Title	**Natural History of Photoreceptor Degeneration Related to USH1b, Clinical Parameters, and Validation of Functional Vision Tests**
Acronyme	**MYO7A**
Principal Investigator	Pr. Isabelle AUDO
Sponsor	Hôpital National de la Vision des Quinze-Vingts, Paris (France)
Justification for the Study	nherited retinal diseases (IRD) are a heterogeneous group of disorders that progressively lead to severe visual impairments with limited therapeutic options. Rod dystrophy, also known as retinitis pigmentosa (RP), is the most common form of IRD, with an estimated global prevalence of 1 in 4,500. Approximately 20 to 30% of rod-cone dystrophy cases are syndromic forms, among which Usher syndrome (USH) is the most frequent (estimated prevalence of 1 to 4 in 25,000), accounting for 50% of cases of combined deafness and blindness in males and 3 to 6% of all childhood deafness cases. Type 1 Usher syndrome (USH1) is the most severe form of USH and typically presents with severe to profound congenital sensorineural deafness, vestibular areflexia, and early-onset rod-cone dystrophy (i.e., during the first decade of life). Mutations in nine genes have been associated with USH1, among which biallelic mutations in MYO7A represent 70% of cases. These specific mutations are known as USH1B syndrome. Currently, there is no treatment available for USH1B, representing a significant unmet medical need for this severe form of USH.
Study Objectives	1. Study of the natural history of retinal degeneration in a large USH1B cohort 2. Validation of functional vision tests based on virtual reality and two patient-reported questionnaires
Study Category and Type	Research with minimal risks and constraints, Category 2 This is a prospective and longitudinal study focusing on the natural history and progression of inherited retinal diseases related to USH1b, as well as the validation of clinical parameters and functional vision tests.
Evaluation Criteria and Parameters	**Functional Tests:** • Letter score from **Best-Corrected Visual Acuity (BCVA)** using the **Early Treatment Diabetic Retinopathy Study (ETDRS)** scale • In case of very low visual acuity: **Berkeley Rudimentary Vision Test (BRVT)** • **Low Luminance Visual Acuity (LLVA)** using ETDRS or HOTV charts • **Color Contrast Sensitivity** using the **Lanthony 15-HUE test** and **Cambridge Colour Test** • **Contrast Sensitivity** with the **backlit Pelli-Robson chart** • **Mesopic Microperimetry** (MAIA) • **Kinetic Visual Field** testing (Octopus 900) • **Static Visual Field** testing (Octopus 900)

	• **Retinal Function** evaluated by **Full-Field Stimulus Threshold (FST)** testing (global photoreceptor sensitivity) • **Retinal Function** assessed by **full-field electroretinogram (ERG)** responses to rod- and cone-specific stimuli (measuring amplitude and peak time) **Structural Tests:** • **Retinography** (Clarus) • **Fundus Autofluorescence (FAF)** imaging using both **short-wavelength autofluorescence (SWAF)** and **near-infrared autofluorescence (NIRAF)** (HRA2) • **Spectral Domain Optical Coherence Tomography (SD-OCT)** • **Optical Coherence Tomography Angiography (OCT-A)** • **Axial Length Measurements** • **Objective Refraction and Non-contact Tonometry** **Quality of Life:** • Responses to the two patient-reported outcome questionnaires: o *The Michigan Vision-Related Anxiety Questionnaire (MAVQ): A Psychosocial Outcomes Measure for Inherited Retinal Degenerations* o *The Michigan Retinal Degeneration Questionnaire (MRDQ): A Patient-Reported Outcome Instrument for Inherited Retinal Degenerations* -
Inclusion Criteria	- Age ≥ 3 years - Clinical diagnosis of Usher Syndrome Type 1 (USH1) in both eyes, defined as profound congenital deafness, vestibular dysfunction, and rod-cone dystrophy, with biallelic class 4 or 5 variants in the MYO7A gene - Affiliation with, or beneficiary of, a social security system (according to article L1121-8-1 of the French Public Health Code) - Additional Inclusion Criteria for Participants in the MOST-VR and VR-ViSA (Streetlab) Tests: - Sufficient understanding of spoken and signed French to ensure proper comprehension of the tasks and instructions - Presence of a cochlear implant allowing for comprehension of auditory instructions during the virtual reality mobility test, with a Mini-Mental State Examination (MMSE) score ≥ 20/25 - Age between 18 and 75 years
Exclusion Criteria	- Inability to attend or complete all study visits - Anticipated participation in an experimental treatment trial at any point during the study - Presence of ocular conditions that could impact retinal status other than retinitis pigmentosa (e.g., history of retinal detachment, glaucoma, vein occlusion, diabetic retinopathy, etc.) - Prior participation in the USH1B gene therapy trial (USHSTAT, NCT01505062) - Pregnant, postpartum, or breastfeeding women (according to article L1121-5 of the French Public Health Code)

