Is the neurodiversity model of autism genetically supported?

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Abstract

Autism spectrum disorder is a neurological disorder that presents with a variety of socially stigmatized behaviors. For much of the past century, treatment for autism has consisted mainly of attempts to treat the behaviors of autistic individuals to make them conform to societal norms. The neurodiversity movement instead embraces the concept of concept of autism being a spectrum to promote destigmatization of autistic behavior and reduce the pathologization of autism. As a broader societal movement, it affects many factors related to the lives of autistics, including treatment and research trends. As such, it's important to ensure that the spectrum model of autism is biologically supported if possible.

This poster presents a literature review of broader societal trends as they relate to autism, as well as a study published in 2015 examining whether dividing autism into smaller subgroupings based on various factors decreased genetic heterogeneity. The study found no significant differences in genetic heterogeneity between phenotypic subgroups, suggesting that the significant phenotypic differences seen between autistic individuals are natural variation from a common core phenotype, rather than representing a group of similar disorders which have distinct genetic sources.

Introduction

Autism spectrum disorder (ASD) or autism is a commonly-misunderstood neurological disorder recognizable by deficits in social communication, and repetitive stereotyped behaviors, and interests (American Psychiatric Association, 2013, pp. 50–59). Before 2013, ASD was divided into a variety of separate disorders such as Asperger's Syndrome, Autistic Disorder, Rett's Disorder, and others. In the DSM IV, these were grouped together as a set of related disorders, but were considered separate diagnoses (American Psychiatric Association, 2000, pp. 130–138). As shown by its diagnostic history, ASD is an extremely heterogeneous disorder, with extreme diversity of symptoms and severity. Some people with ASD require significant support to function, whereas others require more support to handle everyday tasks.

The modern neurodiversity movement works to help autistic people by focusing on reducing stigma and providing support and accommodations for autistic individuals (Pelicano and den Houting, 2022). It is a social movement which is "explicitly inclusive" of all autistic and other neurodivergent people (Pelicano and den Houting). It also relies heavily on the concept that phenotypic differences between neurodivergent individuals are due to natural human variation and should not be selectively pathologized. This movement has important implications for ongoing research on the causes and potential treatment for people with ASD, and as such it's important to verify the conceptual schema of autism as a spectrum.

It is well established that autism is highly heritable and many loci have been associated with ASD in various studies (Bolton et al., 2016). Although no specific biomarkers or pathways are known at the time of writing, one way to evaluate whether ASD is truly one heterogeneous disorder or whether it is actually a grouping of similar disorders might be examining whether genetic heterogeneity decreases if autistic subjects are grouped by phenotypic differences. If so, the current model of autism as a spectrum might need to be reevaluated, along with aspects of the neurodivergence movement.

Methodology

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 2,576 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). Since the Simons-Simplex collection consists solely of families where neither parent and only one child is affected, it is ideal of this type of study (Fischbach and Lord, 2010). Eleven phenotypic subgroups were identified for the study based on diagnosis, IQ and symptom profiles such as repetitive stereotyped behaviors, etc. See Table 1 for the full list of phenotypic subtypes evaluated, as well as the number of cases studied

Single Nucleotide Polymorphisms (SNPs) were evaluated from all individuals, and any SNPs with high noncall rates were removed from the analysis (Chaste, Sanders, et al.). Genetic association, heritability estimates and allele scores were then calculated to be used in the final analysis of the effects of phenotypic subtyping.

Table 1

Subgroup	Abbreviated Name	Criteria	*n* Cases
Whole sample	All ASD	ASD on both ADI-R and ADOS	2575
Restricted Autism Diagnosis	Autism	ADI-R autism and ADOS autism	2088
Verbal IQ > 60	High vIQ	Verbal IQ > 60	1880
Higher ADOS ASD Symptoms	Severe ASD	Overall ADOS CSS ≥ 8	1200
Higher ADOS RRB Symptoms	Severe RBB	ADOS RRB CSS ≥ 8	1589
Higher ADOS Social Affect Impairment	Severe SA	ADOS Social Affect CSS ≥ 8	1091
Higher ADI-R Circumscribed Interests	Sameness1	ADI-R Circumscribed interests ≥ 2	1474
Higher ADI-R Difficulty with Change	Sameness2	ADI-R Difficulty with change ≥ 2	1313
Higher Sensitivity to Noise	Noise	ADI-R Sensitivity to noise ≥ 2	1676
ADOS CSS RRB Higher than SA	RBB > SA	ADOS RRB CSS ≥ Social Affect CSS	1805
ADOS CSS RRB Much Higher than SA	RBB >> SA	ADOS RRB CSS ≥ Social Affect CSS + 2	880

Note: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; CSS, calibrated severity score; RRB, repetitive and restrictive 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.

