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Currently recognized clinically relevant and known genes for human reproduction and related infertility with representation on high-resolution chromosome ideograms

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Abstract

Objective: To provide an update of currently recognized clinically relevant candidate and known genes for human reproduction and related infertility plotted on high resolution chromosome ideograms (850 band level) and represented alphabetically in tabular form.

Method: Descriptive authoritative computer-based website and peer-reviewed medical literature searches used pertinent keywords representing human reproduction and related infertility along with genetics and gene mutations. A master list of genes associated with human reproduction and related infertility was generated with a visual representation of gene locations on high resolution chromosome ideograms. GeneAnalytics pathway analysis was carried out on the resulting list of genes to assess underlying genetic architecture for infertility.

Results: Advances in genetic technology have led to the discovery of genes responsible for reproduction and related infertility. Genes identified (N = 371) in our search primarily impact ovarian steroidogenesis through sex hormone biology, germ cell production, genito-urinary or gonadal development and function, and related peptide production, receptors and regulatory factors.

Conclusions: The location of gene symbols plotted on high resolution chromosome ideograms forms a conceptualized image of the distribution of human reproduction genes. The updated master list can be used to promote better awareness of genetics of reproduction and related infertility and advance discoveries on genetic causes and disease mechanisms.

Keywords

Human reproduction and related infertility; genes; Genetic pathways; Meiosis; Steroidogenesis; Chromosome ideograms

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Conflict of interest

None.

1. Introduction

Infertility is the inability of couples who are sexually active and not taking contraceptives to achieve a pregnancy within one year. About 70 million infertile couples are noted worldwide and 10%–15% of the US population experiences infertility (Silber and Barbey, 2012; Ombelet et al., 2008). Male infertility accounts for about 50% of infertile cases and can be multifactorial in origin; however, structural chromosomal and mitochondrial DNA abnormalities and hormonal/endocrine disturbances are also known. Non-genetic causes can include abnormal testicular development or descent, genital tract abnormalities, infection, age-related factors, chronic illnesses, impotence, medication and immunity status (Shah et al., 2003). Female infertility is caused by hormonal, anatomical, genetic or environmental factors such as fibroids, tubal blockage, cervical mucus or chromosome abnormalities, pelvic inflammatory disease and age-related factors (Olooto et al., 2012). Women beginning in their 30s will experience a greater than 25% chance of becoming infertile (Silber and Barbey, 2012; Ombelet et al., 2008).

An increased prevalence of human infertility and reproductive problems have been observed in westernized societies and is often related to a selected delay in establishing pregnancies by older women and the ensuing increase in genetic and hormonal imbalance with advancing age in both men and women. The increasing worldwide obesity epidemic further impacts reproduction by disturbing energy balance and expenditure often influenced by genetic and hormonal factors contributing to ovulation dysfunction, spontaneous abortions and overall infertility (Silber and Barbey, 2012; Marsh and Hecker, 2014; Pandy et al., 2010; Balen et al., 2006; Gesink Law et al., 2007; Jungheim et al., 2012; Ogden et al., 2006). Genes encode proteins affecting reproductive organs and function, germ cell production and hormonal factors as well as those contributing to caloric intake (i.e., food seeking, eating behavior), body composition (fat and fat-free mass) and energy storage and utilization (physical activity and metabolism) (Jungheim et al., 2012; Choquet and Meyre, 2011a, 2011b; Zaadstra et al., 1993; Rich-Edwards et al., 1994; Metwally et al, 2007). Obesity often complicates reproduction by affecting genetic factors that are known to play a role in the coordination of many encoded proteins released at selected intervals for the establishment of pregnancies (Jungheim er al., 2012; Metwally et al., 2007). For example, genetic-related conditions that correlate with decreased reproduction (e.g., fewer reproductive cycles) include women with polycystic ovarian syndrome (PCOS) and female carriers of the fragile X syndrome (i.e., *FMR1* gene mutation) (Pasquali and Gambineri, 2006; Peng et al., 2014; Ehrmann, 2005). About 5 to 10% of women from the general population are diagnosed with PCOS and over 40 genes are known to play a role in this disorder (Venkatesh et al., 2014).

A recent computer-based search of websites and peer-reviewed medical literature sources (e.g., www.pubmed.org;www.ncbi.nlm.nih.gov) using keywords related to obesity and genetics identified 370 clinically relevant candidate and known genes for obesity and similarly 153 human infertility and reproduction genes when searching keywords related to infertility and reproduction (Butler et al., 2015). Among them, at least 21 genes were found to be associated with both obesity and human infertility. We now report an updated list of clinically relevant and known genes for human reproduction and related infertility with the display of gene symbols on high resolution (850 band level) chromosome ideograms and

also alphabetically arranged in a tabular form. This illustrative effort of showing the location of genes involved with human infertility and reproduction on chromosome ideograms brings a better awareness of the gene(s) that might be involved in a given chromosomal aberration in an infertile couple and thereby render a more precise genetic basis for infertility, enabling a specific gene-based personalized medicine approach to treatment and genetic counseling. Additionally, GeneAnalytics (http://geneanalytics.genecards.org/) was used to assess the underlying genetic architecture of human reproduction and related infertility by mapping the identified genes to tissues and cells, diseases, phenotypes, molecular pathways and biological processes with the greatest overlap and probable relevance.

2. Materials and methods

Our study involved a computer-based internet approach by searching peer-reviewed articles published in the medical literature [e.g., PubMed (www.pubmed.org)] and other relevant computer-based authoritative websites including Online Mendelian Inheritance in Man (www.OMIM.org); GeneCards (www.genecards.org); and the National Center for Biotechnology Information.

(www.ncbi.nlm.nih.gov). We searched keywords including human infertility, reproduction, meiosis, azoospermia, premature ovarian failure, primary ovarian insufficiency, endometriosis, diminished ovarian reserve and estrogen combined with other keywords such as genes, genetics, mutations or gene variants in order to identify sources with evidence for reproductive genetic factors that are supported by clinical, functional or experimental data for the causation of human infertility in both sexes. The title of the research articles found through this web-based search often contained the keywords of human infertility and genes (or genetics). The research articles were then examined for evidence of involvement of genes or genetic factors playing a role in human infertility or reproduction. Specifically, reviews of whole-genome-wide association studies (GWAS), gene linkage or expression patterns with DNA sequencing of infertile individuals identified a list of multiple genes which were compiled to develop an updated master list of such genes. We then plotted the recognized symbols for each gene that is known or is clinically relevant for causing human infertility and/or involved in reproduction onto high resolution (850 band level) chromosome ideograms (Butler et al., 2015; Shaffer et al., 2013). The master list of all identified genes was then alphabetized by gene symbol, full name of the gene and chromosome band location in a tabular form.

