Appendix 2 KER-2828 ‘ Decrease, AR activation leads to hypospadias’ - Empirical evidence

Table 1 Empirical evidence for the KER – animal studies All animal studies included were judged as reliable without restriction or reliable with restriction in the evidence collection.

Flutamide Overall confidence: strong						
Species	**Exposure window**	**Measurement timepoint**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**	**Hypospadias frequency (% males)**	**Reference**
Rat	GD12-21	PD38	--	6.25	6.25 mg/kg/day: 100% 12.5 mg/kg/day: 100% 25 mg/kg/day: 100% 50 mg/kg/day: 100%	(McIntyre et al., 2001)
Mouse	GD12-18	Adult	*	300	100%	(Yu et al., 2020)
Rat	GD16-20	PD5	*	5	6/7 litters	(Pike et al., 2014)
Rat	Gestation	Postnatally	--	3	3 mg/kg/day: 50% 10 mg/kg/day: 100% 30 mg/kg/day: 100%	(Goto et al., 2004)
Rat	GD15-17	PD90	*	100	Not reported	(Zakaria et al., 2000)
Rat	Gestation	Adult	*	150 mg/L	60%	(Källén, 2004)
Rat	GD13-20	PD25 or after	*	20	56.9%	(Kita et al., 2016)
DBP Overall confidence: strong						
Species	**Exposure window**	**Measurement timepoint**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**	**Hypospadias frequency**	**Reference**
Rat	GD3-PD20	From PD38	*	250	250 mg/kg/day: 3.1% 500 mg/kg/day: 21% 750 mg/kg/day: 43%	(Mylchreest et al., 1998)
Rat	GD12-21	Adult	100	500	9%	(Mylchreest et al., 2000)
Rat	GD12-21	Adult	*	500	33.3%	(Saillenfait et al., 2008)
Rat	GD12-21	Adult	100	250	250 mg/kg/day: 1/8 litters 500 mg/kg/day: 40.4%	(Mylchreest et al., 1999)
Rat	GD16-19 GD14-PD3	Adult	500 *	* 500	0 6.2%	(C. J. Wolf et al., 1999)
Rat	GD16-19 GD20-22	Adult	*	750	52% 4.2%	(van den Driesche et al., 2017)
Rat	GD11-15	PD1	*	850	10.9%	(Zhu et al., 2016)
Rat	GD14-18	PD7	*	750	42.9%	(Jiang et al., 2016)
Rat	GD14-18	10 weeks	*	800	Not reported	(Zhou et al., 2022)
Rat	GD14-18	PD10	*	750	Not reported	(Zhou X et al., 2022)
Rat	GD14-18	PD7	*	750	42.3 %	(Zhao et al., 2018)

Rat	GD14-18	PD7	250	500	500 mg/kg/day: 6.8% 750 mg/kg/day: 41.3%	(Jiang et al., 2007)
Rat	GD3-PD20	From PD38	*	500	21%	(Mylchreest et al., 1998)
Rat	GD16-19	Adult	*	750	23%	(van den Driesche et al., 2020)
Rat	GD14-18	PD7	*	750	43.6%	(S. Liu et al., 2012)
Rat	GD14-22	Adult	100	500	31%	(Drake et al., 2009)
Vinclozolin Overall confidence: strong						
Rat	Premating, gestation and through to weaning	Postweaning and adult	20	100	100%	(S. Schneider et al., 2011)
Rat	GD14-PD3	Pubertal and adult	25	50	50 mg/kg/day (adult): 45% 100 mg/kg/day (adult): 100%	(Ostby J et al., 1999)
Mouse	GD12-18	3 and 7 weeks	*	400	100%	(Yu et al., 2021)
Rat	GD16-17 GD18-19 GD14-19	Adult	--	400 400 200	400 mg/kg/day: 41.7% 400 mg/kg/day: 11.1% 200 mg/kg/day: 97.62% malformations[a] 400 mg/kg/day: 91.86% malformations[a]	(C. Wolf et al., 2000)
Rat	GD6-15	Adult	4	100	One case	(W. Schneider et al., 2013)
Rat	GD7-PD16	PD47	24.5	95.9	Increased likelihood for hypospadias	(Christiansen et al., 2008)
DEHP Overall confidence: strong						
Rat	GD12-21	Adult	--	500	500 mg/kg/day: 14.8% 600 mg/kg/day: 37%	(Saillenfait et al., 2009)
Rat	GD14-PD3	Adult	*	750	82%	(Gray et al., 2000)
Rat	GD14-PD3	Adult	*	750	67 ±14%	(C. J. Wolf et al., 1999)
Rat	GD13-20	PD25	*	750	1/38	(Kita et al., 2016)
Procymidone Overall confidence: strong						
Rat	GD14-PD3	Adult	*	100	40%	(C. J. Wolf et al., 1999)
Rat	GD7-PD16	PD16-50	12.5	50	24%	(Hass et al., 2012)
Finasteride Overall confidence: strong						
Rat	GD15-21 GD16-17	Adult Adult	0.03 *	3 20	29% 39%	(Clark et al., 1993)

*Only one dose tested; -- all doses had effects; [a]Genital malformations, including hypospadias

Table 2 Supporting evidence for the KER – human studies. The table lists human studies reporting hypospadias in association with an upstream defect in AR activity, grouped according to the precise effect, and how it was diagnosed (mutation, *in vitro* activity, or blood hormone and metabolite profile). SRD5A2: 5α-reductase 2; HSD17B3: 17β-hydroxysteroid dehydrogenase 3; HSD3B2: 3β-hydroxysteroid dehydrogenase 2; CYP17A1: 17α-hydroxylase.

