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Y Chromosome Infertility

Synonym: Y Chromosome-Related Azoospermia

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Summary

Clinical characteristics

Y chromosome infertility is characterized by azoospermia (absence of sperm), severe oligozoospermia (<1 x 10^6 sperm/mL semen), moderate oligozoospermia (1-5 x 10^6 sperm/mL semen), or mild oligozoospermia (5-20 x 10^6 sperm/mL semen). Males with Y chromosome infertility usually have no obvious symptoms, although physical examination may reveal small testes.

Diagnosis/testing

The diagnosis of Y chromosome infertility is established in a male with characteristic clinical and laboratory features and by identification of a hemizygous deletion of Yq involving the AZF regions or identification of a heterozygous pathogenic variant involving *USP9Y* (located within AZFa).

Management

Treatment of manifestations: Pregnancies may be achieved by in vitro fertilization using intracytoplasmic sperm injection (ICSI), an in vitro fertilization procedure in which spermatozoa retrieved from ejaculate (in males with oligozoospermia) or extracted from testicular biopsies (in males with azoospermia) are injected into an egg harvested from the reproductive partner.

Other: Testicular sperm retrieval for in vitro fertilization is ineffective for males with AZFb and AZFa deletions, but has been successful for most males with AZFc deletions; in males with retrievable spermatozoa, the presence or absence of deletion of the long arm of the Y chromosome has no apparent effect on the fertilization or pregnancy rates; the risk for birth defects is the same as for any infertile couple that achieves a pregnancy using assisted reproductive technology.

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Genetic counseling

Y chromosome infertility is inherited in a Y-linked manner. Because males with Y chromosome deletions are infertile, the deletions are usually *de novo* and therefore not present in the father of the proband. Despite their severely impaired spermatogenesis, some males with deletion of the AZF regions have occasionally spontaneously fathered sons, who are infertile. This will occur in about 4% of couples with severe oligospermia if the female partner is young and very fertile. In pregnancies achieved using ICSI, male offspring have the same deletion as their father, with a high risk of male infertility. Note that certain Y deletions, including the most common Y deletions (gr/gr), do not necessarily cause infertility, but are only a risk factor for infertility. Female fetuses from a father with a Y chromosome deletion have no increased risk of congenital abnormalities or infertility. In pregnancies conceived through assisted reproductive technology (ART) and known to be at risk of resulting in a male with Y chromosome deletion, specific prenatal testing or preimplantation testing could be performed to determine the sex of the fetus and/or the presence of the Y chromosome deletion.

Diagnosis

Suggestive Findings

Y chromosome infertility **should be suspected** in males with the following clinical and laboratory features.

Clinical features

- A history of infertility
- Normal physical examination in ~30%
- Small testes in ~70% (males with Sertoli cell-only syndrome)

Laboratory features

Semen analysis. Ejaculate is examined to determine the number, motility, and morphology of sperm. Semen analysis should follow the WHO guidelines, Laboratory Manual for the Examination and Processing of Human Semen [WHO 2010]. The following categories of sperm count are identified (Table 1).

Table 1. Classification of Sperm Count

Classification of Sperm Count [1]	Sperm Count in Millions/mL [2]
Azoospermia	0
Severe oligozoospermia	<1
Moderate oligozoospermia	1-5
Mild oligozoospermia	5-20
Normal	>20

1. In each category, the morphology and/or motility of the sperm can be normal or abnormal (asthenoteratozoospermia).
2. These estimates have a poor correlation to pregnancy rate, when the count is >5 million/mL. Other than males with gr/gr interstitial AZFc deletions, individuals with deletion of Yq involving the AZF regions never have a sperm count >2 million/mL.

Testicular biopsy. Testicular biopsy may reveal either one or a combination of the following:

- Sertoli cell-only (SCO) syndrome, in which azoospermia is associated with the absence of or only occasional germ cells in tubules that for the most part have only Sertoli cells lining them with no or rare spermatogenesis
- Maturation arrest with spermatocytes but no spermatids or mature sperm

Establishing the Diagnosis

The diagnosis of Y chromosome infertility **is established** in a male with characteristic clinical and laboratory features and **one of the following** identified on molecular genetic testing (see Table 2):

- A hemizygous deletion of Yq involving the AZF regions (see Figure 1) (~99% of affected individuals) [Colaco & Modi 2018]
- A heterozygous *USP9Y* pathogenic (or likely pathogenic) variant in the AZFa region (1% of affected individuals) [Silber 2011]

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *USP9Y* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of Tier 1 testing (**targeted deletion/duplication analysis** or **chromosomal microarray analysis**) and Tier 2 testing (**cytogenetic analysis** and **single-gene testing**).