Genome-wide pathway analysis was carried out for the derived gene master list and all mapped genomic variants associated with human reproduction and related infertility using GeneAnalytics (http://geneanalytics.genecards.org/), a commercially available software program based on proprietary, comprehensive and organized databases from the LifeMap suite. Mammalian genes were organized into functional categories based upon *tissues and cells, diseases, pathways, GO-biological processes, GO-molecular function, phenotypes and compounds* (endogenous or exogenous) with functional link to the queried gene set. Gene ontology (GO) terms (e.g., superpathways and GO-biological function) were scored based upon transformation of the binomial p-value which is equivalent to a corrected p-value with significance defined at $p < 0.0001$. Disease-matching scores were derived based upon the

number of overlapping genes and the nature of the gene-disease association. Tissues and cells were scored using a matching algorithm that weighs tissue specificity, abundance and function of the gene. Related pathways were then grouped into superpathways to improve inferences, pathway enrichment, reduce redundancy, and rank genes within a biological mechanism via the multiplicity of constituent pathways (Belinky et al., 2015).

3. Results and discussion

We developed high resolution chromosome ideograms at the 850 band level and plotted the location of the gene symbol representing each gene onto the ideogram at the precise chromosome band or subband level for each of the 371 genes reported to play a role in human infertility and/or reproduction. The genes were identified by searching the medical literature and computer-based websites. Clinically relevant or known human infertility and/or reproductive genes were found to be distributed on all chromosomes (Fig. 1). Not surprisingly, the largest percentage of human reproduction and related infertility genes (i.e., 59 of 371 genes or 16%) were located on the sex chromosome pair (i.e., X and Y) in relationship to the autosomes or non-sex chromosomes. The gene symbol, expanded name and chromosome location are listed in alphabetical order in Table 1 for each of the 371 human infertility and/or reproductive genes. These genes represented a wide range of functions including sex hormone, peptide receptors, organ development, growth, gene transcription or translational factors, germ cell production and metabolic or neuronal influences (Venkatesh et al., 2014; Layman, 2002; Okada et al., 2010, Hu et al., 2014; Kosova et al., 2012; El Inati et al., 2012; Qiu et al., 2013; Ferfouri et al., 2013; Albertsen et al., 2013; Brannian and Hansen, 2002; Fragouli et al., 2014; Bulun, 2014; Greene et al., 2014; Qin et al., 2014; Abid et al., 2013; Bergh et al., 1993).

The GeneAnalytics program identified 5 superpathways with a significant number of overlapping genes in the compiled list of human reproduction and related infertility genes. The Ovarian Steroidogenesis superpathway received the most significant score (score = 80.2) with 23 out of a total gene set of 51 included on our master list of reproduction genes. Genes associated with 16 disease processes showed significant overlap. The top five diseases were Prostate Cancer (32 out of 313, score = 28.6), Infertility (21 out of 22, score = 25.5), Breast Cancer (32 out of 781, score = 24.8), Obesity (29 out of 576, score = 21.7) and Lung Cancer (30 out of 622, score = 21.0). Significant overlap related to tissue and cell type was found for the testis (124 out of 3818, score = 16.6). Multiple overlapping pathways for biological (27 pathways) and molecular (5 pathways) processes were identified that significantly impacted spermatogenesis, male gonad development, cell differentiation and organismal development involving steroidogenesis, hormone receptor activity, sequence-specific DNA and protein binding. These pathways point to functional roles in cellular growth and development targeting gonadal development, maturation and function as key underlying genetic architecture for reproduction and related infertility.

We summarized evidence from the peer-reviewed medical literature using computer-based search engine websites for genes playing a definitive role in human infertility and reproduction. We thus provided an update on the list of 153 relevant genes in human reproduction and/or infertility that was reported previously (Butler et al., 2015). This

updated list includes a total of 371 clinically relevant and known genes for human infertility and/or reproduction. We also provided a pictorial image of the location and distribution of genes on high resolution chromosome ideograms. Not surprisingly, a preponderance of human reproduction and related infertility genes were found on the sex chromosome pair in relationship to the 22 pairs of autosomes which include 68 genes primarily impacting testis formation or sperm production with 24 located on the Y chromosome and 5 on the X chromosome. Genes that directly influence reproduction or infertility are also involved with testes function and spermatogonial cell production (e.g., *ETV5, SPACA1, TSSK6)*, premature ovarian failure (e.g., *FMR1)* or primary ovarian insufficiency (e.g., *SHOX, CCNH, HSD3B2, GNAS)*, development of obesity or susceptibility (e.g., *FTO, PCSIK,STAR)*, gene expression or transcription activators (e.g., *NFE2L3)* or other transcription and translation factors (e.g., *CRTC1, TCEB3B, NUPR1, EIF2B2)* required for the proper development of somatotrophs, thyrotrophs and gonadotrophs (e.g., *PROP1)*, organization or function of the endoplasmic reticulum and protein export (e.g., *SEC16B*) or recycling (e.g., *MAGEL2)*, testes-specific RNA splicing factors (e.g., *TRA2B*) and transcription factors involved with genito-urinary or gonad development (e.g., *WT1, CFTR*) [genes reviewed in Online Mendelian Inheritance in Man (www.OMIM.org) and in Gene Cards (www.genecards.org)]. Collectively, our list of reproduction and infertility genes impact common hormone pathways encompassing ovarian steroidogenesis along with related peptide production and their receptors, specifically those required for hormone storage and transport, gonadal structure and function and germ cell development as noted in Table 1. These roles also directly influence cellular growth and development relevant to disease states involving cancer risk for multiple cell types (prostate, breast, lung and colon).

Data from genome-wide association studies (GWAS) have shown that the onset of menarche in females is influenced by at least 35 individual genes (Qiu et al., 2013; Montgomery et al., 2014). These include *FTO, TRA2B, ETV5, TMEM18* and *SEC16B* which are also known as obesity-related genes (Choquet and Meyre, 2011a, 2011b; Speliotes et al., 2010; Scherag et al., 2010). Pathways analysis of our tabulated list of human reproduction and infertility genes also identified significant overlap with the Obesity disease state. An example of an obesity-related disorder that is characterized by menstrual irregularities, hyperandrogenism and subfertility is polycystic ovary syndrome (PCOS). About 50% of women with PCOS are also obese (Pasquali and Gambineri, 2006; Erhmann, 2005) with several genes implicated (Venkatesh et al., 2014). Factors contributing to human reproduction and/or infertility identified in our review of involved genes include obesity, hormonal imbalance and protein-based disturbances such as leptin which is a key regulator of appetite produced by adipose tissue and known to inhibit ovarian steroidogenesis (Moschos et al., 2002). This process influences sex hormone binding and androgen receptor sensitivity (Peng et al., 2014) with increased levels of androgen resulting in apoptosis of granulosa cells with conversion of androgens peripherally to estrogens in fat cells. This inhibits gonadotrophin secretion and its level thereby impacting the hormone balance and fertility status of women with obesity (Balen et al., 2006; Metwally et al., 2007; Fragouli et al., 2014; Bergh et al., 1993; Zaadstra et al., 1993). Obesity impacts fertility in women by also decreasing the conception rate with a relative risk for anovulatory infertility estimated at 2.7 (Gesink Law et al., 2007; Wise et al., 2010; Rich-Edwards et al., 1994). Spontaneous conceptions are also known to decrease

with subsequent increases in body mass index (BMI) in women. Obesity, therefore, impacts fertility and reproduction by overlapping shared genetic factors implicated or involved in perturbed metabolic and hormonal function (Venkatesh et al., 2014).

