Genome-wide analysis shows previously undetected abnormalities in parents of affected children

June 24 2012

The use of genome-wide array analysis in parents whose children are suspected of having a genetic disease shows that the parents frequently also have previously undetected genetic abnormalities, a researcher from The Netherlands told the annual conference of the European Society of Human Genetics. Being aware of this is important to parents because it means that their risk of having another affected child is significantly increased.

Dr. Nicole de Leeuw, a clinical laboratory geneticist in the Department of Human Genetics of the Radboud University Nijmegen Medical Centre in Nijmegen, and colleagues performed genome-wide SNP array analysis in 6,500 patients and 1,874 parents. The patients had intellectual disability and/or congenital abnormalities, and the parents of those in whom an aberration was detected were tested in a similar way to determine whether they had the same aberration as their child. Mosaic aberrations, where both genetically normal and abnormal cells are present in an individual, were not only found in one in every 300 patients, but in one in every 270 parents as well. "These abnormalities occurred more frequently than we had expected", said Dr. de Leeuw. "Armed with this knowledge, we can try to understand not only why, but also how genetic disease arises in individuals, and this can help us to provide better genetic counselling."

Analysis of patients' genomes showed 6.5% de novo (spontaneously

arising) genomic imbalances, 9.1% of rare, inherited imbalances, and 0.8% of X-linked abnormalities. Moreover, with the additional data from their SNP array test results, the researchers were able to subsequently find pathogenic mutations in recessive disease genes, uniparental disomies (where a single chromosome is doubled leading to two genetically identical ones), and mosaic aneuploidies (an extra or missing chromosome in some of the cells of the body) in about 30 patients.

"In at least seven families, these findings meant that what we had thought of as a spontaneously arising, non-inherited genetic abnormality in a child was in fact already present in some form in the parent", said Dr. de Leeuw. "Furthermore, when we tested in different cell lines – for example, DNA from blood and that from a mouth swab – we often found that results varied. This is because mosaic aberrations can occur in cells in some organs and not in others, and underlines the importance of not just relying on one type of cell line for this kind of genetic diagnosis."

In two cases these tissue-dependent differences changed over time, and the researchers believe that this was due to an attempt by the body to correct and rescue the situation. "Such rescue attempts are best known in cases of trisomy, where there are three chromosomes instead of two in a cell, or monosomy, where there is only one. In both these cases, the body may try to correct the situation by respectively deleting or adding (doubling) a chromosome. Such rescue mechanisms may be more common than we expected, and by using genome-wide SNP array analysis it will help us to reveal them. For some patients, it would be particularly interesting if we could test multiple samples of these patients over time", said Dr. de Leeuw.

The majority of genetic diseases are not treatable, but in some cases a special diet may reduce the severity of the symptoms ,for example, in

phenylketonuria (PKU) or in coeliac disease, in others the same can be obtained by periodic examination of certain organs (for example in Down syndrome or Marfan syndrome). Sometimes hormone treatment will be of benefit to the patient, for example growth hormone treatment in Turner syndrome. For most patients with a genetic disorder, there is no cure, but knowing the genetic cause of their disease may help and improve the care for these patients through knowledge about other patients with the same disease. And if the family is at risk of a genetic disease, couples considering having children can be better informed as to their options, the researchers say.

"By using genome-wide array analysis to look for imbalances in the human genome, we will uncover more and more accurate findings in patients. This will not only increase our knowledge of genetic disorders and the human genome in general, but if we can also collect the clinical features of these patients in a structured and uniform way, the information will become increasingly valuable. Fortunately, this is becoming easier due to advances in tools and software applications, and many professionals in the academic and commercial world have agreed to collaborate in order to substantially increase the genotype/phenotype collection and make these anonymised data publicly available to medical professionals in order to improve patient care worldwide", Dr. de Leeuw concluded.

Provided by European Society of Human Genetics

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