Rate of Progression of PCDH15-Related Retinal Degeneration in Usher Syndrome 1F (RUSH1F)

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1. To report the natural history of retinal degenaration in patients with biallelic mutations in the PCDH15 gene.2. To identify sensitive structural and functional outcome measures to use for future multicenter clinical trials in PCDH15-related...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Eye disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON50300

Source
ToetsingOnline

Brief title
RUSH1F

Condition

- Eye disorders congenital
- Congenital eye disorders (excl glaucoma)

Synonym
retinal degeneration, Retinal dystrophy, retinitis pigmentosa

Research involving
Human

Sponsors and support

Primary sponsor: JAEB Center for Health Research
Source(s) of monetary or material Support: Foundation Fighting Blindness

Intervention

Keyword: natural history, PCDH15 mutation, Usher Syndrome 1F

Outcome measures

Primary outcome

Visual field sensitivity measured by static perimetry, best corrected visual acuity, mean retinal sensitivity as measured by fundus guided microperimetry, ellipsoid zone area as measured by spectral-domain optical coherence tomography, retinal function using timing in response to rod- and cone-specific stimuli.

Secondary outcome

n/a

Study description

Background summary

USH1F is a subtype of USH1 caused by bi-allelic mutations of the USH1F gene, also called protocadherin 15 (PCDH15). It is assumed that PCDH15 might have a role in the morphogenesis and cohesion of stereocilia bundles and retinal photoreceptor cell maintenance or function. Protocadherin 15 deficiency leads to functionally impaired cones and rods with abnormally shaped outer segments. The current knowledge about the natural course of USH1F is limited, as no systematic observational trials of the retinal phenotype have been published. The phenotype and fast time course of the retinal degeneration in USH1F is comparable with the phenotype of USH1 in general, which is characterized by profound pre-lingual deafness, vestibular ataxia, and childhood onset of retinitis pigmentosa.
Gene-based therapies such as dual-vectors, gene editing or mini genes, and suppression of several PCDH15 mutations by aminoglycosides have been examined. Aminoglycosides can influence the translation of mRNA into protein by inhibiting ribosomal proofreading, thus, leading to read-through of nonsense mutations. A partial read-through of PCDH15 nonsense mutations leading to various levels of the full-length protein was shown by aminoglycosides in vitro and ex vivo. However, more preclinical and clinical research is needed to

determine whether these approaches can restore vision in patients with USH1F or slow down the degeneration process leading to blindness.

Study objective

1. To report the natural history of retinal degenaration in patients with biallelic mutations in the PCDH15 gene.
2. To identify sensitive structural and functional outcome measures to use for future multicenter clinical trials in PCDH15-related retinal degeneration.
3. To identify well-defined subpopulations for future clinical trials of investigative treatments for PCDH15-related retinal degeneration

Study design

This study is designed as a multicenter longitudinal, prospective natural history study. Patients will be defined to 2 cohorts based on their visual acuity and kinetic visual field.

Study burden and risks

We anticipate that study enrollment will be representative of the population of patients with biallelic mutations in the PCDH15 gene.
Participants do not benefit, risks are considered negligible, procedures are non-invasive and take 3 to 6 hours extra time from patient per visit, one visit per year. lt is anticipated that, in the future, patients with PCDH15-related retinal degeneration will benefit from newly developed therapeutic strategies.

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)

Inclusion criteria

1. Willing and be able to complete the informed consent process, by patient self of parents in case of minors
2. Ability to return for all study visits over 48 months if in the natural history study
3. Age 8 years and older
4. Have retinal dystrophy caused by mutations in the PCDH15 gene, as identified by a clinically certified lab

Exclusion criteria

1. Have other mutations in your DNA that could cause retinal degeneration
2. be planning to enter a study, testing treatments for retinal degeneration during the time of this study
3. have a history of treatment that could have affected the retina
4. Have had certain eye surgeries that may affect the tests for this study

Study design

Design

Study type: Observational non invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-03-2022
Enrollment:	2
Type:	Actual

Ethics review

Approved WMO

Date:	23-02-2022
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
ClinicalTrials.gov	NCT04765345
CCMO	NL78682.091.21