Infertility-related genes are noted to be involved with spermatogenesis (e.g.,*ACVR2A,AR,ARNTL)*, testes (e.g., *ANKRD7, BAX, BCL2)* or ovarian follicle development (e.g., *AMH, BMP15, DMC1)*, premature ovarian failure (e.g., *FMR1)* or primary ovarian insufficiency (e.g., *SHOX, CCNH, HSD3B2*, GNAS), development of obesity or susceptibility (e.g., *FTO, PCSK1, STAR)*, gene expression or transcription activators (e.g., *NFE2L3)* or other transcription and translation factors (e.g., *CRTC1, TCEB3B, NUPR1, EIF2B2)* that are required for the proper development of somatotrophs, thyrotrophs and gonadotrophs (*PROP1*), organization or function of the endoplasmic reticulum and protein export (e.g., *SEC16B)* or recycling (e.g., *MAGEL2)*, neuronal influences on body weight regulation (e.g., *TMEM18)*, testes-specific RNA splicing factors (e.g., *TRA2B*) and transcription factors involved with genito-urinary or gonad development (e.g., *WT1, CFTR)* [genes reviewed in OMIM-(www.omim.org) and Gene Cards (www.genecards.org)]. Several obesity-related genes are clearly known to influence infertility by impacting hormonal status and related peptide production. Examples of obesity-related hormonal genes are *LEP, LHB, AMH, INHA, GNRH1, IGF1, FSHB, FST, EPPIN, SHBG* and *IGF2* and examples of obesity-related peptide producing genes and receptors are *AR, ESR1, INSR, FSHR, AMHR2, LHCGR, ACVR1, PPARG, STS, LEPR, VDR* and *IGF1R* (Butler et al., 2015). Thus, infertility susceptibility genes are known to affect common hormonal pathways along with related peptide production and their receptors, specifically those required for hormone storage and transport, gonadal structure and function and germ cell development, as noted in Table 1.

Advances in genetic technology using next generation sequencing of DNA exome or RNA expression data should allow for the discovery of hither to unknown disease-causing genes and their functional regulatory sequences, and thus enable a holistic understanding of commonly disturbed mechanisms in the development of human reproduction, ovulation, sperm production and infertility. This complete systems biological understanding has the potential to lead to targeted avenues of novel treatments and management in a significant number of infertile individuals. Therefore, molecular signatures of human reproduction and infertility-based gene profiles and coding expression patterns with overlap in interconnected disturbed gene pathways of infertility will be important to decipher and study. Further deciphering of infertility genomic perturbation and the resultant changes in the functional hormonal pathways will help characterize the disease mechanisms and processes to provide new targets for drug design and therapy. Characterization of these perturbations on an individual basis should not only lead to targeted more effective treatment modalities, but pave the way for prevention of infertility in the human population.

4. Conclusions

We compiled an updated master list of clinically relevant genes for human reproduction and/or infertility by an extensive search of keywords related to human infertility, reproduction and genetics from peer-reviewed medical research articles and related

nationally sponsored computer-based websites. The symbols for 371 genes were then plotted on high resolution human chromosome ideograms at precise chromosome band locations thereby producing a convenient visual image of the distribution of genetic factors contributing to human infertility and reproduction with alphabetical listing of genes in a tabular form allowing comparison to guide diagnosis, research, counseling and treatment particularly in individuals with chromosomal and/or genomic aberrations. The current number of genes identified in this report will vary in the future when stimulated by the latest advances in genomic technology and augmented by an increased number of subjects analyzed. The authors encourage the use of this current updated collection of clinically relevant candidate and known genes in the evaluation of patients and families in the clinical setting. This genetic information will in-turn encourage additional basic and translational research in human infertility and reproduction.

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Abbreviations:

DNA	deoxyribonucleic acid
RNA	ribonucleic acid
PCOS	polycystic ovarian syndrome
GWAS	genome-wide association studies
OMIM	Online Mendelian Inheritance in Man

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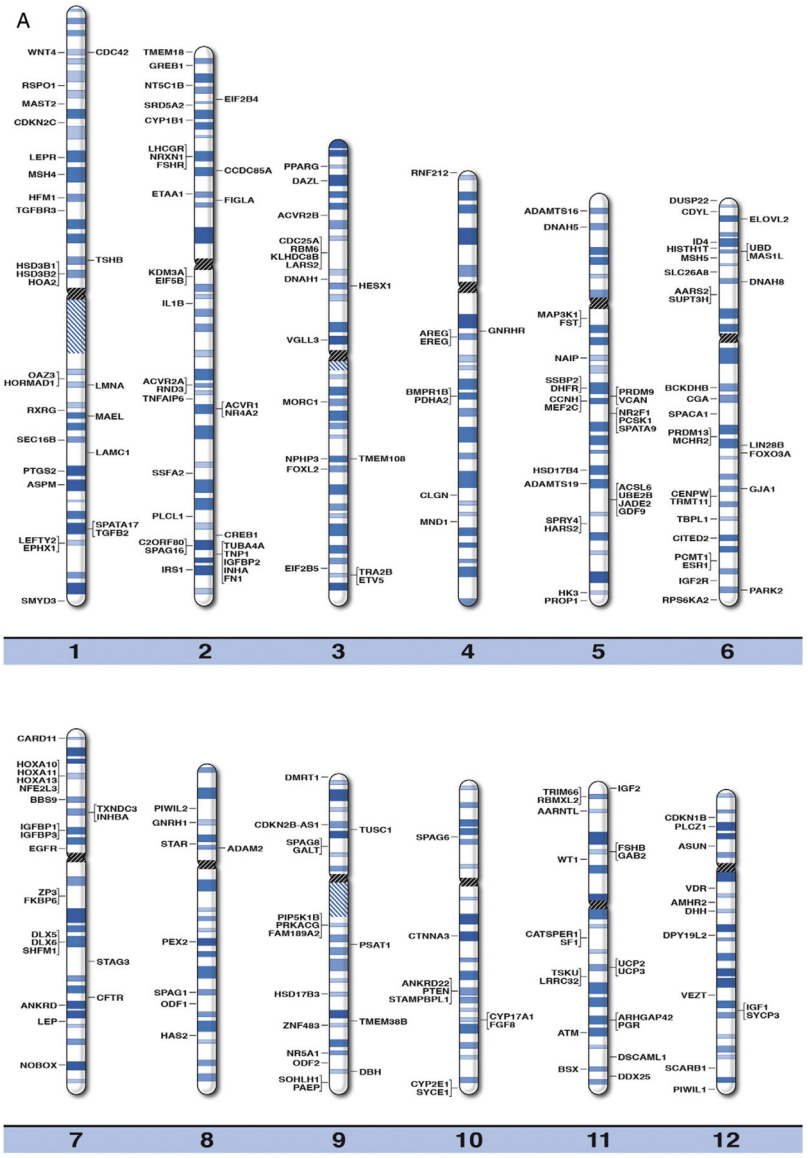

