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The Role of Genetic Mutations in Y Chromosome Infertility Syndrome

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1. Abstract

Sex chromosome Y infertility is a genetic disorder that affects sperm production and causes affected men to become infertile. Most men with Y chromosome infertility syndrome have some sperm cells in their urine that can be extracted for this purpose. As the name implies, this type of infertility is caused by changes in the Y sex chromosome. Infertility of the Y sex chromosome is usually caused by the removal of genetic material in areas of the Y chromosome called Azosperm Factor (AZF) A, B or C.

2. Generalities of Y Chromosome Infertility Syndrome

Sex chromosome Y infertility is a genetic disorder that affects sperm production and causes affected men to become infertile. In addition, men affected by this syndrome may not produce any sperm (azoospermia), have less than normal sperm cells (oligospermia), or produce abnormal sperm cells that do not move properly [1] (Figure 1and 2).

3. Clinical signs and symptoms of Y Chromosome Infertility Syndrome

Some men with the Y sex chromosome infertility syndrome, who have mild to moderate oligospermia, may eventually give birth naturally. Reproductive technologies can help other affected people. Most men with Y chromosome infertility syndrome have some sperm cells in their urine that can be extracted for this purpose. Men are severely affected by this syndrome and do not produce mature sperm cells in the testicles. This form of infertility on the Y chromosome is known as Sertoli cell-only syndrome [1, 2].

Men with the Y sex chromosome infertility syndrome usually have no other signs or symptoms. Sometimes they may have small testicles or testicles descending into the scrotum (cryptorchidism) [1, 3] (Figure 3).

4. Etiology of Y Chromosome Infertility Syndrome

As the name implies, this type of infertility is caused by changes in the Y sex chromosome. Humans usually have 46 chromosomes per cell. There are 44 asexual chromosomes and two sex chromosomes known as X and Y. (Women have two sex chromosomes X (46, XX) and men have one sex chromosome X and one sex chromosome Y (46, XY). Because only men have the Y chromosome, the genes on this chromosome tend to be involved in determining male sex and sexual development [1, 4] (Figure 4).

Infertility of the Y sex chromosome is usually caused by the removal of genetic material in areas of the Y chromosome called Azosperm Factor (AZF) A, B or C. Genes in these regions provide the instructions for the synthesis of proteins involved in the growth of sperm cells, although the specific functions of these proteins are not yet well understood [1, 5].

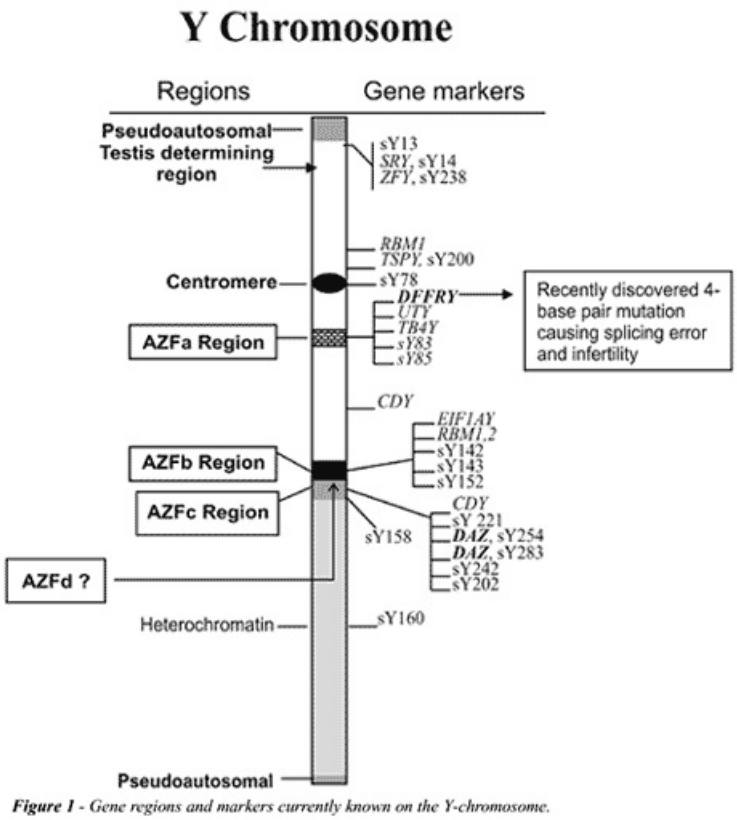

Figure 1: Schematic of AZF regions on the human sex Y chromosome [1].

