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ORIGINAL INVESTIGATION

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The relationship between Y chromosome DNA haplotypes and Y chromosome deletions leading to male infertility

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Abstract Microdeletions on the short arm of the Y chromosome have defined three non-overlapping regions (AZFa, b, c) recurrently deleted among infertile males. These regions contain several genes or gene families involved in male germ-cell development and maintenance. Even though a meiotic origin for these microdeletions is assumed, the mechanisms and causes leading to microdeletion formation are largely unknown. In order to assess whether some Y chromosome groups (or haplogroups) are predisposed to, or protected against, deletion formation during male meiosis, we have defined and compared Y chromosome haplogroup distribution in a group of infertile/subfertile males harbouring Yq deletions and in a relevant Northwestern European control population. Our analyses suggest that Y chromosome deletion formation is, at least in the study populations, a stochastic event independent of the Y chromosome background on which they arise and may be caused by other genetic and/or environmental factors.

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Introduction

Microdeletions of specific regions of the Y chromosome are associated with male infertility. Three non-overlapping regions on the long arm of the Y chromosome, AZFa (azoospermia factor), AZFb and AZFc, are recurrently deleted among infertile males (Vogt et al. 1996) and are associated with either the complete absence of germ cells (azoospermia) or a severe disruption of spermatogenesis (oligozoospermia). These three regions, which appear to affect different and separate phases of male germ-cell development, contain several positional candidate genes involved in spermatogenesis (McElreavey et al. 2000). About 15–20% of azoospermic and about 10% of severely oligospermic men present with microdeletions of Yq (Krausz et al. 1999). Although variations in deletion frequency have been reported in different studies, these appear to be due to factors related to study design (number of patients and markers analysed, different cohort, etc.). AZFa deletions are rare and are usually associated with complete absence of spermatogonia (sertoli cell only syndrome type I). AZFb deletions are infrequent and, in most cases, associated with maturation arrest of germ cells. AZFc deletions are the most common and are associated with both azoo- and oligozoospermia. The physical extent of the AZFc deletion interval is estimated to be approximately 1–3 Mb and, in the vast majority of cases, the deletion appears to remove a common series of markers, suggesting that the deletion breakpoints may be similar in different populations.

The question remains why some individuals have AZF deletions and others do not. It may be that some Y chromosome haplogroups (defined by single stable mutations)

may define certain chromosome structures (e.g. variations in repeat sequences including multicopy gene families, or polymorphisms in Y-specific genes) that are susceptible to, or protective against, Y chromosome rearrangements, such as microdeletions causing infertility.

An association between a particular Y chromosome background and predisposition to Y rearrangements has been previously reported (Jobling et al. 1998a). In the XX male syndrome, the majority of individuals have a portion of the Y chromosome, including the testis determining gene *SRY*, on the short arm of the X chromosome due to ectopic recombination during male meiosis. In one third of cases this involves recombination between a Y chromosomal gene, *PRKY*, and its X homologue, *PRKX* (Schiebel et al. 1997). Individuals with a Y chromosome defined as belonging to a particular haplogroup have a significantly reduced frequency of illegitimate recombination between *PRKY* and *PRKX* compared to men belonging to other Y chromosome haplogroups. This difference appears to be associated with an inversion polymorphism on Yp that includes the *PRKY* gene. Men with the polymorphic segment in one orientation, indicated indirectly through haplotype analysis, have a protection against recombination, whereas others, with the inversion in the opposite orientation, are more susceptible to the rearrangement.

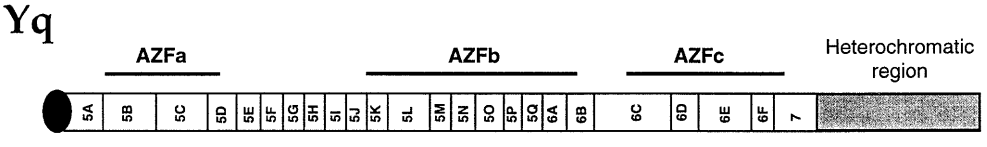
Recurrent deletions of the AZF regions associated with male infertility may also be due to inherent structures of the Y chromosome. Although a meiotic origin of Y deletions has been proposed (Edwards and Bishop 1997), the causes and mechanisms leading to deletion formation remain speculative. Y chromosome deletions might be the consequence of the organisation of Y chromosome genomic sequences. More than the 50% of the human Y chromosome consists of a rich variety of repetitive elements, including SINE (Alu repeats), LINE and a large number of endogenous retroviral sequences and a number of gene families. Deletions could be caused by aberrant recombination between areas of homologous or similar sequence repeats between the X and Y chromosomes, aberrant intrachromosomal recombination by unbalanced sister chromatid exchange, or by slippage during DNA replication. Such events may be indirectly revealed by the definition of Y chromosome haplotypes in Y-deleted men and comparing the haplogroup distribution with that of the general population. This should indicate whether deletions occur on a particular Y chromosome background, or if deletion formation is a stochastic event irrespective of the Y chromosome haplotype. We defined and compared Y chromosome lineages in a group of 50 infertile and subfertile individuals harbouring Y microdeletions and also large terminal deletions of the Y chromosome in four different populations of Northwestern Europe.

