What is Osteoporosis?

- Common disease that affects both sexes by increased thinning and porosity of bone
- Bone mineral density (BMD) is the single best predictor of osteoporosis risk and fracture susceptibility

UK Biobank, BMD and Fracture

BMD can be estimated at the heel (eBMD)
- Using quantitative ultrasound
- Speed of sound (SOS)
- Bone ultrasound attenuation (BUA)

GWAS of eBMD and Fracture

Previously, eBMD GWAS in 142,487 UK Biobank participants identified 203 loci (153 novel)
- Currently, there are no large-scale fracture GWAS

GWAS of eBMD

| eBMD GWAS of 424,183 participants identified 515 loci (301 novel) 1,103 conditionally independent lead SNPs, 20% variance explained |

Fracture GWAS of 53,184 cases and 373,611 controls identified 13 loci
- 14 conditionally independent lead SNPs, all associated with eBMD

Enrichment for Known Bone Genes

- Defined known bone biology or drug target genes from review papers 6
- Strongest enrichment for fine-mapped SNPs with functional annotations

Validated Target Genes with Mice

Origins of Bone and Cartilage Disease
- High-throughput mouse knockout screening for 19 skeletal parameters for bone mineral content, 3D trabecular and cortical bone structure, bone mineralization, and femoral and vertebral bone strength 13
- 126 target gene knockouts enriched for outlier skeletal phenotypes P<0.001 compared against 526 unselected lines

Further Study of DAAM2

- Brief results from hypomorphic Daam2 mice
- Decreased maximum load from a) destructive 3 point bend testing of femurs and from destructive and (b) compression testing of femurs
- Daam2 hypomorphic mice had bone quality less than 250 σ in control (c)

Primary Aims

1. Given the pronounced polygenicity of eBMD, identify target genes
   - Generate and utilize human bone cell functional genomics data
2. Validate as many genes as possible using mouse knockout models
   - In collaboration with the Origins of Bone and Cartilage Disease (ORCID) program
3. Make further insights into the genetic architecture of osteoporosis
   - Profile in-depth novel top candidate genes for osteoporosis with CRISPR/Cas9 in human bone cells

Conclusion

- Increased the number of associated BMD loci to 518 and variance explained to 20%
- Identified methods that mapped associated SNPs to genes enriched for known causal genes
- Provided a DAAM2 target gene in human bone cells and in mice to observe bone phenotypes

References

2. Bassett et al. 2015, PLOS Genet.