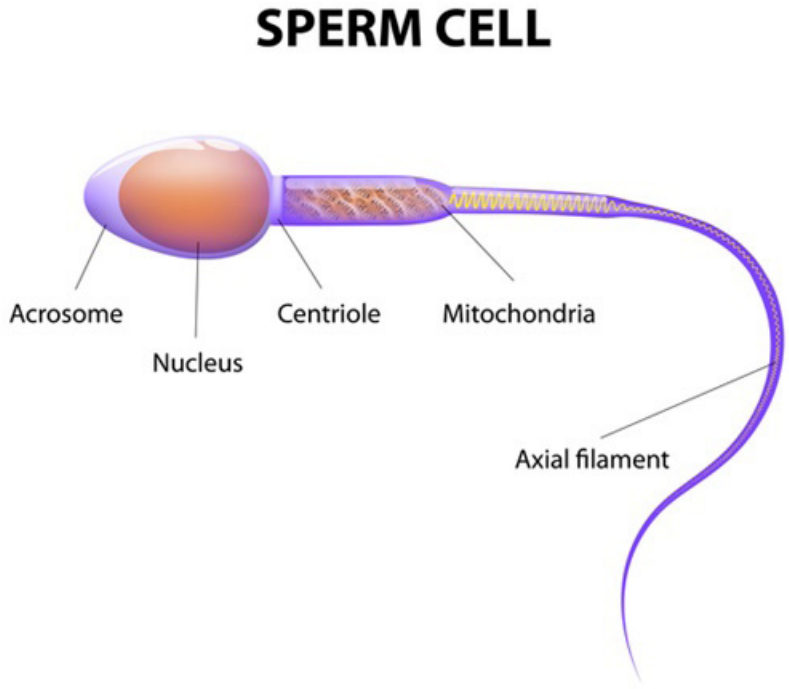

Figure 2: Schematic of human sperm cell structure [1].

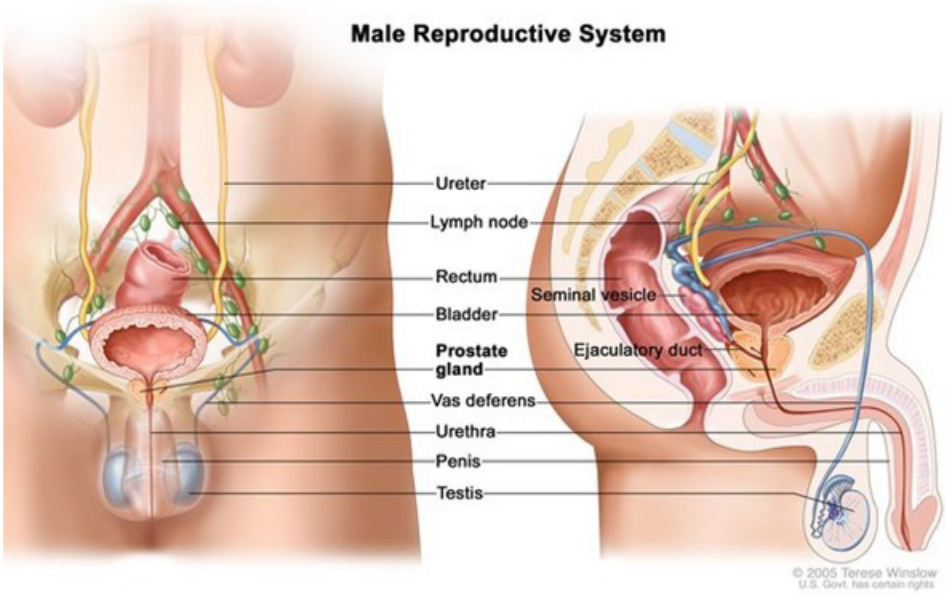

Figure 3: Schematic of the structure of the male reproductive system [1].