Tier 1 Testing

Targeted deletion analysis to detect deletions of the AZF regions on the Y chromosome can be considered first:

- Interstitial AZFa deletion (HERV15yq1-HERV15yq2; region includes *USP9Y* and *DDX3Y*)
- Interstitial AZFb & AZFb+c deletions (P5/proxP1, P5/distP1, P4/distP1)
- Interstitial AZFc deletion (b2/b4, gr/gr)
- Terminal AZF deletion (often representing a pseudodicentric Y chromosome with duplication and deletion)

Note: (1) *USP9Y* deletion has been found in fertile individuals (albeit with reduced spermatogenesis), and severely impaired spermatogenesis only occurs when both *USP9Y* and *DDX3Y* are deleted [Luddi et al 2009]. (2) Duplications involving the AZF regions have been reported and do not appear to affect fertility.

Chromosomal microarray analysis (CMA), which uses oligonucleotide or SNP arrays to detect genome-wide deletions/duplications (including deletions or duplications of the Y chromosome) not detectable by sequence analysis, can be used to detect deletions/duplications of the AZF region (Table 2). However, interpretation of CMA for the detection of Y deletions can be complicated by the fact that many of the genes implicated in Y chromosome infertility are present in multiple copies with similar sequences (see Molecular Genetics).

Tier 2 Testing

Cytogenetic analysis. Routine cytogenetic studies including G-banded karyotype and fluorescence in situ hybridization (FISH) analyses using probes specific for Y-linked genes performed on peripheral blood can distinguish terminal deletions of Yq from complex Y chromosome rearrangements that lead to Yq deletions (e.g., pseudodicentric Y chromosome).

Note: (1) A pseudodicentric Y chromosome results in both deletion of part of Yq and duplication of Yp and proximal Yq. (2) Complex Y chromosome rearrangements (e.g., pseudodicentric Y chromosomes and ring Y chromosomes) are often associated with a 45,X cell line [Lange et al 2009] and can lead to disruption of genes within the pseudoautosomal region (e.g., *SHOX*) and to additional phenotypes including short stature [Jorgez et al 2011] (see Genetically Related Disorders).