Effect on upstream KE	**References**
Effects on Androgen receptor	
AR mutations	(Ahmad et al., 2017; Albers et al., 1997; Batch et al., 1993; Boehmer et al., 2001; Chen, Wang, et al., 2021; Chu et al., 2002; Dougan et al., 2014; Evans et al., 1997; Fu et al., 2016; Galli-Tsinopoulou et al., 2018; Giwercman et al., 2002; H Klocker H et al., 1995; Hage et al., 2021; Hellmann et al., 2012; Hiort et al., 1994; Holterhus et al., 2000, 2005; Kalfa et al., 2013; Kaspar et al., 1993; Klocker et al., 1992; Koçyiğit et al., 2016; Kon et al., 2015; Kulshreshtha et al., 2009; Kumar et al., 2022; Lagarde et al., 2012; Lottrup et al., 2013; Lucas-Herald et al., 2016)
Extended CAG repeat length in *AR*	(Adamovic & Nordenskjöld, 2012; AS Nordenvall et al., 2016; Ogata et al., 2001; Parada-Bustamante et al., 2012)
Reduced AR activity (e.g. low receptor binding) in *in vitro* genital skin fibroblasts	(Amrhein et al., 1977; Bals-Pratsch et al., 1990; Choong et al., 1997; Gooren, 1989; Grino et al., 1989; Jukier et al., 1984; Keenan et al., 1984; Mark et al., 1983; Migeon et al., 2002; Schweikert et al., 1989; Warne GL et al., 1983)
Effects on 5α-reductase activity	
SRD5A2 mutations	(Albers et al., 1997; Alswailem et al., 2019; Bahceci et al., 2005; Baldinotti et al., 2008; Chan et al., 2015; Chen, Wang, et al., 2021; Cheng et al., 2019; Di Marco et al., 2013; Eunice et al., 2008; Fan et al., 2020; Fu et al., 2016; Kon et al., 2015; Q. Liu et al., 2022; Maimoun, Philibert, Bouchard, et al., 2011; Maimoun, Philibert, Cammas, et al., 2011; Mendonca et al., 1996; Nagaraja et al., 2010; Nicoletti et al., 2005; Rahimi et al., 2017; Sahu et al., 2009; Sato et al., 2022; Shabir et al., 2012, 2013, 2015; Silver & Russell, 1999; Sinnecker et al., 1996; Vilchis et al., 2008; Wan et al., 2013; Wang et al., 2004; Zhang et al., 2019)
SRD5A2 deficiency, diagnosed by T/DHT-ratio and/or reduced *in vitro* 5α-reductase activity in genital skin fibroblasts	(Akgun et al., 1986; Al-Attia, 1997; Bartsch et al., 1987; Boehmer et al., 2001; Bose et al., 2022; Das et al., 2020; Imperato-McGinley et al., 1991; Q. Liu et al., 2022)
Effects on upstream steroidogenesis enzymes	
HSD17B3 mutations	(Al-Sinani et al., 2015; Galli-Tsinopoulou et al., 2018; Lee et al., 2007; Luna et al., 2021; Mendonca et al., 2000; Neocleous et al., 2012)
HSD3B2 mutations	(Chen, Huang, et al., 2021; Codner et al., 2004; Donadille et al., 2018; Kon et al., 2015; Rabbani et al., 2012)
CYP17A1 mutation	(Sherbet et al., 2003)
HSD17B3 deficiency, diagnosed by hormone and metabolite profile	(Aaronson et al., 1997; Imperato-McGinley et al., 1979)
HSD3B2 deficiency, diagnosed by hormone and metabolite profile	(Cara et al., 1985; Mendonca et al., 1987; Pang et al., 1983; Perrone et al., 1985)
CYP17A1 deficiency, diagnosed by hormone and metabolite profile	(Aaronson et al., 1997; Ammini et al., 1997; Dean et al., 1984; Kaufman et al., 1983; New, 1970)
Other upstream effects on low testosterone	
Low testosterone due to gonadal dysgenesis or hypogonadism	(Cameron et al., 1997; Hamin et al., 2012; Harasymczuk et al., 2011; Hirose et al., 2007; Jones et al., 1970; Wang et al., 2017, 2022)
Low basal testosterone or low testosterone response to hCG stimulation. Idiopathic or rare mutations.	(Ahmed et al., 2010; Allen & Griffin, 1984; Arsklan Ates et al., 2022; Blanc et al., 2011; Misrahi et al., 1997; Moriya et al., 2010; Yeste et al., 2022)

References

Aaronson, I., Cakmak, M., & Key, L. (1997). Defects of the testosterone biosynthetic pathway in boys with hypospadias. *The Journal of Urology*, *157*(5), 1884–1888.

Adamovic, T., & Nordenskjöld, A. (2012). The CAG repeat polymorphism in the androgen receptor gene modifies the risk for hypospadias in Caucasians. *BMC Medical Genetics*, *13*, 109. https://doi.org/10.1186/1471-2350-13-109

Ahmad, Z., Xing, C., Panach, K., Kittler, R., McPhaulJ, M., & WilsonD, J. (2017). Identification of the Underlying Androgen Receptor Defect in the Dallas Reifenstein Family. *Journal of the Endocrine Society*, *1*(7), 836–842. https://doi.org/10.1210/js.2017-00124

Ahmed, S., Keir, L., McNeilly, J., Galloway, P., O'Toole, S., & Wallace, A. (2010). The concordance between serum anti-Mullerian hormone and testosterone concentrations depends on duration of hCG stimulation in boys undergoing investigation of gonadal function. *Clinical Endocrinology*, *72*(6), 814–819. https://doi.org/10.1111/j.1365-2265.2009.03724.x

Akgun, S., Ertel, N., Imperato-McGinley, J., Sayli, B., & C Shackleton. (1986). Familial male pseudohermaphroditism due to 5-alpha-reductase deficiency in a Turkish village. *The American Journal of Medicine*, *81*(2), 267–274. https://doi.org/10.1016/0002-9343(86)90262-7

Al-Attia, H. (1997). Male pseudohermaphroditism due to 5 alpha-reductase-2 deficiency in an Arab kindred. *POSTGRADUATE MEDICAL JOURNAL*, *73*(866), 802–807. https://doi.org/10.1136/pgmj.73.866.802

Albers, N., Ulrichs, C., Glüer, S., Hiort, O., Sinnecker, G., H, M., & Brodehl, J. (1997). Etiologic classification of severe hypospadias: Implications for prognosis and management. *The Journal of Pediatrics*, *131*(3), 386–392. https://doi.org/10.1016/s0022-3476(97)80063-7

Allen, T., & Griffin, J. (1984). Endocrine studies in patients with advanced hypospadias. *The Journal of Urology*, *131*(2), 310–314. https://doi.org/10.1016/s0022-5347(17)50360-2

Al-Sinani, A., Mula-Abed, W., Al-Kindi, M., Al-Kusaibi, G., Al-Azkawi, H., & Nahavandi, N. (2015). A Novel Mutation Causing 17-β-Hydroxysteroid Dehydrogenase Type 3 Deficiency in an Omani Child: First Case Report and Review of Literature. *Oman Medical Journal*, *30*(2), 129–134. https://doi.org/10.5001/omj.2015.27

Alswailem, M., Alzahrani, O., Alghofaili, L., Qasem, E., Almohanaa, M., Alsagheir, A., Abbas, B. B., Attia, N., Shaikh, A. A., & Alzahrani, A. (2019). Molecular genetics and phenotype/genotype correlation of 5-α reductase deficiency in a highly consanguineous population. *Endocrine*, *63*(2), 361–368. https://doi.org/10.1007/s12020-018-1767-1

Ammini, A., Sharma, D., Gupta, R., Mohapatra, I., Kucheria, K., Kriplani, A., Takkar, D., Mitra, D., & Vijayaraghavan, M. (1997). Familial male pseudohermaphroditism. *Indian Journal of Pediatrics*, *64*(3), 419–423. https://doi.org/10.1007/BF02845218

Amrhein, J., Klingensmith, G., Walsh, P., McKusick, V., & Migeon, C. (1977). Partial androgen insensitivity: The Reifenstein syndrome revisited. *The New England Journal of Medicine*, *297*(7), 350–356. https://doi.org/10.1056/NEJM197708182970703

Arsklan Ates, E., Eltan, M., Sahin, B., Gurpinar Tosun, B., Seven Menevse, T., Geckinli, B., Greenfield, A., Turan, S., Bereket, A., & Guran, T. (2022). Homozygosity for a novel INHA mutation in two male siblings with hypospadias, primary hypogonadism, and high-normal testicular volume. *European Journal of Endocrinology*, *186*(5), K25–K31. https://doi.org/10.1530/EJE-21-1230

AS Nordenvall, Paucar, M., Almqvist, C., Nordenström, A., Frisén, L., & Nordenskjöld, A. (2016). Hypospadias as a novel feature in spinal bulbar muscle atrophy. *Journal of Neurology*, *263*(4), 703–706. https://doi.org/10.1007/s00415-016-8038-y

Bahceci, M., Ersay, A., Tuzcu, A., Hiort, O., Richter-Unruh, A., & Gokalp, D. (2005). A novel missense mutation of 5-alpha reductase type 2 gene (SRD5A2) leads to severe male

pseudohermaphroditism in a Turkish family. *Urology*, *66*(2), 407–410. https://doi.org/10.1016/j.urology.2005.02.021

Baldinotti, F., Majore, S., Fogli, A., Marrocco, G., Ghirri, P., Vuerich, M., Tumini, S., Boscherini, B., Vetri, M., Scommegna, S., Rinaldi, R., Simi, P., & Grammatico, P. (2008). Molecular characterization of 6 unrelated Italian patients with 5alpha-reductase type 2 deficiency. *Journal of Andrology*, *29*(1), 20–28. https://doi.org/10.2164/jandrol.107.002592

Bals-Pratsch, M., Schweikert, H., & Nieschlag, E. (1990). Androgen receptor disorder in three brothers with bifid prepenile scrotum and hypospadias. *Acta Endocrinologica*, *123*(3), 271–276. https://doi.org/10.1530/acta.0.1230271

Bartsch, G., Decristoforo, A., & Schweikert, U. (1987). Pseudovaginal perineoscrotal hypospadias. Clinical, endocrinological and biochemical characterization of a patient. *European Urology*, *13*(6), 386–389.

