Supplementary Table 1: Selection of genes, receptors and endo-/ paracrine factors related to gonadal development in mice and humans

	Expression in testicular tissue/ cells	Expression in non-testicular tissue/ cells	Function	Mutation effects on male gonadal tissue/ cells	Other effects caused by mutations	References
Sex determining region on the Y (SRY)	Bi-potential gonads; Sertoli cell precursor cells	Bi-potential gonads	Testis determination; Proteins interacting with *SRY* have a relevant function in gonadal differentiation	Swyer-Syndrome: Sex-reversal (male to female)	XY-Female; early loss of oocytes after birth in females	Berta et al. 1990, Jäger et al. 1990, Albrecht & Eicher 2001
SRY related HMG box 9 (SOX9)	Bi-potential gonads (under *SF1* regulation); after *SRY* expression only in Sertoli cells; foetal and adult testis	Various tissue during embryogenesis; central nervous system, limbs, kidneys, craniofacial structures; adult head and foetal brain	Predominantly testis promoting activity; Upregulation of anti-Müllerian hormone (AMH) and therefore affection of the differentiating reproductive tract; upregulation of *FGF9* and prostaglandin D2 **(***PGD2*); Sertoli cell differentiation	In humans: sex-reversal (male to female) due to gonadal dysgenesis in XY individuals	Overexpression during early embryogenesis inducing testicular differentiation in transgenic XX mice; In humans: heterozygous mutations: haploinsufficiency resulting in campomelic dysplasia, a polymalformative syndrome (includes sex-reversal due to gonadal dysgenesis in XY individuals)	Sekido & Lovell-Badge 2009, Sekido & Lovell-Badge 2008, Kent et al. 1996, Morais da Silva et al. 1996, Vidal et al. 2001, Foster et al. 1994, Parker et al. 1999
Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain 2 (CITED2)	Bi-potential gonads	Adrenal; adrenogonadal primordium; coelomic epithelium underlying mesenchyme of the genital ridge	Regulation through interaction with *WT1* of *SF1* expression (upstream of the gonadal development cascade); cAMP-responsive element binding protein	Transient development delay in male gonads; reduction of *SOX9* expression; reduction of *SF1* expression; disrupted testicular structures	Spina bifida (erectile dysfunction)	Combes et al. 2009, Buaas et al. 2009, Volcik et al. 2004
Fibroblast growth factor 9 (FGF9)	Bi-potential gonads (near the coelomic surface)	Airway epithelium and visceral pleura	Predominantly testis promoting activity; interaction with related receptor FGFR2; proliferation control of cells giving rise to Sertoli cell progenitors (location of *FGFR2*); maintaining *SOX9* expression and downregulation of *WNT4* expression; in the embryo: mesenchymal proliferation, mesonephric cell migration, Sertoli cell differentiation	Testicular hypoplasia; disruption of FGF9 expression shows no effects on XX gonads, but prevents testicular differentiation and results in sex-reversal in XY mice; *FGF9* knockout results in aborted Sertoli cell differentiation due to decreased expression of *SRY* and *SOX9* in mice	Lung hypoplasia: lethal at the time of birth	Kim et al. 2006, Colvin et al. 2001a, Schmahl et al. 2004, Colvin et al. 2001b, O'Shaughnessy et al. 2007a

Wingless-related MMTV integration site 4 (WNT4)	Foetal gonads (near the mesonephric border)	Developing kidney, mesonephros	Antagonistic signal to FGF9 during the early gonadal differentiation; predominantly ovary promoting activity; paracrine factor that regulates several developmental mechanisms; *WNT4* leads to an increased β-catenin level	Unknown	Absence of an uterus and the androgen excess; clinical entity distinct from the typical Mayer-Kokitansky-Kuster-Hauser syndrome; homozygous: lethal shortly after birth, due to kidney failure; renal, adrenal and pulmonary defects; mental retardation, virilised ovary	Kim et al. 2006, Biason-Lauber & Konrad 2008, Vainio et al. 1999, O'Shaughnessy et al. 2007a, Parker et al. 1999,; Hiort & Gillessen-Kaesbach 2009
