Supplementary Material S1.

Summary of information found in the current published literature for the identified genes suggested contributing to a broad DSD phenotype in 8 individuals with variants in *MAMLD1*

Overall, the genes detected in our 8 studied patients with *MAMLD1* variants have been previously reported in humans with hypospadias, cryptorchidism, small penis, and other urogenital abnormalities. Also, some of them have been associated with specific syndromes (Table 2). The detailed information is summarized below.

- *ATF3* variants were present in patients with hypospadias (Beleza-Meireles et al., 2008; Kalfa et al., 2009; van der Zanden et al., 2012) and this gene is upregulated in prepuce tissue in patients with hypospadias (Wang et al., 2007).
- *BNC2* variants had been related to hypospadias (Baxter et al., 2015; Bhoj et al., 2011; Kon et al., 2015; van der Zanden et al., 2012) and to gonadal development (Jameson et al., 2012). In Bhoj *et al*, the patient also presented with partial anomalous pulmonary venous return (Bhoj et al., 2011).
- Some studies indicate that *CDH23* is an SRY- and SOX9-target (Li et al., 2014) and is overexpressed in male mice gonadal supporting cells (Jameson et al., 2012).
- *COL9A3* is related to male gonadal development (Beverdam and Koopman, 2006; Jameson et al., 2012; Nef et al., 2005).
- *CUL4B* variants were detected in a patient with abnormal genitourinary system (Retterer et al., 2015).
- *CYP1A1* has been related to hypospadias (van der Zanden et al., 2012).
- *FGF10* plays an important role in the morphogenesis of distal genital tubercle structures, like the glans penis (Grinspon and Rey, 2014; Rey et al., 2000) and is linked to increased risk of hypospadias in humans (Carmichael et al., 2013; Svechnikov et al., 2014; van der Zanden et al., 2012).
- *DAPK1* is overexpressed during mice female gonadal development (Jameson et al., 2012).
- An *EVC* mutation has been described in a patient with syndromic (Ellis-van Creveld syndrome) micropenis (D'Asdia et al., 2013; Ibarra-Ramirez et al., 2017) and has also been related to sex development in mice (Beverdam and Koopman, 2006; Jameson et al., 2012).
- *EYA1* is associated to hypospadias (Grinspon and Rey, 2014; Hwang et al., 2014) and one patient with variants presented urinary tract anomalies including hypospadias (Hwang et al., 2014).
- *FLNA* presents high genetic variability. It has been associated to different clinical phenotypes including aortic diseases and cardiopathies (Chen et al., 2018). Two 46,XY brothers were reported with hypospadias, cryptorchidism, testicular atrophy, vaginal duct and diminished nuclear androgen receptor (Carrera-García et al., 2017). It is overexpressed in mice female germ cells during sex development (Jameson et al., 2012).

- *EMX2* variants are present in patients with uterus didelphys (Liu et al., 2015) and in one 46,XY DSD in heterozygosis (Piard et al., 2014). *Emx2* mutant mice lack gonads and genital tracts (Li et al., 2014). *Emx2* expression is necessary for Wolffian and Müllerian duct development in mice (Grinspon and Rey, 2014; Rey et al., 2000), for sex determination (Biason-Lauber, 2010) as it is expressed in early coelomic epithelium in mice (Jakob and Lovell-Badge, 2011; Jameson et al., 2012), and required in the development of the bipotential gonad in mice (Eggers and Sinclair, 2012).
- *FRAS1* is associated to abnormalities in genitourinary system in Fraser syndrome 1 (Kornacki et al., 2017; Retterer et al., 2015).
- *FREM2* is related to Fraser syndrome 2, with congenital genitalia anomalies (De Bernardo et al., 2015) and overexpressed in supporting and stroma cells during mice female gonadal development (Jameson et al., 2012).
- *GLI2* has been associated to hypospadias increased risk (Carmichael et al., 2013), and is considered a growth factor in urogenital development. It participates in masculinization of external genitalia: outgrowth and patterning of external genitalia and urogenital sinus and in the inhibition of apoptosis in penile smooth muscle (Rey et al., 2000).
- *GLI3* has been associated with genitourinary anomalies, hypogonadotropic hypogonadism (Quaynor et al., 2016) and to increased risk of hypospadias (Carmichael et al., 2013). It has been reported to be related to abnormal early morphogenesis of genital primordia (Rey and Grinspon, 2011) and to male gonadal development (Windley and Wilhelm, 2016).
- *HSD3B2* encodes for the steroidogenic enzyme 3-beta-hydroxysteroid dehydrogenase type 2, which is well-known to participate in sex development (Baxter et al., 2015) (Baxter and Vilain, 2013) and steroid hormone synthesis (McCartin et al., 2000). Patients with pathogenic mutations in *HSD3B2* present 46,XY DSD (Codner et al., 2004; Eggers et al., 2016; Kon et al., 2015). Interestingly, although inheritance is mostly AR, some heterozygous patients with hypospadias had been reported (Codner et al., 2004).
- *GRID1* (van der Zanden et al., 2012) has been related to hypospadias.
- *HOXA13* has been associated to hypospadias and to early patterning stage of development (Beleza-Meireles et al., 2007; van der Zanden et al., 2012). It has also been reported in patients with Hand-foot-genital (HFG)/Guttmacher syndrome, which includes hypospadias (Innis et al., 2002), in a patient with HFG and small penis (Goodman et al., 2000) and in another patient with HFG, heart defects & facial anomalies (Jun et al., 2011). It plays a role as growth factor in the development of genital tubercle, accessory sex glands and Wolffian and Müllerian ducts (Grinspon and Rey, 2014; van der Zanden et al., 2012).

