of predictors greatly exceeds the number of samples. False negatives can result from two-stage approaches, where the residuals estimated from a null model adjusted for the subjects' relationship structure are subsequently used as the response in a standard penalized regression model. To overcome these challenges, we develop a general penalized LMM framework that simultaneously selects and estimates ~~variables~~, accounting for between individual correlations, in one step. Our method can accommodate several sparsity-inducing penalties such as the lasso, elastic net and group lasso, and also readily handles prior annotation information in the form of weights. We develop a groupwise-majorization descent algorithm which is highly scalable, computationally efficient and has theoretical guarantees of the convergence. Through simulations, we show that ~~are~~ method has better power over the two-stage approach, particularly for polygenic traits. ~~We apply our method to identify SNPs that predict bone mineral density in the UK Biobank cohort~~. This approach can also be used to generate genetic risk scores and finding groups of predictors associated with the response, such as variants within a gene or pathway. Our algorithms are available in an R package (https://github.com/sahirbhatnagar/ggmix).

1 Introduction

Genome-wide association studies (GWAS) have become the standard method for analyzing genetic datasets owing to their success in identifying thousands of genetic variants associated with complex diseases (`https://www.genome.gov/gwastudies/`). Despite these impressive findings, the discovered markers have only been able to explain a small proportion of the phenotypic variance, known as the missing heritability problem (1). One plausible explanation is that there are many causal variants that each explain a small amount of variation with small effect sizes (2). Methods such GWAS, which test each variant or single nucleotide polymorphism (SNP) independently, ~~are likely to~~ miss these true associations due to the stringent significance thresholds required to reduce the number of false positives (1). Another