Supplementary Information

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Supplementary Table

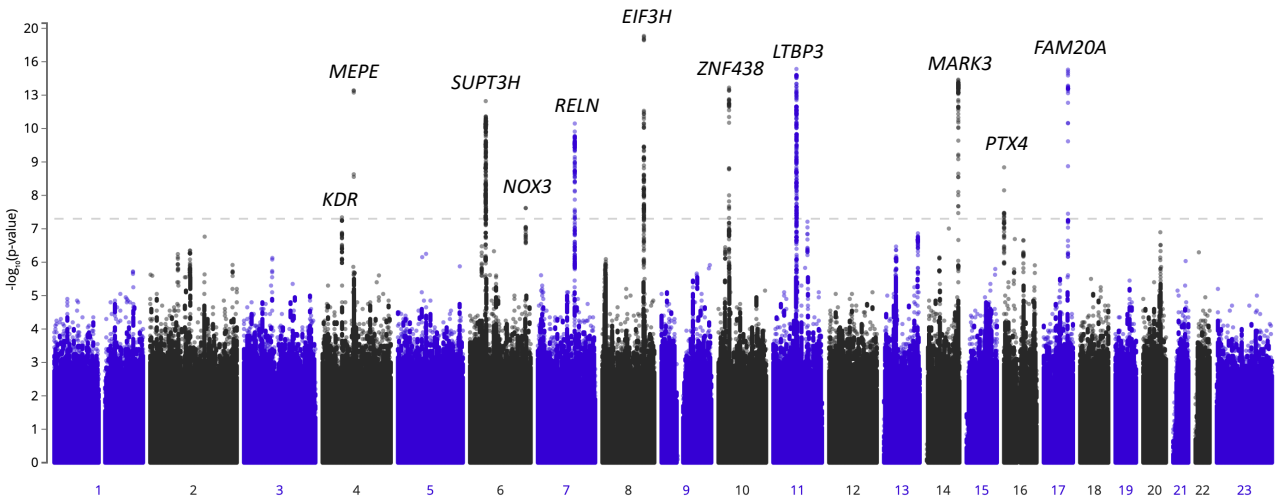
Rsid	Chromosome and position	Nearest Gene	Biological role(s) of proteins coded by nearest genes	Severe skeletal diseases associated with nearest genes	Hearing or skeletal phenotypes in mouse knockout models
rs11683921	2:111714056	*ANAPC1*	*ANAPC1*: *Encodes sc*affold subunit of the anaphase-promoting complex	*ANAPC1*: Rothmund-Thomson Syndrome Type 1 (skeletal and dental abnormalities and short stature)	
rs4917	3:186619924	*AHSG*	*AHSG:* Binds to TGFβ1 and BMPs. Regulator of mineralization through inhibition of calcium phospate precipitation. AHSG knockout mice exhibit increased bone formation with age and ectopic bone formation in response to TGFβ1/BMP signalling.		AHSG: High frequency hearing loss
rs181831514	4:87901594	*MEPE*	*MEPE:* Candidate gene for otosclerosis. Regulator of osteoclast differentiation and mineralization. *IBSP* (3rd nearest gene): Structural protein of bone matrix	*MEPE*: Hereditary congenital facial paresis	
rs13192457	6:44887654	*SUPT3H*	*RUNX2* (2nd nearest gene, overlapping association signal): Transcription factor, regulator of osteoblast and chondrocyte differentiation. *RUNX2* and *SUPT3H* show synteny across several species and the SUPT3H promoter is a potential regulator of the bone-specific Runx2-P1 promoter.	*RUNX2*: Metaphyseal dysplasia with maxillary hypoplasia and brachydactyly, cleidocranial dysostosis	RUNX2: Hearing loss
rs4464751	6:73707844	*CD109*	*CD109*: TGF-β co-receptor, negative regulator of TGF-β signalling		
rs77249084	8:116560300	*EIF3H*		Rs13279799: Associated with otosclerosis and ossification of the posterior longitudinal ligament of the spine	
rs4877080	9:89398813	*SEMA4D*	*SEMA4D*: Expressed in osteoclasts, inhibits bone formation		SEMA4D: Low bone mineral content
rs12270054	11:65555077	*LTBP3*	*LTBP3*: Latent Transforming Growth Factor Beta Binding Protein 3 (LTBP3), a component of the extracellular matrix. Regulates TGFβ activity via extracellular binding.	*LTBP3:* Acromicric dysplasia, Brachyolmia-amelogenesis imperfecta syndrome, Geleophysic dysplasia.	
rs73172296	13:42525753	*TNFSF11*	TNFSF11: Osteoclast differentiation and activation factor	TNFSF11: Osteopetrosis	
rs7995158	13:110459370	*COL4A2 (COL4A2-AS2)*	*COL4A2:* Alpha-2 chain of basement membrane collagen.		
rs10592836	14:103471816	*MARK3*	*MARK3:* Potential regulator of bone mineral density. *CKB* (2nd nearest gene, overlapping association): Regulator of the bone-resorbing function of osteoclasts.		
rs2118612	15:67108152	*SMAD3*	*SMAD3*: Downstream transcription factor in the TGFβ1 signalling pathway	*SMAD3*: Aneurysms-osteoarthritis syndrome	
rs67284550	16:1480948	*PTX4*	*CLCN7* (2nd nearest gene, nearest gene to fine-mapped credible set): Regulator of osteoblast function. *TELO2* (3rd nearest gene): Overexpressed in bone.	*CLCN7*: Osteopetrosis (several types). *TELO2*: You-Hoover-Fong syndrome	
rs4636903	16:54995451	*IRX5*	*IRX5*: Regulator of mineralization in cranial bones.	*IRX5:* Hamamy syndrome (with features including skeletal abnormalities, short stature, enamel hypoplasia, osteopenia with repeated fracture, and hearing loss)	
rs11868207	17:68679579	*FAM20A*	*FAM20A*: Involvement in biomineralization of teeth	*FAM20A*: Amelogenesis imperfecta type IG	
rs8105161	19:41333726	*TGFB1*	*TGFB1*: Candidate gene for otosclerosis. Essential cytokine for skeletal development and bone remodeling. Regulator of osteoblast and osteoclast cell lineages.	*TGFB1*: Gain-of-function mutations predispose to diaphyseal dysplasia (Camurati-Engelman disease)	
rs6066131	20:46941020	*EYA2*			EYA2: Mild hearing loss
rs6066825	20:48723580	*PREX1*	*PREX1*: Potential driver of bone dissemination in breast cancer		

Supplementary Table 1. Annotation of association loci with biological functions and rare disease associations. In several association loci, genes implicated in bone metabolism are in close proximity with the lead variant. Nearest protein coding genes to the lead variants are highlighted in bold. The biological functions of proteins were evaluated based on UniProt and followed up with literature review. ClinVar and GWAS Catalog were queried for associations with severe skeletal or dental diseases. Mouse knockout data were queried using available International Mouse Phenotyping Consortium (IMPC) data and PubMed searches. References to individual studies are listed in Supplementary References.

