Using next generation sequencing to find causative genes in patients with severe microcephaly

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To explore the use of exome sequencing in the diagnostic evaluation of patients with severe microcephaly

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON35505

Source
ToetsingOnline

Brief title
Genetics of microcephaly

Condition

- Neurological disorders congenital

Synonym
microcephaly, small head size

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Exome sequencing, Genes, Microcephaly

Outcome measures

Primary outcome

Number of pathogenic mutations in known genes and newly identified genes causing severe microcephaly

Secondary outcome

Estimated increase in diagnostic yield and speed compared to currently used diagnostic evaluations and sequential genetic testing in patients with severe microcephaly.

Study description

Background summary

Head size is determined by brain development. In severe microcephaly, the head circumference is more than 3 standard deviations below the mean. Usually, severe microcephaly is associated with mental retardation. Severe microcephaly can be caused by a very heterogeneous group of disorders and syndromes. After excluding chromosomal defects, environmental factors (e.g. fetal alcohol syndrome) and recognizable syndromes, the risk of recurrence is still substantial (approximately 20%). This suggests a high contribution of autosomal recessive disorders. To date, multiple genes and gene loci have been identified. However, the analysis of all these individual genes is not widely available and laborious. Moreover, mutations in the currently known genes involved in microcephaly only explain a minority of the cases. So there is a need for a rapid and broad approach to quicken the diagnostic process, increase the diagnostic yield and to identify the other, yet unknown, genes involved.

Study objective

To explore the use of exome sequencing in the diagnostic evaluation of patients with severe microcephaly

Study design

Mutation analysis by exome sequencing

Study burden and risks

The burden and risks associated with participation are minimal. A blood sample is taken only when no DNA is available. There is no direct benefit for the patients. The identification of causative mutations may however reduce the number of other diagnostic evaluations. The identification of causative mutations may also be beneficial for the family. It could improve genetic counselling, aid in decision making in relation to reproduction, enable carrier testing in family members and offer possibilities for prenatal diagnosis.
The study focuses on patients with severe microcephaly because of the expected high contribution of autosomal recessive disorders. This helps in the identification of causative genes based on selection by the presence of at least two mutations (homozygous or compound heterozygous) in the same gene or by shared haplotypes (identical-by-descent).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

A head circumference below -3 SD at birth or below -4 SD at other ages

Exclusion criteria

Causative chromosomal abnormality identified by array CGH

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-01-2011
Enrollment:	750
Type:	Actual

Ethics review

Approved WMO Date:	27-12-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL38198.042.11