Detecting genes for developmental delay

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Developmental delay Charting parts of the genome likely to contain faulty genes is enabling researchers to home in on genes involved in developmental delay and possibly ones behind psychiatric disorders too.

The international study used DNA from 29,000 children who had been diagnosed with developmental delay and compared it with DNA from nearly 20,000 normal adults.

Seven Australian researchers took part in the study, which is reported today in *Nature Genetics* (http://dx.doi.org/10.1038/ng.3092) .

Children with developmental delay reach their milestones - such as making eye contact, sitting and talking - later than other children, explains Professor Jozef Gécz, of the University of Adelaide (http://www.adelaide.edu.au/) , one of the Australians involved.

Their developmental delay may be the first sign of intellectual disability or an autism spectrum disorder, he says.

Children with developmental delay often miss milestones, such as learning to walk. (Lammeyer/iStockphoto)

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Missing chunks of DNA

Such children are usually seen in a specialist clinic, where genetic testing is run, says Professor Evan Eichler of the University of Washington (http://www.washington.edu/) , USA, the leader of the study.

These tests look for chunks of the genome, usually containing several genes, which are either missing altogether (deletions) or erroneously repeated. These errors, consisting of absent or duplicated DNA chunks, are known as 'copy number variants' or CNVs.

Eichler says that the test may find a CNV in a child's genome, but often the clinician has no idea whether it is causing the developmental delay. The CNV may be involved in the developmental delay or it may be benign, he explains, and knowing whether it is the cause "really matters to individual families."

"Twenty-five percent of kids that come into a clinic for diagnosis will have a large CNV, compared with only 10% of the general population; which suggests that 15% of cases of developmental delay have a CNV underlying as a potential risk factor or cause."

This is where the research comes in: by comparing CNVs in the DNA of children with developmental delay with CNVs occurring in normal adults, 70 CNVs were spotted as potential culprits in developmental delay.

Knowing where to look

Eichler's team then spear-headed a new approach: the individual genes causing developmental delay were likely to be found in the 70 CNVs they had charted, they reasoned.

To pin-point these individual faulty genes, DNA was needed from children who had developmental delay, but had apparently normal genomes (ie with no CNVs). These children were likely to have the 'point mutations' (errors in single genes) that the researcher were after. But until the CNV chart had been prepared, no one knew where to look.

So, DNA was taken from nearly 5000 more children with developmental delay, but for whom no CNVs had been found. As a control, DNA was also obtained from around 2000 unaffected siblings.

The CNV chart meant that Eichler's team needed only to sequence those genes that lay in the 70 CNVs - an efficient approach which made the problem tractable.

Aggressive gene

This enabled them to discover 10 genes which had point mutations, rendering them faulty and, as a result, were associated with developmental delay.

One of these genes, ZMYND11, was particularly interesting says Eichler. Children with a mutation in this gene "are higher functioning so they have only mild developmental disability and we know that most of the males... have neuropsychiatric features in addition, such as severe aggression, rage and bipolar disorder."

"I think this may be one of those genes where we may have found it in kids with learning disability, but it is actually more applicable to adult disease like schizophrenia and bipolar disorder," he suggests.

Gécz's team in Adelaide provided DNA from 1200 Australian children with developmental delay. A handful of them turned out to have a ZMYND11 gene mutation, he says, and comparing clinical notes about these patients was very revealing.

"Things surface only when you see multiple patients," he says. "These disorders are rare."

In patients with the ZMYND11 mutation the IQ wasn't affected and there were lots of behavioural problems, Gécz adds.

He says a ZMYND11 mutation has been found in a person with schizophrenia, and suspects therefore, like Eichler, that the gene may prove to be involved in psychiatric disorders.

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