Inadvertent diagnosis of male infertility through genealogical DNA testing

T E King, E Bosch*, S M Adams, E J Parkin, Z H Rosser, M A Jobling

The potentially informative relationship between Y chromosomes and patrilineally inherited surnames has led to a major expansion in the number of commercial companies offering Y chromosomal DNA polymorphism analysis to members of the public; because of the geographical specificity of Y chromosomal types, many companies also offer to deduce “ancestry”. As the number of markers used in these tests increases, so does the probability of inadvertently diagnosing male infertility through the detection of Y chromosomal deletions. Using commercially typed Y markers, we here report the ascertainment of such deletions in general population samples.

METHODS
Samples were collected with informed consent and relevant ethical approval from the Leicester Research Ethics Committee (ref. 5796) and the Committee for Scientific Investigations in Greenland (ref. 505-16).

Deletion analysis was carried out using standard PCR techniques; primer sequences and conditions are given in original references cited for markers in the text below.

RESULTS
As part of a Y chromosomal haplotyping study of 2574 English males ascertained on the basis of surname and geographical origin, we included the binary marker PN25 which defines an important haplogroup, R1b, common in Western Europe. The PN25 polymorphism is an A to C transversion in one of three copies of the PN25 sequence, which lie in the three ampliconic repeat units g1, g2, and g3 of the AZFc region on Yq (fig 1A). In three unrelated males PN25 sequences were absent, and analysis of markers across the AZFc region showed a pattern of presence or absence consistent with these males carrying ~3 Mb deletions caused by non-allelic homologous recombination (NAHR) between the b2 and b4 repeats, previously observed in 47 of 48 infertility AZFc deletion patients.

In a population study of 69 Greenlandic Inuit males, we typed a set of 19 Y-specific microsatellites and a number of binary markers on the Y chromosome. In one male nine of 19 microsatellites and a single binary marker, M173, failed to amplify (fig 1B). Since all of these markers lie in the AZFc region on Yq, this is consistent with this male carrying an AZFc deletion. Testing of further loci in and around the region confirmed this, and showed that the deletion has arisen through a mechanism observed in the majority of AZFc cases; that is, by NAHR between directly repeated HERVs 780 kb apart and flanking the AZFa region.

DISCUSSION
AZF deletions are normally ascertained by testing the DNA of men with idiopathic infertility, and estimates of their frequencies are derived from clinical data. Here, we have ascertained deletions in an unbiased way.

AZFc deletions are the commonest of the classes found in infertile men, with a frequency estimated to be 1 in 4000. We found three deletions in 2574 English males, and can add to these an additional 681 males (mostly from the Iberian peninsula) typed for PN25 in whom we would have expected to detect some deletions had there been any. The frequency we find, three in 3255, is not significantly different from 1 in 4000 (p = 0.20, Fisher exact test).

AZFa deletions are particularly rare, constituting 1–2% of all pathogenic Y chromosomal deletions, and have a likely population frequency of less than 1 in 100 000. We found one deletion in 69 Inuit males, but including 5303 additional undeleted chromosomes from many, mostly Eurasian, populations typed with AZFa region microsatellites in our laboratory, the observed incidence is one case in 5374. A large database (see Roewer et al10 and http://www.yhrd.org) of ~23 000 Y chromosomal microsatellite haplotypes includes DYS389, and contributors would therefore be expected to detect AZFa deletions, although it is possible that such “incomplete” haplotypes would not be submitted. The database contains no examples with null alleles at this locus. Notably, we have found no examples of AZFb deletions, intermediate in frequency between AZFa and c deletions, in our population studies (n = 5374): these would be expected to lack several microsatellites, including the widely typed DYS385 and DYS392.

While the typing of the binary marker PN25, in the AZFc region, is not being offered commercially, at least one major testing company types the highly informative multi-locus microsatellite, DYS391, lying within the r1–r4 ampliconic repeats, and also absent in the three AZFc males we have identified (fig 1A). Microsatellites within the AZFa and b regions are typed by all companies carrying out commercial Y

Abbreviations: NAHR, non-allelic homologous recombination; STS, sequence-tagged site
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**ELECTRONIC-DATABASE INFORMATION**

The URL of the Y-STR Haplotype Reference Database is http://www.yhrd.org.

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