

# Mayer-Rokitansky-Küster-Hauser Syndrome

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## General Discussion

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare disorder that affects women. It 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 normal secondary sexual characteristics during puberty (e.g., breast development and pubic hair), but do not have a menstrual cycle (primary amenorrhea). Often, the 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 mainly the kidneys and the skeleton. Because of the nature of the disorder, MRKH



syndrome can cause significant psychological challenges and counseling is recommended. The exact cause of MRKH syndrome remains largely unknown, but there is now no doubt of a genetic origin. In this respect, an update on the most recent research publications shows the involvement of several chromosomal segments, some of them including genes likely to account for the disorder.

## **Signs & Symptoms**

The symptoms of MRKH syndrome vary greatly from one woman to another. It is important to note that affected individuals may not have all of the symptoms discussed below. Affected individuals should talk to their physician and medical team about their specific case, associated symptoms and overall prognosis.

## **MAYER-ROKITANSKY KÜSTER-HAUSER SYNDROME TYPE I**

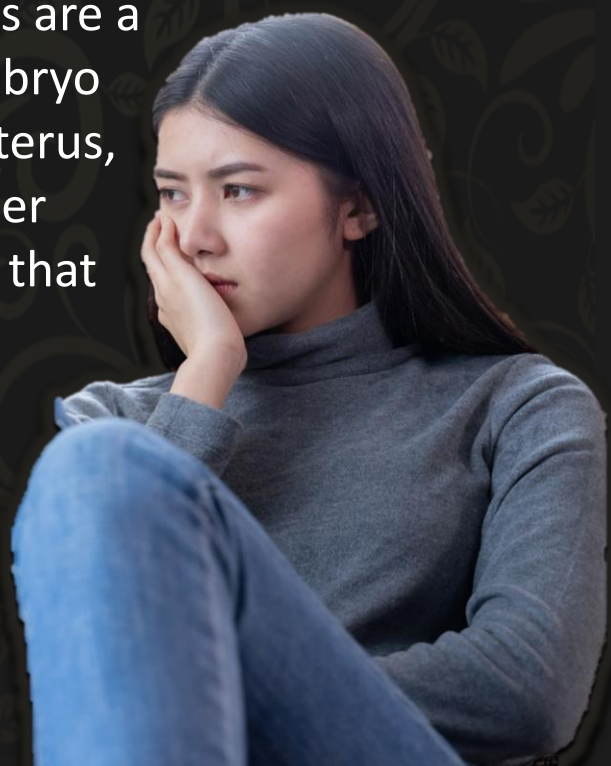
This form of MRKH syndrome is also known as isolated Mullerian aplasia, or Rokitansky sequence. The disorder is characterized by the failure of the uterus and the vagina to develop properly. The severity of MRKH syndrome type I may vary greatly from one person to another. In most cases, the uterus and/or the vagina have not developed (aplasia); in other rare cases, there may be narrowing (atresia) of the upper portion of the



vagina and an underdeveloped or rudimentary uterus. In some cases, the Fallopian tubes may be affected as well. The ovaries of females with MRKH syndrome are unaffected and function normally.

In most cases, the initial symptom of MRKH syndrome type I is the failure to begin menstrual cycles (primary amenorrhea). Despite amenorrhea, affected females do experience normal secondary sexual development including breast development, the growth of hair under the arms and in the pubic area, and an increase in body fat around the hips and other areas. Sex steroid levels, female sexual identification, and level of sexual desire (libido) are all also normal. However, because of the absence of the uterus and properly developed fallopian tubes, all affected women are unable to bear children (infertile). Many affected females also experience difficulty while attempting sexual intercourse due to the shortness of the vagina. Some women may also experience pain during intercourse.

MRKH syndrome type I is sometimes referred to as Mullerian aplasia because the Mullerian ducts are a dual structure within a growing embryo that ultimately develops into the uterus, Fallopian tubes, cervix and the upper portion of the vagina. It is believed that improper development of tissues derived from the Mullerian ducts occurring during embryogenesis, ultimately causes the symptoms of MRKH syndrome.



## MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME TYPE II

When the abnormalities that characterize MRKH syndrome type I occur in association with additional physical findings, the disorder is classified as MRKH syndrome type II or (M)üllerian duct aplasia, (R)enal dysplasia and (C)ervical (S)omite anomalies or MURCS association. The most common abnormalities associated with MRKH syndrome type II are failure of the kidneys to develop properly (renal dysplasia) and various skeletal malformations, mainly vertebral. Much less frequent defects include heart malformations and hearing impairment.

