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The Genetics of Infertility: Current Status of the Field

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Abstract Infertility is a relatively common health condition, affecting nearly 7 % of all couples. Clinically, it is a highly heterogeneous pathology with a complex etiology that includes environmental and genetic factors. It has been estimated that nearly 50 % of infertility cases are due to genetic defects. Hundreds of studies with animal knockout models convincingly showed infertility to be caused by gene defects, single or multiple. However, despite enormous efforts, progress in translating basic research findings into clinical studies has been challenging. The genetic causes remain unexplained for the vast majority of male or female infertility patients. A particular difficulty is the huge number of candidate genes to be studied; there are more than 2,300 genes expressed in the testis alone, and hundreds of those genes influence reproductive function in humans and could contribute to male infertility. At present, there are only a handful of genes or genetic defects that have been shown to cause, or to be strongly associated with, primary infertility. Yet, with completion of the human genome and progress in personalized medicine, the situation is rapidly changing. Indeed, there are 10–15 new gene tests, on average, being added to the clinical genetic testing list annually.

Keywords Chromosome aberrations · Copy number variants · Single-gene disorders · Male infertility · Female infertility · Y chromosome microdeletions

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Introduction

Infertility is a highly complex disorder of the reproductive system. There are two forms of male or female sterility: primary and secondary. The primary form affects germ cell structure or physiology, causing arrest of germ cell development and ultimately cell death. Primary female infertility includes premature ovarian failure (POF), polycystic ovary syndrome (PCOS), endometriosis, and leiomyoma. Primary male sterility disrupts spermatogenesis and is associated with abnormal semen (i.e., abnormal sperm count, morphology, or motility), but often the semen is normal (idiopathic infertility).

Secondary infertility arises because of systemic or syndromic genetic defects, including developmental, endocrine, and metabolic defects. Genetic syndromes that manifest male or female infertility are fragile X syndrome, Kartagener's syndrome, myotonic dystrophy, Noonan syndrome, Fanconi anemia, sickle cell anemia, β-thalassemia, etc. Other notable conditions include disorders of sex development (*DAX1*, *CBX2*, *SRY*, *SOX9*, *RSPO1*) [1–6], reproductive dysgenesis disorders (*AMH*, *AMHR2*, *ARX*, *DHH*, *NR5A1*, *WNT4*, *WT1*) [6], hypogonadotrophic hypogonadism and Kallmann syndrome (*KAL1*, *FGFR1*, *PROKR2*, *GNRH1*, *TAC3*, *LEP*, *NSMF*, *CHD7*, *DAX1*, *KISS1*) [7], ambiguous genitalia and androgen insensitivity (*AR*) [8], and congenital bilateral absence of the vas deferens (*CFTR*); (Tables 1, 2) [9, 10].

Endocrine defects comprise disruption of steroid synthesis and metabolism, and are caused by *CYP17*, *CYP21*, and *CYP21A2* mutations [6, 11, 12]. Also, various metabolic defects (e.g., galactosemia) [13] and mutations in mitochondrial energy pathways (*POLG1* and mitochondrial DNA genes) cause toxic effects and lead to secondary female or male infertility [14]. All

genetic defects can be divided into the following categories: chromosome aberrations, DNA copy number variants (micro deletions and duplications), single-gene disorders, complex conditions, and epigenetic disorders.

Chromosomal Defects in Male Infertility

Constitutional chromosome aberrations are the most frequent cause of male infertility, detected in up to 20 % of infertile men with semen defects; i.e., azoospermia and oligozoospermia [6, 11, 12, 15]. The aberrations include numerical defects, such as the XXY karyotype in Klinefelter syndrome or its variants and structural rearrangements, Robertsonian translocations, balanced reciprocal translocations, and inversions. Rarely, infertile men with normal karyotypes have chromosome aberrations in sperm [16]. Increased germ cell defects have been reported for chromosomes 21, 22, X, and Y [15, 16].

Klinefelter Syndrome

Klinefelter syndrome (KS, karyotype 47,XXY) is the most common chromosomal aberration, detected in up to 14 % of infertile patients with azoospermia [17]. Klinefelter patients manifest language delay and learning and behavioral problems [18]. Their testis histology shows germ cell degeneration, while serum levels of hormones are abnormal, with a decline in testosterone level and elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [12, 17, 18]. The 47,XXY karyotype accounts for nearly 90 % of the patients, while other variants are rare [17]. Usually, the extra X is a result of chromosome nondisjunction in male or female meiosis [18]. Nearly 10 % of KS patients are mosaic 47,XXY/46,XY. Although the sperm of Klinefelter men usually have a normal 23,X or 23,Y haploid genome, an increased rate of autosomal and sex chromosome aneuploidies was reported in KS men's offspring [19].

The 47,XYY Syndrome

This syndrome occurs in 1:1,000 men, but is more common among infertile males [15, 17]. Infertile men with the 47,XYY karyotype are otherwise healthy. While semen analyses of 47,XYY males frequently indicate oligozoospermia or azoospermia, the majority of them are fertile, with normal semen parameters [16]. It has been shown that germ cells with an extra Y chromosome from men with the 47,XYY karyotype have abnormal meiotic pairing, suggesting disrupted meiosis, eventual sperm apoptosis, and subsequent oligozoospermia and infertility [15, 16].

