SEX CHROMOSOME GENETICS '99
Male Infertility and the Y Chromosome

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Although it has been established since the 1970s that deletions of the long arm of the Y chromosome are associated with spermatogenic failure, only in the last few years have these regions been described at the molecular level. In parallel, Y-linked genes and gene families that may explain the phenotypes of men carrying these deletions have been identified. The first association between spermatogenic failure and an underlying genetic cause was demonstrated by Tiepolo and Zuffardi (1976) in a report of six azoospermic patients carrying microscopically detectable deletions of the distal portion of Yq. In four patients, the deletion was de novo—that is, their fathers were tested and were found to carry intact Y chromosomes. On this basis, Tiepolo and Zuffardi (1976) proposed the existence of a spermatogenesis factor, called the "azoospermia factor" (AZF), encoded by a gene on distal Yq. However, the assumption that AZF represented a single Y-linked gene was overturned when Vogt et al. (1996) observed that Y chromosome microdeletions follow a certain deletion pattern, with three recurrently deleted nonoverlapping subregions in proximal, middle, and distal Yq11, designated "AZFa," "AZFb," and "AZFc," respectively. In addition, it became clear that these deletions were not exclusively associated with azoospermia (Reijo et al. 1996*a*). Deletions are associated with a wide range of histological profiles, from Sertoli cell–only syndrome (SCOS) to spermatogenic arrest (SGA) and severe hypospermatogenesis. The physical size of these regions has been estimated to be 1–3 Mb for AZFa and AZFb and ~1.4 Mb for AZFc. Recent studies have shown that ~10%–15% of azoospermic and ~5%-10% of severely oligozoospermic men have Yq microdeletions. However, despite these advances, there are still many unanswered questions, which are the subject of this review.

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Deletion Frequency and Genotype/Phenotype Correlations

Several combined clinical and molecular studies have sought (1) to define recurrently deleted regions of Yq, (2) to determine the incidence of microdeletions among azoospermic and oligozoospermic men, and (3) to correlate the size and position of the deletions that cause the infertile phenotype. The reported incidence of microdeletions in infertile men varies enormously between studies, within the range 1%–55% (Reijo et al. 1995; Quereshi et al. 1996; Stuppia et al. 1996, 1997; Foresta et al. 1997, 1998; Pryor et al. 1997; Simoni et al. 1997; Van der Vent et al. 1997), but study design probably accounts for much of this variation. Study populations have included azoospermic patients, azoospermic and oligozoospermic patients, or azoospermic/oligozoospermic and infertile normospermic patients. Most clinical studies "select" individuals with idiopathic azoospermia or oligozoospermia, although others include "unselected" infertile men with known or unknown causes of infertility. Unfortunately, however, there is no general agreement on what constitutes idiopathic infertility. Varicocele and history of cryptorchidism are considered idiopathic in some studies and nonidiopathic in others. Variation in reported deletion frequency also seems to be affected by the number of patients in the study; in general, studies with low patient numbers report a higher deletion frequency, perhaps because these studies select patients more stringently. Another variable that may also affect Yq deletion frequency is marker density or the position of markers. Despite these caveats, it is possible that differences in deletion frequency and/or localization, between studies, may reflect genuine geographic or ethnic differences, perhaps related to a particular Y chromosome haplogroup, the genetic background, or environmental influences.

Vogt et al. (1996) originally proposed that AZFa deletions result in type I SCOS, in which no spermatogonia develop, whereas deletions in AZFb cause SGA, usually at the spermatocyte stage, and deletions in AZFc are associated with a more variable phenotype, ranging from type II SCOS (absence of germ cells in most testis tubules) to hypospermatogenesis (presence of all germ-cell

types, albeit in reduced numbers). In general, subsequent studies have supported these findings, but there have been exceptions: both AZFa and AZFb deletions have been reported in oligozoospermic men, and we have found oligozoospermia associated with AZFb deletions (authors' unpublished data).

