Q&A

Questions for Thomas Bourgeron: In search of 'second hits'

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To build a **list of genes** with definitive ties to autism — 65 and counting — researchers look for mutations that crop up in children with autism but not their unaffected parents and siblings. But these rare, harmful mutations are just one piece of autism's complex genetic puzzle. They don't explain, for instance, why autism runs in families, or why two people with the same mutation can have vastly different characteristics.

Thomas Bourgeron, professor of genetics at the Institut Pasteur in Paris, is among a group of researchers taking a second look at people who carry a harmful mutation in a known autism gene. Scientists often exclude these individuals from studies under the assumption that the genetic cause of their autism has already been identified, he says. Bourgeron says scouring their genomes may reveal additional mutations or 'second hits' that help to explain how autism is inherited and why it is so diverse.

We asked Bourgeron how painting a more detailed picture of autism's genetic landscape will help to advance the field.

***Spectrum*: Why should scientists look for additional mutations in people with autism who already have a genetic hit?**

Thomas Bourgeron: Our genetic risk is just like a painting that is made up of small dots. Take out one dot and not much changes, but all these dots together make a meaningful painting.

The autism field has progressed so rapidly; it's really amazing. But most of the time we have one column attached to genetic information that says whether or not an individual has autism: yes or no. And sometimes, when we're lucky, we have the intelligence quotient (IQ). But behind these columns, there is a person.

If we only consider that one column — autism: yes or no — it's easy to say that we found the mutation that caused that autism.

But people with autism may have epilepsy, yes or no; sleep problems, yes or no; gastrointestinal problems, yes or no. Autism itself is not yes or no. Some children with **SHANK3** mutations are severely affected and can barely speak, and some are going to college. Can additional genetic hits explain this genetic diversity?

S: Is the field embracing this complexity in autism?

TB: I like to say, as a joke, that I have my monogenic friends and my polygenic friends. My monogenic friends look for a strong single genetic cause in each individual. They find a rare mutation in an affected child and not an unaffected sibling and say, "This is a gene for autism."

Most of my monogenic friends are clinicians who have a patient in front of them and want to be sure and robust when they talk about genetic risk.

My polygenic friends don't care about these rare mutations because they do not explain why autism runs in families. These spontaneous, or *de novo*, variants do not explain the heritability of autism. Studies have shown that the risk of developing autism is inherited, so where is that heritability coming from?

The full answer to autism's genetic puzzle lies in the fact that there are millions of genetic variants. We need to think of the genome as a diverse landscape and look at every genetic variant, whether it has big or small effects. Common variants, the ones that are frequent in the population, add up to weight, height, IQ and quantitative traits such as brain volume. They also play a huge role in autism. But they do so collectively, not individually. And, to date, for autism we don't know where they are or how to measure their effects.

S: Is there a danger in talking about 'autism genes,' because the term implies clinicians should look no further than a single gene?

TB: That is exactly the question I'm exploring. One day I received an Excel file with a list of individuals to include in a sequencing study. Next to several of these patients it said 'excluded.' I asked my colleague why they were excluded, and she said, "Because you already found the gene for autism in this family."

I then decided that I'm only going to work on these 'excluded' families. I've now sequenced the entire genomes of about 20 of them. Some of them have a big hit, such as a mutation in SHANK3. But I think it's important to say, "OK, we have SHANK3, but is there something else?" If you don't look, you will not find it.

S: What are you finding?

TB: This project is in progress, but we do find other mutations. Even in families that have two kids with autism, sometimes one sibling will have a clinically relevant, likely gene-disrupting mutation. But his brother, who also has autism, carries a completely different mutation. Our results replicate those from another whole-genome sequence analysis of siblings with autism **published last year**.

S: Could additional genetic hits counter the effects of a known autism mutation?

TB: I call these people 'The Resilients' or the superheroes. Sometimes I'll see a large chromosomal deletion or clinically relevant mutation in an individual and think, "OK, he has intellectual disability or autism." But it turns out he's the unaffected father or sibling of someone with autism, or a 'control.'

The more we sequence these 'controls,' the more we see people who have a mutation so strong that we'd assume it was the cause of their autism if they had it. But they don't. Why can people cope with very strong deleterious mutations?

My theory is that some mutations are okay in some genomes, or environments, but not others. Imagine throwing a cigarette in the hills in L.A. in August. The chance that it will start a fire is quite high. Take the same cigarette and drop it in Seattle in November and probably nothing will happen. The cigarette is the mutation, and some genomes are protected.

Now that we know the strongest autism risk genes, it's time to look at them across the general population. The first step is to identify everyone in autism and control databases who carries a strong mutation, but who is the unaffected father, mother or sibling of someone with autism. It could seem like a problem for the field if people who don't have autism carry the mutation. But instead of seeing this as problem, I see this as an opportunity.