	- Individuals deprived of liberty by judicial or administrative decision (according to article L1121-6 of the French Public Health Code) - Adults under legal protection or unable to provide informed consent (according to article L1121-8 of the French Public Health Code) - **Additional Exclusion Criteria for Participants in the MOST-VR and VR-ViSA Tests:** - MMSE score (visual items excluded) ≤ 20/25 - Physical or cognitive impairment likely to interfere with mobility - Ongoing treatment with medications that may affect motor, visual, or cognitive function (e.g., antipsychotics, neuroleptics) or that may interfere with study assessments
Criteria for Early Discontinuation or Study Withdrawal	- Occurrence of other medical conditions or treatments likely to interfere with the assessments planned during the study. - Voluntary withdrawal: A participant may decide to discontinue participation at any time, without justification and without affecting their future medical care. - Investigator decision: A participant may also be withdrawn from the study at the discretion of the investigator, for reasons such as safety concerns, protocol non-compliance, or any other reason deemed appropriate.
Constraints and Risks	The procedures involved in this study may expose participants to the following medical risks: - Pupil dilation, performed as part of the ophthalmologic evaluation, may cause side effects, with a risk of acute angle-closure glaucoma estimated at less than 1 in 5000 cases. Risk factors will be systematically screened during the ophthalmologic examination, particularly through slit-lamp evaluation. - Placement of corneal electrodes for the full-field electroretinogram (ERG), as well as the instillation of topical anesthetic eye drops (oxybuprocaine), may occasionally cause corneal erosion or corneal edema, resulting in pain lasting 24 to 48 hours after the examination. This rare complication will be systematically assessed during the fundus examination, and a healing eye drop will be prescribed if necessary. - Completion of patient-reported questionnaires may induce psychological side effects, such as increased anxiety or emotional stress. However, such reactions are typically transient, and participants are free to discontinue at any time if needed.
Population	A total of 60 participants are expected to be recruited for this study. The study is divided into three sub-cohorts: two pediatric cohorts (n=10 patients, ages 3–5 and 6–13 years) and one mixed adolescent and adult cohort (aged 14 and older, n=50).
Research Procedure	See Tables 1, 2, and 3 The following procedures are not part of routine care and are therefore added specifically for the research: - MOST-VR and VR-ViSA tests (Streetlab)

Projected Research Timeline	- **Planned Study Start Date: June 2025** - **Duration of Participation per Participant: 4 years (48 months)** - **Visit Frequency: 6 visits in total (initial visit, reproducibility visit, and 4 follow-up visits)** - **Planned Enrollment Period: 6 months. If recruitment goals are not met within this timeframe, the enrollment period may be extended up to a total of 24 months.** - **Total Study Duration: 72 months (48 months participation + up to 24 months enrollment extension)**
Funding Source	Foundation Fighting Blindness
Reimbursement of Expenses	The study will cover the costs of all examinations beyond standard care, including contrast sensitivity, color contrast vision, mesopic microperimetry, FST, and SS-OCT-A. Additionally, travel and accommodation expenses related to these visits will be reimbursed upon presentation of receipts and prior approval for each evaluation visit.

Table 1. Test Protocol for the Pediatric Cohort Aged 3 to 5 Years

Visits	Initial visit (D+0)	Reproductibility visit (D+1 à D+30)	M12 ± 3M	M24 ± 3M	M36 ± 3M	M48 ± 3M	Duration of the examination (minutes)
Procedures and tests							
Informed Consent	X	-	-	-	-	-	15
Demographics / Medical History	X	-	X	X	X	X	10
Concomitant Medications / Adverse Events	X	-	X	X	X	X	5
Objective Refraction + Air Tonometry	X	-	X	X	X	X	5
Axial Length Measurement	X	-	X	X	X	X	5
Visual Acuity Measurement	X	-	X	X	X	X	15
Full-Field Electroretinogram (ERG)	X	-	X	X	X	X	60
Ophthalmological Examination	X	-	X	X	X	X	5
Retinal Photography	X		X	X	X	X	10
Blue and Near-Infrared Fundus Autofluorescence Imaging (HRA2, 30° and 50°)	X	-	X	X	X	X	15
Spectral-Domain and Swept-Source Optical Coherence Tomography (SD-OCT and OCT-Angiography)	X	-	X	X	X	X	25

[1] The full-field electroretinogram (ERG) will not be performed if previous data showed no detectable response.

