Supplemental data

COHORTS SHORT DESCRIPTION

1982 Pelotas Birth Cohort Study:

The 1982 Pelotas (Brazil) Birth Cohort Study is a longitudinal population-based birth cohort. The maternity hospitals in Pelotas, a southern Brazilian city (current population ~330,000), were visited daily in the year of 1982. The 5,914 live-borns whose families lived in the urban area were examined and their mothers interviewed. Information was obtained for more than 99% of the livebirths. These subjects have been followed-up at the following mean ages: 11.3 months (all children born from January to Abril 1982; n=1457), 19.4 months (entire cohort; n=4934), 43.1 months (entire cohort; n=4742), 13.1 years (random subsample; n=715), 14.7 years (systematic subsample; n=1076); 18.2 (male cohorts attending to compulsory Army recruitment examination; n=2250), 18.9 (systematic subsample; n=1031), 22.8 years (entire cohort; n=4297) and 30.2 years (entire cohort; n=3701). Details about follow-up visits and available data can be found in the two Cohort Profile papers (1, 2). DNA samples (collected at the mean age of 22.8 years) were genotyped for ~2.5 million of SNPs using the Illumina HumanOmni2.5-8v1 array (which includes autosomal, X and Y chromosomes, and mitochondrial variants). After quality control, the data were pre-phased using SHAPEIT and imputed using IMPUTE2 based on 1000 Genomes haplotypes.

Avon Longitudinal Study of Parents and their Children (ALSPAC):

The Avon Longitudinal Study of Parents and their Children (ALSPAC) is a longitudinal population-based birth cohort that recruited pregnant women residing in Avon, UK, with an expected delivery date between 1st April 1991 and 31st December 1992. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. This cohort is described in detail on the website (http://www.alspac.bris.ac.uk) and elsewhere (3) and the total body DXA measures and cohort analyzed in the present paper are described in Kemp et al. (2014) (4). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Bone Mineral Density in Childhood Study (BMDCS):

The Bone Mineral Density in Childhood Study is an ongoing longitudinal study in which boys and girls aged 6-16 year old were recruited between 2002-2003, and whose DXA measurements are obtained annually at five clinical centers in the United States (5, 6).

BPROOF:

B-PROOF is a trial investigating the effect of 2-year supplementation with 400 mcg folic acid and 500 mcg vitamin B12 on fracture incidence in hyperhomoycsteinemic persons aged 65y and older.

CHS:

The Cardiovascular Health Study (CHS) is a prospective investigation of risk factors for CVD in community-dwelling adults aged 65 and older. Participants were identified from Medicare-eligibility lists at four field centers in the U.S. (California, Maryland, North Carolina, and Pennsylvania). Recruitment of an original cohort of 5,201 participants occurred in 1989-90, followed by a supplemental cohort of 697 predominantly African-American individuals in 1992-93. At the exam in 1994-5 1,563 participants underwent DXA using the array beam mode QDR 2000 or 2000+ bone densitometers (Hologic, Inc., Bedford, MA) according to a standardized protocol. See, (7), for a description of the cohort.

Copenhagen Prospective Studies on Asthma (COPSAC) cohort:

The Copenhagen Prospective Studies on Asthma in Childhood is a clinical study. All mothers had a history of a doctor's diagnosis of asthma after 7 years of age. Newborns were enrolled in the first month of life, as previously described in detail (8). The Ethics Committee for Copenhagen and the Danish Data Protection Agency approved this study.

deCODE genetics BMD study:

The deCODE genetics BMD study is an ongoing population based study of all subjects who have undergone a DEXA-Hologic bone mineral density scan at the Landspitali University Hospital, Reykjavik, Iceland. The study samples have been previously described in detail (9). All participants gave informed consent and the study was approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland.

EPIC NorFolk:

The European Prospective Investigation of Cancer (EPIC) began as a large multi-centre cohort study primarily looking at the connection between diet, lifestyle factors and cancer, although the study was broadened from the outset to include other conditions. EPIC-Norfolk is part of a Europe-wide programme (http://www.srl.cam.ac.uk/epic/international/index.shtml). With the help of over 30,000 people living in Norfolk, the aim of the study is to provide data-based evidence for health policies to prevent or delay disease onset and maintain health and independence in older people. EPIC-Norfolk participants are men and women who were aged between 40 and 79 when they joined the study and who lived in Norwich and the surrounding towns and rural areas. They have been contributing information about their diet, lifestyle and health through questionnaires and health checks over two decades.

ERF:

Erasmus Rucphen Family study (ERF) is a family-based cohort study that includes inhabitants of a genetically isolated community in the South-West of the Netherlands, studied as part of the Genetic Research in Isolated Population (GRIP) program. ERF includes over 3,000 individuals who are living descendants of 22 couples, who had at least six children baptized in the community church, and their spouses. All data were collected between June 2002 and February 2005. The population shows minimal

immigration and high inbreeding, therefore frequency of rare alleles is increased in this population. All participants gave informed consent, and the Medical Ethics Committee of the Erasmus University Medical Centre, approved the study.

FENLAND:

The Fenland study is a population-based cohort study that uses objective measures of disease exposure to investigate the influence of diet, lifestyle and genetic factors on the development of diabetes and obesity. The volunteers are recruited from general practice lists in and around Cambridgeshire (Cambridge, Ely, and Wisbech) in the United Kingdom from birth cohorts from 1950–1975 (10).

FHS:

The Framingham Osteoporosis Study (FOS) / Framingham Heart Study (FHS) is a family-based, multigenerational cohort study initiated originally to study the risk factors for cardiovascular disease. (11). The FHS was initiated in 1948 to study determinants of cardiovascular disease and other major illnesses. The Original Cohort included 5,209 men and women, aged 28-62 years at enrolment who have undergone routine biennial examinations (12, 13). In 1971, Offspring of the Original Cohort participants and Offspring spouses including 5,124 men and women, aged 5 to 70 years, were enrolled into the Framingham Offspring Study. Offspring participants have been examined approximately every 4 years (14, 15). In the 1990s, DNA was obtained for genetic studies from surviving Original Cohort and Offspring participants. The body composition measurements used in this analysis have been previously

The Generation R Study:

The Generation R Study is a multiethnic prospective cohort study in which 9,778 pregnant women living in Rotterdam and with delivery date from April 2002 until January 2006 were enrolled. Details of study design and data collection can be found elsewhere (16). Genotype and imputation of this cohort are described elsewhere (17).

GOOD Study:

The Gothenburg Osteoporosis and Obesity Determinants (GOOD) study was initiated to determine both environmental and genetic factors involved in the regulation of bone and fat mass. The GOOD study is a population-based cohort in which male subjects from between 18 and 20 years of age in the Gothenburg area in Sweden were randomly selected using national population registers and invited to participate in this initiative by phone. From the selected candidates 1,068 agreed to participate providing oral and written informed consent. The GOOD study was approved by the local ethics committee at Gothenburg University (18).

HABC:

A population based, prospective cohort study of well-functioning, unrelated men and women aged 70 and older. It was initiated to assess changes in body composition. A detailed description of this cohor can be found elsewhere (19-21).

MROS USA:

The Osteoporotic Fractures in Men (MrOS) Study is a multi-center prospective, longitudinal, observational study of risk factors for vertebral and all non-vertebral fractures in older men, and of the sequelae of fractures in men (22, 23). The original specific aims of the study include: (1) to define the skeletal determinants of fracture risk in older men, (2) to define lifestyle and medical factors related to fracture risk, (3) to establish the contribution of fall frequency to fracture risk in older men, (4) to determine to what extent androgen and estrogen concentrations influence fracture risk, (5) to examine the effects of fractures on quality of life, (6) to identify sex differences in the predictors and outcomes of fracture, (7) to collect and store serum, urine and DNA for future analyses as directed by emerging evidence in the fields of aging and skeletal health, and (8) define the extent to which bone mass/fracture risk and prostate diseases are linked. The MrOS Study enrolled 5,994 community dwelling, ambulatory men aged 65 years or older from six communities in the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA) between 2000 and 2002. Inclusion criteria were designed to provide a study cohort that is representative of the broad population of older men. The inclusion criteria were: (1) ability to walk without the assistance of another, (2) absence of bilateral hip replacements, (3) ability to provide self-reported data, (4) residence near a clinical site for the duration of the study, (5) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (6) ability to understand and sign an informed consent. To qualify as an enrollee, the participant had to provide written informed consent, complete the self-administered questionnaire (SAQ), attend the clinic visit, and complete at least the anthropometric, DXA, and vertebral X-ray procedures. There were no other exclusion criteria. Written informed consent was obtained from all participants, and the Institutional Review Board at each study site approved the study.

Whole body total BMD (g/cm^2) and head BMD (g/cm^2) was measured using dual energy x-ray absorptiometry (DXA) (Hologic, Inc., MA) using Hologic QDR 4500 workstations at the baseline clinic visit. A central quality control lab, certification of DXA operators, and standardized procedures for scanning were used to insure reproducibility of DXA measurements. At baseline, a Hologic whole body phantom was circulated and measured at the 6 clinical sites. The variability across clinics was within acceptable limits, and cross-calibration correction factors were not required.

NEO:

The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected.

OPRA:

The Osteoporosis Risk Assessment Cohort (OPRA) cohort recruited Swedish women aged 75, at which time age-related bone loss is already obvious and fractures prevalent. The study was designed to investigate genetic and lifestyle factors contributing to osteoporosis and fracture risk. Of 1604 women invited between December 1995 and May 1999, 1044 (65%) attended at baseline. No exclusion criteria were applied. All participants answered a detailed questionnaire regarding their general health; BMD and body composition was assessed by DXA. All participants gave written informed consent and the Lund University Ethics Committee approved the study.

ORCADES:

The Orkney Complex Disease Study is an ongoing family-based genetic epidemiology collection in the isolated Scottish archipelago of Orkney. Genetic diversity in this population is decreased compared to Mainland Scotland, consistent with the high levels of endogamy historically. Fasting blood samples were collected and over 300 health-related phenotypes and environmental exposures were measured in each individual. All participants gave informed consent and the study was approved by Research Ethics Committees in Orkney and Aberdeen.

PANIC:

The Physical Activity and Nutrition in Children (PANIC) study is a controlled physical activity and dietary intervention study in a population sample of 506 Finnish children aged 6-8 years at baseline in 2007-2009. Ethical approval was obtained from the Research Ethics Committee of the Hospital District of Northern Savo. All children and their parents gave their written informed consent (24). (http://www.uef.fi/en/web/physical-activity-and-nutrition-in-children/home)

RAINE:

The Raine (West Australian Pregnancy Cohort) Study is a longitudinal population-based pregnancy cohort study, which recruited 2,900 pregnant women from the public antenatal clinic at King Edward

Memorial Hospital and surrounding private clinics in Perth, Western Australia between May 1989 and November 1991 (25). Of the 2868 live births, 1183 had a whole body DXA at 20 years (26).

Rotterdam Study:

The Rotterdam Study is a prospective cohort study of chronic disabling conditions in Dutch elderly individuals that started in 1990 in Ommoord, a suburb of Rotterdam, among 10,994, men and women aged 55 and over (27).

SOF:

The Study of Osteoporotic Fractures (SOF) is a prospective multicenter study of risk factors for vertebral and non-vertebral fractures (28). The cohort is comprised of 9,704 community-dwelling women 65 years old or older recruited from populations-based listings in four U.S. areas: Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley, Pennsylvania. The SOF participants were followed up every four months by postcard or telephone to ascertain the occurrence of falls, fractures and changes in address. To date, follow-up rates have exceeded 95% for vital status and fractures. All fractures are validated by x-ray reports or, in the case of most hip fractures, a review of pre-operative radiographs. The inclusion criteria were: 1) 65 years or older, (2) ability to walk without the assistance of another, (3) absence of bilateral hip replacements, (4) ability to provide self-reported data, (5) residence near a clinical site for the duration of the study, (6) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (7) ability to understand and sign an informed consent.

This study used whole body total BMD (g/cm^2) and head BMD (g/cm^2) measured using dual energy x-ray absorptiometry (DXA) (Hologic, Inc., MA) using Hologic QDR 2000 workstations at the sixth clinic visit. Scans were performed and analyzed at each clinic. Review of scans was done at the UCSF Coordinating Center on random subsets of scans and on problematic scans identified by technicians at the clinic. Some scans were deemed unacceptable and are not included in the data or are set to a special missing value code.

TwinsUK:

The UK Adult Twin Registry (TwinsUK) (www.twinsuk.ac.uk/) was started in 1993 and is comprised of ~12,000 monozygotic and dizygotic twins (83% female) aged 16-85 years recruited by successive media campaigns from all over the UK without selection for any particular disease or trait. The cohort is from Northern European/UK ancestry and has been shown to be representative of singleton populations and the UK population in general (26). All twins received a series of detailed disease and environmental questionnaires and the majority have been assessed in detail clinically at several time points for several hundred phenotypes related to common diseases or intermediate traits. The primary focus of the study has been the genetic basis of healthy aging process and complex diseases, including cardiovascular, metabolic, musculoskeletal, and ophthalmologic disorders.

UKBB:

In 2006-2010, the UK Biobank recruited 502,647 individuals aged between 37-76 years (99.5% were 40-69 years) from across the country. Each participant provided information regarding their health and lifestyle using touch screen questionnaires, physical measurements and agreement to have their health followed and they also provided blood, urine and saliva samples for future analysis. UK Biobank has ethical approval from the Northwest Multi-centre Research Ethics Committee (MREC) and informed consent was obtained from all participants.