Structural Chromosomal Abnormalities (SCAs)

SCAs include deletions, duplications, translocations (balanced, imbalanced, and Robertsonian), and inversions. Overall, SCAs occur in nearly 5 % of infertile men (0.5 % in the general population) [11, 12, 17]. Most frequently, SCAs are found in patients with azoospermia and oligozoospermia. Interestingly, while autosomal defects (3 %) are more common in oligozoospermia, structural aberrations involving sex chromosomes are associated with azoospermia (12.6 %) [20, 21]. There are two alternative models that explain the aberration effect: (1) it blocks spermatogenesis via abnormal chromosome synapsis in crossover and meiosis arrest; (2) the aberration disrupts a dosage-sensitive gene, resulting in spermatogenesis arrest and infertility [15, 16, 20, 21].

Y Chromosome Microdeletions

There are three frequent microdeletions of the azoospermia factor (AZF) region. The AZF deletions are detected in up to 15 % of azoospermic and about 5 % of oligozoospermic patients [17, 22, 23]. The deletions affect three distinct regions: AZFa, AZFb, and AZFc. The AZFa is a nearly 0.8-Mb region that maps to proximal region Yq11.21. AZFb and AZFc map to regions Yq11.22 and Yq11.23, respectively. The AZF deletions influence, overall, 27 unique genes or gene families [24, 25].

AZFa deletions are uncommon and associated with Sertoli cell-only syndrome; testicular histology shows complete germ cell loss and degeneration of seminiferous tubules [15, 17]. The AZFa deletion is a result of nonallelic homologous recombination (NAHR) between two nearly identical DNA repeats. The general view is that the deletion of two genes, *USP9Y* and *DBY* (*DDX3Y*), cause the pathology [22, 24].

AZFb deletions cause spermatogenesis arrest at the spermatocyte stage, loss of mature sperm, and milder azoospermia [17, 22, 24]. The AZFb region has a complex genomic structure and high-identity repeats (palindromic amplicons) that spread in opposite directions up to AZFc [25]. This structure is prone to NAHR between AZFb and AZFc, resulting in two frequent deletions, 6.2 and 7.7 Mb [24, 25]. The 6.2-Mb AZFb deletions remove multiple copies of testis-specific *CDY*, *HSFY*, *RBMY*, and *PRY* genes. The 7.7-Mb deletion spans an extra 1.5 Mb in the AZFc region (AZFb+c deletion).

AZFc deletions are found in around 12 % of infertile azoospermic men and about 6 % with severe oligozoospermia [24, 25]. The AZFc 3.5-Mb region contains multiple copies of five large repeats—*b1*, *b2*, *b3*, *b4*, and *gr*—that are placed in opposite directions and predispose to various partial deletions [25]. Loss of four dosage-sensitive, germ-specific gene families—*BPY2*, *PRY2*, *DAZ*, and *CDY1*—is associated with full AZFc deletions [22, 23, 25]. A common

view is that a low dosage of *DAZ* (Deleted in Azoospermia) causes oligozoospermia. The *DAZ1-4* genes encode germ cell-specific RNA-binding proteins, and their loss affects translation in germ cells and leads to meiosis arrest [25]. Among smaller AZFc deletions, only *gr*/*gr* deletions are associated with increased risk of semen defects. The majority of AZFc deletions occur de novo, while partial *gr*/*gr* deletions can be passed from father to son [17, 25]. It was shown that inherited *gr*/*gr* deletion increases the risk of a complete AZFc deletion in the offspring [11, 12].

Robertsonian Translocations

Robertsonian translocations are the most common SCAs in humans, resulting in a derivative chromosome composed of two long arms from two acrocentric chromosomes (13, 14, 15, 21, and 22). Commonly, RT carriers are healthy but have a high risk of infertility, aberrations in offspring, and spontaneous abortions. The aberrations are found in nearly 1.6 % of infertile male patients. The most frequent RTs are der(13;14) and der(14;21), with incidences of 1:1,000 and 1:5,000, respectively [12, 15, 16, 26, 27]. Nearly 20 % of male carriers of der(13;14) are infertile [27]. Most mature spermatozoa with RT are normal or balanced (75–90 %) as a result of alternate segregation. However, these translocations are associated with disrupted pairing in crossing-over, lead to trivalent formation and subsequent meiotic arrest, and result in oligozoospermia or azoospermia [26, 27]. Male carriers of RTs involving chromosome 21 are more likely to have the disomic gametes likely to produce embryos with trisomy 21. However, male RT carriers are often subfertile, lessening that likelihood [15].

