Genetic Aspects of Male Sterility

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Introduction

The complex cell differentiation process of the male germ cell, spermatogenesis, is a typical example of a regulative biological network based on the interaction of multiple genes, respectively, the interactions of their expression products (RNAs, proteins). This process starts between days 21 and 26 postconception [i.e., in early embryogenesis (1)], and produces the first wave of motile spermatozoa at puberty. Genetic networks are generally nested one inside the other, building up a complex interactive and open system. Thus, the process of spermatogenesis is nested in the process of development of the male gonad. The process of male gonad development is nested in the process of embryo development. As a consequence, male sterility, as a secondary effect, is also caused by the disruption of genes functioning in the development of the male gonad and by disruption of genes functioning in somatic tissues ("pleiotropic male sterility").

From mutation analysis in Drosophila, genes expressed for male fertility were estimated to range from between 1250 and 1750 (2). In men, it is not known how many genes are essential for the male germ line. Because many genes transcribed in the testis do not have a biological function (3), it is difficult to assign a functional role to a certain gene only by analyzing its transcriptional activity in the testis. In order to identify a functional spermatogenic gene, gene-specific mutations are needed that induce disruption of human spermatogenesis. In human genetics, however, this can become a lengthy and cumbersome task unless the gene to be analyzed has a high mutation rate. Before the patients carrying such mutations are diagnosed, therefore, animal models carrying these mutations, such as "transgenic" or "knock-out" mice, are frequently used and analyzed for their fertility and testis histology. Such studies contribute significantly to our knowledge of the specific spermatogenic defects induced by disruption of the genes expressed in the testis. They also show that the genetic control of human spermatogenesis is a complex regulative network.
This chapter presents a short overview of our current knowledge on the genetic aspects of male sterility. This overview, however, is by no means complete. The current rapid expansion of molecular research in the field of reproduction genetics makes it difficult to present a comprehensive review of the topic; therefore, readers engaged in this field who are interested in more detailed information are advised to study other reviews published on the same subject (e.g., Refs. 4, 5). Genetic aspects of male sterility can be studied at two levels: the molecular level, by analyzing gene mutations that disrupt spermatogenesis, and the chromosome level, by analyzing chromosome aneuploidies interfering with meiotic cell divisions. Here, asynaptic chromosome pairing events and/or distortion of the sex vesicle formation are the visible diagnostic indications (6).

The Study of Sex-Specific Gene Expression Patterns

With the exception of postmeiotic germ cells, all human cell nuclei contain two gene copies (two alleles). Genes located on the sex chromosomes (X and Y), however, may have a sex-specific expression pattern because a double dose of the X gene is female specific. Men have only one X chromosome and the male-specific Y chromosome. The genes located in the so-called pseudoautosomal regions (PARs) at the tip of both sex chromosomes may be the exceptions. Due to a high rate of crossing over in these X–Y regions, an identical gene structure is expected on both sex chromosomes (7). A high rate of crossing over, however, is not observed in other parts of the sex chromosomes. As a consequence, in cases where both gene copies on the sex chromosomes are functional, the female-specific sex chromosome constitution (X,X) and the male-specific sex chromosome constitution (X,Y) might display a different functional expression pattern. It is now thought that the Y chromosome provides a sanctuary for spermatogenic genes, both in men, as well as in mice, and in Drosophila (2, 8–10). There is no other known human chromosome that contains so many genes expressed solely in the human testis. Genes for male fertility on the autosomes and on the sex chromosomes will therefore be discussed in separate sections.

Genes for Male Fertility on the Autosomes

Genes on autosomes expressed in the male germ line can be divided into two main groups: (A) genes expressed only in the human testis; (B) genes expressed in multiple human tissues but with a specific expression pattern in testis tissue.

Genes that are expressed only during the meiotic cell cycle are examples of genes in group A (11). Mutations in the meiotic genes are expected to cause chromosome aneuploidies in postmeiotic germ cells. Protamines and transition-