Materials and methods

The study populations and the position and extent of the Y deletions are indicated in Figure 1. The majority of individuals harbored AZFc deletions. Since all individuals were of Northwestern European origin (France, Germany, Ireland and Denmark), they were analyzed using nine UEPs (unique event polymorphisms) that define 11 Y chromosome lineages, or haplogroups, which are polymorphic in European populations. These markers were SRY-2627 (Veitia et al. 1997), SRY-1532 (Kwok et al. 1996), SRY-8299 (Whitfield et al. 1995), 92R7 (Mathias et al. 1994), Tat (Zerjal et al. 1997), YAP (Hammer and Horai 1995), sY81 (Seielstad et al. 1994), LLY22g (E. Righetti and C. Tyler-Smith, unpublished data), and M9 (Underhill et al. 1997). The definition of haplogroups in males who have substantial Yq deletions was compromised by the absence of some of the defining loci (i.e. YAP and M9) and also by the absence of the fathers. To obviate this, haplogroups were deduced on the basis of characteristic DNA codes of the MSY1 minisatellite (Jobling et al. 1998b) which, at least in Europe, can be directly correlated with haplogroups defined by UEPs (MSY1 data are available upon request). MSY1 is located on Yp and, consequently, is present in all individuals.

Results and discussion

The frequency distribution of Y chromosome haplogroups in Y-deleted infertile males is indicated in Table 1, together with those of Northwest European control groups.



Population	AZFa	AZFb	AZFb+c	AZFc	Yq-	Total
French	1	3	2	17	8	31
German		2	1	8		11
Irish				5		5
Danish				3		3
	1	5	3	33	8	50

Fig. 1 The long arm of the human Y chromosome. The relative positions of the three AZF regions in comparison to the 7-interval deletion map of the Y chromosome, defined by Vollrath et al. (1992), are indicated. Underneath, the number of individuals from each of the European population and the relative position of the Y deletion is shown. In eight French samples, a deletion of the entire Y chromosome long arm (Yq–) was detected by cytogenetic analysis and confirmed by PCR analysis

Table 1 Y chromosome haplogroup (*hg*) distribution in Y-deleted males and in the relevant calculated Northwestern European control populations

Population	*N*	hg 1	hg 2	hg 3	hg 9	hg 21	Others
Y-deleted males	50	27 (54.0)	13 (26.0)	7 (14.0)	1 (2.0)	2 (4.0)	–
Calculated control population	50	25.4 (50.8)	11.6 (23.2)	5.1 (10.2)	2.14 (4.3)	2.64 (5.3)	3.2 (6.4)
AZFc-deleted males	33	21 (63.6)	6 (18.2)	5 (15.1)	1 (3.0)	–	–
Calculated control population	33	17.2 (52.1)	7.6 (23.0)	3.5 (10.6)	1.3 (3.9)	1.5 (4.5)	1.9 (5.8)

For statistical comparisons, the control sample was artificially reconstructed, respecting the same ratio of samples to geographic origin, compared to the Y-deleted samples (French:German:Irish:Danish/5:2.5:1.5:1). The most frequent haplogroups (hgs) in the infertile Y-deleted males are hg1 (54%), hg2 (26%) and hg3 (14%) and, at lower frequencies, hg9 (2%) and hg21 (4%). This distribution is consistent with the hg distribution in the general population. Hg1, in western European populations, shows a cline of increasing frequencies towards western Europe, reaching maximum frequencies of more than 80% in Ireland (Hill et al. 2000). Hg2 is widely distributed across the whole European landscape and hg3 has a maximum frequency in eastern Europe, with a decreasing frequency cline towards the southeast and southwest (Rosser et al. in press).

Overall, there is no significant difference in haplogroup distribution between the total Y-deleted study population and the general population. A reanalysis of individuals who are deleted only for the AZFc region, the most common microdeletion among infertile men, again showed no evidence for a significant bias in the haplogroup distribution. A more detailed analysis was performed on samples divided by geographic region using Fisher's exact test 2×5. This indicated no significant differences in any of the four populations (French P=0,8; German P=0,67; Irish P=1; Danish P=0,17). Even if not reaching significance (P<0,05), despite the very small sample size, the highest difference between haplogroup distribution in Y-deleted males and in the relevant control population was found among the Danish population. This result is intriguing in light of the fact that the Danish population has one of the lowest mean sperm counts in Europe (Jensen et al. 2000).

In conclusion, these observations suggest that deletions, at least AZFc, occur irrespective of the Y chromosome background. In this case, deletion formation may be due to stochastic events, perhaps caused by genetic factors located on the X chromosome or autosomes, or due to an environmental influence. However, it must be remembered that we studied low numbers of the much rarer AZFa and AZFb deletions; thus, we cannot exclude the possibility that a particular Y chromosome background may predispose to, or protect against, deletion formation in these cases.

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