CROSS TALK

What constitutes 'environmental' risk for autism?

BY **GREG BOUSTEAD**

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In May, we reported on results from the **largest population study to date** to assess the heritability of autism.

The researchers concluded from their study that “genetic factors explain half of the risk for autism.” Much of the media interpreted this — incorrectly — to mean that environmental factors make up the rest of autism risk.

Among autism researchers, the paper led to vigorous discussion about what exactly the term ‘environmental’ comprises, and about the challenges of calculating the heritability of complex disorders.

As part of our discussion series, **Cross Talk**, we asked researchers who study heritability and quantitative genetics to clarify these points.

What do you think? Share your reactions and follow-up questions in the comments section below.

Michael Wigler

Professor,Cold Spring Harbor Laboratory

Random, not environmental

Professor, Cold Spring Harbor Laboratory
Essential caveats: “This important study from the Karolinska Institutet reports incidence data for autism and autism spectrum disorders for the Swedish population, accrued over the past 20 years. Our point of view was not clearly captured in the**SFARI.org article** on this work. These valuable new data offer a comparison of risk between twins, siblings and half-siblings. The authors conclude that the data support the hypothesis that autism is half genetic and half ‘environmental.’ “Unfortunately, the authors appear to confuse randomness (in outcome) with environment — a very loaded term — as a catch-all for ‘incompletely determined by genetic state.’ Moreover, the model the authors use to reach their conclusion may not be appropriate, and they do not evaluate the data in light of recent thought and evidence for the role of singly highly penetrant rare and *de novo* variants (mutations that are not inherited, but spontaneously occur in a parent’s egg or sperm cells). They also seem to ignore the importance of evaluating the higher moments of sibling risk — riskto children born into families that already have two others with autism — as explained in our **recent review**.”
Alternate conclusions possible: “Full access to the raw data would be valuable to the wider community, who could use other tools to model the data — in which case, a very different set of conclusions might be drawn.”

Greg Gibson

Director,Center for Integrative Genomics, Georgia Institute of Technology

Heritability is about populations, not individuals

Director, Center for Integrative Genomics, Georgia Institute of Technology
Does it matter? **“**Without detracting from the magnitude of the accomplishment and the analyses, which I find compelling, at some level arguing over whether genetics explains 50 percent or 80 percent of the variance for autism is a little like asking whatamount of global warming can be explained by human activity: The bottom line is that the contribution is enormous, but it is not particularly enlightening with respect to specific cases (of autism or environmental catastrophe). Heritability is a statement about populations, not individuals, and any measure is compatible with markedly different genetic contributions in individual cases.”
What does environment mean? *“*On the other hand, the contention that environment is more

important than generally accepted surely only has policy implications if the source of the environmental effect is known. Is it unidentifiable effects, identifiable non-biological effects we can't do much about (urban living, sunlight exposure), identifiable cultural effects we may be able to change (daily exposure to TV or iPads), or identifiable effects we would probably not change even if known (living as nuclear instead of extended families, perhaps)? More important than this is the question of whether the environmental effects are the same for everyone: Perhaps they are triggers for some children, and general susceptibility factors for others."

Rare variants may be overhyped: "It does not seem that **copy number variations**, *de novo* mutations, and segregating rare variants are collectively causal in more than a quarter of cases (causal in the sense that without the variant, the criteria for autism would not be met). This leaves the vast majority of cases unexplained, and there is really strong evidence that thousands of common variants of small effect are contributing to risk. Quite likely they contribute to gene expression profiles that place each of us closer or further from a risk threshold that rare variants or environmental perturbations push some children over. Given this complexity, it is almost certainly the case that environmental factors are also important, so for me, this paper reminds us of the complexity of the disorder."

***Exploring heritability*:** "Geneticists are finding more and more rare and common variants that influence the likelihood of developing autism. It would be great if there were as much research into the genetics and heritability of the disorder's progression and response to interventions through genome-wide association studies."

Kevin Mitchell

Associate Professor of Genetics,Trinity College Dublin

Work does not suggest external, environmental factors

Associate Professor of Genetics, Trinity College Dublin

Questionable model: "The general conclusions from this new work on the heritability of autism **fit with previous studies**, in that they show a large effect of genetic variance and no effect of the shared family environment. However, the precise estimates of the mathematical values of these terms depend on a number of assumptions in the statistical models, which are not universally agreed upon. The numbers that emerge are in general of limited value anyway, given that the

diagnostic category of autism is really an umbrella term for many distinct genetic etiologies and not a specific genotype."

