A new case of Yq microdeletion transmitted from a normal father to two infertile sons

V Gatta, L Stuppia, G Calabrese, E Morizio, P Guanciali-Franchi, G Palka


During the last few years, microdeletions of the long arm of the Y chromosome, involving loci AZFa, AZFb, and AZFc, have been identified as a major cause of infertility, leading to the disruption of genes involved in spermatogenesis. These microdeletions are usually de novo mutations, but in six cases transmission from fertile fathers to infertile sons has been reported. In four cases, the transmission occurred to a single son, and in one of these a widening of the deletion was shown. In the remaining two cases, the microdeletion was transmitted to multiple sons, resulting in different defects of spermatogenesis. Here, we describe a third family with a Yq microdeletion transmitted by a father to his two infertile sons.

CASE REPORTS

Two brothers, aged 36 and 35 years respectively, were examined in 1998 and 2000. The first had azoospermia, shown by repeated semen analyses, while the second had oligozoospermia (sperm count 200 000/ml, with reduced motility and abnormal morphology in 96% of sperm). In both patients, hormone values, ultrasound analysis, and karyotype were normal. Screening for microdeletions was performed in the two brothers and in their 69 year old father using PCR amplification of 20 loci on the Y chromosome (table 1). FISH analysis was performed on fixed metaphase chromosomes from the two sons and the father with specific probes for the DAZ and VCY2 genes. Paternity was confirmed using a panel of STR markers. PCR results were confirmed by FISH with DAZ and VCY2, which showed loss of both genes in 30 metaphases each, while in healthy controls at least 90% of metaphases showed positive signals on the Y chromosome (fig 2). This deletion falls within the region recently identified by Kuroda-Kawaguchi et al as involved in the majority of AZFc deletions. Thus, the size of the deletion can be estimated to be 3.5 Mb.

DISCUSSION

Like the other two reported cases, in our family the father and sons had an identical deletion involving AZFc with loss of the genes DAZ, VCY2, and CDY1 genes. This confirms that AZFc microdeletions can be associated with different phenotypes within the same family, suggesting the presence of genetic or environmental factors affecting the phenotypic effect of AZFc deletions.
 oligozoospermia, to infertility, characterised by severe oligozoospermia or azoospermia. These differences are not age related, since the father was fertile until the age of 34 years, while the sons were already infertile at that age. Other genetic or environmental factors affecting the phenotype of patients with AZFc deletions must be present. Since one in six couples requires assisted reproduction for a pregnancy, knowledge of the phenotype resulting from the transmission of a Yq microdeletion is crucial. While these factors remain unknown, care should be taken in the counselling of patients with AZFc deletions undergoing ICSI, since data from these families suggest that the son will not invariably inherit the same pattern of spermatogenesis. Further studies on families with multiple carriers of the same deletion, but showing different phenotypes will be of help for the identification of these factors.

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Figure 2  FISH analysis with SRY (pink) and DAZ (yellow) specific probes. (A) Normal control male showing signals of both probes on the Y chromosome. (B) First son showing only SRY signal on the Y chromosome, owing to AZFc deletion with loss of the DAZ gene.
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