DiViNAS-II study (Disease Variability in NOTCH3 Associated Small vessel disease - a two year follow-up study): A study investigating phenotype, progression, biomarkers and disease modifiers of CADASIL and CADASIL-like hereditary cerebral small vessel diseases.

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Aim and objectivesThe overall aim of DiViNAS-II is to determine the impact of genotype on 2-year disease progression, to discover other disease modifiers and to identify disease monitoring biomarkers in CADASIL. Primary objectives1. To determine…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON52119

Source
ToetsingOnline

Brief title
DiViNAS-II study

Condition

- Central nervous system vascular disorders

Synonym
NOTCH3-associated small vessel disease

Research involving
Human

Sponsors and support

Primary sponsor: Klinische Genetica
Source(s) of monetary or material Support: ZonMw Vidi

Intervention

Keyword: CADASIL, Disease modifiers, Mutation position, Surrogate markers

Outcome measures

Primary outcome

The occurrence and frequency of CADASIL-associated symptoms in the DiViNAS-II cohort will be assessed over the preceding 2 years (the duration of follow-up) and compared to data gathered in the DiViNAS-I study. In the case of new patients (either with rare CADASIL-like hereditary SVD or new CADASIL patients), all associated symptoms will be assessed over the entirety of the participant*s lifespan.

Clinical end-points/parameters:

- Number of strokes (and age at first stroke) during the 2 year follow-up period (or in the case of rare CADASIL-like hereditary SVD the other associated symptoms will be assessed over the entire lifespan)

- Score on disability scale (mRS)

- Scores on psychometric testing (TMT-A/B, Stroop)

- Death

Neuroimaging:

- White matter hyperintensity volume (WMHv)

- Lacune count and lacune volume

- Cerebral atrophy

Secondary outcome

Clinical end-points/parameters

TIA*s, migraines with- or without aura and other symptoms associated with CADASIL during the 2 year follow-up period (or in the case of rare CADASIL-like hereditary SVD the other associated symptoms will be assessed over the entire lifespan)

Neuroimaging:

- ASL

- DTI

- Microbleed count

- Enlarged perivascular space count

Vessel wall pathology markers (in skin biopsy):

- NOTCH3 score [12]

- GOM classification [7]

Fluid biomarkers in serum and/or CSF (validation and discovery):

- Neurofilament light chain

- NOTCH3

- Vascular panels using commercial platforms e.g. O-link (https://www.olink.com)

Retinal OCT(-A) measures:

- Thickness of the Retinal Nerve Fiber Layer (RNFL)

- Subfoveal Choroidal Thickness (SFCT)

- Vessel density of the Deep Retinal Plexus (DRP)

- Retinal vessel wall thickness

- Arteriolar-to-venular diameter ratio (AVR)

- Retinal perfusion measures

Other study parameters include age, gender, level of education, current medical conditions and relevant medical history, medication, and cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus type 2, daily intake alcohol/drugs, smoking, physical exercise, BMI).

Study description

Background summary

CADASIL is a hereditary cerebral small vessel disease (SVD) that is caused by characteristic cysteine altering mutations in the NOTCH3-gene, leading to mid-adult onset ischemic strokes and vascular dementia. In the past four years, the CADASIL research group of the LUMC has shown that NOTCH3 variants located in epidermal growth-factor like repeat (EGFr) domains 1-6 of the NOTCH3 protein are associated with a more severe SVD phenotype than NOTCH3 variants located in EGFr domains 7-34. To further study the impact of NOTCH3 mutation position on disease severity, the DiViNAS-I baseline study was performed at LUMC between May 2019 and December 2020 (CME P18.164). Approximately 200 individuals with a NOTCH3 mutation participated in DiViNAS, of which approximately half have a mutation located in one of EGFr domains 1-6 and half in one of EGFr domains 7-34. Participants were fully characterized (including medical history, neuroimaging, neuropsychological test battery, skin vessel abnormalities). Our preliminary analysis of DiViNAS-I data validates our hypothesis that the NOTCH3 mutation position is associated with disease severity. Moreover, we find a novel association between NOTCH3 mutation position and CADASIL vessel wall

