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Identifying the Genetic Causes of Inherited Retinal Dystrophies

(HNE_2018-Vers. 24.05.2018)

Information for Study Participants

Dear patient and/or family members,

You or a member of your family has been diagnosed with a form of inherited retinal dystrophy. Hereditary retinal diseases are a group of rare eye diseases that result from a functional deficit in sensing and/or transmitting light in the light-sensitive layer at the back of the eye (= retina). The knowledge about the causes and the origin of these illnesses is still limited although this is important information for proper counseling and future development of cures for these diseases.

In the following, we will inform you about the aims of the study, the collection, use and storage of your biological samples in our research biobank, as well as the procedures and measures for the protection of your personal data in the linked patient database.

Aim of the study

The Molecular Genetic Laboratory at the Institute for Ophthalmic Research, University Hospital Tübingen (MGL) conducts a long-term study on identification of the genetic causes of inherited retinal diseases. Our investigations are aimed at identifying the genes involved in this disease and for detecting disease-causing mutations in the DNA (deoxyribonucleic acid) or the messenger RNA (ribonucleic acid). Starting materials for the isolation of DNA and RNA are blood samples, which we ask you to donate with this information letter. If you agree the collected blood sample and/or the biomaterial prepared thereof is deposited in a local biobank and linked to a secured database with your personal and medical data. The biobank (first

established in 1992) is operated locally by the MGL under the supervision of Dr. Susanne Kohl and Prof. Dr. Bernd Wissinger.

If you consent to this study, genetic tests will be performed on your DNA (and/or RNA) samples. In such genetic studies, the base sequence (DNA sequencing) or the integrity of certain genes (e.g., deletion / duplication analysis, copy number variation) is examined. Such genes are segments in the DNA which yield the information for the synthesis of various proteins important for the structure, function and metabolism of the cells in the retina. Aberrations (mutations) in these genes can cause that the corresponding proteins are not produced or are formed in an insufficient amount or that their biological properties are altered. As a result, the retina may not develop or function properly, or cells of the retina may degenerate.

If the causative gene is as yet unknown, indirect investigations of the DNA can be used for its identification, for instance by means of linkage analysis. This method aims to locate the genome segment containing the disease-causing gene. To this end genetic analysis in whole families, including affected and non-affected family members is required. Through the reconstruction which sections of the genome are transmitted from generation to generation, the very section that is inherited together with the disease can be determined and can help to pinpoint the disease-causing gene. Such family studies require a high level of co-operation in your family. For legal reasons we may not contact your family members without prior consent. In such instances we would therefore ask you to arrange contact with your family members, to arrange a contact from their side, or to obtain a written consent that we may contact them. For the discussion of your illness with other family members we may ask you for release from medical confidentiality obligations.

As an alternative to linkage analyses, modern high-throughput technologies for the sequencing of DNA are also used in this study. These make it possible to determine the base sequence of the coding (= protein-forming) sections of all known genes (= exome) or the entire genome of the investigated proband (= whole genome). These techniques are excellent tools for the identification of previously unknown "disease-causing genes" for inherited retinal diseases; but they also bear the chance of unintentionally detecting further genetic aberrations which may predispose to other diseases that may occur in the future (incidental findings). A systematic search for such aberrations is not intended and not part of this study. Therefore incidental findings will not be disclosed.

The results obtained in the course of this study primarily serve to improve the scientific knowledge and to corroborate and support the clinical diagnosis. A treatment and therapy of your disease cannot be derived thereof at this time in most cases. In the future, however, the investigations may help to develop and implement new treatment concepts, many of which are dependent on the exact knowledge of the exact gene mutation in each individual. The identification of the disease-causing mutation, however, allows for a more precise molecular diagnosis, in addition to the clinical diagnosis, and makes it possible to draw conclusions about the future course of the disease. In addition, the mode of inheritance and the recurrence risk for your children or family members can usually be determined with much higher precision.

Regardless of your participation in this study, you have a right to non-knowledge (nescience), i.e. you can decide whether you want to be informed about the outcome of the investigation or not. By participating in this scientific study, however, no legal claim can be derived for the performance of certain genetic investigations.

Minors

The consent of both parents is required for the genetic analysis of minor patients. Investigations for the purpose of presymptomatic (before the onset of the illness) testing and for carrier testing in minors are not carried out and are not the subject of this study.

Unlimited study duration

The identification of the disease-causing mutation todayis successful in a large fraction of all patients, but not all, and sometimes requires long-lasting efforts and complex research investigations. Moreover, the donated biomaterials are a valuable reference material for new analytical tests and further experimental studies on the genetic nature of the diseases. The study is therefore not limited to a specific time frame, and the biomaterials and data are to be kept for an indefinite period of time and made available for medical research.