Another problem in the definition of genotype/phenotype correlations is the variability of the phenotype in the same man, over time. In one study, an individual with an AZFc deletion showed a progressive decrease in sperm concentration, from severe oligozoospermia to azoospermia, over 30 mo (Girardi et al. 1997). Nevertheless, some patterns have emerged from a survey of the clinical literature on these deletions. First, microdeletions are found almost exclusively in males affected by azoospermia or severe oligozoospermia or, occasionally, in patients with other abnormal andrological findings. Second, a higher frequency of Yq deletions is found in azoospermic men, compared with oligozoospermic men, and in men with well-defined idiopathic infertility, compared with men for whom the etiology of the infertility is known. Third, large deletions generally are associated with more-severe spermatogenic defects. Finally, AZFa deletions, which are relatively uncommon (frequency of 1%–5%), generally are associated with SCOS type I, whereas AZFc and AZFc+AZFb deletions, the most frequent form of these lesions, may be associated with a variety of spermatogenesis defects, including oligozoospermia.

Mechanism of Y Deletions

The relatively high frequency of de novo Y deletions indicates that the Y chromosome is susceptible to the spontaneous loss of genetic material. The instability of the Y chromosome may be related to the high frequency of repetitive elements clustered along the length of the chromosome, and deletions may occur through aberrant recombination events (between areas of homologous or similar sequence repeats, between the X and Y chromosomes, or by Y chromosome unbalanced sister-chromatid exchange) or by slippage during DNA replication. There also may be particular Y chromosome sequences that promote deletion of the AZF regions; consequently, some individuals may be more susceptible to de novo deletions than are others. Indeed, Jobling et al. (1998) defined one Y chromosome haplotype that is susceptible to aberrant X/Y exchange during male meiosis, leading to Y-positive 46,XX maleness and infertility. Advanced paternal age also might promote the loss of Y sequences, although this hypothesis needs to be examined by correlation of deletion incidence with the age of the father at conception. Paternal age effects have been described in Marfan syndrome, neurofibromatosis, and Apert syndrome. However, in most of these cases, the mutations are 1-bp substitutions, rather than deletions.

Y-Specific Genes and Gene Families

Several genes and gene families have been identified on the long arm of the Y chromosome (Lahn and Page 1997; also see Lau 1999 [in this issue]). Some of these genes fall within AZF deletion intervals and therefore may underlie the observed deletion phenotypes (tables 1 and 2). These genes can be divided into those that may be involved in cellular "housekeeping" activities and those that are expressed solely in the testis. The former group (table 1) includes *Drosophila* fats facets related Y (*DFFRY*), dead box Y (*DBY*), ubiquitous tetratricopeptide repeat (TPR) motif Y (*UTY*), the eukaryotic translation-initiation–factor 1A Y isoform (*eIF-1AY*), selected mouse cDNA on the Y (*SMCY*), and the thymosin β4 Y isoform (*Tβ4Y*). These ubiquitously expressed genes each exist in a single copy on the Y chromosome, and each possesses a closely related X-linked homologue that escapes X inactivation. The testis-specific group (table 2) includes the RNA-binding–motif Y chromosome gene (*RBMY*) and its relatives, deleted in azoospermia (*DAZ*), chromodomain Y (*CDY*), XK-related Y (*XKRY*), protein-tyrosine phosphatase BAS-like (PTP-BL)–related Y (*PRY*), and the genes for basic proteins Y1 and Y2 (*BPY1* and *BPY2*). These genes are present in multiple copies on the Y and do not appear to have X homologues.

