Response to Buxbaum et al.

To the Editor: We welcome the response by Buxbaum and colleagues[1] from the Autism Sequencing Consortium (ASC) to our commentary, "Insufficient Evidence for 'Autism-Specific' Genes."[2] We are pleased that there is agreement that the current evidence does not establish specificity of any genes for autism spectrum disorder (ASD), nor does it support the idea that ASD-specific gene panels would have clinical utility.[1,2]

We also agree that mutations in genes implicated in ASD may have variable impact on IQ. The ASC study demonstrated that cohorts ascertained for ASD and severe neurodevelopmental delay (NDD), which very likely differed significantly in IQ distribution, also differed significantly in the distribution of mutations in ASD-associated genes.[3] Classification of genes as either "ASD-predominant" or "ASD with NDD" based on the rate of *de novo* disruptive variants in the ascertainment cohort resulted in two more homogeneous sets of genes that, at the group level, differed significantly in characteristics, including mean IQ, age of walking, frequency of *de novo* protein-truncating variants in parents, and frequency of inherited rare protein-truncating variants within families.[2,3] Our concern was about the potential for inappropriate incorporation of the classification of some genes as "ASD-predominant" into clinical decision making, including ASD-specific gene panels or lists, the value of which has been advocated by some.[4,5] Buxbaum and colleagues[1] correctly point out that they did not advocate for such clinical use of their classification and that it would not be appropriate.

Finally, we agree that larger cohorts will be required to reliably identify specific genes as being enriched in ASD compared to intellectual disability (ID) and other NDDs. Rather than studying cohorts defined by categorical diagnoses, we advocate for completing studies that cross diagnostic boundaries to identify rare *de novo* and inherited variants involved in developmental brain dysfunction and designing experiments to elucidate the origins of variable phenotypic expression. In addition to determining which genes are involved in the primary mutation, factors such as variant type, background oligogenic and polygenic risk, and environmental and stochastic variation are likely to be important. This approach will require uniform phenotyping across participants, including measurement of continuously distributed traits, to allow examination of effect sizes of different sources of variation on phenotypes relevant to ASD, ID, and other neurodevelopmental and neuropsychiatric disorders.

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