Exome sequencing gives cheaper, faster diagnosis in heterogeneous disease

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Nuremberg, Germany: The first report of the diagnostic use of the technique of exome sequencing, where short sequences of DNA are analysed, shows that it can give good results at low cost, a researcher from The Netherlands will tell the annual conference of the European Society of Human Genetics today (Monday). The scientists were able to perform a genetic diagnosis in around 20% of 100 cases of patients with intellectual disability (ID) and 50% of the 25 cases of blindness studied. Not only is the exome test cheaper, but results are available more quickly than with Sanger sequencing[1], they say.

Dr. Marcel Nelen, head of the Core Genome Analysis Laboratory of the Genetics Department at Radboud University Medical Centre, Nijmegen, will describe to delegates how he and colleagues at the University examined exome sequences from 262 patients with six heterogeneous diseases: ID, blindness, deafness, movement disorders, cancer, and OXPHOS diseases[2]. In all, the researchers analysed about 500 exome sequences. In the ID cases, exomes from the father, mother and the child were analysed; in all the other diseases, the exome data from the patient alone was filtered for known causative disease genes.

"The chances of finding a causal mutation in a single gene is small", says Dr. Nelen, "but in a package containing more than 100 genes it is high, as our results from the blindness patients show. This new strategy means that we can analyse up to 20,000 genes with a single generic test, and the high throughput and lower cost means that we can test more for less money. But before we implemented the test more widely in our

laboratory we needed to be sure that it would give us reliable diagnostic results."

Exons are short sequences of DNA representing the regions in genes that are translated into protein. The human genome contains about 180,000 exons, constituting about 1% of the total genome. While exome sequencing is only able to identify those conditions where protein function is affected, scientists believe that the exon regions contain about 85% of all disease-causing mutations. And while Sanger sequencing looks at around 500 base pairs per analysis, NGS looks at millions of sequencing reactions per analysis.

The Dutch researchers were entering new territory and so needed to write the rulebook themselves. "There were no best practice guidelines available for exome sequencing, and so we had to create diagnostic workflows, procedures and criteria. What criteria did we have to set before we could authorise the outcome? What type of informed consent was necessary? How could we organise confirmation of our results? All these questions had to be answered, and we undertook numerous discussions with clinical geneticists, researchers and ethicists before we could get started", Dr. Nelen says.

The results then needed to be confirmed. "We validated our results by using Sanger sequencing, the standard method of genetic diagnosis which has a very high sensitivity and specificity", Dr. Nelen will say. In addition to ID and blindness, confirmed diagnostic results in the other diseases analysed to date were impressive. In deafness disease-causing mutations were found in about 20% of cases, in movement disorders between 15 – 20%, and in OXPHOS diseases causal mutations were found in about 25% of the patients studied.

"Although it is often not possible to treat their diseases, we should take into account that most of these patients will have had a long and

worrying journey through different doctors and hospitals before they are diagnosed", says Dr. Nelen. "Exome sequencing can shorten that route, and it can also simplify the work of clinicians because they don't have to make a decision about which gene to test for – with 100 or more genes per disease, that can be a very difficult decision to make. Exome sequencing tests for all the causative gene mutations at the same time, and that means that fast and accurate diagnoses can be made. Even if there is no treatment available, such diagnoses can help parents, patients and clinicians to make well-informed decisions on treatment and care, as well as being able to plan for the future."

A further advantage of the technique is its flexibility. If a new, clinically relevant gene is discovered, it can be added to the testing list and the data reanalysed if necessary. There are limits as to what exome sequencing can do, the researchers say, but these technical difficulties will diminish as the technique matures and evolves, and for now the fact that so many patients that can benefit from the technique, as opposed to time-consuming and costly Sanger sequencing strategies, easily outweighs these disadvantages.

"We need to be able to reduce the price of the exome test yet further before we can offer it more widely", Dr. Nelen will conclude. "In the future I am sure that genome sequencing will become cheaper, and this is really the gold standard; it provides a single test that detects all possible pathogenic genetic variation, whereas exome sequencing still misses mutations due to its more limited nature. But with whole genome sequencing currently costing on average €10 000 and an exome test between 10 and 20 times less we can see significant cost savings, and the less complex nature of the test means that diagnostic results can be available much more quickly. Genetic diagnosis is becoming more and more important in the clinic and we believe that, as it develops, the exome technique will be one of the first tests to be considered by a doctor where a genetic disease is suspected. "

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