Genome-wide Meta-analysis of 158,000 Individuals of European Ancestry Identifies Three Loci Associated with Chronic Back Pain

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ABSTRACT

OBJECTIVES: To conduct a genome-wide association study (GWAS) meta-analysis of chronic back pain (CBP).

METHODS: Adults of European ancestry were included from 16 cohorts in Europe and North America. CBP cases were defined as those reporting back pain present for >3-6 months; non-cases were included as comparisons ("controls"). Each cohort conducted genotyping using commercially available arrays followed by imputation. GWAS used logistic regression models with additive genetic effects, adjusting for age, sex, study-specific covariates, and population substructure. The threshold for genome-wide significance in the fixed-effect inverse-variance weighted meta-analysis was $p<5\times10^{-8}$. Suggestive ($p<5\times10^{-7}$) and genome-wide significant ($p<5\times10^{-8}$) variants were carried forward for replication or further investigation in an independent sample.

RESULTS: The discovery sample was comprised of 158,025 individuals, including 29,531 CBP cases. A genome-wide significant association was found for the intronic variant rs12310519 in *SOX5* (OR 1.08, $p=7.2\times10^{-10}$). This was subsequently replicated in an independent sample of 283,752 subjects, including 50,915 cases (OR 1.06, $p=5.3\times10^{-11}$), and exceeded genome-wide significance in joint meta-analysis (OR=1.07, $p=4.5\times10^{-19}$). We found suggestive associations at three other loci in the discovery sample, two of which exceeded genome-wide significance in joint meta-analysis: an intergenic variant, rs7833174, located between *CCDC26* and *GSDMC* (OR 1.05, $p=4.4\times10^{-13}$), and an intronic variant, rs4384683, in *DCC* (OR 0.97, $p=2.4\times10^{-10}$).

DISCUSSION: In this first reported meta-analysis of GWAS for CBP, we identified and replicated a genetic locus associated with CBP (*SOX5)*. We also identified 2 other loci that reached genome-wide significance in a 2-stage joint meta-analysis (*CCDC26*/*GSDMC* and *DCC).*

Keywords: GWAS; genetic; genomic; back pain; heritability; meta-analysis

INTRODUCTION

Back pain causes more years lived with disability than any other health condition worldwide.(1) Although most adults experience a new ('acute') episode of back pain at some point in their lives, the societal burden of back pain is driven by the minority of individuals who fail to recover from such episodes and go on to develop persistent ('chronic') back pain.(2) Chronic back pain (CBP) has a number of definitions but is most often considered as back pain of duration ≥3 months in clinical practice, and a duration of ≥6 months is also commonly used in research.(3, 4)

Back pain is moderately heritable. Meta-analysis of 11 twin studies of back pain indicates a heritability of 40%, with a pattern of monozygotic (r_{MZ} = 0.56) and dizygotic (r_{DZ} = 0.28) twin correlations suggesting an additive genetic model ($2r_{DZ} = r_{MZ}$).(5, 6) Heritability is greater for chronic than for acute back pain.(7) Nevertheless, genetic studies attempting to identify specific genetic markers for CBP have to date been limited to small studies using the candidate gene approach.(8, 9) Although CBP is often attributed to anatomic changes such as intervertebral disc degeneration or disc herniation, such findings have only weak association with CBP, (10, 11) and explain only a small proportion (7-23%) of the genetic influence on back pain(12). The unexplained genetic contribution to CBP may involve not only spine pathology but also functional predisposition to chronic pain involving higher-order neurologic processes related to the generation and maintenance of pain.(13-15) Furthermore, psychological factors such as depression are widely recognized as important risk factors for CBP.(16) Given the range of processes that might contribute to CBP, the agnostic genome-wide association approach may identify novel genetic variants associated with CBP and provide insights into underlying biological mechanisms not previously considered.

We conducted a meta-analysis of GWAS of CBP in adults of European ancestry from 16 community- and population-based cohorts. This research was an international collaboration between investigators from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Musculoskeletal Workgroup(17) and the European Union FP7 project Pain-OMICS ('Multi-dimensional omics approach to stratification of patients with low back pain'). The aim was to identify novel associations between specific genetic markers and CBP, and elucidate the biological mechanisms underlying this condition.

METHODS

Study Design and Populations

Discovery meta-analysis included adults of European ancestry from 16 population- and community-based cohorts: Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), Generation Scotland (GS), Johnston County Osteoarthritis Project (JoCo), Osteoporotic Fractures in Men (MrOS) Sweden (MrOS-Gothenburg and MrOS-Malmo), MrOS US, Osteoarthritis Initiative (OAI), Rotterdam Study (RS1, RS2, and RS3), Study of Osteoporotic Fractures (SOF), 10,001 Dalmatians (Vis and Korcula), TwinsUK, and UK Biobank (UKB) participants from the interim data release(18). Replication was conducted in an independent sample of UKB European ancestry participants not included in the discovery stage, and a joint (discovery-replication) meta-analysis was performed. Detailed descriptions of the study cohorts are provided in Table 1 and the Supplemental Methods. The participating cohorts and the conduct of genetic analyses were approved by the medical ethics committees of the respective centers.