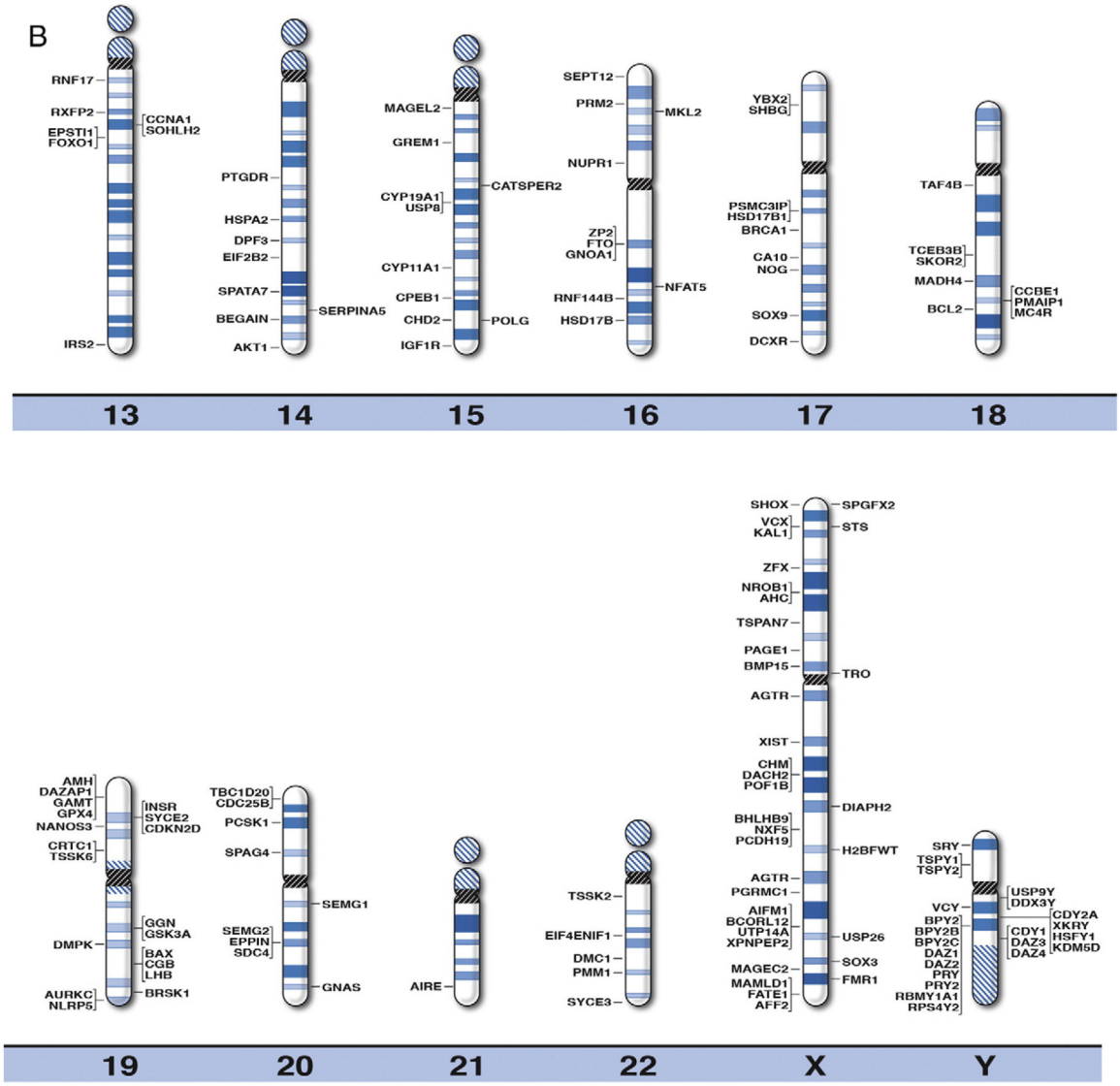

Fig. 1.

High resolution human chromosome ideograms (850 band level) with gene symbols representing genetic biomarkers for infertility and reproduction plotted on chromosome bands for each of the 371 genes. The centromere area is highlighted in black which separates the upper short ‘p’ arm from the lower long ‘q’ arm for each chromosome. The gene symbols are arranged in alphabetical order with the expanded name and precise chromosome band location listed in Table 1.

Table 1.

Currently recognized genes for human reproduction and infertility with their chromosome locations.

GENE SYMBOL	GENE NAME	BAND
AARS2	Leukoencephalopathy, progressive with ovarian failure; LKENP	*6p21:1*
ACSL6	Acyl-CoA synthetase long-chain family member 6	*5q31.1*
ACVR1	Activin A receptor, type I	*2q24.1*
ACVR2A	Activin A receptor, type IIA	*2q22.3*
ACVR2B	Activin A receptor, type IIB	*3p22.2*
ADAM2	A disintegrin and metalloproteinase domain 2	*8p11.22*
ADAMTS16	ADAM metalopeptidase with thrombospondin type I motif, 16	*5p15.32*
ADAMTS19	ADAM metalopeptidase with thrombospondin type I motif, 19	*5q23.3*
AFF2	Fragile X mental retardation 2	*Xq28*
AGTR2	Angiotensin lireceptor, type2	*Xq23*
AHC	Adrenal hypoplasia, congenital	*Xp21.2*
AIFM1	Apoptosis-inducing factor, mitochondrion-associated, 1	*Xq26.1*
AIRE	Autoimmune regulator	*21q22.3*
AKT1	V-Akt murine thymoma viral oncogene homolog 1	*14q32.33*
AMH	Anti-mullerian hormone	*19p13.3*
AMHR2	Anti-mullerian hormone receptor, type II	*12q13.13*
ANKRD7	Ankyrin repeat domain 7	*7q31.31*
ANKRD22	Ankyrin repeat domain 22	*10q23.31*
AR	Androgen receptor	*Xq12*
AREG	Amphiregulin	*4q13.3*
ARHGAP42	Rho GTPase-activating protein 42	*11q22.1*
ARNTL	Aryl hydrocarbon receptor nuclear translocator-like	*11p15.2*
ASPM	ASP (abnormal spindle) homolog, microcephaly associated (Drosophila)	*lq31.3*
ASUN	Asunder spermatogenesis regulator	*12p11.23*
ATM	Ataxia-telangiectasia mutated	*11q22.3*
AURKC	Aurora kinase C	*19q13.43*
BAX	BCL2-associated X protein	*19q13.33*
BBS9	Parathyroid hormone- responsive B1	*7p14.3*