abnormalities, which may shed light on the molecular mechanism underlying the NOTCH3 mutation position effect.
In order to study the effect of NOTCH3 mutation position on disease progression, we aim to now perform a 2-year follow-up study of the DiViNAS-I cohort, in order to improve personalized disease prediction, identify potential disease monitoring biomarkers and discover new (genetic) disease modifiers.
DiViNAS-I and DiViNAS-II are the first prospective studies world-wide assessing the impact of NOTCH3 mutation position on disease severity and disease progression in a cohort of CADASIL patients.
The main aims of DiViNAS-II are i) to study differences in 2-year disease progression between mild and severe genotypes, ii) to identify other major environmental or genetic disease modifiers and iii) to identify (early-disease stage) biomarkers. Secondary aims are comparing CADASIL to novel CADASIL-like small vessel diseases such as CADASIL type 2 and CARASAL, as well as identifying the underlying genetic cause in families with hereditary SVD of unknown etiology (hSVD-u).

Study objective

Aim and objectives
The overall aim of DiViNAS-II is to determine the impact of genotype on 2-year disease progression, to discover other disease modifiers and to identify disease monitoring biomarkers in CADASIL.

Primary objectives
1. To determine differences in 2 year disease progression between patients with NOTCH3 EGFr 1-6 mutations versus 7-34 mutations.
2. To identify biomarkers which are suitable surrogates for monitoring disease progression (e.g. neuroimaging markers, NOTCH3-score and ultrastructural analysis of skin vessels, fluid biomarker levels, retinal abnormalities etc.)
3. To identify additional disease modifiers, using a novel and improved approach by stratifying study participants according to their genotype.

Secondary objectives
1. To create a baseline cohort of patients and families with CADASIL-like hereditary SVDs, such as Cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL), Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), CADASIL type 2 and families with hereditary SVD with unknown genetic cause (hSVD-u).
2. To acquire hiPSCs for in vitro modelling of rare hereditary small vessel diseases, especially to investigate the molecular mechanisms underlying similarities and differences (in collaboration with Prof. Dr. W.M.C. van Roon-Mom from the Department of Human Genetics and Dr. Valeria Orlova from the Department of Anatomy and Embryology). These hiPSCs will be stored in the LUMC Biobank.

Study design

This is a non-intervention 2 year follow-up study including up to circa 200 individuals with cysteine altering NOTCH3 mutations (CADASIL), recruited from participants from the baseline DiViNAS-cohort at LUMC (CME P18.164), who have indicated that they want to be informed about follow-up studies of DiViNAS. An additional small number of individuals (up to max n = 50) with other CADASIL-like hereditary cerebral small vessel diseases and their family members will be asked to participate in DiViNAS-II.
The DiViNAS-II study will be performed at the Leiden University Medical Center (LUMC) at the Department of Clinical Genetics, in collaboration with Radiology (MRI), Neurosurgery (Lumbar puncture), Dermatology and Pathology (Skin biopsy), Ophthalmology (OCT), Neurology and Psychiatry (Neuropsychological test battery and psychiatric inventories). We aim to start the study in May 2021 and complete the study inclusion 1.5 years later in November 2022.
The DiViNAS-II study protocol will be largely identical to the study protocol of DiViNAS-I to ensure compatibility of data (neuroimaging protocol, neuropsychological test battery, interim medical records, skin biopsies, blood withdrawal). In addition, to enable maximum potential for biomarker discovery, a subgroup of individuals with CADASIL will be asked to consent to a lumbar puncture for obtaining CSF and all individuals will be asked to consent to retinal imaging. CSF and retinal measurements will therefore be new baseline measures in DiViNAS-II and will be studied cross-sectionally and serve as novel baseline measures for future follow-up studies.
Pre-defined disease outcome measures (e.g. clinical, neuroimaging, fluid biomarker, (semi-) quantification of skin vessel pathology) will be used to determine 2-year disease progression
Biomarkers identified as promising in DiViNAS, in other LUMC clinical CADASIL studies or in the medical literature will be selected for further study in DiViNAS-II and correlation with disease progression will be assessed. Examples of promising biomarkers are NfL in serum or CSF [10, 26] and neuroimaging markers such as DTI [16]. We also have recently discovered a novel skin vessel biomarker which associates with genotype (manuscript in preparation), which we aim to further assess and validate in DiViNAS-I and DiViNAS-II. Next to assessment of selected biomarkers, there will also be biomarker discovery studies, for example in serum and CSF using biomarker discovery technology platforms such as O-Link. We will also introduce new baseline measures for the study of biomarkers in cerebrospinal fluid and the retina (optical coherence tomography (OCT) and optical coherence tomography-angiography (OCT-A)), as well as introducing new participants with (rare) CADASIL-like hereditary small vessel diseases.
hiPSCs will be generated from a maximum of 10 patients with a rare hereditary cerebral small vessel disease seen in this study.

