UNIVERSITÄTS
KLINIKUM
HEIDELBERG

Institut für Humangenetik I Im Neuenheimer Feld 366 I 69120 Heidelberg

Institute of Human Genetics
Prof. Dr. med. Christian Schaaf
Medical Director
Genetics Clinic
phone: +49 (0)6221 56-5087
fax : +49 (0)6221 56-5080
Diagnostics Laboratories
fax : +49 (0)6221 56-5091
Molecular Genetics: +49 (0)6221 56-32484

Patient information sheet

Information about genetic testing in accordance with the Genetic Diagnostics Act (GenDG)

Dear patient or legal representative,

You or your child has been scheduled for genetic testing. **Genetic tests** in Germany are subject to the regulations of the Genetic Diagnostics Act (GenDG), which stipulates that prior to initiating any genetic testing, detailed medical information must be made available to the patient and **written consent** must be obtained.

Please note that you have the right to withdraw your consent from the analysis entirely or partially at any time without giving a reason. You also have the right not to be informed about the results of an investigation. Also, you may ask for any ongoing analysis to be stopped at any time up to when the results are being communicated, or for any sample material and test results to be destroyed. If you have any further questions about data protection, please contact the data protection officer at Heidelberg University Hospital.[1)]

Please read the following text carefully.

General information on genetic analyses

The aim of a **genetic analysis** is to examine genetic material for alterations that may be the cause of the symptoms or the disease that you / your relatives / the person in your custody are suffering from or are suspected to be suffering from. In our laboratory, we use various testing methods which will be explained to you below.

The results of the genetic testing will be communicated to you by your treating physician in accordance with the Genetic Diagnostics Act (GenDG).

DNA tests carried out among family members may potentially reveal unexpected findings about kinship and family connections, e.g. a wrongly-assigned paternity. We would only disclose this type of information if it were inevitable regarding the completion and interpretation of the requested analysis.

Even though our genetic analyses are very extensive and may cover your whole genome, there is still a small chance that genetic alterations may remain undetected.

Unfortunately, no testing can be 100% error free. Besides methodological challenges related to the analysis itself, sample mix-ups, vague or incorrect information in relation to the symptoms and / or correlations within the family as well as contaminated sample material may lead to incorrect or uninterpretable results. Our laboratory is accredited and thus it strictly adheres to high-quality standards; thus, we ensure that our laboratory test results are of the highest possible quality and validity; nevertheless, incorrect analysis results can never be completely ruled out.

Cytogenetic and molecular cytogenetic studies

In cytogenetic analyses, chromosomes derived from particular body cells (e.g. blood cells, bone marrow, skin, chorion, amniotic fluid or foetal membrane) are examined by light microscopy. Aim of this type of analysis is to examine a set of chromosomes for numerical or structural changes (karyotype).

Please note:

• Occasionally, the set of chromosomes found in the examined tissue may not be representative of the entire body. This is referred to as “chromosomal mosaicism”.

• An inconspicuous set of chromosomes in the examined issue does not rule out the possibility of other tissue samples containing chromosomal aberrations. Neither does an abnormal finding in the examined tissue necessarily allow to conclude that the chromosome set in other tissues is also abnormal.

• Prior to performing a chromosomal analysis, cells usually have to be multiplied in cell culture. This procedure can lead to new chromosomal abnormalities arising in individual cells. In these cases, we speak of “cultivation artefacts” or “pseudo mosaicism”.

• Structural chromosomal alterations can only be detected to the extent as resolution of the light microscope and quality of the respective examination material permit. The quality of our analyses is in line with the guidelines of the Professional Association for Medical Genetics (Berufsverband Medizinische Genetik). In case of deviations, this will be expressly noted in our report.

• There are a number of heritable chromosomal abnormalities which are not of pathological significance. These are referred to as “variants” or “polymorphisms” and will generally not be noted in our reports. In individual cases, it may be difficult to distinguish a variant from a potentially pathological finding. In this case, the variant will be explicitly mentioned in the report and be discussed with you.

Occasionally, it occurs that a person´s appearance and his/her sex chromsomes do not match. There can be biological reasons for this.

Molecular genetic studies (DNA diagnostics) – single gene sequencing

Molecular genetic studies aim to exclude or detect genetic alterations at DNA level using genetic engineering methods.

