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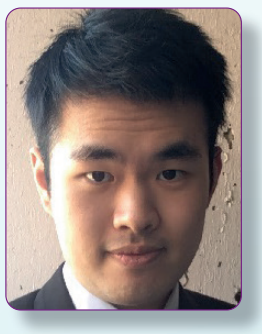

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Identifying Rare Genetic Determinants for Improved Polygenic Risk Prediction of Bone Mineral Density and Fracture Risk

Tianyuan Lu, Vincenzo Forgetta, Sirui Zhou, J Brent Richards and Celia MT Greenwood.

Fracture risk assessment is important for improving health care for the elderly population. Existing genetic risk predictors have been able to integrate a substantial fraction of common genetic components that influence bone mineral density, yet the implications of rare genetic determinants have not been thoroughly investigated.

In this work, we leveraged the largest WES data resource from the UK Biobank to systematically identify rare genetic determinants of bone mineral density. We constructed ggSOS incorporating both common and rare genetic predictors and evaluated to what extent the inclusion of influential rare variants could add value to polygenic risk prediction of osteoporosis and osteoporotic fracture risks.

With whole-exome sequencing data from 436,824 UK Biobank participants, we assigned White British ancestry individuals into a training data set (n = 317,434) and a test data set (n = 74,825). In the training data set, we developed a common variant-based polygenic risk score for heel ultrasound speed of sound (SOS). Next, we performed burden testing to identify genes harboring rare determinants of bone mineral density, targeting influential rare variants with predicted high deleteriousness.

We constructed a genetic risk score, called ggSOS, to incorporate influential rare variants in significant gene burden masks into the common variant-based polygenic risk score. We assessed the predictive performance of ggSOS in the White British test data set, as well as in populations of non-White British European (n = 18,885), African (n = 7165), East Asian (n = 2236), South Asian (n = 9829), and other admixed (n = 1481) ancestries.

Twelve genes in pivotal regulatory pathways of bone homeostasis harbored influential rare variants associated with SOS ($p < 5.5 \times 10-7$), including AHNAK, BMP5, CYP19A1, FAM20A, FBXW5, KDM5B, KREMEN1, LGR4, LRP5, SMAD6, SOST, and WNT1. Among 4013 (5.4%) individuals in the test data set carrying these variants, a one standard deviation decrease in ggSOS was associated with 1.35-fold (95% confidence interval [CI] 1.16–1.57) increased hazard of major osteoporotic fracture.

However, compared with a common variant-based polygenic risk score (C-index = 0.641), ggSOS had only marginally improved prediction accuracy in identifying at-risk individuals (C-index = 0.644), with overlapping confidence intervals. Similarly, ggSOS did not demonstrate substantially improved predictive performance in non-European ancestry populations.

In summary, based on large-scale GWAS and rare variant association testing, we have developed ggSOS to combine common and rare genetic determinants for predicting bone mineral density and fracture risk. We identified potentially influential rare variants that likely confer a strong effect on bone mineral density. Nonetheless, the relatively high cost of sequencing, low prevalence of influential rare variants, limited gain in prediction accuracy, and persistent cross-ancestry generalizability issues largely preclude the immediate clinical utility of ggSOS in population-level risk screening and entail careful considerations in research and in clinics.

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