THE GENOTYPE AND PHENOTYPE CORRELATIONS IN AUTISM SPECTRUM DISORDERS

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Objective of the study: The main objective of this study is to investigate the influence of different genetic mechanisms (risk genes, CNVs and gene expression profiles) in ASD and to study the relation between the genetic heterogeneity and specific...

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

Summary

ID

NL-OMON32673

Source
ToetsingOnline

Brief title
GPASD

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Structural brain disorders
- Developmental disorders NEC

Synonym
autism, autistic disorder

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, Correlations, Genotype, Phenotype

Outcome measures

Primary outcome

Study parameters/outcome of the study:

The parameters of the study are the genotype of common variants for ASD, possible CNVs and gene-expression patterns. The outcome measures are specific subtypes of ASD revealed by clustering of neuropsychological and behavioural symptoms as well as the severity of symptoms as measured with specific clinical instruments (questionnaires, diagnostic interview and observation-instrument and neuropsychological tasks (see chapter clinical phenotyping).

Secondary outcome

None

Study description

Background summary

Background of the study:
Autism spectrum disorders (ASD) form a heterogeneous group of neurodevelopmental disorders characterized by abnormal social interaction, abnormal communication and stereotype behavior. Autism could be seen as the core disease of the ASD and is characterized by a wide range of symptoms in those three fields, with an onset before four years of age. ASD includes autism, Asperger syndrome and Pervasive Developmental Disorder, not otherwise specified (PDD-NOS). Prevalence of autism syndrome and autism related disorders is estimated to be 1:300. The disorder is remarkably common in boys (with a male to female ratio of 4:1.) and most patients need continued intensive clinical care (60%).
The causes of ASD are highly genetic and most research findings to date are

based on studies of patients with autism and their relatives: The prevalence of autism is increased in relatives when compared to the general population (2-8% in siblings; 60-91% in monozygotic twins). Despite this large genetic contribution, finding the causes for ASD has proven challenging. This is largely due to genetic heterogeneity. This means that different genetic abnormalities may increase the risk for ASD.
The genetic data suggest that three basic genetic mechanisms are involved in autism. First, relatively rare single gene disorders (e.g. MECP2 gene in Rett Syndrome) may increase the risk for ASD. Second chromosomal abnormalities may be related to ASD (Freitag CM, 2007). Third, additive effects of several common gene variants may be involved in ASD. When one also considers the possible effects through changes in gene expression levels, the diversity in underlying mechanisms in ASD is even larger.
Chromosomal abnormalities that co-occur with ASD have been described in multiple cases (see figure-1). With the recent advances of DNA-chip technology submicroscopic chromosomal abnormalities (as small as only one or two genes) can be identified. Cytogenetic analysis has shown a relatively high occurrence of chromosomal abnormalities (5%) in ASD patients. The submicroscopic genomic deletions and duplications are often referred to as copy number variants (CNVs). CNVs can be recurrent, inherited events, or arisen de novo on paternal or maternal chromosomes. CNVs are micro deletions or micro duplications of one of the alleles of a chromosome.
The interpretation of copy number changes is complicated by the frequent occurrence of CNVs in both patients and the normal population.
which makes parental studies essential in interpreting subtelomeric copy number changes. To be able to find the relationship between genetic etiologies and phenotypic traits in ASD, we need to investigate CNVs in probands with ASD and their parents. These detection methods have demonstrated that submicroscopic losses and gains of DNA are causally related to ASD in at least 10-20% (Marshall, 2008; Sebat, 2007; Autism Genome Project Consortium, 2007).
Subtelomere FISH is recommended for the investigation of children with unexplained mental retardation (MR) and/or developmental delay (DD) with or without dysmorphic features. Another part of this study is to analyze the clinical utility of micro-array-based comparative genomic hybridization (array-CGH) in the routine diagnostic process for ASD. An array-CGH in clinical practice maximizes the identification of clinically significant chromosome abnormalities, especially subtelomeric rearrangements (CNVs) and can influence clinical diagnostic strategies (Ballif et al., 2007). An array-CGH may help in determining the etiology of a subtype of a disorder and in that way prevent further elaborate diagnostic medical interventions. Also, it leads to more knowledge on which complications (long and short-term) can be expected and lead to prevention or amelioration of these complications. Another important asset is the possibility of genetic counselling for the family members. As the usefulness of an array-CGH is clear in children with developmental delay, the utility of the technique in the routine diagnostic process for probands with ASD and their needs further exploration.
It is important to note that these rates will be even higher with the expected

