Infertility in intracytoplasmic-sperm-injection-derived sons

SIR—Reijo and colleagues (May 11, p 1290)[1] detected microdeletions in the blood of two oligospermic individuals, but not in blood from their fertile fathers. They suggest that the mutation event leading to this microdeletion occurs de novo in the infertile patient and that all infertile men carrying microdeletions will pass them on to their sons through intracytoplasmic sperm injection (ICSI). We suggest that if the de-novo deletion event occurred in the infertile (F1) generation, the infertile patient must be mosaic for an intact Y (inherited from his fertile parental generation father) and a microdeleted Y. Furthermore, routine PCR-based screening procedures are unlikely to detect the microdeletion because of the presence of the intact Y chromosome in the blood sample. Assuming that the infertile individual's somatic cell lineage is mosaic, then presumably the germ-cell lineage would also contain two populations of sperm cells. In this situation, an individual carrying a microdeletion could produce a child with either a microdeleted Y or an intact Y. We propose that the oligospermic patient WHT2712 was not a mosaic since the microdeletion was easily detected in his blood. In this case, the de-novo event leading to this man's infertility had to have occurred spontaneously in the germline of his fertile father, probably as a post-meiotic error. The occurrence of germ-line mosaicism in phenotypically normal parental generation males is well documented, and a case such as this is not surprising.[2-4]

We have completed a study of 32 male-factor infertility patients and their ICSI-derived sons. In this population, we detected a microdeletion associated with one father/son pair. Although the detection of a microdeletion in the germ-cell lineage of patient WHT2712[1] predicts the outcome obtained in our ICSI father/son pair, we suggest that it is unlikely that the de-novo event from which the microdeletion arose occurred in the F1 generation of this presumably non-mosaic individual. A more likely aetiology is the occurrence of a de-novo mutation in the germ-cell lineage of the fertile parental generation.

In two further cases, although a microdeletion was not detected in the blood of the infertile F1 generation fathers, their ICSI-derived sons had microdeletions in the AZF region. Assuming that these infants are direct indicators of the germ-cell lineages of their infertile fathers, we suggest that in these two cases, mosaicism involving an intact Y and a microdeleted Y was present, thus preventing the detection of the microdeletion in the blood of the infertile F1 generation. Although both the sons in these cases inherited their microdeletions from their fathers, we suggest that, dependent on the extent of germ-like mosaicism, it is possible for infertile men such as these to father a child who may inherit an intact Y chromosome. If multiple embryos are produced by couples in which the male partner is known to be mosaic, preimplantation genetic diagnosis might differentiate between Y deleted and Y intact embryos.

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