VIEWPOINT

Explaining ‘resilience’ in autism may seed new therapies

BY **THOMAS BOURGERON**

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A few years ago, I received a phone call from the mother of a young man with autism. She had just learned that her son, who was in his 20s, has a deletion in **SHANK3**, one of the genes my team discovered is mutated in some people with autism. I was surprised by her news because I had met her son and found him to be much less affected than most of the carriers of this type of mutation. He can communicate and attends a mainstream school.

She explained that since he was a baby, she had tried everything to stimulate her son. But if she had known about the mutation, she confessed, “I might have not fought like this. Fighting the

genome, it was impossible."

Her comment made me realize how deeply rooted 'genetic determinism' is. This idea implies that the outcome of a deleterious mutation cannot be changed. In other words, if you carry such a mutation, there's no escape; your fate is sealed.

But this thinking is wrong. And it inspired my research on resilience — the ability to resist the severe consequences associated with a deleterious genetic alteration.

In the past 50 years, we have seen tremendous progress in identifying the genes and biological pathways associated with autism. What we do not understand, however, is how the same mutation can have divergent outcomes. In rare cases, people in the general population or relatives of individuals with autism carry mutations in autism-associated genes but do not show features of the condition.

Understanding how these resilient individuals cope with deleterious mutations might provide important information on how specific genetic backgrounds and environments contribute to major differences in developmental and clinical trajectories[1].

Varied features:

The genetic architecture of autism is heterogeneous. In some people, a single mutation seems to be enough to precipitate autism features. In others, autism is most likely due to the additive effect of thousands of common variants, each one with a weak effect.

The identification of genes that confer autism risk when mutated has significantly advanced our knowledge of the condition's possible causes. These include perturbations in protein production, the remodeling of the protein-DNA complex known as chromatin, and the ability of neuronal junctions, or **synapses**, to change with experience[2].

Identifying these genes has also unintentionally contributed to the emergence of a simplistic conception of autism as a binary trait: Either you have it or you don't. This simplification neglects the heterogeneity — and the range of clinical severity — of the condition.

What's more, mutations associated with autism do not always lead to the condition. Some mutations have complete penetrance; that is, all carriers have autism. In other cases, only, say, 80 percent of people with the mutation have autism.

Identifying why the consequences of a mutation vary among people remains a challenge. But the genome may provide some clues.

Possible protection:

It is well established that the consequence of one mutation can be ‘suppressed’ by another mutation. Studies in yeast reveal that many of these suppressive interactions occur between genes belonging to the same biological pathway[3].

In people, large-scale genetic studies have identified ‘modifier genes’ that provide resilience in HIV infection, sickle cell disease, heart disease and diabetes[4,5,6,7,8].

In a pilot study, we estimated the proportion of resilient individuals in the **Simons Simplex Collection**, a repository of genetic samples from families in which one child has autism. (The collection is funded by the Simons Foundation, *Spectrum*’s parent organization.) In this analysis, we defined ‘resilients’ as any unaffected siblings or parents that carry harmful mutations in a set of 65 genes strongly associated with autism[9].

Preliminary results from 1,776 families reveal the presence of resilience in 2 to 3 percent of family members of individuals with autism. The number of resilients is higher for some genes than for others. For a few genes, we have found no resilient individuals. We are currently ascertaining the number of resilients and of affected individuals for each of the 65 genes. The next step is to identify the factors that allow the resilient individuals to cope with their deleterious mutations.

For example, sex-sensitive brain circuits could modulate how often autism mutations co-occur with autism. Boys are four to eight times as likely to receive an autism diagnosis as girls are. The reasons for this disparity remain poorly understood. But one possibility is that other genes — perhaps even the non-mutated version of the altered gene — act as modifiers.

For example, in resilient people, certain genes might be expressed at higher levels than usual or carry another mutation that buffers the effects of the deleterious mutation.

Boosting resilience:

Finally, access to high-quality treatments might increase resilience. A 2012 study showed that, over time, about 10 percent of children with severe autism bloom and progress significantly[10]. One factor that distinguished these children was their family’s higher socioeconomic status.

Access to treatment has boosted resilience for other heritable conditions. For example, a phenylalanine-free diet can prevent the intellectual disability associated with phenylketonuria — an inherited metabolic condition that can cause a toxic build-up of phenylalanine in the brain — if the diet starts in the first weeks of life[11].

Over time, more and more individuals will have access to their genetic profile. Although this information should lead to more effective treatments and preventive measures, it might also lead to unnecessary distress in the individuals who have a deleterious mutation.

A better understanding of the mechanisms underlying resilience could lead to new avenues for keeping severe clinical outcomes at bay — and also reduce the emotional toll that may result from genetic testing. As Louis Pasteur once said: “The best doctor is nature: She cures three out of four illnesses, and she never speaks ill on her colleagues.”

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