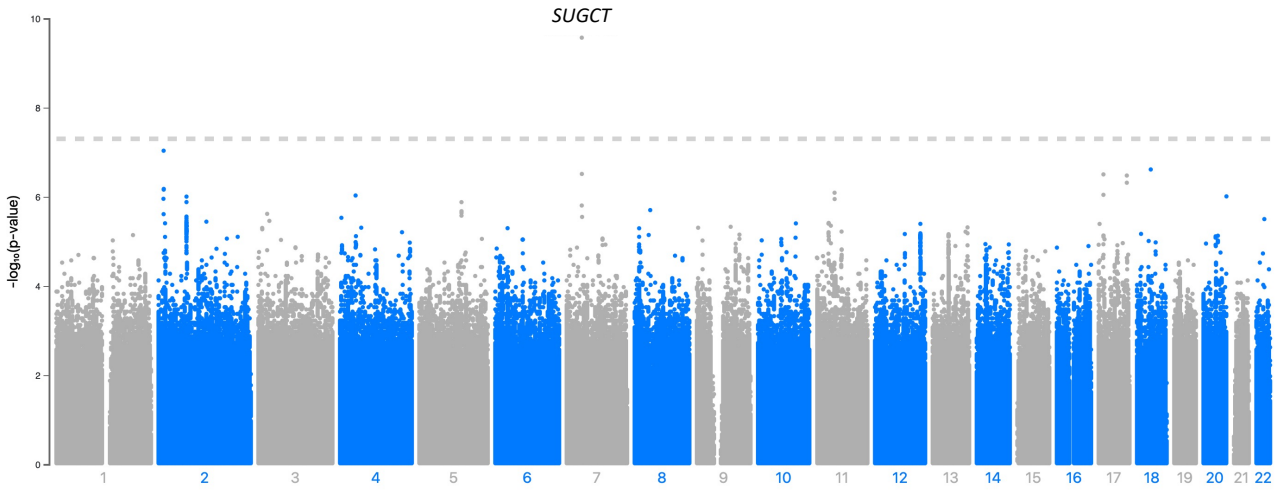
Supplementary Figures

Supplementary Figure 1. Cohort-specific Manhattan plots

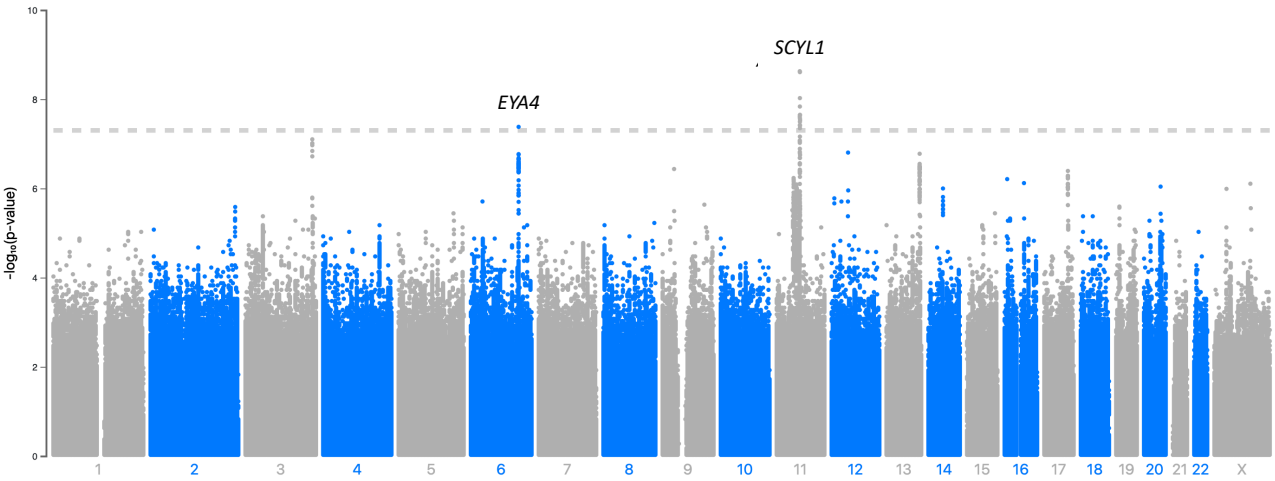
a) FinnGen



b) EstBB

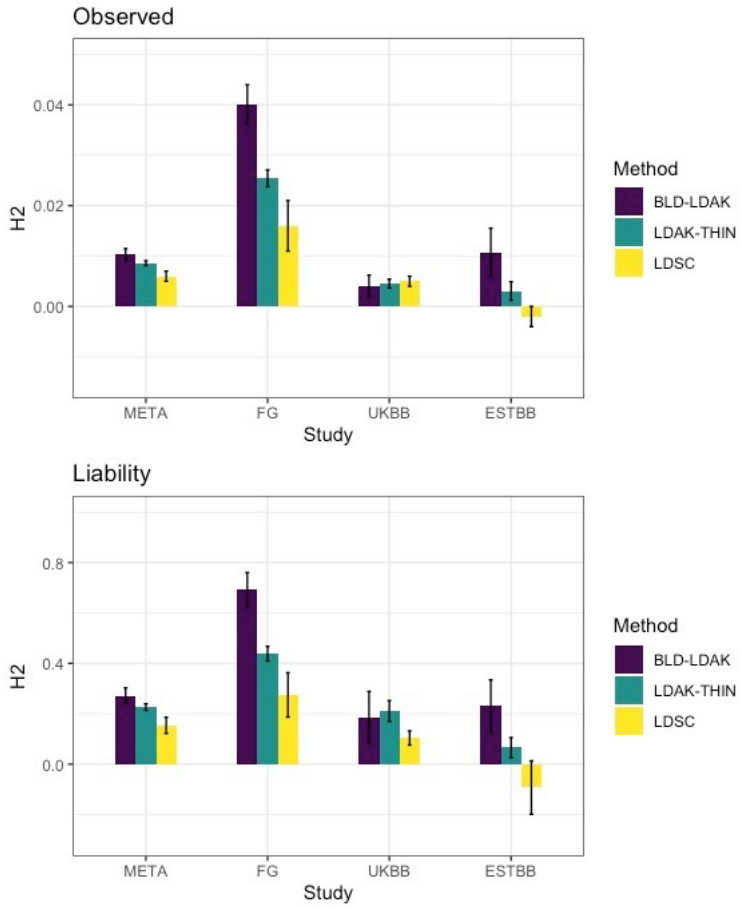


c) UKBB



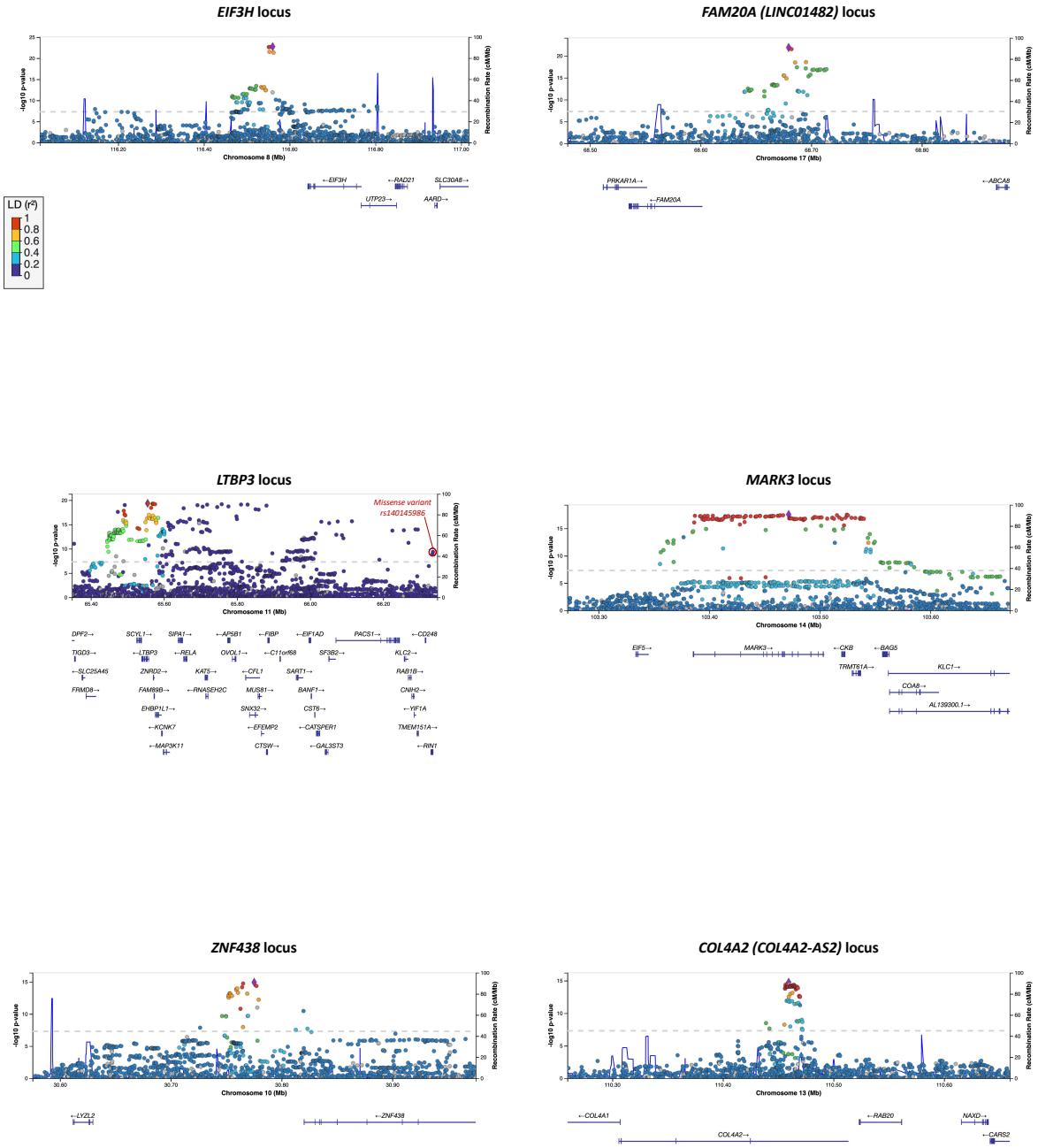
Manhattan plots are presented for the case-control GWAS of otosclerosis in a) FinnGen (1,563 cases and 249,281 controls), b) EstBB (985 cases and 196,516 controls), and c) UKBB (956 cases and 415,401 controls). GWAS for each individual study cohort was performed using a generalized mixed model with the saddlepoint approximation using SAIGE v0.20, using a kinship matrix as a random effect and covariates as fixed effects. Variants with a minor allele frequency > 0.1% and imputation INFO score ≥ 0.7 were included in the analysis. A Bonferroni-corrected two-sided *p*-value threshold of 5×10^{-8} (dashed line) was used to account for multiple comparisons. Colours are used to visually separate chromosomes.

Supplementary Figure 2. SNP-based heritability of otosclerosis in each cohort

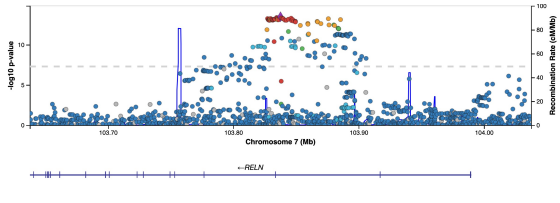