Batch, J., Evans, B., Hughes, I., & Patterson, M. (1993). Mutations of the androgen receptor gene identified in perineal hypospadias. *Journal of Medical Genetics*, *30*(3), 198–201. https://doi.org/10.1136/jmg.30.3.198

Blanc, T., Ayedi, A., El-Ghoneimi, A., Abdoul, H., Aigrain, Y., Paris, F., Sultan, C., Carel, J., & Léger, J. (2011). Testicular function and physical outcome in young adult males diagnosed with idiopathic 46 XY disorders of sex development during childhood. *European Journal of Endocrinology*, *165*(6), 907–915. https://doi.org/10.1530/EJE-11-0588

Boehmer, A., Nijman, R., Lammers, B., ConinckJ, S. de, Hemel, J. V., Themmen, A., Mureau, M., de Jong, F., Brinkmann, A., Niermeijer, M., & Drop, S. (2001). Etiological studies of severe or familial hypospadias. *The Journal of Urology*, *165*(4), 1246–1254.

Bose, S., Das, K., George, B., Raman, V., Shubha, A., Mahadevappa, K., Kumar, P., Bantwal, G., Ayyar, V., & Deb, M. (2022). 46 XY disorder of sex development (DSD) due to 5 alpha (SRD5A2) deficiency—Experience from a multidisciplinary Pediatric Gender Clinic. *Journal of Pediatric Urology*, *18*(4), 492.e1-492.e8. https://doi.org/10.1016/j.jpurol.2022.05.011

Cameron, F., Montalto, J., Byrt, E., Sinclair, A., & Warne, G. (1997). Gonadal dysgenesis: Associations between clinical features and sex of rearing. *ENDOCRINE JOURNAL*, *44*(1), 95–104. https://doi.org/10.1507/endocrj.44.95

Cara, J., Jr Moshang, T., Bongiovanni, A., & Marx, B. (1985). Elevated 17-hydroxyprogesterone and testosterone in a newborn with 3-beta-hydroxysteroid dehydrogenase deficiency. *The New England Journal of Medicine*, *313*(10), 618–621. https://doi.org/10.1056/NEJM198509053131007

Chan, A., But, W., Lee, C., Lam, Y., Ng, K., Loung, P., Lam, A., Cheng, C., Shek, C., Wong, W., Wong, K., Wong, M., & Tse, W. (2015). Aetiological bases of 46,XY disorders of sex development in the Hong Kong Chinese population. *Hong Kong Medical Journal = Xianggang Yi Xue Za Zhi*, *21*(6), 499–510. https://doi.org/10.12809/hkmj144402

Chen, L., Huang, H., Zhang, H., Zhu, G., & Zhu, M. (2021). Three cases of 3β-hydroxysteroid dehydrogenase deficiency: Clinical analysis. *Advances in Clinical and Experimental Medicine : Official Organ Wroclaw Medical University*, *30*(3), 289–299. https://doi.org/10.17219/acem/131220

Chen, L., Wang, J., Lu, W., Xiao, Y., Ni, J., Wang, W., Ma, X., & Dong, Z. (2021). Characterization With Gene Mutations in Han Chinese Patients With Hypospadias and Function Analysis of a Novel AR Genevariant. *Frontiers in Genetics*, *12*, 673732. https://doi.org/10.3389/fgene.2021.673732

Cheng, T., Wang, H., Han, B., Zhu, H., Yao, H., Zhao, S., Zhu, W., Zhai, H., Chen, F., Song, H., Cheng, K., Liu, Y., & Qiao, J. (2019). Identification of three novel SRD5A2 mutations in Chinese patients with 5α-reductase 2 deficiency. *Asian Journal of Andrology*, *21*(6), 577–581. https://doi.org/10.4103/aja.aja_113_18

Choong, C., Sturm, M., Strophair, J., McCulloch, R., & Hurley, D. (1997). Reduced expression and normal nucleotide sequence of androgen receptor gene coding and promoter regions in a family with partial androgen insensitivity syndrome. *Clinical Endocrinology*, *46*(3), 281–288. https://doi.org/10.1046/j.1365-2265.1997.1250941.x

Christiansen, S., Scholze, M., Axelstad, M., Boberg, J., Kortenkamp, A., & Hass, U. (2008). Combined exposure to anti-androgens causes markedly increased frequencies of hypospadias in the rat. *International Journal of Andrology*, *31*(2), 241–248. https://doi.org/10.1111/j.1365-2605.2008.00866.x

Chu, J., Zhang, R., Zhao, Z., Zou, W., Han, Y., Qi, Q., Zhang, H., Wang, J., Tao, S., Liu, X., & Luo, Z. (2002). Male fertility is compatible with an Arg(840)Cys substitution in the AR in a large Chinese family affected with divergent phenotypes of AR insensitivity syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *87*(1), 347–351. https://doi.org/10.1210/jcem.87.1.8167

Clark, R., Anderson, C., Prahalada, S., Robertson, R., Lochry, E., Leonard, Y., Stevens, J., & Hoberman, A. (1993). Critical developmental periods for effects on male rat genitalia induced by finasteride, a 5 alpha-reductase inhibitor. *Toxicology and Applied Pharmacology*, *119*(1), 34–40. https://doi.org/10.1006/taap.1993.1041

Codner, E., Okuma, C., Iñiguez, G., Boric, M., Avila, A., Johnson, M., & Cassorla, F. (2004). Molecular study of the 3 beta-hydroxysteroid dehydrogenase gene type II in patients with hypospadias. *The Journal of Clinical Endocrinology and Metabolism*, *89*(2), 957–964. https://doi.org/10.1210/jc.2002-020873

Das, S., Saikia, U., Saikia, K., Sarma, D., Choudhury, B., Bhuyan, A., Baro, S., Das, D., & S, A. (2020). "Spectrum of 46 XY Disorders of Sex Development": A Hospital-based Cross-sectional Study. *Indian Journal of Endocrinology and Metabolism*, *24*(4), 360–365. https://doi.org/10.4103/ijem.IJEM_98_20

Dean, H., Shackleton, C., & Winter, J. (1984). Diagnosis and natural history of 17-hydroxylase deficiency in a newborn male. *The Journal of Clinical Endocrinology and Metabolism*, *59*(3), 513–520. https://doi.org/10.1210/jcem-59-3-513

Di Marco, C., Bulotta, A., Varetti, C., Dosa, L., Michelucci, A., Baldinotti, F., Meucci, D., Castagnini, C., Lo Rizzo, C., Di Maggi, G., Simi, P., Mari, F., Bertelloni, S., Renieri, A., & Messina, M. (2013). Ambiguous external genitalia due to defect of 5-α-reductase in seven Iraqi patients: Prevalence of a novel mutation. *Gene*, *526*(2), 490–493. https://doi.org/10.1016/j.gene.2013.04.070

Donadille, B., Houang, M., Netchine, I., Siffroi, J., & Christin-Maitre, S. (2018). Human 3beta-hydroxysteroid dehydrogenase deficiency associated with normal spermatic numeration despite a severe enzyme deficit. *Endocrine Connections*, *7*(3), 395–402. https://doi.org/10.1530/EC-17-0306

Dougan, G., Uli, N., & Shulman, D. (2014). Progressive central puberty in a toddler with partial androgen insensitivity. *The Journal of Pediatrics*, *164*(3), 655–657. https://doi.org/10.1016/j.jpeds.2013.11.020

