Genetics and psychopathology in the 22q11.2 deletion syndrome: A follow up study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON47713

Source
ToetsingOnline

Brief title
Genes and psychopathology in 22q11DS: A follow up study

Condition

- Other condition
- Congenital and hereditary disorders NEC
- Schizophrenia and other psychotic disorders

Synonym
Psychosis, Schizophrenia

Health condition

Autisme en taalstoornissen

Research involving

Human

Sponsors and support

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

Intervention

Keyword: 22q11.2 deletion syndrome, Cognition, Genetic association, Psychiatry

Outcome measures

Primary outcome

- schizophrenia development

- diagnosis of autistic spectrum disorder and/or language disorder

- neurocognitive abilities, including intelligence and the longitudinal course

thereof

- proline concentration in the blood

- DNA polymorphisms and RNA expression profile

- Parent of origin

- structural and functional characteristics of the brain obtained with MRI

scanning

Secondary outcome

Not applicable

Study description

Background summary

Schizophrenia and autism are debilitating psychiatric disorders for which a curative treatment is not yet available. The most important reason for the lack of an effective treatment is the currently limited insight in the biological

mechanisms that lead to these diseases. One approach to further our understanding of the (abnormal) biological processes is the identification of genes associated with the disease. A gene encodes a protein, which in turn fulfills a specific biological role. Thus, uncovering an association between a gene and a disease opens ways to new research into the biological functions of the implicated protein. This way the (abnormal) biological processes involved in the disease can be clarified, a first, highly important step towards the development of better treatments for these diseases.

However, despite the available evidence pointing towards an important role of genetics in both autism and schizophrenia, the identification of the actual culprit genes has thus far been very challenging. This may be because (amongst others): 1) in most patients multiple genes with each a modest effect may be involved, 2) in a supgroup of patients extremely rare genetic variants with a large effect may be the cause of the disease, and 3) both autism and schizophrenia are heterogenic diseases; i.e. several different biological pathways may lead to the same clinical phenotype in different patients. The motivation for the the current study can be formulated in the context of these difficulties.

In adults with 22q11.2DS, the prevalence of schizophrenia is strongly elevated in comparison to the general population (respectively 20-30% versus 1% in the general population), also the incidence of autism spectrum disorder in children with 22q11.2DS is 21, 2. Vice versa, the prevalence of 22q11.2 deletions in schizophrenia patients is approximately 30 to 50%.

There are two main reasons why longitudinal studies of the psychiatric symptoms in individuals with 22q11.2DS are of particular value:
a. The 22q11.2DS population can be viewed as one of the strongest high risk groups for psychosis.
b. All 22q11.2DS individuals share a chromosomal deletion which involves the same genomic region.
c. In contrast to the high biological heterogeneity of these diseases in the general population, one can assume that in different patients with schizophrenia and 22q11DS, one and the same biological mechanism is involved.

Thus, the 22q11.2 region is one of several genomic regions associated with schizophrenia. Therefore it can be assumed that one or more genes within this region contribute to psychosis in this population which significantly reduces the number of potential candidate genes to 30 - 50. By comparison: a study of the genetic variants involved in schizophrenia in the general population needs to take intoe account ~25,000 potential risk genes.

Study objective

During the planned follow-up measurements, (T1 and T2), we anticipate that approximately 20% of the cohort will develop schizophrenia. The partition of the sample into *cases* and *controls* with respect to this diagnosis is the basis of all studies proposed in this research project.

Aim 1: The identification of early clinical predictors for schizophrenia.

Aim 2: The identification of susceptibility genetic variants for schizophrenia and autism

Aim 3: The identification of structural and functional brain abnormalities that can be correlated to a) schizophrenia development, b) autism and language abnormalities, and c) genetic variation within the 22q11.2 region.

Study design

At least four hundred individuals with a confirmed 22q11.2 deletion will be measured multiple times (T0, T1, T2 or Tx) with an interval 3 to 4 years, of which at least two hundred and fifty participants will be aged 25 years or older at time of the last assessment.
The measurements will consist of the following examinations:

- psychiatric assessment
- neuropsychological evaluation including cognitive testing and language testing
- assessment of the concentration of proline in the blood
- genotyping for specific DNA polymorphisms as well as genome wide RNA expression profiling
- neuroimaging studies, including functional and structural studies of the brain using MRI techniques.

- DNA study in the biological parents (n=400) in order to examine parent of origin of the chromosome 22 which harbors the deletion in the patient affects the psychiatric phenotype in the patient.

Study burden and risks

Except for the limited risk associated with a blood draw, there are no risks associated with the studies in this protocol. Blood withdrawal for research purposes (DNA and RNA extraction and proline measurement) does however, in principle not cause an extra invasive procedure for the study's participants. The study will take advantage of blood withdrawals that take place as part of normal clinical practice for individuals with 22q11.2DS.

For all youngster with 22q11.2DS, including those who choose not to participate in the study, a psychiatric and neuropsychologic evaluation is part of standard clinical care. Extra burden associated with the participation in the study thus

mainly pertains to the (optional) additional language study the neuro imaging (MRI) study. The MRI study is free of any risk and lasts 90 minutes per measurement, including preparation and explanation time. Also, the amount of blood withdrawn in participants is slightly higher than in those who do not participate. In addition, participants will be asked to fasten overnight (starting at 10 pm) before the morning of the blood withdrawal.

One blood draw in the biological parents of the participants will be performed, exclusively for the purpose of the scientific study.

It is noteworthy that participants and parents are free to elect which components of the study they wish, or do not wish to participate in.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- Confirmed 22q11.2 deletion
- Age range from 13th - 25th year of life (T1)
and for the DNA study in parents:
- biological parents of a youth with a confirmed 22q11.2 deletion

Exclusion criteria

For the psychiatric and genetic studies there are no exclusion criteria.;Exclusion criteria for the Imaging studies:
- Verbal IQ < 55
- Claustrophobia, no potential to lay still during the investigation
- Metal objects in or around the body that cannot be taken off (surgical clips, braces, pacemakers, piercing or others).
- Possibility for pregnancy

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-02-2002
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO Date:	12-05-2009
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-03-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2020
Application type:	Amendment
Review commission:	METC NedMec

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	NL24796.041.08