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A missing piece on the Y

1995 was supposed to be the year that all males unexpectedly became infertile — at least according to the popular novelist P.D. James in her interesting book, *The Children of Men*[1]. Set in 2021, the book depicts a United Kingdom under dictatorial rule, where golf is the national pastime, and where no babies have been born since 1995 (for reasons that are sadly undisclosed). Although James' thesis remains securely in the realm of fiction, curiously a French group reported earlier this year that sperm concentration and motilty have been declining for the past two decades[2]. Other records, however, suggest that infertility rates have been fairly constant during that time, at about 8–11%.

Ever since Biblical times, infertility has been depicted as a distressing and often shameful condition. In the Book of Samuel, Hannah pours out her soul to God, pleading for a son and promising to dedicate his life to the Lord should she conceive. Her prayers were answered and Samuel was born. Meanwhile, men were instructed to have children — with concubines if necessary — who would receive the family name and possessions. If a man died before having a family, his brother would marry the widow in a Levirate marriage, with the resulting children considered to be heirs of the deceased.

Until quite recently, society placed the burden of infertility squarely on women, but it is now accepted that infertility occurs in females and males in roughly equal proportions. The sad fact is that as many as one in five couples have difficulty or are unable to conceive without medical help. In the United States, some 20,000 couples each year undergo *in vitro* fertilization procedures, which have a success rate of about 15%. In males, some of the causes of infertility are well known, including bacterial and viral infections, varicose veins in the testes, anabolic steroid abuse and some hereditary disorders. In all, about 10% of infertile males have either no sperm (azoospermia) or produce few or deformed sperm (oligospermia).

Since the first description of Y-chromosome aberrations in some azoospermic patients in 1976, there have been a number of reports of submicroscopic deletions on the Y chromosome. These culminated in December 1993 with a paper by Ann Chandley, Howard Cooke and colleagues,

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Action down the Y: the *DAZ* candidate gene maps in the critical 'Azoospermia factor region' in the distal portion of the Y euchromatin. (Courtesy R. Reijo).

who described a novel gene called *YRRM* (for 'Y chromosome RNA recognition motif') from part of the distal euchromatic portion of the Y chromosome (see Figure) known colloquially as 'interval 6', which was found to be deleted in several infertile patients[3]. Apart from the incriminating deletion data, this gene family was highly conserved, male-specific and distributed along intervals 5 and 6 of the Y chromosome. But the authors were quick to point out that spermatogenesis is a complex process potentially involving many genes (not necessarily Y-linked). The evidence for *YRRM* being the elusive azoospermia factor, *AZF*, was by no means definitive.

The latest chapter in this story appears on page 383 of this issue, in which David Page and colleagues at the Whitehead Institute in Cambridge, Massachusetts, who three years ago completed the first physical map of the Y chromosome[4], present a meticulous analysis of the Y chromosome from 89 infertile, azoospermic males[5]. Using 84 sequence-tagged-site markers spanning the 30-megabase euchromatic region, Reijo *et al.*[5] looked for Y-chromosome deletions among azoospermic males who had no signs of any physical obstruction. In 12 of their patients (13% of the sample), they found overlapping *de novo* deletions spanning a common region of about 500 kilobases in the distal segment of the Y long arm. Perhaps surprisingly, the available testicular biopsies from these patients revealed that although none of the men were able to produce mature sperm, some were capable of making immature spermatogenic cells. The stage at which spermatogenesis is interrupted, however, does not appear to correlate with the extent of the Y-chromosome microdeletions.

As Reijo *et al.* scrutinized the deleted region in more detail, they were unable to detect any members of the *YRRM* gene family. But by exon trapping, they have identified a novel gene which they have dubbed *DAZ* ('deleted in azoospermia'). Like *YRRM*, *DAZ* is expressed specifically in the testis and bears an RNA recognition motif; however, unlike *YRRM*, *DAZ* is a single-copy gene in humans and chimpanzees (although apparently not in orangutans). However, while this study takes us an important step closer towards identifying *AZF*, more concrete proof, for example in the form of specific mutations in *DAZ* in non-deleted azoospermic or oligospermic patients, would be welcome. It also remains possible that other more proximal regions of the Y chromosome are deleted in some infertile patients, as indeed some groups have reported on occasions, although Riejo *et al.* have not been able to detect any additional rearrangements. For the moment, the precise number of spermatogenesis genes on the Y chromosome remains unclear.

Where does all this leave *YRRM*? There is still good reason to believe that *YRRM* plays some part in gametogenesis[6], but analysis of the gene family (which is classified into four sub-groups based on sequence relationships) is hampered by this redundancy and its extremely specific expression in the nuclei of male germ cells. At the European Society of Human Genetics meeting in Berlin in May, Chandley reported that her group had uncovered a sequence variant in *YRRM* in the RNA-binding domain of one patient, but the patient's father was also found to carry the substitution. According to Cooke, the *YRRM* family also has multiple copies in mice, which will probably prove more amenable to further study.

For Page, there must be a touch of irony about the present states of affairs. In 1987, his group had good evidence to suggest that, in the *ZFY* gene on the distal portion of the Y short arm, they had identified the male testis-determining factor. But their initial analysis had failed to pick up a small deletion near the pseudoautosomal boundary in an X,t(Y;22) female patient[7], in which the genuine sex-determining gene, *SRY*, was eventually located. Now, attention will likely be diverted from the *YRRM* family to the new candidate, *DAZ*, identified by the Whitehead team. But regardless of the ultimate role of *DAZ*, these new results are important in defining a common cause of severe male infertility. When coupled with other exciting developments such as the recent report from Ralph Brinster and colleagues of successful spermatogonial stem-cell transplantation and subsequent sperm production in mice[8], there is a sense of renewed hope for a better understanding of the complexities of spermatogenesis and, possibly, the treatment of male infertility.

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