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1982 Pelotas Birth Cohort:

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ALSPAC Study:

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. The UK Medical Research Council and the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors, and JPK and DME will serve as guarantors for the contents of this paper.. This work is supported by a Medical Research Council program grant (MC_UU_12013/4 to D.M.E). D.M.E is supported by an Australian Research Council Future Fellowship (FT130101709).

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CHS:

Cardiovascular Health Study: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and R01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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deCODE:

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ERF:

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FHS:

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HABC:

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ORCADES:

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Rotterdam Study:

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SOF:

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Functional Group:

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Graham R Williams: Molecular Endocrinology Laboratory, Department of Medicine, Imperial College London, London, UK/ Wellcome Trust Strategic Award 101123/Z/13/A

SUPPLEMENTAL FIGURES

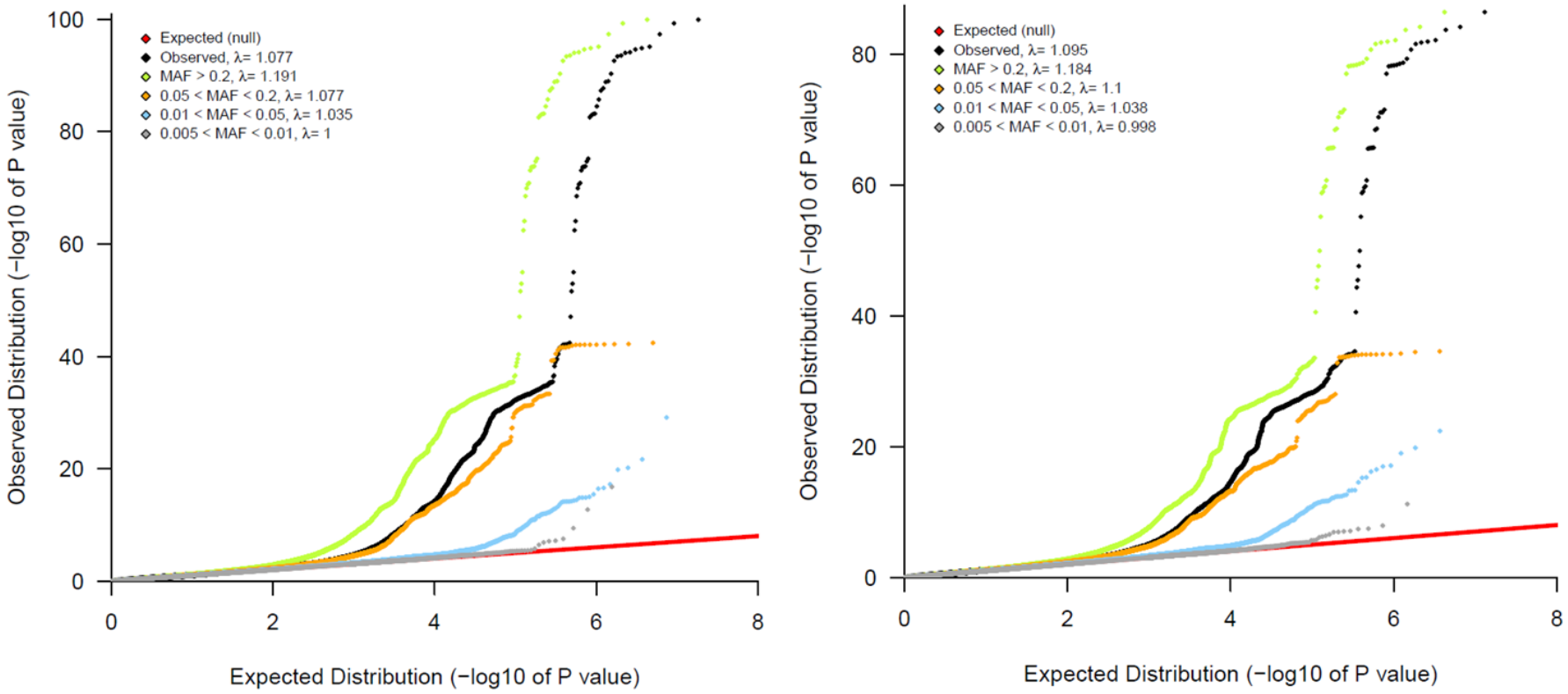


Figure S1. QQ-Plots for the genome-wide association study of TB-BMD. Left panel: Including studies regardless the ethnic background of the participants (N=66, 628). **Right panel:** Including only studies of European ancestry (N=56,284).

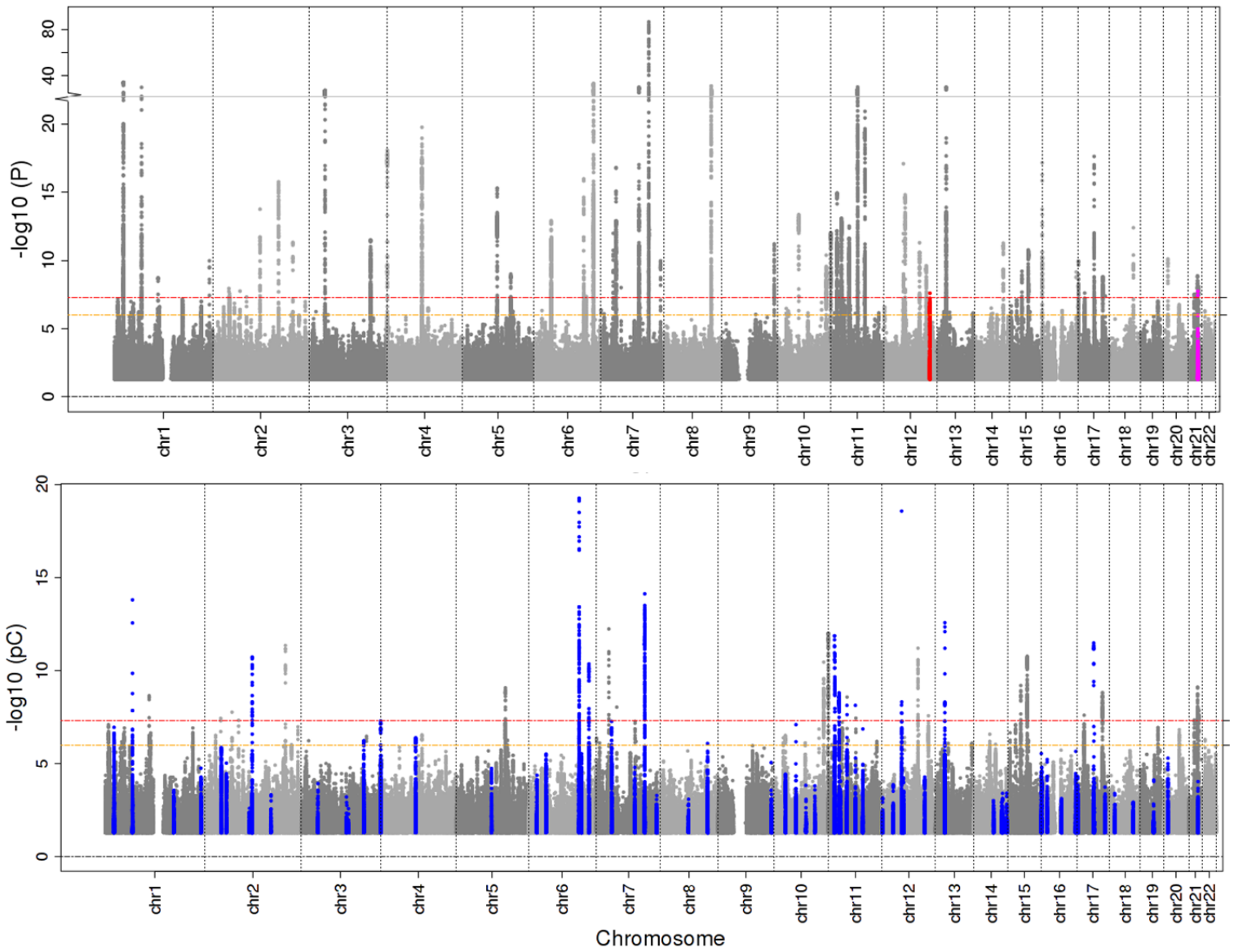
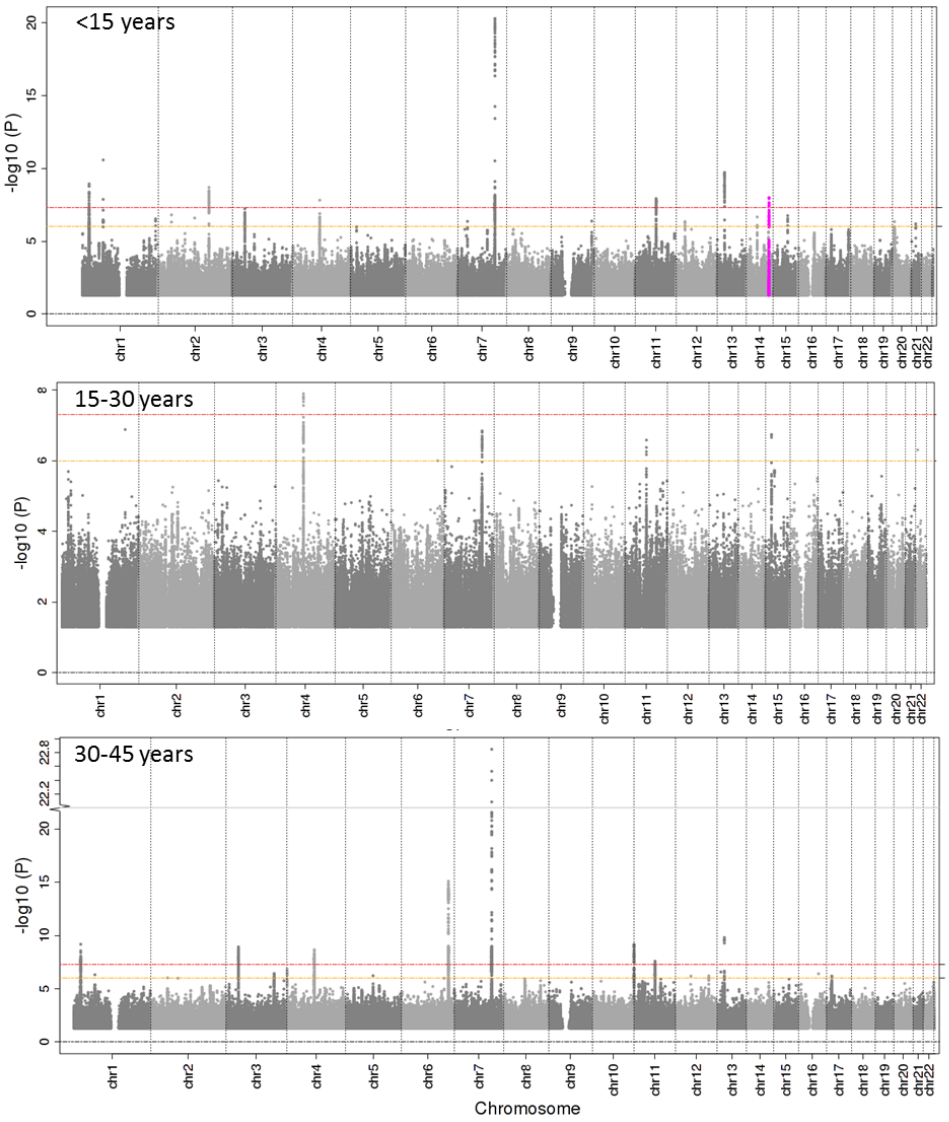


Figure S2. Manhattan plots of association statistics (-log10(P values)) for TB-BMD only-European meta-analysis. Each dot represents a SNP and the x-axis indicates its chromosomal position (Build 37 NCBI). Dashed horizontal red and yellow lines mark the GWS threshold ($P<5x10^{-8}$) and suggestive threshold ($P<1x10^{-6}$), respectively. **Top**: The association P-value (on $-\log_{10}$ scale) in the meta-analysis including only studies comprising individuals of European ancestry. Loci only reaching significance in this analysis are highlighted: the novel 19q12 in red and the known 21q22.13 in magenta. **Bottom:** The association P-value (on $-\log_{10}$ scale) after conditional analysis on all variants. Highlighted in blue previously reported loci (SNPs within ±500Kb of leading SNPs in previous GWAS with different bone traits).