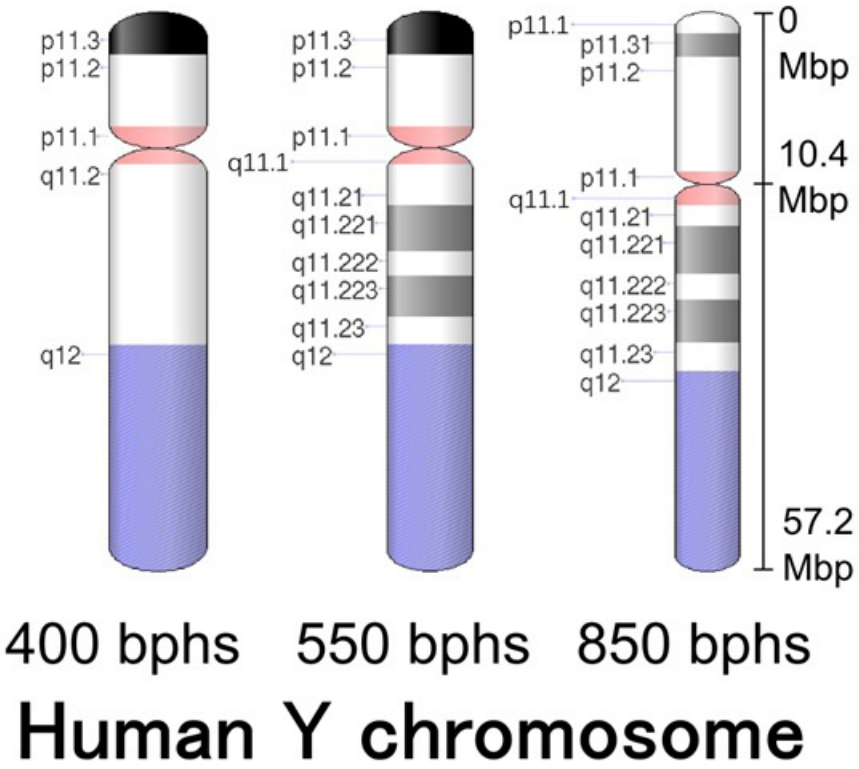

Figure 4: Schematic of the physical map of the human Y sex chromosome [1].

Deletion in AZF regions may affect several genes. Missing genetic material may inhibit the production of a number of proteins needed for normal sperm cells to grow, leading to infertility on the Y chromosome [1, 6].

In rare cases, changes in a single gene called USP9Y, located on the long arm of the Y sex chromosome called Yq11.221 and located in the AZFA region of the Y chromosome, can cause Y chromosome infertility. The USP9Y gene provides the instructions for the synthesis of a protein called protease 9-specific ubiquitin. Few people with Y chromosome infertility syndrome have all or part of the USP9Y gene deleted, while other genes are ineffective in the AZF region. Deletion of the USP9Y gene inhibits the production of protease 9-specific ubiquitin or the production of unusually

short, inactive proteins. Lack of ubiquitin-specific protease 9 impairs sperm cell production and leads to Y chromosome infertility syndrome [1, 7] (Figure 5).

Because Y chromosomal infertility prevents a father from being able to have children, this condition is usually caused by new deletions on the Y chromosome and occurs in men without a family history of the disorder. It is worth noting that when men with Y chromosome infertility have children through fertility enhancement techniques, genetic changes on the Y chromosome are still passed on to all their sons. As a result, boys will also have Y chromosome infertility. This syndrome follows a Y-dependent or paternal inheritance pattern. Girls are not affected by this syndrome because they do not inherit the Y chromosome [1, 8].