Drake, A., van den Driesche, S., Scott, H., Hutchison, G., Seckl, J., & Sharpe, R. (2009). Glucocorticoids amplify dibutyl phthalate-induced disruption of testosterone production and male reproductive development. *Endocrinology*, *150*(11), 5055–5064. https://doi.org/10.1210/en.2009-0700

Eunice, M., Philibert, P., Kulshreshtha, B., Audran, F., Paris, F., Khurana, M., Pulikkanath, P., Kucheria, K., Sultan, C., & Ammini, A. (2008). Molecular diagnosis of 5alpha-reductase-2 gene mutation in two Indian families with male pseudohermaphroditism. *Asian Journal of Andrology*, *10*(5), 815–818. https://doi.org/10.1111/j.1745-7262.2008.00350.x

Evans, B., Hughes, I., Bevan, C., Patterson, M., & Gregory, J. (1997). Phenotypic diversity in siblings with partial androgen insensitivity syndrome. *Archives of Disease in Childhood*, *76*(6), 529–531. https://doi.org/10.1136/adc.76.6.529

Fan, L., Song, Y., Polak, M., Li, L., Ren, X., Zhang, B., Wu, D., & Gong, C. (2020). Clinical characteristics and genotype-phenotype correlations of 130 Chinese children in a high-homogeneity single-center cohort with 5α-reductase 2 deficiency. *Molecular Genetics & Genomic Medicine*, *8*(10), e1431. https://doi.org/10.1002/mgg3.1431

Fu, X., Zhang, W., & Qu, X. (2016). Correlation of androgen receptor and SRD5A2 gene mutations with pediatric hypospadias in 46, XY DSD children. *Genetics and Molecular Research : GMR*, *15*(1), 15018232. https://doi.org/10.4238/gmr.15018232

Galli-Tsinopoulou, A., Serbis, A., KotanidouP, E., Litou, E., Dokousli, V., Mouzaki, K., Fanis, P., Neocleous, V., & Skordis, N. (2018). 46,XY Disorder of Sex Development due to 17-Beta Hydroxysteroid Dehydrogenase Type 3 Deficiency in an Infant of Greek Origin. *Journal of Clinical Research in Pediatric Endocrinology*, *10*(1), 74–78. https://doi.org/10.4274/jcrpe.4829

Giwercman, Y., Nordenskjöld, A., Ritzén, E., Nilsson, K., Ivarsson, S., Grandell, U., & Wedell, A. (2002). An androgen receptor gene mutation (E653K) in a family with congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency as well as in partial androgen insensitivity. *The Journal of Clinical Endocrinology and Metabolism*, *87*(6), 2623–2628. https://doi.org/10.1210/jcem.87.6.8518

Gooren, L. (1989). Improvement of spermatogenesis after treatment with the antiestrogen tamoxifen in a man with the incomplete androgen insensitivity syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *68*(6), 1207–1210. https://doi.org/10.1210/jcem-68-6-1207

Goto, K., Koizumi, K., Takaori, H., Fujii, Y., Furuyama, Y., Saika, O., Suzuki, H., Saito, K., & Suzuki, K. (2004). Effects of flutamide on sex maturation and behavior of offspring born to female rats treated during late pregnancy. *The Journal of Toxicological Sciences*, *29*(5), 517–534. https://doi.org/10.2131/jts.29.517

Gray, L. J., Ostby, J., Furr, J., Price, M., Veeramachaneni, D., & Parks, L. (2000). Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicological Sciences : An Official Journal of the Society of Toxicology*, *58*(2), 350–365. https://doi.org/10.1093/toxsci/58.2.350

Grino, P., Isidro-Gutierrez, R., Griffin, J., & Wilson, J. (1989). Androgen resistance associated with a qualitative abnormality of the androgen receptor and responsive to high dose androgen therapy. *The Journal of Clinical Endocrinology and Metabolism*, *68*(3), 578–584. https://doi.org/10.1210/jcem-68-3-578

H Klocker H, F Neuschmid-Kaspar F, Culig, Z., Cato, A., Hobisch, A., Eberle, J., Cronauer, M., Hittmair, A., Radmayr, C., Uberreiter, S., Glatzl, J., & Bartsch, G. (1995). Androgen receptor alterations in patients with disturbances in male sexual development and in prostatic carcinoma. *Urologia Internationalis*, *54*(1), 2–5. https://doi.org/10.1159/000282684

Hage, M., Drui, D., Francou, B., Mercier, S., Guiochon-Mantel, A., Belaisch-Allart, J., Péréon, Y., Cazabat, L., Mazancourt, P. D., & ML Raffin-Sanson. (2021). Structural analysis of the impact of a novel androgen receptor gene mutation in two adult patients with mild androgen insensitivity syndrome. *Andrologia*, *53*(1), e13865. https://doi.org/10.1111/and.13865

Hamin, J., Arkoncel, F., Lantion-Ang, F., & Sandoval, M. (2012). 46 XY gonadal dysgenesis in adulthood "pitfalls of late diagnosis". *BMJ Case Reports*, *2012*. https://doi.org/10.1136/bcr.12.2010.3626

Harasymczuk, J., Kaminiarczyk-Pyzalka, D., Krawczynski, M., Niedziela, M., Wasko, R., Czarnywojtek, A., & Jankowski, A. (2011). Transverse testicular ectopia with abnormal karyotype—A case report. *Neuro Endocrinology Letters*, *32*(4), 408–410.

Hass, U., Boberg, J., Christiansen, S., Jacobsen, P., Vinggaard, A., Taxvig, C., Poulsen, M., Herrmann, S., Jensen, B., Petersen, A., Clemmensen, L., & Axelstad, M. (2012). Adverse effects on sexual development in rat offspring after low dose exposure to a mixture of endocrine disrupting pesticides. *Reproductive Toxicology (Elmsford, N.Y.)*, *34*(2), 261–274. https://doi.org/10.1016/j.reprotox.2012.05.090

Hellmann, P., Christiansen, P., Johannsen, T., Main, K., Duno, M., & Juul, A. (2012). Male patients with partial androgen insensitivity syndrome: A longitudinal follow-up of growth, reproductive hormones and the development of gynaecomastia. *Archives of Disease in Childhood*, *97*(5), 403–409. https://doi.org/10.1136/archdischild-2011-300584

Hiort, O., Klauber, G., Cendron, M., Sinnecker, G., Keim, L., Schwinger, E., Wolfe, H., & Yandell, D. (1994). Molecular characterization of the androgen receptor gene in boys with hypospadias. *European Journal of Pediatrics*, *153*(5), 317–321. https://doi.org/10.1007/BF01956409

Hirose, Y., Sasa, M., Bando, Y., Hirose, T., Morimoto, T., Kurokawa, Y., Nagao, T., & Tangoku, A. (2007). Bilateral male breast cancer with male potential hypogonadism. *World Journal of Surgical Oncology*, *5*, 60. https://doi.org/10.1186/1477-7819-5-60

Holterhus, P., Sinnecker, G., & Hiort, O. (2000). Phenotypic diversity and testosterone-induced normalization of mutant L712F androgen receptor function in a kindred with androgen insensitivity. *The Journal of Clinical Endocrinology and Metabolism*, *85*(9), 3245–3250. https://doi.org/10.1210/jcem.85.9.6812

Holterhus, P., Werner, R., Struve, D., Hauffa, B., Schroeder, C., & Hiort, O. (2005). Mutations in the amino-terminal domain of the human androgen receptor may be associated with partial androgen insensitivity and impaired transactivation in vitro. *Experimental and Clinical Endocrinology & Diabetes : Official Journal, German Society of Endocrinology [and] German Diabetes Association*, *113*(8), 457–463. https://doi.org/10.1055/s-2005-865770