Figure S3. Regional Plots for all novel loci associated with TB-BMD ($P<5x10^{-8}$). Circles show GWAS meta-analysis P-values and position of SNPs for the overall meta-analysis (N=66,628) unless stated otherwise. Different colors indicate varying degrees of pair-wise linkage disequilibrium with the top marker (1000 Genomes – CEU population, except for 11p13 in which AFR was the reference population). Locus 11p.13 (chr11:35481152−36481152) association is driven by association in non-European populations [S]. Locus 12q24.21 reached significance in the only-European meta-analysis (N=56,284) [Y]. Locus 19q12 reached significance only in the 45-60 age-bin meta-analysis (N=18,805)[Ff]. **Attached file.**

Figure S4. Forest Plots for all novel loci associated with TB-BMD ($P<5x10^{-8}$). Effect estimates for the leading SNPs of the 36 novel BMD loci in the overall meta-analysis. Novel loci detected in the overall and subgroup meta-analyses are displayed. Symbol size proportional to the inverse variance of the SNP main effect. **Attached file**



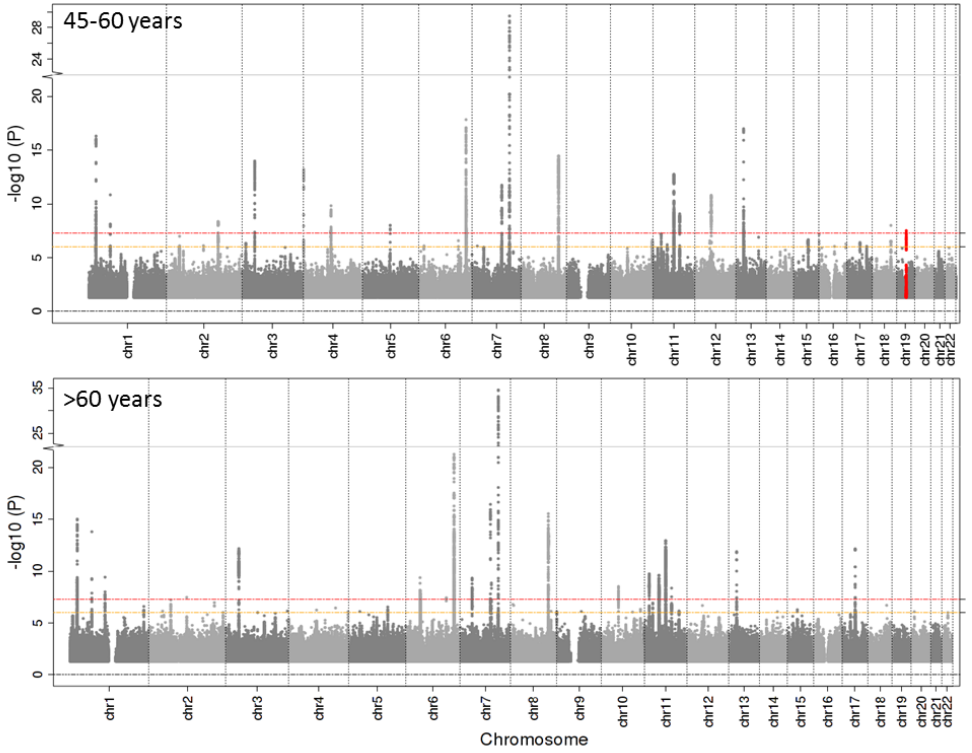


Figure S5. Manhattan plots of association statistics (-log10(P values)) for TB-BMD meta-analyses per age bin. Each dot represents an SNP and the x-axis indicates its chromosomal position (Build 37 NCBI). Dashed horizontal red and yellow lines mark the GWS threshold ($P<5x10^{-8}$) and suggestive threshold ($P<1x10^{-6}$), respectively. Sample sizes vary across the different age bins. <15 years; N= 1,870. 15-30 years; N=4,180. 30-45 years; N=10,062. 45-60 years; N= 18,805. >60 years N=22,504. Highlighted in red the age-specific signals: In red the novel locus 19q2 (45-60 years) and in magenta the known 14q32.12 locus (<15 years).

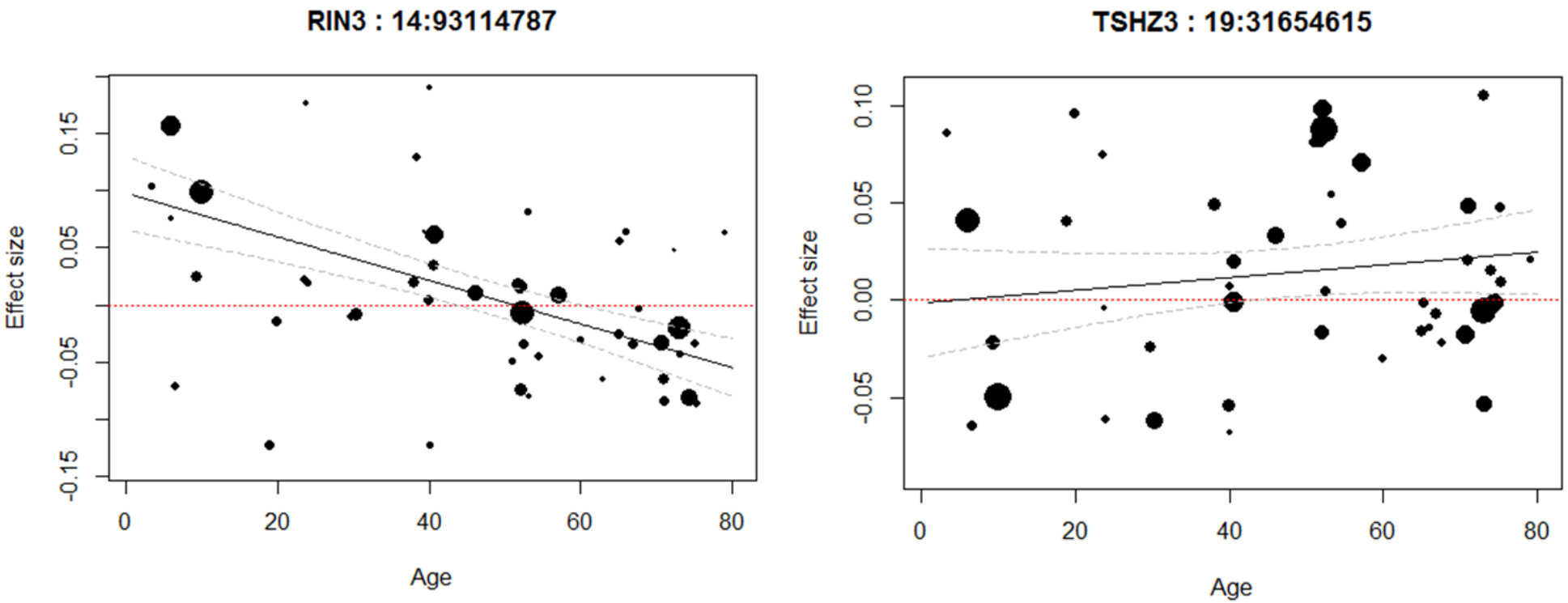


Figure S6. Meta-regression for GWS signals rising exclusively from an age-bin analysis. Left panel: Leading SNP of the signal mapping to 14q32.12 TB-BMD GWS associated only in the <15 years bin (N=11,870). **Right panel:** Leading SNP of the signal mapping to 19q12 TB-BMD GWS associated only in the 45-60 years bin (N=18,805). Each circle represents a study subgroup (i.e., study divided in age strata), with the circle size proportional to the inverse variance of the SNP main effect. At the left, estimates from each age-bin meta-analysis, with the symbol size proportional to the inverse variance of the SNP main effect.

Figure S7. Meta-regression for nominally significant signals in the meta- regression. Left panel: In total for 42 suggestive signals in the overall meta-analysis ($P<5x10^{-6}$) we found nominal evidence of an age-dependent effect of the associated variants. Meta-regression plots for each of the leading SNPs are shown. Each circle represents a study subgroup (i.e., study divided in age strata), with the circle size proportional to the inverse variance of the SNP main effect. At the left, estimates from each age-bin meta-analysis, with the symbol size proportional to the inverse variance of the SNP main effect. **Attached file**.

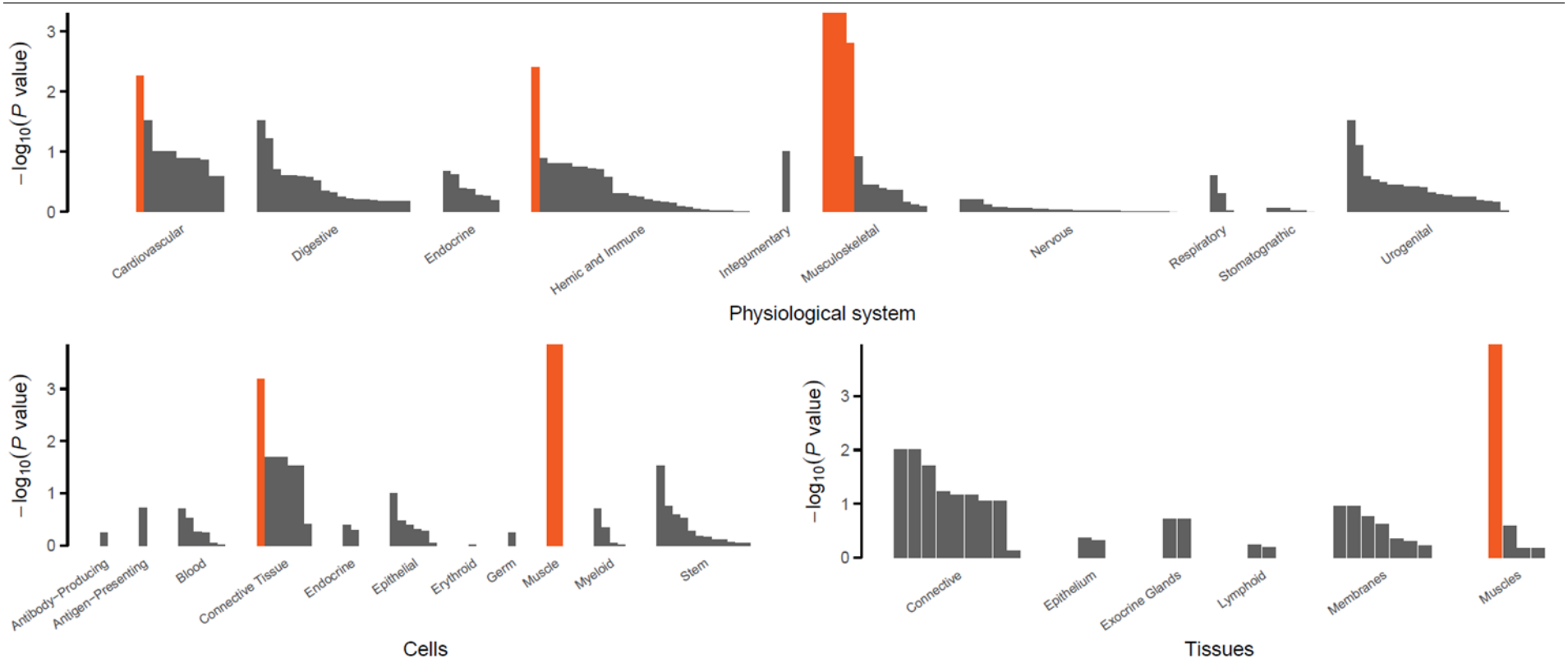


Figure S8. Depict results for cell/tissue enrichment analysis of novel TB-BMD associated regions. Bars represent the level of evidence for genes in the associated loci to be expressed in any of the 209 Medical Subject Heading (MeSH) tissue and cell type annotations. Highlighted in orange are these cell/tissue types significantly (FDR<5%) enriched for the expression of the genes in the associated loci

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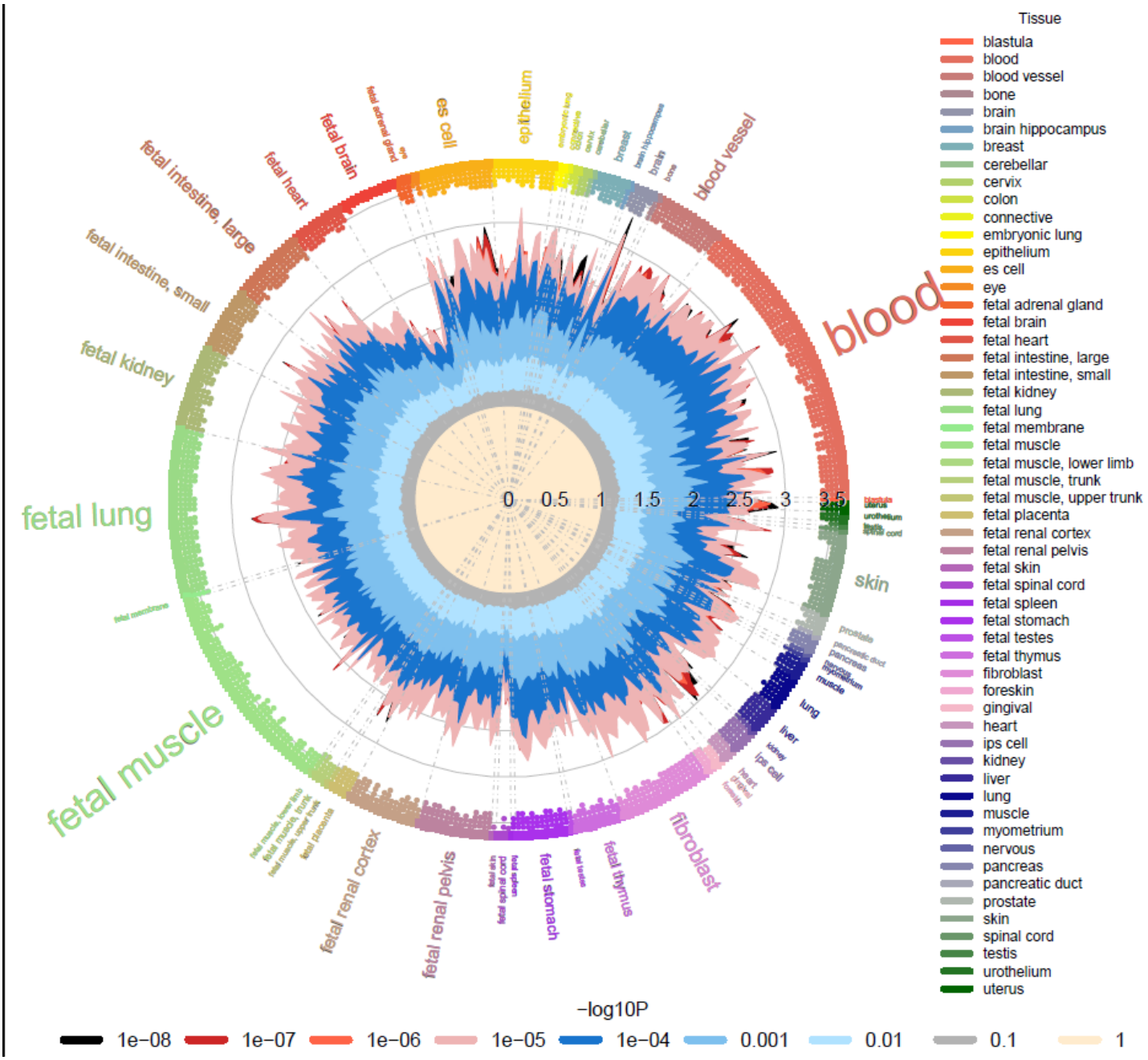