Approximate estimates for the narrow sense heritability of otosclerosis in each cohort and the subsequent meta-analysis were obtained and compared using three different summary statistics based methods: 1) LD Score Regression (LDSC), and 2) BLK-LDAK and 3) LDAK-Thin of the SumHer software. We used summary statistics separately from the meta-analysis and each cohort, restricting the analyses to variants present in HapMap3. For the BLK-LDAK and LDAK-Thin models, we used the European tagging files based on UKBB (http://dougspeed.com/pre-computed-tagging-files/), and for LDSC we used LD Scores computed using 1000 Genomes European data (https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz2). For the liability transformations, a population prevalence approximation of 0.3% was used. Heritability estimates are presented as bars and the standard errors are indicated for each heritability estimate with error bars. A total of 250,844 FinnGen samples, 197,501 Estonian Biobank samples and 416,357 UK Biobank samples were used for heritability estimation. The precise heritability estimates, their standard errors and corresponding Z-scores are presented in Supplementary Data 5.

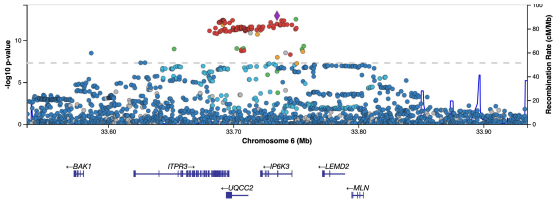
Supplementary Figure 3. LocusZoom plots for significant loci in the meta-analysis



