MECHANISMS IN ENDOCRINOLOGY

Aberrations of the X chromosome as cause of male infertility

Albrecht Röpke and Frank Tüttelmann

Institute of Human Genetics, University of Münster, Münster, Germany,

Correspondence
should be addressed
to F Tüttelmann
Email
frank.tuettelmann@ukmuenster.de

Abstract

Male infertility is most commonly caused by spermatogenetic failure, clinically noted as oligo- or a-zoospermia. Today, in approximately 20% of azoospermic patients, a causal genetic defect can be identified. The most frequent genetic causes of azoospermia (or severe oligozoospermia) are Klinefelter syndrome (47,XXY), structural chromosomal abnormalities and Y-chromosomal microdeletions. Consistent with Ohno's law, the human X chromosome is the most stable of all the chromosomes, but contrary to Ohno's law, the X chromosome is loaded with regions of acquired, rapidly evolving genes, which are of special interest because they are predominantly expressed in the testis. Therefore, it is not surprising that the X chromosome, considered as the female counterpart of the male-associated Y chromosome, may actually play an essential role in male infertility and sperm production. This is supported by the recent description of a significantly increased copy number variation (CNV) burden on both sex chromosomes in infertile men and point mutations in X-chromosomal genes responsible for male infertility. Thus, the X chromosome seems to be frequently affected in infertile male patients. Four principal X-chromosomal aberrations have been identified so far: (1) aneuploidy of the X chromosome as found in Klinefelter syndrome (47,XXY or mosaicism for additional X chromosomes). (2) Translocations involving the X chromosome, e.g. nonsyndromic 46,XX testicular disorders of sex development (XX-male syndrome) or X-autosome translocations. (3) CNVs affecting the X chromosome. (4) Point mutations disrupting X-chromosomal genes. All these are reviewed herein and assessed concerning their importance for the clinical routine diagnostic workup of the infertile male as well as their potential to shape research on spermatogenic failure in the next years.

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Invited Author's profile

Frank Tüttelmann, MD, started his scientific career at the Centre of Reproductive Medicine and Andrology (CeRA), Münster, Germany. He is a certified Clinical Andrologist of the European Academy of Andrology, a specialist in human genetics, senior physician and deputy director of research and teaching at the Institute of Human Genetics (IHG), Münster, Germany. His primary research topic is reproductive genetics with a strong focus on male infertility. The majority of his publications deal with genetic causes of spermatogenic failure. He received several prizes for his research, among other the 'Young Andrologist Award' of the International Society of Andrology. By developing clinical databases at both the CeRA (Androbase) and IHG (Gene.Sys), he improved patient care and research at the same time, e.g. simplifying selection of specific phenotypes based on testicular histology.

Introduction

Male infertility is most commonly caused by spermatogenic failure, clinically noted as oligo- or azoospermia. Concerning the underlying pathophysiology, a substantial genetic contribution can be assumed from family studies as well as from animal – mostly mouse knockout models (1, 2, 3, 4). The most frequent genetic causes of severe oligo- or azoospermia are Klinefelter syndrome (47,XXY), structural chromosomal abnormalities (e.g. translocations) and microdeletions of the AZF ('AZoospermia Factor') regions on the long arm of the Y chromosome (5). Beyond these well-established causes of male infertility, more and more genes are reported to be associated with spermatogenic failure in males. *NR5A1* (6, 7, 8, 9) and *DMRT1* (10, 11) are examples of autosomal genes in which heterozygous mutations are causative. However, sex-chromosomal genes are prime candidates because of their hemizygous state in males and *TEX11* (12, 13) and *RHOX* (14, 15) are recent examples which, if mutated, cause male infertility.

The Y chromosome triggers embryonic male development. Specifically, the *SRY* gene (sex-determining region Y), located on the short arm of the Y chromosome, is responsible for male sex determination (16, 17). Concerning infertility in otherwise healthy men, three partially overlapping but discrete regions were identified on the long arm of the Y chromosome that is essential for normal spermatogenesis. The deletion of any of these regions, designated as AZF microdeletions, regularly leads to infertility due to severe oligo- or azoospermia (18). Ampliconic regions in the male-specific region of the Y chromosome (MSY) explain the mechanism of the different AZF deletions by non-homologous recombination (19). Besides, the Y chromosome of higher mammalian lacks most genes originally located on ancestral Y chromosomes and other genes were moved to autosomes (20, 21). These inserted genes are of special interest because the autosomal gene copies show increased expression in the testis, suggesting an essential role in spermatogenesis, and these genes are possible candidates causing male infertility (20).

In contrast to this evolutionary dramatical loss of genes from the Y chromosome (22), genes on the other sex chromosome, the X chromosome, were predicted to vary little in mammals (23). In fact, the X chromosome is evolutionary stable, but it has been evolving toward a kind of male specialization. It seems that independently

acquired X-linked genes show an important role in male infertility and sperm production (24, 25, 26).

The human X chromosome

The human sex chromosomes (X and Y) originate from an ancestral homologous chromosome pair, which during mammalian evolution lost homology due to progressive degradation of the Y chromosome (20, 27, 28, 29). In contrast to females who inherit an X chromosome from each parent, males own a single, maternal X chromosome. In females, gene dosage resulting from the two X chromosomes is compensated through inactivation of almost the entire genetic content of the second X chromosome (30, 31, 32, 33, 34). Every supernumerary X chromosome, as in 47,XXY or 47,XXX, will be inactivated in the same manner. However, a rather large fraction of about 10% of X-chromosomal genes escape X-inactivation (35). The 'pseudoautosomal' regions (PAR1 and PAR2) are short regions of homology between both distal ends of the X and Y chromosomes as they behave like an autosome and recombine during meiosis (36, 37, 38, 39, 40, 41). Genes inside the PARs share copies on both sex chromosomes, whereas the vast majority of genes outside the PARs are present in only a single copy in the male genome.

Altogether, 1098 genes were annotated to the X chromosome, of which 99 encode proteins expressed in testis and in various tumor types (25). In 1967, it was predicted by Ohno that the X chromosome was evolutionarily very stable, and he assumed that X-linked genes would vary little among mammals (23). To test this hypothesis, the so-called 'Ohno's law', Mueller *et al.* very recently first improved and then compared the sequences of the human and mouse X chromosomes (24). In accord with Ohno's law, they found that most X-linked single-copy genes are shared by humans and mice. However, and in contrast to Ohno's law, approximately 10% of human and 16% of mouse X-chromosomal genes did not have orthologs in the other species. In addition, the majority of these unique genes were found to reside in ampliconic regions, making them rather difficult to sequence. Re-analysis of RNA sequencing data indicated that nearly all these independently acquired genes are expressed in males, but not females, and predominantly in the testes. The authors concluded that, in fact, the X is a 'male

chromosome' (24) highly enriched for genes relevant for spermatogenesis.

Sex chromosome aneuploidy

More than 60 years ago, in 1956, the first human chromosomes were made visible by Tjio and Levan (42), and three years later, the first clinical disorders were identified that are caused by chromosomal aberrations including Klinefelter syndrome (43).

In contrast to the 22 autosomes, which are present in pairs, the X and Y chromosomes are of special interest concerning male infertility because they are only present once in normal males. Thus, any gene located on the sex chromosomes is only present in a single-copy (hemizygous) with the exception of genes located in PAR1 and PAR2 respectively.

Four major sex chromosome aneuploidies are relatively common. Of these, 47,XXY Klinefelter syndrome (1 in 500 newborn boys) and 45,X Turner syndrome (1 in 2500–3000 newborn girls) are regularly associated with infertility. In contrast, 47,XYY (1 in 1000 newborn boys) and 47,XXX Triple X syndrome (1 in 1000 newborn girls) both apparently have little effect on fertility in most patients. However, the supernumerary sex chromosomes are also considered to impair meiosis leading to varying degrees of infertility, but the cause–effect relationship is difficult to assess in individual patients (44, 45, 46, 47).