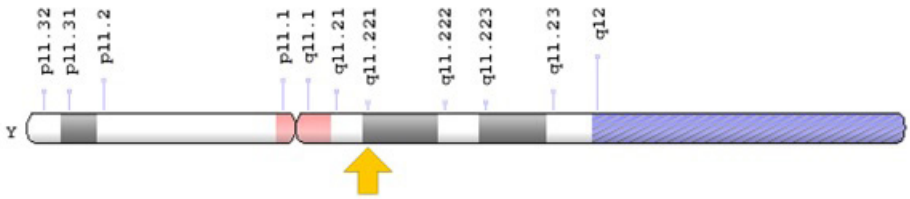

Figure 5: Schematic of the Y sex chromosome where the USP9Y gene is located in the long arm of this chromosome as Yq11.221 [1].

5. Frequency of Y Chromosome Infertility Syndrome

Y chromosome infertility syndrome is a genetic disorder that occurs in about 1 in 2,000 to 1 in 3,000 men of all ethnic groups. This condition accounts for between 5 and 10% of cases of severe azoospermia or oligospermia [1, 9] (Figure 7).

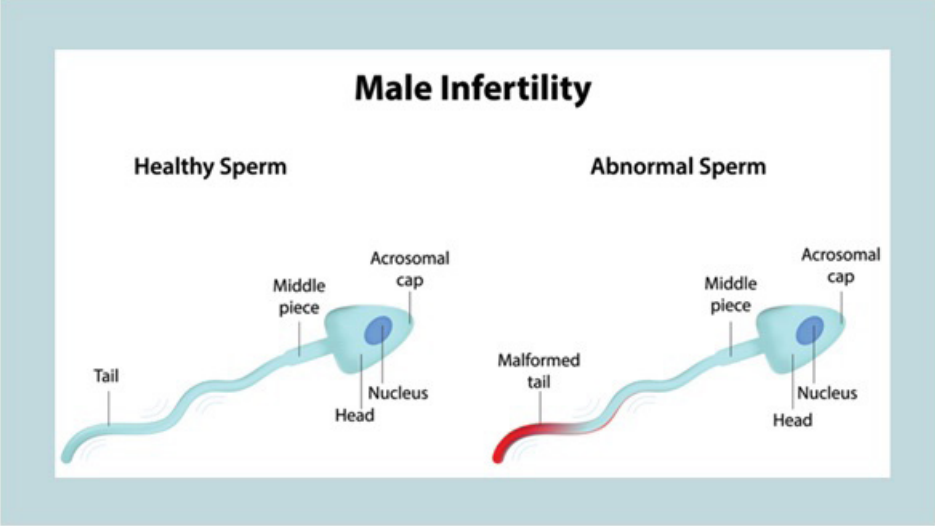

Figure 6: Schematic of a healthy sperm cell (left) versus an abnormal sperm cell (right) [1].

6. Diagnosis of Y Chromosome Infertility Syndrome

Infertility syndrome of sex Y chromosome is determined based on clinical findings of some patients and some pathological tests and spermography. The most accurate way to diagnose this syndrome is to test for molecular genetics for the USP9Y gene and to study the AZF regions on the Y sex chromosome by molecular cytogenetic techniques such as in situ fluorescence hybridization (FISH) [1, 10].

7. Treatment pathways of Y Chromosome Infertility Syndrome

The treatment strategy and management of infertility syndrome of sex Y chromosome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including an infertility specialist, a male reproductive system specialist, a hormone specialist, a reproductive biologist, and other health care professionals. There is no effective treatment for this syndrome and all clinical procedures are aimed at fertilizing injured men to have children. Genetic counseling also has a special place for all parents who want a healthy child [1, 11].

