Genes on the autosomal chromosome related to gametogenesis

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Background

Deletion of the Yq11 region of the Y chromosome long-arm in male subjects with azoospermia was first reported in 1976, as discovered in a study conducted to explore the relationship between human azoospermia and the Y chromosome. This region was named Azoospermic Factor (AZF) [1]. Many investigators have subsequently pursued strenuous studies aimed at analyses of the Y chromosome and the process of spermatogenesis. As a result, several genes have been identified and proposed as spermatogenesis-related genes, such as *USP9Y*, *DBY*, *RBMY*, and *DAZ* (deleted azoospermia) [2].

Occurrence of microdeletion in the AZF region with significantly high frequency in infertile male subjects was reported in about 1996 and thereafter [3]. The success of intracytoplasmic sperm injection (ICSI) technique by Palermo G.D. *et al.* in 1992 [4] has brought about a substantial change in the conventional treatment for male infertility, and has been a great boon to such patients. In the meantime, nevertheless, it has been learned that microdeletion in the Y chromosome might be transmitted via the assisted reproductive technology (ART) represented by ICSI. However, correlation between clinical manifestations and the deletion has not yet been established. Recently, a report demonstrating that a deleted azoospermia-like

autosomal (*DAZLA*) gene, highly homologous to the *DAZ* gene, is localized on the chromosome; 3p24, and has been attracting attention as to its relation with spermatogenesis [5]. The occurrence of *BOULE*, highly homologous to the *DAZ* gene on chromosome 2, has also been reported. It has also been documented that the *SYCP3* gene localized on chromosome 12 has a bearing upon meiosis in the spermatogenic process [5]. Thus, occurrence of genes regulating spermatogenesis not only on the sex-chromosome but also on autosomal chromosome has become generally recognized. *DAZLA* and *BOULE* genes are expressed not only in spermatids but in oocytes, probably taking part in development and maturation. Moreover, as proteins produced by these genes are detected in the cytoplasm of germ cells, the genes are thought to be possibly controlling the genesis of germ cells in concert with mitochondria. It would thus be suggested that mitochondria being the sole extra-nuclear organelle that possesses DNA may be involved in the gametogenesis, and this is yet to be investigated.

DAZ family

DAZ is generally recognized to be localized at AZFc of the Y chromosome, and to have a bearing on meiosis in the spermatogenesis.

Approximately 80% of microdeletions in the Y chromosome are confined to this region. *DAZLA* and *BOULE* genes homologous to *DAZ* are localized on chromosomes 3 and 2, respectively, and both are involved not only in spermatogenesis but in oogenesis as well (Fig. 1). The hypothesis of gene expression of the *DAZ* family in spermatogenesis suggested by Reijo et al. [2] is shown in Figure 2. Expression of the *DAZLA* gene is involved, like *DAZ*, in the entire process of germ cell development, taking part in the genesis of primordial germ cells and in the ensuing differentiation and maturation of those cells. Expression of the *BOULE* gene, on the other hand, culminates during the stage of meiosis. The *DAZ* family is generally thought to be controlling RNA linkage. When the *DAZLA* gene expression was followed with the real-time PCR technique (Fig. 3), it became demonstrable also in the ovary with a delay about 35 cycles later than in the testis. Analysis of the fusion curve showed mutual concordance of ovarian and testicular gene amplification products. According to quantitative analysis of data on ovarian *DAZLA* gene expression by real-time PCR in age-stratified groups of subjects, there was no expression of this gene in a 72-year-old woman, suggesting an aging-related difference in the quantity of this gene expression.

SYCP3

This was reported as a spermatogenesis-related gene by Miyamoto et al. in 2004 [6]. Meiosis is the mode of cell division peculiar to germ cells, and has a bearing on the activity of synaptonemal complex (SC). In view of the fact that *SYCP3* gene knockout leads to cessation of meiosis in mouse testis and gives rise to azoospermia in mice, Miyamoto et al. [6] performed a similar study in humans. Figure 4 illustrates the gene for *SYCP3* and its amino acid sequence. A point mutation (643delA) identified in the study is shown in Figure 5. This point mutation was localized heterologously, so that it

Fig. 1

Fig. 2

Fig. 3

Fig. 4

was considered to have caused formation of a heterogenous protein, giving rise to dyspermatogenesis. They have concluded that SYCP3, unlike the DAZ family, is encoding DNA-binding protein.

Summary

Since the outset of investigation on the relationship between genes with gametogenesis, analyses have been made primarily of sex chromosomes. Studies of the Y chromosome microdeletions in male infertility have progressed through analyses by many investigators and, as a result, their potential transmission to the following generation has come to pose a problem. Not only such genes on sex chromosomes as the DAZ family and SYCP3 genes, but autosomal gene abnormalities should also be taken into account. These are extremely important to reproductive/hereditary counseling for couples wishing offspring (Fig. 6).

Reference

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