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Y Chromosome Infertility

[*Y Chromosome-Related Azoospermia*]

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Summary

Disease 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 and/or cryptorchidism.

Diagnosis/testing. The diagnosis of Y chromosome infertility is suspected in otherwise healthy males with azoospermia or oligozoospermia and/or abnormal sperm morphology/motility for whom other causes of infertility have been eliminated. Routine cytogenetic testing reveals chromosome abnormalities in 5%-10% of these men. Molecular testing reveals microdeletions of the long arm of the Y chromosome in another 5%-10% of these males. Such molecular genetic testing is available clinically.

Management. *Treatment of manifestations:* Pregnancies may be achieved by in vitro fertilization using ICSI (intracytoplasmic sperm injection), 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 Sertoli-cell-only syndrome (SCOS) usually associated with AZFB and AZFA deletions, but has been achieved for 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 not increased in children conceived in this manner.

Genetic counseling. Y chromosome infertility is inherited in a Y-linked manner. Because males with deletion of the AZF (azoospermia factor) regions of the long arm of the Y chromosome are infertile, the deletions are usually *de novo* and therefore not present in the father of the proband. Rarely, within a family, the same deletion of the Y chromosome can cause infertility in some males but not others; hence, some fertile males with deletion of the AZF regions have fathered sons who are infertile. In pregnancies achieved from males with infertility caused by deletion of the AZF regions using ICSI, male offspring have the same deletion as their father, with a high risk of male 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

Clinical Diagnosis

Males with Y chromosome infertility usually have a normal physical examination, although some have small testes and/or cryptorchidism. Of note, some males may have both a Y chromosome abnormality and varicocele, which by itself can cause infertility.

Other causes of male infertility need to be excluded (see Differential Diagnosis).

Semen analysis. Ejaculate is examined to determine the number, motility, and morphology of sperm. 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
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).

Testing

Cytogenetic analysis. Approximately 5%-10% of men with unexplained infertility associated with azoospermia/oligozoospermia and/or abnormalities of sperm morphology/motility have chromosome abnormalities, mostly gonosomal (i.e., involving the sex chromosomes) but also autosomal.

Routine cytogenetic studies performed on peripheral blood **can** detect the following Y chromosome structural abnormalities, when present:

- Terminal deletions of Yq that include the heterochromatic band Yq12 at the end of the long arm of the Y chromosome.
- Other more complex Y chromosome rearrangements that lead to long arm deletions. For example, a pseudodicentric Y chromosome (also called "non-fluorescent Y") results in both deletion of part of the Y long arm and duplication of the Y short arm and proximal Y long arm. The detection of complex Y chromosome rearrangements is important because some of them (pseudodicentric Y chromosomes and ring Y chromosomes) are often associated with a 45,X cell line.

However, cytogenetic analysis alone **cannot**:

- Detect microdeletions of the Y chromosome
- Determine whether a cytogenetically visible deletion extends into the AZF regions
- Detect small interstitial deletions in the AZF regions

Testicular biopsy. Testicular biopsy may reveal either one of the following:

- Sertoli-cell-only syndrome (SCOS), in which azoospermia is associated with the absence of germ cells
- Hypospermatogenesis associated with reduced number of germ cells or arrest of germ cells at different developmental stages

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Y chromosome infertility may be caused by either of the following:

- Microdeletions of the long arm of the Y chromosome (Yq) in the AZF regions (see Figure 1) associated with deletion of multiple genes
- A rare single gene abnormality in *USP9Y*

Clinical uses

- Diagnosis
- Prenatal diagnosis

Clinical testing

- **Deletion/duplication analysis.** The molecular diagnosis of Y chromosome deletion consists of a series of PCR (polymerase chain reaction) amplifications within relatively broad regions of the Y chromosome. Interstitial Yq microdeletions can remove various portions of the long arm, depending on breakpoints. Specific genes (i.e., *USP9Y*, *DDX3Y*, *HSFY1*, *RBMY*, *CDY1*, and *DAZ*) located along the Y chromosome should be included in the analysis to assess Y chromosome integrity.