Women with MRKH syndrome type II may exhibit absence of a kidney (unilateral renal agenesis), malformation of one or the two kidneys (renal dysplasia), underdeveloped (hypoplastic) kidneys and/or improper positioning within the body of one or both kidneys (renal ectopia). Renal abnormalities can cause growth deficiency, kidney stones, an increased susceptibility to urinary tract infections and abnormal accumulation of urine in the kidney due to obstruction (hydronephrosis).

Many females with MRKH syndrome type II also exhibit skeletal malformations.

For example, bones (vertebrae) in the spinal column within the neck (cervical vertebrae) and the upper back (thoracic vertebrae) may develop improperly (dysplasia).

As a result, some of the vertebrae within the neck may be missing



and/or fused, causing shortness of the neck, limited neck motion, and an abnormally low hairline (Klippel-Feil syndrome). In addition, affected females may exhibit asymmetric, fused or wedge vertebrae; malformed or missing ribs; abnormal sideways curvature of the spine (scoliosis); elevation of the shoulder blade (scapula), due to the scapula's failure to move into the appropriate position during fetal development (Sprengel deformity). (For more information on Klippel-Feil syndrome and Sprengel deformity, please see the Related Disorders section of this report.). Abnormalities of the head and face may also occur including an abnormally small jaw (micrognathia), cleft lip, cleft palate and underdevelopment of one side of the face causing facial asymmetry.

Some affected women develop hearing loss due to the failure of sound waves to be conducted through the middle ear (conductive hearing loss), usually due to structural abnormalities of the middle ear. Hearing loss may also be due to impaired ability of the auditory nerve to transmit sensory input to the brain (sensorineural hearing loss).

The degree of hearing impairment may vary. The ears may be malformed (dysplastic) in some cases. When the ears are involved the disorder may be referred to as genital renal ear syndrome (GRES)

In rare cases, some females with MRKH syndrome type II have had additional physical abnormalities including abnormalities of the hands and/or arms and heart malformations.

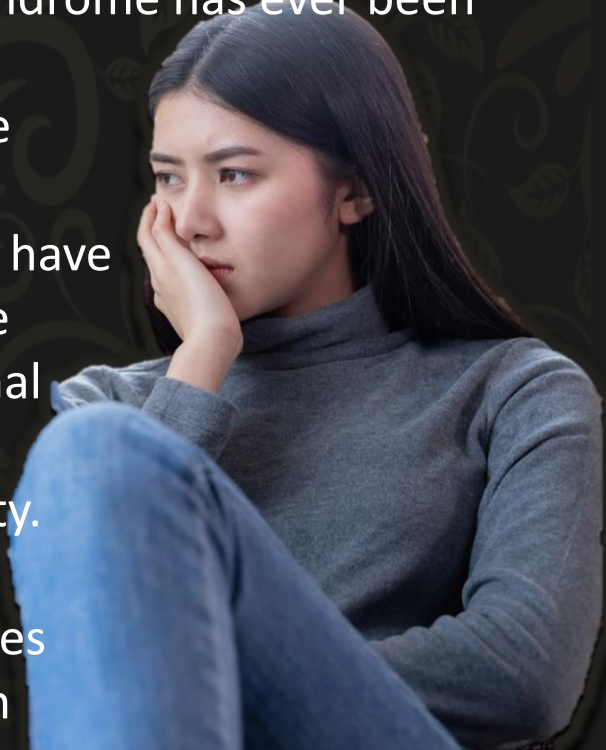


Abnormalities of the extremities may include absence of a portion of one or more fingers or toes (ectrodactyly), webbing of the fingers or toes (syndactyly), duplicated thumb and absence of the long, thin bone of the forearm (absent radius). Heart malformations may include “a hole in the heart” between the two upper chambers of the heart (atrial septal defects), narrowing of the pulmonary valve (pulmonary valvular stenosis) or tetralogy of Fallot, a rare grouping of four different heart defects.

## Causes

The exact cause of MRKH syndrome remains largely unknown but ongoing research has begun to provide some clues to its mechanism. Initially, MRKH syndrome was thought to occur randomly (sporadically) due to the involvement of non-genetic or environmental factors such as gestational diabetes or exposure to a teratogen, which is an agent that can disrupt the development of an embryo. No link between an environmental cause and MRKH syndrome has ever been established.

In recent years, increasing evidence suggests that MRKH syndrome is a genetic disorder. Some researchers have proposed that, in familial cases, the disorder is inherited as an autosomal dominant trait with incomplete penetrance and variable expressivity. Increasing case studies have now reinforced this idea. Genetic diseases are determined by the combination



of genes for a particular trait that are on the chromosomes received from the father and the mother. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or can be the result of a new mutation (gene change) in the affected individual. The risk of passing the abnormal gene from affected parent to offspring is 50 percent for each pregnancy regardless of the sex of the resulting child.

