**Low quality genotype data is not appropriate for family-based analyses**

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**Abstract**

Family-based analyses leverage random genetic variation within families to control for population stratification and distinguish direct from indirect genetic effects. FGWAS and sib-GWAS aim to address confounding issues affecting standard GWAS designs. However, real-world genotype data imperfections, particularly from imputed genotypes, pose challenges that have not been fully explored.

Most GWAS data originate from genotyping arrays followed by imputation using a reference panel. Since imputation does not consider pedigree relationships, low-quality imputed genotypes in parents or siblings may fail to properly control for confounding in FGWAS or sib-GWAS. To examine this, we analyzed 19,290 sibling pairs and 5,324 parent-offspring pairs from the UK Biobank white British subsample.

We found that imputed genotype correlations between relatives decrease as the INFO score declines. For imputed dosages, the mean correlation between siblings across 1,000 SNPs with INFO scores of 0.30–0.31 and minor allele frequency ≥1% was 0.437 (S.E.=0.001), lower than the expected 0.5. Hard-call genotypes had an even lower correlation of 0.376 (S.E.=0.001). Even at INFO scores of 0.96–0.97, hard-call genotype correlations remained slightly below 0.5 (P=1.6x10⁻⁴).

To further assess the impact of imputation quality on family-based analyses and other downstream applications, we leverage newly available whole-genome sequencing data from the UK Biobank. This allows us to compare imputed genotypes with their true counterparts, providing a direct evaluation of imputation accuracy and its consequences for genetic analyses. Our findings underscore the importance of rigorous quality control and the development of pedigree-aware imputation methods in family-based genetic studies.