



Recurrent hydatidiform mole

Recurrent hydatidiform mole is a condition that affects women and is characterized by the occurrence of at least two abnormal pregnancies that result in the formation of hydatidiform moles. A hydatidiform mole is a mass that forms early in pregnancy and is made up of cells from an abnormally developed embryo and placenta. Normally, the embryo would develop into a fetus and the placenta would grow to provide nutrients to the growing fetus. When a hydatidiform mole occurs once, it is known as sporadic hydatidiform mole; if it happens again, the condition is known as recurrent hydatidiform mole.

The first symptom of a hydatidiform mole is often vaginal bleeding in the first trimester of pregnancy. During an ultrasound examination, the abnormal placenta appears as numerous small sacs, often described as resembling a bunch of grapes.

Hydatidiform moles are not naturally discharged from the body and must be surgically removed, typically by the end of the first trimester. After removal, there is up to a 20 percent risk that any tissue left behind will continue to grow and become a cancerous (malignant) tumor called a persistent mole. If the tumor invades the surrounding tissue of the uterus, it is called an invasive mole. In rare cases, this malignant tumor can transform into a different form of cancer called gestational choriocarcinoma that can spread (metastasize) to other tissues such as the liver, lungs, or brain.

Frequency

Hydatidiform moles occur in 1 in 600 to 1,000 pregnancies in western countries. One to six percent of previously affected women will have a recurrent hydatidiform mole. Gestational choriocarcinoma occurs in 1 in 20,000 to 50,000 pregnancies in the United States.

Causes

Mutations in multiple genes have been found to cause recurrent hydatidiform mole. About 55 percent of cases of this condition are caused by *NLRP7* gene mutations and about 5 percent of cases are caused by *KHDC3L* gene mutations. Mutations in other genes each account for a small percentage of cases.

The proteins produced from the *NLRP7* and *KHDC3L* genes are critical for normal egg cell (oocyte) development, which impacts embryonic development. Within oocytes, the exact role of *NLRP7* and *KHDC3L* proteins are not known. However, they are thought to play a role in a phenomenon known as genomic imprinting. Through genomic imprinting certain genes are turned off (inactivated) based on which parent the copy of the gene came from. For most genes, both copies of the gene (one copy inherited from each parent) are active in all cells. However, for a small subset of genes, only one of

the two copies is active and the other is turned off. For some of these genes, the copy from the father is normally active, while for others, the copy from the mother is normally active.

NLRP7 or *KHDC3L* gene mutations result in the production of proteins with impaired function. As a result, oocytes do not develop normally. A pregnancy that results from an abnormal oocyte cannot develop properly, resulting in recurrent hydatidiform mole. *NLRP7* or *KHDC3L* gene mutations can also prevent proper imprinting of multiple genes that contribute to a developing embryo, leading to abnormal gene activity (expression). It is not clear if problems with imprinting also contribute to the development of a hydatidiform mole. In women with *NLRP7* or *KHDC3L* gene mutations, a hydatidiform mole will develop in every pregnancy that occurs with her egg cells.

A small number of cases of recurrent hydatidiform mole have been found to be caused by mutations in genes that play important roles in the production of oocytes and sperm cells. The proteins produced from these genes are involved in the normal process of exchanging genetic material between chromosomes in preparation for cell division during oocyte and sperm cell production. These proteins are needed to make breaks in the chromosomes so that genetic information can be exchanged.

Mutations in these genes prevent the normal function of the proteins involved in the exchange of genetic material. Without the exchange of genetic material, cell division is often stopped. In affected women, this can lead to the production of abnormal oocytes that do not contain chromosomes. When a normal sperm cell fertilizes one of these oocytes, the resulting embryo has only one set of chromosomes. Because the embryo has no genes from the mother, the pregnancy cannot develop normally, resulting in a hydatidiform mole. In women with these rare gene mutations, every pregnancy that occurs with her egg cells will result in a hydatidiform mole or pregnancy loss (miscarriage).

In some cases of recurrent hydatidiform mole, no mutations in any of the genes associated with the condition have been identified. In these instances, the cause of the condition is unknown.