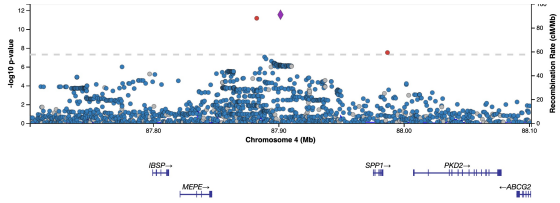
***RELN* locus**



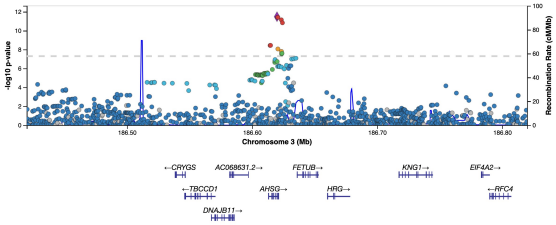
***IP6K3* locus**



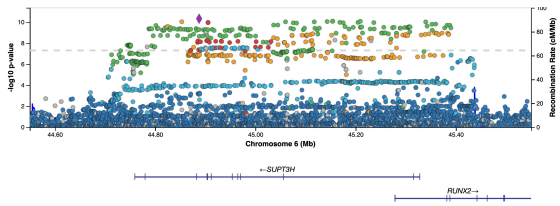
***MEPE* locus**



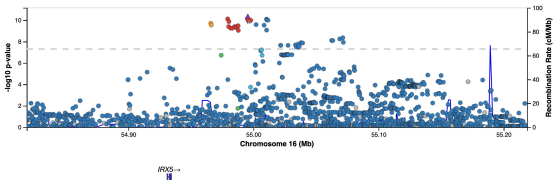
***AHSG* locus**



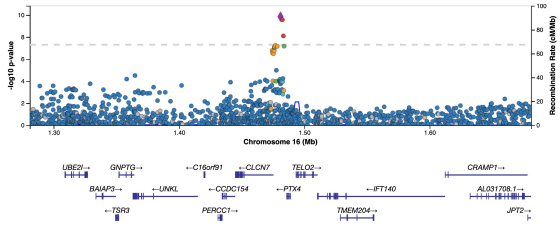
***SUPT3H* locus**



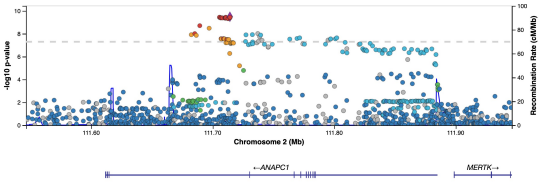
***IRX5* locus**



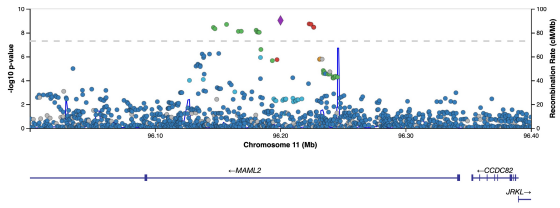
***PTX4* locus**



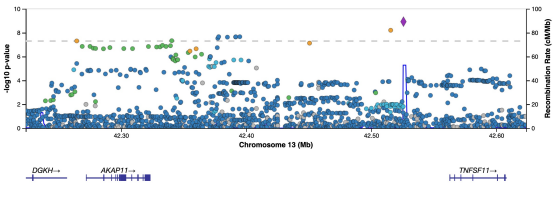
***ANAPC1* locus**



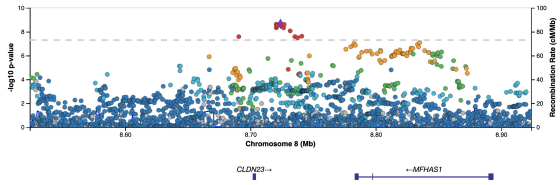
***MAML2* locus**



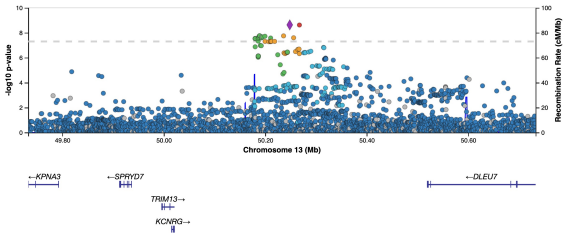
***TNFSF11* locus**



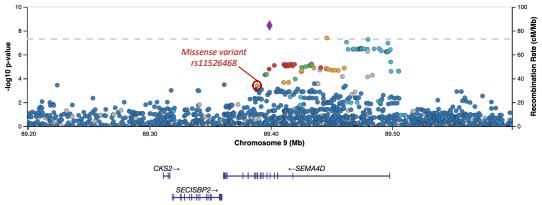
***CLDN23* locus**



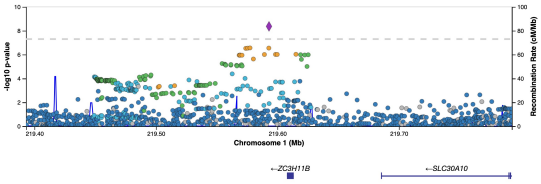
***KCNRG (DLEU1)* locus**



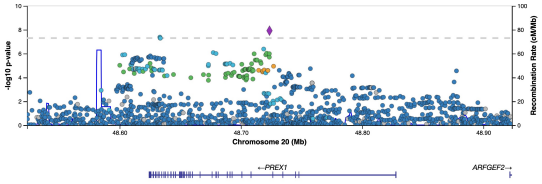
***SEMA4D* locus**



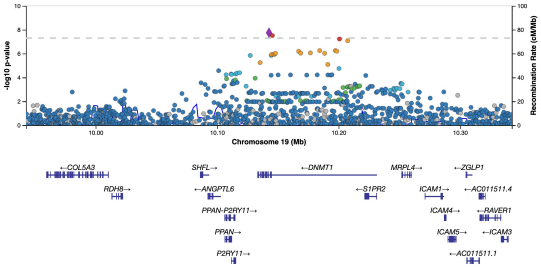
***ZC3H11B* locus**



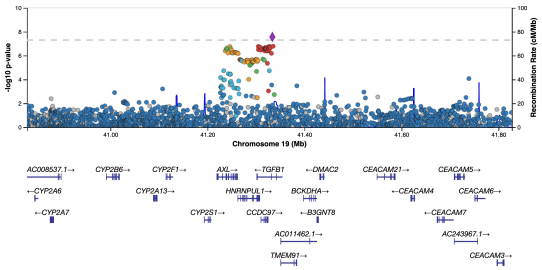
***PREX1* locus**



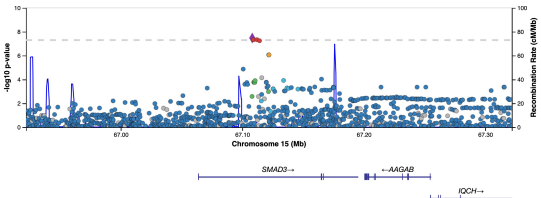
***DNMT1* locus**

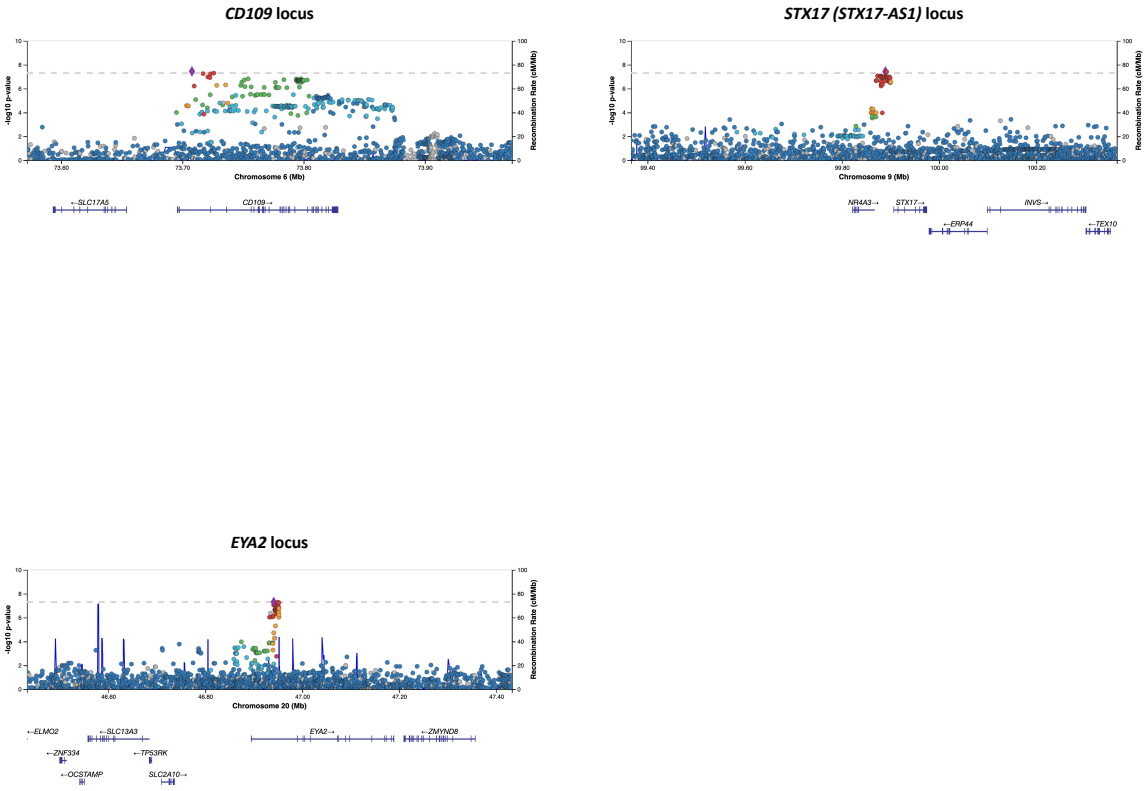


***TGFB1* locus**



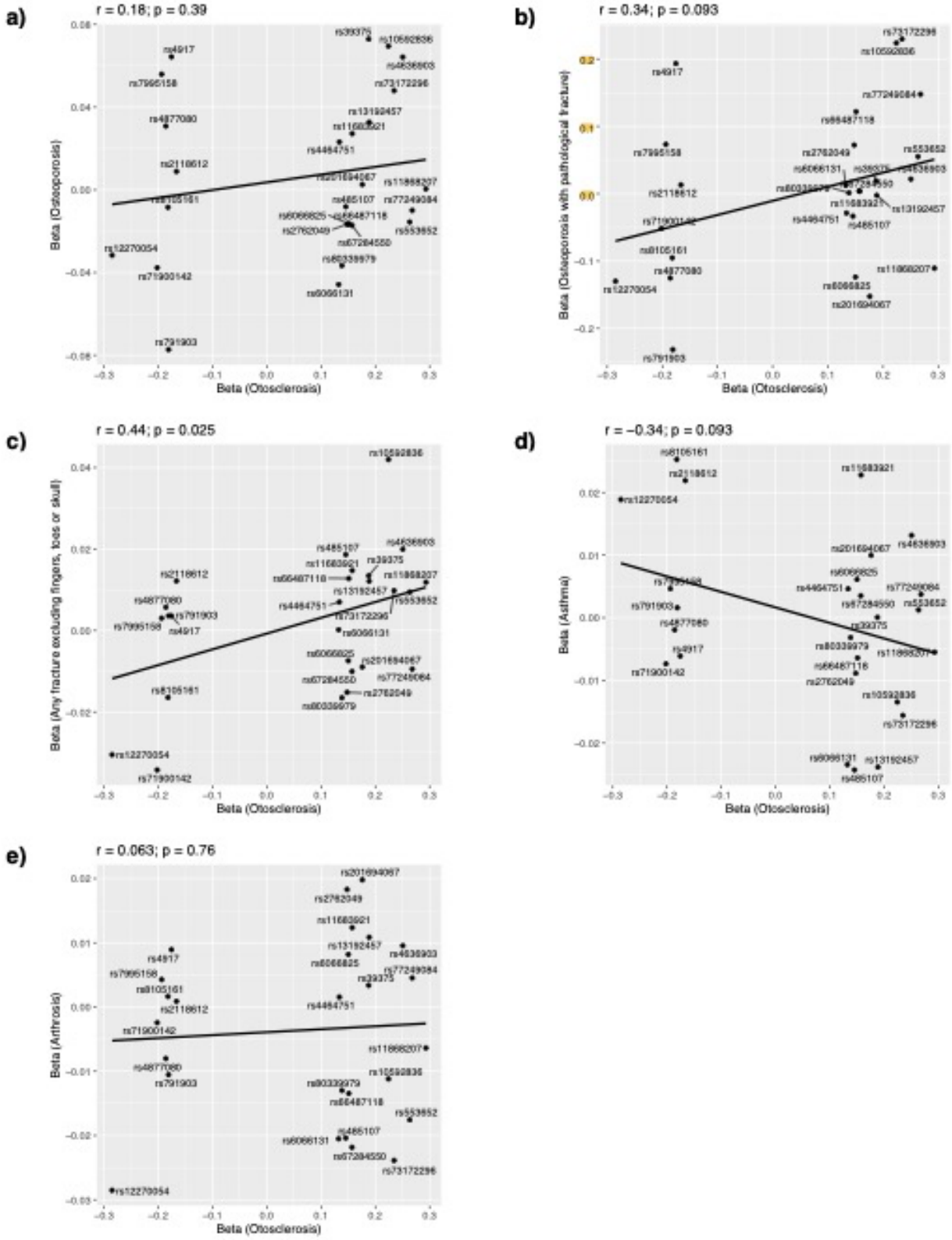
***SMAD3* locus**





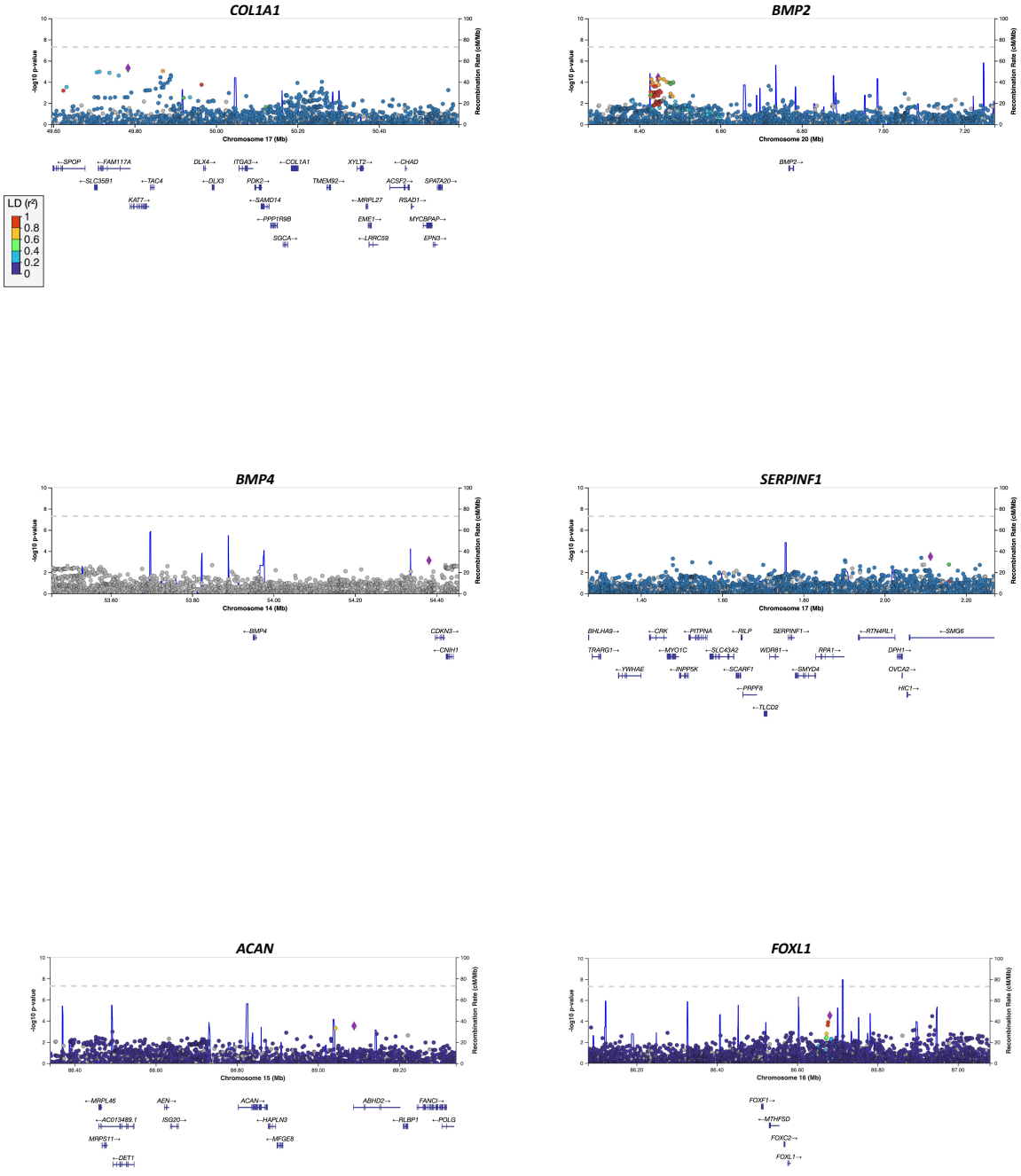
GWAS for each individual study cohort was performed using a generalized mixed model with the saddlepoint approximation using SAIGE v0.20, using a kinship matrix as a random effect and covariates as fixed effects. A fixed-effect meta-analysis of effect estimates from the three cohorts was then performed including a total of 3,504 cases and 861,198 controls. Twenty-seven loci reached genome-wide significance in the meta-analysis (two-sided p-value < 5×10^{-8} to account for multiple comparisons, marked by the dashed line). LocusZoom plots for each significant locus are shown in the same order as in Table 2, and the exact *p*-values corresponding to lead variants in each locus are presented in Table 2. In the LocusZoom plots, variant positions are indicated on the x-axis and $-\log_{10}$(*p*-value) is presented on the y-axis for each variant. The included variants were present in at least two cohorts with a cross-cohort minor allele frequency > 0.1% and imputation INFO score ≥ 0.7. The loci are annotated by the names of the coding genes nearest to the lead variants. Linkage disequilibrium is shown in colour scale with the lead variants as reference, based on publicly available European genome data from the 1000 Genomes Project.