Balanced Translocations

Balanced translocations predispose to the formation of a quadrivalent structure between aberrant chromosomes and their normal homologues in meiotic germ cells. This leads to a high proportion (up to 80 %) of unbalanced spermatozoa [20, 21]. Carriers of balanced aberrations are otherwise healthy but often present with infertility [15, 20, 21]. This infertility is due to fertilization by an abnormal gamete with an unbalanced SCA, leading to an unbalanced embryo unlikely to survive. Thus, preimplantation genetic diagnosis benefits carriers of balanced SCAs by identifying embryos with normal or balanced chromosomes. Although carriers with chromosome inversions are generally healthy, they often present with recurrent pregnancy loss and offspring with abnormal chromosomes [15, 20, 21]. Since inverted segments pair and form an inversion loop in meiosis, its position and inversion size determine the outcome of meiotic pairing. In general, large pericentric inversions (spanning over half of the chromosome) are likely to produce unbalanced SCAs and are frequently observed in infertile men [16, 21].

Testicular Disorder of Sex Development (DSD)

The DSD, known as 46,XX male syndrome, is a rare pathology seen in nearly 1/25,000 newborn males [12, 17]. Most DSD patients have an X;Y translocation with Y-linked gene *SRY* (sex region Y chromosome) placed on one of the X chromosomes [1, 28]. The 46,XX males with *SRY* and testicular DSD have normal male genitalia, but show spermatogenesis arrest and develop severe testicular atrophy and azoospermia [29]. The *SRY* encodes the critical testis-determining transcription factor that activates a number of downstream transcription factors involved in testes formation. SOX9 is a direct target of SRY, and its overexpression can mimic male development without *SRY*. Mutations and small duplications of the *SOX9* upstream regulatory region were demonstrated in *SRY*-negative XX [3, 29] males. Alternatively, increased expression of *SOX9* can be induced by steroidogenic factor 1, *NR5A1*, and *SOX3* [29]. Recently, R-spondin 1 (*RSPO1*) mutations were shown to cause an XX male condition [2].

Complex Structural Chromosome Aberrations (CSAs)

CSAs involve at least three regions in an exchange. Balanced CSAs are rare in individuals with a history of recurrent abortions and infertility. Molecular studies of CSA breakpoints indicate that the complexity and number of breaks cannot predict fertility status. Risk of spontaneous abortion for CSA carriers is estimated at around 50 %. Intracytoplasmic sperm injection is not recommended for male CSA carriers because of the low amount of balanced sperm produced [21, 30].

Genomic Copy Number Variants (CNVs)

CNVs are submicroscopic aberrations of 0.05–3 Mb that cannot be detected by regular chromosome testing. To date, two microarray technologies are used to detect loss or gain CNVs: single nucleotide polymorphism (SNP) array and the comparative genomic hybridization (CGH) array that detects specific probes in comparison to a control specimen. Recent whole-genome and X chromosome CGH studies detected multiple CNVs, with loss and gain that probably affect critical dosage-sensitive genes on sex or autosomal chromosomes [31•, 32, 33]. These studies note that infertile men usually do not have an increased number of CNVs, suggesting that their infertility is likely due to specific defects in single or multiple gene(s). Other studies, using genome-wide SNP arrays, revealed multiple CNVs and regions of homozygosity that could worsen the effect of multiple recessive mutations present in the human genome [34••, 35, 36]. A recent study of

CNVs via SNP array demonstrated various individual CNVs in multiple male germ cell–specific genes [34••]. Of interest are multiple loss-of-function deletions of the *DMRT1* in patients with various types of azoospermia (e.g., Sertoli cell-only syndrome, testicular failure, or maturation arrest). These genomic aberrations range from 0.132 to 2 Mb, deleting a few exons or the entire gene. The gene encodes an ortholog of an avian sex determination factor and was implicated in non-syndromic gonadal dysgenesis [34••]. Two recent studies showed that 200-Kb deletions on the 12q14 chromosome remove testis-specific *DPY19L2*. The deletions are a major cause of globozoospermia (abnormally round sperm head morphology) and detected in nearly 67 % of patients [37, 38••]. The gene encodes a *C. elegans* ortholog involved in initial stages of round spermatid polarization [38••].

Single-Gene Disorders

The study of male infertility caused by single-gene mutations is a rapidly changing field. In the past decade, we have seen a number of reports newly demonstrating the association of various genes with male infertility. Here we present a list of noteworthy single-gene disorders, while a larger list of single-gene mutations with initial reports is shown in Table 1. The best known single-gene disorder is congenital bilateral aplasia of the vas deferens (CBAVD) with obstructive azoospermia. Mutations in cystic fibrosis transmembrane conductance regulator (CFTR) were reported in more than 90 % of CBVAD patients [10, 39]. The gene encodes the ATP-binding chloride channel and regulates chloride secretion and sodium ion absorption [40]. A general view is that a pair of *CFTR* mutations, IVS8-5T in intron 8 and another gene-coding mutation, causes isolated CBAVD. However, if the patient has two coding *CFTR* mutations in both alleles, he will develop classical cystic fibrosis syndrome, including multiple-organ clinical symptoms and male infertility [10].