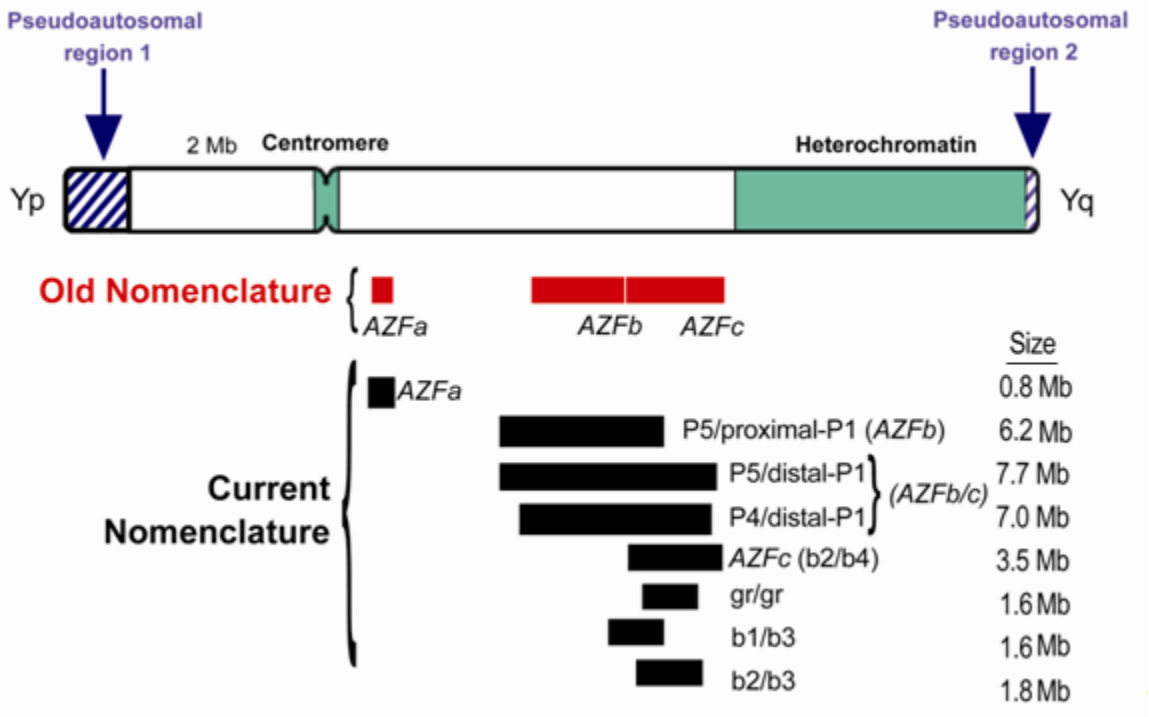

Figure 1. Schematic of the Y chromosome indicating the approximate position of the previously defined regions AZFa, AZFb, and AZFc and the position of recurrent deletions currently defined on the basis of the flanking palindromic repeats (see Establishing the Diagnosis). The short arm (Yp), the centromere, the long arm (Yq) (including the polymorphic heterochromatic band Yq12 of variable length), and the pseudoautosomal regions 1 and 2 are labeled.

The schematic is modified with permission from Repping et al [2002] and Silber [2011].

Single-gene testing. Sequence analysis of *USP9Y* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

Note: Complete deletion of *USP9Y* has been found in fertile individuals (albeit with reduced spermatogenesis), and severely impaired or totally absent spermatogenesis only occurs when both *USP9Y* and *DDX3Y* are both deleted [Luddi et al 2009].

Table 2. Genomic Testing Used in Y Chromosome Infertility

Method	Genetic Mechanism Detected [1]			Total Proportion of Y Chromosome Infertility Detected by Method
	AZF region deletion [2]	Unbalanced Y-chromosome rearrangement	*USP9Y* pathogenic variant	
Targeted deletion/ duplication analysis [3]	X		X [4]	>90%
CMA [5]	X			>90% [6]
Karyotype		X		Rare

Table 2. continued from previous page.

Method	Genetic Mechanism Detected [1]			Total Proportion of Y Chromosome Infertility Detected by Method
	AZF region deletion [2]	Unbalanced Y-chromosome rearrangement	*USP9Y* pathogenic variant	
USP9Y sequence analysis [7]			X	1 reported [8]

1. See Molecular Genetics for more details.
2. AZF regions include interstitial AZFa deletion (HERV15yq1-HERV15yq2); interstitial AZFc deletion (b2/b4); interstitial AZFb & AZFb+c deletions (P5/proxP1, P5/distP1, P4/distP1); and terminal AZF deletion (often representing a pseudodicentric Y chromosome w/duplication & deletion).
3. Targeted deletion analysis methods can include a range of techniques such as FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA), as well as other targeted quantitative methods.
4. Two individuals with intragenic *USP9Y* deletions/duplications reported [Sun et al 1999, Katsumi et al 2014]
5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *USP9Y* and *DDX3Y*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion depends on the type of microarray used and the density of probes in the AZF region. CMA designs in current clinical use target the AZF region.
6. The detection rate by CMA may be higher than that of targeted deletion/duplication analysis depending on the targeted method used.
7. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
8. Sun et al [1999]

Clinical Characteristics

Clinical Description

Males with Y chromosome infertility usually have no symptoms other than infertility. A physical examination may reveal small testes in those with Sertoli cell-only (SCO) syndrome. Physical examination is normal in approximately 30% of males with Y chromosome infertility.

Males with Y chromosome infertility have azoospermia or severe, moderate, or mild oligozoospermia depending on the location and size of the Y chromosome deletion (see Genotype-Phenotype Correlations). Most males with AZFa or AZFb/c deletions have a very poor prognosis for finding any sperm with testicular sperm extraction (TESE). Males with AZFc deletions (b2/b4 or gr/gr) have an extremely favorable prognosis (87%) for finding sperm sufficient for successful intracytoplasmic sperm injection (ICSI).

Oligozoospermia may be compatible with fertility when the female partner is very fertile.

Genotype-Phenotype Correlations

Each AZF region contains several genes that play a role in different stages of spermatogenesis. It is likely that future analysis of these individual genes in infertile males will result in more precise genotype-phenotype correlations. However, the multicopy and polymorphic nature of most fertility genes located on the Y chromosome makes it difficult to define their role precisely.