In contrast to autosomal trisomies, additional copies of the X chromosome are associated with mild phenotypic abnormalities possibly because of dosage compensation by inactivation of the other X chromosome (45, 48).

Another difference to autosomal trisomies concerns the parental origin of the aneuploidies. While autosomal trisomies in the vast majority (>90%) arise during oogenesis, male gametogenesis plays a major role in the generation of sex-chromosomal aneuploidies in the offspring (49, 50). For example, the supernumerary X in Klinefelter syndrome is roughly equally often of maternal and paternal origin (51, 52).

Meiosis and XY pairing

In mammals, meiotic cell division is necessary to produce male and female germ cells. Haploid DNA content in germ cells is achieved by one round of DNA replication, followed by two successive rounds of cell division (meiosis). To successfully segregate chromosomes to daughter cells in the first meiotic cell division, homologous chromosomes must find each other and stably pair. Autosomal

chromosomes are homologous along their entire length and are hence able to pair from end to end. In contrast, the X and Y chromosomes are not homologous save for the short segments at the end of each chromosome arm, the PARs (39). Both chromosomes differ dramatically in size and gene content and X-Y chromosome homology search and pairing can, therefore, only be mediated by the PARs, conceivably making X-Y segregation particularly difficult (22, 28, 53).

Klinefelter syndrome

A supernumerary X chromosome resulting in the karyotype 47,XXY as the genetic cause for the Klinefelter syndrome (KS) was first described in 1959 (43). KS is one of the most frequent cytogenetic anomalies found in infertile men. The prevalence increases from approximately 3% in unselected to up to 15% in azoospermic patients (54, 55, 56). The most common karyotype found in 80–90% of KS men is 47,XXY and the others comprise sex-chromosomal mosaicism (e.g. 47,XXY/46,XY), additional sex chromosomes (48,XXXY; 48,XXYY; 49,XXXXY) or structurally abnormal X chromosomes (4, 57, 58). The supernumerary X chromosome is derived either from meiotic non-disjunction during gametogenesis of the parents or from post-zygotic mitotic cell divisions during early embryogenesis (48).

As hallmark features, KS men regularly have small testes (<6 mL bi-testicular volume), azoospermia and high gonadotropin levels (LH and FSH). In rare cases, some spermatozoa may be found in the ejaculate of KS men and very few natural conceptions by KS men have been described. Depending on the testosterone levels, KS men often exhibit varying symptoms of hypogonadism such as undervirilization, gynecomastia or erectile dysfunction (58, 59, 60).

The phenotype of patients with polysomy of the sex chromosomes (48,XXXY; 48,XXYY; 49,XXXXY; 49,XXYY; 49,XXYYY; 49,XYYYY) has to be seen quite separate from patients with a 47,XXY karyotype (48, 58, 61). These types of sex chromosome aneuploidy are very rare and only few case reports have been published so far. Although it has been shown that also the additional X chromosomes are inactivated (62, 63), as mentioned above, some loci escape inactivation and may function in a disomic (in case of XXY, XXYY or XXYYY), trisomic (XXXXY or XXXYY) or tetrasomic (XXXXY) states. This is likely the predominant reason for the more severe phenotypic abnormalities associated with these karyotypes (64, 65, 66).

Nonsyndromic 46,XX testicular disorders of sex development (XX-male syndrome/DSD)

Nonsyndromic 46,XX testicular disorders of sex development (46,XX testicular DSD; formerly known as XX-males) are characterized by the combination of male external genitalia, testicular differentiation of the gonads and a 46,XX karyotype identified by conventional cytogenetic analysis. Most 46,XX testicular DSD males arise from translocations of parts of the short arm of the Y chromosome to one of the X chromosomes (67, 68). Translocations of a DNA segment that contains the testis-determining gene *SRY* from the Y to the X chromosome takes place during paternal meiosis (69). The presence of the *SRY* gene is sufficient to cause the initially indifferent gonad to develop into a testis. Individuals with 46,XX testicular DSD typically have normal external genital development, but micropenis, hypospadias or cryptorchidism may be seen. In addition, males with 46,XX karyotype regularly have decreased testosterone levels with high levels of LH and FSH (70). As reported above, 46,XX testicular DSD-males are infertile because of azoospermia and sertoli-cell-only syndrome or complete degeneration of the seminiferous tubules upon histological examination (70, 71). The X-Y rearrangements cannot be detected using conventional cytogenetic analysis and, thus, molecular cytogenetic analysis using a specific probe for the *SRY* locus or array-comparative genomic hybridization (CGH) should be carried out in all cases of 46,XX testicular DSD.

Very few cases have been reported on Y-autosomal translocations including the *SRY* gene leading to 46,XX testicular DSD (72, 73).

SRY-positive X-Y rearrangements are generally not inherited because they result from *de novo* translocations and the affected males are infertile. When *SRY* is translocated to another chromosome or when fertility is preserved, sex-limited autosomal dominant inheritance is observed (69, 74).

Males with an 46,XX karyotype having no *SRY* gene are rare with about 10% of all 46,XX testicular DSD and the testicular development may be activated due to other genetic aberrations (70). Copy number variations (CNVs) affecting *SOX9* or *SOX3* as well as *RSPO1* mutations have been implicated in this respect (75, 76, 77).

X-autosome translocations in males

Meiosis in males with X-autosome translocations is typically affected due to failure in XY pairing (see above)

and practically all males with X-autosome translocations are infertile due to spermatogenic arrest (54, 78) for which disruption in the formation of the sex vesicle is the obvious cause (53, 79). The proper sex vesicle formation is necessary for normal spermatogenesis, and any interference will compromise the process of sperm development (53). In cases of X-autosome translocations, the formation of quadrivalents was proposed, in which the PARs of the Y chromosome associate with the homologous parts of the X chromosome on the derivative X chromosome and the derivative autosome (80). In this context, also Y-autosomal translocations, with an autosomal breakpoint other than an acrocentric short arm, may result in the disruption of the sex vesicle leading to infertility (81). However, for both scenarios, if spermatozoa can be recovered, albeit in very small numbers, *in vitro* fertilization (IVF) using intracytoplasmic sperm injection (ICSI) may be attempted, but associated with a potentially high risk for generation of unbalanced chromosomal aberrations in the offspring (82). Prenatal genetic diagnostics (PGD) can be offered to the couple after genetic counseling to screen for balanced or unaffected embryos.

X-chromosomal deletions

Since genome-wide technologies (array-comparative genomic hybridization (array-CGH) or single-nucleotide polymorphism (SNP) arrays) have been available to identify submicroscopic deletions and duplication, these are analyzed on a large scale in many diseases and are termed CNVs. It immediately became clear that CNVs add to the normal variation in our genome and that the majority of CNVs has probably no or little relevance for disease (83). At the same time, however, many novel microdeletion syndromes are being described with increasing pace, of which many are associated with intellectual disability and malformations (84).

The Y-chromosomal AZF deletions are an example for CNVs with a clear cause-effect relationship for male infertility and have been part of the clinical routine diagnostic for many years. In contrast, genome-wide CNV analyses in infertile men are thus far only performed in research settings (10, 85, 86, 87), of which some have focused specifically on the X chromosome (88, 89, 90). When comparing infertile (oligo- or azoospermic) with fertile (or normozoospermic) men, the consistent finding of the available studies is a significantly higher overall 'burden' of microdeletions, especially on the sex chromosomes (10, 85, 88, 89). In addition, one study has

reported an increase of single nucleotide variations (SNVs) in infertile men compared with controls (10), and it has been speculated that infertility may be associated with an increased overall genome instability. To date, no CNVs with a definite cause–effect relationship comparable to the Y-chromosomal AZF deletions have been identified and replicated in an independent study. Thus, CNV analyses can currently not be advised for clinical diagnostics. However, analyses of CNVs can be used to identify novel candidate genes for male infertility. A recent example is *TEX11*, in which CNVs as well as SNVs cause non-obstructive azoospermia (see below) (12).