Imperato-McGinley, J., Miller, M., Wilson, J., Peterson, R., Shackleton, C., & Gajdusek, D. (1991). A cluster of male pseudohermaphrodites with 5 alpha-reductase deficiency in Papua New Guinea. *Clinical Endocrinology*, *34*(4), 293–298. https://doi.org/10.1111/j.1365-2265.1991.tb03769.x

Imperato-McGinley, J., Peterson, R., Stoller, R., & Goodwin, W. (1979). Male pseudohermaphroditism secondary to 17 beta-hydroxysteroid dehydrogenase deficiency:

Gender role change with puberty. *The Journal of Clinical Endocrinology and Metabolism*, *49*(3), 391–395. https://doi.org/10.1210/jcem-49-3-391

Jiang, J., Ma, L., Yuan, L., Wang, X., & Zhang, W. (2007). Study on developmental abnormalities in hypospadiac male rats induced by maternal exposure to di-n-butyl phthalate (DBP). *Toxicology*, *232*(3), 286–293. https://doi.org/10.1016/j.tox.2007.01.018

Jiang, J., Zhong, C., Zhu, Y., XuL, D., Wood, K., Sun, W., Li, E., Liu, Z., Zhao, W., Ruan, Y., & Xia, S. (2016). Prenatal exposure to di-n-butyl phthalate (DBP) differentially alters androgen cascade in undeformed versus hypospadiac male rat offspring. *Reproductive Toxicology (Elmsford, N.Y.)*, *61*, 75–81. https://doi.org/10.1016/j.reprotox.2016.02.016

Jones, J., Isaacs, H. J., Edelbroc, H., & Donnell, G. (1970). Reifenstein's syndrome: Hereditary familial hypogonadism with hypospadias and gynecomastia. *The Journal of Urology*, *104*(4), 608–611. https://doi.org/10.1016/s0022-5347(17)61793-2

Jukier, L., Kaufman, M., Pinsky, L., & Peterson, R. (1984). Partial androgen resistance associated with secondary 5 alpha-reductase deficiency: Identification of a novel qualitative androgen receptor defect and clinical implications. *The Journal of Clinical Endocrinology and Metabolism*, *59*(4), 679–688. https://doi.org/10.1210/jcem-59-4-679

Kalfa, N., Philibert, P., Werner, R., Audran, F., Bashamboo, A., Lehors, H., Haddad, M., Guys, J., Reynaud, R., Alessandrini, P., Wagner, K., Kurzenne, J., Bastiani, F., Bréaud, J., Valla, J., Lacombe, G., Orsini, M., Daures, J., Hiort, O., … Sultan, C. (2013). Minor hypospadias: The "tip of the iceberg" of the partial androgen insensitivity syndrome. *PloS One*, *8*(4), e61824. https://doi.org/10.1371/journal.pone.0061824

Källén, B. (2004). Valproic acid is known to cause hypospadias in man but does not reduce anogenital distance or causes hypospadias in rats. *Basic & Clinical Pharmacology & Toxicology*, *94*(1), 51–54. https://doi.org/10.1111/j.1742-7843.2004.pto_940109.x

Kaspar, F., Cato, A., Denninger, A., Eberle, J., Radmayr, C., Glatzl, J., Bartsch, G., & Klocker, H. (1993). Characterization of two point mutations in the androgen receptor gene of patients with perineoscrotal hypospadia. *The Journal of Steroid Biochemistry and Molecular Biology*, *47*(1), 127–135. https://doi.org/10.1016/0960-0760(93)90066-6

Kaufman, F., Costin, G., Goebelsmann, U., Stanczyk, F., & Zachmann, M. (1983). Male pseudohermaphroditism due to 17,20-desmolase deficiency. *The Journal of Clinical Endocrinology and Metabolism*, *57*(1), 32–36. https://doi.org/10.1210/jcem-57-1-32

Keenan, B., McNeel, R., & ET, G. (1984). Abnormality of intracellular 5 alpha-dihydrotestosterone binding in simple hypospadias: Studies on equilibrium steroid binding in sonicates of genital skin fibroblasts. *Pediatric Research*, *18*(2), 216–220. https://doi.org/10.1203/00006450-198402000-00020

Kita, D., Meyer, K., Venturelli, A., Adams, R., Machado, D., Morais, R., Swan, S., Gennings, C., & Martino-Andrade, A. (2016). Manipulation of pre and postnatal androgen environments and anogenital distance in rats. *TOXICOLOGY*, *368*, 152–161. https://doi.org/10.1016/j.tox.2016.08.021

Klocker, H., Kaspar, F., Eberle, J., Uberreiter, S., Radmayr, C., & Bartsch, G. (1992). Point mutation in the DNA binding domain of the androgen receptor in two families with Reifenstein syndrome. *American Journal of Human Genetics*, *50*(6), 1318–1327.

Koçyiğit, C., Sarıtaş, S., Çatlı, G., Onay, H., & Dündar, B. (2016). A Novel Mutation in Human Androgen Receptor Gene Causing Partial Androgen Insensitivity Syndrome in a Patient Presenting with

Gynecomastia at Puberty. *Journal of Clinical Research in Pediatric Endocrinology*, *8*(2), 232–235. https://doi.org/10.4274/jcrpe.2637

Kon, M., Suzuki, E., Dung, V., Hasegawa, Y., Mitsui, T., Muroyas, K., Ueoka, K., Igarashi, N., Nagasaki, K., Oto, Y., Hamajima, T., Yoshino, K., Igarashi, M., Kato-Fukui, Y., Nakabayashi, K., Hayashi, K., Hata, K., Matsubara, Y., Moriya, K., … Fukami, M. (2015). Molecular basis of non-syndromic hypospadias: Systematic mutation screening and genome-wide copy-number analysis of 62 patients. *HUMAN REPRODUCTION*, *30*(3), 499–506. https://doi.org/10.1093/humrep/deu364

Kulshreshtha, B., Philibert, P., Eunice, M., Audran, F., Paris, F., Khurana, M., Ammini, A., & Charles, S. (2009). Phenotype, hormonal profile and genotype of subjects with partial androgen insensitivity syndrome: Report of a family with four adult males and one child with disorder of sexual differentiation. *Andrologia*, *41*(4), 257–263. https://doi.org/10.1111/j.1439-0272.2009.00921.x

Kumar, A., Sharma, R., Faruq, M., Kumar, M., Sharma, S., Werner, R., Hiort, O., & Vandana, J. (2022). Clinical, Biochemical, and Molecular Characterization of Indian Children with Clinically Suspected Androgen Insensitivity Syndrome. *Sexual Development : Genetics, Molecular Biology, Evolution, Endocrinology, Embryology, and Pathology of Sex Determination and Differentiation*, *16*(1), 34–45. https://doi.org/10.1159/000519047

Lagarde, W., Blackwelder, A., Minges, J., Hnat, A., French, F., & Wilson, E. (2012). Androgen receptor exon 1 mutation causes androgen insensitivity by creating phosphorylation site and inhibiting melanoma antigen-A11 activation of NH2- and carboxyl-terminal interaction-dependent transactivation. *The Journal of Biological Chemistry*, *287*(14), 10905–10915. https://doi.org/10.1074/jbc.M111.336081

Lee, Y., Kirk, J., Stanhope, R., Johnston, D., Harland, S., Auchus, R., Andersson, S., & Hughes, I. (2007). Phenotypic variability in 17beta-hydroxysteroid dehydrogenase-3 deficiency and diagnostic pitfalls. *Clinical Endocrinology*, *67*(1), 20–28. https://doi.org/10.1111/j.1365-2265.2007.02829.x