Single-gene sequencing is specifically designed to investigate an individual´s genetic make-up (alterations in individual genes). Its aim is not a genome-wide exclusion or detection of genetic alterations. Basically, there are two different methods to be distinguished, i.e. the “direct” and the “indirect” approach.

Please note:

• In direct genetic diagnostic testing, disease-causing alterations (pathogenic variants) in a hereditary disposition (a gene) can clearly be detected or ruled out. The detection of a pathogenic variant has usually a high quality of evidence. An inherited gene mutation without any impact on the individual´s health (polymorphism), will normally not be mentioned in our report. If, according to our current knowledge, it is not certain whether a variant has an impact, this will be noted in our reports and be discussed with you.

• Even if no pathogenic variants are detected by means of direct genetic diagnostic testing, disease-causing variants may still be present either in the examined gene or in other genes, depending on the type of the disease, the hereditary disposition as well as the scope of the analysis.

If, in individual cases, a direct test should not be possible, an indirect genetic test can be performed. In this test, so-called genetic “markers” that are located within or near the disease-associated genes, are examined. This indirect genetic test can only provide probabilities; its accuracy always depends on the genetic linkage between disease-causing gene and marker. In some cases, markers may be completely “uninformative”; in these cases, the test does not allow any conclusions to be drawn.

Molecular genetic testing as gene panel sequencing or exome-wide analysis based on genome sequencing

Next Generation Sequencing (NGS), enables us to analyse several or all genes at once. As a result, a large number of sequence variants are identified in bulk and need to be assessed as regards their clinical relevance.

Please note:

• For a correct interpretation of results, detailed clinical information about the patient is essential.

• Genes which have been known for a long time and thus -in the majority of cases- represent the cause of the issue being investigated (known disease-associated genes), will be examined first. Later, the investigation can be extended to genes that have only been described sporadically in the literature as potentially being related to the prevalent symptoms.

• To date, only certain regions of a gene are examined; consequently, the sensitivity remains limited.

It is possible that variants are discovered, whose clinical relevance is unclear at the time of discovery (VUS).

Incidental findings

In more extensive genetic analyses, e.g. exome-wide analyses based on genome sequencing, incidental findings that are unrelated to the original diagnostic question, may be discovered by chance, depending on the evaluation strategy used. For instance, a genetic predisposition to a tumour disease or a predisposition to cardiac arrhythmia could emerge as an incidental finding within a "developmental disorder". However, there is no systematic screening for genetic mutations outside the actual question. Knowing about such incidental findings may be medically relevant, but also cause emotional strain or pressure or have consequences for future life situations (e.g. life insurance).

• In principle, we only report incidental findings that are medically actionable. Our laboratory does not report incidental findings for a gene for a non-treatable disease or carrier status.

• Incidental findings can be reported but they do not necessarily have to. You alone decide whether incidental findings will be reported (not ticking this box is considered as NO).

• In the case of children, it is their legal representatives who decide whether incidental findings that only become medically significant in adulthood, should be reported. It must be considered that this could potentially result in disadvantages for insurance claims in the future.

In the case of children, medically highly relevant incidental findings are always reported, regardless of the parents' consent, if withholding them would result in harm for the child.

Genetic findings in the patient data system

Genetic findings merit specific protection. Protecting your data is a top priority for us.

Your documents and findings are stored in an internal laboratory organisation system of the Institute for Human Genetics at Heidelberg University Hospital. Access to the internal laboratory organisation system is personal and password-protected and - due to the unity of diagnostics and patient care at our institute- is granted to all employees working in these areas. Once the finding has been medically validated and released, the report becomes visible within the UKHD patient data system (ISHmed), that is embedded in the internal clinic network. This means that UKHD employees who are logged in with their name and password are able to view these genetic findings in our patient data system for a limited period of time, provided that their department is involved in the care and treatment of you / your relative / the person in your custody. This is the only way we can ensure that the findings will be promptly considered by the treating physician for preventative therapy or treatment planning.

1) Data protection officer at Heidelberg University Hospital; Im Neuenheimer Feld 672, 69120 Heidelberg, 06221-56 7036, email: Datenschutz@med.uni-heidelberg.de