AR (androgen receptor) encodes testis-specific testosterone receptor. The gene has been associated with androgen insensitivity (AIS) disorder, which ranges from females with testes (complete AIS) to normal and otherwise healthy infertile males (partial AIS) [8]. To date, more than 300 gene mutations have been reported, with multiple forms of testosterone insensitivity and abnormal development of internal and external genitalia. Recently, two studies using conventional and Cre/Lox conditional *Ar*-null male mice recreated human disorders [41, 42]. They showed female external sex development and testis atrophy with spermatocyte-stage arrest, resembling AIS human pathology.

AURKC (aurora kinase C) is highly expressed in testis and encodes a protein that is probably involved in cytokinesis during germ cell mitosis and meiosis [43, 44]. Mutations in the gene were reported in a number of infertile males with entirely abnormal sperm morphology and sperm polyploidy [45]. The initial report identified a founder loss-of-function mutation; however, subsequent studies have expanded the list of gene mutations, supporting the importance of *AURKC* for sperm morphology [46].

HSF2 encodes a testis-expressed heat-shock transcription factor 2. Recent study of *Hsf2*-null male mice demonstrated embryonic lethality, neuronal defects, and a reduced spermatogenesis that includes meiotic disruption and increased sperm apoptosis with seminiferous tubule dysgenesis [47, 48]. A subsequent study of *HSF2* in 766 azoospermic males revealed missense mutations in approximately 1 % of patients, suggesting high heterogeneity of the azoospermia [49].

KLHL10 (kelch-like 10) is exclusively expressed in elongating and elongated spermatids. The gene encodes a sperm-specific substrate-targeting module of Cullin 3 ubiquitin ligase and regulates protein ubiquitination and sperm maturation [50]. Null *Klhl10* in male mice causes haploinsufficiency with meiotic arrest, absence of mature spermatozoa in semen and male infertility [50]. A study of human oligozoospermia identified missense and splicing mutations in *KLHL10* in nearly 2 % of patients that were not observed in controls [51]. Further functional analysis reported a damaging effect of missense mutations. Some gene mutations showed variable effects, ranging from severe to mild oligozoospermia.

NR5A1 encodes steroidogenic factor 1 (SF1), crucial in male and female gonadal development and steroidogenesis. *Nr5a1*-null male mice present with adrenal agenesis, female internal genitalia, and gonadal absence [52]. Initial human studies of the gene reported mutations associated with female sex development and infertility in males. However, two recent studies of male infertility found different *NR5A1* missense mutations associated with 1–4 % of men with oligozoospermia [53, 54••].

PRM1 encodes the testis-specific nuclear protein protamine 1 that replaces histones in postmeiotic sperm. Null *PRM1* mutations in male mice showed a haploinsufficiency effect and had a chromatin compaction defect, sperm DNA damage, and severe teratozoospermia [55]. A study of *PRM1* in men with similar semen defects identified missense mutations in 10 % of infertile patients [56, 57]. However, later studies used insufficient patient and/or control populations and led to conflicting results [57–59]. Recently, the mutation search was expanded to *PRM2*, *PRM3*, and *TNP2* located adjacent to the protamine gene cluster, reporting novel mutations [60].

SLC26A8 encodes a sperm-specific sulfate exchange channel (also known as testis anion transporter, *TAT1*) that regulates *CFTR* and is vital for sperm motility [61]. Male mice with null *SLC26A8* show sperm with abnormal heads, no motility, and male sterility [62]. Recently, two studies revealed that nearly 2–5 % of patients with

asthenozoospermia (reduced sperm motility) have various gene mutations with deleterious effects [63, 64•].

SOHLH1 (spermatogenesis- and oogenesis-specific basic helix-loop-helix 1) encodes a critical testis-specific transcription factor essential for spermatogonial differentiation [65]. Male mice with homozygous deletion of *Sohlh1* demonstrated spermatocyte arrest, testicular failure, and azoospermia [65]. A subsequent study of the gene in male patients with testicular failure and nonobstructive azoospermia (NOA) supported this notion [66•]. Two missense and one splicing mutation in the *SOHLH1* were detected in about 3 % of patients with NOA. Further in vitro functional assay provided evidence that the mutations had a damaging effect [66•].

SPATA16 (spermatogenesis-associated protein 16) encodes a testis-specific Golgi apparatus protein with a tetratricopeptide motif. The original study of one consanguineous family with male infertility and globozoospermia (abnormally round-headed sperm) reported homozygous mutations in the autosomal gene, *SPATA16*, in three affected brothers [67]. It was shown that the sperm head defects were due to SPATA16 protein involvement in acrosome formation.

ZPBP1 encodes zona pellucida binding protein 1. The protein is located in the acrosomal extracellular matrix of mature sperm and is involved in the initial steps of oocyte fertilization. *Zpbp1*-null male mice show acrosome fragmentation and abnormal sperm head morphology resembling globozoospermia [68]. A study of human *ZPBP1* revealed that nearly 4 % of patients with abnormal sperm-head morphology have missense and splicing gene mutations [69].