Liu, Q., Yin, X., & Li, P. (2022). Clinical, Hormonal, and Genetic Characteristics of 5α-Reductase Type 2 Deficiency in 103 Chinese Patients. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, *28*(9), 859–866. https://doi.org/10.1016/j.eprac.2022.06.002

Liu, S., Ma, Z., Sun, W., Sun, X., Hong, Y., Ma, L., Qin, C., Stratton, H., Liu, Q., & Jiang, J. (2012). The role of androgen-induced growth factor (FGF8) on genital tubercle development in a hypospadiac male rat model of prenatal exposure to di-n-butyl phthalate. *Toxicology*, *293*(1), 53–58. https://doi.org/10.1016/j.tox.2011.12.010

Lottrup, G., Jørgensen, A., NielsenE, J., Jørgensen, N., Duno, M., Vinggaard, A., Skakkebæk, N., & Meyts, E. R.-D. (2013). Identification of a novel androgen receptor mutation in a family with multiple components compatible with the testicular dysgenesis syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *98*(6), 2223–2229. https://doi.org/10.1210/jc.2013-1278

Lucas-Herald, A., Bertelloni, S., Juul, A., Bryce, J., Jiang, J., Rodie, M., Sinnott, R., Boroujerdi, M., Johansen, M. L., Hiort, O., Holterhus, P., Cools, M., Guaragna-Filho, G., Guerra-Junior, G., Weintrob, N., Hannema, S., Drop, S., Guran, T., Darendeliler, F., … Ahmed, S. (2016). The Long-Term Outcome of Boys With Partial Androgen Insensitivity Syndrome and a Mutation

in the Androgen Receptor Gene. *The Journal of Clinical Endocrinology and Metabolism*, *101*(11), 3959–3967. https://doi.org/10.1210/jc.2016-1372

Luna, S., Wegner, D., Gale, S., Yang, P., Hollander, A., St Dennis-Feezle, L., Nabhan, Z., Ory, D., Cole, F., & Wambach, J. (2021). Whole exome sequencing and functional characterization increase diagnostic yield in siblings with a 46, XY difference of sexual development (DSD). *The Journal of Steroid Biochemistry and Molecular Biology*, *212*, 105908. https://doi.org/10.1016/j.jsbmb.2021.105908

Maimoun, L., Philibert, P., Bouchard, P., Ocal, G., Leheup, B., Fenichel, P., Servant, N., Paris, F., & Sultan, C. (2011). Primary amenorrhea in four adolescents revealed 5 alpha-reductase deficiency confirmed by molecular analysis. *FERTILITY AND STERILITY*, *95*(2). https://doi.org/10.1016/j.fertnstert.2010.08.007

Maimoun, L., Philibert, P., Cammas, B., Audran, F., Bouchard, P., Fenichel, P., Cartigny, M., Pienkowski, C., Polak, M., Skordis, N., Mazen, I., Ocal, G., Berberoglu, M., Reynaud, R., Baumann, C., Cabrol, S., Simon, D., Kayemba-Kay's, K., De Kerdanet, M., … Sultan, C. (2011). Phenotypical, biological, and molecular heterogeneity of 5α-reductase deficiency: An extensive international experience of 55 patients. *The Journal of Clinical Endocrinology and Metabolism*, *96*(2), 296–307. https://doi.org/10.1210/jc.2010-1024

Mark, E., Castells, S., Glassberg, K., Choi, S., Tolete-Velcek, F., David, K., & Migeon, C. (1983). Deficiency of androgen receptors in male pseudohermaphroditism. *Urology*, *21*(2), 168–171. https://doi.org/10.1016/0090-4295(83)90017-1

McIntyre, B., Barlow, N., & Foster, P. (2001). Androgen-mediated development in male rat offspring exposed to flutamide in utero: Permanence and correlation of early postnatal changes in anogenital distance and nipple retention with malformations in androgen-dependent tissues. *Toxicological Sciences : An Official Journal of the Society of Toxicology*, *62*(2), 236–249. https://doi.org/10.1093/toxsci/62.2.236

Mendonca, B., Bloise, W., Arnhold, I., Batista, M., Toledo, S., Drummond, M., Nicolau, W., & Mattar, E. (1987). Male pseudohermaphroditism due to nonsalt-losing 3 beta-hydroxysteroid dehydrogenase deficiency: Gender role change and absence of gynecomastia at puberty. *Journal of Steroid Biochemistry*, *28*(6), 669–675. https://doi.org/10.1016/0022-4731(87)90396-7

Mendonca, B., Inacio, M., Arnhold, I., Costa, E., Bloise, W., Martin, R., Denes, F., Silva, F., Andersson, S., Lindqvist, A., & Wilson, J. (2000). Male pseudohermaphroditism due to 17 beta-hydroxysteroid dehydrogenase 3 deficiency. Diagnosis, psychological evaluation, and management. *Medicine*, *79*(5), 299–309. https://doi.org/10.1097/00005792-200009000-00003

Mendonca, B., Inacio, M., Costa, E., Arnhold, I., Silva, F., Nicolau, W., Bloise, W., Russel, D., & Wilson, J. (1996). Male pseudohermaphroditism due to steroid 5alpha-reductase 2 deficiency. Diagnosis, psychological evaluation, and management. *Medicine*, *75*(2), 64–76. https://doi.org/10.1097/00005792-199603000-00003

Migeon, C., Wisniewski, A., Gearhart, J., Meyer-Bahlburg, H., Rock, J., Brown, T., Casella, S., Maret, A., Ngai, K., Money, J., & Berkovitz, G. (2002). Ambiguous genitalia with perineoscrotal hypospadias in 46,XY individuals: Long-term medical, surgical, and psychosexual outcome. *Pediatrics*, *110*(3), e31. https://doi.org/10.1542/peds.110.3.e31

Misrahi, M., Meduri, G., Pissard, S., Bouvattier, C., Beau, I., Loosfelt, H., Jolivet, A., Rappaport, T., Milgrom, E., & Bougneres, P. (1997). Comparison of immunocytochemical and molecular

features with the phenotype in a case of incomplete male pseudohermaphroditism associated with a mutation of the luteinizing hormone receptor. *The Journal of Clinical Endocrinology and Metabolism*, *82*(7), 2159–2165. https://doi.org/10.1210/jcem.82.7.4039

Moriya, K., Mitsui, T., Tanaka, H., Nakamura, M., & Nonomura, K. (2010). Long-term outcome of pituitary-gonadal axis and gonadal growth in patients with hypospadias at puberty. *The Journal of Urology*, *184*(4), 1610–1614. https://doi.org/10.1016/j.juro.2010.04.022

Mylchreest, E., Cattley, R., & Foster, P. (1998). Male reproductive tract malformations in rats following gestational and lactational exposure to Di(n-butyl) phthalate: An antiandrogenic mechanism? *Toxicological Sciences : An Official Journal of the Society of Toxicology*, *43*(1), 47–60. https://doi.org/10.1006/toxs.1998.2436

Mylchreest, E., Sar, M., Cattley, R., & Foster, P. (1999). Disruption of androgen-regulated male reproductive development by di(n-butyl) phthalate during late gestation in rats is different from flutamide. *Toxicology and Applied Pharmacology*, *156*(2), 81–95. https://doi.org/10.1006/taap.1999.8643

Mylchreest, E., Wallace, D., Cattley, R., & Foster, P. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to Di(n-butyl) phthalate during late gestation. *Toxicological Sciences : An Official Journal of the Society of Toxicology*, *55*(1), 143–151. https://doi.org/10.1093/toxsci/55.1.143

Nagaraja, M., Rastogi, A., Raman, R., Gupta, D., & Singh, S. (2010). Molecular diagnosis of 46,XY DSD and identification of a novel 8 nucleotide deletion in exon 1 of the SRD5A2 gene. *Journal of Pediatric Endocrinology & Metabolism : JPEM*, *23*(4), 379–385. https://doi.org/10.1515/jpem.2010.059