The regions initially defined as AZFb and AZFc have been found to partially overlap (Figure 1) [Repping et al 2002]. Much of the literature still refers to these regions; thus, the authors include reference to these regions by the palindromic repeats that now define the deletions more precisely [Silber 2011].

- Interstitial or terminal deletions that include all of AZFa are rare and usually result in the severe phenotype of Sertoli cell-only (SCO) syndrome [Silber 2011] (see Differential Diagnosis). The interstitial

deletions are mediated by recombination between the HERV15yq1 and HERV15yq2 repeats. One single-copy gene (*USP9Y*) located in AZFa has been directly implicated in the infertility phenotype, following detection of a single-nucleotide variant and a deletion limited to this gene in two infertile males with hypospermatogenesis but without SCO syndrome [Sun et al 1999]. Complete deletion of *USP9Y* has been found in fertile individuals, albeit with hypospermatogenesis [Luddi et al 2009], suggesting that SCO syndrome usually associated with AZFa deletion is not caused by *USP9Y* deletion alone but must include deletion of at least one adjacent gene, *DDX3Y*, to result in azoospermia. Complete AZFa deletions thus involve loss of two genes, *USP9Y* and *DDX3Y*, and result in a much more severe phenotype than mutation of *USP9Y* alone.

- Interstitial or terminal deletions that include AZFb and/or AZFb+c (hereafter designated AZFb/c) are mediated by recombination between palindromic repeats, either P5/proxP1, P5/distP1, or P4/distP1. These deletions are uncommon and usually result in severe azoospermia due to mature arrest [Repping et al 2002, Silber 2011]. Partial deletion of AZFb that removes the entire P4 palindrome decreases spermatocyte maturation but can be transmitted [Kichine et al 2012].
- Interstitial or terminal deletions that include AZFc only are mediated by recombination between the b2/b4 palindromic repeats and result in a variable infertility phenotype, ranging from azoospermia and SCO syndrome to severe oligozoospermia [Oates et al 2002, Silber 2011]. This type of deletion is common. Eighty-seven percent of males with this deletion will have some spermatozoa either in the ejaculate or at testicular sperm extraction that can lead to successful intracytoplasmic sperm injection [Silber 2011].
- Two partial deletions of AZFc, called b1/b3, b2/b3, are considered benign copy number variants (polymorphisms) [Repping et al 2003, Fernandes et al 2004, Machev et al 2004, Ferlin et al 2007].
- Another partial deletion of AZFc, gr/gr, may have some impact on fertility depending on ethnicity and geographic region [Stouffs et al 2011]. Males with gr/gr deletions can also have compensatory duplications of genes [Noordam et al 2011]. The gr/gr deletion removes two of the four copies of *DAZ* in the AZFc region, and is a risk factor for oligospermia. The role of *DAZ* in spermatogenesis is quantitative. Usually the loss of all four copies of *DAZ* does not prevent some spermatogenesis from occurring because of the compensatory function of *DAZL* on chromosome 3.
- Duplication of the AZFa or AZFc regions has been reported and does not appear to be associated with an abnormal phenotype [Bosch & Jobling 2003, Giachini et al 2008].

Penetrance

Rarely within a family, the same deletion of the Y chromosome has been reported to occasionally cause infertility in some males but not in others [Repping et al 2003]. These observations have been misinterpreted as representing variable penetrance. However, they result from the fact that even a severely oligospermic male with a Y chromosome deletion in the AZF regions can occasionally impregnate a very fertile partner.

Prevalence

The prevalence of Y chromosome deletions and microdeletions is estimated at 1:2,000 to 1:3,000 males [de Vries et al 2002; de Vries et al, personal communication].

The frequency of Yq microdeletions in males with azoospermia or severe oligozoospermia is about 5% [Kim et al 2017].

Differences in prevalence based on ethnicity have not been observed. However, the gr/gr deletion may have a different impact on fertility depending on ethnicity and geographic region [Stouffs et al 2011]. The gr/gr deletion is extremely common (25%) in Japanese men, for example, and represents simply a "risk factor" for male infertility.

Genetically Related Disorders

No disorders other than infertility are known to be caused by deletions of the long arm of the Y chromosome in the AZF regions. Men with Y chromosome deletions and infertility are otherwise healthy. However, complex Y chromosome rearrangements can lead to disruption of genes within the pseudoautosomal region (e.g., *SHOX*) and to additional phenotypes such as short stature [Jorgez et al 2011].