Epigenetic and Posttranscriptional Modifications

Epigenetic abnormalities were recently reported in male infertility. One study tested genome-wide methylation defects in 27,000 CpG dinucleotides in sperm from men with abnormal sperm chromatin packaging and patients displaying defective spermatogenesis [70]. It described altered DNA methylation patterns in 3 out of 43 patients, suggesting that a systemic methylation defect contributes to male infertility. A second study identified novel posttranscriptional *UBE2B* mRNA mutations in approximately 4 % of patients with severe oligozoospermia [71•]. This report is consistent with results of earlier study of *Ube2b*-null male mice with spermatogenic meiotic disruption, increased apoptosis, and male sterility and suggests that such modifications substantially contribute to an abnormal protein load and sperm disruption [72].

Female Infertility

Reproductive defects and genital tract developmental defects are not uncommon in women, yet little is known about the genetics behind them. During sexual development, congenital malformations of the reproductive tract may occur that affect fertility; these include anatomical abnormalities of the Mullerian ducts, uterus, endometrium, Fallopian tubes, and ovaries [6]. Premature menopause in women of reproductive age and the increasing prevalence of intentionally delayed pregnancy, in Western countries at least, also contribute to female infertility [73].

Chromosomal Aberrations

The 47,XXX Syndrome

The 47,XXX syndrome, also known as trisomy X, is one of the most common causes of premature ovarian insufficiency (POI); it occurs in 1 in 1,000 female births. While the majority of women with trisomy X present as normal, some suffer from POI or from malformations of the genitourinary tract [74].The aberration happens because of chromosome nondisjunction errors in meiosis I or II in oogenesis.

Turner Syndrome

Turner syndrome, also known as monosomy X or 45,XO, chromosome disorder in females, has an incidence of 1:2,000 births. The loss of chromosome X in the oocyte is a result of chromosome nondisjunction in meiosis. The 45,XO females display skeletal abnormalities, congenital heart defects, and physical attributes such as short stature, a webbed neck, low hairline, flat chest, and gonadal dysgenesis with signs of amenorrhea or ovarian failure. Females mosaic for Turner syndrome present with a milder form, often noted because of infertility. 45,X/47,XXX is not a common mosaic presentation, but does present similarly to 45,X/46,XX, with ovarian function declining quickly and leading to infertility [75].

Genomic Aberrations, Copy Number Variants (CNVs)

Recently, a number of microarray studies reported genomic regions associated with female infertility, including the complex disorders endometriosis and primary ovarian failure (POF). They provided stepping stones toward in-depth whole-genome analysis and the discovery of novel genes that would not have been detected with the use of older technologies. One SNP array study identified 6 novel microdeletions affecting at least 1 gene each from a total of 198 autosomal CNVs (microdeletions and microduplications) in 89 women with POF [76•]. Among deleted genes, two previously described POF genes, *SYCE1* and *CPEB1*, were found. Null mutations in these two genes

Table 1 Genes, chromosome aberrations, genomic CNVs, and disorders of male infertility

Disorder		Gene	Ch. location	OMIM no.
Chromosomal aberrations				
Klinefelter syndrome (KS)	1:1,000	47, XXY	–	–
47, XYY		47, XYY	–	–
Numerical chromosome aberrations		–	Ch 21, 22, X, Y	–
Structural chromosome abnormalities (SCA)		–	Ch X, Y	–
		t(SRY; X)	Ch Y; X	
	1:1,000	der(13;14)	Ch13,14	–
Robertsonian translocations (RT)	1:5,000	der(14;21)	Ch14,21	–
		der(14;15)	Ch14,15	–
Y-chromosome microdeletions/ AZF regions		AZFa	Yq11.21	400042
		-*USP9Y*	Yq11.21	400005
		-*DBY*	Yq11.21	400010
		AZFb	Yq11.22	400005
		-*CDY*	Yq11.23	400016
		-*HSFY*	Yq11.222	400029
		-*RBMY*	Yq11.223	400006
		-*PRY*	Yq11.223	400019
		AZFc	Yq11.23	400010
		-*BPY2*	Yq11.223	400013
		-*PRY2*	Yq11.223	400041
		-*DAZ*	Yq11.223	400003
		-*CDY1*	Yq11.23	400016
Testicular disorder of sex development/ 46, XX (DSD)	1:25,000	*SRY*	Yp11.3	480000
		SOX9	17q24.3	608160
		NR5A1	9q33.3	184757
		SOX3	Xq27.1	313430
		RSPO1	1p34.3	609595
		DAX1	Xp21.2	300473
Reproductive dysgenesis disorders		*WT1*	11p13	607102
		NR5A1	9q33.3	184757
		CBX2	17q21.3	602770
		AMH	19p13.3	600957
		AMHR2	12q13.13	600956
		ARX	Xp21.3	300382
Kallman syndrome/hypogonadotrophic hypogonadism		*KAL1*	Xp22.31	300836
		FGFR1	8p11.23-p11.22	136350
		PROKR2	20p12.3	607123
		GNRH1	8p21.2	152760
		TAC3	12q13.3	162330
		LEP	7q32.1	164160
		NSMF	9q34.3	608137
		CHD7	8q12.1-q12.2	608892
		DAX1	Xp21.2	300473
		KISS1	1q32.1	603286
Genomic aberrations/CNVs				
Azoospermia/gonadal dysgenesis		*DMRT1*	9p24.3	602424
		del(12q14)	12q14	–
		DPY19L2	12q14.2	613893
Single gene disorders				
Congenital bilateral aplasia of the vas deferens		*CFTR*	7q31.2	602421
Androgen insensitivity disorder (AIS)		*AR*	Xq12	313700