Figure S9. GARFIELD functional enrichment analyses. The wheel plot displays functional enrichment for associations with TB-BMD within DHS hotspot regions in ENCODE and Roadmap Epigenomics studies. The radial axis shows fold enrichment calculated at each of eight GWAS P-value thresholds ($P < 1\times10^{-1}$ to $P < 1\times10^{-8}$) for each of 424 cell types. Cell types are sorted by tissue, represented along the outside edge of the plot with font size proportional to the number of cell types from that tissue. Fold enrichment values at the different thresholds are plotted with different colors inside the plot (indicated at the bottom of the figure). Dots along the inside edge of the plot denote significant enrichment (if present; $P<1x10^{-4}$) for a given cell type at $P < 1\times10^{-5}$ (outermost dot) to $P < 1\times10^{-8}$ (innermost dot). Results show overall well-spread enrichment.

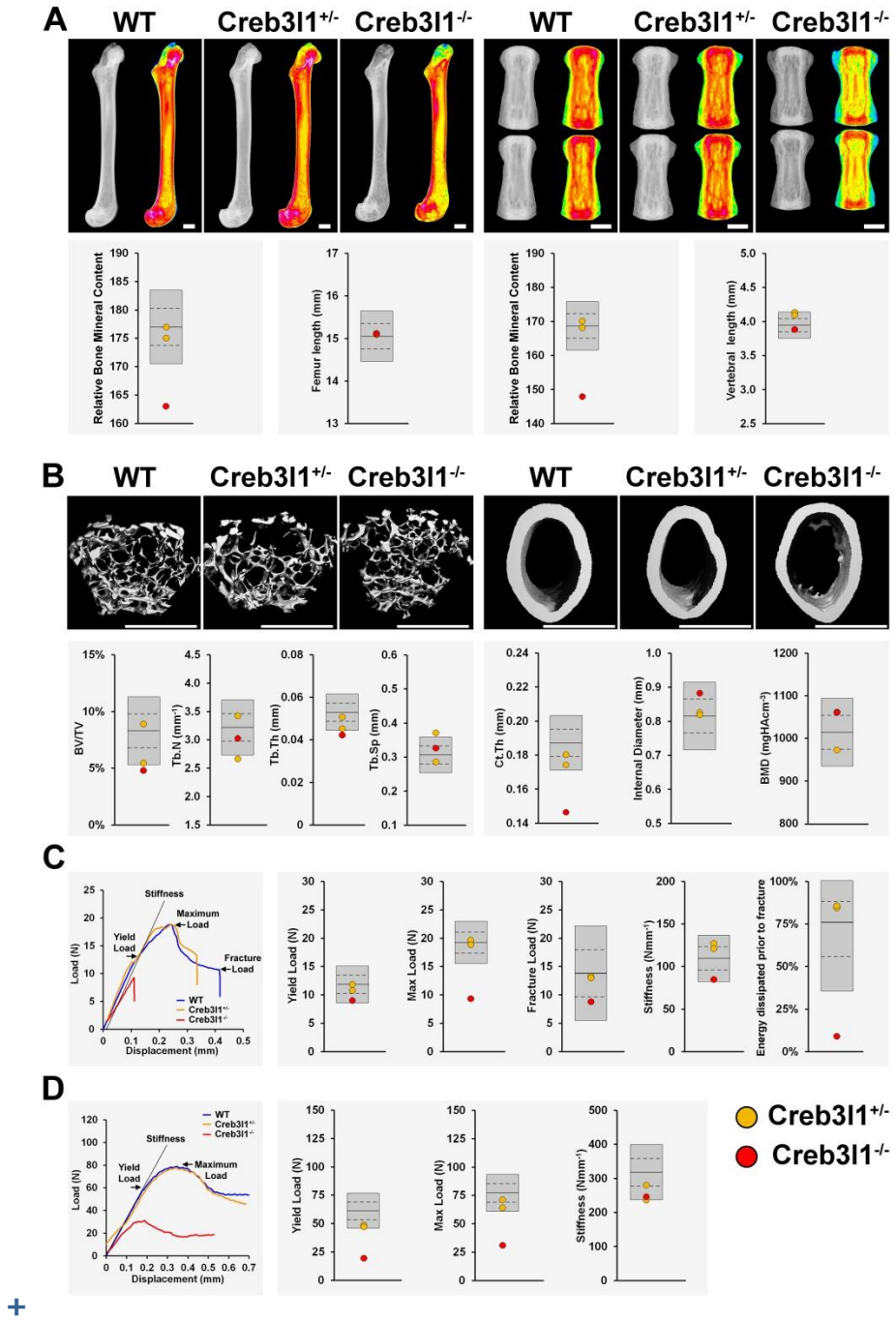

Figure S10. Skeletal phenotype screening of Cyclic AMP-responsive element-binding protein 3-like 1 (Crebl1) knockout mice. Decreased bone mass and strength in adult Creb3l1 knockout mice. **A.** X-ray microradiography (Faxitron MX20) of femur and caudal vertebrae from female wild-type (WT), heterozygous (*Creb3l1*$^{+/-}$) and homozygous (*Creb3l1*$^{-/-}$) knockout mice at postnatal day 112 (P112). Pseudocolored grey-scale images in which low bone mineral content (BMC) is blue/green and high BMC is pink. Reference ranges are derived from >300 WT mice of identical age, sex and genetic background (C57BL/6), mean (solid line), 1.0SD (dotted lines) and 2.0SD (grey box). Values for parameters from individual animals are shown as orange dots (*Creb3l1*$^{+/-}$ n=2) and red dots (*Creb3l1*$^{-/-}$ n=1). Scale bar: 1mm. **B.** Micro-CT images (Scanco MicroCT-50) of proximal femur trabecular bone (left) and mid-diaphysis cortical bone (right) from WT, *Creb3l1*$^{+/-}$ and *Creb3l1*$^{-/-}$ mice. Graphs showing trabecular bone volume/tissue volume (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp), cortical thickness (Ct.Th), internal cortical diameter and cortical bone mineral density (BMD). Scale bar: 1mm. **C**. Representative load displacement curves from destructive 3-point bend testing (Instron 5543 load frame) of WT, *Creb3l1*$^{+/-}$ and *Creb3l1*$^{-/-}$ femurs. Yield load, maximum load, fracture load and gradient of the linear elastic phase (stiffness) are indicted for the WT curve. Graphs showing yield load, maximum load, fracture load, stiffness and energy dissipated prior to fracture (Toughness). **D.** Representative load displacement curves from destructive compression testing (Instron 5543 load frame) of WT, *Creb3l1*$^{+/-}$ and *Creb3l1*$^{-/-}$ caudal vertebra showing yield load, maximum load and stiffness.

SUPPLEMENTAL TABLES

Table S1. Descriptives per cohort of genotype data for analysis. Attached Excel file