Short stature may occur in individuals with Yq deletions that extend close to the centromere in a region containing a putative growth-controlling gene, *GCY* [Kirsch et al 2002, Kirsch et al 2004].

Terminal deletions often associated with severely impaired spermatogenesis remove either all or part of the AZF regions along with the terminal q12 band of the Y chromosome. These so-called "terminal deletions" are usually not terminal, but rather are more complex rearrangements such as isodicentric Y chromosomes, which are often unstable and associated with a mosaic 45,X cell line. In fact, Turner syndrome (45,X) can be caused by the loss of an isodicentric Y chromosome [Lange et al 2009].

Differential Diagnosis

Infertility affects 15%-20% of couples of reproductive age. Infertility, dependent to a great extent on the age of the female partner, has been estimated to be male related in about half of those couples, but this often-quoted figure is poorly documented. Most likely, oligospermia sufficiently severe to cause infertility would only be present in 10% of infertile couples. Causes of male infertility other than deletion of the Y chromosome are numerous and often controversial. In most cases, male infertility is of unknown etiology. Possible causes of male infertility other than Y chromosome deletion include the following conditions:

- **Obstruction of the ejaculatory ducts,** which should be evaluated by physical examination [Practice Committee of the American Society for Reproductive Medicine 2004]. Congenital absence of the vas deferens (see Cystic Fibrosis) should be considered in this evaluation.

  CFTR-related disorders include cystic fibrosis (CF) and congenital absence of the vas deferens (CAVD). All males with CF are infertile as a result of azoospermia caused by absent, atrophic, or fibrotic wolffian duct structures. CAVD more commonly occurs in men without pulmonary or gastrointestinal manifestations of CF and usually results from compound heterozygosity of a classic (severe, loss-of-function) *CFTR* pathogenic variant with a mild (retaining some function) *CFTR* pathogenic variant (e.g., the 5T allele). These men make about 10% of the normal amount of CTFR protein, which is typically enough to prevent clinical CF, but not enough to allow fetal wolffian duct development [Chillón et al 1995]. Affected men have azoospermia and are thus infertile. Homozygosity for two *CFTR* 5T alleles can also result in CAVD without pulmonary or gastrointestinal manifestations of CF. CF is inherited in an autosomal recessive manner.

- **Immunologic abnormalities** caused by anti-sperm antibodies (controversial)

- **Infection** (e.g., mumps orchitis, epididymitis, urethitis); uncommon, and can generally be differentiated from Y chromosome infertility by past history

- **Vascular abnormalities** (varicocele); may be identified on physical examination, but their relevance to male infertility has been robustly questioned by most reproductive endocrinologists and is very controversial [Silber 2001]

- **Trauma;** distinguished by history and very rare

- **Endocrine abnormalities;** also rare (e.g., congenital adrenal hyperplasia [see 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia], isolated follicle-stimulating hormone (FSH) deficiency, and hyperprolactinemia). These can be differentiated through hormone studies. Kallmann syndrome (KS), the association of isolated GnRH deficiency (IGD) and anosmia (absence of smell), needs to be considered. Some males with KS have micropenis and cryptorchidism as neonates. Adults with KS have incomplete development of secondary sexual characteristics and prepubertal testicular volume (i.e., <4 mL). To date, more than 20 genes have been associated with KS. Of these, pathogenic variants in *ANOS1* (*KAL1*) and *FGFR1* account for approximately 15%-25% of KS. Non-reproductive phenotypes:
  - In males with *ANOS1* (*KAL1*) pathogenic variants. Synkinesia (mirror movement) of the digits, unilateral renal agenesis, sensorineural hearing loss, high-arched palate
  - In males with *FGFR1* pathogenic variants. Synkinesia of digits, cleft lip and/or palate, dental agenesis, brachydactyly or syndactyly, corpus callosum agenesis
- **Testicular tumor,** or other tumor caused by exposure to toxic agents
- **Exposure to toxic agents** such as radiation, chemotherapy; heat exposure (evaluated by full medical history)
- **Klinefelter syndrome (XXY),** which can be detected by cytogenetic analyses or CMA in men with non-obstructive azoospermia (NOA) and severe oligospermia and accounts for approximately 8% of azoospermic men. Klinefelter syndrome can be associated with hypoandrogenism and reported reduced intellectual function. However, most men with XXY are healthy except for their infertility.
- **Balanced chromosomal rearrangements,** which can be detected by cytogenetic evaluation in about 1.5% of men with NOA and oligospermia. In this case, there may also be a family history of multiple miscarriages and/or various phenotypic anomalies.