Chronic Back Pain (CBP) Phenotype

There is no “gold-standard” definition for CBP. Consistent with the most commonly accepted clinical and research definitions for CBP (3, 4), CBP cases were defined in this study as those reporting back pain that had been present for a minimum of 3-6 months, by one of 3 definitions depending on the cohort: 1) ≥3 months of back pain, 2) ≥6 months of back pain, and 3) ≥1 month of back pain in consecutive years (see Table 1). The comparison group (“controls”) was comprised of those who reported not having back pain or reported back pain of insufficient duration to be included as a case.

Genotyping

Details of genotyping, quality control, imputation methods, and genome-wide analysis for each cohort were study-specific (Supplemental Tables S2-3). In brief, genotyping was performed using commercially available genome-wide arrays. Imputation of single nucleotide polymorphisms (SNPs) and insertions/deletions (indels) was performed using reference panels from 1000 Genomes phase 1 version 3 or phase 3,(19) or the Haplotype Reference Consortium.(20)

Statistical Analysis

We conducted genome-wide association analyses in each of the 16 cohorts, and subsequent meta-analysis of autosomal SNPs to combine results from all cohorts. Each site conducted GWAS using logistic regression models with additive genetic effects to test for associations between each variant and CBP as a binary trait. These models adjusted for age, sex, study-specific covariates, and population substructure using principal components (Supplemental Table S3). Height and body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, were not included as covariates in site-specific GWAS, since these traits might lie along the causal pathway or (in the case of BMI) reflect a consequence of CBP. Harmonization and quality control of GWAS results from each cohort were conducted using the EasyQC

software package in the R statistical environment (v3.2.2), using methods described previously.(21) After removal of SNPs with very low minor allele frequencies (MAF <0.005 to <0.03, depending on cohort) and other filters (Supplemental Methods), the number of SNPs included in the meta-analysis ranged from 6,205,227 (Croatia-Vis) to 9,775,703 (MrOS-Gothenburg) (Supplemental Table S3). Fixed-effect inverse-variance weighted meta-analysis was performed using METAL, version 2011-03-25 (http://csg.sph.umich.edu/abecasis/metal/). Quality control and meta-analysis were conducted twice, independently of each other, by researchers at the University of Washington (MP and PS) and at PolyOmica (YT, YA, and LCK). The results from the two centers were compared to ensure accuracy. We used linkage disequilibrium (LD) score regression (LDsr) to examine the potential for confounding.(22) The genome-wide significance level was defined as $p<5\times10^{-8}$, and suggestive significance level was defined as $p<5\times10^{-7}$, after using the LDsr intercept as a correction factor. Q-Q and Manhattan plots were generated in R. We conducted GCTA-COJO (Genome-Wide Complex Trait Analysis conditional and joint analyses, http://cnsgenomics.com/software/gcta/#About) to examine associations conditional on the most significant variant at each locus.

The most highly-associated variants at genome-wide significant loci were subjected to replication in the independent sample of UKB participants. Analysis in the independent sample used logistic regression with additive genetic effects, adjusting for age, sex, array, and principal components (Supplemental Table S3); significant replication was defined using a Bonferroni-corrected threshold of p<0.05 divided by the number of genome-wide significant loci. The most highly-associated variants at loci with suggestive significance were selected for a joint (discovery-replication) meta-analysis using $p<5\times10^{-8}$ to define genome-wide significance. Further details regarding analysis are provided in Supplemental Methods.

For genome-wide significant variants and those in LD (r^2 >0.6) we examined previously reported GWAS associations with other phenoypes using PhenoScanner v1.1 (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner), and conducted functional annotation using FUMA (http://fuma.ctglab.nl). FUMA draws upon multiple publicly available databases, annotating variants for consequences on gene functions using the combined annotation dependent depletion (CADD) score,(24) potential regulatory functions (RegulomeDB score),(25) and effects on gene expression using expression quantitative trait loci (eQTLs) of different tissue types (GTExv6) (26, 27) (Supplemental File). The higher the CADD score, the more potentially deleterious is the variant. A CADD score of ≥10 indicates a variant predicted to be among the 10% most deleterious substitutions involving the human genome, a score of ≥20 indicates a variant among the 1% most deleterious, and so forth.(24) We used data from the Roadmap Epigenomics Project to evaluate whether the lead variants at each locus reside in enhancer regions for selected tissues with possible conceptual connections to the spine via roles involving chondrogenesis, vertebral development,

muscle, and pain processing the central nervous system.(28, 29). Because two significant variants were found to be associated with height in prior published GWAS, we conducted *post hoc* region-specific GWAS secondary analyses accounting for height, among UKB participants from the discovery stage. Further details of functional annotation and secondary analyses are provided in Supplemental Methods.

