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Autism in neurofibromatosis type 1: misuse of covariance to dismiss autistic trait burden

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EDITOR–We read with interest the report by Morotti et al.[1] which raises several important points regarding neurodevelopmental phenotypes in individuals with neurofibromatosis type 1 (NF1). Notably, the authors replicated previously published observations of a pathological shift in autistic trait burden in NF1 and substantial correlations between autistic trait scores and attention-deficit/hyperactivity disorder (ADHD) symptom ratings (Spearman's *rho*=0.66).

Unfortunately, a principal aspect of the authors' approach was to use the covariance with ADHD (effect size=0.40) to mathematically 'explain away' the comparably-sized effect of NF1 on autistic trait burden. As in a similar prior attempt to use behavioral data to explain away an even larger main effect,[2] we challenge the appropriateness of pitting one phenotype against another in a regression or covariance model. Simply put, if NF1 actually causes *both* ADHD and autistic trait aggregation (which the preponderance of prior research and even this small study support[1,3]), asserting that one symptom explains away the other is no more appropriate than it would be to assert that optic glioma prevalence is not elevated in NF1 because it is accounted for by an excess of café-au-lait spots.

Nearly all studies of autism in the population have documented genetic overlap of autistic trait liability with ADHD symptomatology on the order of 50%. NF1 represents a rare and valuable monogenic example of this overlap; using the ADHD–autistic trait correlation to dismiss a main effect of NF1 on autistic trait burden risks losing a major biological lead with a partially overlapping consequence of the mutation. The importance of specifying autistic trait burden is underscored by the observation that NF1 exhibits mutational specificity for its severity and therefore represents, in essence, a quantitative trait locus for autistic variation across the range from subclinical to clinical level symptomatology with preliminary associations with specific sequence variants.[4,5]

Moreover, there are significant problems with drawing inferences regarding the case rate for clinical autistic syndromes from either electronic health records (clinical diagnosis of autism in NF1 is only starting to gain traction in the community), or the clinically ascertained sample (Appendix S1, online supporting information). The representativeness of the latter is severely compromised, given the bimodal distribution

of Social Responsiveness Scale, Second Edition (SRS-2) scores in this cohort, which differs radically from the continuous distribution of SRS-2 scores observed in more representative samples, as published from the INFACT analysis.[4]

Understanding the nature of the cooccurrence of ADHD and autistic trait symptoms, and the extent to which they may accentuate one another over the course of development (as observed for the association of autistic traits with other 'comorbid' behavior impairments), is a next priority for prospective developmental studies of NF1. In addition, the extent to which individual *NF1* gene mutations amplify cooccurring behavioral impairments or selectively engender cases with greater or less concordance in autistic and ADHD trait burden remains to be explored.

Definitive elucidation of the relationships between NF1 and its disparate neurodevelopmental manifestations awaits accrual of fully representative samples in which genotype, variation in quantitative behavioral traits, and diagnosis are simultaneously ascertained. The current body of research on the association between NF1 and autism represents a valuable lead that warrants thorough scientific interrogation of the relationship between genotype and phenotype in this recurrent monogenic syndrome.

Future studies aimed at understanding the genomic, genetic, cellular, and circuit-level etiologies for the neuropsychiatric consequences of loss-of-function mutations in NF1 will position the field to better anticipate the symptom burden of affected individuals and enable earlier intervention to ameliorate symptoms.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Methodological limitations.

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