Sertoli cell-only (SCO) syndrome is the term applied to the finding of germinal aplasia in males. It has numerous causes including Y deletion, exposure to toxic chemotherapy agents or irradiation, mumps orchitis, Down syndrome, Klinefelter syndrome (47,XXY), congenital adrenal hypoplasia, isolated FSH deficiency, and hyperprolactinemia. For each of these, the medical history, the presence of other anomalies or symptoms, or chromosome analysis should differentiate them from Y chromosome infertility. In most cases, the etiology of SCO syndrome is unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Y chromosome infertility, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Semen analysis to determine the number, motility, and morphology of sperm
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A couple in which the male has Y chromosome infertility can be offered the option of in vitro fertilization using ICSI (intracytoplasmic sperm injection) [Silber 2011]. In this procedure, spermatozoa retrieved from ejaculate (in males with oligozoospermia) or extracted from testicular biopsies (in males with azoospermia) are injected by ICSI into a harvested egg by IVF (in vitro fertilization) [Silber et al 1998].

Retrieval of sperm has been successful for most males with deletions of AZFc, but rarely for males with deletions of AZFb or AZFa. The reason for this is that an autosomal copy of *DAZ* (*DAZL*) may serve as a "backup gene," which would help preserve a tiny amount of residual spermatogenesis in males with AZFc deletions that remove the *DAZ* genes. There are no such autosomal "backup" copies for genes in AZFa and AZFb.

The definition of Sertoli cell-only (SCO) syndrome has been the subject of confusion in the literature. There are two main causes of non-obstructive azoospermia (NOA): maturation arrest and Sertoli cell-only. With maturation arrest, there is a failure of spermatocytes to progress beyond meiosis I. But in 60% of individuals, a few spermatocytes do progress to sperm and can be retrieved from the testis. Similarly, in about 60% of males with SCO syndrome a tiny number of tubules actually contain a few spermatozoa resulting from small foci of spermatogenesis.

It is important to discuss the possibility of transmission of Y chromosome infertility to male offspring (see Genetic Counseling) prior to attempting fertilization by ICSI and IVF [Stouffs et al 2005].

In males with retrievable spermatozoa, the presence or absence of deletion of the long arm of the Y chromosome has no apparent effect on fertilization or pregnancy rates [Silber 2011]. The risk for birth defects is not different from that of any infertile couple that achieves a pregnancy through assisted reproductive technology [Davies et al 2012].

Agents/Circumstances to Avoid

Hormones or nutritional supplements could reduce severe oligospermia to complete azoospermia [Hughes & Page 2015].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Ongoing studies are evaluating the use of skin biopsy in azoospermic men to make induced pluripotent stem cells (iPSC) differentiate into primordial germ cells and ultimately sperm [Author, personal communication].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

Testicular sperm retrieval for in vitro fertilization is ineffective for males with AZFb and AZFa deletions, but has been achieved for the majority of males with AZFc deletions [Silber 2011].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Y chromosome infertility is inherited in a Y-linked manner.

Risk to Family Members

Parents/father of a proband

- Because males with deletion of the AZF regions of the long arm of the Y chromosome are typically infertile, the deletions are usually *de novo* and therefore not present in the father of the proband (except for gr/gr; see below).
- Rarely, a male with an AZFc deletion of the Y chromosome has fathered a son, who is infertile [Faddy et al 2001, Silber & Repping 2002]. However, it should be stressed that in these families, the fathers with an AZFc deletion were all severely oligospermic, but had a young and very fertile partner who conceived despite her partner's low sperm count.
- Men with gr/gr deletions have variable fertility, and can readily transmit the deletion to future generations [Silber 2011].

  The gr/gr deletion is a "partial AZFc deletion" of only two of the four copies of *DAZ*; gene dosage therefore affects the severity of the defect in spermatogenesis [de Vries et al 2002] (see Genotype-Phenotype Correlations).
- Deletions of b1/b3 and b2/b3 are inconsequential, and have no effect on male fertility.
- Note: Using ICSI-IVF (see Treatment of Manifestations), most azoospermic men can conceive children despite the most severe spermatogenic defect; male offspring will inherit the same AZFc deletion as their azoospermic father [Silber 2011].