Table 1 continued

Disorder	Gene	Ch. location	OMIM no.
Abnormal sperm morphology and/or motility	*AURKC*	19q13.43	603495
	PRM1	16p13.13	182880
	SLC26A8	6p21.31	608480
	SPATA16	3q26.31	609856
	ZPBP	7p12	608498
Azoospermia	*HSF2*	6q22.31	140581
	SOHLH1	9q34.3	610224
	ETV5	3q27.2	601600
	GILZ	Xq22.3	300506
	PRM2	16p13.13	182890
Oligozoospermia	*NR5A1*	9q33.3	184757
	KLHL10	17q21.2	608778
Azoospermia/oligozoospermia	*PRM3*	16p13.13	–
	TNP2	16p13.13	190231
Posttranscriptional abnormalities			
	UBE2B	5q31.1	179095
Genetic syndromes			
Sickle cell anemia (OMIM 603903)	*HBB*	11p15.4	141900
Kartagener's syndrome (OMIM 244400)	*DNAI1*	9p13.3	604366
Myotonic dystrophy (OMIM 160900)	*DMPK*	19q13.32	605377
Fanconi anemia (OMIM 227650)	*FANCA*	16q24.3	607139
β-thalassemia (OMIM 613985)	*HBB*	11p15.4	141900

Incidence and OMIM numbers are shown when available for respective disorders. *Ch. location* chromosome location, *del(,)* deletion

were responsible for ovarian failure in female mice [77, 78]. Another CGH study tested genomic CNVs in 74 patients with POF and ovarian dysfunction [79•]. Multiple genes, such as *PLCB1*, *RB1CC1*, *MAP4K4*, *RBBP8*, *IMMP2L*, *FER1L6*, and *MEIG1*, involved in meiosis, DNA repair, or folliculogenesis, were identified as possible candidate genes for POF and ovarian dysfunction. Following CGH studies identified new infertility-associated candidate genes and unveiled new details of the pathophysiology [79•, 80].

Single-Gene Disorders

Fragile X Syndrome

Fragile X syndrome is a disorder characterized mainly by mental retardation, long faces, large ears, and prominent jaws. The syndrome was first reported in 1969 with constriction of the long arm on the X chromosome [81]. It has an incidence of 1:5,161 [82]. The critical gene for fragile X is *FMR1*, fragile X mental retardation gene, located at Xq27.3. The pathology is caused by expansion of the CGG repeat in the gene's 5′ untranslated region to a premutation state of between 56 and 199 repeats (a complete mutation has over 200 repeats). Generally, *FMR1* premutations are found in 16 % of POF females, with about 2 % of the cases being sporadic and 14–21 % familial [82, 83]. Carrier screening of *FMR1* premutation is recommended for women of advanced maternal age or with a family history of fragile X.

Galactosemia

Many women with galactosemia manifest hypergonadotropic hypogonadism, presenting with secondary amenorrhea [84, 85]. Premature ovarian failure is independent of age. A candidate gene that has been shown to be associated with galactosemia and endometriosis is the *GALT* gene, although conflicting results in various studies have reduced its likelihood of being causal [13, 84]. Early genetic counseling about the related risk of infertility and pediatric endocrinologist assistance greatly improve the prognosis of ovarian failure for girls with galactosemia [13, 86]. Since most women with galactosemia are infertile, pregnancy is achieved by oocyte or pre-embryo donation.

Primary Ovarian Failure (POF)

POF is defined as either complete or incomplete failure of the ovaries (also known as primary ovarian insufficiency, POI). Recently, several genes have been discovered that show

Table 2 Genes, chromosome aberrations, genomic CNVs, and disorders of female infertility