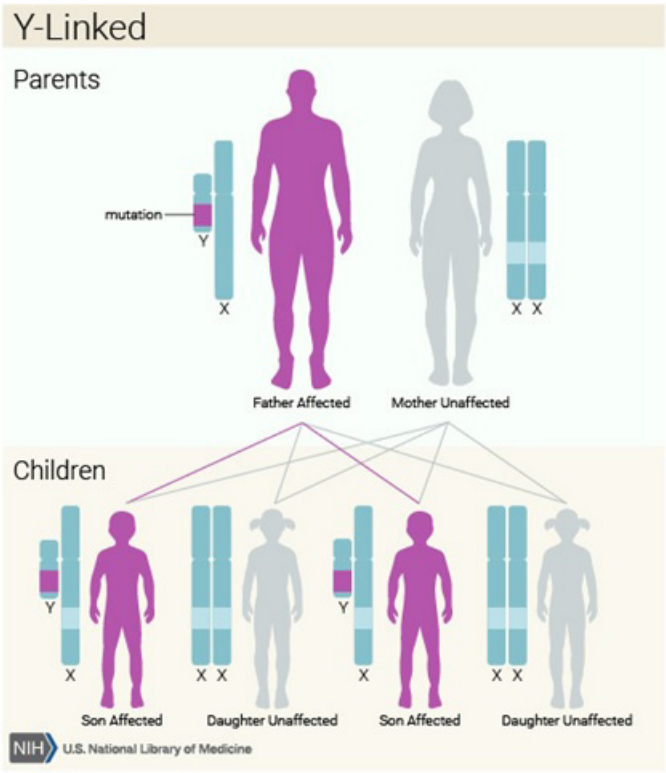

Figure 7: Schematic of the Y-dependent hereditary pattern that the Y sex chromosome infertility syndrome also follows [1].

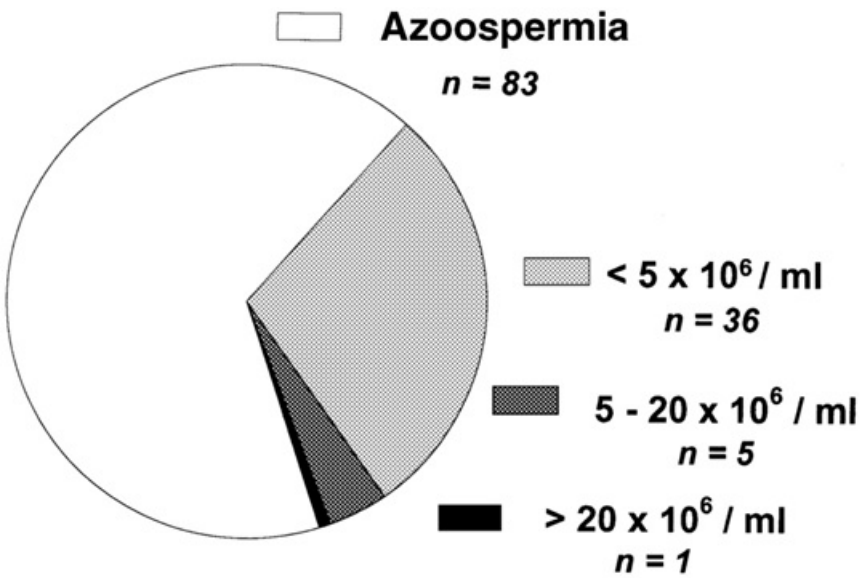

Figure 8: Pie chart of sperm cell count in semen of a man with azoospermia [1].

8. Discussion

Y chromosome infertility is a condition that affects the production of sperm, making it difficult or impossible for affected men to father children. An affected man's body may produce no sperm cells (azoospermia), a smaller than usual number of sperm cells (oligospermia), or sperm cells that are abnormally shaped or that do not move properly. This condition accounts for between 5 percent and 10 percent of cases of azoospermia or severe oligospermia. As its name suggests, this form of infertility is caused by changes in the Y chromosome, one of the sex chromosomes. Y chromosome infertility is usually caused by deletions of genetic material in regions of the Y chromosome called azoospermia factor (AZF) A, B,

or C. Genes in these regions are believed to provide instructions for making proteins involved in sperm cell development, although the specific functions of these proteins are not well understood. In rare cases, changes to a single gene called USP9Y, which is located in the AZFA region of the Y chromosome, can cause Y chromosome infertility [1, 12]. Some men with Y chromosome infertility who have mild to moderate oligospermia may eventually father a child naturally. Assisted reproductive technologies may help other affected men. Because Y chromosome infertility impedes the ability to father children, this condition is usually caused by new deletions on the Y chromosome and occurs in men with no history of the disorder in their family. When men with Y chromosome infertility do father children, either naturally or with the aid of assisted reproductive technologies, they pass on the genetic changes on the Y chromosome to all their sons. As a result, the sons will also have Y chromosome infertility [1, 13].

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