# Genotype-phenotype relation within families with various forms of hereditary hemochromatosis

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Which combinations of mutations in the HFE and HJV and other genes involved in iron metabolism are associated to iron overload?

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Endocrine disorders congenital |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON29963

**Source**
ToetsingOnline

**Brief title**
Genotype-phenotype relation in various forms of HH

### Condition

- Endocrine disorders congenital
- Iron and trace metal metabolism disorders

**Synonym**
iron overload disease

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** genotype, hereditary hemochromatosis, iron

## Outcome measures

### Primary outcome

Iron and ironbindingparameters

Genotype of iron genes

Hepcidin

### Secondary outcome

not applicable

# Study description

### Background summary

Hereditary Hemochromatosis (HH) is a genetic condition characterized by excess iron absorption and pathologic iron deposition in tissue. Usual treatment consists of the removal of body iron by phlebotomy treatments performed weekly until iron parameters are normal, after which these parameters are maintained at normal range by phlebotomies 2-8 times yearly. Hemochromatosis leads to infertility, liver cirrhosis, diabetes, and mortality as a result of liver cirrhosis or heart failure without treatment. If discovered before iron deposition occurs, irreversible damage can be prevented by treatment (phlebotomies).
The most important gene associated with hemochromatosis is the hemochromatosis gene (HFE), which was identified in 1996. Homozygous C282Y-mutations or compound heterozygosity C282Y/H63D is observed in 80-100% of patients with HH. In recent years, other genes which code for proteins involved in the iron metabolism have been discovered: hemojuvelin, (HJV), hepcidin (HAMP), transferrin receptor 2 (TFR2), and ferroportin (SLC40A1). Mutations in these genes are responsible for rare, non-HFE-related forms of HH.
The hemochromatosis family study (HEFAS, a multicentre study amongst 1st grade relatives of patients with homozygous C282Y mutations in the HFE gene), amongst others, showed that not all C282Y homozygotes developed iron deposition during their lifetime. These differences are mainly unexplained. Almost certainly this is the result of an interaction between the environment (the balance between iron available from the diet and iron loss) and genes other than the HFE gene.

There have been reports of families with mutations in two genes, which are involved in the iron metabolism. This is called digenic inheritance. The model of digenic inheritance is mainly criticized because of the low number of well-documented cases. We need to learn more about which genotypes (combinations of mutations) predispose to iron loading to be able to develop an effective strategy to identify people with an increased risk of iron overload. Recently, we identified a combination of a new mutation in the hemojuvelin (HJV) gene with the C282Y mutation in the HFE gene in an index patient with juvenile hemochromatosis from a large family, with hemochromatosis in 4 large sib ships. Furthermore, we collect index patients, where the HFE genotype does not seem to explain the severity of the disease. Using cascade research, we would like to collect a large pool of persons with different combinations of genotypes to relate their genotypes to the severity of iron overload.
We now have the opportunity to study the different combinations of HJV and HFE mutations in detail in different persons who vary in age. In the long run, this research can provide important information about which genotypes are most strongly associated with a predisposition for iron overload. Since it is important for the participants to know whether they load iron, results of the laboratory results on iron parameters and on genotype as well as an advice based on these results will be reported to the general practitioner of the patient, based on current standards (Health Council Report)

**Study objective**

Which combinations of mutations in the HFE and HJV and other genes involved in iron metabolism are associated to iron overload?

**Study design**

1. After deliberation with the proband, family members are informed in writing (Appendix 1 *wervingsbrief HJV-HEFAS.doc*) and are invited to a meeting, in which the background of the disease and the research is explained. Before this meeting , they are asked to fill out a questionnaire and to sign the informed consent (Appendix 2 *vragenlijstinformedconsentHEFASHJV.doc*). This questionnaire was used before in the HEFAS (persons with the homozygous C282Y mutation and their family members) and NBS (a survey of the general population in the city of Nijmegen) investigations, facilitating comparison of the results with other populations.
2. Questionnaires and informed consent are collected at the meeting. If the informed consent permits it, blood (3x 10 ml) is drawn for the determination of creatinin, LDH, CRP, hemocytometrics (to exclude pathologies that influence iron parameters), iron and iron binding, ferritin, hepcidin and ALAT (a measure for liver damage), and DNA to investigate the presence of mutations. Also, 10 ml of urine is collected for the determination of hepcidin and creatinin.
3. Results are reported to the general practitioner of the patient, with a referral to a specialist of iron metabolism if applicable (Appendix 3

*UitslagbriefHA.doc*).

**Study burden and risks**

see ABR form

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Family members of a patient with hereditary hemochromatosis

### Exclusion criteria

At least 18 years of age

## Study design

### Design

**Study type:** Observational invasive

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-04-2006 |
| Enrollment: | 120 |
| Type: | Anticipated |

## Ethics review

Approved WMO

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| 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 | NL11616.091.06 |