A[n/a]; p.(G212S) | Sanger sequencing | *SRY* (NM_003140.3) | c.227G>T[n/a]; p.(R76L) | [25] |
| | | | *FGF10* (NM_004465.2) | c.610A>G[n/a]; p.(M204V) | [25] |
| 46,XY DSD Micropenis | c.1223A>C[1]; p.(H408P) | WES | *MAP3K1* (NM_005921.2) | c.3418A>G[1]; p.(M1140V) | [26] |
| | | | *CTU2* (NM_001012759.3) | c.710C>T[1]; p.(A237V) | [26] |
| 47,XXY Opposite sex DSD | c.50G>T[1]; p.(G17V) | WES | *AMH* (NM_000479.5) | c.300C>T[1]; p.(F100=) | [27] |
| 47,XY Severe DSD | c.218G>C[1]; p.(C73S) | WES | *SRD5A2* (NM_000348.4) | c.265C>G[3]; p.(L89V) | [27] |
| 47,XY Severe DSD | c.219C>G[1]; p.(C73W) | WES | *SZT2* (NM_015284.4) | c.4039C>T[1]; p.(R1347C) | [27] |
| | | | *ALMS1* (NM_015120.4) | c.4207A>G[1]; p.(T403A) | [27] |
| | | | *BTD* (NM_000060.4) | c.1330G>C[1]; p.(D444H) | [27] |
| | | | *TREX1* (NM_033629.6) | c.206T>C[1]; p.(L69P) | [27] |
| | | | *PDHB* (NM_000925.4) | c.701-3C>T[1] | [27] |
| | | | *VCAN* (NM_004385.5) | c.1412C>T[1]; p.(T471M) | [27] |
| | | | *SYNE1* (NM_033071.5) | c.14732G>A[1]; p.(R4911H) | [27] |
| | | | *ARID1B* (NM_020732.3) | c.369_392dup[1]; p.(Q124_Q131dup) | [27] |

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| | | | *RELN* (NM_005045.4) | c.865A>G[1]; p.(N289D) | [27] |
| | | | *ARMC4* (NM_018076.5) | c.1386+5G>A[1] | [27] |
| | | | *DYNC2H1* (NM_001377.3) | c.4295T>C[1]; p.(I1432T) | [27] |
| | | | *HEPACAM* (NM_152722.5) | c.139G>A[1]; p.(V47M) | [27] |
| | | | *GALC* (NM_000153.4) | c.1685T>C[1]; p.(I562T) | [27] |
| | | | *OCA2* (NM_000275.3) | c.1025A>G[1]; p.(Y342C) | [27] |
| | | | *GAA* (NM_000152.5) | c.2065G>A[1]; p.(E689K) | [27] |
| | | | *SIK1* (NM_173354.5) | c.1784G>A[1]; p.(R595Q) | [27] |
| 46,XY Opposite sex DSD | c.680T>C[1]; p.(I227T) | WES | *POR* (NM_000941.3) | c.859G>C[1]; p.(A287P) | [27] |

DSD, disorders/differences of sex development; CGD, complete gonadal dysgenesis; WES, whole-exome sequencing; GD,gonadal dysgenesis; PGD, primary gonadal dysgenesis; CAIS, complete androgen insensitivity; CNV, Copy number variations; BPES: blepharoptosis–ptosis–epicanthus syndrome; POI: primary ovarian insufficiency.[1] Heterozygous variant [2] Hemizygous variant; [3] Homozygous variant; n/a: not available. *The clinical phenotype is indicated when available and according to the description in the corresponding publication.

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