Dangerous terminology: "The conclusions of an important effect for the environment should be tempered, especially given how they can be misinterpreted and misrepresented. The fact that monozygotic twins are not always concordant for the disorder suggests there are some non-genetic factors that contribute to whether individuals develop the disorder or not. In the analytical models used here, these sources of variance are bundled into a statistical term called the 'non-shared environment.' This term is used here in a technical sense that does not correspond to the colloquial meaning. In particular, it should not be taken as evidence of effects of some causal factors out in the environment.

Unique development: "Brain development is incredibly complex and inherently variable, even for the same genotype and in the same environment. The probabilistic nature of neurodevelopmental events at the cellular level can manifest as quite different phenotypic outcomes at the organismal level. By the time they are born, the brains of monozygotic twins are thus already highly distinct from each other. This does not represent effects of external factors — this variability is entirely intrinsic to the developing organism itself."

"Given that they are likely to contribute to the already rampant misinformation regarding causes of autism, headlines suggesting that this study demonstrates an important role for external, environmental factors should therefore be avoided."

Peter Visscher

Professor and Chair of Quantitative Genetics,University of Queensland

Common variation does not contradict rare contributions

Professor of Quantitative Genetics, Queensland Brain Institute, University of Queensland

What it tells us: "This is the largest population-based study to date on autism risk for relatives of individuals with the disorder. The authors use the observed risk to relatives to estimate heritability on the unobserved scale of 'liability.' They estimate that about 50 percent of variation in liability to autism in the Swedish population is due to additive genetic factors. The study confirms that autism is a 'complex trait,' just like other traits and disorders in humans, all the way from height to schizophrenia."

New mutations: “The population parameter of heritability is ‘blind’ in terms of the number of genes, their effect size and frequency in the population, so this study is not informative in that respect. The mathematical model that fit the observations best was one for which variation in liability is due to additive genetic effects (which are shared by relatives in proportion to the degree of relationship) and ‘environmental’ factors that are specific to an individual. The study is not informative about what these ‘environmental’ effects might be, other than to conclude that they cannot be attributed to the shared environment of family members and hence are considered to be unique to individuals. But they can also include the effect of new mutations.”
Parsing liability: “The observed risk to relatives of this study is remarkably consistent with the researchers’ hypothesized model of liability, since on that scale the risk halves with each degree of relatedness, all the way from monozygotic twins to cousins. The results are also consistent with similar studies on schizophrenia and bipolar disorder. For those disorders, many common genetic variants have been found that explain some of the heritability, using genome-wide association studies. Notably, the experimental sample sizes for genome-wide association studies on autism have been much smaller than those for other psychiatric disorders, even though evidence for the existence of common genetic variation for autism **has been reported**. A role of common genetic variation does not contradict a contribution of rare and *de novo* mutations to risk of autism.”

Lonnie Zwaigenbaum

Professor,University of Alberta

Highlights challenges of modeling heritability

Professor of Pediatrics, University of Alberta
Recurring insight: “The authors provide estimates of autism recurrence risk for each of the types of relatives (from twins, to siblings, half-siblings and cousins), which may be helpful in counseling families. It is important to note that these risk estimates (for example, 12.9 percent in siblings) are based on risk at age 20 years, in contrast to other recent studies in which recurrencerisk was based on assessment at a much younger age. For instance, **Sally Ozonoff** and her colleagues **reported in 2011** that 18.7 percent of younger siblings of children with autism also have the diagnosis at age 3 years.
“It is intriguing that they do not find any trend towards increasing recurrence risk of autism in

relatives over the study period. This is consistent with Danish birth registry data **reported last year** by Therese Koops Grønborg and her colleagues, despite trends towards higher rates of autism diagnosis in the general community. Such trends are widely regarded to be influenced, at least in part, by the clinical diagnostic criteria for autism broadening over time (that is, to a broader 'spectrum'). If this is truly the main driver, one might expect to observe trends towards higher recurrence rates as well."

Challenging model: "It's important to emphasize, though, that heritability estimates do not have a straightforward interpretation for individual families. For example, there are families in which two affected siblings carry different rare pathogenic variants, a circumstance that certainly challenges how we have modeled heritability."