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The Role of Mutations on Gene WNT4 in Müllerian Aplasia and Hyperandrogenism Syndrome

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Abstract

Molar aplasia and hyperandrogenism is a genetic disorder that affects the reproductive system in women. This condition is caused by abnormal growth of the molar ducts, which are structures in the fetus that form into the uterus, fallopian tubes, cervix, and upper vagina. A mutation in the WNT4 gene, located at the short arm of chromosome 1 at 1p36.12, causes molar aplasia and hyperandrogenism. This gene belongs to a family of WNT genes that play an important role in evolution before birth.

Keywords

WNT4 deficiency, Genetic Mutation, WNT4 Gene, Infertility

Clinical Signs and Symptoms of Müllerian Aplasia and Hyperandrogenism Syndrome

Molar aplasia and hyperandrogenism is a genetic disorder that affects the reproductive system in women. This condition is caused by abnormal growth of the molar ducts, which are structures in the fetus that form into the uterus, fallopian tubes, cervix, and upper vagina. People with molar aplasia and hyperandrogenism usually have an underdeveloped or absent uterus and may also have other abnormalities in the reproductive organs. Women with the disease have some female external genitalia, and during puberty, breasts typically grow and skin hairs form on their penis. However, their menstrual cycle does not begin until they are 16 years old (early amenorrhea) and they will probably never experience menstruation. Women with Müllerian aplasia syndrome and hyperandrogenism are unable to have children (infertile) [1].

Women with molar aplasia and hyperandrogenism have excessively high levels of male sex hormones called androgens in their blood (hyperandrogenism), which can cause acne and facial hair (facial hirsutism). In addition, kidney abnormalities may be present in some people with this syndrome [1,2].

Etiology of Müllerian Aplasia and Hyperandrogenism Syndrome

A mutation in the WNT4 gene, located at the short arm of chromosome 1 at 1p36.12, causes molar aplasia and hyperandrogenism. This gene belongs to a family of WNT genes that play an important role in evolution before birth. The WNT4 gene provides the instructions

for protein production that are important for the formation of the female reproductive system, the kidneys, and several hormone-producing glands. During the development of the female reproductive system, the WNT4 protein regulates the formation of molar ducts. This protein is also involved in the growthof the ovaries from birth to adulthood and is very important for the growth and maintenance of egg cells ('s) in the ovaries. In addition, the WNT4 protein regulates the production of androgens (**Fig-1)** [1,3].

Mutations in the WNT4 gene alter the single-amino acid structural blocks in the WNT4 protein. The researchers suspect that the modified protein could not be released normally from the cells. Therefore, the modified protein is not able to perform its normal functions. Lack of regulation by WNT4 is likely to impair the development of the female reproductive system, leading to abnormal androgen production, leading to features of Müllerian aplasia syndrome and hyperandrogenism (**Fig-2**) [1,3].

Müllerian aplasia syndrome and hyperandrogenism follow an autosomal dominant pattern. Therefore, a copy of the WNT4 mutant gene is needed in each cell to cause this syndrome. It is important to note that girls with molarine aplasia and hyperandrogenism do not inherit the mutation from their mother because women with the disorder cannot have children (infertile). However, it is not clear how a person with the mutation inherits the mutation from his or her father or if the disease is caused by new mutations in the WNT4 gene, leading to Müllerian aplasia syndrome and hyperandrogenism. Molar aplasia and hyperandrogenism may also occur in people with no family history of the disorder [1,4].