Supplementary Figure 4. Correlation analysis of lead variant associations for otosclerosis and selected traits in FinnGen



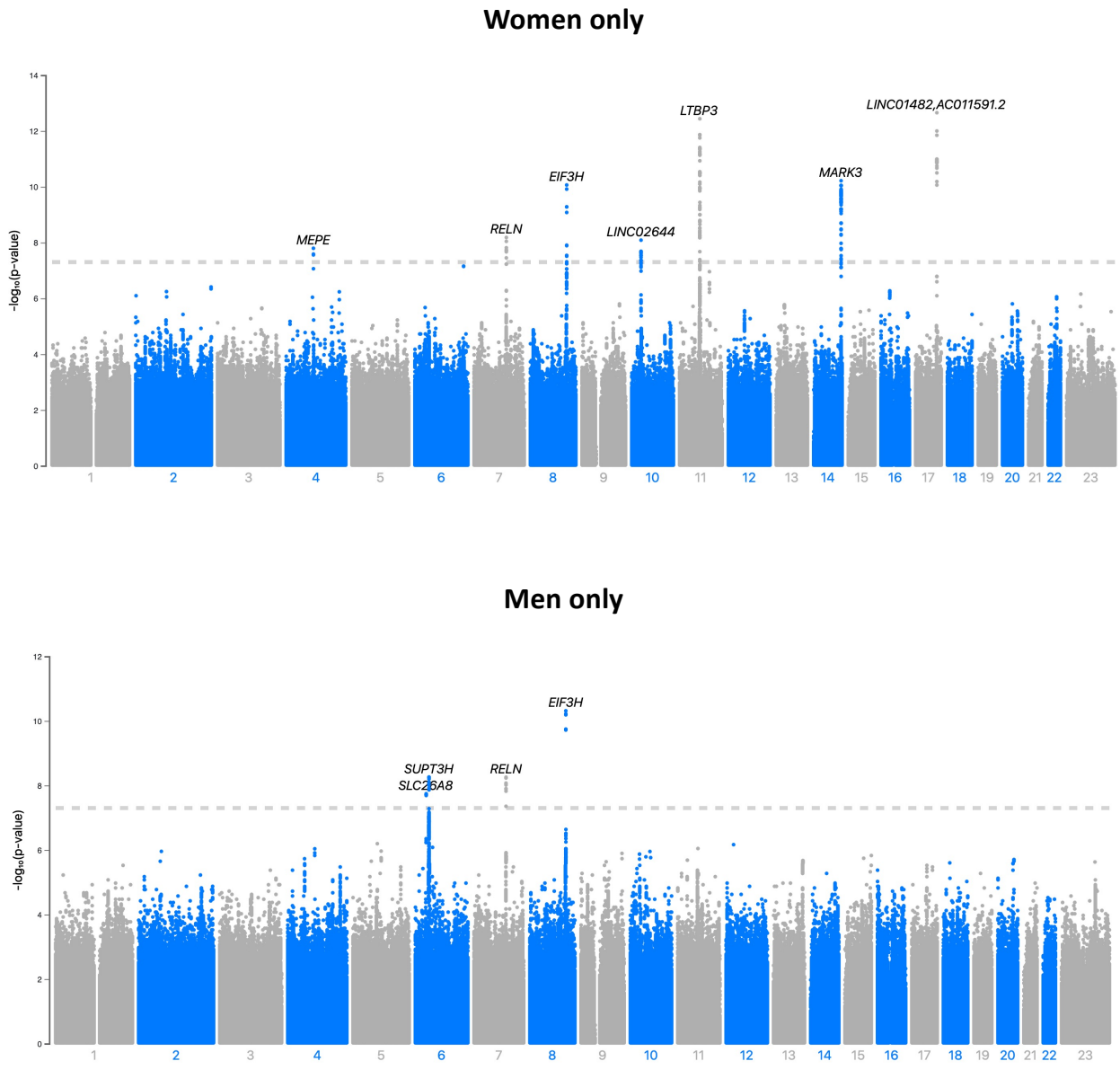
Lead variants from the 27 significant otosclerosis GWAS meta-analysis loci were analyzed with respect to their association with selected traits in FinnGen (prioritized based on the earlier phenome-wide association study). The beta estimate for otosclerosis is represented on the x-axis, and the beta estimate for the trait under comparison is represented on the y-axis. Included traits were a) osteoporosis, b) osteoporosis with pathological fracture, c) any fracture excluding fracture of fingers, toes or skull, d) asthma, e) arthrosis. Pearson's correlation coefficients and corresponding *p*-values (using the t-distribution) were computed for all comparisons. A two-sided *p*-value threshold of 0.01 was used to account for multiple comparisons.