Paired box gene 2 (PAX2)	Foetal gonads	Mesonephros, metanephros, adrenals, spinal cord, hindbrain and optic and otic vesicles; urogenital system	Regulation of *WT1* expression and mesenchyme- to-epithelium transition	Developmental failure of urogenital derivates; absent gonads	Essential for the development of vital embryonic structures; CHARGE syndrome; KO: lack of kidneys, genital tracks, ureters; kidney hypoplasia (*pax2* point mutation)	Torres et al. 1995, Dehbi et al. 1996, Tellier et al. 2000
SRY related HMG box 8 (SOX8)	Foetal gonads (beyond 16 dpc in Sertoli cells)	Central nervous system, limbs, kidneys, craniofacial structures	Embryonic development; gonadal, central neuron system, neural crest and skeletal development	Activation of *AMH* transcription; (less efficient than *SOX9*)	Involved in ART16: haemoglobin H related mental retardation; haematological abnormalities, mental retardation and craniofacial defects	Schepers et al. 2000, Schepers et al. 2003
Wingless-related MMTV integration site 2B (WNT2B)	Gonads	Kidney, lung, salivary gland, gut, adrenal gland, pancreas	Testicular development; kidney organogenesis	Regulation of several developmental mechanisms	Lethal shortly after birth	O'Shaughnessy et al. 2007a, Lin et al. 2005
Helicase 2, X-linked (ATRX or XH2)	Gonads	Widespread	Nucleotide excision repair and initiation of transcription; might be involved in chromatin remodelling like *SRY*	Gonadal dysgenesis in XY individuals	Mental retardation, α-thalassemia	Gibbons et al. 1995, Ion et al. 1996
Steroidogenic factor 1 (SF1)	Gonadal ridges	Hypothalamus and pituitary, adrenal gland primordia	Orphan nuclear receptor; transcriptional regulation of *StAR*, steroid hydroxylases, gonadotropins, aromatase, AMH and *DAX1*; stabilization of intermediate mesoderm, follicle development and ovulation	Gonadal and sex reversal (usually, but not always); dosage-sensitive mechanism in human sex differentiation, since mutations at the heterozygous state are sufficient to induce sex reversal in XY individuals	Adrenal primordia degeneration, adrenal insufficiency	Taketo et al. 1995, Morohashi 1999, Parker et al. 1999, Ikeda et al. 1996, Achermann et al. 1999, Correa et al. 2004, Mallet et al. 2004, Hasegawa et al.

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Dosage-sensitive sex reversal-congenital adrenal hypoplasia critical region on the X-chromosome protein 1 (DAX1)	Testis	Ovary, several endocrine organs throughout the hypothalamic pituitary-adrenal/gonadal axis (including the ventro-medial hypocampus and anterior pituitary adrenal cortex)	Predominantly ovary promoting activity; normal testicular cord formation	Overexpression impairs testis differentiation in XY mice; abnormally low or high expression results in abnormal gonadal differentiation; eventual germ cell loss in XY; dosage-sensitive sex-reversal (DSS)	Disruption does not prevent ovarian formation, delayed puberty, adrenal hypoplasia congenital (AHC)	Yu et al. 1998, Bouma et al. 2005, Park et al. 2008, Ludbrook & Harley 2004
R-spondin homolog (Xenopus laevis) (RSPO1)	Testis	Upregulated in mice in XX somatic cells and controls the differentiation of the ovary (probably); ovary, adrenal glands, thyroid and trachea	Predominantly ovary promoting activity	In absence of *SRY*: female to male sex-reversal	Palmoplantar hyperkeratosis, predisposition to squamous cell carcinoma of the skin; hearing impairment; corneal opacities, loss of function mutation in humans and gene ablation in mice results in the formation of ovotestes in the XX-foetus (probably upregulation of *SOX9*); XX germ cells fail to enter meiosis	Chassot et al. 2008, Sekido & Lovell-Badge 2009, Tomaselli et al. 2008, Parma et al. 2006, Hiort & Gillessen-Kaesbach 2009
PRDI-BF1-RIZ domain containing 14 (PRDM14)	PGC precursors	Breast cancer cells	Specification of PGC through competent cells of the proximal epiblast expressing *PRDM1* and *14*	Only few *PRDM1* positive cells; repression of *SOX2*; Infertility	Stimulation of breast cancer cell growth	Edson et al. 2009, Nishikawa et al. 2007