Disorder		Gene	Ch. location	OMIM #
Chromosomal aberrations				
47,XXX	1:1,000	–	–	–
Turner syndrome (45,XO)	1:2,000	–	–	–
Noonan syndrome (OMIM 163950)	1:1,000–2,500	*PTPN11*	12q24.13	176876
		SOS1	2p22.1	182530
Sickle cell anemia	1:1,146	*HBB*	11p15.4	603903
Genomic aberrations/CNVs				
Premature ovarian failure (POF)/ovarian dysfunction (OD)		*SYCE1*	10q26.3	611486
		CPEB1	15q25.2	607342
		PLCB1	20p12.3	607120
		RB1CC1	8q11.23	606837
		MAP4K4	Ch 2	604666
		RBBP8	18q11.2	604124
		IMMP2L	7q31.1	605977
		FER1L6	8q24.1	–
		MEIG1	10p13	614174
Single gene disorders				
Fragile X syndrome (OMIM 300624)	1:5,161	*FMR1*	Xq27.3	309550
Galactosaemia (OMIM 230400)	1:47,000	*GALT*	9p13.3	606999
Blepharophimosis, ptosis, epicanthus inversus syndrome (OMIM 110100)		*FOXL2*	3q22.3	605597
Premature ovarian failure (POF)/premature ovarian insufficiency (POI)		*FMR1*	Xq27.3	309550
		BMP15	Xp11.22	300247
		FOXL2	3q22.3	605597
		GDF9	5q31.1	608697
		FIGLA	2p13.3	601918
		SALL4	20q13.2	607343
		AR	Xq12	313700
		FSHR	2p16.3	136435
		FOXO1a	13q14.11	136533
		FOXO3a	6q21	602681
		NOBOX	7q35	610934
		CDKN1B	12p13.2	600778
		INHA	2q35	147380
		CYP19A1	15q21.2	107910
		LHX8	1p31.1	604425
		NANOS3	19p13.13	608229
Leiomyomas (OMIM 150699)		*MED12*	Xq13.1	300188
		t(12;14)	12q	–
		del(7q22-q32)	7q	–
		COL4A5 -	Xq22.3	303630
		COL4A6	Xq22.3	303631
		HMGA2	12q14.3	600698
		RAD51B	14q24.1	602948
Polygenic/multifactorial				
Endometriosis (OMIM 131200)		*HSD17B2*	16q23.3	109685
		CYP19A1	15q21.2	107910
		STAR	8p11.23	600617
		SF1	11q13.1	601516

Table 2 continued

Disorder	Gene	Ch. location	OMIM #
	Ch region	10q26	–
	Ch region	1p36	–
Polycystic ovarian syndrome (PCOS)	*PCOS1*	19p13.2	184700
	SRD5A1	5p15.31	184753
	SRD5A2	2p23.1	607306
	CYP11A1	15q24.1	118485
	FBN3	19p13.3	608529
	INS	11p15.5	176730
	INSR	19p13.2-p13.2	147670
	TCF7L2	10q25.2-p25.3	602228
	CAPN10	2q37.3	605286
	FTO	16q12.2	610966
	SHBG	17p13.1	182205
	Ch region	2p16.3	–
	Ch region	2p21	–
	DENND1A	9q33.3	613633

Incidence and OMIM are shown when available for respective disorders. *Ch. location* chromosome location, *t(,)* translocation, *del(,)* deletion, *COL* collagen, *Ch region* chromosome region

incomplete loss of function of the ovary, leading to the term "primary ovarian insufficiency" (POI). A number of genes have been associated with POF/POI. X-linked genes include *FMR1* and bone morphogenetic protein 15 (*BMP15*) located at the Xp11.2 region [87, 88]. Among autosomal gene mutations often found in women with POF/POI are *AR*, *CDKN1B*, *CYP19A1*, *GDF9*, *FIGLA*, *FOXL2*, *FOXO1a*, *FOXO3a*, *INHA*, *LHX8*, *NOBOX*, *NANOS3*, *FSHR*, and *SALL4* (Table 2).

FOXL2 encodes an ovarian development-specific transcription factor with forkhead box L2. The forkhead box is a DNA-binding domain that plays a key role in the protein function. Dominant mutations in *FOXL2* cause premature ovarian failure 3 [89]. The gene is also responsible for the blepharophimosis, ptosis, and epicanthus syndrome, which may include POF [90].

GDF9 (growth/differentiation factor 9) and *GDF9B* (*BMP15*) are necessary for ovarian folliculogenesis and somatic cell function in both mice and humans. Initial genetic studies in women with POF discovered multiple missense mutations in 3–4 % of patients [91]. Subsequent studies of POF in women of various ethnic backgrounds reported more mutations in these two genes.

FIGLA (factor in germline alpha) is located at 2p13.3 and encodes a germ cell-specific basic helix-loop-helix transcription factor. It regulates the expression of the zona pellucida- and oocyte-specific genes. A knockout of FIGLA in female mice prevents the formation of primordial follicles, and oocyte numbers drop rapidly after birth [92]. The initial study of *FIGLA* identified mutations in approximately 4 % of POF patients [93]. Two women had missense mutations and two had other gene deletions that resulted in a frameshift and haploinsufficiency [93].

NOBOX (newborn ovary homeobox) is located at 7q35 and encodes a transcriptional regulator with a homeobox motif. Study of *Nobox*-null female mice indicates that this gene is critical for early folliculogenesis [94], and an independent human study found *NOBOX* defects in POF patients [95]. Later, two missense mutations in the homeobox domain were found in 6.2 % of patients of Caucasian or African descent [96•].

SALL4 (SAL-like 4) is located at 20q13.2 and encodes putative zinc finger transcription factor and plays a role in the pluripotency of oocytes. In *Nobox*-deficient mouse ovaries, SALL4 is downregulated, suggesting it is activated by NOBOX [94]. In a study of 100 Han Chinese women with nonsyndromic POF, two probable gene mutations were discovered in POF subjects and not in the control group [97]. Remaining known genes associated with POF have been recessive, producing a variety of phenotypes and causing idiopathic infertility (Table 2) [6].