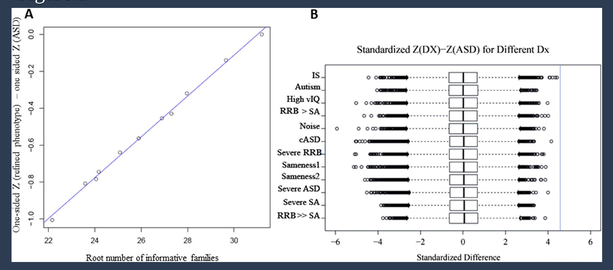
Note: The Autism Spectrum Infinity Awareness Symbol is a more generally accepted symbol for autism awareness than the puzzle piece given the complex history of groups such as Autism Speaks with the autistic community. It is a common representation of the modern shift towards the neurodiversity movement within the broader autistic community. Adapted from: (last name unknown), E. (2022). Autism spectrum infinity awareness symbol. Wikimedia Commons. Wikimedia Commons. Retrieved December 7, 2022, from https://commons.wikimedia.org/wiki/File:Autism_spectrum_infinity_awareness_symbol.svg.

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 1A). 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 1B). In both cases, phenotypic subtyping had no effect on genetic heterogeneity. In fact, the correlation seen in Figure 1A is almost perfect.

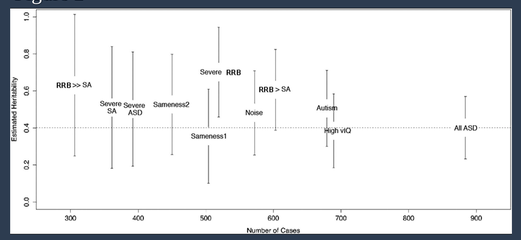
The researchers also examined the effects of phenotypic subtyping on heritability and found that the subgroups defined by excess repetitive behaviors (denoted RRB), had higher average heritability than other subgroups (Figure 2). Although this overall trend was noted, the researchers found no significant difference in mean heritability between subgroups. The researchers also generated allele scores for the subgroups, but there was no apparent trend in allele scores based on phenotypic subtype, nor was there a significant difference in mean allele score based on subtype.

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.

Figure 2



Note: (A) Heritability estimates in each phenotypic subset of the whole sample. All ASD, whole sample; Autism, restricted autism diagnosis; High vIQ, verbal IQ > 60; Noise, higher sensitivity to noise; RBB > SA, ADOS CSS RRB higher than SA; RBB ≫ SA, ADOS CSS RRB much higher than SA; Sameness1, higher ADI-R circumscribed interests; Sameness2, higher ADI-R difficulty with change; Severe ASD, higher ADOS ASD symptoms; Severe RBB, higher ADOS RRB symptoms; Severe SA, higher ADOS social affect impairment. ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; CSS, calibrated severity score; RBB, 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 may be due to normal human variation around a common set of behaviors rather than representing a grouping of separate disorders. This result validates the decision taken in the DSM V to unify the ASD into a single diagnosis and also suggests that the neurodiversity model does in fact have credible scientific backing. Particularly telling are the results in Figure 1A which show almost no variation from the expected z-scores based on sample size. Although the sample size of this study was relatively low for a GWAS, which meant that this study was somewhat underpowered, the results are very consistent with the idea that all manifestations of ASD have a common biological basis.

For researchers, this suggests that grouping subjects based on phenotypic measurements such as ADI-R scores or similar metrics is unlikely to yield better results in genetic studies. The fact that high RRB phenotypic subtypes were more heritable could also be of interest to future researchers, particularly since it may represent a behavioral phenotype more directly controlled by genetic factors. This could make it a fruitful research area for scientists to examine potential neurodevelopmental pathways in ASD

An important caveat to these results is that this study measured a very specific set of phenotypic subtypes, and it might be that other subgroupings not studied here, possibly with metrics not available in this study, might identify subgroupings with lower genetic heterogeneity. Given that, the importance of continuing similar studies should not be discounted, particularly if new metrics are identified which weren't available in this study. Additionally, this study only examined the relationship between genetic heterogeneity and phenotypic heterogeneity, and studies of epigenetic factors might also yield different results.

Since the neurodiversity model of autism relies so heavily on the spectrum model of ASD, it is encouraging that initial studies into the DSM V model of phenotypic heterogeneity in ASD appear to validate the idea that the phenotypic heterogeneity present in ASD are due to natural variation around a common phenotype.

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