„Clinical characterization of patients with achromatopsia due to CNGA3 mutations and patients with retinitis pigmentosa due to PDE6A mutations“

Information for patients

Thank you for your interest in the study. Please read this information carefully before you decide whether you wish to participate as a subject. If anything is unclear, please feel free to ask the study doctor or other team member.

1. Introduction and purpose of the study

Retinitis pigmentosa (RP) is a clinically and genetically heterogenous group of hereditary retinal disorders, being one of the most common types of retinal degenerations with a prevalence of 1:4000. More than 45 genes have been associated with RP so far, whose defects cause a progressive loss of rod photoreceptor function, followed by cone photoreceptor dysfunction often leading to complete blindness. With the help of improved genetic and functional diagnostic tools an early recognition and differentiation has become possible. Still, up to date no established therapy is available, therefore, social and professional consequences are essential tasks to deal with.

Achromatopsia, also known as rod monochromatism, is a rare inherited ocular disorder with a prevalence of 1:30.000, and is characterized by lack of cone photoreceptor function. Due to the complete unresponsiveness of cones, achromatopsia is considered a severe ocular disease with very poor visual acuity, severe photophobia at normal daylight conditions and complete color blindness that is accompanied mostly by a pendular nystagmus.

The modern ophthalmological functional diagnostic tools enable a precise characterisation and early recognition of such retinal diseases. The detailed results and information can help to extend our understanding of the pathological mechanisms involved

in these diseases. Up to date, no established therapies are available, however, enormous efforts have been made in research in recent years and the new therapeutic approaches are underway and look very promising. One possibility in RP patients could be electronic subretinal implants, of which the ARGUS 2011 device has already been licensed. Another promising approach is the transcorneal electrical stimulation, which is in evaluation in clinical studies at the moment.

Our aim is to achieve a better clinical characterisation of these diseases and to provide a better understanding of the nature of retinal disorders.

In this study we intend to investigate patients with a genetically confirmed diagnosis (the correct diagnosis should be underlined):

Retinitis pigmentosa due to *PDE6A* mutations

Or

Achromatopsia due to *CNGA3* mutations

hereby assessing the function and structure of the retina with an extensive battery of tests. We intend to examine 50 adult patients in each group.

2. Procedures

The examinations in Tübingen are performed at the outpatient departments of the Department of Ophthalmology, University of Tübingen (duration: up to 7 hours). First, the study physician will gather information about your visual impairment and ask about other affected family members to find out whether you are eligible to participate in the study. If eligible, and if you wish to take part in the study, you will be asked for written consent that you agree to participate.

The examinations planned in the study are as follows:

- a **complete eye examination** of both eyes will be carried out with determination of visual acuity and if applicable, the required correction calculated. A slitlamp examination and measurement of the eye pressure will be performed.
- A **colour vision test** will then be carried out in which you have to sort coloured caps according to their shade (Farnsworth-Munsell 28 Hue Test). Another method is the anomaloscope examination, where you have to look into the eyepiece of a device, which is similar to a microscope. You see a circle, which is divided into two different coloured halves. Your task is to try to adjust the colours and the brightness with the help of different knobs. *Duration: 20 minutes*.
- **Contrast sensitivity** will be tested with the Pelli-Robson chart. Your task is to read as many letters as you can. The letters have different contrast levels. *Duration 10 minutes*.
- The extent of the **visual field** will be measured. For this test you will sit in front of a dimly lit hemisphere and fixate a central red cross. Small bright test spots are then presented to different areas in the visual field and you will be asked to report by pressing a buzzer which ones you have seen. *Duration: 30 minutes (with breaks).*

- **Microperimetry** is a type of visual field examination, but it also allows the examiner to monitor the eyes' background through a camera. This allows a more precise investigation of the function of the eye. *Duration: 30 minutes.*
- Changes in pupil size after stimulation of the retina with light flashes may also be examined (**pupillography**). During these measurements you will sit in the dark with your head resting on a chin-rest and fixate a test point. During the measurement red or blue light stimuli will be presented and the changes of the pupil size during examination will be recorded with an infrared camera., which will then be analyzed by a special software. *Duration: 20 minutes.*

After these examinations, the pupils will be dilated (with tropicamide 1% [registration number: 6037055.00.00] and phenylephrine hydrochloride 2.5% [registration number 6008852.01.00]), and after 30 minutes in the dark, the following investigations will be conducted:

- First, the absolute threshold of light perception will be measured with a small light stimulus (**dark adaptation thresholds**). To do this, you will sit in front of a hemisphere and press a button when you have seen the light stimulus. *Duration: 40 minutes with dark adaptation.*
- This is followed by further **electroretinographical recordings**. You will sit in front of a small hemisphere as in the previous study, or in front of a computer. The hemisphere is illuminated with light flashes at different levels of brightness and colours: on the computer screen a flickering pattern is viewed. During these examinations you will have to fixate on a red cross. For these examinations, electrodes have to be placed on your forehead and temples. To achieve good results your skin has to be cleaned before the electrodes can be fixed with an electrode paste. Furthermore, a thin fibre electrode will be placed under your eyelid (after corneal anesthesia with Novesine 0,4%® [registration number: 6499318.00.00]) to detect the small potentials produced by your eyes during the measurement. *Duration without dark adaptation: 50 minutes.*
- To capture the structure of the retina **optical coherence tomography (OCT)** and **autofluorescence examinations** will be carried out. You will again be asked to fixate a small light while looking into a camera. The examination itself is barely noticeable. For the autofluorescence recording, a blue fluorescent light is used. *Duration: 15 minutes*.
- With the help of **adaptive optics** an even more detailed examination the retinal structure in a high resolution can be performed. You will again be asked to fixate a small light while looking into a camera. *Duration 30 minutes.*
- Finally **fundus photographs** of the back of the eye will be taken. You will be asked to look straight ahead into the camera and to fixate steadily while the photos are being taken. *Duration: 5 minutes.*

In certain cases blood (2 x 9 ml) will be taken for molecular genetic analysis to verify the already known genetic results. For this, you will be asked for written consent that you agree with the examination. You have the right to know the results of the genetic analysis.

Duration: 10 minutes.

3. Risks and side effects

All instruments required for the examinations are tested for safety and are used routinely in the clinic. All methods are non-invasive, meaning they require no external injuries, except for when taking the blood sample.

The following minor and transient side effects may also occur:

- The mechanical irritation of the cleaning paste, required before attaching the electrodes for the electroretinographical recordings may bring about redness of the skin. Rarely there is an allergic reaction to the cleaning paste or the contact gel.
- After the eye drops have been administered, when the pupils are enlarged, there is an increased sensitivity to light and difficulty in viewing an object at a close range. **Driving and active participation in road traffic is not possible for 6 hours after pupil dilation.** Headaches sometimes result. Allergic reactions (redness of the eyes, burning, itching) might also occur. In very rare cases, acute angle closure glaucoma is caused. In one case an anaphylactic (allergic) shock has been reported in the literature. In emergency cases your study doctor and colleagues from the intensive care will be at your immediate help.
- Systemic side effects of tropicamide and phenylephrine are very rare (frequency of occurance: 0.1-1%): mouth dryness, redness of the skin, cardiac problems, increased temperature, dizziness.
- In susceptible persons, the light stimulation during the electroretinographical recordings can trigger an epileptic seizure.
- While taking the blood sample pain and redness may occur at the puncture site in sensitive persons. Some patients can blackout during the venipuncture because of the psychological stress. A bruise is formed at the puncture site, which heals by itself within a few days. In very rare cases, a clot can block the blood vessel, or inflammation or infection at the puncture site can occur, which can also cause local pain. Sometimes, when puncturing, a nerve or artery can be damaged. However, this is extremely rare, because only experienced personnel are permitted to take blood.

4. Personal benefit

The study physicians in the Department of Ophthalmology, University of Tübingen can provide information about your vision. Your data will be stored in a database to help select suitable patients for future therapeutic measures, so that you have the opportunity to be informed and to participate at an early stage in such studies. You may benefit from the patient counseling, which can provide important information for career choice, or family planning.

5. Privacy policy

The data collected are subject to medical confidentiality. All data is encrypted, i.e. your person is assigned several characters, which are stored along with your data instead of your name. This means that the data collected can be later assigned only to individual subjects with the help of a decoding list, which is kept in a locked cabinet. For the data analysis and publication, only encrypted data are used. The encrypted data will be kept for 15 years.

If you agree with the data collection, analysis and publishing in the form described above, please sign the consent form, which will be provided to you at the first visit.

6. Participation

Participation in the study is entirely voluntary. You can withdraw your consent to participate at any time, without notice, for any reason and without affecting treatment. Examinations can be paused or aborted at any time at your convenience. If you withdraw from the study, there will be no disadvantages for you.

7. Insurance

During the study, you are insured under the public liability insurance of the University Hospitals. An additional accident insurance will be contracted by Ecclesia Versicherungsdienst GmbH (Klingenbergstrasse 4, 32758 Detmond, Tel: 05231/6030).

8. Contact person and address of the study

Study physician

Dr. med. Ditta Zobor
Department of Ophthalmology Tübingen, Tel.: 0 70 71 29 87033

In an emergency or if Dr. Zobor cannot be reached, the duty doctor of the Department of Ophthalmology (Tel: 07071-29-84761) are responsible for emergency treatment.

Please ask if you have not understood something, or if you want to know more about the examinations.