GENE SYMBOL	GENE NAME	BAND
BCKDHB	Branched-chain keto acid dehydrogenase E1, beta polypeptide	*6q14.1*
BCL2	B-cell CLL/lymphoma 2	*18q21.33*
BCORL1	BCL6 corepressor-like 1	*Xq26.1*
BECAIN	Brain-enriched granylate kinase-associated	*14q32.2*
BHLHB9	Basic helix-loop-helix domain- containing protein, class B9	*Xq22.1*
BMP15	Bone morphogenetic protein 15	*Xq11.22*
BMPR1B	Bone morphogenetic protein receptor, type 1B	*4q22.3*
BPY2	Basic charge, Y-linked, 2	*Yq11.223*
BPY2B	Basic charge, Y-linked, 2B	*Yq11.223*
BPY2C	Basic charge, Y-linked, 2C	*Yq11.223*
BRCA1	Breast cancer 1, early onset	*17q21.31*
BRDT	Bromodomain, testis-specific	*1p22.1*
BRSK1	BR serine/threonine kinase 1	*19ql3.42*
BSX	Brain specific homeobox	*11q24.1*
CA10	Carbonic anhydrase X	*17q21.33*
CATSPFR1	Cation channel, sperm associated 1	*11q13.1*
CATSPER2	Cation channel, sperm associated 2	*15q15.3*
CARD11	Caspase recruitment domain family, member 11	*7p22.2*
CCBE1	Collagen and calcium-binding EGF domain containing protein 1	*18q21.32*
CCDC85A	Coiled-coil domain containing 85A	*2p16.1*
CCNA1	Cyclin A1	*13q13.3*
CCNH	Cyclin H	*5q14.3*
CDC25A	Cell division cycle 25A	*3p21.31*
CDC25B	Cell division cycle 25B	*20p13*
CDC42	Cell division cycle 42	*1p3612.*
CDC6	Cell division cycle 6	*17q21.2*
CDKN1B	Cyclin-dependent kinase inhibitor 1B	*12p13.1*
CDKN2B-AS1	CDKN2B antisense RNA 1	*9p21.3*
CDKN2C	Cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	*1p32.3*
CDKN2D	Cyclin-dependent kinase inhibitor 2D (p19, inhibits CDK4)	*19p13.2*
CDY1	Chromodomain protein, Y- linked, 1	*Yq11.23*

GENE SYMBOL	GENE NAME	BAND
CDY2A	Chromodomain protein, Y- linked, 2A	*Yq11.222*
CDYL	Chromodomain protein, Y-like	*6p25.1*
CENPW	Centromeric protein W	*6q22.32*
CFTR	Cystic fibrosis transmembrane conductance regulator	*7q31.2*
CGA	Chorionic gonadotropin, alpha chain	*6q14.3*
CGB	Chorionic gonadotropin, beta polypeptide	*19q13.33*
CHD2	Chromodomain helicase DNA- binding protein 2	*15q26.1*
CHM	Choroideremia	*Xq21.2*
CITED2	CBP/p300-interacting transactivator, with glu/asp- rich C-terminal domain 2	*6q24.1*
CLGN	Calmegin	*4q31.1*
CPEB1	Cytoplasmic polyadenylation element-binding protein 1	*15q25.2*
CREB1	cAMP response element- binding protein 1	*2q33.3*
CRTC1	CREB-regulated transcription co-activator 1	*19p13.11*
CTNNA3	Catenin (Cadherin-associated protein), alpha 3	*10q21.3*
CYP11A1	Cytochrome p450, family 11, subfamily A, polypeptide 1	*15q24.1*
CYP17A1	Cytochrome p450, family 17, subfamily A, polypeptide 1	*10q24.32*
CYP19A1	Cytochrome p450, family 19, subfamily A, polypeptide 1	*15q21.2*
CYP1B1	Cytochrome p450, family 1, subfamily B, polypeptide 1	*2p22.2*
CYP2E1	Cytochrome p450, family 2, subfamily E, polypeptide 1	*10q26.3*
C20RF80	Chromosome 2 open reading frame 80	*2q34*
DACH2	Dachshund, Drosophila, homolog 2	*Xq21.2*
DAZ1	Deleted in azoospermia 1	*Yq11.223*
DAZ2	Deleted in azoospermia 2	*Yq11.223*
DAZ3	Deleted in azoospermia 3	*Yq11.23*
DAM	Deleted in azoospermia 4	*Yq11.23*
DAZAP1	DAZ associated protein 1	*19p13.3*
DAZL	Deleted in azoospermia-Like	*3p24.3*
DBH	Dopamine α-hydroxylase	*9q34.2*
DCXR	Dicarbonyl/L-xylulose reductase	*17q25.3*
DDX25	DEAD (asp-glu-ala-asp) box helicase 25	*11q24.2*
DDX3Y	DEAD (asp-glu-ala-asp) box helicase 3, Y-linked	*Yq11.21*