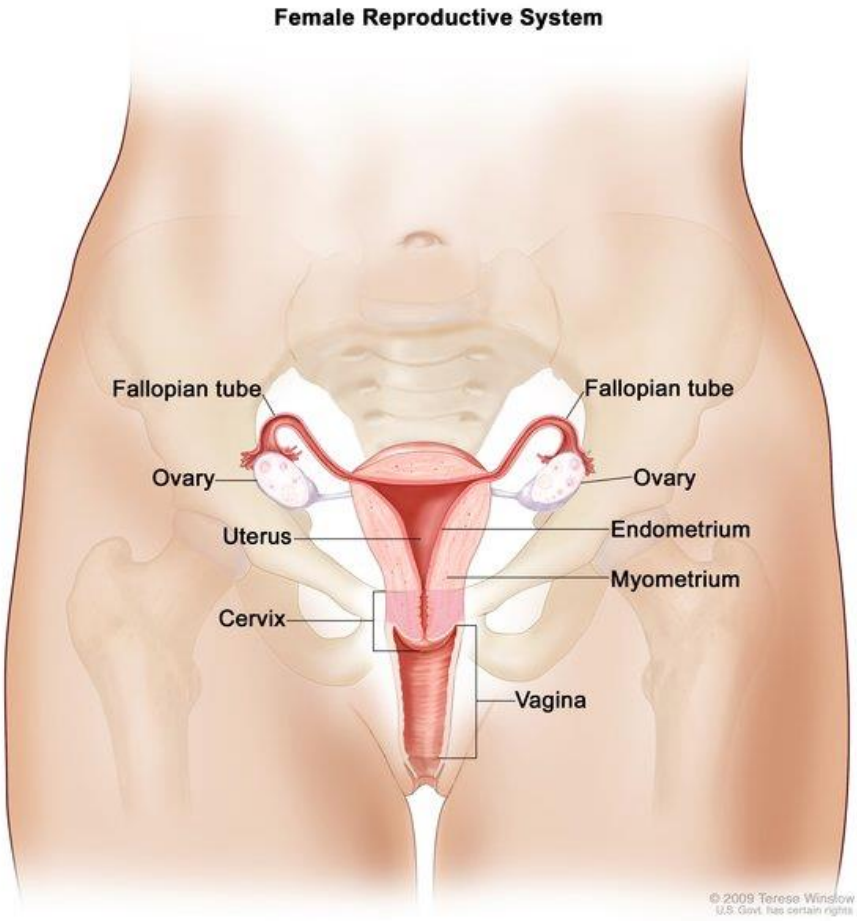

Fig-1:

Schematic of the anatomy of the female reproductive system. Organs in the female reproductive system include the uterus, ovaries, fallopian tubes, cervix, and vagina. The uterus has an outer layer of muscle called the myometrium and an inner layer called the endometrium.[1]

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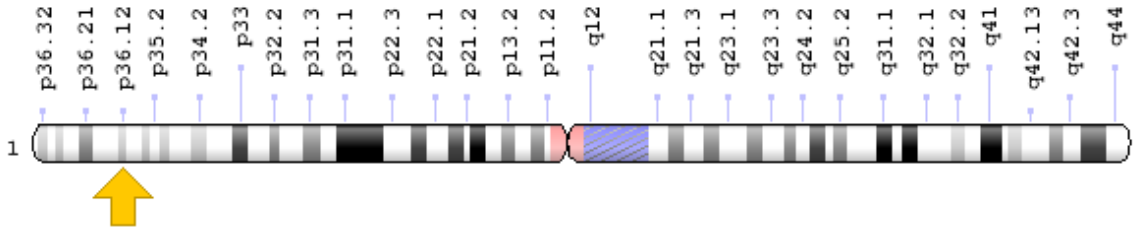

Fig-2:

Schematic view of chromosome 1 where the WNT4 gene is located in the short arm of this chromosome as 1p36.12.[1]

Frequency of Müllerian Aplasia and Hyperandrogenism Syndrome

Müllerian aplasia syndrome and hyperandrogenism is a very rare genetic disorder that only a small number of people with this syndrome have been reported in the world [1,4].

Diagnosis of Müllerian Aplasia and Hyperandrogenism Syndrome

Müllerian aplasia syndrome and hyperandrogenism can be diagnosed based on the clinical findings of some patients and some pathological tests. The most accurate way to diagnose this syndrome is to test the molecular genetics for the WNT4 gene to check for possible mutations (**Fig-3**) [1,5].

Treatment options for Müllerian Aplasia and Hyperandrogenism Syndrome

The treatment and management strategy of Müllerian aplasia syndrome and hyperandrogenism is symptomatic and supportive only for female genital and renal disorders. No reliable treatment has been

