Uncovering molecular mechanisms and neuronal pathways involved in SETBP1 disorder using human cell culture models

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Our research aims to establish informative tools in the laboratory for studying the molecular and cellular pathways that are altered in SETBP1 disorder.

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

Summary

ID

NL-OMON48020

Source
ToetsingOnline

Brief title
The SETBP1 molecular study

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Mental impairment disorders

Synonym
neurodevelopmental disorder, SETBP1 disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Max Planck Society;Germany; SETBP1 Society;USA

Intervention

Keyword: de novo mutations, neurodevelopmental disorders, SETBP1 disorder, speech impairments

Outcome measures

Primary outcome

* To identify differences in cellular morphologies between human iPSCs and

iPSC-neuronal models derived from samples obtained from SETBP1 patients and

controls.

* To identify alterations in gene expression and chromatin accessibility

* To categorise genes that show alterations in gene expression and chromatin

accessibility into biological pathways with gene ontology tools

Secondary outcome

Not applicable

Study description

Background summary

Haploinsufficiency of the SETBP1 gene causes a neurodevelopmental syndrome involving expressive speech impairment and mild-moderate developmental delay. The precise functions of SETBP1, encoding the SET-binding protein 1, are yet to be discovered. Therefore, the molecular mechanisms or neuronal pathways by which rare loss-of-function SETBP1 mutations lead to disorder remain largely unknown. For neurodevelopmental disorders, relevant tissues (brain tissues) and cell types (neurons) are difficult to obtain. Therefore, patient-derived induced pluripotent stem cells (iPSCs) that can be differentiated into any cell lineage provide an important model system. For this purpose, we will use patient-derived cells including blood lymphocytes and skin fibroblasts to establish iPSCs. Disease-relevant neuronal models will be established from these iPSCs in the laboratory for studying the molecular mechanisms and neural pathways that go awry in SETBP1 disorder.

Study objective

Our research aims to establish informative tools in the laboratory for studying the molecular and cellular pathways that are altered in SETBP1 disorder.

Study design

This study is a laboratory-based study using cell-culture models derived from SETBP1 patient fibroblasts and peripheral blood mononuclear cells (PBMCs). Subjects with SETBP1 disorder and healthy human donors who give written informed consent will undergo skin biopsy and blood sampling. The collected tissue samples will be used to generate iPSCs according to standard procedures, which will be subsequently differentiated into particular neuronal subtypes e.g. cortical neurons using established protocols. Functional analyses using transcriptomic/epigenetic approaches and morphological characterisation will be performed to identify alternations in gene expression, chromatin remodeling and cellular morphologies between patient- and control-derived iPSC models.

Study burden and risks

There are no risks associated with participation. The burden for patients will be small, and the study can only be done using this patient group as SETBP1 disorder is rare. At this stage, virtually nothing is known about the molecular mechanisms or neuronal pathways by which rare loss-of-function variants of SETBP1 lead to disorder. Therefore, we aim to establish informative cell-culture models in the laboratory for studying the fundamental neuronal mechanisms that go awry in SETBP1 disorder. Results from our study may help towards future therapeutic development for the disorder.

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

The subjects must carry a de novo pathogenic variant in the SETBP1 gene, where properties and functions of the encoded protein are likely to be affected; and display neurodevelopmental phenotypes

Exclusion criteria

Subjects with another (possibly) pathogenic variant (CNV, SNV) that might contribute to the neurodevelopmental phenotype

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:	Recruiting
Start date (anticipated):	12-10-2020
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	08-10-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL69164.091.19