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GENE SYMBOL	GENE NAME	BAND
DHFR	Dihydrofolate reductase	*5q14.1*
DHH	Desert hedgehog	*12q13.12*
DIAPH2	Diaphanous, Drosophila, homolog of, 2	*Xq21.33*
DLX5	Distal-less homeobox 5	*7q21.3*
DLX6	Distal-less homeobox 6	*7q21.3*
DMC1	Disrupted meiotic cDNA 1	*22q13.1*
DMPK	Dystrophia myotonica-protein kinase	*19q13.32*
DMRT1	Doublesex -and MAB3- related transcription factor 1	*9p24.3*
DNAH1	Dynein, axonemal, heavy chain 1	*3p21.1*
DNAH5	Dynein, axonemal, heavy chain 5	*5p15.2*
DNAH8	Dynein, axonemal, heavy chain 8	*6p21.2*
DPF3	D4, zinc, and double PHD fingers, family, member 3	*14q24.2*
DPY19L2	DPY19-like 2	*12q14.2*
DSCAML1	Down syndrome cell adhesion molecule-like 1	*11q23.3*
DUSP22	Dual specificity phosphatase 22	*6p25.3*
EGFR	Epidermal growth factor receptor	*7p11.2*
EIF2B2	Eukaryotic translation initiation factor 2b, subunit 2	*14q24.3*
EIF2B4	Eukaryotic translation initiation factor 2b, subunit 4	*2p23.3*
E1F2B5	Eukaryotic translation initiation factor 2b, subunit 5	*3q27.1*
EIF5B	Eukaryotic translation initiation factor 5b	*2q11.2*
EIF4ENIF1	Eukaryotic translation initiation factor 4E nuclear import factor 1	*22q12.2*
EL0VL2	Elongation of very long chain fatty acids-like 2	*6p24.2*
EPHX1	Epoxide hydrolase 1	*1q42.12*
EPPIN	Epididymal peptidase inhibitor	*20q13.12*
EPSTI1	Epithelial stromal interaction 1	*13q14.11*
EREG	Epiregulin	*4q13.3*
ESR1	Estrogen receptor 1	*6q25.1*
ETAA1	Ewing tumor-associated antigen 1	*2p14*
ETV5	ETS variant gene 5	*3q27.2*
FAM189A2	Family with sequence similarity 189, member A2	*9q21.11*
FATE1	Fetal and adult testis expressed 1	*Xq28*

GENE SYMBOL	GENE NAME	BAND
FCF8	Fibroblast growth factor 8	*10q24.32*
F1GLA	Folliculogenesis specific basic helix-loop-helix	*2p13.3*
FKBP6	FK506 binding protein 6	*7q11.23*
FMN2	Formin 2	*1q43*
FMR1	Fragile X mental retardation 1	*Xq27.3*
FM	Fibronectin 1	*2q35*
FOXL2	Forkhead box L2	*3q22.3*
FOXO1	Forkhead box O1	*13q14.11*
FOXO3A	Forkhead box O3A	*6q21*
FST	Follistatin	*5q11.2*
FSHB	Follicle stimulating hormone, beta polypeptide	*11p14.1*
FSHR	Follicle stimulating hormone receptor	*2pl6.3*
FTO	Fat mass-and obesity- associated gene	*16q12.2*
GAB2	GRB2-associated binding protein 2	*UqU.1*
GALT	Galactose 1 phosphate uridylyl transferase	*9p13.3*
GAMT	Guanidinoacetate N-methyl transferase	*19p13.3*
GDF9	Growth/differentiation factor 9	*5q31.7*
GGN	Gametogenetin	*19q13.2*
GJA1	GAP junction protein, alpha −1	*6q22.31*
GNAO1	Guanine nucleotide-binding protein, alpha activating activity polypeptide O	*16q12.2*
GNAS	Guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1	*20q13.32*
GNRH1	Gonadotropin-releasing hormone 1	*8p21.2*
GNRHR	Gonadotropin-releasing hormone receptor	*4q13.2*
GPR3	G protein-coupled receptor 3	*1p36.11*
GPX4	Glutathione peroxidase 4	*19p13.3*
GREB1	Growth regulation by estrogen in breast cancer 1	*2p25.1*
GREM1	Gremlin 1 homolog, cystine knot superfamily	*15q13.3*
GSK3A	Glycogen synthase kinase 3 alpha	*19q13.2*
H2BFWT	H2B histone family, member W, testis-specific	*Xq22.2*
HAO2	Hydroxyacid oxidase 2	*1p12*
HARS2	Histidyl-tRNA synthetase2	*5q31.3*

GENE SYMBOL	GENE NAME	BAND
HAS2	Hyaluronan synthase 2	*8q24.13*
HESX1	HESX homeobox 1	*3p14.3*
HFM1	Premature ovarian failure 9; POF9	*1p22.2*
HIST1H1T	Histone gene cluster 1, HI histone family, member T	*6p22.2*
HK3	Hexokinase 3	*5q35.2*
HORMAD1	HORMA domain containing 1	*1q21.3*
HOXA10	Homeobox A10	*7p15.2*
HOXA11	Homeobox A11	*7p15.2*
HOXA13	Homeobox A13	*7p15.2*
HSD3B1	3-beta-hydroxysteroid dehydrogenase I	*1p12*
HSD3B2	3-beta-hydroxysteroid dehydrogenase II	*1p12*
HSD17B1	17-beta-hydroxysteroid dehydrogenase 1	*17q21.2*
HSD17B2	17-beta-liydroxysteroid dehydrogenase II	*16q23.3*
HSD17B3	17-beta-hydroxysteroid dehydrogenase III	*9q22.32*
HSD17B4	17-beta-hydroxysteroid dehydrogenase IV	*5q23.1*
HSFY1	Heat shock transcription factor, Y-linked 1	*Yq11.222*
HSPA2	Heat shock 70kDa protein 2	*14q23.3*
ID4	Inhibitor of DNA binding 4	*6p22.3*
IGF1	Insulin-like growth factor 1	*12q23.2*
IGF1R	Insulin-like growth factor 1 receptor	*15q26.3*
IGF2	Insulin-like growth Factor 2	*11p15.5*
IGF2R	Insulin-like growth factor 2 receptor	*6q25.3*
IGFBP1	Insulin-like growth factor- binding protein 1	*7p12.3*
IGFBP2	Insulin-like growth factor- binding protein 2	*2q35*
IGFBP3	Insulin-like growth factor- binding protein 3	*7p12.3*
IL1B	Interleukin 1, beta	*2q13*
INCENP	Inner centromere protein antigens 135/155kDa	*11q12.3*
INHA	Inhibin alpha	*2q35*
INHBA	Inhibin, beta A	*7p14.1*
INSR	Insulin receptor	*19p13.2*
IRS1	Insulin receptor substrate 1	*2q36.3*

