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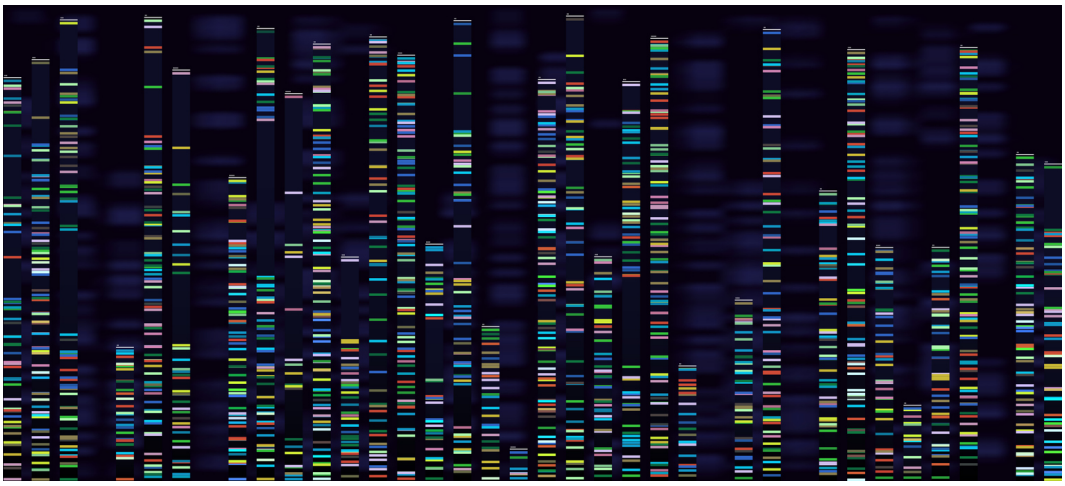
Smarter Through Whole Genome Sequencing?

Study investigates the diagnostic utility of GS in congenital heart defects

Berlin, March 07, 2023 - The molecular genetic causes of congenital heart defects are diverse and not yet fully understood. Could whole genome sequencing help improve diagnosis, therapy and prevention of severe congenital heart defects? A team of researchers led by human geneticist Marc-Phillip Hitz is now investigating this using sample donations from participants in the National Registry.



Visualization of a genome analysis. Where are the spelling mistakes in the genome?
Foto |© iStockphoto.com, Tetiana Lazunova

The development of digital technology has helped the examination of the entire genome by means of genome sequencing, or GS for short, to take a quantum leap. Whereas data acquisition initially took many months and was very costly, the visualization of the entire genome is now taking place at high speed. This has now made it possible to identify "writing errors" in the genome of a large number of tissue and blood samples, which can cause confusion in cell communication and thus lead to severe congenital heart malformations, for example.

The clinical application of the GS could therefore be of groundbreaking importance for progress in diagnostics and therapy of severe heart defects.

This is now being investigated for the first time by a team of researchers led by human geneticist Marc-Phillip Hitz, director of the University Institute of Medical Genetics at the Oldenburg University Medical Center. The researchers are comparing a large number of exome data sets from people with congenital heart defects with the results from genome sequencing. For this purpose, the broad-based study can access tissue and blood samples from about 1,000 participants in the National Registry. "The structure of the National Registry, which has been systematically built up over the years with its own biobank in the research network of the Competence Network for Congenital Heart Defects, creates ideal conditions for this," says study leader Marc-Phillip Hitz.

Tracking Down the Causes of Severe Congenital Heart Defects

Back in 2016, the research team led by Marc-Phillip Hitz achieved a breakthrough in the study of severe congenital heart defects. Using exome sequencing, the researchers discovered three new gene mutations involved in the formation of severe syndromic heart defects. At the same time, they found that non-syndromic heart defects are inherited more frequently than previously thought. (https://www.kompetenznetz-ahf.de/en/researchers/research/results/discovery-of-new-heart-disease-genes/). "However, exome sequencing alone cannot assign such gene mutations to individual heart defects. We may find the needles in the haystack, but not the straws perforated by them. For targeted measures of diagnostics, therapy and counseling, the unambiguous assignment is the decisive prerequisite. For this, we need to investigate more broadly and more deeply at the same time," explains Hitz.

Holistic Research Approach

The researchers now want to achieve this assignment by comparing the data from exome sequencing with data from genome analysis. In the process, they are also subjecting the heart tissue samples to a transcriptome analysis, in which individual genes transcribed from DNA into RNA can be precisely localized in the cell and in the tissue. For all patients for whom exome and genome sequencing do not yet yield conclusive results, the researchers go one step further. Using samples of blood serum and blood plasma from the relevant cohort, the researchers are also identifying novel biomarkers. With this holistic approach, it may be possible to identify previously unknown gene variants and evaluate their

effects on cellular processes, gene transcription, protein interactions, and degradation as well as metabolic processes. The research team hopes that this will make it possible to identify further genes, proteins and metabolites, intermediate products in the metabolic process of a cell, which are involved in the development of congenital heart defects.

Improving the Treatment of Severe Congenital Heart Defects

Beyond previous findings from basic molecular genetic research, the researchers hope that this will lead in the medium term to an improvement in diagnostics and counseling, also in the case of severe syndromic heart defects. In the long term, this could create the conditions for improving therapy and even new cures. "We are already well on the way to translation, i.e. the transfer of our research results into clinical practice," says Marc-Phillip Hitz.

Already, findings from research at the Competence Network for Congenital Heart Defects serve as an early warning system for hereditary heart defects, for example. "Through human genetic counseling, we can intervene preventively in such cases and warn and treat potential patients without symptoms more quickly," says the human geneticist. If the knowledge gained could also be used to better treat severe congenital heart defects in the near future, that would indeed be groundbreaking.

This study is supported by Illumina.

Reader Service:

Do you or your child have a congenital heart defect? By registering in the National Registry for Congenital Heart Defects, you support medical progress. Here you will also receive important information on current research projects and support services. Find out more at: https://www.kompetenznetz-ahf.de/patienten/.
Membership is free of charge and can be revoked at any time.
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