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New diagnostic method identifies genetic diseases

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People with genetic diseases often have to embark on an odyssey from one doctor to the next. Fewer than half of all patients who are suspected of having a genetic disease actually receive a satisfactory diagnosis. Scientists from the Charité - Universitätsmedizin Berlin and the Max Planck Institute for Molecular Genetics have now developed a test procedure that significantly increases the prospect of a diagnosis for affected patients. The procedure is freely available to the relevant medical institutions and can be used with immediate effect.

The first step to the right treatment is an accurate diagnosis - even in untreatable cases, it is invaluable. "At the least, it provides the reassurance that the illness is not self-inflicted," says Peter Robinson, one of the developers of the PhenIX diagnostic procedure. PhenIX stands for "Phenotypic Interpretation of eXomes". In the past, only a genetic analysis was carried out for such diseases. However, this is often not enough to accurately detect the illness. The problem with all the tests is that the individual diversity of patients makes a diagnostic analysis difficult – among the millions of genetic deviations from the norm inherent in every single person, the crucial difference must be found.

To solve this problem, the Berlin-based scientists developed an innovative diagnostic procedure. In contrast to previous diagnostic tests, PhenIX combines the analysis of genetic irregularities with the patient's clinical presentation. In the first step, a specific search is conducted for around 3,000 genes that are known to cause diseases. To find out which ones they are, the scientists systematically search through publicly

available databases and create a list of known genetic defects. Once this is complete, several hundred genetic irregularities usually still remain in the patient's genome as candidates for the cause of the disease.

In the second step, the attending doctor browses the Human Phenotype Ontology (HPO), a database already developed at the Charité, to search for the patient's symptoms. This also contains a list of genetic defects that could be responsible for the disease. When the doctor then examines the overlap between the two analysis methods, he or she is left with a list of candidates of often no more than 20 possible causes of the illness, including a ranking in order of probability. It is relatively easy to go through this list and test it.

In a pilot study, a group of patients, whose genetic disease was already known, were examined. In every single case, PhenIX diagnosed the illness correctly. Other sick persons also presented for treatment. These were individuals who had not been able to obtain a diagnosis, despite intensive and in some cases years of effort and investigation. More than 25 percent of these patients were able to find out the exact cause of their illness when the PhenIX method was used.

PhenIX is already available to hospitals that have the necessary technical equipment. "Through a combination of clinical findings and genetic analysis, we have taken a major step forward – the new method means just two hours of work for the doctor," says Robinson. And he promises: "Even in the future, a free version of this programme will always be available." He sees the potential for further improvement in a more standardised handling of the databases. "Doctors sometimes do not know exactly how they should describe a symptom, or they know a particular symptom under a different name." Certain guidelines could make the search process more successful, so that the diagnosis can be even faster and more accurate in the future.

More information: Tomasz Zemojtel, Sebastian Köhler, Luisa Mackenroth, Marten Jäger, Jochen Hecht, Peter Krawitz, Luitgard Graul-Neumann, Sandra Doelken, Nadja Ehmke, Malte Spielmann, Nancy Christine Øien, Michal R. Schweiger, Ulrike Krüger, Götz Frommer, Björn Fischer, Uwe Kornak, Ricarda Flöttmann, Amin Ardeshirdavani, Yves Moreau, Suzanna E. Lewis, Melissa Haendel, Damian Smedley, Denise Horn, Stefan Mundlos, Peter N. Robinson. "Effective diagnosis of genetic disease by computational phenotype analysis of the disease-associated genome." *Science Translational Medicine*, 3 September 2014 RA3009262/S/MEDICINE

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