  Note: (1) Although guidelines for testing (including the use of positive and negative control samples for PCR analysis) have been published [Simoni et al 2004], the testing recommended is insufficient, especially in regard to specific genes that should be included. (2) Commercial kits have been designed but need further evaulation [Aknin-Seifer et al 2005].

  Originally, three AZF regions were defined: AZFA, AZFB, and AZFC (azoospermia factors a, b, and c), which map on the long arm (Yq) in order from the centromere to the telomere and are thought to be non-overlapping. However, subsequent studies showed that AZFB and AZFC overlap [Repping et al 2002] (see Figure 1). Because the deletions tend to occur between large palindromic repeats, a more appropriate nomenclature for the types of recurrent deletions is to use the name of the flanking repeats [Yen 2001, Repping et al 2002].

Research testing

- **Single gene defects.** Mutations involving the *USP9Y* gene, located in the AZFA region (see Figure 1) have been reported in rare cases [Sun et al 1999]. These types of mutations are usually not detectable by PCR analyses and thus require other types of testing (e.g., sequence analysis) that are presently done on a research basis only.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Y Chromosome Infertility

Test Method	Genetic Mechanism	Phenotype	Mutation Detection Frequency [1]	Test Availability
Deletion/ duplication analysis	Interstitial AZFA deletion (HERV15yq1-HERV15yq2) [2]	SCOS	9%	Clinical Testing
	Interstitial AZFC deletion (b2/b4) [2]	Oligozoospermia	6%	
		Azoospermia	13%	
	Intermediate AZFB and AZFB+C deletions (P5/proxP1, P5/distP1, P4/distP1) [2]	Azoospermia	1%-2%	
	Terminal AZF	ND	ND	

SCOS = Sertoli-cell-only syndrome

ND = No data

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

2. Indicates the flanking repeats [Kamp et al 2000, Sun et al 2000, Kamp et al 2001, Yen 2001, Oates et al 2002, Repping et al 2002]

Testing Strategy

Sperm counts and morphology/motility should be assessed and routine cytogenetic analysis performed together with molecular genetic testing for microdeletions of the long arm of the Y chromosome.

Genetically Related (Allelic) 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.

A single study suggested that one of the deletions of the Y chromosome in AZFC region (designated gr/gr) also causes a slight increase in susceptibility to testicular germ cell tumors [Nathanson et al 2005].

Clinical Description

Natural History

Males with Y chromosome infertility usually have no obvious symptoms, although physical examination may reveal small testes and/or cryptorchidism. Males with Y chromosome infertility have azoospermia or severe, moderate, or mild oligozoospermia (Table 1). Mild oligozoospermia may be compatible with fertility in rare instances.

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].

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.

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 author

includes reference to these regions and to the palindromic repeats that now define the deletions more precisely.

- Interstitial or terminal deletions that include AZFA, often mediated by recombination between the HERV15yq1-HERV15yq2 repeats, usually produce the severe phenotype of Sertoli-cell-only syndrome (SCOS) [Kamp et al 2001].
- 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 usually result in azoospermia [Repping et al 2002].
- Interstitial or terminal deletions that include AZFC only are mediated by recombination between the b2/b4 palindromic repeats and result in a variable phenotype, ranging from azoospermia and SCOS to severe or mild oligozoospermia [Oates et al 2002]. This type of deletion can occasionally be associated with normal fertility in younger males, with the phenotype worsening with age [Chang et al 1999, Saut et al 2000].
- Two partial deletions of AZFC, called b1/b3 and gr/gr, are considered polymorphisms [Repping et al 2003, Fernandes et al 2004, Machev et al 2004, Ferlin et al 2007].
- Duplication of the AZFA region has been reported and does not appear to be associated with an abnormal phenotype [Bosch & Jobling 2003].
- So far, only one gene *(USP9Y)* located in AZFA has been directly implicated in the infertility phenotype, following detection of a point mutation and a deletion limited to this gene in two infertile males with hypospermatogenesis but without SCOS [Sun et al 1999]. This study suggests that the SCOS phenotype usually associated with AZFA deletion is not caused by *USP9Y* deletion alone but must include deletion of at least one other gene, *DDX3Y*, to result in the severe phenotype. These findings underscore the complexity of the AZF region, which contains multiple genes, each of which is present in multiple copies.