- No patients with *IGFBP2* variants have been reported to date. This gene is considered candidate gene in ovary development (Clement et al., 2007) and overexpressed in mice female gonadal development (Jameson et al., 2012; Munger et al., 2013).
- *IRX5* and *IRX6* have been associated to hypospadias in humans (Geller et al., 2014; Grinspon and Rey, 2014).
- *MAML1*, a MAMLD1-related gene, has not been related to DSD yet, but some patients with *MAML1* variants showed cardiomyopathy (left-ventricular outflow tract obstructions) (Preuss et al., 2016).
- *MAML2* (MAMLD1-related) has not been related to DSD to date.
- *MAML3* (MAMLD1-related) is overexpressed during mice female gonadal development (Jameson et al., 2012).
- *MYO7A* is considered SRY- and SOX9-target (Li et al., 2014) and overexpressed in mice male gonadal supporting cells during gonadal development (Jameson et al., 2012).
- *NOTCH1* activity is maintained by FGF10 and SHH to promote prostate growth (Grinspon and Rey, 2014) and it has been related to male gonadal development (Windley and Wilhelm, 2016).
- *NOTCH2* has been related to primary ovarian failure (Patiño et al., 2017) and mice male gonadal development (Jameson et al., 2012; Windley and Wilhelm, 2016).
- *NRP1* has been reported in a female patient with no uterus and absent Fallopian tubes, inguinal testes with calcifications and abnormal histology, deafness and impaired cognition (Baxter et al., 2015) and in another patient with truncus arteriosus, but no DSD (Shaheen et al., 2015). This gene interacts with *Sem3a* (hypogonadotropic hypogonadism and Kallmann syndrome) (Hanchate et al., 2012). It is overexpressed in mice developing gonadal cells (Jameson et al., 2012).
- *PIK3R3* is an SRY target (Li et al., 2014) and related to mice female gonadal development: overexpressed in mice female gonadal cells (Beverdam and Koopman, 2006; Jameson et al., 2012).
- *PPARGC1B* has been considered candidate gene for hypospadias (van der Zanden et al., 2012).
- *PROP1* has been related to human central causes of hypogonadism (combined pituitary hormone deficiency and hypogonadotropic hypogonadism) (Baxter et al., 2015; Baxter and Vilain, 2013; Eggers et al., 2016; Reynaud et al., 2005).
- *PTPN11* presented pathogenic variants in Noonan-syndrome patients with cryptorchidism (Tartaglia et al., 2002) and pulmonic stenosis (Lee et al., 2014; Tartaglia et al., 2002).
- Mutations in *RECQL4* have been detected in a patient with hypospadias and bilateral inguinal hernia (Rothmund-Thomson syndrome) (Kellermayer et al., 2005).
- *RET* deleterious mutations have been detected in syndromic patients with cryptorchidism (CAKUT syndrome) (Chatterjee et al., 2012). In addition, *RET* is overexpressed in germ cells during gonadal development (Jameson et al., 2012) and is a *SRY* target gene in mice (Li et al., 2014).

- *RIPK4* has been related to genital hypoplasia (Kalay et al., 2012; Mitchell et al., 2012), micropenis, hypoplastic scrotum and inguinal hernia (Kalay et al., 2012) in patients with Popliteal Pterygium/Bartsocas-Papas syndrome.
- *TGFBI* is related to gonadal development in both sexes (Beverdam and Koopman, 2006; Clement et al., 2007; Jameson et al., 2012).
- Little is known about *WNT9A*. It seems that it is overexpressed at early mice female gonadal development (Beverdam and Koopman, 2006; Nef et al., 2005).
- *WNT9B* variants have been found in Mayer-Rokitansky-Küster-Hauser syndrome (no uterus, no vagina) (Waschk et al., 2016), in one patient with congenital anomalies of the kidney and urinary tract (Nicolaou et al., 2016) and in another patient with bicornuate uterus (Waschk et al., 2016). WNT9B is secreted by Wolffian ducts to inhibit elongation of Müllerian ducts (Grinspon and Rey, 2014) and is believed to be involved in mesenchymal to epithelial transition in organogenesis of mammalian urogenital system (Carroll et al., 2005; Grinspon and Rey, 2014).
- Variants in *WDR11* have been detected in patients with 46,XY DSD (Fan et al., 2017), patients with hypospadias (Eggers et al., 2016; Fan et al., 2017), small testes (Fan et al., 2017) and with hypogonadotropic hypogonadism (Dong et al., 2016; Eggers et al., 2016).
- *ZBTB16* mutations have been reported in a syndromic patient (deletion 11q23) with cryptorchidism and micropenis (Fischer et al., 2008).

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