Finally, we used LDsr of summary-level GWAS results from the discovery stage to estimate heritability due to common autosomal SNPs and genetic correlations.(22) We transformed the observed SNP heritability to the liability scale, in order to make heritability estimates for CBP comparable with traditional heritability estimates from twin studies.(30) We used cross-trait LDsr and publicly available meta-GWAS results from LDhub to examine genetic correlations with selected traits with possible links to CBP: anthropometrics (adult height, infant/childhood height, waist/hip circumference, BMI, and overweight/obesity), depression and depressive symptoms, osteoarthritis, and rheumatoid arthritis.(31, 32)

RESULTS

Characteristics of the discovery sample

The discovery sample included 29,531 CBP cases of the total 158,025. The characteristics of cohorts included in the meta-analysis are shown in Table 1. The mean age of participants in each cohort ranged between 53-76 years. Within cohorts, mean age, BMI, and proportion of females was more often higher among CBP cases than among those without CBP.

Meta-analysis of GWAS of CBP

A quantile-quantile plot comparing the meta-analysis association results with those expected by chance is presented in Figure 1. The LDsr intercept was 1.007, providing no evidence of inflation of p-values from population stratification. Meta-analysis results are summarized in the Manhattan plot shown in Figure 2.

A genome-wide significant association (OR 1.08, $p=7.2\times10^{-10}$) was found for rs12310519 on chromosome 12 in an intronic region of *SOX5*, with little evidence for heterogeneity ($I^2=0$, $p=0.95$) (Table 2, Supplemental Figure S1). Several other signals were in high LD ($r^2>0.8$) with the top signal (Supplemental Figure S2), but none were independently associated with CBP in analyses conditional on rs12310519.

No other variants achieved genome-wide significance, but variants in three other loci reached suggestive significance (Table 2, Supplemental Table S4, Supplemental Figures S3-8): rs1453867 (OR 0.95, $p=7.7\times10^{-8}$), located in an intronic region of chromosome 2 within *DIS3L2*; rs7833174 (OR 1.06, $p=1.0\times10^{-7}$), located in an intergenic region on chromosome 8 between *CCDC26* (a long non-coding RNA) and *GSDMC*; and rs4384683 (OR 0.95, $p=3.2\times10^{-7}$), located in an intronic region of chromosome 2 within *DCC*. In each of these 3 regions, there was no other variant reaching the suggestive significance level in analyses conditional on the lead SNP in the region.

Genome-wide Meta-analysis of Back Pain

We examined the 4 top variants in an independent sample of 283,752 UKB individuals that included 50,915 cases (Table 2). For all 4 variants, the direction of association was the same in discovery and replication. The association for rs12310519 in *SOX5* replicated in the independent sample (OR 1.06, p=5.3×10^{-11}), and exceeded genome-wide significance in the joint analysis (OR=1.07, p=4.5×10^{-19}). Of the 3 suggestive-significance variants from the discovery stage, rs7833174 at *CCDC26/GSDMC* (OR 1.05, p=4.4×10^{-13}) and rs4384683 in *DCC* (OR 0.97, p=2.4×10^{-10}) exceeded genome-wide significance in the joint meta-analysis, but rs1453867 in *DISL32* (OR 0.98, p=3.9×10^{-7}) did not (Table 2). Thus, we demonstrate genome-wide significant associations of CBP with loci tagged by rs12310519 (*SOX5),* rs7833174 (*CCDC26/GSDMC)*, and rs4384683 (*DCC*), with replication for rs12310519 in *SOX5*.

Characterization of variants in SOX5, CCDC26/GSDMC, and DCC

The variant rs9804988, in LD with the lead SNP in *SOX5* rs12310519, was associated with height (p=9.6×10^{-6}) in a prior GWAS (Supplemental Table S5). The T allele at rs9804988 was associated both with greater height and greater CBP risk (OR = 1.08). The highest CADD score among *SOX5* variants was 10.52 for the lead SNP in the region rs12310519, indicating it is predicted to be among the 10% most deleterious possible substitutions in the human genome (Supplemental File). However, the overall regulatory potential of these variants was low according to RegulomeDB score (scores of 6 [‘minimal binding evidence’]). The lead SNP rs12310519 and variants in LD contain active enhancer marks in chondrogenic cells (Figure 3).

