Next-generation DNA sequencing to improve diagnosis for muscular dystrophy

March 5 2012

Scientists at The University of Nottingham have used a revolutionary new DNA-reading technology for a research project that could lead to correct genetic diagnosis for muscle-wasting diseases.

The technique could be used to offer people with muscular dystrophy, or a related neuromuscular condition, a more accurate prognosis, which would enable them to make more informed choices on life decisions, including family planning.

The researchers used a next-generation DNA sequencing machine to investigate the condition of a patient who had previously been misdiagnosed with the wrong type of muscular dystrophy.

The research, led by Professor Jane Hewitt in the University's School of Biology, was funded by the Muscular Dystrophy Campaign through a PhD studentship for Andreas Leidenroth.

Andreas said: "Our case study demonstrates how genetic diagnostics will be done in the future. New DNA sequencing machines will be cheap to run, easy to use, fit on a desk and decode an entire human genome in minutes. High-throughout DNA sequencing in the NHS is no longer a question of 'if', but of 'when'. The biggest challenge will be to develop standardised filtering guidelines so that we can easily extract medically relevant information from these large DNA datasets."

The study, published in the *European Journal of Human Genetics*,

focused on a person who had previously been diagnosed with facioscapulohumeral muscular dystrophy (FSHD) — a type of muscular dystrophy that predominantly affects muscles of the face, shoulder and upper arm. However, when the researchers studied her DNA more closely they found several inconsistencies and realised that she was highly unlikely to have FSHD.

To gain a genetic diagnosis for this, traditionally genes known to be involved in muscular dystrophies would have to be tested one by one, which can be a laborious and time consuming process. This would also have limited the search to a small number of genes and risked missing the mutation.

Instead, the Nottingham team used whole genome sequencing which, rather than reading the code of a single gene at a time, can simultaneously decipher the more than 25,000 genes of the human genome. This had the advantage of almost guaranteeing to examine the mutated gene but also poses a serious challenge: human DNA can vary from one person to the next so how could they tell which was a harmful genetic mutation rather than a harmless 'spelling difference' unique to that person?

The Nottingham researchers used different data filters to carefully narrow them down. First they ignored all spelling differences that had already been reported in the genomes of healthy people, assuming them to be harmless. This left 950 differences, of which 450 looked like they might be harmful mutations. When they compared this shortlist to 30 known muscular dystrophy genes, they found two matches: the patient had two mutations in a gene known to cause limb-girdle muscular dystrophy (LGMD) type 2A, correcting the genetic diagnosis of this patient.

Due to the complexities of these diseases, more than 20 per cent of all

people with muscular dystrophy or a related neuromuscular condition are currently living without a genetic diagnosis, leaving around 10,000 people in the UK without accurate information about how their condition will progress. Treatments are on the horizon for many of these conditions and to access these patients will need an accurate diagnosis.

The study demonstrates the power of next generation sequencing as a diagnostic tool. While health services like the NHS are likely to adopt similar technologies in the near future, these methods are still rapidly evolving and research-based case studies such as this one will provide important guidance for other researchers and prove the feasibility of these methods.

Dr Marita Pohlschmidt, Director of Research at the Muscular Dystrophy Campaign said: "Diagnosing neuromuscular disorders can be extremely difficult — there are currently thousands of people in the UK living in a state of limbo with no definite answers about their condition. Not only is it psychologically difficult but it can have real consequences upon people's lives, making decisions about treatment options and having children much harder. This research is extremely promising and will bring hope to many families."

The Nottingham researchers worked on the DNA sequencing in collaboration with colleagues at the Norwegian High-Throughput Sequencing Centre in Oslo, which was enabled by a Nottingham Robert's Money Building Experience and Skills Travel Scholarship (BESTS).

More information: The full paper can be found at www.nature.com/ejhg/journal/va … abs/ejhg201242a.html

Provided by University of Nottingham