Penetrance

Rarely within a family, the same deletion of the Y chromosome can cause infertility in some males but not others [Chang et al 1999, Saut et al 2000, Gatta et al 2002, Repping et al 2003]; hence, some fertile males with deletion of the AZF regions have fathered sons who are infertile.

Prevalence

The prevalence of Y chromosome deletions and microdeletions is estimated to be about 1:2000 to 1:3000 males.

The frequency of Yq microdeletions in males with azoospermia or severe oligozoospermia is about 5%-10% [Vogt 1997, Silber et al 1998, Oates et al 2002]. Some reports indicate that males with azoospermia apparently caused by other factors, such as hypogonadotropic hypogonadism, varicocele, or infection, may also have an increased incidence of Yq deletions [Krausz et al 1999].

Differences in prevalence based on ethnicity have not been observed.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Infertility affects 15%-20% of couples of reproductive age. Infertility is male related in about half of those couples. Causes of male infertility other than deletion of part of the long arm of the Y chromosome are numerous and include the following conditions:

- **Obstruction of the ejaculatory ducts,** which should be evaluated by physical examination [AUA / ASRM 2004]. Congenital bilateral absence of the vas deferens (see *CFTR*-Related Disorders) should be considered in this evaluation. *CFTR*-related disorders include cystic fibrosis (CF) and congenital bilateral absence of the vas deferens (CBAVD). More than 95% of males with CF are infertile as a result of azoospermia caused by absent, atrophic, or fibrotic Wolffian duct structures. CBAVD can also occur in men without pulmonary or gastrointestinal manifestations of CF. Affected men have azoospermia and are thus infertile. CF is inherited in an autosomal recessive manner.
- **Immunologic abnormalities** caused by anti-sperm antibodies
- **Infection** (for example, mumps orchitis, epididymitis, urethitis); these can generally be differentiated from Y chromosome infertility by past history.
- **Vascular abnormalities** (varicocele), which can be identified on physical examination. Note, however, that a Y chromosome deletion has been reported in some males with varicocele [Moro et al 2000].
- **Trauma** (distinguished by history)
- **Endocrine abnormalities** (for example, congenital adrenal hyperplasia, isolated follicle-stimulating hormone (FSH) deficiency, and hyperprolactinemia). These can be differentiated through hormone studies. Kallmann syndrome (KS), the association of idiopathic hypogonadotrophic hypogonadism (IHH) 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). *KAL1* and *FGFR1* are the only two genes known to be associated with Kallmannn syndrome. Together, mutations in the two genes account for approximately 15%-25% of KS. Non-reproductive phenotypes:
  - In males with *KAL1* mutations: synkinesia (mirror movement) of the digits, unilateral renal agenesis, sensorineural hearing loss, high-arched palate
  - In males with *FGFR1* mutations: 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 analysis, recommended for men with non-obstructive azoospermia and oligospermia.
- **Balanced chromosome rearrangements,** which can be detected by cytogenetic evaluation, recommended for men with non-obstructive azoospermia and oligospermia. In this case, there may also be a family history of multiple miscarriages.

  In the remaining males, infertility is of unknown etiology.

Sertoli-cell-only syndrome (SCOS) is the term applied to the finding of germinal aplasia in males. It has numerous causes including exposure to toxic chemotherapy agents or irradiation, mumps orchitis, Down syndrome, Klinefelter syndrome (47,XXY), congenital adrenal

hypoplasia, isolated follicle-stimulating hormone (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 many males, the etiology of SCOS is unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Y chromosome infertility:

- Semen analysis to determine the number, motility, and morphology of sperm

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). In this procedure, spermatozoa retrieved from ejaculate (in males with oligozoospermia) or extracted from testicular biopsies (in males with azoospermia) are injected into a harvested egg by IVF (in vitro fertilization).