X-linked candidate genes

Numerous mouse models that have linked hundreds of genes with azoospermia and infertility provide insight into the molecular mechanisms responsible for this condition in mice (91). However, over the last few years, some of these genes have been reported to be mutated in men, but most of these studies have so far not been replicated and their role in human gonadal development and function currently remains unclear. A recurring problem is the interpretation of detected ‘mutations’, which may comprise rare but still non-pathogenic variants or variants that are associated with specific ethnic groups. This underlines the need for (1) strict *in silico* assessment of the pathogenicity, which should follow the established guidelines (e.g. American College of Medical Genetics and Genomics, ACMG (92)) and (2) functional studies to ascertain the pathogenicity of mutations.

Nevertheless, genes on the sex chromosomes are prime factors for sexual differentiation and gonadal function. Many X-linked genes are expressed in the testis and are thought to be involved in gametogenesis.

Androgen receptor (AR)

Mutations in the X-linked *AR* gene cause three different diseases (1) androgen insensitivity syndrome (AIS) (93), (2) spinal and bulbar muscular atrophy (SBMA or Kennedy disease) (94) and (3) prostate cancer (95, 96, 97).

For the wide spectrum of AIS phenotypes, *AR* mutations may lead to complete androgen insensitivity (CAIS) with a female phenotype in karyotypic males, partial forms (PAIS) in patients with ambiguous genitalia or mild forms (MAIS) in men with hypospadias, gynecomastia and spermatogenic impairment (98, 99, 100). However, patients with MAIS may have normal male genitalia and

infertility as the only symptom. Therefore, *AR* mutational analysis should be prompted in cases of a high Androgen Sensitivity Index (ASI) but mutations in the *AR* gene seem to be a rare cause of isolated male infertility (101, 102, 103).

Two polymorphisms, the CAG and GGN polymorphisms, located in exon 1 of the *AR* gene, code for polyglutamine and polyglycine stretches respectively. Longer lengths of the CAG repeat are associated with decreased transcriptional activity of the *AR* protein *in vitro*, suggesting that longer polyglutamine tracts may be related to male infertility (104, 105, 106). Thus, the CAG repeat length has been extensively studied for their role in male infertility. However, overall statistically significant, but very small and thus clinically irrelevant differences have been determined between infertile men and controls (105, 107, 108, 109). Variations of the GGN polymorphism are frequently found in the general male population and are not associated with male infertility (109, 110, 111, 112, 113).

TEX11

The X-linked *TEX11* (testis-expressed 11) gene encodes a protein critical for male germ cell meiotic DNA recombination (114). *Tex11*-knockout male mice exhibit azoospermia with meiotic arrest at the pachytene stage due to an inability to repair double-strand DNA breaks (114). Recently, Yatsenko *et al.* identified *TEX11* as a new genetic marker for spermatogenic arrest in men with idiopathic infertility (12). Using array-CGH, a loss of approximately 99 kb on chromosome Xq13.2, involving three exons of *TEX11*, was found in two azoospermic patients. Subsequent mutational screening identified five additional *TEX11* mutations in overall 2.4% of azoospermic patients, which were absent in normozoospermic controls. Importantly, five of those *TEX11* mutations were detected in 33 patients (15%) diagnosed with azoospermia and meiotic arrest, resembling the *Tex11*-deficient mouse meiotic arrest phenotype. Immunohistochemical analysis showed specific cytoplasmic *TEX11* expression in late spermatocytes, as well as in round and elongated spermatids, in normal human testes. In contrast, testes from azoospermic patients with *TEX11* mutations showed meiotic arrest and lacked any *TEX11* expression (12). This finding relied on the combination of genetics and phenotyping by testicular histology. Hemizygous mutations in *TEX11* were confirmed as an important cause for meiotic arrest already in another study (13). Exome sequencing was also

recently used to identify a homozygous mutation in the closely related, but autosomal gene *TEX15* as a cause for meiotic arrest (115).

RHOX

The human reproductive homeobox (*RHOX*) genes are clustered on the X chromosome and comprise three genes: *RHOXF1*, *RHOXF2* and *RHOXF2B*, which are selectively expressed in human oocytes and male germ cells (116, 117, 118). Several mutations in *RHOXF1* and *RHOXF2/2B* found in patients with severe oligozoospermia stress the importance of these genes in male infertility (14, 15). It has been shown that *RHOXF2/2B* mutations significantly impair the ability to regulate downstream genes such as transcription factors and chaperons from the HSP70 family (15).

ANOS1 (KAL1)

ANOS1 (formerly known as *KAL1*), located on the short arm of the X chromosome (Xp22.31), encodes the extracellular matrix protein anosmin 1 that plays an important role in the migration of gonadotropin-releasing hormone (GnRH)-producing neurons to olfactory axons of the hypothalamus (119, 120). Gene deletions and point mutations were identified in patients with hypogonadotropic hypogonadism (HH) with or without anosmia (121, 122, 123, 124, 125).

USP26

The *USP26* gene is located on Xq26 and belongs to a large family of deubiquitinating enzymes (DUBs) (126), which are responsible for processing inactive ubiquitin precursors, removing ubiquitin from cellular adducts and rescuing macromolecules from degradation (127, 128, 129). The *USP26* protein assembles with the androgen receptor (AR) and modulates its ubiquitination. Therefore, *USP26* influences AR transcriptional activity, which is, as described previously, fundamental for the proper maintenance of spermatogenesis (130). In recent years, numerous nucleotide variations in *USP26* gene have been reported both in fertile and infertile men, but the conflicting results of these studies render the association of variations in *USP26* with male infertility unclear (108, 131, 132, 133, 134).

TAF7L

In mice, *Taf7l* is highly expressed in germ cells and *Taf7l*-knockout mice exhibit structurally abnormal sperm, a reduced sperm count, motility and fertility (135, 136). Thus, it has been speculated that the human *TAF7L* gene may be essential for the maintenance of spermatogenesis (137). However, sequence analysis of infertile patients and controls revealed no clear association to male infertility (108, 138).

Summary

The supposedly ‘female’ human X chromosome plays a predominant role in spermatogenesis and several X-chromosomal aberrations are known to cause male infertility. The genetic spectrum ranges from an additional X chromosome found in Klinefelter patients to point mutations in several recently published genes. Furthermore, patients with spermatogenic failure carry a higher CNV burden on the sex chromosomes compared with fertile males.

Two different types of genes are located on the X chromosome: highly conserved genes according to Ohno’s law combine with acquired adaptive genes in ampliconic gene families. These acquired X-linked genes are predominantly expressed in the testes and mutations may impact male reproduction as it was recently found in *TEX11* or *RHOXF1* and *RHOXF2/2B*. These genes emphasize the importance of the X chromosome for male gonadal development.

In summary, the diverse X-chromosomal defects found in patients with spermatogenic failure point out that the X chromosome is, besides the well-known X-linked developmental genes, also a ‘male’ chromosome, containing a multitude of genes orchestrating different stages of male gonadal and especially germ cell development.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

Both authors outlined, wrote and finalized the manuscript together.