Study burden and risks

The burden and potential risks of this study are moderate. All examinations will take place in the LUMC during a single visit of maximally 7 hours, including breaks. Prior to the examination day, patients will be asked to fill in questionnaires. During the day the patients will undergo two 4mm punch skin biopsies, blood withdrawal (maximum of 70 ml), neuropsychological testing, optical coherence tomography of the retina, an MRI-scan and in a subgroup also a lumbar puncture.

MRI risks
The risks of MRI are minimal and may include movement of paramagnetic objects in the body and claustrophobia. Prior to the procedure, patients will be screened by a physician for the identification of MRI contra-indications. The MRI-procedure will be described in great detail to reduce possible stress experienced by the participant. Patients may stop the scanning procedure at any given time.

Skin biopsy risks
In rare cases, skin biopsies may lead to site infection or post-procedure bleeding. This risk is minimalized by disinfecting the site prior to the procedure and observing the biopsy site for excessive bleeding afterwards.

Neuropsychological testing burden
A potential risk of neuropsychological testing is temporary psychological distress and fatigue during and after the examination.

OCT/OCT-A risks
The examinations will be performed without dilation of the pupil. There are no health risks associated with OCT and OCT-A without pupil dilatation.

Lumbar puncture
A subgroup of patients will also undergo a lumbar puncture. A lumbar puncture is a relatively safe procedure, but complications may arise and most commonly include post-LP headache, back pain and minor neurologic symptoms such as radicular pain and numbness. Rare complications include infection, bleeding and cerebral herniation in patients with intracranial tissue displacement or possible raised intracranial pressure. To minimize the risks of lumbar puncture, the patient, together with the researcher, will fill in a questionnaire prior to the research day over the telephone to exclude the presence of any contra-indications in addition to screening of the medical history and medication list by the study physician. On the study site, the study physician will additionally screen the patient with blood work-up. The procedure will be performed by an experienced consultant Neurosurgeon or senior Neurosurgery resident.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For all participants in DiViNAS-II, the following inclusion criteria apply:
o Is 20 years of age or older.
o Is able to travel to the LUMC.
o Is able to give informed consent.
o Has participated in DiViNAS-I and/or has visited the CADASIL/CHA-clinic at the LUMC and/or has been recruited via a family member who has visited the LUMC.

For the study sub-populations, there are additional inclusion criteria, as listed below:
1) DiViNAS-II CADASIL cohort
o Has a confirmed NOTCH3 cysteine altering variant.

2) CADASIL-CSF cohort
o Has a cysteine altering variant in exon 4 (EGFr 1-6) of the NOTCH3 gene

3) CADASIL-like hereditary-SVD cohort:
o Has, or is a family member of a patient with, a pathogenic or likely pathogenic variant in one of the following hereditary SVD genes: CTSA or HTRA1
OR
o Has, or is a family member of a patient with, a cerebral small vessel disease with unknown genetic aetiology with clear Mendelian inheritance in the pedigree, defined as follows: has clinical and neuroimaging features highly indicative of cerebral SVD, and has at least two affected family members, of whom the index patient and at least one first- or second degree family member have already had extensive clinical and genetic work-up at the CHA- clinic of the LUMC.

Exclusion criteria

- Contra-indications for MRI-scan
• Claustrophobia
• Pacemakers and defibrillators
• Nerve stimulators
• Intracranial clips
• Intraorbital or intraocular metallic fragments
• Cochlear implants
• Ferromagnetic implants
• Hydrocephalus pump
• Intra-uterine device (not all types)
• Permanent make-up
• Tattoos above the shoulders (only those older than 20 years)

In CADASIL-CSF subgroup:
1. Contra-indications for lumbar puncture:
• Known or possible raised intracranial pressure (ICP) with risk for cerebral herniation or intracranial tissue displacement (either clinically or as observed on MRI scan)
• Occlusion of spinal canal
• Thrombocytopenia or other bleeding diathesis including ongoing anticoagulant therapy
• Local infection of the skin or suspected spinal epidural abscess
• Lumbar neural tube defects

2. Presence of central nervous system disease other than CADASIL

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-06-2021
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO

Date:	04-05-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	15-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	14-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	NL75697.058.20