Declaration of consent to participate in the study on

Identification and characterisation of genetic alterations in rare diseases

at the Institute of Human Genetics / University Centre of Rare Diseases Leipzig

Family number: Subject number:

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

UZSEL – ZENTRUM FÜR SELTENE ERKRANKUNGEN LEIPZIG

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Dear patients, dear parents, dear relatives,

As part of our research assignment at the University Center for Rare Diseases Leipzig, we are interested in patient care as well as for the exact description and clarification of previously unknown diseases. We have a special focus on the identification of genetic causes, the exact description of the clinical spectrum, and the understanding of the origin (so-called pathomechanisms). Involved departments of the University Medical Center Leipzig are Pediatric and Juvenile Medicine, Pediatric Dentistry, Pediatric Radiology, Pediatric Oncology, Hematology and Hemostaseology, Hematology and Internal Oncology, Neonatology, Cervical, Nasal, 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, Anaesthesiology and Intensive Therapy, Orthopedics, Traumatology, Plastic Surgery, Neurology, Day Clinic for Cognitive Neurology, Visceral, Transplantation, thorax and vascular surgery, angiology, virology, ophthalmology and the Max Planck Institute for Human Cognitive and Brain Sciences.

Diseases in focus of the University Center for Rare Diseases Leipzig

At the Center for Rare Diseases Leipzig we investigate all diseases with a very low frequency in the general population. These are diseases that affect only one organ system as well as syndromic diseases. Grouped under the name "syndromic diseases" are a variety of clinical pictures, due to a single genetic cause presenting with several characteristic symptoms such as external abnormalities, malformations, developmental and behavioral disorders. In the Center for Rare Diseases in Leipzig, we would counsel you on the background of the respective rare diseases and examine you with routine diagnostics and treat if necessary. For this, we have established an interdisciplinary network with participation of many disciplines (see also our website: http://www.uniklinikum-leipzig.de/r-universitaeres-zentrum-fuer-seltene-erkrankungen-a-7597.html). Diseases that can not be clarified in the context of routine diagnostics, are interesting for various research questions. In some cases, research is carried out at the University Hospital Leipzig, sometimes in cooperation with colleagues in Germany or foreign countries. In particular, we are interested in neurological disorders (both neurodevelopmental and neurodegenerative). These include, above all, developmental delay. These are characterized by an intelligence quotient (IQ) of less than 70 and by adaptation disorders. Furthermore, we are interested in epilepsy disorders (seizure) as well as diseases with malformations of brain structures. With respect to neurodegenerative diseases, we examine a broad spectrum, such as ataxias, neuropathies, paraplegias and dementia. Another scientific focus of the Center for Rare Diseases Leipzig are endocrine diseases, in particular in children. This mainly includes abnormalities of growth and body weight.
Despite significant medical advances, the underlying cause of the disease remains unknown in many children and adults. This leads to a great distress for the families, to suboptimal medical care and in some cases to missed opportunities for therapy. Based on the current state of knowledge, it can be assumed that a genetic cause exists in many of the children and adults with developmental disorders, seizure disorders, brain malformations, organ malformations, ataxias, neuropathies, dementia, paraplegia, growth retardation, obesity, and hormonal abnormalities.
Using the new sequencing technologies (so-called massive parallel sequencing or *Next Generation Sequencing* NGS) as well as subsequent functional analyzes, we want to elucidate yet unknown genetic causes. Via cooperation of different medical disciplines at the University Center for Rare Diseases Leipzig we want to achieve a comprehensive description of the spectrum of symptoms. The investigations will also be in collaboration with national and international scientific and medical colleagues. This may elucidate the cause of the disease in you, your child or siblings.