References

- 1 Meschede D, Lemcke B, Behre HM, Geyer C De, Nieschlag E & Horst J. Clustering of male infertility in the families of couples treated with intracytoplasmic sperm injection. *Human Reproduction* 2000 **15** 1604–1608. (doi:10.1093/humrep/15.7.1604)
- 2 Zorrilla M & Yatsenko AN. The genetics of infertility: current status of the field. *Current Genetic Medicine Reports* 2013 **1** 247–260. (doi:10.1007/s40142-013-0027-1)
- 3 Golde RJT van, Avoort IaM van der, Tuerlings JHAM, Kiemeny LA, Meuleman EJH, Braat DDM & Kremer JAM. Phenotypic characteristics of male subfertility and its familial occurrence. *Journal of Andrology* 2004 **25** 819–823. (doi:10.1002/j.1939-4640.2004.tb02860.x)
- 4 Gekas J. Chromosomal factors of infertility in candidate couples for ICSI: an equal risk of constitutional aberrations in women and men. *Human Reproduction* 2001 **16** 82–90. (doi:10.1093/humrep/16.1.82)
- 5 Behre HM, Bergmann M, Simoni M & Tüttelmann F. Primary testicular failure. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. *Source Endotext* [Internet]. South Dartmouth (MA): MDText.com, 2015 p 2000.
- 6 Röpke A, Tewes AC, Gromoll J, Kliesch S, Wieacker P & Tüttelmann F. Comprehensive sequence analysis of the NR5A1 gene encoding steroidogenic factor 1 in a large group of infertile males. *European Journal of Human Genetics* 2013 **21** 1012–1015. (doi:10.1038/ejhg.2012.290)
- 7 Bashamboo A, Ferraz-de-Souza B, Lourenço D, Lin L, Sebire NJ, Montjean D, Bignon-Topalovic J, Mandelbaum J, Siffroi JP, Christin-Maitre S *et al.* Human male infertility associated with mutations in NR5A1 encoding steroidogenic factor 1. *American Journal of Human Genetics* 2010 **87** 505–512. (doi:10.1016/j.ajhg.2010.09.009)
- 8 Ferraz-de-Souza B, Lin L & Achermann JC. Steroidogenic factor-1 (SF-1, NR5A1) and human disease. *Molecular and Cellular Endocrinology* 2011 **336** 198–205. (doi:10.1016/j.mce.2010.11.006)
- 9 Ferlin A, Rocca MS, Vinanzi C, Ghezzi M, Nisio A Di & Foresta C. Mutational screening of NR5A1 gene encoding steroidogenic factor 1 in cryptorchidism and male factor infertility and functional analysis of seven undescribed mutations. *Fertility and Sterility* 2015 **104** 163.e1–169.e1. (doi:10.1016/j.fertnstert.2015.04.017)
- 10 Lopes AM, Aston KI, Thompson E, Carvalho F, Gonçalves J, Huang N, Matthiesen R, Noordam MJ, Quintela I, Ramu A *et al.* Human spermatogenic failure purges deleterious mutation load from the autosomes and both sex chromosomes, including the gene DMRT1. *PLoS Genetics* 2013 **9** e1003349. (doi:10.1371/journal.pgen.1003349)
- 11 Tewes AC, Ledig S, Tüttelmann F, Kliesch S & Wieacker P. DMRT1 mutations are rarely associated with male infertility. *Fertility and Sterility* 2014 **102** 816–820. (doi:10.1016/j.fertnstert.2014.05.022)
- 12 Yatsenko AN, Georgiadis AP, Röpke A, Berman AJ, Jaffe T, Olszewska M, Westernströer B, Sanfilippo J, Kurpisz M, Rajkovic A *et al.* X-linked TEX11 mutations, meiotic arrest, and azoospermia in infertile men. *New England Journal of Medicine* 2015 **372** 2097–2107. (doi:10.1056/NEJMoa1406192)
- 13 Yang F, Silber S, Leu NA, Oates RD, Marszalek JD, Skaletsky H, Brown LG, Rozen S, Page DC & Wang PJ. TEX11 is mutated in infertile men with azoospermia and regulates genome-wide recombination rates in mouse. *EMBO Molecular Medicine* 2015 **7** 1198–1210. (doi:10.15252/emmm.201404967)
- 14 Frainais C, Kannengiesser C, Albert M, Molina-Gomes D, Boitrelle F, Bailly M, Grandchamp B, Selva J & Vialard F. RHOXF2 gene, a new candidate gene for spermatogenesis failure. *Basic and Clinical Andrology* 2014 **24** 3. (doi:10.1186/2051-4190-24-3)
- 15 Borgmann J, Tüttelmann F, Dworniczak B, Röpke A, Song HW, Kliesch S, Wilkinson MF, Laurentino S & Gromoll J. The human RHOX gene cluster: target genes and functional analysis of gene variants in infertile men. *Human Molecular Genetics* 2016 **25** 4898–4910. (doi:10.1093/hmg/ddw313)
- 16 Goodfellow PN & Lovell-Badge R. SRY and sex determination in mammals. *Annual Review of Genetics* 1993 **27** 71–92. (doi:10.1146/annurev.ge.27.120193.000443)
- 17 Sinclair AH, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ, Foster JW, Frischauf AM, Lovell-Badge R & Goodfellow PN. A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* 1990 **346** 240–244. (doi:10.1038/346240a0)
- 18 Krausz C, Hoefsloot L, Simoni M & Tüttelmann F. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: state-of-the-art 2013. *Andrology* 2014 **2** 5–19. (doi:10.1111/j.2047-2927.2013.00173.x)
- 19 Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, Repping S, Pyntikova T, Ali J, Bieri T *et al.* The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* 2003 **423** 825–837. (doi:10.1038/nature01722)
- 20 Hughes JE, Skaletsky H, Koutseva N, Pyntikova T & Page DC. Sex chromosome-to-autosome transposition events counter Y-chromosome gene loss in mammals. *Genome Biology* 2015 **16** 104. (doi:10.1186/s13059-015-0667-4)
- 21 Mendez FL, Poznik GD, Castellano S & Bustamante CD. The divergence of neandertal and modern human Y chromosomes. *American Journal of Human Genetics* 2016 **98** 728–734. (doi:10.1016/j.ajhg.2016.02.023)
- 22 Charlesworth B & Charlesworth D. The degeneration of Y chromosomes. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences* 2000 **355** 1563–1572. (doi:10.1098/rstb.2000.0717)
- 23 Ohno S. *Sex chromosomes and sex-linked genes. (Monographs on endocrinology, Vol. 1.)*, 1967. In: Berlin, Heidelberg, New York: Springer-Verlag. (doi:10.1007/978-3-642-88178-7)
- 24 Mueller JL, Skaletsky H, Brown LG, Zaghul S, Rock S, Graves T, Auger K, Warren WC, Wilson RK & Page DC. Independent specialization of the human and mouse X chromosomes for the male germ line. *Nature Genetics* 2013 **45** 1083–1087. (doi:10.1038/ng.2705)
- 25 Ross MT, Grafham DV, Coffey AJ, Scherer S, McLay K, Muzny D, Platzer M, Howell GR, Burrows C, Bird CP *et al.* The DNA sequence of the human X chromosome. *Nature* 2005 **434** 325–337. (doi:10.1038/nature03440)
- 26 Lin F, Xing K, Zhang J & He X. Expression reduction in mammalian X chromosome evolution refutes Ohno's hypothesis of dosage compensation. *PNAS* 2012 **109** 11752–11757. (doi:10.1073/pnas.1201816109)
- 27 Charlesworth D & Charlesworth B. Sex chromosomes: evolution of the weird and wonderful. *Current Biology* 2005 **15** R129–R131. (doi:10.1016/j.cub.2005.02.011)
- 28 Graves JAM. Sex chromosome specialization and degeneration in mammals. *Cell* 2006 **124** 901–914. (doi:10.1016/j.cell.2006.02.024)
- 29 Veyrunes F, Waters PD, Miethke P, Rens W, McMillan D, Alsop AE, Grützner F, Deakin JE, Whittington CM, Schatzkammer K *et al.* Bird-like sex chromosomes of platypus imply recent origin of mammal sex chromosomes. *Genome Research* 2008 **18** 965–973. (doi:10.1101/gr.7101908)