Table S2. Participant description per cohort and age strata. Attached Excel file

CHR	BP	Rsid	locus	Phenotype	Reference	A1	EAF	beta_TB	P_TB	beta_LS	P_LS	beta_FN	P_FN
1	22490724	rs7521902	1p36.12	FN-BMD, LS-BMD	Estrada et al.	A	0.24	-0.066	3.32E-23	-0.034	0.002	-0.037	6.60E-05
1	22711473	rs6426749	1p36.12	FN-BMD, LS-BMD	Estrada et al.	C	0.18	0.101	2.73E-42	0.088	1.2E-13	0.082	5.9E-16
1	68639385	rs17482952	1p31.3	FN-BMD, LS-BMD	Estrada et al.	G	0.08	-0.065	8.21E-10	-0.045	0.008	-0.043	0.003
1	68647716	rs12407028	1p31.3	FN-BMD, LS-BMD	Estrada et al.	C	0.38	-0.051	1.10E-18	-0.063	4.3E-12	-0.046	5.07E-09
1	172199573	rs479336	1q24.3	FN-BMD	Estrada et al.	G	0.28	0.032	1.18E-06	0.034	9.74E-04	0.043	9.08E-07
1	240597214	rs9287237	1q43	Trabecular vBMD	Paternoster et al.	T	0.17	0.056	3.29E-12	0.037	0.002	0.039	1.47E-04
2	42250549	rs7584262	2p21	FN-BMD	Estrada et al.	T	0.24	0.033	5.41E-07	0.009	0.392	0.044	1.34E-06
2	54659707	rs4233949	2p16.2	LS-BMD	Estrada et al.	C	0.37	0.031	2.47E-07	0.055	1.49E-03	0.044	0.002
2	112500035	rs17040773	2q13	FN-BMD	Estrada et al.	C	0.22	-0.021	0.008	-0.004	0.714	-0.023	0.012
2	119038598	rs1878526	2q14.2	LS-BMD	Estrada et al.	A	0.22	0.012	0.092	0.038	4.29E-04	0.006	0.529
2	119154872	rs6542457	2q14.2	LS-BMD	Zheng et al.	C	0.09	0.048	2.19E-05	0.083	6.53E-06	-0.005	0.757
2	119545994	rs11692564	2q14.2	LS-BMD	Zheng et al.	T	0.01	0.229	7.09E-15	0.238	4.1E-09	0.116	7.23E-04
2	166601046	rs1346004	2q24.3	FN-BMD, LS-BMD	Estrada et al.	A	0.47	-0.051	3.62E-19	-0.052	8.7E-09	-0.058	7.15E-14
3	41128564	rs430727	3p22.1	FN-BMD, LS-BMD	Estrada et al.	T	0.45	-0.070	1.53E-34	-0.056	5.3E-10	-0.061	2.02E-15
3	113370010	rs1026364	3q13.2	FN-BMD	Estrada et al.	T	0.37	0.023	1.50E-04	0.013	0.171	0.024	0.003
3	118183783	rs1949542	3q13.2	INT-BMD, TRO-BMD	Pei et al.	A	0.40	0.006	0.282	-0.013	0.150	-0.019	0.015
3	156555984	rs344081	3q25.31	LS-BMD	Estrada et al.	C	0.16	-0.056	7.40E-12	-0.047	4.28E-04	-0.035	0.002
4	994414	rs3755955	4p16.3	FN-BMD, LS-BMD	Estrada et al.	A	0.16	-0.074	2.10E-19	-0.049	5.05E-05	-0.044	2.87E-05
4	88773849	rs6532023	4q22.1	FN-BMD, LS-BMD	Estrada et al.	T	0.34	0.060	1.31E-23	0.048	2.34E-07	0.034	2.78E-05
5	88376061	rs1366594	5q14.3	FN-BMD	Estrada et al.	C	0.49	-0.048	2.35E-17	-0.007	0.435	-0.079	5.44E-25
6	21384613	rs9466056	6p22.3	FN-BMD, LS-BMD	Estrada et al.	A	0.39	-0.028	1.90E-06	-0.039	1.81E-05	-0.038	8.86E-07
6	44639184	rs11755164	6p21.1	LS-BMD	Estrada et al.	T	0.41	-0.041	7.13E-12	-0.024	0.010	-0.013	0.108
6	127167072	rs13204965	6q22.33	FN-BMD, LS-BMD	Estrada et al.	C	0.23	-0.062	1.02E-18	-0.039	2.81E-04	-0.052	1.39E-08
6	133350936	rs3012465	6q23.2	Skull BMD	Kemp et al.	A	0.33	-0.022	2.61E-04	0.016	0.079	0.025	0.002
6	151895456	rs6909279	6q25.1	Cortical vBMD	Paternoster et al.	G	0.44	-0.072	2.52E-35	-0.055	1.3E-09	-0.051	8.07E-11
6	151907748	rs4869742	6q25.1	FN-BMD, LS-BMD	Estrada et al.	T	0.33	-0.070	5.20E-30	-0.061	2.8E-08	-0.052	1.75E-08
6	151946658	rs7751941	6q25.1	FN-BMD, LS-BMD	Estrada et al.	A	0.21	-0.044	1.45E-10	-0.059	9.8E-08	-0.031	0.001
7	37938422	rs10226308	7p14.1	LS-BMD	Estrada et al.	G	0.18	0.033	1.06E-05	0.059	2.48E-07	0.025	0.012
7	38128326	rs6959212	7p14.1	FN-BMD, LS-BMD	Estrada et al.	T	0.34	-0.043	7.34E-13	-0.066	2.6E-12	-0.033	5.12E-05
7	96120675	rs4727338	7q21.3	FN-BMD, LS-BMD	Estrada et al.	G	0.32	-0.073	6.07E-33	-0.059	5.8E-10	-0.063	5E-15
7	120742980	rs148771817	7q31.31	FA-BMD	Zheng et al.	T	0.01	0.154	7.88E-04	0.136	0.006	0.011	0.798
7	120785064	rs13245690	7q31.31	LS-BMD	Estrada et al.	G	0.37	-0.057	4.06E-22	-0.028	0.002	-0.023	0.003
7	120903815	rs4609139	7q31.31	TB-BMD	Medina-Gomez et al.	T	0.35	-0.046	1.17E-14	-0.015	0.117	-0.013	0.114
7	120974765	rs3801387	7q31.31	FN-BMD	Estrada et al.	G	0.27	0.135	1.15E-100	0.073	1.7E-13	0.054	3.26E-10
7	150919829	rs7812088	7q36.1	FN-BMD	Estrada et al.	A	0.12	0.058	3.54E-11	0.035	0.010	0.044	1.61E-04
8	71591203	rs7017914	8q13.3	Fem FN-BMD	Estrada et al.	G	0.48	-0.008	0.151	0.011	0.219	-0.016	0.045
8	120007420	rs2062377	8q24.12	FN-BMD, LS-BMD	Estrada et al.	T	0.41	0.064	1.47E-28	0.081	6.6E-19	0.060	1.64E-14
9	133478827	rs7851693	9q34.11	FN-BMD	Estrada et al.	G	0.35	-0.046	5.73E-14	-0.017	0.074	-0.040	9.62E-07
10	28479942	rs3905706	10p12.1	LS-BMD	Estrada et al.	T	0.23	0.009	0.176	0.055	7.69E-07	-0.014	0.157
10	54427825	rs1373004	10q21.1	FN-BMD, LS-BMD	Estrada et al.	T	0.15	-0.067	1.22E-14	-0.056	1.10E-04	-0.045	2.81E-04
10	79401316	rs7071206	10q22.3	LS-BMD	Estrada et al.	C	0.21	0.016	0.027	0.053	8.60E-07	-0.014	0.122
10	101813802	rs7084921	10q24.2	FN-BMD	Estrada et al.	T	0.41	0.024	3.94E-05	0.018	0.043	0.026	9.35E-04
11	15710084	rs7108738	11p15.1	FN-BMD	Estrada et al.	G	0.18	0.056	9.06E-14	0.043	2.05E-04	0.083	8.07E-17
11	16296412	rs1347677	11p15.1	Hip BMD	Yang TL et al.	C	0.21	0.045	5.41E-11	0.030	0.006	0.039	3.37E-05
11	27505677	rs10835187	11p14-p13	LS-BMD	Estrada et al.	C	0.48	0.044	4.38E-14	0.026	0.004	0.009	0.275
11	30951674	rs163879	11p14.1	FN-BMD, LS-BMD	Estrada et al.	C	0.34	0.031	3.02E-07	0.039	6.17E-05	0.018	0.026
11	46722221	rs7932354	11p11.2	FN-BMD, LS-BMD	Estrada et al.	T	0.34	0.043	9.33E-12	0.036	4.23E-04	0.041	1.64E-06
11	68201295	rs3736228	11q13.2	FN-BMD, LS-BMD	Estrada et al.	T	0.15	-0.102	5.03E-34	-0.078	2.9E-10	-0.049	4.79E-06
11	68263370	rs12272917	11q13.2	SK-BMD	Kemp et al.	C	0.25	-0.077	2.74E-31	-0.074	4.6E-13	-0.045	2.89E-07
11	86853997	rs597319	11q14.2	BUA and VOS	Moayyeri et al.	G	0.32	-0.055	1.72E-19	-0.042	1.25E-05	-0.026	0.002
12	1638171	rs2887571	12p13.33	FN-BMD, LS-BMD	Estrada et al.	G	0.24	0.038	6.83E-09	0.034	8.57E-04	0.022	0.012
12	28017159	rs7953528	12p11.22	FN-BMD	Estrada et al.	A	0.17	0.018	0.019	-0.011	0.349	0.038	1.35E-04
12	49474605	rs12821008	12q13.12	LS-BMD	Estrada et al.	T	0.38	0.034	1.94E-08	.	.	0.012	0.525
12	53727955	rs2016266	12q13.13	FN-BMD, LS-BMD	Estrada et al.	G	0.34	0.048	1.55E-15	0.056	6.7E-09	0.039	1.89E-06
12	54417576	rs736825	12q13.13	FN-BMD, LS-BMD	Estrada et al.	G	0.37	-0.017	4.09E-03	-0.062	2.7E-11	-0.043	8.70E-08
12	107367225	rs1053051	12q23.3	FN-BMD	Estrada et al.	C	0.49	0.032	2.46E-08	0.024	0.006	0.023	0.003
13	42951449	rs9533090	13q14.11	FN-BMD, LS-BMD	Estrada et al.	T	0.45	-0.060	1.09E-25	-0.082	5.2E-20	-0.035	6.19E-06
13	43116133	rs1021188	13q14.11	Cortical BMD	Paternoster et al.	C	0.19	-0.037	5.79E-07	-0.026	0.024	-0.020	0.051
14	70456699	rs227425	14q24.2	LS-BMD	Zhang et al.	G	0.49	-0.013	0.026	-0.035	1.13E-04	-0.010	0.185
14	91442779	rs1286083	14q32.11	FN-BMD, LS-BMD	Estrada et al.	C	0.20	0.053	1.95E-13	0.065	1E-08	0.038	7.66E-05
14	93114787	rs754388	14q32.12	TB-BMD, LL-BMD	Kemp et al.	A	0.17	-0.010	0.167	-0.007	0.543	-0.004	0.670
14	103883633	rs11623869	14q32.32	FN-BMD, LS-BMD	Estrada et al.	T	0.34	-0.029	1.11E-06	-0.020	0.029	-0.029	2.96E-04
16	375782	rs9921222	16p13.3	FN-BMD, LS-BMD	Estrada et al.	T	0.48	-0.048	1.76E-17	-0.053	3.2E-09	-0.050	6.36E-11
16	1532463	rs13336428	16p13.3	FN-BMD, LS-BMD	Estrada et al.	A	0.44	-0.025	1.56E-05	-0.027	0.003	-0.039	8.33E-07
16	15129459	rs4985155	16p13.11	FN-BMD, LS-BMD	Estrada et al.	G	0.34	0.021	4.35E-04	0.035	2.09E-04	0.022	0.007
16	50986308	rs1564981	16q12.1	LS-BMD	Estrada et al.	A	0.49	-0.025	6.86E-06	-0.044	7.95E-07	-0.032	2.38E-05
16	51021803	rs1566045	16q12.1	FN-BMD	Estrada et al.	C	0.20	0.027	8.05E-04	0.012	0.317	0.043	2.90E-05
16	86710660	rs10048146	16q24.1	FN-BMD, LS-BMD	Estrada et al.	G	0.18	-0.048	2.09E-10	-0.064	4.5E-08	-0.056	2.31E-08

CHR	BP	Rsid	locus	Phenotype	Reference	A1	EAF	beta_TB	P_TB	beta_LS	P_LS	beta_FN	P_FN
17	2068932	rs4790881	17p13.3	FN-BMD, LS-BMD	Estrada et al.	C	0.29	-0.038	1.04E-09	-0.035	3.41E-04	-0.050	2.92E-09
17	41798824	rs4792909	17q21.31	FN-BMD, LS-BMD	Estrada et al.	T	0.40	0.039	5.96E-11	0.047	3.07E-07	0.048	1.52E-09
17	42225547	rs227584	17q21.31	FN-BMD, LS-BMD	Estrada et al.	C	0.34	0.032	2.16E-07	0.043	4.05E-05	0.048	2.69E-08
17	43977827	rs1864325	17q21.31	LS-BMD	Estrada et al.	T	0.21	-0.023	0.008	-0.052	2.48E-04	-0.019	0.103
17	69949016	rs7217932	17q24.3	FN-BMD	Estrada et al.	A	0.48	0.025	1.14E-05	0.006	0.501	0.033	1.89E-05
18	13708574	rs4796995	18p11.21	FN-BMD	Estrada et al.	G	0.37	-0.022	2.23E-04	-0.025	0.006	-0.037	2.56E-06
18	60054857	rs884205	18q21.33	FN-BMD, LS-BMD	Estrada et al.	A	0.24	-0.053	4.39E-15	-0.062	2.8E-09	-0.042	2.71E-06
19	33599127	rs10416218	19q13.11	LS-BMD	Estrada et al.	C	0.29	0.028	1.19E-05	0.070	8.3E-09	0.042	2.93E-05
20	10639988	rs3790160	20p12.2	FN-BMD, LS-BMD	Estrada et al.	C	0.50	-0.035	7.99E-10	-0.051	1.50E-08	-0.029	1.94E-04
21	37848334	rs170183	21q22.13	Hip BMD-Female	Zhang et al.	G	0.50	0.026	6.80E-06	0.016	0.082	0.020	0.009

Table S3 Known independent markers associated with bone phenotypes. Index SNPs of the GWS association reported for the specific bone phenotype [fifth column] in the reference stated [sixth column]. All effect sizes (β) are reported for the minor allele (A1). EAF=Effect Allele Frequency, TB= total body BMD, assessed in this study, LS=lumbar spine BMD, assessed in Zheng et al. , FN=Femoral Neck BMD, assessed in Zheng at al. Phenotype for which association was previously reported and the correspondent reference are given.

Table S4. Genome-wide significant SNPs for the overall TB-BMD meta-analysis. Estimates were derived from the overall approach. Beta coefficients and allele frequency (EAF) are reported for the A1 allele. **Attached Excel file**.

Table S5. Genome-wide significant SNPs for the TB-BMD meta-analysis in European cohorts. Estimates were derived from the all-age combined approach. Beta coefficients and allele frequency (EAF) are reported for the A1 allele. **Attached Excel file.**

CHR	BP	Rsid	A1	A2	EAF	beta	P.value	HetISq	HetPVal	N	locus	unreported
1	22700351	rs34920465	a	g	0.7968	-0.1008	9.41E-16	0	0.6114	22467	1p36.12	no
1	68656697	rs2566752	t	c	0.6119	-0.0776	1.55E-14	0	0.841	22380	1p31.3	no
1	110475971	rs7548588	t	c	0.6075	-0.0617	3.80E-10	34.4	0.07127	22324	1p13.3	yes
2	119529829	rs55983207	t	c	0.9474	-0.1409	3.37E-08	36.1	0.06437	22187	2q14.2	no
3	41171177	rs2371447	t	g	0.4846	-0.0711	6.58E-13	0	0.5362	22460	3p22.1	no
6	45144224	rs184065563	a	g	0.3052	-0.0623	7.14E-09	7.9	0.3586	22491	6p21.1	no
6	127423055	rs1936792	a	g	0.2652	0.0607	3.72E-08	20	0.2109	22458	6q22.33	no
6	151910126	rs6557155	t	g	0.428	-0.0981	5.18E-22	0	0.9731	22490	6q25.1	no
7	38136277	rs1524058	t	c	0.4044	-0.0604	7.43E-10	10.7	0.3237	22479	7p14.1	no
7	96134115	rs6465511	c	g	0.3265	-0.0849	1.16E-16	0	0.5605	22493	7q21.3	no
7	99130834	rs34670419	t	g	0.0387	-0.1603	1.40E-09	0	0.7425	22223	7q22.1	yes
7	120974765	rs3801387	a	g	0.7266	-0.1337	2.82E-35	13.3	0.2911	22423	7q31.31	no
8	120012700	rs11995824	c	g	0.4289	0.0806	2.80E-16	0	0.6858	22476	8q24.12	no
10	54425325	rs10824760	t	c	0.8217	0.0886	3.05E-09	0	0.9745	22453	10q21.1	no
11	16348061	rs7131442	a	t	0.7918	-0.0762	1.81E-10	0	0.6208	22497	11p15.1	no
11	46783435	rs61884328	t	c	0.9013	-0.1063	2.46E-10	29.7	0.1088	22502	11p11.2	no
11	68218290	rs11228240	t	c	0.254	-0.0848	1.12E-13	16.7	0.2501	22483	11q13.2	no
11	86873599	11:86873599:I	d	i	0.7333	0.0768	4.34E-09	0	0.6918	18952	11q14.2	no
13	42951449	rs9533090	t	c	0.4555	-0.0663	8.41E-12	53.8	0.002882	22493	13q14.11	no
17	41826839	rs2741856	c	g	0.0764	0.1391	7.03E-13	2.6	0.4249	22392	17q21.31	no
1	22697860	rs6679981	a	g	0.1811	0.1162	4.81E-17	34.1	0.1257	18784	1p36.12	no
1	68656697	rs2566752	t	c	0.6056	-0.075	1.42E-11	0	0.7436	18734	1p31.3	no
2	166618262	rs1968294	t	c	0.4895	-0.0632	4.41E-09	0	0.9458	18786	2q24.3	no
3	41127606	rs444561	c	g	0.5642	0.0831	1.02E-14	0	0.9578	18782	3p22.1	no
4	1008386	rs56396408	t	c	0.1529	-0.1198	1.37E-13	16.2	0.2938	16206	4p16.3	no
4	88831249	rs11934731	a	g	0.6784	-0.0718	3.71E-10	0	0.7177	18802	4q22.1	no
5	88354675	rs10037512	t	c	0.5173	0.0604	2.10E-08	0	0.6152	18780	5q14.3	no
6	151910126	rs6557155	t	g	0.4255	-0.0968	1.42E-18	11.1	0.3381	18802	6q25.1	no
7	96133871	rs6465510	a	c	0.6498	0.0787	1.79E-12	0	0.464	18802	7q21.3	no
7	120974765	rs3801387	a	g	0.7348	-0.1359	3.49E-30	0	0.4875	18735	7q31.31	no
8	119946656	rs7010267	a	c	0.4438	0.0838	3.34E-15	0	0.7913	18728	8q24.12	no
11	68220905	rs57502260	a	g	0.8295	0.1088	1.81E-13	36.4	0.1075	18792	11q13.2	no
11	86880458	rs540403	a	g	0.3312	-0.0699	1.36E-09	0	0.859	18791	11q14.2	no
12	49379537	rs118115924	t	g	0.0143	-0.3132	6.10E-10	23.7	0.2178	18764	12q13.12	no
12	53659448	rs7398996	t	c	0.6855	-0.0762	1.56E-11	0	0.4527	18787	12q13.13	no
13	42969049	rs9533095	t	g	0.4647	-0.091	1.32E-17	0	0.4543	18797	13q14.11	no
18	60054857	rs884205	a	c	0.2479	-0.072	9.97E-09	0	0.532	18757	18q21.33	no
19	31654615	rs6510186	t	c	0.2602	0.0677	3.11E-08	0	0.614	18782	19q12	yes*
1	22682366	rs12742784	t	c	0.2193	0.1126	6.64E-10	0	0.6669	10049	1p36.12	no
3	41112656	rs62259232	a	g	0.4885	0.0899	1.21E-09	0	0.8597	10050	3p22.1	no
4	88852643	rs10005067	t	c	0.5212	0.0883	2.16E-09	0	0.545	10062	4q22.1	no
6	151874122	rs9478217	a	g	0.4637	-0.1173	4.33E-15	13.1	0.3249	10055	6q25.1	no
7	120983343	rs10242100	a	g	0.7296	-0.1614	8.22E-23	4.1	0.4007	10025	7q31.31	no
11	242859	rs55781332	a	g	0.7823	-0.1088	6.98E-10	8.7	0.3624	9965	11p15.5	yes
11	68218290	rs11228240	t	c	0.2576	-0.0974	2.58E-08	0	0.9399	10049	11q13.2	no
13	42965694	rs8001611	t	c	0.5404	0.0947	1.54E-10	0	0.8615	10059	13q14.11	no