Inheritance Pattern

Recurrent hydatidiform mole is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Recurrent hydatidiform mole seems to have an autosomal recessive inheritance pattern even when the genetic cause of the condition is unknown.

Other Names for This Condition

- familial recurrent hydatidiform mole
- FRHM
- recurrent androgenetic hydatidiform mole
- recurrent biparental hydatidiform mole

Diagnosis & Management

Formal Diagnostic Criteria

- Soper JT, Mutch DG, Schink JC; American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. *Gynecol Oncol.* 2004 Jun;93(3):575-85. Review. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/15196847>

Genetic Testing Information

- What is genetic testing?
</primer/testing/genetictesting>
- Genetic Testing Registry: Hydatidiform mole
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3463897/>
- Genetic Testing Registry: Hydatidiform mole, recurrent, 2
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3280352/>

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22recurrent+hydatidiform+mole%22+OR+%22Gestational+Trophoblastic+Disease%22+OR+%22Hydatidiform+Mole%22>

Other Diagnosis and Management Resources

- American Cancer Society: Signs and Symptoms of Gestational Trophoblastic Disease
<https://www.cancer.org/cancer/gestational-trophoblastic-disease/detection-diagnosis-staging/signs-symptoms.html>
- MedlinePlus Encyclopedia: Choriocarcinoma
<https://medlineplus.gov/ency/article/001496.htm>
- MedlinePlus Encyclopedia: Hydatidiform Mole
<https://medlineplus.gov/ency/article/000909.htm>

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Choriocarcinoma
<https://medlineplus.gov/ency/article/001496.htm>
- Encyclopedia: Gestational Trophoblastic Disease
<https://medlineplus.gov/ency/article/007333.htm>
- Encyclopedia: Hydatidiform Mole
<https://medlineplus.gov/ency/article/000909.htm>
- Health Topic: Female Infertility
<https://medlineplus.gov/femaleinfertility.html>
- Health Topic: Miscarriage
<https://medlineplus.gov/miscarriage.html>
- Health Topic: Tumors and Pregnancy
<https://medlineplus.gov/tumorsandpregnancy.html>

Genetic and Rare Diseases Information Center

- Hydatidiform mole
<https://rarediseases.info.nih.gov/diseases/10263/hydatidiform-mole>

Additional NIH Resources

- National Cancer Institute: General Information about Gestational Trophoblastic Disease
<https://www.cancer.gov/types/gestational-trophoblastic/patient/gtd-treatment-pdq>
- Office on Women's Health: Infertility Fact Sheet
<https://www.womenshealth.gov/a-z-topics/infertility>

Educational Resources

- Centers for Disease Control and Prevention: Infertility FAQs
<https://www.cdc.gov/reproductivehealth/Infertility/>
- MalaCards: recurrent hydatidiform mole
https://www.malacards.org/card/recurrent_hydatidiform_mole
- March of Dimes
<https://www.marchofdimes.org/complications/molar-pregnancy.aspx>
- Merck Manual Consumer Version
<https://www.merckmanuals.com/home/women-s-health-issues/cancers-of-the-female-reproductive-system/hydatidiform-mole>
- Orphanet: Hydatidiform mole
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99927

Patient Support and Advocacy Resources

- Heartstrings
<http://www.heartstringsupport.org/>
- RESOLVE: The National Infertility Association
<https://resolve.org/>
- Share Pregnancy & Infant Loss Support, Inc.
<http://nationalshare.org/>
- The International Council on Infertility Information Dissemination, Inc. (INCIID)
<http://www.inciid.org/>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28hydatidiform+mole%5BTI%5D%29+AND+%28recurrent%5BALL%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- HYDATIDIFORM MOLE, RECURRENT, 1
<http://omim.org/entry/231090>
- HYDATIDIFORM MOLE, RECURRENT, 2
<http://omim.org/entry/614293>

Medical Genetics Database from MedGen

- Complete Hydatidiform Mole
<https://www.ncbi.nlm.nih.gov/medgen/195706>
- Gestational trophoblastic disease
<https://www.ncbi.nlm.nih.gov/medgen/444101>

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Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/recurrent-hydatidiform-mole>

Reviewed: December 2018

Published: January 15, 2019

Lister Hill National Center for Biomedical Communications
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