PRDI-BF1-RIZ domain containing 1 (PRDM1)	PGC precursors	Multiple tissues (e.g. maturating B-lymphocytes)	Specification of PGC through competent cells of the proximal epiblast expressing *PRDM1* and *14*	Reduction of PGCs in heterozygous and nearly zero PGCs in homozygous mutants; variable expression of *SOX2*	KO mice are lethal during embryogenesis; LOF-mutants: B-T cell lymphoms	Edson et al. 2009
C-Kit	PGCs, differentiated spermatogonia	Neurons and some glial cells, embryonic lung, kidney, gut and brain	Migration, survival and proliferation of PGCs as an interaction between SCF and C-Kit	PGC defects: germ cell deficiency, due to impaired PGC migration	Hematopoietic defects; KO mice: severe anaemia; lethality late in gestation	Motro et al. 1991, Buehr et al. 1993, Pesce et al. 1993, Matsui et al. 1990, O'Shaughnessy et al. 2007a
Activator protein 2 gamma (AP2γ or TFAP2C)	Gonocytes, undifferentiated spermatogonia	Skin, heart , neural crest, neural tube, urogenital tissue; pancreas; breast carcinoma; extra-	Important for differentiation of trophoblasts and germ cells; Regulation of *KIT* expression; RA-inducible gene	Germ cell tumour formation	Lethal, due to malformation of extra-embryonic tissue; in humans: neoplasia; breast cancer formation	O'Shaughnessy et al. 2007a, Hong et al. 2005, Motonaga et al. 2002,

		embryonic ectoderm				Hoei-Hansen et al. 2004
FGFR3 (Fibroblast growth factor receptor 3)	Gonocytes, spermatogonia, spermatocytes, spermatids	During embryogenesis, expression in differentiating hair cells of the cochlear duct and in the cartilage of developing bone; In adult tissues: expression in brain, skin, lung, kidney, spinal cord, liver, pancreas, and embryonic stem cells, prostate	Negative regulator of endochondral bone growth; regulates cell proliferation, migration, differentiation and survival	Promotion of clonal expansion of spermatogonia in congenital disorders and testicular tumours; spermatogenesis-preserving gain-of-function mutation (in a non-mosaic Klinefelter patient); infertility	Skeletal disorders: achondroplasia (ACH), hypochondroplasia (HCH), thanatophoric dysplasia type I (TDI) and type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN); craniofacial disorders and multiple myeloma; Epidermal nevi and bladder cancer	Von Kopylow et al. 2010; Juul et al. 2007; Goriely et al. 2009; Harada et al. 2009; Hernández et al. 2007, Cotton et al. 2008
DSG2 (desmoglein 2)	Gonocytes, spermatogonia	Widespread	Important for embryonal stem cell and early embryo survival; part of the blood-testis-barrier in the adult testis	Impairment of the blood-testis-barrier	Loss of DSG2 protein expression contributes to an aggressive phenotype during tumorigenesis; arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) type 10	Von Kopylow et al. 2010, Cheng & Mruk 2009, Eshkind et al. 2002, Brennan et al. 2007, Herren et al. 2009
FGFR5 (Fibroblast growth factor receptor 5)	Spermatogonia	Widespread	Regulates cell proliferation, migration, differentiation and survival	Infertility	Skeletal diseases and cancer	Cotton et al. 2008
UTF1 (undifferentiated embryonic cell transcription factor 1)	Spermatogonia	Pluripotent cells; duct deferens, epididymis, and prostate	Critical for the differentiation of embryonic stem (ES) cells and for maintaining proliferation rates of embryonic carcinoma and ES cells; maintance of proliferation and self-renewal in adult male germ cells	Unknown	Failure of proper induction of ES cell differentiation	Von Kopylow et al. 2010, Thummer et al. 2010, Kristensen et al. 2010, Kristensen et al. 2008
FGFR2 (Fibroblast growth factor receptor 2)	Spermatocytes, spermatids, Leydig cells, Sertoli cells	Differentially expressed in the mesenchyme and epithelium of fusing palatal shelves and in dental follicle development	Regulates cell proliferation, migration, differentiation and survival	Genital malformations; sex reversal (male to female) in mice; infertility	Hypospadias; cleft palate associated with craniosynostosis; induction of proliferation and survival of tumour cells; Crouzon syndrome, Jackson-Weiss syndrome, Apert syndrome, Pfeiffer syndrome, and Beare-Stevenson syndrome	Hiort & Gillessen-Kaesbach 2009, Beleza-Meireles et al. 2007, Pitteloud et al. 2006, Katoh & Katoh 2009, Cotton et al.