4	88815986	rs77034375	t	c	0.3089	-0.1397	1.26E-08	0	0.5184	4180	4q22.1	no
1	22444975	rs10737462	t	c	0.2267	-0.0925	1.67E-09	22	0.2685	11807	1p36.12	no
1	68658266	1:68658266:I	d	i	0.4541	0.0947	2.60E-11	39.9	0.1553	11360	1p31.3	no
2	166573776	rs35969972	t	c	0.5148	0.0771	2.01E-09	26.3	0.2369	11807	2q24.3	no
4	88831249	rs11934731	a	g	0.6716	-0.0777	1.52E-08	0	0.6512	11807	4q22.1	no
7	121018857	rs917726	a	t	0.7269	-0.137	5.07E-21	36.4	0.1644	11807	7q31.31	no
11	68252123	rs12364620	t	g	0.7508	0.0848	1.29E-08	0	0.8874	11807	11q13.2	no
13	43128577	rs9525638	t	c	0.5826	-0.0844	1.90E-10	0	0.9245	11360	13q14.11	no
14	93114787	rs72699866	g	a	0.8247	0.0994	1.01E-08	54.3	0.05281	11807	14q32.12	no*

Table S6. Index Genome-wide significant SNPs in the age-bin meta-analyses. Genomic coordinates are on build 37 of the human genome. Beta coefficients and allele frequencies (EAF) are reported for the A1 allele. * Only GWS in the particular age-bin.

Table S7. Nominally significant variants after meta-regression analysis. Only suggestively associated variants ($P<5x10^{-6}$) in the TB-BMD overall meta-analysis were subjected to meta-regression assessment. Genomic coordinates are on build 37 of the human genome. Allele frequencies (EAF) are reported for the A1 allele. C.L-C.U, 95% Confidence interval lower and upper limit. **Attached Excel file**

CHR	BP	locus	rsnumber	A1	EAF	beta	P	N	betaJ	PJ
1	22484575	1p36.12	rs3971300	T	0.71	0.069	7.41E-23	57561	0.071	2.56E-24
1	22700351	1p36.12	rs34920465	A	0.82	-0.101	2.67E-35	59625	-0.103	7.68E-37
1	68635879	1p31.3	rs145119306	A	0.07	-0.026	0.03436	58593	-0.088	2.77E-11
1	68656697	1p31.3	rs2566752	T	0.61	-0.074	6.79E-31	59727	-0.091	7.06E-40
1	110480220	1p13.3	rs7364724	A	0.40	-0.038	1.84E-09	60973	-0.038	2.20E-09
1	240581653	1q43	rs12044944	T	0.19	0.052	1.06E-10	58925	0.052	8.86E-11
2	40630678	2p22.1	rs10490046	A	0.77	0.042	1.13E-08	59278	0.043	9.30E-09
2	42280066	2p21	rs78572108	A	0.13	-0.054	2.66E-08	55121	-0.054	2.35E-08
2	68962137	2p13.3	rs10048745	A	0.25	-0.041	1.76E-08	58660	-0.041	1.68E-08
2	85483350	2p11.2	rs2043230	A	0.44	0.034	4.77E-08	61631	0.034	4.59E-08
2	119507607	2q14.2	rs115242848	T	0.01	0.312	1.75E-14	35647	0.305	6.28E-14
2	119632724	2q14.2	rs12621139	A	0.20	-0.060	3.88E-12	48934	-0.058	1.12E-11
2	166577489	2q24.3	rs7586085	A	0.52	0.051	1.72E-16	60651	0.051	1.76E-16
2	202803881	2q33.2	rs6716216	A	0.88	-0.066	4.71E-12	61489	-0.066	4.40E-12
3	41129297	3p22.1	rs415997	A	0.53	0.068	2.64E-28	60766	0.068	3.61E-28
3	156474152	3q25.31	rs344024	A	0.77	0.050	3.11E-12	62621	0.050	2.61E-12
4	996165	4p16.3	rs6831280	A	0.16	-0.080	8.26E-19	53031	-0.080	1.06E-18
4	88831249	4q22.1	rs11934731	A	0.68	-0.062	1.69E-20	61124	-0.062	1.09E-20
5	88376061	5q14.3	rs1366594	A	0.52	0.051	5.03E-16	60698	0.051	3.01E-16
5	122847622	5q23.2	rs11745493	A	0.75	0.044	9.90E-10	61202	0.044	8.30E-10
6	44636919	6p21.1	rs7741085	T	0.59	0.047	1.19E-13	60657	0.047	1.61E-13
6	127167072	6q22.33	rs13204965	A	0.76	0.062	1.05E-16	57298	0.085	5.46E-27
6	127446790	6q22.33	rs9482772	T	0.55	-0.039	5.70E-10	59203	-0.061	3.17E-20
6	151910126	6q25.1	rs6557155	T	0.42	-0.079	2.97E-34	58412	-0.074	3.00E-30
6	151994910	6q25.1	rs7765040	A	0.84	0.059	5.37E-12	58188	0.054	7.30E-10
6	152008982	6q25.1	rs2941741	A	0.41	0.058	1.29E-20	62437	0.040	4.26E-10
7	30957702	7p14.3	rs28362721	T	0.18	-0.061	1.02E-12	53488	-0.062	6.40E-13
7	37965963	7p14.1	rs28457747	T	0.18	0.039	9.85E-07	61792	0.045	1.89E-08
7	38136277	7p14.1	rs1524058	T	0.40	-0.054	1.73E-17	60883	-0.057	2.72E-19
7	50901491	7p12.1	rs1548607	A	0.69	0.041	9.71E-09	52156	0.041	9.02E-09
7	96133319	7q21.3	rs6965122	A	0.68	0.077	4.64E-31	61668	0.076	1.52E-30
7	96656572	7q21.3	rs3757493	T	0.42	-0.036	1.28E-08	60079	-0.035	4.29E-08
7	120790559	7q31.31	rs56335989	T	0.55	-0.023	0.0001878	59259	-0.045	5.38E-09
7	120902676	7q31.31	rs4731006	T	0.35	-0.040	5.45E-10	60966	-0.060	2.85E-14
7	120959155	7q31.31	rs2536195	A	0.68	-0.089	1.11E-29	43891	-0.068	1.46E-14
7	120974765	7q31.31	rs3801387	A	0.73	-0.138	3.31E-87	60474	-0.163	7.27E-91
7	120985854	7q31.31	rs2041490	C	0.18	0.017	0.04031	59352	0.084	9.83E-21
7	121178195	7q31.31	rs73717393	T	0.93	-0.094	4.69E-13	55499	-0.088	8.04E-12
7	150933044	7q36.1	rs10233479	T	0.12	0.062	1.20E-10	63298	0.062	9.70E-11
8	120012700	8q24.12	rs11995824	C	0.44	0.074	5.21E-32	59397	0.074	8.68E-32
9	133471891	9q34.11	rs10901216	A	0.35	-0.045	6.20E-12	58789	-0.045	6.84E-12
10	54423853	10q21.1	rs12258451	C	0.88	0.075	4.32E-14	56851	0.075	5.63E-14

10	124015986	10q26.13	rs10788264	A	0.49	-0.041	4.10E-11	60632	-0.041	3.43E-11
11	243268	11p15.5	rs505404	T	0.76	-0.052	9.04E-13	60292	-0.052	9.75E-13
11	15708792	11p15.2	rs7926837	A	0.79	-0.052	7.46E-12	60590	-0.054	1.76E-12
11	15814794	11p15.2	rs11023718	T	0.04	0.128	7.30E-13	52490	0.118	5.96E-11
11	16248894	11p15.1	rs12800049	T	0.26	0.056	1.11E-15	61150	0.048	1.43E-11
11	16630779	11p15.1	rs35199438	T	0.31	-0.047	2.24E-12	60906	-0.040	4.72E-09
11	27308483	11p14-p13	rs10450586	C	0.62	-0.048	8.17E-14	60024	-0.051	2.26E-15
11	27593899	11p14-p13	rs1352479	A	0.27	0.039	6.88E-08	57320	0.042	5.05E-09
11	35083633	11p13	rs2553773	C	0.43	-0.034	8.09E-08	60038	-0.036	1.79E-08
11	46856536	11p11.2	rs10838622	T	0.36	0.049	3.04E-13	56422	0.045	2.54E-11
11	47252107	11p11.2	rs4647728	A	0.03	-0.124	5.88E-11	49763	-0.111	5.94E-09
11	68174189	11q13.2	rs4988321	A	0.04	-0.160	4.08E-23	54286	-0.114	1.63E-11
11	68218290	11q13.2	rs11228240	T	0.26	-0.084	3.57E-31	56682	-0.069	3.51E-19
11	86887931	11q14.2	rs634277	A	0.67	0.062	2.19E-20	58914	0.062	2.01E-20
12	49379537	12q13.12	rs118115924	T	0.01	-0.277	8.01E-18	39253	-0.304	6.84E-21
12	49385679	12q13.12	rs10875906	T	0.27	0.053	1.07E-12	53734	0.061	1.57E-16
12	53737840	12q13.13	rs12424778	A	0.28	0.054	2.23E-15	61906	0.054	1.16E-15
12	90334829	12q21.33	rs10777212	T	0.35	0.045	5.00E-12	58906	0.045	6.15E-12
12	107297862	12q23.3	rs6539288	A	0.50	-0.040	2.44E-10	60592	-0.040	1.86E-10
12	116555786	12q24.21	rs73200209	A	0.80	0.045	2.52E-08	56109	0.045	2.54E-08
13	42952145	13q14.11	rs9594738	T	0.47	-0.072	5.00E-31	60695	-0.069	2.43E-28
13	43153869	13q14.11	rs117543324	A	0.96	-0.162	3.13E-17	46599	-0.147	2.42E-14
14	91445162	14q32.11	rs1286079	T	0.19	0.055	5.42E-12	59543	0.055	5.30E-12
15	51126002	15q21.2	rs34293575	A	0.82	-0.025	0.002497	60821	-0.049	1.80E-08
15	51524292	15q21.2	rs2414095	A	0.35	-0.040	6.22E-10	60408	-0.054	7.30E-15
15	67420680	15q22.33	rs1545161	A	0.54	0.038	1.16E-09	61086	0.036	7.67E-09
15	67562214	15q22.33	rs12901789	A	0.76	-0.049	1.68E-11	59612	-0.047	1.22E-10
16	392318	16p13.3	rs8047501	A	0.49	0.056	6.83E-18	55097	0.056	8.38E-18
16	86714715	16q24.1	rs71390846	C	0.19	-0.050	6.95E-10	58067	-0.050	7.94E-10
17	2048713	17p13.3	rs7209460	T	0.70	0.044	1.15E-10	59907	0.044	1.20E-10
17	17843396	17p11.2	rs8070624	A	0.44	0.036	2.45E-08	57633	0.036	2.45E-08
17	41798621	17q21.31	rs66838809	A	0.08	0.109	2.35E-18	50133	0.110	1.59E-18
17	42283037	17q21.31	rs9910055	T	0.25	0.044	3.13E-09	57268	0.045	1.37E-09
17	63840961	17q24.1	rs9907056	A	0.32	0.041	1.61E-09	59188	0.041	1.38E-09
18	60054857	18q21.33	rs884205	A	0.25	-0.053	3.96E-13	58528	-0.053	3.96E-13
20	10640877	20p12.2	rs6040063	A	0.51	0.040	7.75E-11	60605	0.040	1.01E-10
21	36970350	21q22.12	rs9976876	T	0.46	-0.038	1.35E-09	59146	-0.038	1.48E-09
21*	37836973	21q22.13	rs7277076	T	0.43	0.036	1.82E-08	59889	0.036	1.21E-08
21	40350744	21q22.2	rs11910328	A	0.84	-0.049	8.51E-09	59137	-0.050	5.82E-09

Table S8. Independent variants associated with TB-BMD in the only –European meta-analysis. Genomic coordinates are on build 37 of the human genome. Beta coefficients and allele frequencies (EAF) are reported for the A1 allele. *J* suffix refers to the summary statistics in the join analysis fitting all variants together. * Only significant in the meta-analysis of European individuals.