Leiomyomas

Leiomyomas, also referred to as fibroids, are benign tumors found in the smooth muscle layers of the uterus. It is not uncommon to have irregular bleeding and pain, sometimes necessitating a hysterectomy. The number of tumors varies among those affected and can change in conjunction with hormones. During pregnancy, the tumor lesions have a tendency to increase in size. There is a prevalence of lesions among black women, who undergo hysterectomies twice as often as whites [98••, 99]. Somatic chromosomal rearrangements or deletions are found in the 12q and 7q regions, respectively [100]. Deletions within 7q are

observed in about 20 % of leiomyomas [100]. Whole genome sequencing implicated *CUX1*, *ZNHIT1*, and *CUL1* as key genes within 7q deletions [101••]. In addition, mutations affecting oncogenes, metabolism, and follicle-stimulating hormone signaling, and changes in *COL4A5-COL4A6*, *HMGA2* and *RAD51B* were identified [101••]. New studies using conventional and next-generation sequencing techniques identified mutations in the *MED12* gene as a major contributor to leiomyoma [102, 103••, 104]. Nearly 60 % of patients with the pathology have *MED12* mutations.

Polygenic, Complex Female Infertility

Endometriosis

Endometriosis is a complex disease, characterized by the inflammation and bleeding of the endometrium. It affects 5–10 % of females. Often there is infertility and pain due to endometrial tissue in the pelvic region outside of the uterus [98••, 105]. Those with affected first degree relatives have five to eight times increased risk for the disease. Genetic association and linkage studies have identified some candidate genes, SNPs, and CNVs, but follow-up studies are needed to replicate the studies and narrow down critical regions (Table 2). One study determined a significant linkage to 10q26, but the linkage peak was too broad to identify a single gene as a causative factor of endometriosis [106]. Among two genome-wide association (GWAS) studies conducted in Australia and Japan in 2011 and 2010 [107, 108], only one common locus was found—in the 1p36 region—which contains *WNT4*, a gene responsible for cell proliferation and that plays a key role in embryogenesis [109]. Prior studies have also noted this region's involvement in endometriosis [98••].

Polycystic Ovarian Syndrome (PCOS)

PCOS is a complex endocrine disorder with heterogeneous genetic causes. It is found in about 7 % of women of reproductive age. Aside from metabolic issues that may be associated with PCOS, such as obesity and type 2 diabetes mellitus, common symptoms are irregularities in the menstrual cycle, polycystic ovaries, secondary amenorrhea, anovulation, hirsutism, and reduced fertility due to oversized, dysfunctional follicles [99, 110–112]. The adrenal-form adult-onset disorder is due primarily to enzyme deficiencies, often causing pseudo-hermaphroditism and hirsutism. Nonadrenal PCOS phenotypes differ in how they manifest and in their pathophysiology. There appears to be dominant inheritance, yet no specific gene(s) has been identified as the cause for PCOS, rendering it idiopathic [99]. Studies of multiple candidate genes including *FBN3*, *FST*, *INS*, *INSR*, *TCF7L2*, *CAPN10*, *FTO*, *SHBG*, *PCOS1*, *SRD5A1*, *SRD5A2*, and *CYP11A1* have shown association with PCOS [98••, 111–122]. However, these genes have also shown significant associations with other disorders such as obesity, diabetes, and insulin resistance, which are commonly associated with PCOS. These results suggest the complex nature of PCOS. To date, a direct correlation with PCOS has been shown for one gene, *INSR*. The insulin receptor gene has shown the highest likelihood as a susceptibility gene in the Han Chinese after being identified in a GWAS study, which also identified three additional PCOS loci (2p16.3, 2p21, 9q33.3) [114]. Two studies were able to replicate the results for one identified gene of interest, *DENND1A*, a guanine nucleotide exchange factor [114, 123]. As yet, the cause of PCOS is unknown; both, genetic and environmental factors must be taken into consideration. Current treatment and management of the symptoms of PCOS include ovulation induction [112].

Conclusion

Many men and women affected by infertility or disorders that lead to decreased fertility have turned to assisted reproductive technology (ART). Recent estimates show nearly 5 million newborns have been assisted by ART [124]. It is known that a woman's fecundity decreases with advancing age. Also, the modern tendency to delay childbirth contributes to the increased use of ART. Yet, there are several concerns about the safety and possible negative outcomes of the ICSI treatment, such as pregnancy complication or termination, risk of various birth defects, and childhood developmental and mental defects [124]. It is important that all couples undergoing infertility treatment should be informed of the risks, benefits, and possible outcomes through the use of genetic testing and counseling. As more genes are discovered, and the etiology of infertility disorders become better understood, the management and treatment of infertility will improve as well.

Compliance with Ethics Guidelines

Conflict of Interest M. Zorrilla and A.N. Yatsenko have received research grants and travel reimbursements from the NIH.

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