Deletions and duplications in the exome can help pinpoint cause of unexplained genetic diseases

June 1 2014

Analysis of genetic variation in the exome, the DNA sequence of genes that are translated into protein, can aid in uncovering the cause of conditions for which no genetic cause could previously be found, and this can directly impact clinical management, the annual conference of the European Society of Human Genetics will hear today. Dr Jayne Hehir-Kwa, Assistant Professor of Bioinformatics in the Translational Research group, Department of Human Genetics, Radboud UMC, Nijmegen, The Netherlands, will describe results from her group's study that set out to determine whether copy number variants (CNVs), large genomic deletions or duplications, can contribute to diseases other than intellectual disability.

The role of CNVs in intellectual disability is well known, but their implication in other conditions is less so. "There are, for example, case reports describing deletions in blindness, but no-one has determined the full extent of CNVs in other patient groups," Dr Hehir-Kwa will say.

The team screened 600 patients for which no diagnosis or causal mutation could be found using current whole exome sequencing (WES) methodology, and looked genome-wide for a causal deletion or duplication. It is, they say, the first time anyone has screened systematically for a disease mechanism in such a large and diverse patient group, including five heterogeneous conditions – intellectual disability, deafness, blindness, metabolic disorders, and movement

disorders.

"For these patient groups, targeted gene approaches have been traditionally used for mutation screening and hence the contribution of CNVs to these disease groups has never been established and genome-wide testing rarely applied," says Dr Hehir-Kwa. "Our results show that CNVs are a relatively common, clinically-relevant event."

CNVs were found in patients with many different kinds of disorders, for example retinitis pigmentosa (blindness), Usher syndrome (deafness), Bethlem/Ulrich myopathy (a congenital form of muscular dystrophy), hypotonia-cystinuria syndrome (a neonatal-onset metabolic disorder) and X-linked immunodeficiency (an inherited disorder of the immune system).

"Although WES is not perfect in terms of completely cataloguing genomic variation, our work has shown that it can play an important part in diagnosis. In addition to helping us devise better clinical management strategies for patients, it also affects their prognosis and provides information which can aid us with reproductive counselling for affected individuals," says Dr Hehir-Kwa. "As a result, we are now offering the CNV screening performed in our study as a standard diagnostic procedure in exome analysis for patients where the genetic cause of their condition has not been found previously."

The diagnostic yield differs between the different disease categories, the researchers say. Traditional screening for genetic mutations can explain 27% of intellectual disability, 52% of blindness, and up to 20% of individuals with mitochondrial and movement disorders. "This means that between 48-80% of patients screened with WES are not given a genetic diagnosis. By looking for CNVs in the exon regions of these undiagnosed patients we estimate that we can find such a diagnosis in about a further four percent. In particular, the blindness conditions seem

to have the highest yield of CNVs – up to seven percent," says Dr Hehir-Kwa. "I would like to see screening for more types of genomic variants become standard procedure in genetic diagnostics. The genome of an individual can contain all kinds of different variants, in all shapes and sizes, and it is important that we take all these variations into account." WES, when offered as a first tier diagnostic test, can give a high diagnostic yield, and the result is faster diagnostics at lower cost.

"The more complete and thorough we can make such a diagnostic test, the more accessible we make genetic testing for the public. However, clinical health care professionals need to be well informed about the different genetic disease mechanisms to provide the best possible counselling for patients," Dr Hehir-Kwa will conclude.

Provided by European Society of Human Genetics