GWAS of biomarker variance in UK Biobank identifies evidence of GxG and GxE interaction effects

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1. Introduction

- Effect modification describes the situation where an exposure-outcome relationship varies in the presence of a third variable known as the modifier
- Detecting effect modification is important to identify groups of individuals who may benefit most from an intervention or who may experience unwanted side-effects
- Effect modification of an exposure-outcome relationship produces heteroscedastic residuals when the outcome is regressed only on the exposure
- This research aims to evaluate the Breusch-Pagan test [1,2] to detect SNP-biomarker effect modification where the modifier is unknown or unmeasured.
- Additionally, we aim to follow up variance QTLs (vQTLs) with formal gene-gene (GxG) and gene-environment (GxE) interaction tests

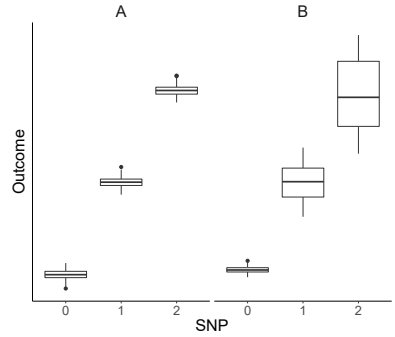

Figure 1. A, SNP has a homogenous main effect producing homoscedastic residuals. B, SNP has a main and interaction effect on the outcome giving heteroscedastic residuals when the outcome is regressed on the exposure without specifying the interaction term. SNP, allele dosage.

2. Simulation study design

- Test power to detect SNP effect modification was evaluated using the Breusch-Pagan test and Levene's test implemented in OSCA [3] (Figure 2)
- A SNP x continuous modifier N(0,1) interaction effect was simulated to produce effect modification of the SNP-outcome relationship
- Normal, lognormal and t-distribution (df=4) were used as trait residuals to provide normal, kurtotic and skewed distributions, respectively
- Effects were set using methodology from Brookes et al [4]. The main effect δ was fixed to have 80% power with a sample size inflation factor $\lambda = 1$. The interaction effect $\theta = \delta\phi$ was set relative to the main effect and the outcome was generated with these simulated values $y = (\delta - \theta)x + \theta xu + e$

3. Simulation study results

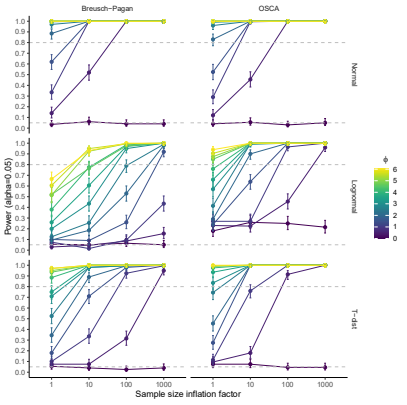

Figure 2. Power to detect SNP-trait effect modification using the Breusch-Pagan test [1,2] and Levene's test implemented in OSCA [3]. Phi is the size of the interaction effect relative to the main effect. The sample size inflation factor is a multiplier of the anticipated sample size required to detect the main effect with 80% power as described in Brookes et al [4]. T-dist, four degrees of freedom.

- The power to detect effect modification was generally low (Figure 2). For example, power was approximately 50% when the interaction effect was half the size of the main effect using a sample size 10x that needed to detect the main effect with 80% power.
- Both methods had similar power for normally distributed data; OSCA had higher power for non-normal distributions.
- OSCA also had elevated type 1 error under the lognormal distribution while Breusch-Pagan showed better control for non-normal data

4. GWAS of variance effects in UK Biobank

- Genome-wide association studies of SNP effects on biomarker variance were performed in ~330k white British unrelated UK Biobank participants using the Breusch-Pagan test adjusted for age, sex and top ten genetic principal components

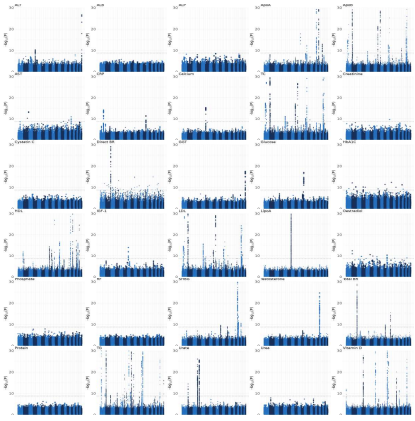

Figure 3. Manhattan plots for GWAS of variance effects using the Breusch-Pagan test on 30 blood biomarkers in UK Biobank

5. Identification of GxG and GxE interaction effects

- Pairwise GxG and candidate GxE interaction tests of biomarker vQTLs were performed (Figures 4 & 5).

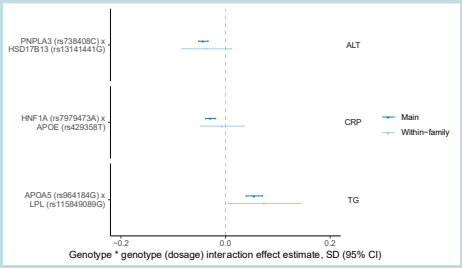

Figure 4. Top GxG effects ($P < 5 \times 10^{-8}$) in main analysis and within-family sensitivity studies. All models adjusted for age, sex and top ten genetic principal components.

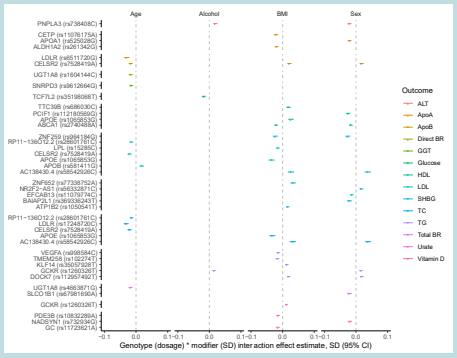

Figure 5. Top 50 GxE effects adjusted for age, sex and top ten genetic principal components.

- We found evidence of GxG effects ($P < 5 \times 10^{-8}$) on ALT, CRP and TG concentration supported by within-family studies and GxE effects on 15/30 biomarkers ($P < 5 \times 10^{-8}$) interacting with at least one of: age, alcohol intake, BMI, sex and smoking status (top 50 GxE effects shown).
- Therapies targeting the product of these genes may show subgroup effects on biomarker concentration. These findings could have implications for drug development and prescribing policy.

6. Conclusion

- Heteroscedasticity testing can be applied to rapidly detect SNP-trait associations for effect modification when the modifier is unknown or unmeasured
- The Breusch-Pagan test has lower type 1 error than Levene's test (OSCA[3]) for skewed data but also lower power for non-normal traits
- We found GxE and GxG effects on 15/30 and 3/30 biomarkers respectively ($P < 5 \times 10^{-8}$)
- Detection of interaction effects could have important implications for targeting interventions to those who would most benefit and are least likely to suffer adverse effects

7. References

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