Retrieval of sperm has been successful mainly for males with deletions of AZFC, and rarely for males with deletions of AZFB or AZFA. This procedure should not be performed in males with SCOS, in which no sperm are present [Krausz et al 2000, Stouffs et al 2005, Reyes-Vallejo et al 2006].

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 the fertilization or pregnancy rates [Oates et al 2002, Kihaile et al 2004]. The risk for birth defects is not increased in children conceived in this manner [Choi et al 2004].

Males with SCOS do not have germ cells in their testes; thus, testicular sperm extraction is not an option.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Testicular sperm retrieval for in vitro fertilization is ineffective for males with SCOS, usually associated with AZFB and AZFA deletions, but has been achieved for males with AZFC deletions [Krausz et al 1999, Stouffs et al 2005, Reyes-Vallejo et al 2006].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 infertile, the deletions are usually *de novo* and therefore not present in the father of the proband.
- Rarely within a family, the same deletion of the Y chromosome can cause infertility in some individuals but not others [Chang et al 1999, Saut et al 2000, Gatta et al 2002, Repping et al 2003]; hence, some fertile males with deletion of the AZF regions have fathered sons who are infertile.
- Theoretically, a father could be mosaic for the deletion of the AZF regions; however, this situation has not yet been reported.

Sibs/brothers of a proband. Because a Y chromosome deletion found in an infertile male is usually *de novo*, the risk to the brothers of a proband is low. On rare occasions, however, the brothers of a proband may be at risk because within a family the same deletion of the AZF regions can result in infertility in some individuals but not in others [Chang et al 1999, Saut et al 2000, Repping et al 2003].

Offspring of a proband

- Pregnancies have been achieved from males with infertility caused by deletion of the AZF regions using intracytoplasmic sperm injection (ICSI).
- Male fetuses have the same deletion as their father, with a high risk of male infertility [Page et al 1999, Oates et al 2002]. However, if germ cell mosaicism were present in the infertile male undergoing ICSI (no such individual has been reported to date), some of his sons may not have the deletion.
- Female fetuses from a father with a Y chromosome deletion have no increased risk of congenital abnormalities or infertility.

Other family members. It is unlikely that extended family members are at increased risk for Y chromosome infertility. However, because AZF deletions can be expressed differently in family members, male relatives (e.g., a proband's paternal uncles and their sons) may be at risk.

Related Genetic Counseling Issues

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration

should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies conceived through assisted reproductive technology (ART) and at risk of resulting in a male with Y chromosome deletion is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Testing includes determining the sex of the fetus and/or the presence of a Y chromosome deletion. Prenatal diagnosis is also available for pregnancies at risk for chromosome abnormalities (such as 45,X mosaicism) resulting from a paternal Y chromosome rearrangement (e.g., pseudodicentric Y or ring Y).

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for pregnancies conceived through assisted reproductive technology (ART) and at risk of resulting in a male with Y chromosome deletion. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Molecular Genetics of Y Chromosome Infertility

- Click here to view the Y chromosome using the NCBI Map Viewer. Use the **Zoom** feature at left to see the complete list of genes.
- For a list of gene symbols and descriptions by cytogenetic location, click here.

