Universal Rare Gene Study: A Registry and Natural History
Study of Retinal Dystrophies Associated with Rare Disease-Causing Genetic Variants

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

Summary

ID

NL-OMON56829

Source
ToetsingOnline

Brief title
Uni-Rare

Condition

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

Synonym
genetic eye disease, retinal dystrphy

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: diseasecausing genetic variants, inherited retinal diseases, rare, retinal dystrophies

Outcome measures

Primary outcome

The list of candidate endpoints to measure and understand IRD progression is vast. Visual function outcomes, such as visual acuity (VA), contrast sensitivity, color vision, microperimetry (MP), full-field stimulus threshold (FST) and full-field electroretinogram (ffERG), measure performance of the components of the visual system in the clinical environment and represent the measures of what is clinically meaningful. Structural or anatomical measures, such as fundus autofluorescence (FAF) and optical coherence tomography (OCT), represent candidate biomarkers or surrogate endpoints that hold the potential to predict clinical benefit. Structural measures are an expanding area of IRD research due to new technologies and better imaging acquisition and interpretation techniques and is an area of priority identified by gap analyses.

Secondary outcome

Functional vision measures, which are designed to reflect real-life challenges in daily activities, include patient-reported outcomes. Although a variety of tools exist, little is known about their applicability within each genotype.

Study description

Background summary

Inherited retinal degenerations (IRDs) affect approximately 2 to 3 million people worldwide.The rise of promising treatment approaches has increased rapidly in recent years, include gene editing and augmentation (early-stage disease), neuroprotection (mid-stage disease), prosthetics, optogenetics, and cell therapy to restore some light sensation (late-stage disease). Despite advancements in therapy development, and a growing number of interventional trials (https://www.clinicaltrials.gov/) for IRDs, there remain significant hurdles to designing trials and moving therapy through the development process. Several papers have reviewed unmet needs and identified top priorities to move the promise of treatment forward amongst a complex landscape of IRD research. The common theme among the recommendations is the vital need for natural history studies, the foundational basis for trial design and drug development.

Study objective

IRDs are genetically diverse (280 causative genes have been identified to date) (https://sph.uth.edu/retnet/) and have vastly different clinical manifestations, including age of onset, severity of disease, rate of progression, and structural and functional abnormalities. Understanding this phenotypic heterogeneity is a major challenge for potential therapy developers. It is critical to identify genetic factors impacting disease severity and progression, including the impact of mutation-specific variations within genes. Natural history data, both longitudinal and cross-sectional, within each gene population is needed to understand these differences, and ideally these studies would include enough cases to evaluate a variety of subgroups across genetic, phenotypic, and environmental factors. The cornerstone of good trial design is a good endpoint. Identifying the best candidate endpoint for evaluating progression of disease, and ultimately treatment effects in a trial, requires consideration of many properties. These include sensitivity, reproducibility, correlation with other measures of disease progression, how much within-person change is beyond measurement variability, and whether within-person change is clinically meaningful. For a given treatment, the best measure also depends on the expected benefit; restoration of vision versus slowing of progression. Since IRDs are genetically diverse, understanding these properties within each gene is important.

Study design

Individual natural history studies for each rare RD gene are not feasible. Many

centers have as few as one (1) - two (2) patients for a particular RD gene and may not be able to devote resources needed to implement each study. Individual studies also require considerable startup time (e.g., contracts, IRB/Ethics Committee approvals) and study management expenses regardless of the number of patients. A single, universal protocol under which all rare RD genes may be enrolled would address these inefficiencies. Because of the vast phenotypic diversity, simultaneous open enrollment of all rare RD genes directly into a longitudinal natural history study is problematic. Unfocused enrollment efforts spread across hundreds of genes will dilute timelines for data collection and analysis objectives within targeted genes. A solution is to create a universal registry open to all rare RD genes, to cross-sectionally characterize patients within all rare RD genes (mild, moderate, and severe vision loss) so they are ready to be enrolled into a subsequent universal longitudinal natural history study as their gene is selected. This two-phase platform will (1) eliminate repetitive processes like certification, training, regulatory approval, contract agreements, (2) reduce costs and accelerate timelines for longitudinal studies and (3) leverage a large sample size and standardized data collection in the cross-sectional study to explore the extent to which genes with common mechanisms of disease have similar clinical manifestations (e.g., determine if and how some genes may be pooled in some analyses).

Study burden and risks

Known Potential Risks
Most examination procedures are considered part of standard care for retinal degenerations. This study will be capturing some information about participants that include identifiable, personal information, like date of birth (will be collected if permitted by site*s regulatory bodies). The study has procedures in place to protect that information. However, there is a chance that a loss of that protection could occur. This would be a loss of confidentiality. There are special efforts being made to ensure that this does not happen.
The sections below summarize the risks and discomforts that may be occur during the period of prospective data collection.
• Risks associated with testing VA, KP, SP, MP, FST, ERG, OCT, and PROs may include boredom and frustration, but no lasting adverse effects are associated with these noninvasive tests
• Dilating eye drops will be used as part of the ophthalmic examination and before some tests. Dilating eye drops may sting, cause light-sensitivity, or an allergic reaction. There is a small risk of inducing a narrow-angle glaucoma attack from the pupil dilation. However, all participants will have had prior pupil dilation usually on multiple occasions and therefore the risk is extremely small. If glaucoma occurs, treatment is available.
• In rare instances, the cornea may be scratched during measurement of IOP or use of a contact lens electrode. An abrasion like this may be painful, but it heals quickly with no lasting effects. If a participant experiences a corneal abrasion, a tear ointment may be administered, and an eye patch or gauze may be placed over the eye.

Known Potential Benefits
Study participants are not expected to benefit directly from participation in this study. Study participants participating in this study may benefit from close attention from the study personnel and Investigator(s). The risks of participating in the study are outweighed by the benefits. Benefits include increased attention from the study personnel and the ability to contribute to increased understanding of the cross-sectional description and natural history of retinal degenerations due variants in rare genes, which may contribute to future development of treatments.

The risk level for this protocol is considered no greater than minimal risk. A risk-based monitoring approach will be followed, consistent with the FDA *Guidance for Industry Oversight of Clinical Investigations * A Risk-Based Approach to Monitoring* (August 2013).

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

• Have retinal degeneration
• Have one or more mutations in one of your genes that is the cause of your retinal degeneration
• Be willing and able to give consent
• Be willing to have annual study phone calls over four years
• Have eyes in which photographic imaging is possible
• Be at least 4 years old

Exclusion criteria

• Have a history of treatment that could have affected the retina
• Have a history of certain eye conditions or 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):	27-09-2024
Enrollment:	40
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	19-06-2024
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	NL85416.091.23