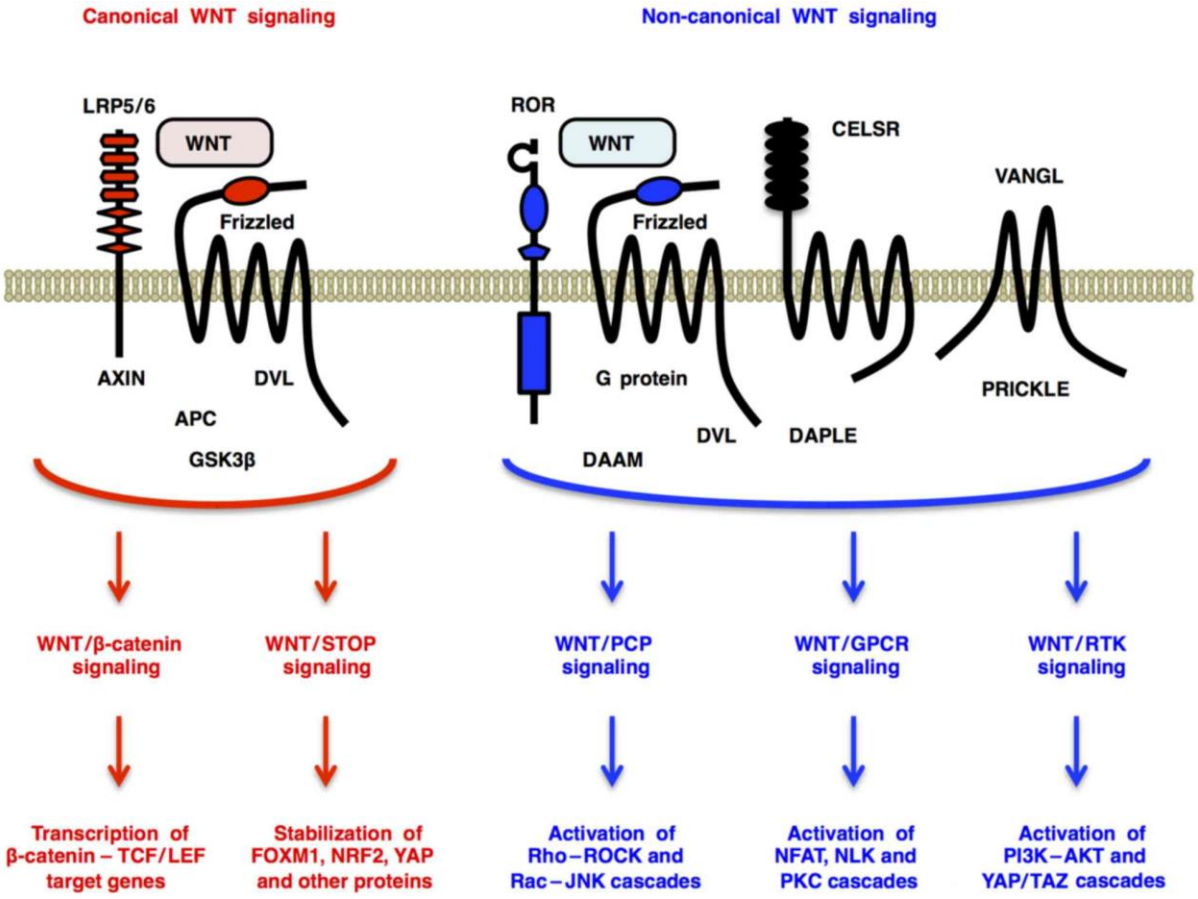

Fig-3:

Schematic of the WNT4 signaling path.[1]

identified for infertility in women with this syndrome. Genetic counseling is also essential for all parents who want a healthy baby. In women with mullerian aplasia, nonsurgical techniques, including the use of vaginal dilators, may increase the depth of the vagina to a normal length. Such treatment can ease the pain and difficulty that may be associated with sexual intercourse. Nonsurgical techniques are considered the first-line approach. Vaginal dilators are specially designed plastic tubes that are used to help enlarge or create a vagina. The most common method is known as Franck's dilator method. With this method, a physician (and then woman herself) applies a vaginal dilator, which progressively stretches and widens the vagina. This daily procedure may be continued for up to six weeks to several months. In some cases, plastic surgery may be necessary to create an artificial vagina (vaginoplasty). There are a variety of different surgical techniques that may be used and there is no consensus as to which technique is best. Females who undergo surgery to create an artificial vagina will most likely need to use vaginal dilators after the surgery to enhance the chance of success (**Fig-4**) [1,6].

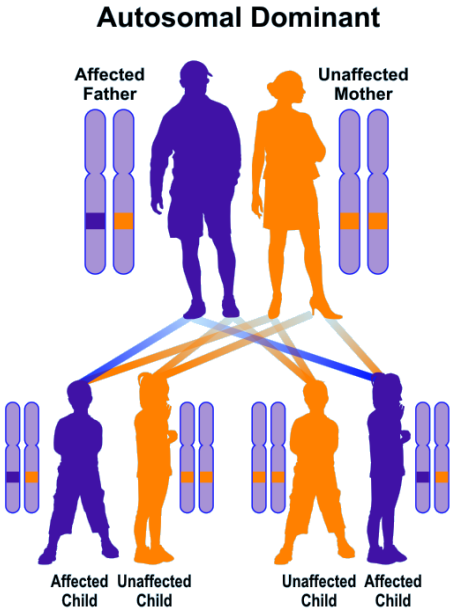

Fig-4:

Schematic of the dominant autosomal inherited pattern followed by Müllerian aplasia and hyperandrogenism syndrome.[1]

Discussion and Conclusion

Women with molar aplasia and hyperandrogenism have excessively high levels of male sex hormones called androgens in their blood (hyperandrogenism), which can cause acne and facial hair (facial hirsutism). The WNT4 gene provides the instructions for protein production that are important for the formation of the female reproductive system, the kidneys, and several hormone-producing glands. During the development of the female reproductive system, the WNT4 protein regulates the formation of molar ducts. No reliable treatment has been identified for infertility in women with this syndrome. WNT4 deficiency is extremely similar to another rare disorder known as Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. Many women who have WNT4 deficiency may have originally received a diagnosis of MRKH syndrome. Although the two disorders have similar signs and symptoms, most women with MRKH syndrome who have been tested do not have mutations of the WNT4 gene. MRKH syndrome is characterized by the failure of the uterus and the vagina to develop properly in women who have normal ovarian function and normal external genitalia. Women with this disorder develop secondary sexual characteristics during puberty (e.g., breast development and pubic hair), but do not have a menstrual cycle (primary amenorrhea). As with WNT4 deficiency, failure to begin the menstrual cycle is the initial clinical sign of MRKH syndrome. The range and severity of MRKH syndrome can vary greatly and the disorder is generally broken down into type I, which occurs as an isolated finding, and type II, which occurs with abnormalities of additional organ systems including the kidneys and the skeleton. The exact cause of MRKH syndrome is unknown [1-6].

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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