Monogenic defects responsible for intellectual disability and related disorders

September 21 2011

(Medical Xpress) -- For over 15 years, genome research has focussed – largely unsuccessfully – on the quest for common genetic risk factors for widespread diseases and conditions, such as diabetes, high blood pressure, schizophrenia and cancer. One of the reasons for this is that many different genetic disorders can be hidden behind these diseases, and not uncommonly defects in individual genes are involved. However, most of these genetic defects are still unexplained.

Researchers at the Max Planck Institute for Molecular Genetics in Berlin and their colleagues in Iran have now succeeded in identifying 50 hitherto unknown genetic causes of intellectual disability. Moreover, there is good reason to believe that several of these new genetic defects are also responsible for related disorders, such as autism, schizophrenia and epilepsy.
To date, almost 7,000 ‘monogenic’ diseases are known, and the corresponding genetic defect identified for around half of them. Around 17 percent of children who are admitted to hospital suffer from these diseases, and the percentage of total healthcare costs generated by their treatment is considerably higher. Nonetheless, many monogenic diseases are still unknown. They often remain undiagnosed as they involve cases that are not associated with an identifiable family history or patients with supposedly complex common diseases and conditions.

An international consortium, of which the Max Planck Institute for Molecular Genetics is a prominent member, has now discovered 50 hitherto unknown genetic causes of intellectual disability in children.

This disorder only arises if the – usually healthy – parents have a predisposition for a certain genetic defect and both pass on a mutated copy of the same gene to their children. Very little has been known about such 'recessive' genetic defects up to now, as the scientists need families with several affected members, in other words very large families, to explain them.

Such families are rare in Germany and other Western countries; however, this is not the case among the populations of the Near and Middle East. Moreover, many parents in these countries are related and this could explain why intellectual disability is around three times more common there than in Germany. Therefore, the Max Planck researchers are collaborating closely with a research centre in Iran. "We all carry genetic defects in us. However, there is a much higher risk that the same genetic defect is involved in diseases suffered by blood relatives," says Hilger Ropers. The sick children of blood-related parents have two identical copies of the responsible genetic defect and the surrounding chromosome sections are also completely identical. This makes it easier for the researchers to find the defective gene.

Since the beginning of the cooperative study in 2003, over one thousand mostly Iranian families with children with an intellectual disability have undergone tests. In 136 of these families, the researchers were able to locate the defect in the genome with sufficient accuracy and, in 78 with the help of new sequencing techniques.

In addition to mutations in 22 already known disease genes, the German-Iranian research team discovered conspicuous mutations in 50 additional genes. Apart from a few exceptions, these genes could be allocated to known regulatory signalling pathways. Many products of the conspicuously mutated genes interact directly with other proteins in these networks, which are coded by genes already known to play a role in intellectual disability. "This is a direct indication that the genes we

found are actually responsible for the disability," says Ropers.

Surprisingly, a majority of these genes and gene products are not solely active in the human brain but in other organs as well. The researchers suspect that this could be related to the fact that, due to the enormous complexity of the central nervous system, the brain is particularly vulnerable to disorders of the cellular metabolism and other fundamental cellular functions. The final proof that the gene mutations discovered by the researchers influence brain function will be provided by ongoing tests on animal models.

These findings, which are being published online in the journal Nature, demonstrate the enormous genetic diversity of intellectual disabilities and subdivide them into different monogenic defects, which are limited to individual families in most cases. "Our findings will help to reduce significantly the time taken by families to obtain a reliable diagnosis – a process that often took years in the past – and offer them new options in relation to family planning," says Hilger Ropers.

Moreover, the studies provide a model for the explanation of related disorders, such as autism, schizophrenia and epilepsy, and for other complex diseases with a genetic background, for which genome-wide association studies have been largely unsuccessful. There are indications that such disorders are often related to intellectual disability: around 30 percent of all patients with an intellectual disability also suffer from epilepsy, and as many as 70 to 80 percent of autistic individuals suffer from an intellectual disability. The results of the tests are therefore of enormous significance for the explanation of these complex conditions.

More information: Hossein Najmabadi, et al. "Deep sequencing reveals 50 novel genes for recessive cognitive disorders," *Nature*, 22. September 2011

Provided by Max-Planck-Gesellschaft