Review	A Röpke and F Tüttelmann	Aberrations of the X chromosome	177:5	R256
30	Lyon M. Gene action in the X-chromosome of the mouse (<i>Mus musculus</i> L.). <i>Nature</i> 1961 190 372–373. (doi:10.1038/190372a0)	50	Shi Q, Spriggs E, Field LL, Ko E, Barclay L & Martin RH. Single sperm typing demonstrates that reduced recombination is associated with the production of aneuploid 24,XY human sperm. <i>American Journal of Medical Genetics</i> 2001 99 34–38. (doi:10.1002/1096-8628(20010215)99:1<34::aid-ajmg1106>3.0.co;2-d)	
31	Ng K, Pullirsch D, Leeb M & Wutz A. Xist and the order of silencing. <i>EMBO Reports</i> 2007 8 34–39. (doi:10.1038/sj.embor.7400871)	51	Thomas NS & Hassold TJ. Aberrant recombination and the origin of Klinefelter syndrome. <i>Human Reproduction Update</i> 2003 9 309–317. (doi:10.1093/humupd/dmg028)	
32	Kalantry S, Purushothaman S, Bowen RB, Starmer J & Magnuson T. Evidence of Xist RNA-independent initiation of mouse imprinted X-chromosome inactivation. <i>Nature</i> 2009 460 647–651. (doi:10.1038/nature08161)	52	Tüttelmann F & Gromoll J. Novel genetic aspects of Klinefelter's syndrome. <i>Molecular Human Reproduction</i> 2010 16 386–395. (doi:10.1093/molehr/gaq019)	
33	Sudbrak R, Wiczorek G, Nuber UA, Mann W, Kirchner R, Erdogan F, Brown CJ, Wöhrle D, Sterk P, Kalscheuer VM <i>et al.</i> X chromosome-specific cDNA arrays: identification of genes that escape from X-inactivation and other applications. <i>Human Molecular Genetics</i> 2001 10 77–83. (doi:10.1093/hmg/10.1.77)	53	Heard E & Turner J. Function of the sex chromosomes in mammalian fertility. <i>Cold Spring Harbor Perspectives in Biology</i> 2011 3 a002675. (doi:10.1101/cshperspect.a002675)	
34	Barr M & Bertram E. A morphological distinction between neurones of the male and female, and the behaviour of the nucleolar satellite during accelerated nucleoprotein synthesis. <i>Nature</i> 1949 163 676. (doi:10.1038/163676a0)	54	Assche E Van, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, Steirteghem A Van & Liebaers I. Cytogenetics of infertile men. <i>Human Reproduction</i> 1996 11 (Supplement 4) 1–24.	
35	Disteche CM. Escape from X inactivation in human and mouse. <i>Trends in Genetics</i> 1995 11 17–22. (doi:10.1016/S0168-9525(00)88981-7)	55	Tüttelmann F, Werny F, Cooper TG, Kliesch S, Simoni M & Nieschlag E. Clinical experience with azoospermia: aetiology and chances for spermatozoa detection upon biopsy. <i>International Journal of Andrology</i> 2011 34 291–298. (doi:10.1111/j.1365-2605.2010.01087.x)	
36	Rouyer F, Simmler MC, Johnsson C, Vergnaud G, Cooke HJ & Weissenbach J. A gradient of sex linkage in the pseudoautosomal region of the human sex chromosomes. <i>Nature</i> 1986 319 291–295. (doi:10.1038/319291a0)	56	Vincent MC, Daudin M, De MP, Massat G, Miesusset R, Pontonnier F, Calvas P, Bujan L & Bourrouillout G. Cytogenetic investigations of infertile men with low sperm counts: a 25-year experience. <i>Journal of Andrology</i> 2002 23 18–22. (doi:10.1002/j.1939-4640.2002.tb02597.x)	
37	Burgoyne PS. Genetic homology and crossing over in the X and Y chromosomes of Mammals. <i>Human Genetics</i> 1982 61 85–90. (doi:10.1007/BF00274192)	57	Bojesen A, Juul S & Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. <i>Journal of Clinical Endocrinology and Metabolism</i> 2003 88 622–626. (doi:10.1210/jc.2002-021491)	
38	Polani PE. Pairing of X and Y chromosomes, non-inactivation of X-linked genes, and the maleness factor. <i>Human Genetics</i> 1982 60 207–211. (doi:10.1007/BF00303003)	58	Lanfranco F, Kamischke A, Zitzmann M & Nieschlag E. Klinefelter's syndrome. <i>Lancet</i> 2004 364 273–283. (doi:10.1016/S0140-6736(04)16678-6)	
39	Helena Mangs A & Morris BJ. The human pseudoautosomal region (PAR): origin, function and future. <i>Current Genomics</i> 2007 8 129–136. (doi:10.2174/138920207780368141)	59	Groth KA, Skakkebaek A, Høst C, Gravholt CH & Bojesen A. Clinical review: Klinefelter syndrome – a clinical update. <i>Journal of Clinical Endocrinology and Metabolism</i> 2013 98 20–30. (doi:10.1210/jc.2012-2382)	
40	Freije D, Helms C, Watson M & Donis-Keller H. Identification of a second pseudoautosomal region near the Xq and Yq telomeres. <i>Science</i> 1992 258 1784–1787. (doi:10.1126/science.1465614)	60	Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA & Ferlin A. Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. <i>Journal of Endocrinological Investigation</i> 2017 40 123–134. (doi:10.1007/s40618-016-0541-6)	
41	Rappold GA. The pseudoautosomal regions of the human sex chromosomes. <i>Human Genetics</i> 1993 92 315–324. (doi:10.1007/BF01247327)	61	Frühmesser A & Kotzot D. Chromosomal variants in Klinefelter syndrome. <i>Sexual Development</i> 2011 5 109–123. (doi:10.1159/000327324)	
42	Tjio JH & Levan A. The chromosome number of man. <i>Hereditas</i> 1956 42 1–6. (doi:10.1111/j.1601-5223.1956.tb03010.x)	62	Böök J & Santesson B. Nuclear sex in triploid XXY human cells. <i>Lancet</i> 1961 278 318. (doi:10.1016/S0140-6736(61)90612-2)	
43	Jacobs PA & Strong JA. A case of human intersexuality having possible XXY sex-determining mechanism. <i>Nature</i> 1959 183 302–303. (doi:10.1038/183302a0)	63	Plath K, Mlynarczyk-Evans S, Nusinow DA & Panning B. Xist RNA and the mechanism of X chromosome inactivation. <i>Annual Review of Genetics</i> 2002 36 233–278. (doi:10.1146/annurev.genet.36.042902.092433)	
44	Rives N, Simeon N, Milazzo JP, Barthelemy C & Mace B. Meiotic segregation of sex chromosomes in mosaic and non-mosaic XYY males: case reports and review of the literature. <i>International Journal of Andrology</i> 2003 26 242–249. (doi:10.1046/j.1365-2605.2003.00421.x)	64	Tartaglia N, Davis S, Hench A, Nimishakavi S, Beauregard R, Reynolds A, Fenton L, Albrecht L, Ross J, Visootsak J <i>et al.</i> A new look at XYY syndrome: medical and psychological features. <i>American Journal of Medical Genetics Part A</i> 2008 146A 1509–1522. (doi:10.1002/ajmg.a.32366)	
45	Otter M, Schrander-Stumpel CTRM & Curfs LMG. Triple X syndrome: a review of the literature. <i>European Journal of Human Genetics</i> 2010 18 265–271. (doi:10.1038/ejhg.2009.109)	65	Ottesen AM, Aksglaede L, Garn I, Tartaglia N, Tassone F, Gravholt CH, Bojesen A, Sørensen K, Jørgensen N, Meyts ER De <i>et al.</i> Increased number of sex chromosomes affects height in a nonlinear fashion: a study of 305 patients with sex chromosome aneuploidy. <i>American Journal of Medical Genetics, Part A</i> 2010 152 1206–1212. (doi:10.1002/ajmg.a.33334)	
46	Kim IW, Khadilkar AC, Ko EY & Sabanegh ES. 47,XXY syndrome and male infertility. <i>Reviews in Urology</i> 2013 15 188–196. (doi:10.1016/j.urology.2012.09.005)	66	Visootsak J, Aylstock M & Graham JM. Klinefelter syndrome and its variants: an update and review for the primary pediatrician. <i>Clinical Pediatrics</i> 2001 40 639–651. (doi:10.1177/000992280104001201)	
47	Bojesen A & Gravholt CH. Klinefelter syndrome in clinical practice. <i>Nature Clinical Practice Urology</i> 2007 4 192–204. (doi:10.1038/ncpuro0775)			
48	Visootsak J & Graham JM. Klinefelter syndrome and other sex chromosomal aneuploidies. <i>Orphanet Journal of Rare Diseases</i> 2006 1 42. (doi:10.1186/1750-1172-1-42)			
49	Shi Q & Martin RH. Aneuploidy in human spermatozoa: FISH analysis in men with constitutional chromosomal abnormalities, and in infertile men. <i>Reproduction</i> 2001 121 655–666. (doi:10.1530/rep.0.1210655)			

