Autism: from phenotype to genotype and back

Published: 25-03-2015
Last updated: 24-04-2024

1. To identify genetic variants associated with an increased risk of ASD using different genetic models (dominant, recessive, interaction).2. To determine the relationship between different genetic variants and the associated neuropsychiatric ASD...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Developmental disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON41644

Source
ToetsingOnline

Brief title
Genes of Autism

Condition

- Developmental disorders NEC

Synonym
Autism spectrum disorders, Pervasive developmental disorders

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: Autism, Deep phenotyping, Genetic variation, Whole genome sequencing

Outcome measures

Primary outcome

(1) Non-synonymous single nucleotide changes in DNA coding sequence

(2) Copy number variants

Secondary outcome

(1) Nature and severity of autistic symptoms

(2) Nature and severity of co-morbid psychiatric symptoms

Potential confounding factors including age, gender, years and level of

education, years and level of parental education, medication use.

Study description

Background summary

ASDs are debilitating mental disorders2, characterized by defects in communication and social interaction. Together with rigidity and repetitive behaviours, these symptoms often remain manifest throughout the entire life of affected individuals3. ASD includes autism, Asperger syndrome and Pervasive Developmental Disorder, not otherwise specified (PDD-NOS). The spectrum of clinical impairment is broad, ranging from patients with mild symptoms and relatively good language skills, a.k.a. Asperger syndrome, to patients with severe symptoms often accompanied by low IQ and epilepsy. Our current understanding of the neurobiological abnormalities underlying ASD is limited; partly as a consequence, there are at present no adequate treatments available that can restore or ameliorate the core deficits that characterize this disorder.

In recent years, whole genome sequencing studies have revealed that each human individual carries a high number of genetic variants that are very rare (minor allele frequency <0.1%4) or virtually unique and that a substantial fraction of these variants has a relevant impact on protein function5.
Even though the heritability of autism is very high, i.e. 90%12, the three

largest published Genome Wide Association Studies (GWAS) so far have failed to provide convincing evidence for the role of common genetic variants in ASD13 (although the role of common variants cannot be ruled out). In contrast, an increasing number of rare variants are discovered in autism14,15,16. These rare variants have modest to relatively large effect sizes and typically occur at rates of 0.3 * 0.6% in the autistic population17. Importantly, when taken together, the risk variants known to date are estimated to explain approximately 5 * 15% of all ASD cases18.

In clinical practice three important problems stand out, against which the relevance of this proposal can be expressed:

First, an etiologic diagnosis can only be provided to a minority of ASD patients. An explanatory diagnosis is, amongst others, highly relevant with respect to prognosis, acceptance and life planning19,20. The current study aims to identify genetic variants associated with increased ASD risk. Identifying novel genetic risk variants for ASD will enhance the yield of clinical genetic testing, providing an etiological diagnosis for an increased number of ASD patients.
Second, the essential reason for the current lack of effective treatments for ASD is that the underlying biological processes are not understood. The discovery of ASD risk genes offers a unique *bottom up* approach into its biological underpinnings. Once identified, the precise functions of the encoded proteins can be further studied. This information is crucial to further our biological understanding of ASD and is needed to open new venues for the development of treatment.
Third, the heterogeneity of research findings indicates that ASD is not the consequence of one unifying etiology, but separable into different etiological subgroups21. Indeed, a pattern starts to emerge, indicating that autism risk genes may converge into a limited number of different neurobiological pathways22. However, the number of different risk-contributing genetic variants is likely to be high (~200-300)23,24,25, with only a small proportion of alleles identified so far. The lack of insight into the different ASD-subtypes is currently one of the greatest obstacles towards the development of etiology-specific treatments26. Etiological subtypes of bleeding disorders are defined based on genetic causes and require type-specific treatments. Similarly, it is likely that genetically defined subtypes exist in ASD27 which, consequently may benefit from subtype-specific treatments. The identification of causative genetic variants, the aim of this proposal, is a necessary step towards the definition of such genetic ASD-subtypes28 which in turn will allow the development of tailored treatments.

In conclusion, ASD is a group of severely handicapping mental disorders. Our current insight into the biology of autism is limited, which is a major obstacle towards the development of novel, more efficient treatment strategies. Recently, an increasing number of rare causal genetic variants for ASD have

been discovered. Although this represents a true breakthrough in our understanding of autism, these findings still represent only a small proportion of all genetic variants that are thought to contribute to ASD risk in the population. The current proposal aims to identify novel genetic ASD risk variants (first stage, core cohort study) and in the second stage studies, confirm statistical association and elucidate the associated ASD phenotype via the extended family and deep phenotyping studies respectively.