DFFRY, DBY, and *UTY* all fall within the AZFa deletion interval; therefore, one or more of these genes may be implicated in SCOS or other male-fertility disorders. AZFb includes copies of *CDY* and *XKRY,* as well as of *SMCY, eIF-1AY,* and *RBMY.* Although sequences related to *RBMY* are found throughout the Y chromosome, functional copies appear to be restricted to AZFb, since deletions of distal AZFb lead to the absence of RBMY epitopes in testicular sections (Elliott et al. 1997). A number of transcripts are found within AZFc. At least six copies of *DAZ* are found in this region (Saxena et al. 1996; Yen et al. 1997), as are multiple copies of *PRY, BPY2, CDY,* and *XKRY.* Any of these genes may contribute to the AZFc-deletion phenotype, and most AZFc deletions probably remove all these genes. Individuals with AZFc deletions can present with oligozoospermia, and some even father children; hence, it is clear that these genes are not essential for spermatogenesis.

Function of Y-linked Genes in Spermatogenesis

At present, we know very little about the biochemistry or biology of Y-encoded proteins. Only RBMY and DAZ have been studied extensively. More than 30 *RBMY* genes and pseudogenes occur over both arms of the Y

Table 1

Ubiquitously Expressed Housekeeping Genes That Map to AZF-Deleted Regions and That Have Been Implicated in Male Infertility

Gene Symbol	Gene Name	Comment(s)	X-Linked Homologue	Amino Acid Identity (%)
DFFRY	*Drosophila* fats facets related Y	Homologous to *Drosophila* deubiquinating enzyme (Brown et al. 1998)	*DFFRX*	91
DBY	Dead box Y	Contains a DEAD (amino acid sequence Asp-Glu-Ala-Asp) box motif; may function as an RNA helicase (Linder et al. 1989)	*DBX*	91
Tβ4Y	Thymosin β4 Y	May be involved in actin sequestration (Gondo et al. 1987)	*Tβ4X*	93
UTY	Ubiquitous TPR motif Y	Contains 10 tandem TPR motifs that may be involved in protein-protein interactions (Greenfield et al. 1996)	*UTX*	85
SMCY	Selected mouse cDNA on the Y	Encodes an H-Y antigen epitope (Agulnik et al. 1994*a*, 1994*b*)	*SMCX*	84
eIF-1AY	Eukaryotic translation-initiation–factor 1A	Eukaryotic translation-intiation factor (Pestova et al. 1998).	*eIF1-1AX*	98

NOTE.—These genes are present in a single copy on the Y, but they all have X homologues that escape X inactivation. In all cases, the degree of sequence identity between the X and Y homologues is ⩾84%.

chromosome (Ma et al. 1993; Prosser et al. 1996; Chai et al. 1997), and these sequences can be divided into several subfamilies. The *RBMY1* subfamily has at least seven members, all of which appear to be clustered in the AZFb region (Prosser et al. 1996; Chai et al. 1997, 1998). These genes encode germ-cell specific nuclear proteins that contain an RNA-binding motif (RBM), as well as four copies of an SRGY (Serine-Arginine-Glycine-Tryosine motif) repeat. *RBMY2* genes share 88% homology with *RBMY1* genes and encode an RBM and a single SRGY repeat. The *RBMY1* sequence is 67% similar to the autosomally expressed hnRNPG (ribonucleoprotein G) protein, a nuclear glycoprotein with RNA-binding activities but with no known biological function (Soulard et al. 1993). *RBMY1* genes may derive from an *hnRNPG* gene that translocated to the Y chromosome and subsequently was amplified (Delbridge et al. 1997). In humans, RBMY1 can be detected by immunostaining of pachytene spermatocytes, an interesting observation in view of the SGA often seen in association with AZFb deletions (Elliott et al. 1997, 1998). In spermatocytes, RBMY1 colocalizes with pre–mRNA-splicing components in a discrete area of the nucleus, but, by late meiosis, it is found diffusely throughout the nucleoplasm of round spermatids. Hence, RBMY1 may play distinct roles during different phases of spermatogenesis.