Review	A Röpke and F Tüttelmann	Aberrations of the X chromosome	177:5	R257
67	Ferguson-Smith MA. X-Y chromosomal interchange in the aetiology of true hermaphroditism and of XX Klinefelter's syndrome. <i>Lancet</i> 1966 2 475–476. (doi:10.1016/S0140-6736(66)92778-4)	83	Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, Fiegler H, Shapero MH, Carson AR, Chen W <i>et al.</i> Global variation in copy number in the human genome. <i>Nature</i> 2006 444 444–454. (doi:10.1038/nature05329)	
68	Rigola MA, Carrera M, Ribas I, Egozcue J, Miró R & Fuster C. A comparative genomic hybridization study in a 46,XX male. <i>Fertility and Sterility</i> 2002 78 186–188. (doi:10.1016/S0015-0282(02)03165-5)	84	Craddock N, Hurles ME, Cardin N, Pearson RD, Plagnol V, Robson S, Vukcevic D, Barnes C, Conrad DF, Giannoulatos E <i>et al.</i> Genome-wide association study of CNVs in 16,000 cases of eight common diseases and 3,000 shared controls. <i>Nature</i> 2010 464 713–720. (doi:10.1038/nature08979)	
69	Weil D, Wang I, Dietrich A, Poustka A, Weissenbach J & Petit C. Highly homologous loci on the X and Y chromosomes are hot-spots for ectopic recombinations leading to XX maleness. <i>Nature Genetics</i> 1994 7 414–419. (doi:10.1038/ng0794-414)	85	Tüttelmann F, Simoni M, Kliesch S, Ledig S, Dworniczak B, Wieacker P & Röpke A. Copy number variants in patients with severe oligozoospermia and sertoli-cell-only syndrome. <i>PLoS ONE</i> 2011 6 e19426. (doi:10.1371/journal.pone.0019426)	
70	Vorona E, Zitzmann M, Gromoll J, Schüring AN & Nieschlag E. Clinical, endocrinological, and epigenetic features of the 46,XX male syndrome, compared with 47,XXY Klinefelter patients. <i>Journal of Clinical Endocrinology and Metabolism</i> 2007 92 3458–3465. (doi:10.1210/jc.2007-0447)	86	Eggers S, DeBoer KD, Bergen J van den, Gordon L, White SJ, Jamsai D, McLachlan RI, Sinclair AH & O'Bryan MK. Copy number variation associated with meiotic arrest in idiopathic male infertility. <i>Fertility and Sterility</i> 2015 103 214–219. (doi:10.1016/j.fertnstert.2014.09.030)	
71	Chapelle A de la. The etiology of maleness in XX men. <i>Human Genetics</i> 1981 58 105–116. (doi:10.1007/BF00284157)	87	Stouffs K, Vandermaelen D, Massart a, Menten B, Vergult S, Tournaye H & Lissens W. Array comparative genomic hybridization in male infertility. <i>Human Reproduction</i> 2012 27 921–929. (doi:10.1093/humrep/der440)	
72	Dauwerse JG, Hansson KBM, Brouwers AAM, Peters DJM & Breuning MH. An XX male with the sex-determining region Y gene inserted in the long arm of chromosome 16. <i>Fertility and Sterility</i> 2006 86 463.e1–465.e1. (doi:10.1016/j.fertnstert.2005.12.062)	88	Giacco D Lo, Chianese C, Ars E, Ruiz-Castañe E, Forti G & Krausz C. Recurrent X chromosome-linked deletions: discovery of new genetic factors in male infertility. <i>Journal of Medical Genetics</i> 2014 51 340–344. (doi:10.1136/jmedgenet-2013-101988)	
73	Queralt R, Madrigal I, Vallecillos MA, Morales C, Ballescá JL, Oliva R, Soler A, Sánchez A & Margarit E. Atypical XX male with the SRY gene located at the long arm of chromosome 1 and a 1qter microdeletion. <i>American Journal of Medical Genetics Part A</i> 2008 146A 1335–1340. (doi:10.1002/ajmg.a.32284)	89	Chianese C, Gunning AC, Giachini C, Daguin F, Balercia G, Ars E, Giacco D Lo, Ruiz-Casta E, Forti G & Krausz C. X chromosome-linked CNVs in male infertility: discovery of overall duplication load and recurrent, patient-specific gains with potential clinical relevance. <i>PLoS ONE</i> 2014 9 1–7. (doi:10.1371/journal.pone.0097746)	
74	Wang I, Well D, Levilliers J, Affara NA, la Chapelle A de & Petit C. Prevalence and molecular analysis of two hot spots for ectopic recombination leading to XX maleness. <i>Genomics</i> 1995 28 52–58. (doi:10.1006/geno.1995.1105)	90	Krausz C, Giachini C, Giacco D Lo, Daguin F, Chianese C, Ars E, Ruiz-Castane E, Forti G & Rossi E. High resolution X chromosome-specific array-CGH detects new CNVs in infertile males. <i>PLoS ONE</i> 2012 7 e44887. (doi:10.1371/journal.pone.0044887)	
75	Sutton E, Hughes J, White S, Sekido R, Tan J, Arboleda V, Rogers N, Knowler K, Rowley L, Eyre H <i>et al.</i> Identification of SOX3 as an XX male sex reversal gene in mice and humans. <i>Journal of Clinical Investigation</i> 2011 121 328–341. (doi:10.1172/JCI42580)	91	Matzuk MM & Lamb DJ. The biology of infertility: research advances and clinical challenges. <i>Nature Medicine</i> 2008 14 1197–1213. (doi:10.1038/nm.f.1895)	
76	Huang B, Wang S, Ning Y, Lamb AN & Bartley J. Autosomal XX sex reversal caused by duplication of SOX9. <i>American Journal of Medical Genetics</i> 1999 87 349–353. (doi:10.1002/(sici)1096-8628(19991203)87:4<349::aid-ajmg13>3.0.co;2-n)	92	Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E <i>et al.</i> Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. <i>Genetics in Medicine</i> 2015 17 405–423. (doi:10.1038/gim.2015.30)	
77	Parma P, Radi O, Vidal V, Chaboissier MC, Dellambra E, Valentini S, Guerra L, Schedl A & Camerino G. R-spondin1 is essential in sex determination, skin differentiation and malignancy. <i>Nature Genetics</i> 2006 38 1304–1309. (doi:10.1038/ng1907)	93	McPhaul MJ, Marcelli M, Zoppi S, Wilson CM, Griffin JE & Wilson JD. Mutations in the ligand-binding domain of the androgen receptor gene cluster in two regions of the gene. <i>Journal of Clinical Investigation</i> 1992 90 2097–2101. (doi:10.1172/JCI116093)	
78	Ma S, Yuen BH, Penaherrera M, Koehn D, Ness L & Robinson W. ICSI and the transmission of X-autosomal translocation: a three-generation evaluation of X;20 translocation: case report. <i>Human Reproduction</i> 2003 18 1377–1382. (doi:10.1093/humrep/deg247)	94	Spada AR La, Wilson EM, Lubahn DB, Harding AE & Fischbeck KH. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. <i>Nature</i> 1991 352 77–79. (doi:10.1038/352077a0)	
79	Turner JMA. Meiotic sex chromosome inactivation. <i>Development</i> 2007 134 1823–1831. (doi:10.1242/dev.000018)	95	Röpke A, Allhoff E & Wieacker P. Mutationen des androgenrezeptor-gens als mögliche ursache der antiandrogenresistenz beim prostatakarcinom. <i>Journal of Reproductive Medicine and Endocrinology</i> 2004 1 194–201.	
80	Perrin A, Douet-Guilbert N, Bris MJ Le, Keromnes G, Langlois ML, Barrière P, Amice J, Amice V, Braekeleer M De & Morel F. Segregation of chromosomes in sperm of a t(X;18)(q11;p11.1) carrier inherited from his mother: case report. <i>Human Reproduction</i> 2008 23 227–230. (doi:10.1093/humrep/dem359)	96	Röpke A, Erbersdobler A, Hammerer P, Palisaar J, John K, Stumm M & Wieacker P. Gain of androgen receptor gene copies in primary prostate cancer due to X chromosome polysomy. <i>Prostate</i> 2004 59 59–68. (doi:10.1002/pros.10356)	
81	Röpke A, Stratis Y, Dosow-Scheele D, Wieacker P, Kliesch S & Tüttelmann F. Mosaicism for an unbalanced Y;21 translocation in an infertile man: a case report. <i>Journal of Assisted Reproduction and Genetics</i> 2013 30 1553–1558. (doi:10.1007/s10815-013-0122-y)	97	McCrea E, Sissung TM, Price DK, Chau CH & Figg WD. Androgen receptor variation affects prostate cancer progression and drug resistance. <i>Pharmacological Research</i> 2016 114 152–162. (doi:10.1016/j.phrs.2016.10.001)	
82	Perrin A, Vialard F, Douet-Guilbert N, Gomes DM, Guthauser B, Braekeleer M De, Selva J & Morel F. Meiotic segregation of X-autosome translocation in two carriers and implications for assisted reproduction. <i>Reproductive Biomedicine Online</i> 2009 18 850–855. (doi:10.1016/S1472-6483(10)60036-3)			

