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Information

on the study

Genetics of rare diseases based on Next Generation Sequencing

at the Institute of Human Genetics and the Centre for Rare Diseases of the University Medical Centre Leipzig

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Dear patient,
Dear parents and legal representatives,
Dear relatives and caregivers,

You, your child or guardian/caregiver have been diagnosed with or suspected of having a rare disease. With this letter, we invite you to participate in the above study. As part of our research mission at the University Hospital Leipzig, we, as the University Center for Rare Diseases of the Institute of Human Genetics, are interested, in addition to patient care, in the precise description and clarification of previously little or unknown disease patterns. Here we have a special focus on the identification of genetic causes, the exact description of the clinical spectrum, as well as the understanding of the development (the so-called pathomechanisms).

The participating departments at Leipzig University Medical Center are Pediatrics and Adolescent Medicine, Pediatric Dentistry, Pediatric Radiology, Pediatric Oncology, Hematology and Hemostaseology, Hematology and Internal Oncology, Neonatology, Otolaryngology, Rheumatology, Hepatology, Diagnostic and Interventional Radiology, Nuclear Medicine, Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Pathology, Human Genetics, Psychosomatic Medicine and Psychotherapy, Endocrinology and Nephrology, Anesthesiology and Intensive Care, Orthopedics, Trauma Surgery, Plastic Surgery, Neurology, Day Clinic for Cognitive Neurology, Visceral, Transplant, Thoracic and Vascular Surgery, Virology, Ophthalmology, as well as the Max Planck Institute for Human Cognitive and Brain Sciences and Immunology at St. George Hospital.

Disease patterns in the focus of the Institute of Human Genetics at the University of Leipzig

At the Institute of Human Genetics in Leipzig, we investigate all diseases with a very low incidence in the general population. These are diseases that affect only one organ system as well as syndromal diseases. The term "syndromal diseases" covers a large number of clinical pictures in which, due to a single genetic cause, several characteristic symptoms such as external abnormalities, malformations, developmental and behavioral disorders are present at the same time. At the Center for Rare Diseases in Leipzig, we would advise you regarding the respective rare diseases and examine and, if necessary, treat them on the basis of routine diagnostics. For this purpose, we have established an interdisciplinary network with participation of many departments (see also our website: https://www.uniklinikum-leipzig.de/einrichtungen/humangenetik). In our studies we put a special focus on the investigation of neurodegenerative diseases and neurodevelopmental disorders. These include developmental delays, intelligence impairment, adaptive disorders, and epileptic seizures. We are also interested in other heterogeneous disorders, such as short stature, malformations, visual and hearing impairment, immunodeficiencies, and many other rare, more monogenic disorders. Particularly important is the study of diseases for which the diagnostic possibilities have already been exhausted and no diagnosis could be made so far. We want to alleviate the associated difficulties, especially with regard to treatment and psychological burden, by developing and applying methods that are not (yet) established in routine medical practice and are therefore not covered by health insurance.

In particular, the following should be considered before consenting to participate in the study:

Since new causes of disease are being investigated, the analysis may require a longer period of time. For the purpose of re-evaluating our results, we keep excess test material indefinitely until revocation. If new possibilities for investigation arise as a result of scientific progress, we apply them to cases that have not yet been clarified or for re-evaluation. We strongly recommend that you have the overall results of the study explained to you in a personal human genetics consultation and are available for this purpose at our in-house genetic consultation hours. Information about your individual results will also be forwarded to the physicians through whom you were included in the study. Findings may be limited in their significance: Not all genetic alterations can be detected with the currently available methods. There is also the possibility that test results are not clearly interpretable in their meaning. Only in rare cases can therapeutic or prognostic statements currently be derived from the results of the examination.

Despite the greatest care in handling the data and samples, a mix-up of these can never be completely ruled out.

In the case of family examinations, it is possible that the stated family relationship, such as paternity, may be questioned. We would not inform you of the outcome in this special case.

The planned investigations, analyses and findings

In order to perform genetic diagnostics or, at the latest, to participate in the study, it is indispensable to obtain blood samples from probands as well as affected and healthy persons of a family. Samples from apparently healthy relatives are necessary to be able to assess the significance of the test results in the affected persons. In addition, we will collect as comprehensive clinical data as possible (medical findings, imaging, laboratory values) including body measurements and, if necessary, data on video and photo documentation and will evaluate, store and publish them pseudonymously (publications, photo galleries, databases, registers), taking into account the data protection guidelines and your consent.

As part of the previous treatment or with consent in this study, exome sequencing or in the future also genome sequencing was/will be performed. This means that protein-coding sections of the genome (exome) or the entire genome are read out. This generates an enormous amount of genetic data, which is not only important for the research question, but may also provide information about other health aspects: These findings are called additional findings (see next paragraph for details) and are only communicated to the persons involved if they have given their explicit consent. Should the above-mentioned examinations produce clinically useful results with regard to the research question (clear, and diagnosis-relevant genetic findings), we will inform you in detail, if you are interested.