Hypotheses:
1. Novel, thus far unidentified genetic variants that are rare on the population level can contribute substantially to the vulnerability of ASD on an individual level. Such variants can be either de novo or inherited.
a. In case of a de novo variant a dominant model for genetic impact is relevant.
b. In case of inherited variants a recessive model of impact and / or interaction model involving the effect of genetic modifiers elsewhere on the genome can both be relevant.
2. Specific genetic variants may be associated with specific neuropsychiatric ASD phenotypical profiles.

Given that the essence of this study is the comparison of genetic variants between affected and unaffected individuals, the participation of ASD patients and unaffected subjects is required. Since the genetic variants that are the focus of this study are rare, or in some cases may even be unique, the analysis of family members is needed in order to establish patterns of segregation. Hence, this study can only be carried out with the participation of autistic subjects and their family members.

Study objective

1. To identify genetic variants associated with an increased risk of ASD using different genetic models (dominant, recessive, interaction).

2. To determine the relationship between different genetic variants and the associated neuropsychiatric ASD phenotype.

Study design

This study is a non-intervention study conducted in two stages. The setting of the study is the department of psychiatry at the UMC Utrecht. There is a regular flow of children who are referred to this clinic because of behavioral problems and a suspicion of the possibility of ASD. For these children a regular assessment procedure is in place which includes the use of standardized measures and the withdrawal of blood for clinically motivated genetic analyses including the standard screening for Fragile X.
The duration of this study is estimated to be eight years; given the rate of

new ASD patients in our department we expect to have recruited 40% of the core cohort in three years, this will provide sufficient data to start selection for the stage 2 studies, while continuing the completion of the stage 1 core cohort.

The first stage consists of the recruitment of a large sample (n=1000) of ASD probands and their parents through the clinic (psychiatry clinic and outpatient clinic at the University Medical Center Utrecht). With regard to the assessment (phenotyping), participation at this stage does not imply extra tests or interviews in addition to what is required for normal good clinical practice (i.e. probands who do not wish to participate in the study will undergo the same assessments). Similarly, laboratory analyses using patient blood are part of the standard clinical assessment in patients assessed for ASD in the Netherlands29. For those patients who agree to participate in the study the blood draw for clinical purposes is taken advantage of by drawing two extra tubes of blood for the purpose of the study. At stage 1 the parents will be asked to provide two tubes of blood for the purpose of the study.

All participants and their parents will be explicitly informed at the start that, provided their consent, they may be re-contacted for stage 2:
- Based on family structure (i.e. patients who have two or more second degree relatives affected by ASD) and/or severity of the ASD in the proband, approximately 150 families will be contacted and asked to participate in the stage 2 *family subsamples a,b,c*.
- Based on the genetic findings approximately 200 patients and their parents will be asked to participate in a more thorough phenotypic assessment in the stage 2 follow-up *deep phenotyping subsample*. Please note that for all participants feed-back on the findings of the genetic study is provided, since it is part of the standard clinical assessment.

Study burden and risks

Risk of participation in the core cohort (stage 1) study is negligible; the burden is minimal for participating probands, for parents small. Participation in one of the stage 2 studies does not increase any risk but requires additional efforts; however taken together the burden remains relatively small.

Total research burden is dependent on study participation; participation in the core cohort study alone represents a relatively small burden; however the burden increases when selected to participate in any of the stage 2 studies, and varies with the specific stage 2 study. In the protocol, on pages 22, 28 and 32 - 40, the research burden is summarized and detailed for each study component.

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)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

The diagnosis of ASD in the proband, according to the DSM-IV (APA 1994) or DSM-5criteria, established by an expert clinician.
Proband age between 5 and 25 years.
Availability of at least 1 biological parent

Exclusion criteria

Proband younger than 5 or older than 25 years of age.

Family members of the proband: no age exclusion criteria.
Epilepsy and/or mental retardation are not criteria for exclusion
Known genetic disorders at entry (e.g. fragile X) are not a reason for exclusion, however such conditions will be noted in the participant*s research file.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4500
Type:	Anticipated

Ethics review

Approved WMO

Date:	25-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL45866.041.13