Review	A Röpke and F Tüttelmann	Aberrations of the X chromosome	177:5	R258
98	Wilson JD, Harrod MJ, Goldstein JL, Hemsell DL & MacDonald PC. Familial incomplete male pseudohermaphroditism, type 1. Evidence for androgen resistance and variable clinical manifestations in a family with the Reifenstein syndrome. <i>New England Journal of Medicine</i> 1974 290 1097–1103. (doi:10.1056/NEJM197405162902001)	112	Rajender S, Rajani V, Gupta NJ, Chakravarty B, Singh L & Thangaraj K. No association of androgen receptor GGN repeat length polymorphism with infertility in Indian men. <i>Journal of Andrology</i> 2006 27 785–789. (doi:10.2164/jandrol.106.000166)	
99	Quigley CA, Bellis A De, Marschke KB, el-Awady MK, Wilson EM & French FS. Androgen receptor defects: historical, clinical, and molecular perspectives. <i>Endocrine Reviews</i> 1995 16 271–321. (doi:10.1210/edrv-16-3-271)	113	Lundin KB, Giwercman A, Richthoff J, Abrahamsson PA & Giwercman YL. No association between mutations in the human androgen receptor GGN repeat and inter-sex conditions. <i>Molecular Human Reproduction</i> 2003 9 375–379. (doi:10.1093/molehr/gag048)	
100	Brinkmann AO. Molecular basis of androgen insensitivity. <i>Molecular and Cellular Endocrinology</i> 2001 179 105–109. (doi:10.1016/S0303-7207(01)00466-X)	114	Adelman CA & Petrini JHJ. ZIP4H (TEX11) deficiency in the mouse impairs meiotic double strand break repair and the regulation of crossing over. <i>PLoS Genetics</i> 2008 4 e1000042. (doi:10.1371/journal.pgen.1000042)	
101	Hiort O, Holterhus PM, Hörter T, Schulze W, Kremke B, Bals-Pratsch M, Sinnecker GHG & Kruse K. Significance of mutations in the androgen receptor gene in males with idiopathic infertility. <i>Journal of Clinical Endocrinology and Metabolism</i> 2000 85 2810–2815. (doi:10.1210/jc.85.8.2810)	115	Okutman O, Muller J, Baert Y, Serdarogullari M, Gultomruk M, Piton A, Rombaut C, Benkhalifa M, Teletin M, Skory V <i>et al.</i> Exome sequencing reveals a nonsense mutation in <i>TEX15</i> causing spermatogenic failure in a Turkish family. <i>Human Molecular Genetics</i> 2015 24 5581–5588. (doi:10.1093/hmg/ddv290)	
102	Goglia U, Vinanzi C, Zuccarello D, Malpassi D, Ameri P, Casu M, Minuto F, Foresta C & Ferone D. Identification of a novel mutation in exon 1 of androgen receptor gene in an azoospermic patient with mild androgen insensitivity syndrome: case report and literature review. <i>Fertility and Sterility</i> 2011 96 1165–1169. (doi:10.1016/j.fertnstert.2011.08.033)	116	Song HW, Anderson RA, Bayne RA, Gromoll J, Shimasaki S, Chang RJ, Parast MM, Laurent LC, de Rooij DG, Hsieh TC <i>et al.</i> The RHOX homeobox gene cluster is selectively expressed in human oocytes and male germ cells. <i>Human Reproduction</i> 2013 28 1635–1646. (doi:10.1093/humrep/det043)	
103	Ferlin A, Vinanzi C, Garolla A, Selice R, Zuccarello D, Cazzadore C & Foresta C. Male infertility and androgen receptor gene mutations: clinical features and identification of seven novel mutations. <i>Clinical Endocrinology</i> 2006 65 606–610. (doi:10.1111/j.1365-2265.2006.02635.x)	117	Richardson ME, Bleiziffer A, Tüttelmann F, Gromoll J & Wilkinson MF. Epigenetic regulation of the RHOX homeobox gene cluster and its association with human male infertility. <i>Human Molecular Genetics</i> 2013 1–12. (doi:10.1093/hmg/ddt392)	
104	Gao T, Marcelli M & McPhaul MJ. Transcriptional activation and transient expression of the human androgen receptor. <i>Journal of Steroid Biochemistry and Molecular Biology</i> 1996 59 9–20. (doi:10.1016/S0960-0760(96)00097-0)	118	Wayne CM, MacLean JA, Cornwall G & Wilkinson MF. Two novel human X-linked homeobox genes, hPEPP1 and hPEPP2, selectively expressed in the testis. <i>Gene</i> 2002 301 1–11. (doi:10.1016/S0378-1119(02)01087-9)	
105	Pan B, Li R, Chen Y, Tang Q, Wu W, Chen L, Lu C, Pan F, Ding H, Xia Y <i>et al.</i> Genetic association between androgen receptor gene CAG repeat length polymorphism and male infertility: a meta-analysis. <i>Medicine</i> 2016 95 e2878. (doi:10.1097/MD.0000000000002878)	119	Cariboni A, Pimpinelli F, Colamarino S, Zaninetti R, Piccolella M, Rumio C, Piva F, Rugarli EI & Maggi R. The product of X-linked Kallmann's syndrome gene (KAL1) affects the migratory activity of gonadotropin-releasing hormone (GnRH)-producing neurons. <i>Human Molecular Genetics</i> 2004 13 2781–2791. (doi:10.1093/hmg/ddh309)	
106	Tut TG, Ghadessy FJ, Trifiro MA, Pinsky L & Yong EL. Long polyglutamine tracts in the androgen receptor are associated with reduced trans-activation, impaired sperm production, and male infertility. <i>Journal of Clinical Endocrinology and Metabolism</i> 1997 82 3777–3782. (doi:10.1210/jcem.82.11.4385)	120	Layman LC. The molecular basis of human hypogonadotropic hypogonadism. <i>Molecular Genetics and Metabolism</i> 1999 68 191–199. (doi:10.1006/mgme.1999.2912)	
107	Meyts ERD, Leffers H, Petersen JH, Andersen AG, Carlsen E, Jørgensen N & Skakkebaek NE. CAG repeat length in androgen-receptor gene and reproductive variables in fertile and infertile men. <i>Lancet</i> 2002 359 44–46. (doi:10.1016/S0140-6736(02)07280-X)	121	Hardelin JP, Leveilliers J, Blanchard S, Carel JC, Leutenegger M, Pinard-Bertelto JP, Bouloux P & Petit C. Heterogeneity in the mutations responsible for X chromosome-linked Kallmann syndrome. <i>Human Molecular Genetics</i> 1993 2 373–377. (doi:10.1093/hmg/2.4.373)	
108	Tüttelmann F, Rajpert-De Meyts E, Nieschlag E, Simoni M, de Meyts ER, Nieschlag E & Simoni M. Gene polymorphisms and male infertility – a meta-analysis and literature review. <i>Reproductive BioMedicine Online</i> 2007 15 643–658. (doi:10.1016/S1472-6483(10)60531-7)	122	Behre HMM, Tüttelmann F, Ledig S & Wieacker P. Hypogonadotroper hypogonadismus aufgrund eines IHH oder Kallmann-Syndroms beim Mann. <i>Medizinische Genetik</i> 2011 23 254–258. (doi:10.1007/s11825-011-0278-8)	
109	Davis-Dao CA, Tuazon ED, Sokol RZ & Cortessis VK. Male infertility and variation in CAG repeat length in the androgen receptor gene: a meta-analysis. <i>Journal of Clinical Endocrinology and Metabolism</i> 2007 92 4319–4326. (doi:10.1210/jc.2007-1110)	123	Tornberg J, Sykiotis GP, Keefe K, Plummer L, Hoang X, Hall JE, Habuchi H, Kimata K, Pitteloud N & Bülow HE. Heparan sulfate 6-O-sulfotransferase 1, a gene involved in extracellular sugar modifications, is mutated in patients with idiopathic hypogonadotrophic hypogonadism. <i>PNAS</i> 2011 108 11524–11529. (doi:10.1073/pnas.1102284108/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1102284108)	
110	Ferlin A, Bartoloni L, Rizzo G, Roverato A, Garolla A & Foresta C. Androgen receptor gene CAG and GGC repeat lengths in idiopathic male infertility. <i>Molecular Human Reproduction</i> 2004 10 417–421. (doi:10.1093/molehr/gah054)	124	Costa-Barbosa FA, Balasubramanian R, Keefe KW, Shaw ND, Al-Tassan N, Plummer L, Dwyer AA, Buck CL, Choi JH, Seminara SB <i>et al.</i> Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. <i>Journal of Clinical Endocrinology and Metabolism</i> 2013 98 E943–E953. (doi:10.1210/jc.2012-4116)	
111	Ruhayel Y, Lundin K, Giwercman Y, Halldén C, Willén M & Giwercman A. Androgen receptor gene GGN and CAG polymorphisms among severely oligozoospermic and azoospermic Swedish men. <i>Human Reproduction</i> 2004 19 2076–2083. (doi:10.1093/humrep/deh349)	125	Oliveira LMB, Seminara SB, Beranova M, Hayes FJ, Valkenburgh SB, Schipani E, Costa EME, Latronico AC, Crowley WF & Vallejo M. The importance of autosomal genes in Kallmann	

