Collection of biomaterial for iPSCs to study the molecular mechanisms underlying monogenic epilepsies

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Ethical review	Approved WMO
Status	Pending
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational non invasive

Summary

ID

NL-OMON57349

Source
ToetsingOnline

Brief title
Epilepsy disease modelling study

Condition

- Congenital and hereditary disorders NEC
- Encephalopathies

Synonym
Monogenic epilepsy, seizures

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW,EpilepsieNL

Intervention

Keyword: Cerebral organoids, iNeurons, iPSCs, Monogenic epilepsy

Outcome measures

Primary outcome

The main study parameter is the differences in tissue architecture, cellular function and MEA phenotypes, including baseline phenotypes and responses to ASMs or other treatments, between patient and healthy control neurons/neuronal organoids.

Secondary outcome

n.v.t.

Study description

Background summary

Monogenic variants can be found in up to 40% of people with a rare and complex epilepsy. A significant portion of monogenic epilepsies include channelopathies, where a pathogenic variant can result in a gain or loss of function of voltage- or ligand-gated ion channels leading to a variety of phenotypes. An example of such a monogenic epilepsy is caused by pathogenic variants in SCN1A, which is associated with a range of epileptic disorders, including Dravet syndrome (DS), generalised epilepsy with febrile seizures plus (GEFS+) and febrile seizures (FS). Approximately 30% of epilepsies are highly drug resistant, and there is an unmet need for tolerable and effective treatments that reduce seizure frequency and improve quality of life. Induced pluripotent stem cells (iPSCs), derived from patients* biomaterial, provide us with a unique opportunity to study the neurological diseases in relevant human cell types. iPSCs can be generated into model systems of varying complexities, from very simple cultures containing only one cell type to neuronal organoid structures that are able to self-organise into a brain-like structure. For epilepsies, we currently do not know how relevant the different model systems are in terms of face and predictive validity. Therefore, a major challenge in using iPSC-derived models for translational purpose is to identify model systems that show high face and predictive validity while being as simple,

robust, cheap, and scalable as possible.

Study objective

We aim to collect blood cells from 40 patients with monogenic epilepsy, with a preference for patients with a pathogenic variant in SCN1A, reprogram these cells into iPSCs and use these iPSCs for differentiation into neurons and neuronal organoids to study the relevance of these models for future testing of antiseizure medications (ASMs).

Study design

Laboratory study, using patient-specific blood for the generation of iPSCs and neurons/neuronal organoids. These models will be grown on micro electrode arrays (MEAs) and exposed to ASMs, including cannabidiol (CBD), and other possible precision treatments, to test the relevance of the model systems.

Study burden and risks

This study will only be carried out in individuals with a monogenic epilepsy with variable phenotypes and treatment response, for example, variants in SCN1A, CDH2, TSC2, RHEB and MTOR. Rare and complex epilepsies are mostly diagnosed in individuals that are young and/or mentally incapacitated. 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 epilepsy.
Subjects will be asked to give a one-time blood sample (2x5mL for individuals with an age of 4 years or older, for between the age of 2 and 4 years old this will be reduced to 1x 5mL), which can result in pain at the site of venepuncture and/ or hematoma. The collection of blood cells for the generation of iPSCs and their subsequent use for neuronal cell culture models does not give risk for adverse events and/or unsolicited findings, which will be clearly communicated to the participants in the recruitment phase. The methods used for the collection of patient material are classified as *procedures with minimal risk and burden* according to the guideline *Toetsing van Onderzoek met Minderjarige proefpersonen*.

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)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Written informed consent (IC) to participate in this study

Having a (likely) pathogenic variant in an epilepsy gene, such as SCN1A, CHD2, TSC2, RHEB, or MTOR, where properties and functions of the encoded protein are likely to be affected resulting in an epilepsy syndrome.

Medication use (including both patients with seizure-freedom following medication and patients with drug resistant epilepsy, and responders and non-responders from the CBD study)

Exclusion criteria

Subjects who do not meet the inclusion criteria

Subjects with epilepsy that does not have a monogenic cause

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2024
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	11-03-2025
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	NL86514.091.24