Supplementary Figure 5. Meta-analysis LocusZoom plots for candidate gene regions

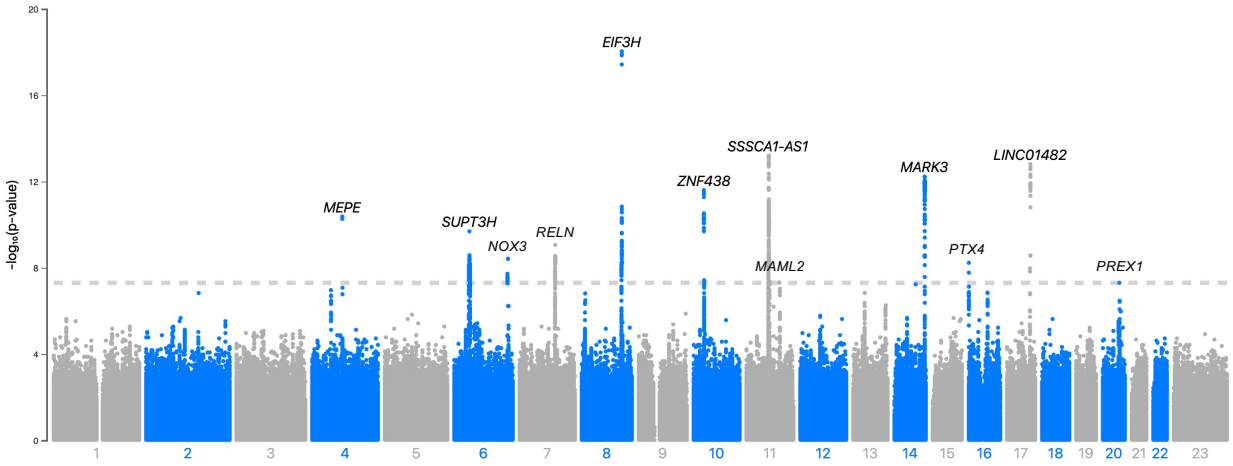


GWAS for each individual study cohort was performed using a generalized mixed model with the saddlepoint approximation using SAIGE v0.20, using a kinship matrix as a random effect and covariates as fixed effects. A fixed-effect meta-analysis of effect estimates from the three cohorts was then performed including a total of 3,504 cases and 861,198 controls. LocusZoom plots are presented for the regions of four candidate genes based on previous studies (*COL1A1*, *BMP2*, *BMP4*, and *SERPINF1*). In the LocusZoom plots, variant positions are indicated on the x-axis and $-\log_{10}$(*p*-value) is presented on the y-axis for each variant. The included variants were present in at least two cohorts with a cross-cohort minor allele frequency > 0.1% and imputation INFO score ≥ 0.7. The loci are annotated by the names of the coding genes nearest to the lead variants. Linkage disequilibrium is shown in colour scale with the lead variants as reference, based on publicly available European genome data from the 1000 Genomes Project. Odds ratios and *p*-values for candidate variants are also presented in Supplementary Data 20.

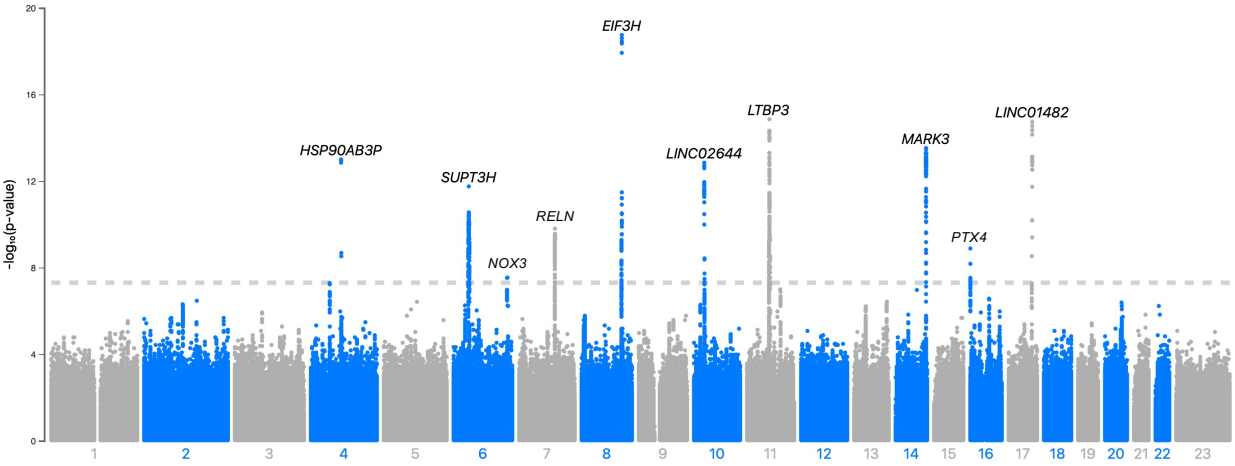
Supplementary Figure 6. Additional genome-wide association studies of otosclerosis in FinnGen



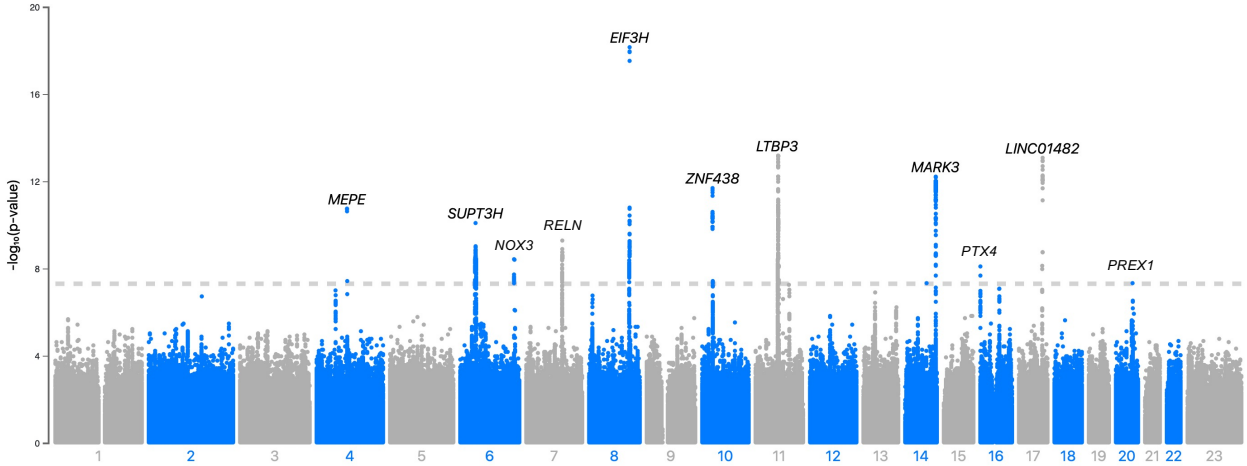
Controls limited to individuals aged > 65