Neocleous, V., Sismani, C., Shammas, C., Efstathiou, E., Alexandrou, A., Ioannides, M., Argyrou, M., Patsalis, P., Phylactou, L., & Skordis, N. (2012). Duplication of exons 3-10 of the HSD17B3 gene: A novel type of genetic defect underlying 17 beta-HSD-3 deficiency. *GENE*, *499*(2), 250–255. https://doi.org/10.1016/j.gene.2012.03.031

New, M. (1970). Male pseudohermaphroditism due to 17 alpha-hydroxylase deficiency. *The Journal of Clinical Investigation*, *49*(10), 1930–1941. https://doi.org/10.1172/JCI106412

Nicoletti, A., Baldazzi, L., Balsamo, A., Barp, L., Pirazzoli, P., Gennari, M., Radetti, G., Cacciari, E., & Cicognani, A. (2005). SRD5A2 gene analysis in an Italian population of under-masculinized 46,XY subjects. *Clinical Endocrinology*, *63*(4), 375–380. https://doi.org/10.1111/j.1365-2265.2005.02348.x

Ogata, T., Muroya, K., Ishii, T., Suzuki, Y., Nakada, T., & Sasagawa, I. (2001). Undermasculinized genitalia in a boy with an abnormally expanded CAG repeat length in the androgen receptor gene. *Clinical Endocrinology*, *54*(6), 835–838. https://doi.org/10.1046/j.1365-2265.2001.01205.x

Ostby J, Monosson E, Kelce WR, & Gray, L. J. (1999). Environmental antiandrogens: Low doses of the fungicide vinclozolin alter sexual differentiation of the male rat. *Toxicology and Industrial Health*, *15*(1), 48–64. https://doi.org/10.1177/074823379901500106

Pang, S., Levine, L., Stoner, E., Opitz, J., Pollack, M., Dupont, B., & New, M. (1983). Nonsalt-losing congenital adrenal hyperplasia due to 3 beta-hydroxysteroid dehydrogenase deficiency with normal glomerulosa function. *The Journal of Clinical Endocrinology and Metabolism*, *56*(4), 808–818. https://doi.org/10.1210/jcem-56-4-808

Parada-Bustamante, A., Lardone, M., Madariaga, M., Johnson, M., Codner, E., Cassorla, F., & Castro, A. (2012). Androgen receptor CAG and GGN polymorphisms in boys with isolated

hypospadias. *Journal of Pediatric Endocrinology & Metabolism : JPEM*, *25*(1), 157–162. https://doi.org/10.1515/jpem.2011.379

Perrone, L., Criscuolo, T., Sinisi, A., Graziani, M., Manzo, T., Sicuranza, R., Bellastella, A., & Faggiano, M. (1985). Male pseudohermaphroditism due to 3 beta-hydroxysteroid dehydrogenase-isomerase deficiency associated with atrial septal defect. *Acta Endocrinologica*, *110*(4), 532–539. https://doi.org/10.1530/acta.0.1100532

Pike, J., McDowell, E., McCahan, S., & Johnson, K. (2014). Identification of gene expression changes in postnatal rat foreskin after in utero anti-androgen exposure. *REPRODUCTIVE TOXICOLOGY*, *47*, 42–50. https://doi.org/10.1016/j.reprotox.2014.05.011

Rabbani, B., Mahdieh, N., Ashtiani, M. H., Setoodeh, A., & A Rabbani. (2012). In silico structural, functional and pathogenicity evaluation of a novel mutation: An overview of HSD3B2 gene mutations. *Gene*, *503*(2), 215–221. https://doi.org/10.1016/j.gene.2012.04.080

Rahimi, M., Ghanbari, M., Fazeli, Z., Rouzrokh, M., Omrani, S., Mirfakhraie, R., & Omrani, M. (2017). Association of SRD5A2 gene mutations with risk of hypospadias in the Iranian population. *Journal of Endocrinological Investigation*, *40*(4), 391–396. https://doi.org/10.1007/s40618-016-0573-y

Sahu, R., Boddula, R., Sharma, P., Bhatia, V., Greaves, R., Rao, S., Desai, M., Wakhlu, A., Phadke, S., Shukla, M., Dabadgha, P., Mehrotra, R., & Bhatia, E. (2009). Genetic analysis of the SRD5A2 gene in Indian patients with 5alpha-reductase deficiency. *Journal of Pediatric Endocrinology & Metabolism : JPEM*, *22*(3), 247–254. https://doi.org/10.1515/jpem.2009.22.3.247

Saillenfait, A., Sabaté, J., & Gallissot, F. (2009). Effects of in utero exposure to di-n-hexyl phthalate on the reproductive development of the male rat. *Reproductive Toxicology (Elmsford, N.Y.)*, *28*(4), 468–476. https://doi.org/10.1016/j.reprotox.2009.06.013

Saillenfait, A., SabatéP, J., & Gallissot, F. (2008). Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat. *Reproductive Toxicology (Elmsford, N.Y.)*, *26*(2), 107–115. https://doi.org/10.1016/j.reprotox.2008.07.006

Sato, T., Nakano, S., Asanuma, H., Ishii, T., & Hasegawa, T. (2022). Effectiveness of dihydrotestosterone ointment on glans penis size increment in a 5-alpha-reductase type 2 deficiency patient. *Pediatrics International : Official Journal of the Japan Pediatric Society*, *64*(1), e15079. https://doi.org/10.1111/ped.15079

Schneider, S., Kaufmann, W., Strauss, V., & B van Ravenzwaay. (2011). Vinclozolin: A feasibility and sensitivity study of the ILSI-HESI F1-extended one-generation rat reproduction protocol. *Regulatory Toxicology and Pharmacology : RTP*, *59*(1), 91–100. https://doi.org/10.1016/j.yrtph.2010.09.010

Schneider, W., Marxfeld, H., Gröters, S., Buesen, R., & van Ravenzwaay B. (2013). Vinclozolin—No transgenerational inheritance of anti-androgenic effects after maternal exposure during organogenesis via the intraperitoneal route. *Reproductive Toxicology (Elmsford, N.Y.)*, *37*, 6–14. https://doi.org/10.1016/j.reprotox.2012.12.003

Schweikert, H., Schlüter, M., & Romalo, G. (1989). Intracellular and nuclear binding of [3H]dihydrotestosterone in cultured genital skin fibroblasts of patients with severe hypospadias. *The Journal of Clinical Investigation*, *83*(2), 662–668. https://doi.org/10.1172/JCI113930

Shabir, I., Khurana, M., Joseph, A., Eunice, M., Mehta, M., & Ammini, A. (2015). Phenotype, genotype and gender identity in a large cohort of patients from India with 5α-reductase 2 deficiency. *Andrology*, *3*(6), 1132–1139. https://doi.org/10.1111/andr.12108

Shabir, I., Khurana, M., Marumudi, E., Khadgawat, R., & Ammini, A. (2013). Novel nucleotide insertions in two unrelated Indian patients with 5α reductase 2 deficiency leading to premature termination of SRD5A2 enzyme. *Steroids*, *78*(12), 1159–1163. https://doi.org/10.1016/j.steroids.2013.08.010

Shabir, I., Marumudi, E., Khurana, M., & Khadgawat, R. (2012). Novel mutation of SRD5A2 gene in a patient with 5α-reductase 2 deficiency from India. *BMJ Case Reports*, *2012*. https://doi.org/10.1136/bcr-2012-007060

Sherbet, D., Tiosano, D., Kwist, K., Hochberg, Z., & RJ Auchus. (2003). CYP17 mutation E305G causes isolated 17,20-lyase deficiency by selectively altering substrate binding. *The Journal of Biological Chemistry*, *278*(49), 48563–48569. https://doi.org/10.1074/jbc.M307586200