Review	A Röpke and F Tüttelmann	Aberrations of the X chromosome	177:5	R259
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- syndrome: genotype-phenotype correlations and neuroendocrine characteristics. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 1532–1538. (doi:10.1210/jcem.86.4.7420)
- 126 Glickman MH & Ciechanover A. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. *Physiological Reviews* 2002 **82** 373–428. (doi:10.1152/physrev.00027.2001)
- 127 Wilkinson KD. Regulation of ubiquitin-dependent processes by deubiquitinating enzymes. *FASEB Journal* 1997 **11** 1245–1256.
- 128 Wing SS. Deubiquitinating enzymes – the importance of driving in reverse along the ubiquitin-proteasome pathway. *International Journal of Biochemistry and Cell Biology* 2003 **35** 590–605. (doi:10.1016/S1357-2725(02)00392-8)
- 129 Nijman SMB, Luna-Vargas MPA, Velds A, Brummelkamp TR, Dirac AMG, Sixma TK & Bernards R. A genomic and functional inventory of deubiquitinating enzymes. *Cell* 2005 **123** 773–786. (doi:10.1016/j.cell.2005.11.007)
- 130 Dirac AMG & Bernards R. The deubiquitinating enzyme USP26 is a regulator of androgen receptor signaling. *Molecular Cancer Research* 2010 **8** 844–854. (doi:10.1158/1541-7786.MCR-09-0424)
- 131 Stouffs K, Lissens W, Tournaye H, Steirteghem A Van & Liebaers I. Possible role of USP26 in patients with severely impaired spermatogenesis. *European Journal of Human Genetics* 2005 **13** 336–340. (doi:10.1038/sj.ejhg.5201335)
- 132 Christensen GL, Griffin J & Carrell DT. Sequence analysis of the X-linked USP26 gene in severe male factor infertility patients and fertile controls. *Fertility and Sterility* 2008 **90** 851–852. (doi:10.1016/j.fertnstert.2007.06.096)
- 133 Ribarski I, Lehavi O, Yogev L, Hauser R, Bar-Shira Maymon B, Botchan A, Paz G, Yavetz H & Kleiman SE. USP26 gene variations in fertile and infertile men. *Human Reproduction* 2009 **24** 477–484. (doi:10.1093/humrep/den374)
- 134 Asadpor U, Totonchi M, Sabbaghian M, Hoseinifar H, Akhound MR, Zari Moradi S, Haratian K, Sadighi Gilani MA, Gourabi H & Mohseni Meybodi A. Ubiquitin-specific protease (USP26) gene alterations associated with male infertility and recurrent pregnancy loss (RPL) in Iranian infertile patients. *Journal of Assisted Reproduction and Genetics* 2013 **30** 923–931. (doi:10.1007/s10815-013-0027-9)
- 135 Zhou H, Grubisic I, Zheng K, He Y, Wang PJ, Kaplan T & Tjian R. Taf7l cooperates with Trf2 to regulate spermiogenesis. *PNAS* 2013 **110** 16886–16891. (doi:10.1073/pnas.1317034110)
- 136 Pointud JC. The intracellular localisation of TAF7L, a paralogue of transcription factor TFIID subunit TAF7, is developmentally regulated during male germ-cell differentiation. *Journal of Cell Science* 2003 **116** 1847–1858. (doi:10.1242/jcs.00391)
- 137 Akinloye O, Gromoll J, Callies C, Nieschlag E & Simoni M. Mutation analysis of the X-chromosome linked, testis-specific TAF7L gene in spermatogenic failure. *Andrologia* 2007 **39** 190–195. (doi:10.1111/j.1439-0272.2007.00789.x)
- 138 Stouffs K, Willems A, Lissens W, Tournaye H, Steirteghem A Van & Liebaers I. The role of the testis-specific gene hTAF7L in the aetiology of male infertility. *Molecular Human Reproduction* 2006 **12** 263–267. (doi:10.1093/molehr/gal020)

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