ELECTRONIC LETTER

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

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*J Med Genet* 2002;**39**:e27 (http://www.jmedgenet.com/cgi/content/full/39/6/e27)

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.[1–4] In the remaining two cases, the microdeletion was transmitted to multiple sons, resulting in different defects of spermatogenesis.[5 6] Here, we describe a third family with a Yq microdeletion transmitted by a father to his two infertile sons.

- A very few cases of transmission of a Yq microdeletion from a fertile father to multiple sons have been reported. The present study describes the molecular analysis of the Y chromosome in two infertile brothers and in their father. The two brothers had different phenotypes, since sperm count showed azoospermia in the first son and oligozoospermia in the second one.
- The presence of Yq microdeletions was investigated in the two patients and in their father using PCR and FISH analyses with specific primers and probes for the Y chromosome.
- Both the father and the two sons showed a similar deletion involving the AZFc locus, with loss of the *DAZ*, *VCY2* (*BPY2*), and *CDY1* genes.
- This case confirms that Yq 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.

**Table 1** STS loci of Yq investigated in the two patients and in their father

| | 1st son | 2nd son | Father |
|---|---|---|---|
| AZFa | | | |
| *USP9Y* | + | + | + |
| sY86 | + | + | + |
| sY87 | + | + | + |
| *DBY* | + | + | + |
| AZFb | | | |
| sY100 | + | + | + |
| *CDY2* | + | + | + |
| sY128 | + | + | + |
| sY130 | + | + | + |
| sY134 | + | + | + |
| *RBMY* | + | + | + |
| AZFc | | | |
| sY153 | + | + | + |
| sY152 (*DAZ*) | Del | Del | Del |
| sY254 (*DAZ*) | Del | Del | Del |
| sY255 (*DAZ*) | Del | Del | Del |
| *VCY2* | Del | Del | Del |
| *CDY1* | Del | Del | Del |
| sY243 | Del | Del | Del |
| sY269 | Del | Del | Del |
| sY158 | Del | Del | Del |
| sY160 | + | + | + |

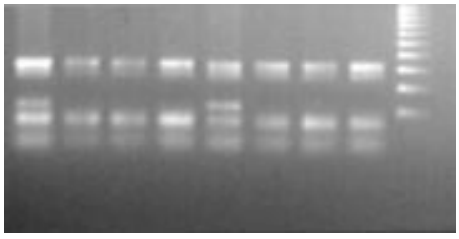

**Figure 1** Duplex PCR reaction using primers for the SRY gene and for STSs sY152 (lanes 1-4) and sY254 (lanes 5-8). Lanes 1 and 5 = normal male control; lanes 2 and 6 = first son; lanes 3 and 7 = second son; lanes 4 and 8 = father.

## 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.

In both patients, PCR analysis disclosed an identical deletion encompassing loci sY152 to sY158 (AZFc), with loss of the *DAZ*, *VCY2,* and *CDY1* genes (fig 1, table 1). The Y chromosome was then tested in their father and the same AZFc deletion was detected. Paternity was confirmed using a panel of STR markers. PCR results were confirmed by FISH with probes for *DAZ* and *VCY2*,[7] which showed loss of both genes in the father and in his sons 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*[8] 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*, but showed different phenotypes.[5 6] This confirms that AZFc microdeletions can be associated with features ranging from normal fertility, to mild

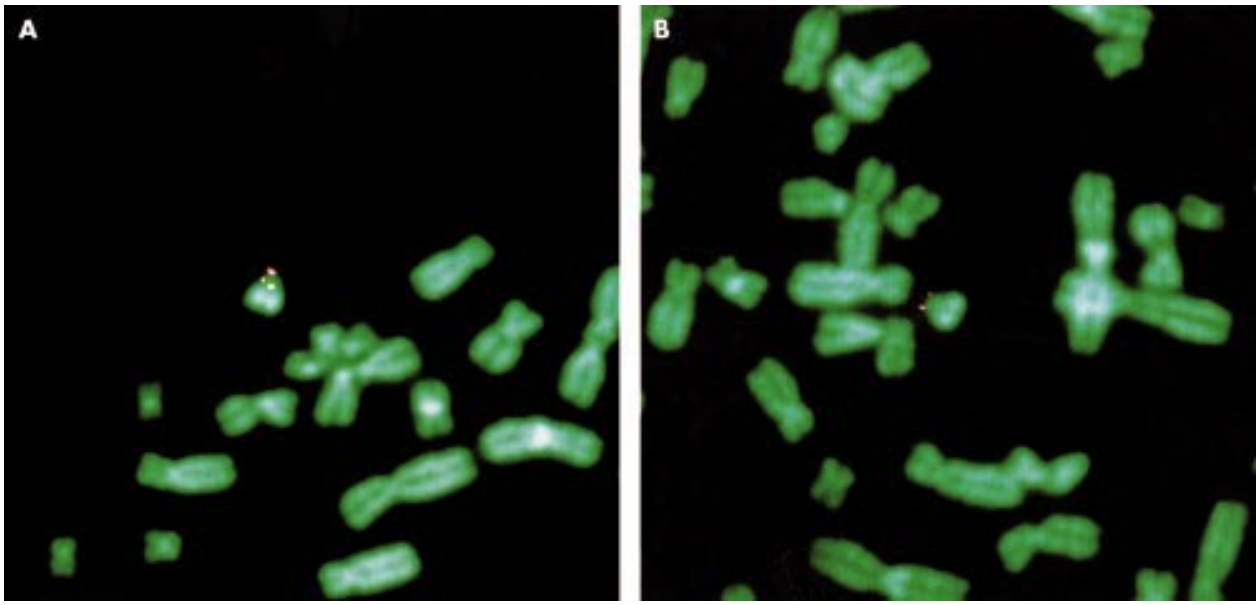


**Figure 2** FISH analysis with SRY (pink) and DAZ (yellow) specific probes. (A) Normal control male showing signals of both probes on the Y chromosome. (B) First son showing only SRY signal on the Y chromosome, owing to AZFc deletion with loss of the DAZ gene.

oligozoospermia,[9] 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.

## ACKNOWLEDGEMENTS

The financial support of Telethon Italy (Grant No E.832) is gratefully acknowledged.

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