The planned investigations and analyzes

For analyzes, a blood sample (about 5 ml) is usually taken once by the affected persons in a family and by healthy relatives (especially parents). The blood samples of healthy persons are necessary to interpret the results of the affected persons. Blood collection may cause bruising and, in very rare cases, accidental nerve injury, puncture of an artery or infection. Such very rare complications are cared for by standard medical care. A separate insurance for blood collection for this study was not made. In particular cases it may also be useful to examine a tissue sample, for example, a small piece of an organ which was taken for diagnostic or therapeutic purposes. Such an investigation is not covered within the scope of the enclosed declaration of consent and will be discussed separately with you, if this is indicated. As a rule, there are no additional risks. Also it is sometimes informative to obtain an oral mucosal smear.
In addition, we will record comprehensive clinical data (medical findings, imaging, laboratory data) including body measurements and photo documentation and will evaluate and store them in accordance with the Privacy Policy and your consent. We will then perform a so-called exome, genome or transcriptome-sequencing. This means that all protein coding sections of the genome, their expression or all genetic material will be sequenced. This generates an enormous amount of genetic data, which is not only useful for the disease in question, but could possibly provide information about other aspects (incidental findings, see below).

Should the above-mentioned investigations produce clinically useful results regarding the disease in question, that is, clear and diagnostic-relevant genetic findings, we will inform you, in detail, if you are interested. Should we elucidate interesting findings, that are clinically not yet relevant in the context of a routine diagnostic, we would pursue them at the research level, and if necessary, carry out further research by cooperating with scientists and physicians in Germany and worldwide. This could lead to significant results that we would publish in scientific journals in anonymized form.
It is always possible to revoke participation in this study without giving any reason, without affecting it your further medical care.

Before agreeing to participate in the study, please consider the following

Family investigations: family investigations can lead to questioning the stated relationships, for example paternity. We would not tell you about this.
Findings may be limited in their informative value: the currently available methods do not cover all genetic alterations. There is also the possibility that test results are not clearly interpretable in their meaning. Only in rare cases, therapeutic or prognostic statements can currently be derived from the results of the investigation. Although biggest care is taken, mix-up of probes can never be completely ruled out.
Handling of samples and results: as new causes of the disease are researched, the analysis can take a long time. Excess probe material is retained for the purpose of reviewing our results. Should new possibilities of investigation arise through the scientific progress, we apply these in cases not yet solved. We strongly recommend having the overall results of the study explained to you in a personal genetic counseling session, and we are happy to assist you with this. Information about your individual results will also be forwarded to the doctor through whom you were included in the study.

Incidental / additional findings

Incidental or additional findings may be found in high-throughput sequencing projects that are of clinical significance to individuals in the context of other diseases and they may be important for the prevention and / or treatment of other diseases. An example includes genetic changes that increase the risk of cancer or cardiovascular disease and this knowledge could enable special preventive care or early therapy. In the framework of this study, such findings are not intentionally looked for. However, should such changes can be found by chance and if deemed to be relevant, we forward these findings on the basis of your consent. Currently, the consensus is that clear mutations (so-called pathogenic and likely pathogenic variants according to Richards et al., 2015) in one of currently 56 genes (so-called actionable genes, list of genes is likely to be extended in the future), will be forwarded, since clinical consequences could arise because of this knowledge. This information will only be provided to you if you consented in principle to a notification of incidental / additional findings. As an adult you can consent for yourself and your affected children or patronized persons. Findings for healthy minors in the family are not communicated. Otherwise, with the exception of clinically releveant genetic findings in the context of the neurological disorder in question, we will not communicate individualized findings to study participants.

Data protection and input of variant databases

The study collects personal data (name, date of birth, contact address) electronically. During the investigations, samples receive a number. They are only processed in this pseudonymized form or passed on to cooperating working groups. A publication in a scientific journal also takes place without naming the personal data. The publication of photos, if any, will only be made in accordance with your consent. All persons who have access to the stored data are required to maintain secrecy and to maintain data secrecy.
Only by combining larger data sets is it possible to identify relevant genes and to assess genetic variants. Therefore, in databases that are also accessible to other scientists, we will provide a compressed listing of the symptoms as well enter a list of identified variants. Conclusions about your identity or that of your child are not possible for third parties without additional information.

In the case of a change of address and request for result notification, we ask you or your doctor to communicate the new address. To participate in the study, we would like to ask you to carefully read through the enclosed declaration and send it us completed and signed.

We thank you for your participation and are happy to answer your questions.
Your Institute for Human Genetics and the University Center for Rare Diseases Leipzig