GENE SYMBOL	GENE NAME	BAND
IRS2	Insulin receptor substrate 2	*13q34*
JADE2	PHD finger protein 15	*5q31.1*
KALI	Kallmann syndrome 1	*Xp22.31*
KDM3A	Lysine (K)-specific demethylase 3A	*2p11.2*
KDM5D	Lysine (K)-specific demethylase 5D	*Yq11.222*
KLHDC8B	Kelch domain-containing protein 8B	*3p21,31*
LAMC1	Laminin, gamma 1	*1q25.3*
LARS2	Leucyl-tRNA synthetase 2	*3p21.31*
LEFTY2	Left-right determination factor 2	*1q42.12*
LEP	Leptin	*7q32.1*
LEPR	Leptin receptor	*1p31.3*
LHB	Luteinizing hormone beta polypeptide	*19q13.33*
LHCGR	Luteinizing hormone/choriogonadotropin receptor	*2p16.3*
L1N28B	LIN 28, C. elegans, homolog of, B	*6q16.3*
LMNA	Lamin A	*1q22*
LRRC32	Leucin-rich repeat containing protein 32	*11q13.5*
MADH4	Mothers against decapentaplegic homolog 4	*18q21.2*
MAGEC2	Melanoma antigen, family C, 2	*Xq27.2*
MAEL	Maelstrom spermatogenic transposon silencer	*1q24.1*
MAGEL2	MAGE (melanoma-associated antigen)-like 2	*15q11.2*
MAMLD1	Mastermind-like domain- containing protein 1	*Xq28*
MAP3K1	Mitogen-activated kinase kinase kinase 1	*5q11.2*
MAS1L	MAS! oncogene-like	*6p22.1*
MAST2	Microtubule associated serine/threonine kinase 2	*1p34.1*
MCHR2	Melanin-concentrating hormone receptor 2	*6q16.2*
MC4R	Melanocortin 4 receptor	*18q2l.32*
MEF2C	MADS box transcription enhancer factor 2, polypeptide C	*5q14.3*
MKL2	MKL/myocardin-like 2	*16p13.12*
MND1	Meiotic nuclear divisions 1 homolog (S. cerevisia)	*4q31.3*
MORC1	MORC family CW-type zinc finger 1	*3q13.13*
MSH4	MutS homolog 4	*1p31.1*

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GENE SYMBOL	GENE NAME	BAND
MSH5	MutS homolog 5	*6p21,33*
NA1P	NLR family, apoptosis inhibitory protein	*5q13.2*
NANOS3	NANOS, Drosophila, homolog 3	*19p13.13*
NFAT5	Nuclear factor of activated T cells 5	*16q22.1*
NFE2L3	Nuclear factor erythroid 2-like 3	*7p15.2*
NLRP5	NLR family, Pyrin domain containing 5	*19q13.43*
NOBOX	Newborn ovary homeobox	*7q35*
NOG	Noggin	*17q22*
NPHP3	Nephronopthisis 3	*3q22.1*
NR0B1	Nuclear receptor subfamily 0, group B, member 1	*Xp21.2*
NR2F1	Nuclear receptor subfamily 2, group F, member 1	*5q15*
NR4A2	Nuclear receptor subfamily 4, group A, member 2	*2q24.1*
NR5A1	Nuclear receptor subfamily 5, group A, member 1	*9q33.3*
NRXN1	Neurexin	*2p16.3*
NT5C1B	5’-nucleotidase, cytosolic IB	*2p24.2*
NUPR1	Nuclear protein, transcriptional regulator, 1	*16p11.2*
NXF5	Nuclear RNA export factor, 5	*Xq22.1*
OAZ3	Ornithine decarboxylase antizyme 3	*1q21.3,*
ODF1	Outer dense fiber of sperm tails 1	*8q22.3*
ODF2	Outer dense fiber of sperm tails 2	*9q34.11*
PAEP	Progestagen-associated endometrial protein	*9q34.3*
PACE1	P antigen family, member 1 (prostate associated)	*Xp11.23*
PARK2	Parkin RBR E3 ubiquitin protein ligase	*6q26*
PCDH19	Protocadherin 19	*Xq22.1*
PCMT1	Protein-L-isoaspartate (D- Aspartate) O- methvltransferase	*6q25.1*
PCSK1	Proprotein convertase, subtilisin/kexin-type 1	*5qJ5*
PCSK2	Proprotein convertase, subtilisin/kexin-type 2	*20p12.1*
PDHA2	Pyruvate dehydrogenase, alpha-2	*4q22.3*
PGR	Progesterone receptor	*11q22.1*
PGRMC1	Progesterone receptor membrane component 1	*Xq24*
PIP5K1B	Phosphatidylinositol 4- phosphate 5-kinase, type1, beta	*9q21.11*

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GENE SYMBOL	GENE NAME	BAND
PIWIL1	PIWI-like RNA-mediated gene silencing 1	*12q24.33*
PIWIL2	PIWI-like RNA-mediated gene silencing 2	*8p21.3*
PLCL1	Phospholipase C-like 1	*2q33.1*
PLCZ1	Phospholipase C, zeta 1	*12p12.3*
PMAIP1	Phorbol-12-myristate-13- acetate-induced protein 1	*18q21.32*
PMM1	Phosphomannomutase	*22q13.2*
POF1B	Premature ovarian failure, IB	*Xq21.2*
POLG	Polymerase, DNA, gamma	*15q26.1*
PPARG	Peroxisome proliferator- activated receptor-gamma	*3p25.2*
PRDM9	PR domain containing 9	*5p14.2*
PRDM13	PR domain containing 13	*6q16.2*
PRKACG	Protein kinase, cAMP- dependent, catalytic, gamma	*9q21.11*
PRM2	Protamine 2	*16p13.13*
PROP1	PROP paired-like homeobox 1	*5q35.3*
PRY	PTPBL-related gene on Y	*Yq11.223*
PRY2	PTPBL-related gene on Y, 2	*Yq11.223*
PSAT1	Phosphoserine aminotransferase 1	*9q21.2*
PSMC3IP	Proteasome 26S subunit, ATPase, 3-interacting protein	*17q21.2*
PTEN	Phosphatase and tensin homolog	*10q23.31*
PTGDR	Prostaglandin D2 receptor	*14q22.1*
PTGS2	Prostaglandin-endoperoxide synthase 2	*1q31.1*
PEX2	Peroxisomal biogenesis factor 2	*8q21.11*
RBM6	RNA-binding motif protein 6	*3p21.31*
RBMXL1	RNA binding motif protein, X- linked-like 1	*1p22.2*
RBMXL2	RNA binding motif protein, X- linked like 2	*11p15.4*
RBMY1A1	RNA binding motif protein, Y- linked, family 1, member A1	*Yq11.223*
RND3	RHO family GTPase 3	*2q23.3*
RNF144B	Ring finger protein 144B	*6p22.3*
RNFI7	Ring finger protein 17	*13q12.12*
RNF212	Ring finger protein 212	*4p16.3*
RPS4Y2	Ribosome protein S4,Y-linked 2	*Yq11.223*