Voluntariness and Revocation

Participation in this study is strictly voluntary. If you do not want to participate or wish to withdraw your consent later, you will not incur any disadvantages. With

your participation you declare your consent to the use of your blood, DNA and/or RNA samples for the above-mentioned investigations for an indefinite time or until you withdraw your consent. You may, at any time, withdraw your consent to participate in written or verbal form, without giving reasons. For a withdrawal, please contact: Molecular Genetic Laboratory, Research Institute for Ophthalmology, University of Tübingen, Elfriede-Aulhorn-Str. 5-7, 72076 Tübingen, Germany. In this case, your blood, DNA and/or RNA sample will be destroyed, your personal data will be deleted from our files and the results so far obtained will be anonymized. Data from prior analyzes cannot be removed anymore but will be anonymized.

Transfer of samples to third parties

To support complementary genetic studies, a fraction of your blood, DNA and/or RNA sample may be transferred to other universities, research institutes and research companies for medical research purposesin an encrypted (pseudonymized) manner. The samples and data can thereby not be assigned to your person without the involvement of our facility.

Sample material and risks in blood collection

The blood collection (in the case of DNA 10 - 20 ml venous whole blood, EDTA tube, in the case of RNA 10 - 20 ml blood in PaxGene tubes) is carried out by a doctor or trained specialist. In rare cases local haematomas, thromboses, thrombophlebitis, bleeding, infections, accidental puncture of an artery or nerve can occur, which can also be associated with prolonged discomfort, dizziness and syncope, and usually will disappear within a few days. Blood collection may also be done by your GP, doctor or physician and the samples can be sent by mail. In this case, please provide your signed consent together with the samples.

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Identifying the Genetic Causes of Inherited Retinal Dystrophies

(HNE_2018-Vers. 24.05.2018)

Information and consent to privacy and data protection

Information:

Within the study "**Identifying the Genetic Causes of Inherited Retinal Dystrophies**" personal data (names date of birth, addresses, previous (clinical, genetic) findings, study-related findings including imaging procedures, results of study-related genetic examinations, etc.) are collected, stored and processed. Your medical data will also be included in the processing, if necessary. Your data is collected, processed and archived in paper form and / or in a protected electronic database at the Department for Ophthalmology of the University Hospital Tübingen, to which only authorized employees (including PhD students) who are obliged to professional confidentiality and data secrecy, have access. All employees involved are subject to confidentiality.

Any collection, storage, and transfer of data from your biomaterials as part of our research projects involves confidentiality risks (such as the ability to identify you), particularly with regard to information about your genetic material. These risks cannot be completely ruled out and will increase the more data can be linked, especially if you yourself (for example by genealogy research) publish genetic data (i.e. family pedigrees, genetic data) on the internet. The data immediately identifying you (name, date of birth, address, etc.) will remain in the facility where the samples and data were obtained. Information concerning your health (medical data) is stored separately from the biomaterials. Therefore, these data cannot be assigned to you without the involvement of our institution.

A transfer of your identifying personal data to researchers or other unauthorized third parties, such as insurance companies or employers, does not occur.

The prerequisite for the use of biomaterials and data for a specific medical research project is, in principle, that the research project has been assessed by an ethics committee. This study was also positively advised by the local ethics committee (Ethics vote 116 / 2015BO2 of 15.06.2018).

The biomaterial and data collected during the study can also be used and further processed for future research projects at the clinic or institute.
The processing and use of the biomaterial and data is carried out within the framework of the RetDis biobank and database for an indefinite period of time.
The information obtained in the course of this study may also be shared for scientific purposes, with cooperation partners subject to the European General Data Protection Regulation as well as cooperation partners outside Europe, i.e. to countries with lower data protection levels (this also applies to the US).
The research results from the study will be published pseudonymized or anonymously in journals or in scientific databases. When publishing the research results, your identity will not be disclosed. However, with the help of a patient list, we can link back the data to your sample in case of queries.
We will not publish or deposit the totality of your genetic information (whole exome or genome) at any database.
You can request information about your stored data at any time and have the right to correct incorrect data. You can also request at any time that your data be deleted or anonymised, so that a reference to your person can no longer be established.
The study leader (Prof. Dr. Bernd Wissinger, Dr. Susanne Kohl, Molecular Genetic Laboratory, Institute for Ophthalmic Research, Department for Ophthalmology, University of Tübingen, Elfriede-Aulhorn-Str 7, 72076 Tübingen) is responsible for data processing and compliance to the legal data protection regulations.
If you have any complaints, you can contact the data protection officer of the University Hospital Tübingen or the state data protection officer of the state of Baden-Württemberg:

Data Protection Officer of the University Clinics Tübingen
Martin Schurer, Datenschutzteam,
Calwerstraße 7/4, 72076 Tübingen,
Tel. 07071 29-87667,
E-Mail: dsb@med.uni-tuebingen.de

Country Representative for Data Protection and Freedom of Information in Baden-Württemberg
Dr. Stefan Brink,
Postfach 10 29 32, 70025 Stuttgart
Tel.: 0711/615541-0, FAX: 0711/615541-15,
E-Mail: poststelle@lfdi.bwl.de

For the collection, storage, use and disclosure of your data, your explicit consent by signing the declaration of consent to privacy and data protection is required.

