Genetic origin of recurrent hydatidiform moles

Published: 10-05-2013
Last updated: 24-04-2024

This study has two objectives:1) The first objective is to determine the frequency of mutations in NLRP7 and KHDC3L in patients with recurrent HM in the Netherlands.2) The second objective is to identify additional candidate genes associated with (...

Ethical review	Approved WMO
Status	Pending
Health condition type	Placental, amniotic and cavity disorders (excl haemorrhages)
Study type	Observational invasive

Summary

ID

NL-OMON38464

Source
ToetsingOnline

Brief title
Genetic origin of hydatidiform moles

Condition

- Placental, amniotic and cavity disorders (excl haemorrhages)

Synonym
molar pregnancy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Veni ZonMw

Intervention

Keyword: etiology, genetics, hydatidiform mole, NLRP7

Outcome measures

Primary outcome

1) To determine the frequency of mutations in NLRP7 or KHDC3L in patients with

recurrent hydatidiform moles in the Netherlands.

2) To identify additional candidate genes associated with (familial) recurrent

HM.

Secondary outcome

Not applicable.

Study description

Background summary

Hydatidiform mole (HM) is a non viable form of pregnancy with a cystic appearance of chorionic villi, most often in the absence of an embryo. HM occurs in approximately 1 in 1000 pregnancies. Hydatidiform moles can be divided in complete and partial HM. Complete hydatidiform moles (CHM) commonly have a diploid karyotype (46,XX, occasionally 46,XY), representing reduplication of the haploid genome of the sperm in an enucleated oocyte or the fusion of two sperms with an enucleated oocyte. Foetal development or foetal erythroblasts are not observed in complete moles, trophoblastic proliferation and hydropic villi are usually more prominent and diffuse. In contrast, partial hydatidiform moles (PHM) are generally triploid (69,XXX or 69,XXY). This results from fertilisation of a normal ovum by one sperm followed by reduplication of the haploid paternal genome, or from dispermic fertilisation. Foetal development, such as embryonic structures, stromal capillaries and amniotic tissue are often present.

Following molar evacuation by uterine curettage, remaining trophoblastic tissue resolves spontaneously in most cases. However some HM persist and even metastasise. This is called persistent trophoblastic disease (PTD). PTD is a clinical diagnosis and is determined by the production of serum human chorionic gonadotropin (hCG). According to the FIGO criteria, PTD is defined as 1) a

plateau in weekly serum hCG concentrations for 3 consecutive weeks, 2) an increase of the serum hCG level for 2 weeks and 3) persistence of detectable hCG levels for more than 6 months after evacuation. PTD occurs in approximately 15% of all complete molar pregnancies. Less often (0.5-5.6%) partial moles develop malignant sequelae.
Some non-gestational malignancies can also produce hCG. In most cases these can be distinguished from a gestational trophoblastic tumour by histopathological examination. In difficult cases, genetic testing can be useful in determining the correct diagnosis.

Diploid moles are most often androgenetic with two identical (homozygous) or different sets of paternal chromosomes (heterozygous) [9, 10]. Beside the more common androgenetic diploid moles, in rare cases (4%) a diploid biparental genome is observed. This is usually associated with familial recurrent hydatidiform mole.
Recurrent hydatidiform mole occurs in about 1 - 6% of patients with a sporadic hydatidiform mole. Familial biparental hydatidiform moles are usually complete. Familial and non-familial recurrent hydatidiform moles are associated with mutations in particular genes resulting in a defect in imprinting. Linkage to chromosome locus 19q13.4 and autosomal recessive mutations of the NLRP7 gene in that region have been found in a small number of families with recurrent biparental diploid HM, although in other families with recurrent hydatidiform mole no association with the NLRP7 gene was observed. Recent studies implicated a second gene in this class of moles, KHDC3L (C6orf221). It is speculated that NLRP7 and KHDC3L interact as components of an oocyte complex that is directly or indirectly required for determination of epigenetic status on the oocyte genome.

The goal of this study is to explore genetic mutations explaining HM. A systematic screen of the described genes NLRP7 or KHDC3L will show the prevalence of mutations in these genes in Dutch women with HM. By using exome sequencing in blood of patients with recurrent HM, without NLRP7 or KHDC3L mutations, we aim to identify novel genes involved in the development of HM. Identification of additional candidate genes responsible for recurrent (familial) HM will lead to a better understanding of the aetiology of HM, PTD and possibly other forms of recurrent aberrant pregnancy.

Study objective

This study has two objectives:
1) The first objective is to determine the frequency of mutations in NLRP7 and KHDC3L in patients with recurrent HM in the Netherlands.
2) The second objective is to identify additional candidate genes associated with (familial) recurrent HM.

Study design

The study design for the two objectives:
1) Women were identified who had two or more hydatidiform moles. Evacuation tissue of these women will be retrospectively and prospectively collected from the pathology laboratories of their hospitals and will be reviewed by an expert pathologist to be certain of the diagnosis of HM. In addition, a blood sample will be obtained from the patients. After isolating DNA from the blood samples of the patients, the frequency of mutations in NLRP7 and KHDC3L in Dutch patients with recurrent HM can be determined. In collaboration with the department of Human Genetics we will apply Sanger sequencing to screen these two known genes for point mutations.
2) In a second step we will investigate 5-10 of the patients without mutations in the known genes NLRP7 and KHDC3L, preferably including patients with the highest frequency of HMs. In order to identify novel genes for this disorder, we will apply exome sequencing by using the blood that was obtained for the first objective.

Study burden and risks

Since all patients have finished their treatments for HM, this research will not interfere with the patients treatment schedule. The burden consists of obtaining a blood sample from the patients and their parents.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525 GA
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

objective 1:
- patients with a history of at least two or more hydatidiform moles;objective 2:
- patients from objective 1 without a known mutation in NLRP7 or KHDC3L

Exclusion criteria

objective 1:
- patients with a history of less than two molar pregnancies;objective 2:
- patients from objective 1 with a mutation in NLRP7 or KHDC3L

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2013
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO Date:	10-05-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL43653.091.13