GENE SYMBOL	GENE NAME	BAND
RPS6KA2	Ribosomal protein S6 kinase 90kDa, polypeptide 2	*6q27*
RSPO1	R-spondin 1	*1p34.3*
RXFP2	Relaxin/insulin-like family peptide receptor 2	*13q13.1*
RXRG	Retinoid X receptor, gamma	*1q23.3*
SCARB1	Scavenger receptor class B, member 1	*12q24.31*
SDC4	Syndecan 4	*20q13.12*
SEC16B	SEC16 homolog B	*1q25.2*
SEMG1	Semenogelin I	*20q13.12*
SEMG2	Semenogelin II	*20q13.12*
SEPT12	Septin 12	*16p13.3*
SERP1NA5	SERP1N peptidase inhibitor, clade A, member 5	*14q32.13*
SF1	Splicing factor 1	*11q13.1*
SHBG	Sex hormone-binding globulin	*17p13A*
SHFM1	Split hand/foot malformation (ectrodactyly) type 1	*7q21.3*
SHOX	Short stature homeobox	*Xp22.33*
SKOR2	SKI family transcriptional corepressor 2	*18q21.1*
SLC26A8	Solute carrier family 26 (anion exchanger), member 8	*6p21.31*
SMYD3	SET and MYND domain containing protein 3	*1q44*
SOHLH1	Spermatogenesis and oogenesis-specific basic helix- loop-helix protein 1	*9q34.3*
SOHLH2	Spermatogenesis and oogenesis specific basic helix- loop-helix 2	*13q13.3*
SOX3	SRY (sex determining region Y) -box 3	*Xq27.1*
SOX9	SRY-box 9	*17q24.3*
SPACA1	Sperm acrosome associated 1	*6q15*
SPAG1	Sperm associated antigen 1	*8q22.2*
SPAG4	Sperm associated antigen 4	*20q11.22*
SPAG6	Sperm associated antigen 6	*10p12.2*
SPAG8	Sperm associated antigen 8	*9p13.3*
SPAG16	Sperm associated antigen 16	*2q34*
SPATA7	Spermatogenesis associated 7	*14q31.3*
SPATA9	Spermatogenesis associated 9	*5q15*
SPATA17	Spermatogenesis associated 17	*1q41*

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GENE SYMBOL	GENE NAME	BAND
SPGFX2	Spermatogenic failure, X- linked, 2	*Xp22.33*
SPRY4	Sprouty homolog 4 (Drosophila)	*5q31.3*
SRD5A2	Steroid 5-alpha-reductase 2	*2p23.1*
SRY	Sex-determining region Y	*Yp11.31*
SSBP2	Single-stranded DNA binding protein 2	*5q14.1*
SSFA2	Sperm specific antigen 2	*2q31.3*
STAG3	Stromal antigen 3	*7q22.1*
STAMBPL1	STAM binding peotein -like 1	*10q23.31*
STAR	Steroidogenic acute regulatory protein	*8p11.23*
STS	Steroid sulfatase (microsomal), isozyme S	*Xp22.31*
SUPT3H	Suppressor of Ty 3, S. cerevisiae homolog	*6p21.1*
SYCE1	Synaptonemal complex central element protein 1	*10q26.3*
SYCE2	Synaptonemal complex central element protein 2	*19p13.2*
SYCE3	Synaptonemal complex central element protein 3	*22q13.33*
SYCP3	Synaptonemal complex protein 3	*12q23.2*
TAF4B	TAF4B RNA polymerase II, TATA box-binding protein- associated factor	*18q11.2*
TBC1D20	TBC1 domain family, member 20	*20p13*
TBPL1	TBP-like 1	*6q23.2*
TCEB3B	Transcription elongation factor B, polypeptide 3B	*18q21.1*
TGFB2	Transforming growth factor, beta 2	*1q41*
TGFBR3	Transforming growth factor- beta receptor, type III	*1p22.1*
TMEM18	Trans membrane protein 18	*2p25.3*
TMEM38B	Transmembrane protein 38B	*9q31.2*
TMEM108	Transmembrane protein 108	*3q22.1*
TNFAIP6	Tumor necrosis factor-alpha- induced protein 6	*2q23.3*
TNP1	Transition protein 1	*2q35*
TRA2B	Transformer 2, Drosophila, homolog of beta	*3q27.2*
TR1M66	Tripartite motif-containing protein 66	*11p15.4*
TRMT11	tRNA methyl transferase 11	*6q22.32*
TRO	Trophinin	*Xp11.21*
TSHB	Thyroid-stimulating hormone, beta chain	*1p13.2*

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GENE SYMBOL	GENE NAME	BAND
TSKU	Tsukushin, small leucine rich proteoglycan	*11q13.5*
TSPAN7	Tetraspanin 7	*Xp11.4*
TSPY1	Testis-specific protein, Y- l inked 1	*Yp11.2*
TSPY2	Testis-specific protein,Y-linked 2	*Yp11.2*
TSSK2	Testis-specific serine kinase 2	*22q11.21*
TSSK6	Testis-specific serine kinase 6	*19p13.11*
TUBA4A	Tubulin, alpha-4A	*2q35*
TUSC1	Tumor suppressor candidate 1	*9p21.2*
TXNDC3	Thioredoxin domain- containing protein 3	*7pl4.1*
UBD	Ubiquitin D	*6p22.1*
UBE2B	Ubiquitin-conjugating enzyme E2B	*5q31.1*
UCP2	Uncoupling protein 2	*11q13.4*
UCP3	Uncoupling protein 3	*11q13.4*
USP8	Ubiquitin-specific protease 8	*15q21.2*
USP26	Ubiquitin-specific protease 26	*Xq26.2*
USP9Y	Ubiquitin-specific protease9, Y-linked	*Yq11.21*
UTP14A	U3 small nucleolar ribonucleoprotein, homolog A	*Xq26.1*
VCAN	Versican (chondroitin sulfate proteoglycan 2)	*5q14.2*
VCX	Variable charge, X-linked	*Xp22.31*
VCY	Variable charge, Y-linked	*Yq11.221*
VDR	Vitamin D receptor	*12q13.11*
VEZT	Vezatin, adherens junctions transmembrane protein	*12q22*
VCLL3	Vestigial-like 3	*3p12.1*
WNT4	Wingless-type MMTV integration site family, member 4	*1p36.12*
WT1	Wilms tumor 1	*11p13*
XIST	X inactivation-specific transcript	*Xq13.2*
XKRY	XK, Kell blood group complex subunit-related, Y-linked	*Yq11.222*
XPNPEP2	X-propyl aminopeptidase 2	*Xq26.1*
YBX2	Y box binding protein 2	*17p13.1*
ZFX	Zink finger protein, X-linked	*Xp22.11*
ZNF483	Zinc finger protein 483	*9q31.3*

GENE SYMBOL	GENE NAME	BAND
ZP2	Zona pellucida glycoprotein 2 (sperm receptor)	*16p12.2*
ZP3	Zona pellucida glycoprotein 3 (sperm receptor)	*7q11.23*