Height as a Model for Heterogeneity: Dissecting Traits Variation Using Skeletal Components Derived from Deep Learning DXA Imaging

Background:
Understanding heterogeneity in complex traits and diseases remains challenging, particularly when biological subcomponents cannot be directly measured. Human height provides a tractable model for studying genetic heterogeneity because it can be decomposed into measurable skeletal components. We leveraged UK Biobank DXA imaging data to extract skeletal components and investigate whether genetic variants affect height through heterogeneous effects across skeletal components.

Methods:
We applied the HRNet-UDP deep learning architecture for keypoint detection on dual-energy X-ray absorptiometry (DXA) images from 89,580 UK Biobank participants, achieving high accuracy. After quality control, 81,703 participants with measurements of four skeletal traits (head-neck, torso, femur, tibia) and total height were included in the analysis. Genome-wide association studies (GWAS) were performed for each trait. Pedigree-based genetic variance is estimated using average information restricted maximum likelihood (AI-REML) with genomic relationship matrices. Partitioned heritability and genetic covariance were estimated using SBayesRC and S-LDSC, respectively. We developed a mathematical framework to test for heterogeneity that exploits the constraint that height equals the weighted sum of its skeletal components. Colocalization analysis was conducted to distinguish between distinct causal variants and shared variants with heterogeneous effect sizes across skeletal components.

Results:
At the phenotypic level, skeletal components explained 92% of height variance. Genetic analysis revealed that skeletal traits accounted for 43.4% of height's SNP-based heritability, with high genetic correlations between height and skeletal components (range: 0.78-0.85). Functional annotation showed heritability enrichment in limb regions, consistent with tissue-specific biology. Genetic covariance partitioning identified shared regulatory regions and conserved elements between skeletal traits and height. Preliminary heterogeneity testing identified 37,871 SNPs passing Bonferroni correction that also reached genome-wide significance ($p < 5\times10^{-8}$) in at least one trait, indicating widespread heterogeneity in genetic effects between height and skeletal components. Colocalization analysis demonstrated strong colocalization patterns across skeletal components.

Conclusions:
Decomposing height into skeletal components provides a framework for studying genetic heterogeneity in complex traits and diseases.