Trait	PMID	year	rg	se	Z	P
Age.at.menarche	25231870	2014	-0.05	0.028	-1.801	0.072
Age.at.Menopause	26414677	2015	0.002	0.043	0.054	0.957
Anorexia.nervosa	24514567	2014	-0.027	0.034	-0.791	0.429
Asthma	17611496	2007	0.02	0.063	0.312	0.755
Autism.spectrum.disorder	www.med.unc.edu	2015	-0.059	0.064	-0.925	0.355
Bipolar.disorder	21926972	2011	0.035	0.052	0.669	0.504
Birth.length	25281659	2015	-0.109	0.059	-1.84	0.066
Birth.weight	23202124	2013	-0.023	0.059	-0.39	0.697
Body.mass.index.2010	20935630	2010	0.108	0.029	3.748	0.0002
Childhood.intelligence.quotient	23358156	2014	-0.012	0.065	-0.183	0.855
Childhood.obesity	22484627	2012	0.091	0.049	1.858	0.063
Cholesterol.esters.in.large.HDL	27005778	2016	-0.077	0.107	-0.721	0.471
Cholesterol.esters.in.large.LDL	27005778	2016	0.036	0.068	0.535	0.593
Cholesterol.esters.in.large.VLDL	27005778	2016	-0.078	0.106	-0.735	0.463
Cholesterol.esters.in.medium.HDL	27005778	2016	0.076	0.094	0.807	0.42
Cholesterol.esters.in.medium.LDL	27005778	2016	-0.062	0.104	-0.598	0.55
Cognitive.performance	25201988	2014	0.057	0.039	1.472	0.141
College.completion	23722424	2013	0.059	0.042	1.43	0.153
Creatinine	27005778	2016	0.093	0.069	1.354	0.176
Crohn's.disease	26192919	2015	-0.044	0.042	-1.042	0.297
Depressive.symptoms	27089181	2016	-0.051	0.039	-1.307	0.191
Ever.vs.never.smoked	20418890	2010	-0.015	0.044	-0.335	0.737
Extreme.body.mass.index	23563607	2013	0.094	0.044	2.122	0.034
Extreme.height	23563607	2013	-0.087	0.044	-1.978	0.048
Extreme.waist.to.hip.ratio	23563607	2013	-0.035	0.072	-0.486	0.627
Fasting.glucose	22581228	2012	0.065	0.047	1.388	0.165
Fasting.insulin	22581228	2012	0.027	0.058	0.459	0.647
Femoral.neck.bone.mineral.density	22504420	2012	0.923	0.035	26.03	2.25E-149
Forced.expiratory.volume.in.1.second	21946350	2011	0.054	0.062	0.877	0.381
forced.vital.capacity	21946350	2011	0.056	0.044	1.272	0.203
Former.vs.current.smoker	20418890	2010	-0.019	0.067	-0.289	0.772
Free.cholesterol.in.IDL	27005778	2016	-0.101	0.106	-0.952	0.341
Free.cholesterol.in.large.HDL	27005778	2016	0.117	0.114	1.02	0.308
Free.cholesterol.in.large.LDL	27005778	2016	0.04	0.068	0.59	0.555
Free.cholesterol.in.large.VLDL	27005778	2016	-0.049	0.108	-0.453	0.651
Free.cholesterol.in.medium.HDL	27005778	2016	0.073	0.085	0.861	0.389
Free.cholesterol.in.medium.VLDL	27005778	2016	-0.068	0.072	-0.952	0.341
Free.cholesterol.in.serum	27005778	2016	-0.162	0.129	-1.258	0.208
Free.cholesterol.in.small.VLDL	27005778	2016	-0.102	0.093	-1.091	0.275
Glucose	27005778	2016	0.079	0.069	1.145	0.252
Glycated hemoglobin.HbA1C	20858683	2010	0.122	0.06	2.033	0.042
HDL.cholesterol	20686565	2010	-0.07	0.033	-2.116	0.034

Height.2010	20881960	2010	-0.057	0.031	-1.846	0.065
Hip.circumference	25673412	2015	-0.038	0.032	-1.174	0.24
Homeostasis.model.assessment-B	20081858	2011	0.026	0.059	0.44	0.66
Homeostasis.model.assessment-IR	20081858	2011	0.057	0.069	0.825	0.409
Infant.head.circumference	22504419	2012	0.258	0.074	3.493	0.0005
Inflammatory.bowel.disease	26192919	2015	-0.112	0.038	-2.908	0.004
Insulin.like.growth.factor.1	27329260	0	0.174	0.062	2.798	0.005
Leptin	26833098	2016	-0.028	0.065	-0.424	0.671
Leptin.adjusted.for.body.mass.index	26833098	2016	-0.081	0.07	-1.163	0.245
Lumbar.spine.bone.mineral.density	22504420	2012	0.99	0.035	28.097	1.06E-173
Lung.cancer.all	24880342	2016	0.009	0.067	0.136	0.891
Major.depressive.disorder	22472876	2013	0.004	0.048	0.073	0.942
Mean.platelet.volume	22139419	2011	0.109	0.048	2.278	0.023
Neuroticism	27089181	2016	-0.107	0.036	-3.012	0.003
Obesity.class.1	23563607	2013	0.077	0.032	2.422	0.015
Obesity.class.2	23563607	2013	0.029	0.04	0.714	0.475
Obesity.class.3	23563607	2013	-0.008	0.055	-0.14	0.889
Overweight	23563607	2013	0.097	0.033	2.902	0.004
PGC.cross.disorder.analysis	23453885	2013	0.012	0.048	0.259	0.796
Platelet.count	22139419	2011	-0.056	0.041	-1.379	0.168
Rheumatoid.Arthritis	24390342	2014	-0.028	0.051	-0.548	0.584
Subjective well being	27089181	2016	0.124	0.045	2.759	0.006
Total.cholesterol	20686565	2010	-0.085	0.038	-2.278	0.023
Triglycerides	20686565	2010	-0.027	0.04	-0.68	0.497
Type.2.diabetes	22885922	2012	0.108	0.05	2.153	0.031
Ulcerative.colitis	26192919	2015	-0.145	0.043	-3.358	0.001
Urinary.albumin/creatinine	26631737	2015	0.065	0.063	1.038	0.299
Urinary.albumin/creatinine.non.diabetes	26631737	2015	0.087	0.084	1.038	0.299
Waist.circumference	25673412	2015	-0.012	0.027	-0.435	0.664
Waist.to.hip.ratio	25673412	2015	0.038	0.032	1.171	0.241
Years.of.schooling	23722424	2013	0.053	0.038	1.366	0.172

Table S9. Genetic correlation of TB-BMD with different traits. The genetic correlation was calculated based on the summary statistics of the only-Europeans meta-analysis in LD-Hub using its current dataset. Significant results are shown in **Figure 3**.

CHR	BP	rsID	A1	A2	Freq1	P-value	Gene Name	Codons	SNP Type	SIFT	Polyphen2	OMIM Disease
1	68603586	rs983034	C	T	0.62	1.21E-08	*GPR177*	GTC-aTC	Nonsynonymous	Tolerated	benign	
1	68624878	rs3748705	C	T	0.66	3.77E-09	*GPR177*	GCG-GCa	Synonymous	.	.	
2	166535918	rs777346	C	T	0.52	5.08E-16	*CSRNP3*	ACC-ACt	Synonymous	.	.	
3	156570703	rs414683	A	G	0.79	1.88E-08	*AC117392.3*	CAA-CAg	Synonymous	.	.	
4	994414	rs3755955	A	G	0.16	2.10E-19	*IDUA*	CGG-CaG	Nonsynonymous	Tolerated	benign	Scheie Syndrome
4	995305	rs6815946	T	C	0.84	7.16E-18	*IDUA*	AAT-AAc	Synonymous	.	.	Scheie Syndrome
4	995868	rs114806891	C	T	0.93	1.21E-10	*IDUA*	AAC-AAt	Synonymous	.	.	Scheie Syndrome ; Hurler Syndrome
4	995919	rs6830825	C	G	0.16	3.63E-18	*IDUA*	GCG-GCc	Synonymous	.	.	Scheie Syndrome
4	995997	rs6811373	A	G	0.84	4.21E-18	*IDUA*	AGA-gGA	Nonsynonymous	Not Predicted	benign	
4	996012	rs6831021	C	G	0.16	5.57E-18	*IDUA*	GCG-cCG	Nonsynonymous	Not Predicted	benign	
4	996165	rs6831280	A	G	0.16	9.66E-19	*IDUA*	GCG-aCG	Nonsynonymous	Tolerated	benign	Scheie Syndrome
4	996248	rs6836258	C	G	0.16	2.56E-18	*IDUA*	ACG-ACc	Synonymous	.	.	Scheie Syndrome
4	996560	rs115790973	C	G	0.84	4.35E-18	*IDUA*	ACC-ACg	Synonymous	.	.	Scheie Syndrome
4	996690	rs73066479	A	G	0.16	2.97E-17	*IDUA*	GTC-aTC	Nonsynonymous	Tolerated	benign	Scheie Syndrome
4	996888	rs115929690	T	C	0.16	2.59E-18	*IDUA*	CGC-CGt	Synonymous	.	.	Scheie Syndrome
4	1019011	rs4647932	C	T	0.93	2.52E-11	*FGFRL1*	CCA-CtA	Nonsynonymous	Damaging*	benign	
4	88732692	rs1054627	A	G	0.29	7.98E-14	*IBSP*	GGA-GaA	Nonsynonymous	Tolerated	benign	
4	88732918	rs1054629	A	T	0.71	1.26E-13	*IBSP*	GAA-GAt	Nonsynonymous	Tolerated	benign	
6	151859314	rs4870034	A	G	0.32	7.04E-15	*C6orf97*	GAA-GAg	Synonymous	.	.	
6	151894340	rs12205837	T	C	0.11	6.63E-13	*C6orf97*	GCT-GtT	Nonsynonymous	Tolerated	benign	
6	151936677	rs6929137	A	G	0.33	1.28E-15	*C6orf97*	GTC-aTC	Nonsynonymous	Tolerated	benign	
6	151939181	rs3734804	A	G	0.52	2.88E-15	*C6orf97*	GTC-aTC	Nonsynonymous	Tolerated	benign	
7	120876835	rs35793694	A	G	0.93	2.26E-13	*C7orf58*	GAA-GgA	Nonsynonymous	Tolerated	benign	
7	120969769	rs2908004	A	G	0.46	1.43E-89	*WNT16*	GGG-aGG	Nonsynonymous	Tolerated	benign	
7	120979089	rs2707466	T	C	0.46	4.79E-88	*WNT16*	ACA-AtA	Nonsynonymous	Tolerated	benign	
7	150915948	rs7782699	T	C	0.12	5.93E-11	*ABCF2*	GCG-GCa	Synonymous	.	.	
8	119964052	rs2073618	C	G	0.48	1.54E-19	*TNFRSF11B*	AAC-AAg	Nonsynonymous	Tolerated	benign	Paget Disease, Juvenile
10	**124089036**	**rs2421013**	**G**	**A**	**0.48**	**3.33E-09**	***BTBD16***	**CGG-CaG**	**Nonsynonymous**	**Tolerated**	**benign**	
11	**198062**	**rs11605246**	**C**	**G**	**0.78**	**5.37E-14**	***ODF3***	**CCT-CgT**	**Nonsynonymous**	**Tolerated**	**benign**	
11	**280464**	**rs77447196**	**C**	**G**	**0.79**	**5.39E-11**	***NLRP6***	**CCG-gCG**	**Nonsynonymous**	**Tolerated**	**benign**	
11	46339011	rs35652107	A	G	0.08	1.15E-08	*CREB3L1*	GCA-aCA	Nonsynonymous	Tolerated	benign	
11	46387868	rs1317826	A	G	0.68	2.07E-09	*DGKZ*	CAG-CgG	Nonsynonymous	Tolerated	benign	
11	46406767	rs2067482	A	G	0.16	2.10E-12	*CHRM4*	ACC-ACt	Synonymous	.	.	
11	46886077	rs117936904	A	T	0.98	9.97E-10	*LRP4*	CTT-CaT	Nonsynonymous	Damaging*	prob. damaging	
11	46893108	rs2306029	T	C	0.48	6.99E-13	*LRP4*	AGC-gGC	Nonsynonymous	Tolerated	benign	
11	46898771	rs6485702	T	C	0.37	1.19E-13	*LRP4*	ATT-gTT	Nonsynonymous	Tolerated	benign	Cenani-Lenz Syndactyly Syndrome
11	46916179	rs72897663	T	G	0.96	3.44E-08	*LRP4*	AAC-cAC	Nonsynonymous	Tolerated	benign	
11	68174189	rs4988321	A	G	0.04	7.64E-30	*LRP5*	GTG-aTG	Nonsynonymous	Damaging	prob. damaging	Van Buchem Disease, Type 2; Osteopetrosis, Autosomal Dominant 1; Exudative Vitreoretinopathy 4; Osteoporosis-Pseudoglioma Syndrome; Osteoporosis; Hyperostosis Corticalis Generalisata, Benign Form Of Worth, With Torus