Incomplete penetrance means that some individuals who inherit the gene for a dominant disorder will not be affected by the disorder. Variable expressivity a dominant disorder can have widely varying signs and symptoms among affected individuals.

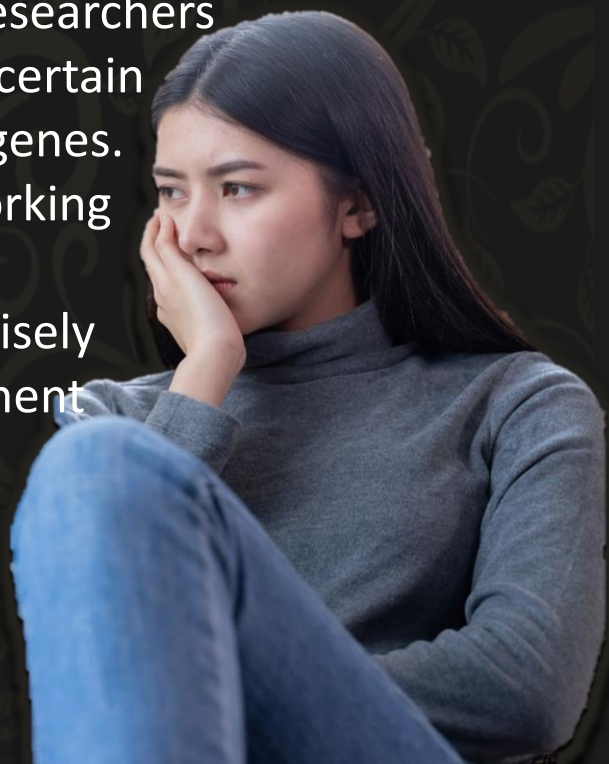
Polygenic multifactorial inheritance has also been proposed as a cause of MRKH syndrome. Polygenic multifactorial inheritance refers to the interaction of many genes (polygenic) in the development of a disorder with each gene having a small effect on the overall development of the disorder.

Research is ongoing to determine the exact underlying causes of MRKH syndrome including identifying the gene or gene(s) involved in the development of the disorder and whether environmental factors play a role. It is now clear that different genes can each account for the disease, when they are mutated or involved in a chromosome segmental anomaly (deletion or duplication).



Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q”. Chromosomes are further sub-divided into many bands that are numbered. For example, “chromosome 1q21.1” refers to band 21.1 on the long arm of chromosome 1. The numbered bands specify the location of the thousands of genes that are present on each chromosome.

To date, seven deletions and one duplication of chromosomal segments have been identified in several persons affected by MRKH syndrome. These anomalies have been found independently in different persons (i.e., one and only one of these chromosomal anomalies per person). These anomalies are of varying length and can contain one gene or many different genes. This has allowed researchers to hypothesize the involvement of certain genes, which are called candidate genes. These researchers are currently working on the characterization of these candidate genes to determine precisely their responsibility in the development of MRKH syndrome. At the present time, the seven segmental deletions likely to be involved in MRKH syndrome have been identified in chromosomes 1





(1q21.1), 4 (4q34-qter), 8 (8p23.1), 10 (10p14-15), 16(16p11.2), 17 (17q12) and 22 (22q11.21), and the duplication was found on the chromosome X (Xpter-p22.32). This has led researchers to define several candidate genes: HNF1B (formerly TCF2), LHX1, TBX6, ITIH5 and SHOX, which are currently under investigation.

These new data demonstrate the genetic origin of the MRKH syndrome. They also show that several different genes defects can cause the syndrome. In this case, the disease can be considered as of multigenic origin, meaning that different genes can independently be responsible for the syndrome.

## **Affected Populations**

MRKH syndrome is estimated to affect 1 in 4,000-5,000 women in the general population. It is the second most common cause of primary amenorrhea. The disorder is thought to be underdiagnosed making it difficult to determine the true frequency of MRKH syndrome in the general population. The disorder is present at birth (congenital) but is often not identified until early adolescence.

By definition, MRKH syndrome only affects females. However, some researchers have noted similar symptoms in males. Affected males have exhibited absence or underdevelopment of the Wolffian duct, an organ that is present in a developing embryo that eventually evolves into certain structures



such as the tube connecting the testes to the urethra (vas deferens). Affected males may also have low levels of live sperm in their semen (azoospermia), kidney abnormalities, spinal malformations, hearing impairment and additional physical findings. This condition is sometimes referred to as ARCS (Azoospermia, Renal anomalies, Cervicothoracic Spine dysplasia). The relationship, if any, between ARCS and MRKH syndrome remains unsolved. However, rare cases of ARCS and MRKH in the same family have been reported, making both syndromes likely to be of identical genetic origin.

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