Table A. Molecular Genetics of Y Chromosome Infertility

Chromosome Region	Gene Symbol	Chromosomal Locus	Protein Name
AZFc	*CDY1*	Yq11	Testis-specific chromodomain protein Y 1
AZFc	*DAZ1*	Yq11	Deleted in azoospermia protein 1
AZFa	*DDX3Y*	Yq11	ATP-dependent RNA helicase DDX3Y
AZFb	*HSFY1*	Yq11	Heat shock transcription factor, Y-linked
AZFb	*RBMY1A1*	Yq11	RNA-binding motif protein, Y chromosome, family 1 member A1
AZFa	*USP9Y*	Yq11	Probable ubiquitin carboxyl-terminal hydrolase FAF-Y

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Y Chromosome Infertility

400003	DELETED IN AZOOSPERMIA; DAZ
400005	UBIQUITIN-SPECIFIC PROTEASE 9, Y CHROMOSOME; USP9Y
400006	RNA-BINDING MOTIF PROTEIN, Y CHROMOSOME, FAMILY 1, MEMBER A1; RBMY1A1
400010	DEAD/H BOX 3, Y-LINKED; DBY
400016	CHROMODOMAIN PROTEIN, Y CHROMOSOME, 1; CDY1
400029	HEAT-SHOCK TRANSCRIPTION FACTOR, Y-LINKED; HSFY
415000	SPERMATOGENIC FAILURE, NONOBSTRUCTIVE, Y-LINKED

Table C. Genomic Databases for Y Chromosome Infertility

Gene Symbol	Entrez Gene	HGMD
CDY1	9085 (MIM No. 400016)	
DAZ1	1617 (MIM No. 400003)	DAZ1
DDX3Y	8653 (MIM No. 400010)	DDX3Y
HSFY1	86614 (MIM No. 400029)	
RBMY1A1	5940 (MIM No. 400006)	
USP9Y	8287 (MIM No. 400005)	USP9Y

For a description of the genomic databases listed, click here.

Locus symbols: Originally, three azoospermia regions (a, b, and c) were defined as AZFA, AZFB, and AZFC. However, because AZFB and AZFC overlap, a new nomenclature was developed to distinguish deletions based on the flanking palindromic repeat names [Repping et al 2002]. It is likely that additional deletion types will be discovered (see Table 2).

Gene symbols: For a listing of genes located on the long arm of the Y chromosome, refer to NCBI, where the functional annotation of the genes is kept current. Specific genes are included in the AZF regions. *USP9Y* and *DDX3Y* are located in AZFA. *HSFY1*, *XKRY*, *RBMY1A1*, *DAZ*, *JARID1D*, *EIF1AY*, *RPS4Y2*, *PRY*, *CDY1*, *CDY2*, *BPY2*, *CsSPG4LY*, *GOLGA2LY*, and eightf *TTTY* transcripts are located in AZFB and C.

Chromosomal locus: The male infertility phenotype maps to relatively broad regions defined on the Y chromosome (Figure 1). The regions have been defined on the basis of deletion intervals found in infertile males. These massive interstitial deletions are mediated by recombination between palindromic repeats on the Y chromosome.

AZFA is 792 kb long and just distal to the centromere of the Y chromosome [Kamp et al 2001]. Recombination between two HERV15 (HERV15yq1-HERV15yq2) proviral sequences located around AZFA has been identified as the mechanism that generates AZFA deletions [Kamp et al 2000, Sun et al 2000, Kamp et al 2001].

AZFB and AZFC overlap, with distal AZFC located just proximal to the Y chromosome heterochromatic band Yq12. The most common Y chromosome deletion, formerly known as AZFC deletion, removes 3.5 Mb between palindromes b2 and b4 [Kuroda-Kawaguchi et al 2001, Vogt 2005]. Two of the largest interstitial deletions in the AZFB/C region remove either 6.2 Mb between palindromes P5 and proximal P1 (formerly known as AZFB deletion) or 7.7 Mb between palindromes P5 and distal P1 (formerly, deletion AZFB plus AZFC) [Repping et

al 2002]. Additional deletions, for example a 7-Mb deletion between palindromes P4 and distal P1, have been described but are less common.

Some Y deletions appear to be terminal by cytogenetic and PCR analyses. These deletions remove either all or part of the AZF regions along with the terminal q12 band of the Y chromosome, depending on the breakpoints. They may be associated with pseudodicentric or ring Y chromosomes.