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FGFR4 (Fibroblast growth factor receptor 4)	Spermatogonia, spermatocytes, elongating spermatids, Leydig cells, Sertoli cells	Widespread	Regulates cell proliferation, migration, differentiation and survival	Infertility	Skeletal diseases and cancer	Cotton et al. 2008
Fibroblast growth factor receptor 1 (FGFR1)	Seminiferous epithelium and interstitium, peritubular cells, Leydig cells, elongating spermatids	Developing olfactory bulbs, along the GnRH migration pathway; mature hypothalamic GnRH neurons; differentially expressed in the mesenchyme and epithelium of fusing palatal shelves and in dental follicle development	Regulates cell proliferation, migration, differentiation and survival	Cryptorchidism; infertility	Kallmann's syndrome; hypogonadotropic hypogonadism, delayed or absent puberty	Salenave et al. 2008, Pitteloud et al. 2006, Cotton et al. 2008
Wilms tumor associated gene 1 (WT1)	Immature Sertoli cells and rete testis	Urogenital ridges derivates; coelomic epithelium, granulosa cells; gonadal stromal cells; embryonic tunica albugiuea	DNA- and RNA-binding protein with transcriptional and post transcriptional regulation capacity	Gonadal dysgenesis; often male to female sex-reversal; male pseudohermaphroditism, cryptorchidism	Nephroblastoma (Wims´ tumour), nephritic syndrome owing to glomerular diffuse mesangial sclerosis; often Deny's-Drash syndrome (DSS) and Frasier syndrome; diffuse mesenglial sclerosis associated with pseudohermaphroditism, gonadal tumours	Bardeesy & Pelletier 1998, Pritchard Jones et al. 1990, Pelletier et al. 1991a, Charles et al. 1997, Mundlos et al. 1993, Hanley et al.1999, Pelletier et al. 1991b, Royer-Pokora et al. 2004, Jeanpierre et al.1998, Hossain & Saunders 2001,Hiort & Gillessen-Kaesbach 2009
Anti-Müllerian hormone (AMH) or MIS (Müllerian	Foetal Sertoli cells; produced by Sertoli cells; adult testis	Adult ovaries; granulosa cells of the postnatal ovary	Regression of the Müllerian duct; Leydig cell differentiation; Sertoli cell-	Failure in testosterone production; Leydig cell hyperplasia	Persistent Müllerian duct syndrome; Female sex differentiation	Arango et al. 1999, Cate et al. 1986,

inhibiting substance)			specific factor involved in male differentiation of the internal genitalia; together with androgens and *INSL3* involved in testicular descent			Behringer et al. 1994, Viger et al. 2005
Follicle stimulating hormone receptor (FSHR)	Sertoli cells	Granulosa cells	Important for spermatogenesis and oogenesis	Reduced fertility in males; reduction of testis size (caused be a reduction of Sertoli cells numbers), reduction of circulating testosterone levels	Effects of reduced circulating testosterone	O'Shaughnessy et al. 2007a, Huhtaniemi et al. 1987, Krishnamurthy et al. 2001, Simoni et al. 1997
Kit ligand (or stem cell factor (SCF) or steel factor (SF) or C-Kit ligand)	Somatic cells; Sertoli cells (postnatal)	Olfactory bulb, cerebral cortex, hippocampus region and cerebellum; neurons in certain areas; hematopoietic tissues; follicular cells of the ovary	Reduction of PGC apoptosis in vitro; migration, survival and proliferation of PGCs as an interaction between SCF and C-Kit	PGC defects: germ cell deficiency, due to impaired PGC migration	Hematopoietic defects; KO mice: severe anaemia; lethality late in gestation; neural crest derived melanocytes	Motro et al. 1991, Buehr et al. 1993, Pesce et al. 1993, Matsui et al. 1990, O'Shaughnessy et al. 2007a
Wingless-related MMTV integration site 5A (WNT5A)	Sertoli cell (probably), gonads	Gonads	Testicular development; expression is androgen regulated	Overexpression may be deleterious to normal testis function in the adult	Robinow syndrome	O'Shaughnessy et al. 2007a, O'Shaughnessy et al. 2007b, Person et al. 2010