Sibs/brothers of a proband

- Because most Y chromosome deletions found in an infertile male are *de novo*, the risk to the brothers of a proband is very low. However, if the proband has a gr/gr deletion, risk to the brothers of a proband is increased, as there is a higher likelihood that their father also has a gr/gr deletion.
- On very rare occasions, the brothers of a proband may be at risk because within a family the same deletion of the AZFc region may appear to result in infertility in some individuals but not in others [Chang et al 1999, Saut et al 2000, Repping et al 2003]. However, it should be made clear that all men with the AZFc deletion have a severe spermatogenic defect, which is only rarely compensated for by high fertility in their partner.

Offspring of a proband

- Pregnancies have been achieved from males with infertility caused by Y chromosome deletion using ICSI.
- Male fetuses have the same Y chromosome deletion as their father, with a high risk for male infertility. The deletion is not amplified or corrected in subsequent generations [Oates et al 2002].
- Female fetuses from a father with a Y chromosome deletion are not at increased risk for congenital abnormalities or infertility [Silber et al 1998, Silber & Repping 2002].

Other family members. It is unlikely that extended family members are at increased risk for Y chromosome infertility since Y chromosome deletions are almost always *de novo* events that occur in 1/2,000 sperms in the testis of a father with normal spermatogenesis. Furthermore, the possibility of transmission of AZF deletions is extremely remote.

Related Genetic Counseling Issues

Family planning. It is appropriate to inform men with non-obstructive azoospermia or severe oligospermia who undergo TESE-ICSI (testicular sperm extraction – intracytoplasmic sperm injection) that their condition is

likely genetic and could be due to a Y chromosome deletion, translocation, or Klinefelter syndrome (47, XXY). (Note: Most men with Klinefelter syndrome appear clinically asymptomatic.)

Prenatal Testing and Preimplantation Genetic Testing

Once the causative genetic alteration has been identified in a male with Y chromosome infertility, prenatal testing for pregnancies conceived through assisted reproductive technology (ART) and at risk of resulting in a male with Y chromosome deletion is possible. Testing includes determining the sex of the fetus and/or the presence of a Y chromosome deletion.

Prenatal testing is also possible for pregnancies at risk for chromosome abnormalities (e.g., 45,X mosaicism) resulting from a paternal Y chromosome rearrangement (e.g., pseudodicentric Y or ring Y), although such Y chromosome alterations would rarely be associated with residual spermatogenesis.

Preimplantation genetic testing may be an option for some pregnancies conceived through ART and at risk of resulting in a male with Y chromosome deletion.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Y chromosome infertility
- **InterNational Council on Infertility Information Dissemination, Inc. (INCIID)**
  Phone: 703-379-9178
  Fax: 703-379-1593
  Email: INCIIDinfo@inciid.org
  www.inciid.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Y Chromosome Infertility: Genes and Databases

Chromosome Region	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AZFa	*Not applicable*	Yq11.2	Not applicable			
AZFb	*Not applicable*	Yq11.2	Not applicable			
AZFc	*Not applicable*	Yq11.2	Not applicable			
	DDX3Y	Yq11.221	ATP-dependent RNA helicase DDX3Y	DDX3Y database	DDX3Y	DDX3Y
	USP9Y	Yq11.221	Probable ubiquitin carboxyl-terminal hydrolase FAF-Y	USP9Y database	USP9Y	USP9Y

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Y Chromosome Infertility (View All in OMIM)

400003	DELETED IN AZOOSPERMIA 1; DAZ1
400005	UBIQUITIN-SPECIFIC PROTEASE 9, Y CHROMOSOME; USP9Y
400006	RNA-BINDING MOTIF PROTEIN, Y CHROMOSOME, FAMILY 1, MEMBER A1; RBMY1A1
400010	DEAD-BOX HELICASE 3, Y-LINKED; DDX3Y
400012	VARIABLY CHARGED, Y CHROMOSOME; VCY
400013	BASIC PROTEIN, Y CHROMOSOME, 2; BPY2
400015	XK-RELATED PROTEIN ON Y CHROMOSOME
400016	CHROMODOMAIN PROTEIN, Y-LINKED, 1; CDY1
400018	CHROMODOMAIN PROTEIN, Y-LINKED, 2A; CDY2A
400019	PTPBL-RELATED GENE ON Y; PRY
400026	DELETED IN AZOOSPERMIA 2; DAZ2
400027	DELETED IN AZOOSPERMIA 3; DAZ3
400029	HEAT-SHOCK TRANSCRIPTION FACTOR, Y-LINKED; HSFY
400030	RIBOSOMAL PROTEIN S4, Y-LINKED, 2; RPS4Y2
400041	PTPBL-RELATED GENE ON Y, 2; PRY2
400042	SPERMATOGENIC FAILURE, Y-LINKED, 1; SPGFY1
415000	SPERMATOGENIC FAILURE, Y-LINKED, 2; SPGFY2
426000	LYSINE DEMETHYLASE 5D; KDM5D