advances in technology. Probably, the screening for this type of small chromosomal abnormalities will become part of diagnostics in the future. Especially in relation to the CNV studies, it is important to mention the importance of gene expression studies briefly. To be pathogenic, a (rare) CNV must change the coding sequence of a gene (haplo-insufficiency). For example, in some cases a micro deletion leads to reduced gene expression, but not always. Consequently, study of gene-expression profiles with well-described CNVs will be of great value for the study of the pathogenesis of ASD. While this is a major discovery, the genetic explanation (i.e. causality) of these findings remains ambiguous. For example, the assumption that gene-expression profiles of brain tissue can also be observed in peripheral blood. So far, genome wide gene expression (GWGE) with ASD patients has only been reported in a few studies. But the sample sizes did not allow drawing definite conclusions. Though linkage- and association studies have led to potential risk genes for ASD (see table-1, 2, 3) results didn*t show a homogeneous picture. This may be due to several confounders such as small sample sizes, but possibly also because individual ASD genes are of small effect. In addition, in only a minority of the studies replication in an independent sample has been performed. More powerful research designs such as joint analysis has only been performed in our own association study, while genome-wide association data is not yet available.
In summary, genetic studies with ASD patients gradually leads to insight into the meaning of various genetic mechanisms involved in autism.
The phenotype (including a wide range of symptoms and possibly several subgroups) as defined on the basis of a DSM-IV classification (American Psychiatric Association, 2000b) will be too limited to relate the phenotypic traits with the heterogeneity of the genotype. Genetic studies that stratified their cases into more homogeneous subgroups have been proven to be more successful. Phenotypic features that were found to be promising in genetic studies were: language related difficulties, repetitive or rigid behaviours and head circumference. Therefore phenotypic information is needed to characterize individuals with ASD and their relatives, to be able to investigate the relationship between genetic etiologies and phenotypic traits.

Study objective

Objective of the study:
The main objective of this study is to investigate the influence of different genetic mechanisms (risk genes, CNVs and gene expression profiles) in ASD and to study the relation between the genetic heterogeneity and specific clinical phenotypical traits as described in this disorder.

Study design

Study design:
All subjects will be at least 4 years of age. For basic ASD evaluation the

parents of the subjects will be asked to participate in a structured interview about the (early) development of the subject, and the subjects are asked to participate in a standardized observation to confirm the clinical diagnosis. For more detailed assessment of phenotypical characteristics, parents (or subjects if appropriate) are asked to fill out some questionnaires and to participate in a short neuropsychological assessment to measure cognitive flexibility and attention to detailed information. Neuropsychological tasks provide a more objective way to measure rigidity than self-report with a questionnaire alone and cognitive functioning might be more closely related to brain development under genetic influences than behavior in daily life situations. Lastly, subjects will be asked to provide a sample for genetic analysis, either by blood or saliva. Information from medical records will be obtained and head circumference and body length will be measured.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
There are no known risks associated with any of the proposed methodologies, and we believe the impact on subjects will be negligible. Vena puncture can be a burden, but can be replaced by the use of the saliva. Research into the genetic basis of neurobiological deficits in ASD will improve our insight into the pathophysiology of these disorders. Studies that elucidate the neurobiology of ASD will ultimately facilitate future design of new and effective ways to treat this disorder.
The evaluation of the utility of the array-CGH in ASD might lead to improvement of genetic counselling to the families of probands with ASD. It can reduce unnecessary medical procedures to unravel an etiology of ASD and lead to prevention strategies for complications for individual probands with ASD.
In concurrence with this research project, a routine medical evaluation will be performed, which is a standard procedure in our diagnostic process for ASD patients. All children are screened in collaboration with our consulting clinical geneticist on whether a more elaborate genetic work-up is necessary. If so, the patient will be referred to the diagnostic department of Medical Genetics in our hospital. The parents of these patients will receive the results of this diagnostic procedure and will receive genetic counselling.
Because neurocognitive testresults will be collected for research purposes only, parents en patients can*t be informed about the data in a diagnostic framework. If they do have any questions, they can contact one of the associated psychologist.
If a result of DNA-analysis in the research project proves to have relevance for the future health of the patient, whom has not been referred to a diagnostic genetic setting, we will refer the patient in collaboration with our consulting clinical geneticist

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

General Inclusion criteria
1) Aged at least 4 years ;Inclusion criteria for subjects with ASD
2) DSM-IV (APA, 1994) diagnosis in the autism spectrum, according to ADI-R interview and ADOS;Inclusion criteria for controls
2) No psychiatric disorders or behavioural problems as reflected by scores on the CBCL in the normal range.
3) no significant social problems as reflected by a score on the SRS in the normal range
4) No ASD in their first degree relatives.
5) IQ > 70

Exclusion criteria

Exclusion criteria
1) Major illness of the cardiovascular, the endocrine, the pulmonal or the gastrointestinal system
2) History of or present neurological disorder
3) For individuals over 12 years of age: legal incompetence, defined as the obvious inability to comprehend the information that is presented by the investigator and is outlined in the Information letter and on which the decision to participate in the study is to be based

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):	07-01-2009
Enrollment:	1600
Type:	Actual

Ethics review

Approved WMO

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	NL23938.041.08