Androgen receptor (AR)	Sertoli cells, Leydig cells and peritubular cells	Widespread	Regulation of *WNT5A* expression; steroid receptor; Sertoli-germ-cell interaction	Cryptorchidism; male infertility; impaired spermatogenesi;s androgen resistance	Kennedy Disease; hypospadias; congenital lipoid adrenal hyperplasia (lipoid CAH); gynaecomastia;	Tan et al. 2005, Matzuk et al. 2008, Charest et al. 1991, Sharpe et al. 2003
GATA4	Gonadal somatic cells; foetal and adult Leydig cells; increased in Sertoli cells; peritubular myoid cells	Gut and heart cells	Normal *SRY* expression and therefore normal testis development; activation of *StAR, CYP11A, CYP17, CYP19* and *HSD3B2*	Failure in steroidogenic gene expression	Cardiac defect during embryonic development	Manuylov et al. 2008, Viger et al. 2005, O'Shaughnessy et al. 2007a, Ketola et al. 1999
GATA6	Leydig and Sertoli cells in the foetal testis,	Gut and heart cells	Testicular development	Unknown	Early embryonal lethality	O'Shaughnessy et al. 2007a,

	peritubular myoid cells					Ketola et al. 2003
Aristaless-related (X-linked) homeobox (ARX)	Peritubular myoid cells, interstitial fibroblast-like cells, vessel endothelial cells and tunica albuginea in the embryonic testis (mice: E14.5)	Foetal and adult brain; skeletal muscle	Neuronal proliferation, interneuronal migration and differentiation in the embryonic forebrain; differentiation of the testis	Block of Leydig cell differentiation; dysgenetic gonads; cryptorchidism	Ambiguous external genitals; X-linked lissencephaly, epilepsy and temperature instability	Hiort & Gillessen-Kaesbach 2009, Ruggieri et al. 2010, Kitamura et al. 2002,; Matzuk et al. 2008, Jagla et al. 2008
Chromosome X open reading frame 6 (CXORF6)	Leydig and Sertoli cells	Müllerian ducts, forebrain, somites, neural tube, pancreas, somatic cells in the ovary	Testicular development	Ascribed to Leydig cell dysfunction	Abnormal genitalia; hypospadias	O'Shaughnessy et al. 2007a, Fukami et al. 2006
Steroidogenic acute regulatory protein (StAR)	Leydig cells; Sertoli cells (foetal and adult testes)	Ovarian theca, granulosa, ovarian corpora lutea cells, (foetal and adult ovaries), steroidogenic tissue (adrenal cortex, foetal mouse giant trophoblast cells, adrenals, adrenal tumours), brain	Initial and rate-limiting step in steroidogenesis; cholesterol transport from the outer to the inner mitochondrial membrane	Negative effect on testosterone production; disrupts the synthesis of all adrenal and gonadal steroid; male undermasculinization; infertility	Congenital lipoid adrenal hyperplasia (lipoid CAH); female external genitalia; failures in normal growth; die prematurely, presumably as a result of adrenocortical insufficiency; male undermasculinization	Viger et al. 2005, Stocco 2001
P450 side chain cleavage enzyme (CYP11A)	Foetal Leydig cells	Inner mitochondrial membrane in all steroidogenic cells	Cholesterol conversion to pregnenolone	Negative effect on testosterone production; disrupts the synthesis of all adrenal and gonadal steroids; male undermasculinization; infertility	Congenital lipoid adrenal hyperplasia (lipoid CAH); male undermasculinization	Viger et al. 2005, Tajima et al. 2001
Insulin-like factor 3 (INSL3)	Foetal and adult Leydig cells	Pancreatic beta-cells	Together with androgens and AHM involved in testicular descent; first stage of testicular descent	Related to cryptorchidism	Overexpression in female mice leads to descended ovaries	Viger et al. 2005