Like *RBMY, DAZ* encodes a testis-specific protein that has a single RBM and a series of 8–24 copies of a 24–amino-acid unit termed the "DAZ repeat" (Reijo et al. 1995; Yen et al. 1997). The biological function of this motif is unknown, and *DAZ* genes differ substantially in the sequence and organization of these repeats (Yen et al. 1997). *DAZ* is homologous to an autosomal gene with a single DAZ repeat, named "*DAZL1*" (*DAZ*-like autosomal 1; Saxena et al. 1996; Yen et al. 1996), and the Y-linked *DAZ* probably originated from the translocation and amplification of this ancestral autosomal gene. Mice lack the Y-located *DAZ* gene, but they do carry a single autosomal *Dazl1* gene (Cooke et al. 1996; Reijo et al. 1996*b*). Immunostaining has revealed human DAZ in the innermost layer of male germ-cell epithelium and in the tails of spermatozoa (Habermann et al. 1998). This observation is consistent with the expression of DAZ transcripts just inside the perimeter of seminiferous tubules in spermatogonia (Menke et al. 1997). However, some caution must be used when these results are interpreted, since cross-hybridization with *DAZL* mRNA or protein cannot be excluded.

Insights into human *DAZ* function may come from the analysis of its autosomal homologues in other species. Targeted disruption of *Dazl1* in mice leads to a complete absence of gamete production in both testis and ovary, demonstrating that Dazl1 is essential for the development or survival of germ cells (Ruggiu et al. 1997). In *Drosophila,* mutation of the *boule* gene, another homologue of *DAZL,* results in spermatocyte arrest at the G2/M transition and complete azoospermia (Castrillon et al. 1993; Eberhart et al. 1996). The boule protein occurs in the nucleus of primary spermatocytes until the end of the meiotic prophase, after which it is found in the cytoplasm. In *Xenopus, Xdazl* is expressed in premeiotic germ cells in adult testis (Houston et al. 1998). Interestingly, the *Xenopus Xdazl* gene can rescue

Table 2

Genes and Gene Families with Expression Restricted to the Testis and That Map to the AZF-Deleted Regions of the Y chromosome

Gene Symbol	Gene Name	Comment(s)	X-Linked or Autosomal Homologue
RBMY	RNA-binding–motif Y	Subfamilies include *RBMY1* and *RBMY2;* RBMY1 may be functional and is predicted to bind RNA	*RBMY* may be an ancestral *hnRNPG* gene
DAZ	Deleted in azoospermia	Predicted to bind RNA, as *Xenopus* Dazl does in vitro	*DAZL1* chromosome 3p25
XKRY	XK-related Y	Similar to XK, a putative membrane-transport protein (Ho et al. 1994)	None known
CDY	Chromodomain Y	Contains chromodomain (James and Elgin 1986); may be involved in chromatid modification during spermatogenesis	None known
PRY	PTP-BL–related Y	Similar to PTP-BL, a putative membrane-transport protein (Hendriks et al. 1995)	None known
BPY1	Basic protein Y1	Basic protein of unknown function	None known
BPY2	Basic protein Y2	Basic protein of unknown function	None known

NOTE.—Table modified from the report by Lahn and Page (1997).

meiotic entry of spermatocytes in *Drosophila boule* mutants, suggesting functional conservation of the *DAZ* family over evolutionary time (Houston et al. 1998). Xdazl protein has RNA-binding properties in vitro, and perhaps other members of the *DAZ* family play a role in RNA metabolism during gamete development (Houston et al. 1998).

Other genes on the long arm of the Y also may be involved in RNA metabolism. *DBY* is predicted to act as an RNA helicase (Lahn and Page 1997), and *eIF-1AY* encodes an essential translation-initiation factor (Pestova et al. 1998). During the latter stages of spermatogenesis, transcription terminates and posttranscriptional regulation plays a primary role (see reviews by Braun [1998] and Hecht [1998]). RNA synthesis peaks during the spermatocyte stage, is gradually reduced in subsequent stages, and ceases as round spermatids differentiate into elongated spermatids. Numerous mRNA that are under posttranslational control during spermatogenesis have been identified. It is tempting to speculate that many of the factors encoded by Y-linked genes play key roles in this process.

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