[2] Axial length measurement may be difficult to perform in some subjects depending on their level of concentration.

Table 2. Testing protocol for the pediatric cohort aged 6 to 13 years

Visits	Initial visit (D+0)	Reproductibility visit (D+1 à D+30)	M12 ± 3M	M24 ± 3M	M36 ± 3M	M48 ± 3M	Duration of the examination (minutes)
Procedures and tests							
Informed Consent	X	-	-	-	-	-	15
Demographics / Medical History	X	-	X	X	X	X	10
Concomitant Medications / Adverse Events	X	-	X	X	X	X	5
Objective Refraction + Air Tonometry	X	-	X	X	X	X	5
Axial Length Measurement[2]	X	-	X	X	X	X	5
Best Corrected Visual Acuity (ETDRS or BRVT)	X	-	X	X	X	X	15
Low Luminance Best Corrected Visual Acuity (LLVA)	X	-	X	X	X	X	10
Color Contrast Sensitivity (15 HUE Lanthony Test)	X	-	X	X	X	X	30
Contrast Sensitivity (Pelli-Robson)	X	-	X	X	X	X	15
Kinetic Visual Field (Octopus 900)	X	-	X	X	X	X	45
Full-field Electroretinogram (ERG)[1]	X	-	X	X	X	X	60
Ophthalmological Examination	X	-	X	X	X	X	5
Retinophotography	X	-	X	X	X	X	10
Blue and Near-Infrared Fundus Autofluorescence (HRA2, 30° and 50°)	X	-	X	X	X	X	15
Spectral-Domain and Swept-Source Optical Coherence Tomography (SD-OCT and SS-OCT-A)	X	-	X	X	X	X	25

[1] L'électrorétinogramme plein champ ne sera pas effectué si les données antécédentes n'ont montré aucune réponse détectable.

[2] La mesure de la longueur axiale peut être difficilement réalisée chez certains sujets en fonction de leur concentration

Table3. Test Protocol for the Adolescent (≥14 years) and Adult Cohort

Visits	Initial visit (D+0)	Reproductibility visit (D+1 à D+30)	M12 ± 3M	M24 ± 3M	M36 ± 3M	M48 ± 3M	Duration of the examination (minutes)
Procedures and tests							
Informed Consent	X	-	-	-	-	-	15
Demographics / Medical History	X	-	X	X	X	X	10
Concomitant Medications / Adverse Events	X	-	X	X	X	X	5
Objective Refraction + Air Tonometry	X	-	X	X	X	X	5
Axial Length Measurement	X	-	X	X	X	X	5
Best Corrected Visual Acuity (ETDRS or BRVT)	X	-	X	X	X	X	15
Low Luminance Best Corrected Visual Acuity (LLVA)	X	-	X	X	X	X	10
Color Contrast Sensitivity (Cambridge Color Test, Triverctor protocol)	X	-	X	X	X	X	30
Contrast Sensitivity (Pelli-Robson)	X	-	X	X	X	X	15
Mesopic Microperimetry (MAIA)	X	X	X	X	X	X	30
Static Visual Field (Octopus 900)	X	-	X	X	X	X	60
Kinetic Visual Field (Octopus 900)	X	-	X	X	X	X	45
Full-field Stimulus Threshold (FST)	X	-	X	X	X	X	90
Full-field Electroretinogram (ERG)[1]	X	-	X	X	X	X	60
Ophthalmological Examination	X	-	X	X	X	X	5
Retinophotography	X		X	X	X	X	10
Blue and Near-Infrared Fundus Autofluorescence (HRA2, 30° and 50°)	X	-	X	X	X	X	15
Spectral-Domain and Swept-Source Optical Coherence Tomography (OCT and OCT-A)	X	-	X	X	X	X	25
Patient-Reported Outcome Questionnaires (MVAQ and MRDQ)	X	-	X	X	X	X	30
Streetlab Tests (MOST-VR, VR-ViSA)[2]	X	X		X			150

1. The full-field electroretinogram (ERG) will not be performed if prior data showed no detectable response.

2. MOST-VR and VR-ViSA tests will only be conducted in participants aged 18 years and older who meet the inclusion criteria specified in the table "Inclusion Criteria for MOST-VR and VR-ViSA Tests."