The legal basis for the processing of your data are Articles 6, 7, 9, 89 of the General Data Protection Regulation in conjunction with §§ 4, 5, 6, 8, 9, 12, 13 of the State Data Protection Act of Baden-Württemberg in the 25th May 2018 valid version.

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Declaration of consent to privacy and data protection

I declare that I consent to the collection, storage and processing, as well as the encrypted (pseudonymised) disclosure of data as described in the study patient information.
I agree that authorized persons may inspect my personal medical record for data , and release the attending physician from his/her medical confidentiality.
I am aware that the results of this study will be published in scientific journals, albeit anonymously or pseudonymized, so that a direct link to my person cannot be made.
I have been informed that I can request information about my stored data and the correction of incorrect data at any time.
I know that at any time, for example when withdrawing my consent to this study, I can request that my previously collected personal data are deleted and prior analyses and data are anonymized immediately.
I declare that I have been informed about the collection and processing of my data and rights in this study.
I agree to the use of data collected in this study in the form described above.

Date, City	(Signature Study Participant or Legal Guardian)
Date, City	(Signature Physician)

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

Patient Information

UNIVERSITÄTS KLINIKUM TÜBINGEN

.....
Name: Surname:

.....
Date of Birth.: Tel.:

.....
Street

.....
Zip Code City

Declaration of consent

for the collection and storage of biomaterials (blood, DNA and RNA samples), as well as for the conduct of genetic investigations within the scientific study described in the information letter

„Identifying the Genetic Causes of Inherited Retinal Dystrophies“

Please read this consent carefully and tick the answers that apply to you:

I have received, read and understood the information letter (HNE-2018-Vers.24.05.2018) on participation in the study "Identifying the Genetic Causes of Inherited Retinal Dystrophies". With my signature, I give my consent to the genetic investigations necessary to clarify this question, to the required blood collection, as well as the collection and storage of my personal and clinical data. I had ample opportunity to discuss open questions.

I agree/request that the findings of the genetic investigation(s) will be sent to the following physicians / persons:

.....
Attending or referring physician

I agree to the investigation of my DNA / RNA samples by high-throughput sequencing (e.g., exome or genome sequencing). ☐ yes ☐ no

I would like to be informed about the results of the genetic investigations related to my retinal disease. ☐ yes ☐ no

I consent that the attending and/or referring physicians collect personal data, in particular information about my health including medical records, and that such data are sent and stored together with my biomaterials to the Molecular Genetics Laboratory, Institute for Ophthalmic Research, Centre for Ophthalmology, University Tübingen to support this study. ☐ yes ☐ no

The legal regulations determine that your personal data, and medical and genetic results and findings must be completely destroyed after 10 years. However, this information may still be relevant to you or your family (i.e. offsprings). With your consent, we may retain this data beyond the statutory period of 10 years. Do you agree that your data / documents are kept indefinitely? ☐ yes ☐ no

The collected data also serve the scientific gain in knowledge. I agree that collected genetic and clinical data and results on the disease in question are used in an encrypted (pseudonymized) way for scientific purposes and used anonymously for teaching purposes and may be published in scientific journals. ☐ yes ☐ no

My biomaterials (blood / DNA / RNA samples) may be used indefinitely for medical research projects. ☐ yes ☐ no

My biomaterial (blood / DNA / RNA samples) may be sent pseudonymised to universities, research institutes and research companies for medical research purposes. ☐ yes ☐ no

I have been advised that I may withdraw my consent in whole or in part at any time without stating any reasons, without incurring any disadvantages, and that I have the right to request information on the investigations and results, but also not to receive test results at any time. Upon revocation, at my request, the remaining biomaterials and my personal data are destroyed, deleted or made anonymous. Data from prior analyses cannot be removed anymore but are anonymized. I have received a copy of the patient / study participant information and consent form. The original remains with the Department for Ophthalmology, University of Tübingen or your physician.

..... City, Date	..... Signature Study Participant or Legal Guardian	.... For legal guardian: Name, Address