P450 17α-hydroxylase (CYP17)	Leydig cells	Steroidogenic tissue (e.g. adrenal cortex), ovary	Pregnenolone transformation to testosterone	Negative effect on testosterone production, male pseudohermaphroditism; male undermasculinization; infertility	Patients with sexual infantilism and hypertension, congenital adrenal hyperplasia	Viger et al. 2005, Auchus 2001, Di Cerbo et al. 2002
P450 aromatase (CYP19)	Leydig cells	The placenta, various sites in the brain and in	Testosterone aromatized to estradiol	Negative effect on testosterone production; male	Male undermasculinization	Viger et al. 2005,

		adipose tissue; granulosa cells and corpus luteum of the ovary		undermasculinization; infertility		Kim et al. 2009
17β-hydroxysteroid dehydrogenase type 3 (17βHSD3)	Leydig cells	Steroidogenic cells	Pregnenolone transformation to testosterone	Negative effect on testosterone production; male pseudohermaphroditism; male undermasculinization; infertility	Male undermasculinization	Viger et al. 2005, Boehmer et al. 1999
3β-hydroxysteroid dehydrogenase (3βHSD)	Leydig cells	Microsomal compartment of steroidogenic cells	Pregnenolone transformation to testosterone	Negative effect on testosterone production; male undermasculinization; infertility	Male undermasculinization; congenital adrenal hyperplasia (CAH)	Viger et al. 2005, Simard et al. 2000
Luteinizing hormone and choriogonadotropin receptor gene (LHCGR/LHR)	Leydig cells	Ganulosa-lutein and theca cells	Binding of LH or hCG	No testosterone production; no Leydig cells ; arrest spermatogenesis, male pseudohermaphroditism; Leydig cell hypoplasia (LCH) ; infertility	Delayed puberty; no prostate, and derivates of the Wolfian ducts	Viger et al. 2005, Huhtaniemi 2002, Kossack et al. 2008, Gromoll et al. 2000, Lei et al. 2001
7-dehydrocholesterol reductase (DHCR7)	Leydig cells	Widespread (highly in liver, brain and adrenal tissue)	Reduction of 7DHC to yield cholesterol (final step of cholesterol biosynthesis)	Disturbed steroidogenesis	Variable ambiguous to external genitals; Smith-Lemli-Opitz syndrome with facial abnormalities, clino- and syndactyly defect; mental retardation	Hiort & Gillessen-Kaesbach 2009, Eacker et al. 2008
POR (P450-oxidoreductase)	Leydig cells	Steroidogenic cells	Flavoprotein and electron donor to all microsomal P450 enzymes	Disturbed steroidogenesis	Ambiguous to male external genitals; Antley-Bixler syndrome with craniosynostosis	Hiort & Gillessen-Kaesbach 2009, But et al. 2010
Foorkhead box L2 (FOXL2)	Suppressed by *SOX9* in Sertoli cells of the XY foetus	Human and murine ovary (not expressed in oocytes of the adult mouse ovary); involved in granulosa cell differentiation; mesenchyme of the protruding ridges of developing mouse eyelids	Predominantly ovary promoting activity, due to granulosa cell differentiation; repression of *SOX9* (postnatal stages)	Unknown	Blepharophimosis-ptosis-epicanthus inversus syndrome (BPSE) type 1 and type 2; Type 1: premature ovarian failure (POF), Type 2: eyelid defects; upregulation of *SOX9* in the XX gonad; formation of Sertoli cell-like and Leydig cell-like cells; adult ovarian failure; development of streak gonads and initiation of the male	Ottolenghi et al. 2005, Uhlenhaut et al. 2009, Crisponi et al. 2001, Schmidt et al. 2004, Wilhelm et al. 2009, De Baere et al. 2001,

					differentiation programme, but no XX male has been reported	Prueitt & Zinn 2001, Loffler et al. 2003
Homeobox A13 (HOXA13)	Reproductive tracts	Developing kidneys, axial skeleton	Involved in the formation of the bipotential gonad	Cryptorchidism	Hypospadias; hand and foot abnormalities; mice are lethal during embryonic development, due to kidney failure	Hiort & Gillessen-Kaesbach 2009, Wang et al. 2007