What does exome mean?

Human genetic material consists of DNA, which contains the instructions for the structure of all the different proteins in our body, known as genes. Although genes represent only a small part of the entire DNA, their significance in the development of diseases is significant. Currently, about 20,000 genes are known, but the function of all of them is not yet understood. The whole exome (WES) typically covers all known genes and their adjacent regions, which constitute about 2% of the entire human genome. On the other hand, clinical exome (CES) is narrower and includes only those genes currently associated with a disease. The content of clinical exome varies among different laboratories, and the clinical exome at Tyks Genomics Laboratory currently includes 5500 genes.

Characteristics of exome studies

Every individual is unique, and there are numerous small differences in genetic material between individuals. The majority of these changes are benign in nature, and only a fraction of them cause known diseases or predisposition to diseases. Interpreting different genetic variations, called variants, can sometimes be challenging. The majority of variants are completely harmless (not associated with any disease), some are of uncertain significance (VUS, Variant of Uncertain Significance), and some are highly likely or definitely disease-causing. To clarify VUS variants, your attending physician may suggest additional tests or, in some cases, testing of relatives for the identified variant. VUS variants do not lead to treatment or monitoring decisions.

Due to the investigation of numerous known disease-related genes in exome studies, international recommendations exist for reporting incidental findings. The American College of Medical Genetics (ACMG) has published recommendations on genes that should be included in exome studies if the patient gives consent. Errors in these genes can cause various disease susceptibilities, and early diagnosis and preventive monitoring can influence the risk and prognosis. In addition to the genes recommended by ACMG, incidental findings in other genes may be reported in the exome study report if they are considered directly relevant to the patient's health and if the result can influence the risk of developing a disease. Incidental findings are included as part of the laboratory report.

Variants of uncertain significance (VUS) are not reported as incidental findings, only changes that are considered highly likely or definitely disease-causing.

Consent

Separate consent is always requested in connection with exome studies so that the laboratory knows whether incidental findings should be reported. Since this is a comprehensive genetic study that also includes the possibility of relevant incidental findings,

written consent is always requested from the patient/guardian regarding incidental findings before the study. Before the study, the attending physician should discuss not only the main aspects of the study but also the possibility and significance of incidental findings.

Trio studies

In particular, for pediatric patients, the analysis of exome studies can be significantly improved if the samples of both parents are also examined as control samples (trio exome). This way, especially the aforementioned VUS findings can often be classified more accurately. Trio exome has been proven to improve the diagnostic accuracy compared to analyzing only the patient's sample.

Samples

Generally, genetic studies are performed on DNA isolated from blood samples, but it is also possible to perform studies on other tissues. For example, during pregnancy, fetal DNA can be examined from amniotic fluid or placental samples. For patients who have undergone stem cell transplantation, it is often recommended to examine skin samples instead of blood samples. The turnaround time for gene panel studies is usually around 2 months, but in urgent cases, results can be obtained significantly faster.

Result evaluation

The final assessment of the correlation between the genetic study result and the patient's symptoms is made by the ordering physician. In some cases, additional investigations such as blood tests, imaging studies, or targeted investigations of relatives may be necessary to assess the significance of the result in the patient's case.

If a detected genetic alteration remains unclear in its significance despite additional investigations, the case can often be revisited later when more information has been gathered about the specific alteration, allowing for reclassification. Most uncertain changes eventually turn out to be benign changes related to individual variation.