Specific genes within the deletions have been mapped. However, so far only one gene *(USP9Y)* has been implicated in the infertility phenotype by the finding of gene-limited mutations in two individuals [Sun et al 1999].

Normal allelic variants: The normal Y chromosome contains all AZF regions. A complete sequence analysis of the Y chromosome and a listing of Y-linked genes have been reported [Skaletsky et al 2003]. All genes located in the AZF regions on the Y chromosome and specifically expressed in testis (e.g., *RBMY1A1*, *DAZ*, *VCY*, *XKRY*, *CDY1*, *CDY2*, *HSFY1*, *PRY*, *BPY2*) are candidates for a role in male fertility, though their exact function may be presently unknown. Genes that are ubiquitously expressed or expressed in more than one tissue (e.g., *RPS4Y2*, *USP9Y*, *DDX3Y*, *UTY*, *JARID1D*, *EIF1AY*) and other still uncharacterized transcripts could also play a role in male fertility. *USP9Y* is the only gene that has been directly implicated in male fertility, based on the finding of gene alterations in two infertile males [Sun et al 1999]. The reader is referred to the NCBI Web site for current annotation of Y-linked genes. Below is a short description of some of the genes that are thought to 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.

- *USP9Y* (also called *DFFRY*) is a single-copy gene located in the proximal AZFA region [Brown et al 1998]. *USP9Y* has a homologue on the X chromosome, *USP9X* (also called *DFFRX*). Both X and Y genes are ubiquitously expressed. These genes are homologous to the *Drosophila melanogaster* gene *faf* (fat facets) that plays a role in eye development and in female germ cell function. *USP9Y*-limited alterations in two infertile males have directly implicated this gene in male fertility [Sun et al 1999].
- *DDX3Y* (previously called *DBY*) is another single-copy gene located in AZFA that has a homologue on the X chromosome, *DDX3* (previously called *DBX*). *DDX3* and *DDX3Y* are ubiquitously expressed, but *DDX3Y* produces an alternative transcript in testis [Lahn & Page 1997].
- *HSFY1* is a member of the family of heat shock transcription factors. Its expression is restricted to Sertoli cells and spermatogenic cells [Shinka et al 2004, Vinci et al 2005].
- *RBMY* (previously called *YRRM*) is a multi-copy gene family located in region AZFB and in other regions on the short and long arms of the Y chromosome. There are about 15-20 copies of *RBMY*. A homologue, *RBMX* (previously called *HNRPG*), is located on the X chromosome [Delbridge et al 1999]. *RBMY2* is expressed only in testis.
- *DAZ* is a multi-copy gene family. The *DAZ* gene family on the human Y chromosome is organized in a repeat cluster containing four copies [Saxena et al 2000]. *DAZ* has a homologue on human chromosome 3 *(DAZL)*. The *DAZ* gene is homologous to *bol* in *Drosophila melanogaster*, in which mutations of *bol* cause meiotic arrest and

azoospermia [Yen 2004, Reynolds & Cooke 2005]. Knock-out of *Dazl* in mouse results in azoospermia [Ruggiu et al 1997].

- *CDY* is a processed transposon from an autosomal gene that has been amplified on the Y chromosome in the simian lineage. The *CDY* gene is specifically expressed in testis [Dorus et al 2003].

Pathologic allelic variants: The abnormality of the Y chromosome associated with male infertility results in deletion of genes. The Y chromosome deletions are usually very large and thus result in deletion of multiple genes. Several regions of the Y chromosome long arm have been implicated (Figure 1). One gene, *USP9Y*, has been directly implicated in male infertility. Two allelic variants represent mutations limited to the *USP9Y* gene in two infertile males.

Note: OMIM lists one AZF locus, AZF1, which comprises AZFA, B, C, and SCOS.

Normal gene product: Several genes are included in the AZF regions deleted in males with infertility. However, as discussed above, their role in normal spermatogenesis is not fully known. Refer to NCBI for a current list of Y-linked genes and their annotation in terms of protein product.