Molecular Pathogenesis

Introduction. Three azoospermia regions on the Y chromosome have been defined as AZFa, AZFb, and AZFc. The normal Y chromosome contains all AZF regions. Most genes located in the AZF regions on the Y chromosome are specifically expressed in testis and are candidates for a role in male fertility. Other, still uncharacterized transcripts could also play a role in male fertility. Note that many Y-linked genes are multicopy and thus interpretation of sequence variants is difficult. Pathogenic variants in two single-copy genes, *USP9Y* and *DDX3Y*, cause Y chromosome infertility:

- *USP9Y* is a single-copy gene located in the proximal AZFa region. *USP9Y* and its X-linked paralog *USP9X* encode proteins similar to ubiquitin-specific proteases. Deletion of *USP9Y* is associated with mild hypospermatogenesis and fertility [Luddi et al 2009].
- *DDX3Y* is a single-copy gene located in AZFa that has a paralog on the X chromosome, *DDX3*. These genes encode DEAD box proteins and are ubiquitously expressed, but *DDX3Y* produces an alternative transcript in testis [Lahn & Page 1997]. Translation of *DDX3Y* is detected only in the male germline, predominantly in spermatogonia [Ditton et al 2004].

Other Y chromosome genes, such as *VCY*, *KDM5D*, *RPS4Y2*, *PRY*, *DAZ*, and *CDY*, may play a role in male fertility. The role of these genes in the disorder is still putative and derives from the gene location, its expression in germ cells, and/or homology to genes involved in fertility in other species. It should be noted that several of the Y-linked genes are present in multiple copies on the Y chromosome; the presence of multiple copies complicates the unraveling of their roles in male fertility.

Mechanism of disease causation. Massive interstitial Y chromosome deletions associated with male infertility are mediated by recombination between palindromic repeats on the Y chromosome. The regions have been defined on the basis of deletion intervals found in infertile males.

AZFa:

- 792 kb long and just distal to the centromere
- Recombination between two HERV15 (HERV15yq1-HERV15yq2) proviral sequences [Kamp et al 2000, Sun et al 2000, Kamp et al 2001]

AZFb and AZFc:

- Just proximal to the Yq12 heterochromatic band
- The most common Y chromosome deletion removes 3.5 Mb between palindromes b2 and b4 [Kuroda-Kawaguchi et al 2001, Vogt 2005].
- Recurrent deletions:
  - 6.2 Mb (AZFb/c) between palindromes P5 and proximal P1
  - 7.7 Mb between palindromes P5 and distal P1
  - 7 Mb between palindromes P4 and distal P1
- Smaller deletions (AZFb) between palindromes gr/gr, b1/b3, or b2/b3 are generally considered benign but may be associated with infertility in certain ethnic groups [Stouffs et al 2011].
- Partial deletion in AZFb that removes the entire P4 palindrome apparently decreases spermatocyte maturation but can be transmitted [Kichine et al 2012].

Y chromosome infertility due to pathogenic variants in *USP9Y* or *DDX3Y* occurs through a loss-of-function mechanism.

Laboratory considerations for Y chromosome infertility: nomenclature. Sequencing of AZFc and of the complete Y chromosome has more accurately depicted the Y deletions. For example, AZFc is referred to as b2/b4. AZFb overlaps AZFc and is referred to more accurately as P5/proximal p1. AZFb+c deletions are p5 or p4 distal p1. Nonetheless, the most commonly used (though less accurate) nomenclature is still AZFa,b,+c.

Table 3. Laboratory Considerations for Genes Causing Y-Chromosome Infertility

Gene [1]	Special Consideration
DDX3Y	Has high homology to *DDX3X*
USP9Y	Has high homology to *USP9X*

1. Genes are in alphabetic order.

Chapter Notes

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