Collection of biomaterial for iPSCs to study the molecular mechanisms underlying Witteveen-Kolk syndrome

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We aim to collect skin and blood cells from two to three WitKoS patients, reprogram these cells into iPSCs and use the iPSCs for differentiation into neurons/neural organoids to study the molecular underpinnings of WitKoS.

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

Summary

ID

NL-OMON53284

Source
ToetsingOnline

Brief title
WitKoS molecular study

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Witteveen-Kolk syndrome; SIN3A syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: NWO NWA research along routes of consortia

Intervention

Keyword: Brain development, Molecular mechanisms, Neurodevelopmental disorder, Witteveen-Kolk Syndrome

Outcome measures

Primary outcome

The main study parameter is the differences in cell morphology, tissue

architecture, transcriptomic profile and cellular function between patient and

healthy control derived organoids.

Secondary outcome

- Study the effect of medication on WitKoS patient-derived iPSC based models.

- Study whether iPSCs derived from blood will form neural organoids equally

well compared to organoids from skin cell derived iPSC lines.

Study description

Background summary

Witteveen-Kolk syndrome (WitKoS), a neurodevelopmental disorder (NDD), is caused by mutations in the SIN3A gene. The underlying mechanism by which mutations in SIN3A cause abnormalities in brain development and result in NDD is poorly understood. Induced pluripotent stem cells (iPSCs), derived from patients* biomaterial, provide us with a unique opportunity to study the underlying molecular mechanisms in relevant human cell types, such as neurons or neural tissue. Advancing the molecular understanding of WitKoS is required to understand disease variability and to be able to develop syndrome-specific therapies in the future.

Study objective

We aim to collect skin and blood cells from two to three WitKoS patients, reprogram these cells into iPSCs and use the iPSCs for differentiation into neurons/neural organoids to study the molecular underpinnings of WitKoS.

Study design

Laboratory study, using patient-specific skin cells and blood for the generation of iPSCs and subsequently for neurons/neural organoids

Study burden and risks

This study can only be carried out in individuals with neurodevelopmental problems (NDD), since SIN3A causes NDD when mutated. WitKoS is very rare and generally only diagnosed in individuals that are young and/or have neurocognitive problems. Therefore including subjects with NDD is inherent to the study question. The results of this study will contribute to an increase in knowledge and understanding of the underlying mechanisms in WitKoS. Subjects will be asked to give a one-time blood sample (2x10ml) - which can result in pain at the site of venapuncture and/ or hematoma - and a skin biopsy - which can leave a small scar. The collection of these materials for the generation of iPSCs and their subsequent use for neuronal cell culture models has a minimal risk for adverse events and/or unsolicited findings, which will be clearly communicated to the participants in the recruitment phase

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Written informed consent to participate in this study
- Having a (likely) pathogenic variant in SIN3A
- Clinical diagnosis of WitKoS as judged by the principal investigator
- Age >= 18 years

Exclusion criteria

- Subjects who do not meet the inclusion criteria
- Subjects with another genetic variant (e.g. copy number variation, single nucleotide variant) that most likely contributes 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):	31-10-2023
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	08-08-2023
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	NL83902.091.23