Intergenerational changes of CAG repeat size in the Huntington disease gene

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To include Dutch subjects in a Canadian study to establish the frequency of intergenerational CAG size changes for individuals with an intermediate allele (27-35 CAG) for Huntington disease. This will allow us to understand the evolution of HD...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational non invasive

Summary

ID

NL-OMON33000

Source
ToetsingOnline

Brief title
Intergenerational changes of CAG repeat size in the HTT gene

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Movement disorders (incl parkinsonism)

Synonym
Huntington chorea, Huntington disease

Research involving
Sex cells

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Universiteit van British Columbia;Vancouver;Canada

Intervention

Keyword: CAG repeat expansion, Huntington disease, intermediate allele

Outcome measures

Primary outcome

To establish the frequency that an intermediate allele (27-35 CAG) will expand

into the HD range (>35 CAG) during transmission to the next generation.

Secondary outcome

Secondary study parameters may include factors known to influence the

likelihood of repeat instability such as parental age, family history, and HD

haplotype if applicable.

Study description

Background summary

Direct mutation analysis for Huntington disease (HD) became possible in 1993 with the identification of an expanded CAG trinucleotide repeat within the HD gene as the mutation underlying the disease. Expansion of CAG length beyond 35 repeats is associated with the clinical presentation of HD. Intermediate alleles for HD are defined as being below the affected CAG range but have the potential to expand to >35 CAG repeats within one generation. Therefore, intermediate allele carriers are not at risk to develop HD themselves, but due to CAG trinucleotide repeat instability, their offspring are at risk of inheriting an expanded allele with a CAG size in the disease-associated range. The current CAG range for intermediate alleles is between 27 and 35 repeats.

Risk figures that quantify the likelihood that an intermediate allele will expand into the HD range when passed to the next generation would be valuable for clinical services. Intermediate allele carriers require accurate risk estimates in which to base their reproductive decision-making on. Further, it is essential that we consider the magnitude and frequency of intermediate allele expansion when developing clinical standards of care. Determining accurate risk estimates for inclusion in policy is vital in order to provide accurate and standardized care. Only one study to date has published risk estimates for intermediate allele repeat expansion into the HD range. However

these risk estimates are extremely limited due to the use of an exceedingly small sample size and failure to account for the influence of CAG size on repeat instability. Given these limitations they are not suitable for use in clinical practice. This will be the first study to establish CAG size-specific frequencies of intermediate allele repeat expansion into the HD range for use in health services.

The allele frequency of intermediate CAG repeats in the HTT gene in the Netherlands is high (high background risk). Adding known carriers from our patient population to the Canadian study would imply a substantial increase of eligible subjects.

Study objective

To include Dutch subjects in a Canadian study to establish the frequency of intergenerational CAG size changes for individuals with an intermediate allele (27-35 CAG) for Huntington disease. This will allow us to understand the evolution of HD chromosomes and the origins of new mutations for HD.

Study design

Observational study.

Study burden and risks

There are no known risks to participating in this study. Some participants may feel awkward or embarrassed about collecting the sample. A questionnaire will be completed.

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

Males with an intermediate CAG repeat in the Huntington gene.

Exclusion criteria

Azoospermia.
Vasectomy.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-01-2010
Enrollment:	30

Type:	Actual

Ethics review

Approved WMO Date:	17-11-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	NL28243.000.09