

## Leveraging Polygenic Scores to Go Beyond Examinations of Pathology Among Gender-Diverse Individuals

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Gender is defined as the attitudes, feelings, and behaviors that a culture associates with a person's sex assigned at birth (1). Strong evidence indicates that across adolescence and adulthood, there is diversity in the experience of gender, with as many as 35% of cisgender adults (who identify with the gender associated with their sex assigned at birth) feeling to some extent like a gender not associated with their sex at birth (2). This is consistent with findings from a large community sample of young adolescents in which 20% of the participants at ages 10 to 11 years did not feel totally and exclusively like the gender associated with their sex at birth (3). These findings document that gender diversity is not rare and occurs outside of people who identify as transgender. Given this, gender diversity should be considered as an important construct in neuroscience studies—outside of those focused on minority populations. However, many, if not most, studies still assess gender with categorical items that assess only gender identity. The recent article by Thomas *et al.* (4) demonstrates that rigorous neuroscience research using a more nuanced measure of gender can shed light on how gender influences health and behavioral outcomes.

Thomas *et al.* (4) examine the central question of whether gender diversity is related to polygenic scores for known behavioral traits. Specifically, polygenic scores from large genome-wide association studies (GWASs) for 16 behaviors (mental health diagnoses, personality traits, cognitive performance, and nonheterosexual sexual behavior [NHSB]) were examined. The study is methodologically rigorous and uses the Gender Self Report (5), a dimensional measure of gender that yields scores for both binary (male/female) and nonbinary dimensions of gender. This captures a more nuanced experience of gender that is then leveraged to shed light on polygenic scores associated with gender diversity. In this study, the gender self-report captured gender diversity among individuals with a cisgender gender identity, further supporting the relevance of individual differences in gender beyond people who identify as transgender.

The selection of the 16 polygenic scores used in this study was driven by the polygenic associations found in a previous GWAS of NHSB (6). That study was conducted using a large sample from the UK Biobank and found overlap between polygenic risk genes for NHSB and those for mental health conditions and risk-taking behaviors (6). While gender and sexuality are independent constructs, the occurrence of NHSB is higher among gender-diverse adults in the United States (7). In the absence of an adequately powered GWAS of gender diversity, the decision to ground the current study in the NHSB

GWAS is justifiable. The selection of mental health constructs for examination is particularly important given the rates of mental illness among gender-diverse individuals (8). Currently, the relative contributions of biological factors (genetics, hormones, etc.) and societal factors (interpersonal violence, discrimination, and harassment) that result in higher mental illness among gender-diverse individuals are undetermined.

The central finding of the article is that the strongest polygenic association with gender diversity is cognitive performance, followed by NHSB. The associations with polygenic scores for psychopathology and personality were not statistically significant. These findings are very important because they suggest that the higher rates of mental illness among gender-diverse people are not primarily genetic in origin—and likely reflect the victimization and discrimination that is also well documented among gender-diverse individuals. Very little scientific work has tested for advantages associated with minority populations, and this study provides a model for the inclusion of both positive and negative traits in future studies. The results of this study also support current conceptualizations of gender diversity aimed at removing the lens of pathology that has often been used as a default in studies of gender diversity.

The current study used 2 samples from the SPARK (Simons Foundation Powering Autism Research for Knowledge) project (9). SPARK is a US autism study that includes more than 300,000 participants and genomic, behavioral, and medical information on participants. SPARK participants include adults and children with autism, as well as parents and siblings without an autism diagnosis. For the current study, SPARK participants age 14 years and older were invited to participate by completing the Gender Self Report (5) and additional questionnaires measuring mental health, sexuality, and gender, which were linked to their SPARK data. This sample lends itself to exploration of gender diversity because individuals with autism have higher rates of gender diversity, and gender diverse individuals have higher levels of autistic-like traits than peers (10). However, the use of this sample posed some methodological challenges. Specifically, autism diagnosis, age, and sex assigned at birth were all confounded with gender diversity. The authors used multiple statistical approaches to probe these associations including entering autism, age, and sex as covariates in the models; residualizing age, sex, and autism before running the models; and running separate models among individuals with and without autism. The findings of polygenic scores for cognitive performance being associated with gender diversity were robust to these different approaches.

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Overall, this article provides intriguing evidence for an association between gender diversity and the polygenic score for cognitive performance—and for no robust relationship between gender diversity and polygenic scores associated with mental health problems. Future research will clarify whether this relationship is seen in samples that are not enriched for autism spectrum disorder and will explore environmental factors that may explain the relationship between gender diversity and mental health outcomes.

### Acknowledgments and Disclosures

This work was supported by the National Institutes of Health (Grant Nos. U01DA051039 and U24 DA041147 [to ASP]).

The author reports no biomedical financial interests or potential conflicts of interest.

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Received Mar 24, 2024; accepted Mar 27, 2024.

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