Controls limited to individuals without hearing loss

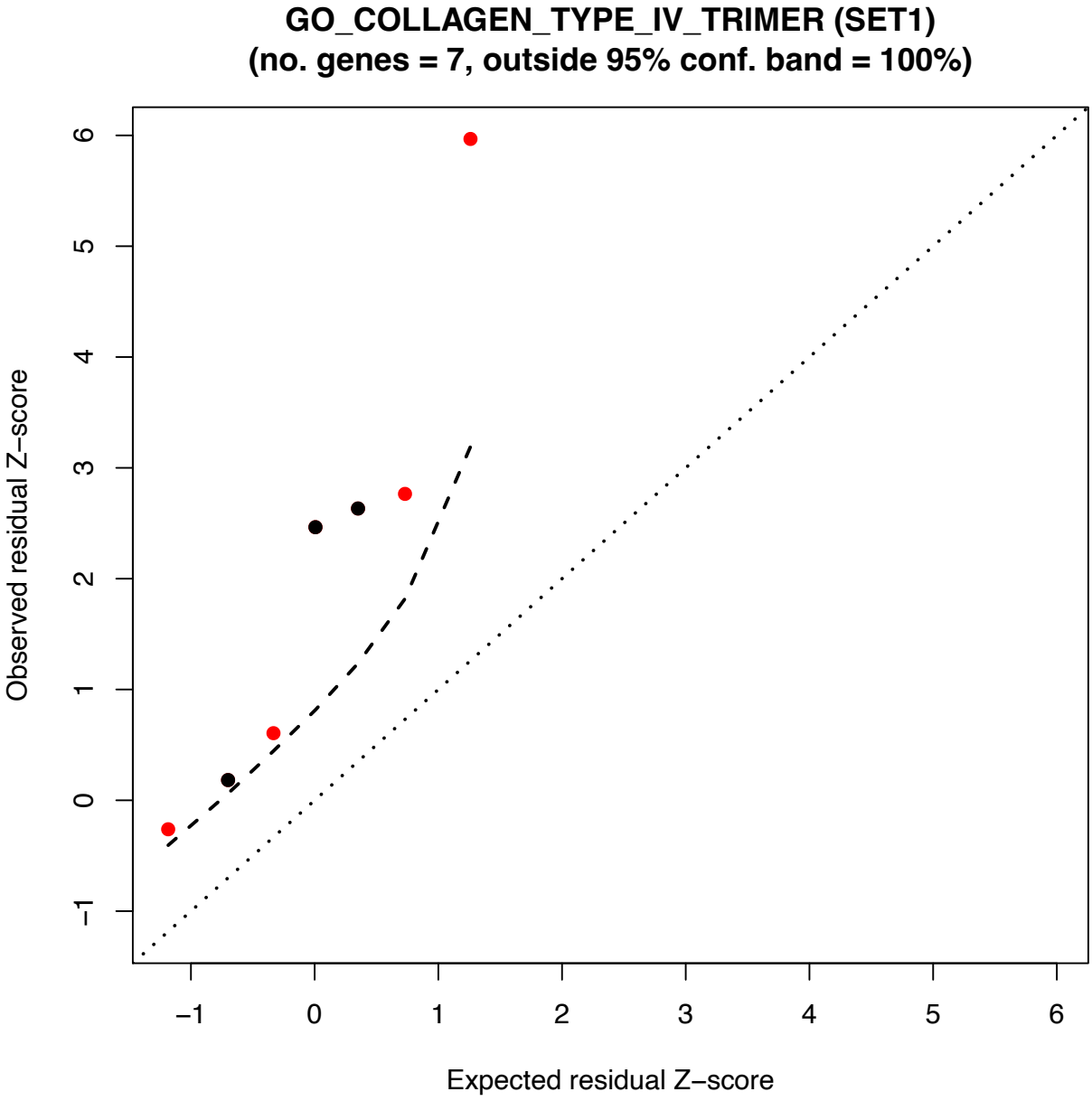


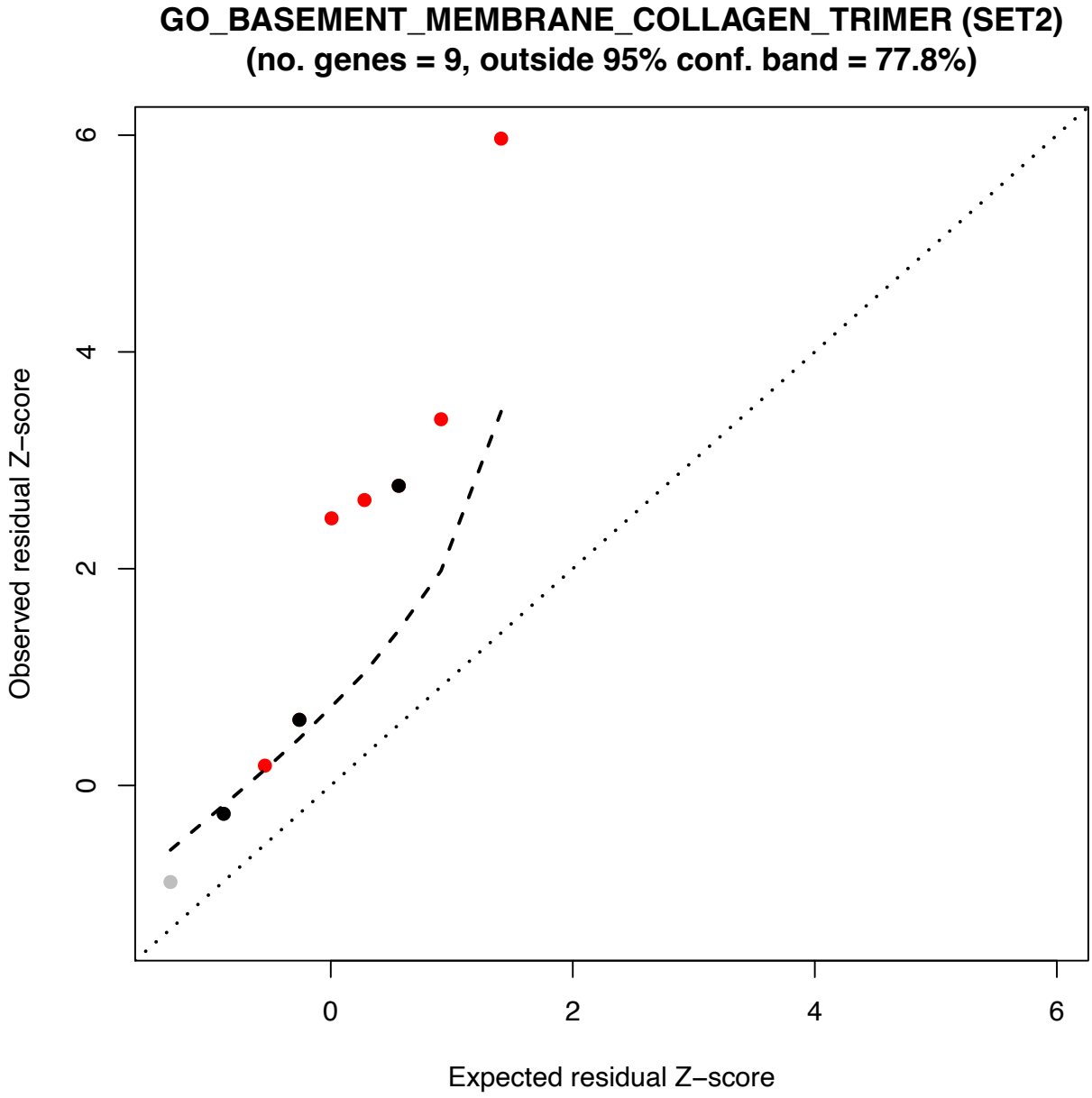
Controls limited to individuals aged > 65 without hearing loss



Additional GWAS were conducted in FinnGen for women (1002 cases and 140,222 controls) and men (561 cases and 109,059 controls). GWAS were also performed comparing all 1,563 cases with controls filtered to include only individuals over age 75 (110,166 controls), individuals without a diagnosis of hearing loss (231,502 controls) and individuals over age 75 without a diagnosis of hearing loss (96,564 controls). GWAS were performed using a generalized mixed model with the saddlepoint approximation using SAIGE v0.20, using a kinship matrix as a random effect and covariates as fixed effects. A Bonferroni-corrected two-sided genome-wide *p*-value threshold of $5x10^{-8}$ was used to account for multiple comparisons. Colours are used to visually separate chromosomes.

Supplementary Figure 7. QQ-plots from post hoc permutation analyses with MAGMA





Based on the results from the gene-based analysis of the meta-analysis summary statistics, a competitive gene set based analysis was performed using 10,182 GO term based gene sets downloaded from the Molecular Signature Database v7.1, using a Bonferroni-corrected *p*-value threshold ($\alpha = 0.05/10{,}182$). Set-specific QQ plots were produced by permutation analysis to evaluate for the influence of outliers.

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Simonne Longerich	Merck, Kenilworth, NJ, United States
Caroline Fox	Merck, Kenilworth, NJ, United States
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Robert Yang	Janssen Biotech, Beerse, Belgium
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Antti Hakanen	Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland
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Markus Perola	THL Biobank / Finnish Institute for Health and Welfare (THL), Helsinki, Finland
Jukka Partanen	Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Anne Pitkäranta	Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki
Taneli Raivio	Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki
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