

CROSS TALK

Are girls really protected from autism?

BY GREG BOUSTEAD

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A new study **we covered earlier this month** adds powerful support for an emerging concept: Girls need more mutations than do boys to cross the threshold into an autism diagnosis.

Known as the 'female protective effect,' this theory may explain the **fourfold imbalance** in autism rates between males and females. But, combined with research suggesting that **autism characteristics differ by gender**, it also raises thorny questions about potential biases in assessing girls for autism.

We asked researchers who study autism in females whether they believe that girls need a bigger mutation load to be recognized as having autism, as part of our discussion series, **Cross Talk**.

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



Catherine Lord

Director, Center for Autism and the Developing Brain, Weill Cornell Medical College

Girls with autism are just as diverse as boys

Director, Center for Autism and the Developing Brain, Weill Cornell Medical College, Columbia University

Girl power: "The new paper by **Evan Eichler** and colleagues adds more detailed genetics about a

so-called ‘female protective effect’ in terms of the size of the **copy number variations** (large deletions or duplications of DNA), the significance of the genes associated with them and how these are related to gender differences — not only in autism but also in other neurodevelopmental disorders. It puts autism findings in the context of other disorders that have similarly higher prevalence rates in males than in females, though often not quite as high a male-female ratio as in autism. The investigators, with a large sample size, were able to find gender differences. Often with smaller samples, differences in intelligence quotient (IQ) distribution exceed gender differences, and so there is not enough power to analyze both.”

Not all the same: “I think we tend to forget — this is not a criticism of the paper at all, but of all of us — that girls with autism are just as diverse as boys. Part of the problem in identifying subsets of symptoms in girls with autism is that they are not all the same and there are proportionately fewer of them in IQ ranges of 100 or higher. Thus I strongly support the proposal of the authors of the new paper that we need more carefully phenotyped and genotyped samples, **with oversampling of girls.**”

Likely bias: “Ideally, epidemiology and the surveillance studies from the Centers for Disease Control and Prevention could help us here, but because of our dependence on existing records in the U.S. and on registries in other countries, the chances of both of these sources of information being biased are very high. Perhaps analogous studies determining these possible biases would be helpful, so that accurate inferences could be made from the more easily accessible data sources.”



David Skuse

Professor, University College London

Where are all the girls with autism?

Chair, Behavioural and Brain Sciences, University College London

Important questions remain: “Are we failing to identify higher-functioning girls with autism? What do we expect to see in a typical female with the condition? Are they being overlooked because their behavior differs from that of boys, **leading to their misdiagnosis?**”

Misleading behavior: “Symptoms in boys and girls with normal-range IQ are quite different. Language delay, aggression and disruptive behavior are often the reasons why boys come to

clinical attention. Externalizing symptoms characterize the psychiatric problems of boys in general. Girls with serious **social communication disorders** are more likely to internalize their symptoms, and have greater insight. From an early preschool age, like any other girls, they are socially aware and try to emulate typical female behavior.

“They may do this very successfully for a while. Desperate to fit in, they remain quiet and behave in an exemplary way at school so as not to draw attention to their problems. At home, they often act out their frustrations, leading to families seeking support from professionals, only for the conclusion to be drawn that there is family dysfunction. Nobody ever considers the possibility that this delightful child, who the school says is a pleasure to teach, could have a form of autism. Yet the underlying social communication problems are identical in nature and severity to those of boys.”

Looking under the lamppost. “Clinical evaluation requires an unbiased history — most diagnostic interviews and questionnaires are derived from male stereotypes. Overfocused special interests in girls are frequently socially appropriate (pop music, film stars, makeup, shoes). Cognitive rigidity and routines usually reflect more social preoccupations, such as self-image or eating behavior. Many serious manifestations — including school refusal, overt anxiety, depression, self-harm and worse — may not emerge until adolescence.

“Conclusions regarding genetic risk are biased by ascertainment: Genomic disruptions in girls that predispose to the condition remain undiscovered unless they have affected IQ. Our **failure to identify girls with ‘covert’ autism** has serious implications for their welfare. Let’s stop looking for our lost keys under the lamppost.”



Angelica Ronald

Reader, Centre for Brain and Cognitive Development, Birkbeck, University of London

Assessing an increased burden

Director, Genes Environment Lifespan laboratory, and Reader, Centre for Brain and Cognitive Development, Birkbeck, University of London

Tackling a messy tangle: “This new study is impressive in its scope in investigating sex differences in autism at the genetic level. It also exposes the messy tangle of factors that feed into the sex differences in autism rates beyond DNA, which include societal norms, diagnostic

traditions, cognitive impairment and comorbidity. More work like this, and cross talk between molecular geneticists and behavior geneticists, epidemiologists, neuroscientists and clinicians, will help us unravel these (hopefully not too tightly) tangled threads.”

Agreement with other studies: “The authors are sensible in their statements about the possible role of ascertainment bias in driving their genetic results: Girls are more likely to be recognized and diagnosed with autism if they **have additional comorbidities** and low IQ, and this ascertainment bias could drive findings at the genetic level. Yet their results can be seen to concur with **our work on the female protective effect** using a general population **cohort of dizygotic twins**, which had mutually exclusive biases and relied on a different (nonclinical) sample design.”

Terribly greedy: “It is terribly greedy of me — since the study is so comprehensive — but I would love to know if the siblings of the females with neurodevelopmental disorders have an increased burden of deleterious autosomal copy number variations compared with the siblings of the males with neurodevelopmental disorders. This would be another form of evidence that girls need to be in a family with, on average, more genetic risk factors present to show autism compared with boys. Perhaps a bright spark will follow this up.”