Molecular phenotyping of MCA/ID patients to improve diagnosis

Published: 17-02-2016
Last updated: 19-04-2024

- Using "Molecular Phenotyping" to increase diagnosis rate of MCA/ID patients with complex SV's- Discovery of pathogenic mechanisms and novel disease-associated genes in MCA/ID patients.With "molecular phenotyping" we will...

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

Summary

ID

NL-OMON45939

Source
ToetsingOnline

Brief title
Molecular phenotyping of MCA/ID patients

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Congenital abnormalities, intellectual disability

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: NWO Vici aan prof. E.Cuppen

Intervention

Keyword: ATAC-Seq, ChIP-Seq, RNA-Seq, Structural variation, WGS

Outcome measures

Primary outcome

This study will generate a genomics dataset from patient-parent trios at the DNA, RNA and epigenome level. These data will help to better diagnose this group of patients. Therefore, results from this study can help in the routine diagnostic care of this patient group. These results will then be shared with the clinical geneticists involved in this study through routine care mechanisms.

Secondary outcome

The results from this study could also generate new genes and/or mechanisms that are important in the etiology of MCA/ID as a syndrome.

Study description

Background summary

Many patients with Multiple Congenital Abnormalities and Intellectual Disability (MCA/ID) remain undiagnosed in the current clinical setting. MCA/ID patients often have complex structural genome variation as a pathogenic cause. Is has been shown that MCA/ID patients have a high burden of genomic imbalance through Copy Number Variations (CNVs) (Girirajan et al. Plos Genetics 2011). However, structural variation can also be balanced and these cases cannot be detected using standard arrayCGH and WES methods (Gilissen et al., Nature 2014). In addition, it is difficult to reliably identify pathogenic mechanisms in these patients since there are many genes involved in these complex structural variation cases. Genomic rearrangements can lead to misexpression of certain genes or can lead to changes in the non-coding portion of the genome (e.g. Promoters/enhancers, see van Heesch et al., Cell Reports 2014). The current diagnostic pipeline does not generate or support this type of data analysis. Using an data-integrative approach consisting of Whole-Genome

Sequencing, RNA-Seq and ChIP-Seq we hope to increase the diagnosis rate of MCA/ID patients with complex SV and identify pathogenic mechanisms in this patient group.

Study objective

- Using "Molecular Phenotyping" to increase diagnosis rate of MCA/ID patients with complex SV's

- Discovery of pathogenic mechanisms and novel disease-associated genes in MCA/ID patients.

With "molecular phenotyping" we will use a combination of Whole-Genome Sequencing, RNA-Seq and ChIP-Seq/ATAC-Seq to better identify pathogenic mechanisms and increase diagnosis of the MCA/ID patient group. Trio-based WGS will be used to better identify genome variation in these patients. RNA-Seq will allow us to look for gene-expression changes on a genome-wide level between parents and patient. ChIP-Seq and ATAC-Seq for chromatin conformation capture (e.g.active enhancers) will allow us to chart the changes in the epigenomic landscape of promoters and enhancers between patient and parents. This integrative "Multi-Omics" data gathering approach will allow us to better zoom in on candidate pathogenic regions in this patientgroup, hence contributing to both an increased diagnosis rate and the etiology of MCA/ID.

Study design

- Selection of MCA/ID patients without clear diagnosis through the regular diagnostic pipeline from the division of Medical Genetics UMCU (also see Study population section below).
- 6 ml peripheral blood sampling from patient and 20 ml of the parents.
- Isolation of PMBCs from blood for DNA, RNA and ChIP-Seq/ATAC-Seq.
- DNA isolation and Next Generation of Whole-Genome Sequencing on Illumina X10 platform.
- mRNA isolation (polyA-enriched mRNA) and RNA-sequencing on Illumina NextSeq platform (Utrecht Sequencing Facility).
- Chromatin isolation and immunoprecipitation for H3K4me3 (active promoters) and H3K27ac (active enhancers), ChIP-Seq of Chromatin-bound DNA on NextSeq platform.
- Data mapping and analysis in collaboration with the Bioinformatics team of the Cuppen group (Dr. Ies Nijman, Dr. Joep de Ligt, Sander Boymans)
- Identification of possible pathogenic events from this integrated genomic landscape dataset
- Reporting of findings in peer-reviewed journals. In specific cases: communication of results to the diagnostic team of clinical Genetics if the findings aid diagnosis.

Study burden and risks

The only invasive procedure will be a venapuction for peripheral blood. The risk of this routine procedure is minimal. See section E for more details.

Contacts

Public
Universitair Medisch Centrum Utrecht

Universiteitsweg 100
Utrecht 3584 CG
NL
Scientific
Universitair Medisch Centrum Utrecht

Universiteitsweg 100
Utrecht 3584 CG
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

* Patient has MCA/ID and is already in the diagnostic clinical genetic circuit at the UMCU.
* Patient lack a diagnosis from regular diagnostic testing (aCGH, WES)

* Both parents are available for blood sampling
* Parents have to give consent for the patient

Exclusion criteria

* One or both Parents do not give consent
* MCA/ID patient carries a recurrent/described SV with a causal variant (i.e. patient has a diagnosis: only undiagnosed MCA/ID patients will be included in this cohort).
* One or more of the parents is not available for blood sampling
* Patients are younger than 2 years of age
* Blood sampling is not possible from the patient for medical reasons

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2016
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO

Date:	17-02-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	03-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-08-2017
Application type:	Amendment
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	NL55260.041.15

Study results

Date completed:	19-04-2018
Actual enrolment:	110