Abnormal gene product: The Y chromosome deletions result in absence of gene products. The deletions often comprise more than one gene or multiple copies of the gene. In the case of *USP9Y*, a deletion limited to the gene was found as well as one mutation (4-bp deletion) that results in skipping of an exon and protein truncation [Sun et al 2000].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The InterNational Council on Infertility Information Dissemination, Inc (INCIID)
PO Box 6836
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Fax: 703-379-1593
Email: inciidinfo@inciid.org
www.inciid.org

RESOLVE
910 Woodmont Avenue Suite 1350
Bethesda MD 20814
Phone: 888-623-0744 (helpline)
Email: info@resolve.org
www.resolve.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Male Infertility Best Practice Policy Committee of the American Urological Association; Practice Committee of the American Society for Reproductive Medicine (2004) Report on evaluation of the azoospermic male. *Fertil Steril* 82 Suppl 1:131-6 [Medline]

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Chapter Notes

Revision History

- 19 March 2007 (me) Comprehensive update posted to live Web site
- 28 February 2006 (cmd) Revision: Diagnosis: Cytogenetic analysis
- 16 September 2004 (me) Comprehensive update posted to live Web site
- 6 February 2004 (cd) Revision: change in gene name
- 31 October 2002 (me) Review posted to live Web site
- January 2001 (cmd) Original submission

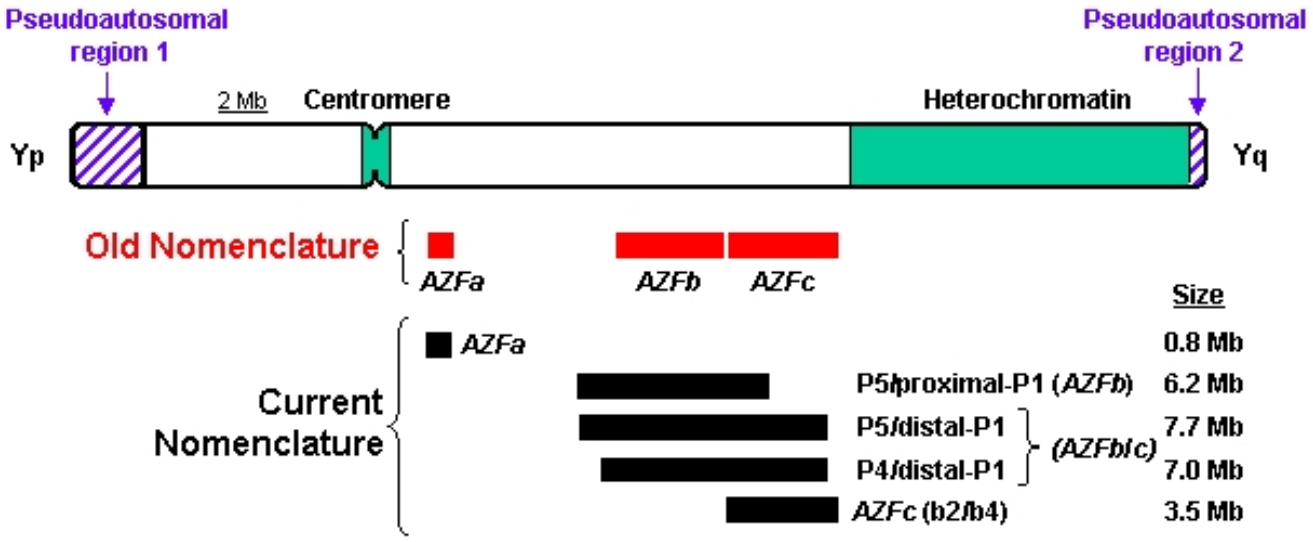

Figure 1. Schematic of the Y chromosome indicating the approximate position of the previously defined regions AZFA, AZFB, and AZFC and the position of recurrent deletions currently defined on the basis of the flanking palindromic repeats (see Table 2) (see the NCBI Web site for additional Y-linked genes). 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).