Is the neurodiversity model of autism genetically supported?

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ABSTRACT

An important question for researchers and autism advocates is whether phenotypic differences in autism would be better represented by separate disorders. Since autism is highly heritable, one way to evaluate this question is to examine genetic factors to see if their heterogeneity decreases within phenotypic subtypes of autism. Understanding this not only helps researchers learn more about autism, but also has important implications for public policy and social work.

INTRODUCTION

The neurodiversity movement is a social movement which is "explicitly inclusive" of all autistic and other neurodivergent people (Pelicano and den Houting, 2022). Rather than focusing on a "cure" for autism, neurodivergent treatment models focus on reducing stigma and providing support and accommodations to neurodivergent individuals (Pelicano and den Houting). Autism spectrum disorder (ASD) is the current diagnostic model for autism in the DSM V, and it encompasses a wide range of heterogeneous phenotypes (American Psychiatric Association, 2013, pp. 50-59; American Psychiatric Association, 2000, pp. 130-138). If the ASD model of autism is correct, then it provides support for the neurodiversity movement and should also affect the type of research being performed on ASD. If ASD is in fact a set of loosely associated disorders, you would expect genetic heterogeneity to decrease with decreasing phenotypic heterogeneity.

METHODS

To evaluate whether genetic heterogeneity was associated with phenotypic heterogeneity, we searched the GWAS catalog for studies of autism (Buniello, McArthur, et al., 2019). We then evaluated the studies listed and found only one study examining the relationship between phenotypic and genetic heterogeneity in ASD. This study evaluated subjects from the Simons-Simplex Collection, grouped them into phenotypic subgroups and compared genetic heterogeneity between the subgroups and the broader ASD phenotype (Chaste, Sanders, et al., 2015; Fischbach and Lord, 2010). 11 phenotypic subgroups were identified for the study based on diagnosis, IQ and symptom profiles.

Phenotypic subtyping **does not** decrease genetic heterogeneity in autism.

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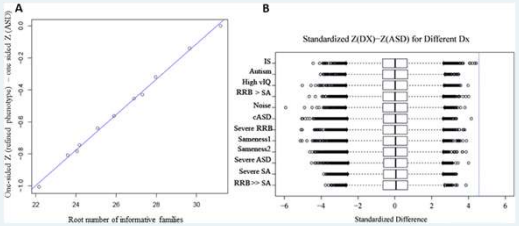
RESULTS

The study showed no difference in SNP association for any of the 11 subgroups in the study. The authors evaluated this by calculating the average z-scores of SNPs with p-values < 0.1 for ASD association, then plotting the standardized difference between them. (Figure 1). The authors also graphed the standardized difference against the root number of informative families to ensure that the effects seen weren't due to sample sizes (Figure 2). In both cases, phenotypic subtyping had no effect on genetic heterogeneity.

Figure 1



Note: (A) Relationship between the number of informative families and the average difference in Z statistics for selected single nucleotide polymorphisms (SNPs). For SNPs with p value < .01 for association in the full sample, the difference in average Z statistics is calculated as the absolute value of the Z statistic for the full sample minus the absolute value of the Z statistic achieved for the subsample and the average is taken over all qualifying SNPs. The straight line shows the expected relationship for the difference if the samples were drawn at random from the full sample. (B) Box plot of difference of one-sided Z in each phenotypic subset of the whole sample from one-sided Z score in all autism spectrum disorders (ASD). The difference was standardized. The vertical line in the plot is drawn at the one-sided Z score of 4.58, corresponding to p = .05/21,351. cASD, European ancestry ASD; DX, diagnosis; IS, insistence on sameness; RRB, restricted and repetitive behavior; SA, social affect; vIQ, verbal IQ. Adapted from "A Genome-wide Association Study of Autism Using the Simons Simplex Collection: Does Reducing Phenotypic Heterogeneity in Autism Increase Genetic Homogeneity?" by P. Chaste et al., 2015, *Biological Psychiatry*, *77(9)*, p. 779. Copyright 2015 Society of Biological Psychiatry.

DISCUSSION

The fact that phenotypic subtyping has no effect on genetic heterogeneity in ASD suggests that the wide spectrum of phenotypic differences in autism may be due to natural human difference, rather than representing separate disorders. This research validates the approach taken by the DSM V and suggests that future studies should focus on potential novel biomarkers to identify ASD pathways rather than spending time attempting to identify haplotypes associated with phenotypic subgroups of ASD. Nonetheless, the number of subjects in this study were relatively low for a GWAS, and larger studies might find trends which this one was underpowered for. Additionally, although this study found no genetic differences between the 11 phenotypic subgroups identified here, it's possible that other phenotypic subgroups not analyzed in this study could derive from a more monolithic haplotype.