In the context of genetic diagnostics, however, it also happens that a genetic cause is suspected on the basis of the detection of so-called variants of unclear significance, but no specific diagnosis can be made because research into these variants is not yet sufficiently advanced. In these cases, it makes sense to take further sample material from the affected person and from affected persons in a family as well as from healthy relatives (especially parents). Since not all examinations are possible from EDTA blood or from an oral mucosal swab, it is useful in some cases to take PAXgene blood for the analysis of messenger RNA (also called mRNA), heparin blood for the establishment of a lymphoblastoid cell line or ACD blood for the analysis of extracellular vesicles (also called exosomes; contain molecules that are released into the blood by various tissues of the body). Blood collection may result in bruising and, in very rare cases, injury to a nerve, accidental puncture of an artery, or infection. Any follow-up treatment that may be necessary will be covered by regular health insurance. Also, it is of scientific interest for this study to obtain an oral mucosal swab, hair or nail samples. These are primarily used to check whether genetic changes are present in the germline or only in certain tissues (mosaic). There are usually no additional risks associated with this.

In specific cases, it makes sense to take a skin sample in the form of a small dermal biopsy (2-4 mm). In very rare cases, this may result in injury to a nerve or blood vessel or in infection. Tissue removal results in a scar, which can be exaggerated (conspicuous) if the patient has the appropriate, rare predisposition. We perform such a removal with the use of local anesthesia. Therefore, this extraction requires a little more time. Such an examination will be discussed with you separately if it is indicated. From the tissue sample, fibroblast cultures (cells of connective tissue) are obtained in the laboratory, with which it is possible to perform cell-based tests. This includes, among other things, the analysis of proteins, metabolites, gene expression or genetic modification of the obtained cells (silencing or overexpression of certain genes). The studies are also carried out in collaboration with national and international scientific and medical colleagues. Misuse beyond that which would be theoretically conceivable with only blood collection is not possible. Tests with cell cultures, analysis of messenger RNA, chromosomes, extracellular vesicles or hair or nail samples usually yield essential information about the potential disease-causing genetic alterations. This may provide the opportunity to clarify the cause of the disease in you, your child or sibling. In any case, this research project will provide us with new knowledge for a better understanding of rare diseases, which we would publish anonymously in scientific journals. It is possible to withdraw your participation in this study at any time without giving reasons, without this having any influence on your possible further medical care.

Additional findings

In the course of high-throughput sequencing projects, additional findings may occur that may have clinical significance for individuals in the context of other diseases and may be important for the prevention and/or therapy of other diseases. An example of this would be genetic variations that lead to an increased risk of cancer or cardiovascular disease and whose knowledge would enable special preventive examinations or early therapy. Such findings are not intentionally searched for within the scope of the studies conducted. However, if such changes are found by chance and deemed relevant, we will arrange for their disclosure to individual study participants based on the applicable consensus. Currently, the consensus is that the clearly disease-causing mutations (so-called pathogenic and likely pathogenic variants according to Richards et al. Genet Med 2015) in one of currently 56 genes (so-called actionable genes, list of genes will likely be expanded in the future) will be reported, as medical consequences may arise based on this knowledge. This information will only be provided if you have agreed in principle to feedback of additional findings in informed consent. You can consent as an adult and person of full age for yourself and for your affected children or legally represented persons. Otherwise, with the exception of genetic findings that have clinical relevance in the context of the neurological disease in question, we will not return individualized findings to study participants.

Data protection and entry into variant databases

In the course of the study, personal data (name, date of birth, contact address) will be stored electronically in our patient management systems and on servers of the University Medical Center. Inspection of the data protection concept is possible upon request from the persons or institutions mentioned at the beginning. During the examinations, the samples are assigned a specific unique number (consisting of family number and personal number). They will only be processed in this pseudonymized form or passed on to cooperating working groups. Publication in a scientific journal also takes place without naming the personal data and also without this number, so that subsequent traceability is made more difficult. The publication of videos and photos, if any, will only be done in accordance with the declaration of consent made by you and only if the videos and photos represent an added value. All persons who have insight into the stored data are obliged to maintain confidentiality and data secrecy.

Only by combining larger data sets is it possible to identify relevant genes and assess genetic variants. Therefore, we will enter a compressed listing of symptoms (in standardized form, so-called HPO, and thus non-specific) as well as a list of identified variants into databases, which are also accessible to other scientists. Conclusions about your identity or that of your child are not possible for third parties without additional information. In case of a change of address and wish to receive the results, please inform us or your physician of the new address. For participation in the study, we would like to ask you to carefully read the enclosed consent form, fill it out, sign it and send it to us.

We thank you for your participation and will be pleased to answer any questions you may have.
Sincerely, Your Institute of Human Genetics and the Leipzig University Center for Rare Diseases