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Preview

# Toward a deeper understanding of gene-by-sex interaction models

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**In this issue of *Cell Genomics*, Zhu et al.[1] propose amplification as the primary mode for gene-by-sex interactions in complex traits. Khramtsova et al. preview their modeling approach and discuss implications for the future work on the genomics of sex differences.**

Sex differences in complex traits and diseases are influenced by multiple factors, including genetics, hormones, and sex chromosome complement.[2] Recent advancements in genomic technologies are shedding light on mechanisms driving sex differences.[3] A deeper understanding of their contributions will reveal the fundamental biology of sex differences and disease processes and enable precision medicine.

Conventional approaches to test for sex differences in genetic effects, including single-locus, genetic correlation and heritability analysis, do not fully explain the observed sex differences for a majority of traits. For example, Bernabeu et al.[4] show that of the roughly 530 traits analyzed in the UK Biobank, approximately 5%–7% of binary and up to 49% of quantitative traits show a sex difference in trait heritability or the proportion of phenotypic difference explained by genetic variation. In recent work, Zhu et al. set out to investigate whether gene-by-sex interaction (GxSex) effects are the major drivers for sex differences.[1] Zhu et al. propose that GxSex most commonly acts through "amplification", or in other words, through sex difference in effect size, rather than difference in specific causal variants or their direction of the effect.

Acknowledging that there is not a strict one-to-one relationship between sex chromosome karyotype and biological sex, and choosing the terms male and female as a proxy for individuals with XY and XX chromosome complement, respectively, Zhu et al. performed several sex-combined and sex-stratified analyses on 27 quantitative traits measured on the UK Biobank participants. Testing for differences in heritability between sexes is a commonly used approach to detect genetic sex differences; however, as Zhu et al. propose, sex differences in heritability may be explained by multiple polygenic models: (1) no GxSex but due to differences in environmental variance, (2), weakly or negatively correlated genetic effects, (3) highly correlated effect with a difference in magnitude ("amplification"), and (4) a mixture of covariance relationships (Figure 1 in Zhu et al.).

For some traits, such as testosterone, single-locus and narrow-sense heritability analyses may reveal substantial discordance between sexes with a low genetic correlation; however, for many traits, the genetic correlation between sexes is greater than 0.9 even when phenotypic variance exists and relatively large sex differences in heritability are observed. Furthermore, Zhu et al. demonstrate that GxSex can present in multiple forms for the same trait. For example, the observation that sex-specific heritabilities are higher than combined-sex heritability for most traits suggests that genetic variance differs between sexes. Additionally, the observation that the trait variance explained by the polygenic score (PGS) differs between males and females provides evidence for amplification. However, using PGS to test for presence of amplification should be exercised with caution because sample size differences between male and female cohorts may lead to biased prediction in one sex versus another.[5]

These observations motivated the authors to examine the covariance between male and female genetic effects, as unique GxSex patterns might exist among subsets of genetic factors. Zhu et al. estimated the mixture of weights using multivariate adaptive shrinkage, quantifying the proportion of variants that follow specific magnitude and correlation patterns (Figure 3 in Zhu et al.). The findings suggest that amplification of genetic effects is the primary model of GxSex. Testosterone is the only trait for which a large fraction ($\geq$10%) of non-zero effects were negatively correlated between sexes. Most effects were instead perfectly or near-perfectly correlated. Overall, the low weights on matrices representing negative correlation do not support opposite allelic direction flips across sexes as a major mechanism of GxSex. For half of the traits analyzed, the majority of weights point to larger effects in one of the sexes (x axis in Figure 4A in Zhu et al.).

Importantly, for some traits (e.g., hemoglobin A1C and diastolic blood pressure), previously considered non-sex specific because of high genetic correlation between sexes, the authors find evidence

for substantial GxSex through amplification. Heritability estimates indicate that diastolic blood pressure has a significantly higher female narrow-sense heritability relative to heritability estimated from combined-sex analysis, but this is not the case for HbA1c (Figure 1 in Zhu et al.). The observation that sex-biased amplification may be high for traits with low phenotypic variance ratio (Figure 4A in Zhu et al.) further supports the recommendation to systematically test for genetic sex differences, irrespective of the magnitude of phenotypic sex differences.[3] The difference between the fraction of male-larger effects and the fraction of female-larger effects correlates strongly with male-to-female phenotypic variance ratio (Pearson r = 0.87, p value = $6 \times 10^{-9}$, Figure 4A in Zhu et al.). Additionally, Zhu et al. show that considering polygenic covariance structure in PGS prediction outperform those that consider additive models only for most traits (20/27; Figure S12 in Zhu et al.), implicating the utility of considering polygenic covariance structure in polygenic prediction.

Further, Zhu et al. hypothesize that cues and exposures may further modulate GxSex magnitude and, possibly, direction of effect. For example, gendered environmental differences may also differentially impact genetic signatures of amplification. Testing the effect of confounders and reverse causality attenuated the signal with testosterone, highlighting the importance of sensitivity analyses while also considering reduction of power when interpreting results.

Lastly, Zhu et al. propose a model for incorporation of the captured GxSex into measures of sexually antagonistic selection. While this model provides evidence for sexually antagonistic polygenic selection on testosterone, the authors note that such analyses may be sensitive to and confounded by differences in study participation by sex[6] and technical artifact,[7] complicating implementation of existing models to study sexually antagonistic selection and requiring new methods development.[8]

By demonstrating that GxSex is pervasive and acts through a variety of mechanisms, including amplification, Zhu et al. provide a rationale and an analytical framework for testing for GxSex at scale. We believe that this analysis approach should become best practice for testing models of sex differences, and an important next step is to investigate whether the approach proposed by Zhu et al. would reveal amplification as a driver for sex differences in complex traits and diseases.

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## DECLARATION OF INTERESTS

E.A.K. is an employee of Janssen Pharmaceutical Companies of Johnson & Johnson.

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