NEWS

Seeking genes that protect from autism

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In the past few years, scientists have uncovered a handful of genes that increase the risk of autism. In an interesting twist, others are instead looking for genetic factors that protect from autism.

“Exactly like there are gene variants that will confer vulnerability toward the disease, its very easy to see that conceivably there could also be gene variants that will make an individual more resistant,” says Antonio Persico, an associate professor of physiology at the University Campus Bio-Medico in Rome.

The dividends of this approach are attractive from a therapeutic perspective: knowing how some people avoid autism could provide crucial insights into potential treatments.

Protective gene variants, or alleles, have been identified[1] in other diseases such as malaria and Alzheimer disease, but the evidence for them in autism has been scarce because of the focus on risk factors, says Persico. “People sort of look in one direction and often times don't look in the opposite direction,” he says.

Still, there is reason to believe that protective genetic factors are relevant in autism. Unaffected siblings of people with autism presumably share similar genetic and environmental risk factors, yet they somehow avoid the disorder. Protective factors might also explain why girls develop autism less frequently than boys; males with autism outnumber females, four to one.

Researchers have canvassed the sex chromosomes looking to explain this difference. Last year, British researcher **David Skuse** and his colleagues turned up an X-linked gene called EFHC2 that might be relevant to autism[2].

A rare variant of EFHC2 is associated with social difficulties in Turner syndrome, a condition in which a female has only one X chromosome. Given the striking behavioral similarities between Turner syndrome and girls with Asperger syndrome, the same rare variant may also play a role in autism, says Skuse, professor of behavioral and brain sciences at University College London.

Like children with Asperger syndrome, girls with Turner syndrome have normal language

development, but struggle socially. Interestingly, both groups seem aware of their social awkwardness, and attempt to make up for it by emulating the social behavior of their peers. “It feels a little like they are acting,” Skuse says.

EFHC2 may help compensate for social skills that are compromised by other risk factors, Skuse suggests. In that case, inheriting the rare variant on one X chromosome without the common variant on another X chromosome to counterbalance it ? as is the case in Turner's syndrome and, possibly, in males with autism ? could prevent someone from compensating effectively for social difficulties. The common variant of EFHC2 could be thought of as protective in autism, Skuse says.

Suggestive data:

In a study published in July, Persico?s group identified a genetic variant that might also protect from autism[3]. The gene, called SLC25A12, encodes a protein that transports molecules within the mitochondria.

This particular variant was found in unaffected siblings more frequently than expected. Such an ‘over transmission? of a variant could indicate some benefit, such as protection from autism, Persico says.

However, the over transmission was only a trend, not reaching statistical significance, and there was no complementary ‘under transmission? in those with autism, as expected for a protective allele, notes **Ed Cook**, professor of psychiatry at the University of Illinois in Chicago.

“I would call the data suggestive,” says **James Sutcliffe**, associate professor of molecular physiology and biophysics at Vanderbilt University. “But in this business it is absolutely crucial that these findings be replicated in an independent sample of families with unaffected siblings.”

Persico himself agrees that the evidence is preliminary. “It is not enormously strong,” he says, “but it is definitely strong enough that we are pursuing it.”

SLC25A12 encodes a transporter protein called AGC1 that contributes to the production of ATP, the energy currency of cells, in the mitochondria. Persico says that a protective version of this transporter might help stave off oxidative stress in the brain, which has been implicated in autism.

He also has similar, albeit weaker, evidence of a protective variant of GLO1, a gene encoding an enzyme involved in another biochemical pathway[4].

In some ways, looking for protective alleles is no different from searching for risk alleles. For every risk allele identified for autism, says Cook, there is typically a version that doesn?t increase risk, making it relatively protective.

“You basically have alleles that push you toward autism or away from autism,” Cook says. “[They?re] yin and yang. You can't interpret one without comparing it to the other.”

References:

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