CHR	BP	rsID	A1	A2	Freq1	P-value	Gene Name	Codons	SNP Type	SIFT	Polyphen2	OMIM Disease
11	68177510	rs2306862	T	C	0.16	1.34E-33	*LRP5*	AAC-AAt	Synonymous	.	.	Van Buchem Disease, Type 2; Osteopetrosis, Autosomal Dominant 1; Exudative Vitreoretinopathy 4; Osteoporosis-Pseudoglioma Syndrome; Osteoporosis; Hyperostosis Corticalis Generalisata, Benign Form Of Worth, With Torus
11	68192690	rs556442	A	G	0.65	6.53E-25	*LRP5*	GTG-GTa	Synonymous	.	.	Van Buchem Disease, Type 2; Osteopetrosis, Autosomal Dominant 1; Exudative Vitreoretinopathy 4; Osteoporosis-Pseudoglioma Syndrome; Osteoporosis; Hyperostosis Corticalis Generalisata, Benign Form Of Worth, With Torus
11	68201295	rs3736228	T	C	0.15	5.03E-34	*LRP5*	GCG-GtG	Nonsynonymous	Not scored	benign	Van Buchem Disease, Type 2; Osteopetrosis, Autosomal Dominant 1; Exudative Vitreoretinopathy 4; Osteoporosis-Pseudoglioma Syndrome; Osteoporosis; Hyperostosis Corticalis Generalisata, Benign Form Of Worth, With Torus
12	49168798	rs3730071	A	C	0.03	6.95E-10	*ADCY6*	GCC-tCC	Nonsynonymous	Tolerated	benign	
12	53662624	rs6580942	C	A	0.30	2.56E-16	*ESPL1*	GCC-GaC	Nonsynonymous	Tolerated	benign	
12	53670545	rs1318648	A	C	0.63	3.32E-12	*ESPL1*	AGC-AGa	Nonsynonymous	Damaging	prob. damaging	
12	53682326	rs1110720	A	G	0.63	6.26E-12	*ESPL1*	GGG-GGa	Synonymous	.	.	
12	53682457	rs56358776	A	G	0.34	2.95E-13	*ESPL1*	CGG-CaG	Nonsynonymous	Tolerated	benign	
13	43148546	rs138818878	C	G	0.97	5.47E-14	*TNFSF11*	CCT-CgT	Nonsynonymous	Damaging*	prob. damaging	Osteopetrosis, Autosomal Recessive 2
15	**67528374**	**rs7173826**	**T**	**G**	**0.67**	**7.49E-09**	***AAGAB***	**ATC-cTC**	**Nonsynonymous**	**Tolerated**	**benign**	
16	396264	rs1805105	A	G	0.34	5.40E-10	*AXIN1*	GAT-GAc	Synonymous	.	.	Caudal Duplication Anomaly; Hepatocellular Carcinoma
17	**17698254**	**rs8067439**	**G**	**A**	**0.39**	**4.69E-08**	***RAI1***	**CCG-CCa**	**Synonymous**	**.**	**.**	
17	**17997209**	**rs2230316**	**G**	**A**	**0.44**	**3.23E-08**	***DRG2***	**TCG-TCa**	**Synonymous**	**.**	**.**	
17	42254417	rs7212854	A	G	0.71	3.53E-09	*C17orf65*	CGT-CGc	Synonymous	.	.	
17	42287519	rs2071167	T	C	0.27	5.00E-09	*UBTF*	AAG-AAa	Synonymous	.	.	

Table S10. Genome-wide Significant coding variants. P-values are derived from the overall meta-analysis including all ethnicities. Bold rows correspond to SNPs mapping to novel loci for the first time described in this GWAS analysis. * Low confidence

Locus	Ensembl gene ID	Gene symbol	P value	FDR
1p13.3	**ENSG00000184371**	***CSF1***	**1.91E-03**	**<0.05**
1p31.3	ENSG00000116729	*WLS*	4.84E-03	<0.05
1p36.12	ENSG00000162552	*WNT4*	2.79E-03	<0.05
1p36.23	**ENSG00000142599**	***RERE***	**1.44E-04**	**<=0.01**
2p11.2	**ENSG00000152284**	***TCF7L1***	**7.41E-04**	**<0.05**
2p21	ENSG00000162878	*PKDCC*	3.74E-04	<0.05
2q14.2	ENSG00000163064	*EN1*	2.23E-04	<=0.01
2q33.2	**ENSG00000155760**	***FZD7***	**1.19E-03**	**<0.05**
3q25.31	ENSG00000163659	*TIPARP*	3.41E-06	<=0.01
4p16.3	ENSG00000127418	*FGFRL1*	1.09E-03	<0.05
4q22.1	ENSG00000152595	*MEPE*	5.51E-06	<=0.01
5q14.3	ENSG00000248309	*MEF2C-AS1*	4.44E-03	<0.05
6p21.1	ENSG00000124813	*RUNX2*	2.80E-09	<=0.01
6q22.33	ENSG00000146374	*RSPO3*	9.63E-06	<=0.01
7p12.1	**ENSG00000106070**	***GRB10***	**6.19E-03**	**<0.05**
7p14.1	ENSG00000106483	*SFRP4*	1.39E-05	<=0.01
7p14.3	**ENSG00000240583**	***AQP1***	**1.18E-03**	**<0.05**
7q21.3	ENSG00000105880	*DLX5*	7.75E-05	<=0.01
7q22.1	**ENSG00000197037**	***ZSCAN25***	**5.15E-05**	**<=0.01**
7q31.31	ENSG00000106034	*CPED1*	2.71E-04	<=0.01
8q24.12	ENSG00000164761	*TNFRSF11B*	1.19E-03	<0.05
10q25.2	**ENSG00000138166**	***DUSP5***	**8.22E-03**	**<0.05**
11p11.2	ENSG00000157613	*CREB3L1*	2.66E-04	<=0.01
11p11.2	ENSG00000165917	*RAPSN*	3.09E-03	<0.05
11p11.2	ENSG00000165915	*SLC39A13*	3.50E-03	<0.05
11p14-p13	ENSG00000176697	*BDNF*	1.55E-03	<0.05
11p14-p13	ENSG00000245573	*BDNF-AS1*	2.37E-03	<0.05
11p14-p13	ENSG00000205213	*LGR4*	5.31E-04	<0.05
11p15.1	ENSG00000110693	*SOX6*	2.02E-04	<=0.01
11p15.2	ENSG00000188487	*INSC*	2.24E-03	<0.05
11q13.2	ENSG00000162337	*LRP5*	5.67E-04	<0.05
11q13.3	**ENSG00000110092**	***CCND1***	**4.08E-05**	**<=0.01**
11q24.1	**ENSG00000255248**	**-**	**1.81E-03**	**<0.05**
12p13.33	ENSG00000111186	*WNT5B*	1.45E-03	<0.05
12q13.12	ENSG00000167548	*MLL2*	5.32E-06	<=0.01
12q13.12	ENSG00000125084	*WNT1*	1.65E-03	<0.05
12q13.13	ENSG00000257194	-	5.05E-04	<0.05
12q13.13	ENSG00000185591	*SP1*	4.12E-03	<0.05
12q13.13	ENSG00000170374	*SP7*	1.64E-07	<=0.01
13q13.3	**ENSG00000120693**	***SMAD9***	**4.15E-03**	**<0.05**
15q22.33	**ENSG00000166949**	***SMAD3***	**4.05E-05**	**<=0.01**
16q24.1	ENSG00000176678	*FOXL1*	7.57E-04	<0.05

17p11.2	**ENSG00000108557**	***RAI1***	**3.50E-04**	**<0.05**
17p13.3	ENSG00000070366	*SMG6*	8.74E-03	<0.05
17q21.31	ENSG00000161664	*ASB16*	4.18E-03	<0.05
17q21.31	ENSG00000161649	*CD300LG*	2.73E-03	<0.05
17q21.31	ENSG00000108840	*HDAC5*	7.24E-03	<0.05
17q21.31	ENSG00000005102	*MEOX1*	7.38E-03	<0.05
17q21.31	ENSG00000167941	*SOST*	6.18E-05	<=0.01
17q21.31	ENSG00000108312	*UBTF*	7.66E-03	<0.05
20p12.2	ENSG00000101384	*JAG1*	3.66E-04	<0.05
20q12	**ENSG00000204103**	***MAFB***	**3.85E-04**	**<0.05**
21q22.12	**ENSG00000159216**	***RUNX1***	**2.24E-03**	**<0.05**

Table S11. DEPICT Gene prioritization (FDR<5%). Based on genome-wide significant variants in the overall TB-BMD meta-analysis. Bold rows correspond to genes mapping to novel loci not previously described in this GWAS analysis of bone phenotypes.

Table S12. DEPICT Gene-set enrichment analysis (FDR<5%). Based on genome-wide significant variants in the overall TB-BMD meta-analysis. These 182 gene-sets were further clustered in 25 'metagene-sets' shown in **Figure 4**. **Attached Excel file.**

Position	Lead SNP	*Proxy SNP*	LD	Host gene	Related miRNA	Ancestral A	Derived A	Conservation	Change contex score	Functional class
7q22.1	**rs34670419**	***rs34670419***	1	***ZKSCAN5***	**mir-382-3p**	**G**	**T**	**4**	**0.09**	**Create**
11p15.5	**rs11601356**	***rs6541***	0.86	***PSMD13***	**mir-942-5p**	**A**	**G**	**0**	**0.02**	**Create**
7q36.1	rs73169649	*rs73169654*	0.88	*ABCF2*	mir-140-3p	C	T	1	0.09	Create
2q24.3	rs7586085	*rs13429321*	0.84	*GALNT3*	mir-499-3p	T	A	6	0.2	Disrupte
2p21	rs78572108	*rs1044305*	0.93	*PKDCC*	mir-1470	T	C	9	0.25	Create
5q22.2	**rs818427**	***rs2545167***	1	***REEP5***	**mir-4444**	**C**	**A**	**0**	**0.2**	**Create**
11q13.2	rs11228240	*rs4988291*	0.95	*PPP6R3*	mir-138-3P	G	A	5	0.02	Disrupte
15q22.33	**rs3743347**	***rs10518716***	1	***AAGAB***	**mir-380/mir-424-3p**	**C**	**G**	**2&6**	**0.22/0.19**	**Disrupte/Create**
17p11.2	**rs8070128**	***rs1052299***	1	***TOM1L2***	**miR-133a, 138-3p**	**T**	**C**	**1**	**0.3**	**Create**

Table S13. Putative effect of the TB-BMD top associated variants in miRNA-binding sites. The effect of the derived allele in the creation/disruption of a binding site (functional class) of a specific miRNA (miRNA) is described (using PolymiRTS database v3.0). Shown are 9 SNPs, including the lead SNP rs34670419 *in ZKSCAN5* and proxy SNPs of other 8 lead SNPs, located in predicted miRNA binding sites. Loci not previously reported are in bold font. Proxy SNP, SNP with r2 > 0.8, limit distance 500 kb, population panel CEU and in 1000 Genome project; Conservation, Occurrence of the miRNA site in other vertebrate genomes in addition to the query genome; LD, linkage disequilibrium; Related miRNA, miRNA that the SNP is predicted to create/disrupt its binding site; Context score predicts the binding of a miRNA to the gene 3'UTR by summing over contributions made by individual sites within the 3'UTR that have perfect sequence complementarity to the miRNA seed region. Change contex score, A more negative value of the context score difference indicates an increased likelihood that the miRNA targeting is disrupted or newly created by the SNP in the target sites.

Table S14. Skeletal phenotype data from the International Mouse Phenotyping Consortium and Mouse Genome Informatics databases and expression data from murine osteoblasts, osteocytes and osteoclasts. Data was collected for the 55 genes prioritized by DEPICT. Detailed bone phenotyping from the Origins of Bone and Cartilage Disease (OCBD) is presented in Table S15. **Attached Excel file**

Table S15. Detailed bone phenotyping of knockout models from the Origins of Bone and Cartilage Disease (OCBD) initiative. Knockout lines with a skeletal parameter greater than 2 standard deviations from the reference mean are highlighted in orange. The standard deviation from the reference mean for each parameter is shown with those greater than 2 highlighted (Black above the mean: Red below the mean). **Attached Excel file.**

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