

## Brain development gene emerges as strong autism candidate

Kate Yandell  
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**Distinctive faces:** People with ADNP mutations tend to have high hairlines, prominent foreheads and thin upper lips.

In April 2013, Evan Eichler attended a meeting on the genetics of autism and intellectual disability in Troina, Sicily.

Eichler, professor of genome sciences at the University of Washington, had planned to present his new data on candidate genes for autism. He and his collaborators had discovered these genes by sequencing the exomes — the protein-coding regions of the genome — of 209 people with autism, and then re-sequencing a promising subset of genes in 5,189 people with autism or developmental delay.

In this list was a gene called ADNP, which Eichler’s team had found to be mutated in four people with both autism and developmental delay, as well as in one control.

In a smaller group meeting later over lunch, cognitive geneticist Frank Kooy of the University of Antwerp in

Belgium showed pictures of two more children with ADNP mutations his team had identified. Eichler pulled out a picture of one of his ADNP cases.

The three children — two Belgian and one Italian — looked remarkably alike, with high hairlines, prominent foreheads and unusually shaped eyes. “Everybody was just like, ‘Wow, this is going to be a new syndrome,’” Eichler recalls.

Kooy and Eichler decided to work together to find more people with ADNP mutations. In the year and a half since, they have found that these individuals have a syndrome that combines autism, developmental delay and distinctive facial features, including a thin upper lip and broad nasal bridge.

In two papers published this year, the researchers identified a total of 11 children with autism symptoms and ADNP mutations<sup>1, 2</sup>. In July, an independent group led by Eric Morrow of Brown University in Providence, Rhode Island, reported one more case: a girl with autism who has an ADNP mutation<sup>3</sup>. Kooy says he knows of three other such children, bringing the total to 15. In all but one of the published cases, the mutations are *de novo*, meaning that the children’s parents do not have them. In the final case, the parents were not available for testing.

“This is a new autism gene,” says Kooy.

## Shared genes:

Among the many hundreds of genes linked to autism, only a few have been clearly characterized. Typically, researchers hoping to zero in on disease subtypes identify people with similar characteristics and then sequence their DNA in hopes of uncovering mutations that contribute to the disorder.

By contrast, the ‘genotype-first’ approach begins by identifying people who have a known genetic risk factor and attempts to chart their symptoms in detail. Researchers are increasingly finding that these genetic risk factors don’t always result in autism. In many cases, they lead only to developmental delay, for example. ADNP is one of a group of genes, including CHD8 and TBR1, that appear to lead to autism in a substantial proportion of cases.

“When recurrently hit, ADNP seems to be enriched in autism as opposed to just broadly defined developmental delay,” Eichler says.

Eichler, however, eschews the idea that there is such a thing as a “pure’ autism gene.” He notes that only some of the children with ADNP mutations have been diagnosed with autism using the gold-standard diagnostic measures.

Among the 12 children — 7 male and 5 female — described so far, all have developmental delay, ranging from mild to severe. Apart from autism, these children also seem to have overly flexible joints and low muscle tone, are prone to infections, and have vision and gastrointestinal problems.

In 11 of the cases, the mutations are in the same section of the gene and tell the cell to stop reading the DNA. Because this section is at the end of the gene, however, the mutated gene is still transcribed into messenger RNA, and may even be translated into protein, Kooy says.

The mutation in the other case is in a more central part of the gene, and almost certainly prevents the protein from being produced, he says.

## Chromatin connection:

ADNP is relatively new to the autism world, but Illana Gozes of Tel-Aviv University in Israel has been studying it for 15 years. Gozes and her colleagues identified the gene in mice in 1999<sup>4</sup> and cloned the human equivalent in 2001<sup>5</sup>.

ADNP appears to be essential for brain development. In mice lacking both copies of the gene, the neural tubes don’t close during fetal development, and the animals die *in utero*. With just one missing copy, the mice have cognitive deficits and develop brain pathology reminiscent of Alzheimer’s disease. Gozes is trying to assess whether these mice would serve as a model for autism.

ADNP is known to interact with the BAF complex, a group of proteins that wind and unwind DNA — a process known as chromatin remodeling — to either suppress or promote gene expression. “Any changes in this system, for instance caused by a lack of ADNP, will have severe consequences for development,” Kooy says.

Other autism-linked genes, including CHD8, have been increasingly linked to chromatin remodeling. ADNP has been identified as a target of CHD8.

ADNP’s work on chromatin remodeling takes place in the nucleus of the cell, where the DNA resides.

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But in neurons, the protein is also present outside the nucleus, where it appears to play a separate role through eight amino acids that make up its so-called 'NAP motif.'

Researchers have tested NAP as a treatment for schizophrenia, mild cognitive impairment and other brain disorders, with mixed success. The peptide easily crosses the blood-brain barrier and appears to be safe, leading researchers to speculate that it may also treat people with ADNP mutations.

"The NAP domain is intriguing," says Kooy. "We can try to see, would just NAP also be able to rescue some of the autistic features in animal models?"

In the meantime, researchers are searching for people with ADNP mutations. An international group of researchers is sequencing ADNP, among a couple of hundred other genes, in around 10,000 people with developmental delay or autism and thousands of controls.

Analyzing a greater variety of mutations in the gene may help explain how the protein functions and the range of symptoms the mutations trigger.

"I still think it's too early to understand the full scope of the phenotype," Morrow says. "I think we're getting a sense of it."

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