Silver, R., & Russell, D. (1999). 5alpha-reductase type 2 mutations are present in some boys with isolated hypospadias. *The Journal of Urology*, *162*(3), 1142–1145. https://doi.org/10.1097/00005392-199909000-00064

Sinnecker, G., Hiort, O., Dibbelt, L., Albers, N., Dörr, H., Hauss, H., Heinrich, U., Hemminghaus, M., Hoepffner, W., Holder, M., Schnabel, D., & Kruse, K. (1996). Phenotypic classification of male pseudohermaphroditism due to steroid 5 alpha-reductase 2 deficiency. *American Journal of Medical Genetics*, *63*(1), 223–230. https://doi.org/10.1002/(SICI)1096-8628(19960503)63:1%253C223::AID-AJMG39%253E3.0.CO;2-O

van den Driesche, S., Kilcoyne, K., Wagner, I., Rebourcet, D., Boyle, A., Mitchell, R., McKinnell, C., Macpherson, S., Donat, R., Shukla, C., Jorgensen, A., Meyts, E., Skakkebaek, N., & Sharpe, R. (2017). Experimentally induced testicular dysgenesis syndrome originates in the masculinization programming window. *JCI Insight*, *2*(6), e91204. https://doi.org/10.1172/jci.insight.91204

van den Driesche, S., Shoker, S., Inglis, F., Palermo, C., Langsch, A., & Otter, R. (2020). Systematic comparison of the male reproductive tract in fetal and adult Wistar rats exposed to DBP and DINP in utero during the masculinisation programming window. *Toxicology Letters*, *335*, 37–50. https://doi.org/10.1016/j.toxlet.2020.10.006

Vilchis, F., Valdez, E., Ramos, L., Garcia, R., Gomez, R., & Chavez, B. (2008). Novel compound heterozygous mutations in the SRD5A2 gene from 46,XY infants with ambiguous external genitalia. *JOURNAL OF HUMAN GENETICS*, *53*(5), 401–406. https://doi.org/10.1007/s10038-008-0274-2

Wan, R., Dong, Z., Wang, W., Xiao, Y., Ni, J., & Wang, D. (2013). Mutation analysis of the SRD5A2, AR and SF-1 genes in 52 Chinese boys with hypospadias. *Journal of Pediatric Endocrinology & Metabolism : JPEM*, *26*(9), 887–893. https://doi.org/10.1515/jpem-2012-0316

Wang, Y., Gong, C., Qin, M., Liu, Y., & Tian, Y. (2017). Clinical and genetic features of 64 young male paediatric patients with congenital hypogonadotropic hypogonadism. *Clinical Endocrinology*, *87*(6), 757–766. https://doi.org/10.1111/cen.13451

Wang, Y., Li, Q., Xu, J., Liu, Q., W Wang, Lin, Y., Ma, F., Chen, T., Li, S., & Shen, Y. (2004). Mutation analysis of five candidate genes in Chinese patients with hypospadias. *European Journal of Human Genetics : EJHG*, *12*(9), 706–712. https://doi.org/10.1038/sj.ejhg.5201232

Wang, Y., Qin, M., Fan, L., & Gong, C. (2022). Correlation Analysis of Genotypes and Phenotypes in Chinese Male Pediatric Patients With Congenital Hypogonadotropic Hypogonadism. *Frontiers in Endocrinology*, *13*, 846801. https://doi.org/10.3389/fendo.2022.846801

Warne GL, Gyorki S, Risbridger GP, Khalid BA, & Funder JW. (1983). Fibroblast studies on clinical androgen insensitivity. *Journal of Steroid Biochemistry*, *19*(1), 583–586. https://doi.org/10.1016/0022-4731(83)90221-2

Wolf, C. J., Lambright, C., Mann, P., Price, M., Cooper, R., Ostby, J., & Gray, L. J. (1999). Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicology and Industrial Health*, *15*(1), 94–118. https://doi.org/10.1177/074823379901500109

Wolf, C., LeBlanc, G., Ostby, J., & Gray, L. J. (2000). Characterization of the period of sensitivity of fetal male sexual development to vinclozolin. *Toxicological Sciences : An Official Journal of the Society of Toxicology*, *55*(1), 152–161. https://doi.org/10.1093/toxsci/55.1.152

Yeste, D., Aguilar-Riera, C., Canestrino, G., Fernández-Alvarez, P., Clemente, M., & Camats-Tarruella, N. (2022). A New MAMLD1 Variant in an Infant With Microphallus and Hypospadias With Hormonal Pattern Suggesting Partial Hypogonadotropic Hypogonadism-Case Report. *Frontiers in Endocrinology*, *13*, 884107. https://doi.org/10.3389/fendo.2022.884107

Yu, H., Wen, K., Zhou, X., Zhang, Y., Yan, Z., Fu, H., Zhu, J., & Zhu, Y. (2020). Role of unfolded protein response in genital malformation/damage of male mice induced by flutamide. *Human & Experimental Toxicology*, *39*(12), 1690–1699. https://doi.org/10.1177/0960327120937049

Yu, H., Yang, J., Zhang, Y., Fu, H., Yan, Z., & Zhu, Y. (2021). Vinclozolin-induced mouse penile malformation and "small testis" via miR132, miR195a together with the Hippo signaling pathway. *Toxicology*, *460*, 152842. https://doi.org/10.1016/j.tox.2021.152842

Zakaria, O., Shono, T., Imajima, T., & Suita, S. (2000). Comparative studies of fertility and histologic development of contralateral scrotal testes in two rat models of unilateral cryptorchidism. *Pediatric Surgery International*, *16*(7), 498–501. https://doi.org/10.1007/s003830000400

Zhang, W., Shi, J., Zhang, C., Jiang, X., Wang, J., Wang, W., Wang, D., Ni, J., Chen, L., Lu, W., Xiao, Y., Ye, W., & Dong, Z. (2019). Identification of gene variants in 130 Han Chinese patients with hypospadias by targeted next-generation sequencing. *Molecular Genetics & Genomic Medicine*, *7*(8), e827. https://doi.org/10.1002/mgg3.827

Zhao, S., Li, D., Bei, X., Zhu, Z., Sun, W., Shen, C., Wood, K., Han, B., & Jiang, J. (2018). Maternal exposure to di-n-butyl phthalate (DBP) promotes epithelial-mesenchymal transition via regulation of autophagy in uroepithelial cell. *Toxicology*, *406*, 114–122. https://doi.org/10.1016/j.tox.2018.07.013

Zhou, X., Wang, S., Zhou, R., Zhang, T., Wang, Y., Zhang, Q., Cong, T., Ji, C., Luan, J., Yao, L., Zhou, X., & Song, N. (2022). Erectile dysfunction in hypospadiac male adult rats induced by maternal exposure to di-n-butyl phthalate. *Toxicology*, *475*, 153227. https://doi.org/10.1016/j.tox.2022.153227

Zhou X, Zhang X, Zhou X, Abulimiti G, Wang Y, Zhang Q, Cong R, Ji C, Luan J, Yao L, Yang J, & Song N. (2022). Identification of endocrine-disrupting chemicals targeting the genes and pathways of genital anomalies in males. *Ecotoxicology and Environmental Safety*, *247*, 114241. https://doi.org/10.1016/j.ecoenv.2022.114241

Zhu, Y., Li, E., Sun, W., Xu, D., Liu, Z., Zhao, W., Wood, K., Xia, S., & Jiang, J. (2016). Maternal exposure to di-n-butyl phthalate (DBP) induces combined anorectal and urogenital malformations in male rat offspring. *Reproductive Toxicology (Elmsford, N.Y.)*, *61*, 169–176. https://doi.org/10.1016/j.reprotox.2016.04.007