Variants in the intergenic *CCDC26/GSDMC* locus were significantly associated with height in prior GWAS (lowest p=1.0×10^{-41}, Supplemental Table S5); alleles associated with greater height were also associated with greater CBP risk. Variants in *CCDC26/GSDMC* that were suggestively associated with CBP were also associated with lumbar microdiscectomy for sciatica in a recent GWAS of Icelandic adults (Supplemental Table S6, lowest p=5.6×10^{-12}), with the same direction of effect (i.e. alleles associated with greater risk of lumbar discectomy for sciatica were also associated with greater CBP risk). The highest CADD score among these variants was 18.75 for rs6470778, indicating that this SNP is predicted to be among the 5% most deleterious substitutions in the human genome, and the overall regulatory potential of these variants was substantial according to Regulome DB score (highest RegulomeDB score of 2b [‘likely to affect binding’]) (Supplemental File). These variants were also eQTLs for *GSDMC* expression in esophageal mucosa, skin, and skeletal muscle (Supplemental File, p<5×10^{-8}). The lead SNP rs7833174 and variants in LD contain active enhancer marks located in regulatory regions for mesodermal cells, astrocytes, chondrogenic cells, and osteoblasts (Figure 3).

No variants in the intronic *DCC* locus were associated with other phenotypes in prior GWAS. The highest CADD score among these variants was 11.21 for rs2116378, indicating that it is predicted to be among

the 10% most deleterious substitutions in the human genome, but the overall regulatory potential of these variants was low according to Regulome DB score (Supplemental File, highest RegulomeDB score of 5). The lead SNP rs4384683 and variants in LD contain active enhancer marks in H9 human embryonic stem cell-derived neural cells (Figure 3).

Secondary analyses to examine interrelationships with height

Post hoc analyses among UKB participants from the discovery sample (n=120,023) indicated that associations with CBP for the lead variant in *SOX5* were similar with and without adjustment for height as a covariate, and in conditional analyses accounting for height (Supplemental Table S7). Associations with CBP for the lead variant in *CCDC26*/*GSDMC* were also similar with and without adjustment for height as a covariate. However, associations with CBP were markedly diminished when conditional on the lead height-associated variant in the region, and associations with height were markedly diminished when conditioned on the lead CBP-associated variant in the region. This suggests that the same functional variant is responsible for association of *CCDC26*/*GSDMC* locus with height and CBP, although an alternative explanation is two functional variants in tight LD.

Heritability of CBP and genetic correlations

SNP heritability of CBP on the liability scale was 7.6%. Genetic correlations of nominal significance (range of r_g 0.17- 0.31, $p<0.05$) were found with anthropometric traits involving obesity or body fat distribution (waist circumference, hip circumference, waist-hip ratios, overweight/obesity classes, and BMI), but not with height (Supplemental Table S8). Larger magnitude nominally significant ($p<0.05$) genetic correlations were also found with depression-related phenotypes (range of r_g 0.46-0.52), self-reported osteoarthritis (r_g=0.63), and ICD-10-defined osteoarthritis (r_g=0.49) phenotypes.

DISCUSSION

This study is the first meta-GWAS of CBP. This collaboration between two international consortia for genomic studies of complex traits in the USA and Europe incorporated data from 16 cohorts and more than 441,000 participants of European ancestry across discovery and replication samples. Our study identifies three novel associations with CBP for loci at *SOX5, CCDC26*/*GSDMC,* and *DCC*.

CBP was most strongly associated with rs12310519 in an intronic region of the *SOX5* gene. The *SOX* genes are a family of transcription factors involved in virtually all phases of embryonic development, and are thought to determine the fate of many cell types. The *SOX* genes are defined by containing the HMG ('high mobility group') box of a gene involved in sex determination called SRY ('sex determining region') (33). *SOX5*

and *SOX6* have overlapping functions and work together in close coordination that is necessary for efficient chondrogenesis (34). Inactivation of *SOX5* leads to minor defects in cartilage and skeletogenesis in mice, whereas *SOX5/SOX6* double knockouts have severe chondrodysplasia (35). Together with *SOX9*, *SOX5* and *SOX6* are sometimes referred to as the 'master chondrogenic SOX trio' (34, 36). Prior work indicates an important role for *SOX5* in articular cartilage and osteoarthritis (37, 38), and such a role was also supported by our functional annotation showing that rs12310519 (and SNPs in high LD) overlapped with potential regulatory regions for chondrogenic cells. *SOX5/6* are also essential for notochord development, and through this role they are critical in the formation of the vertebral column, including the intervertebral discs (39). Inactivation of *SOX5* and/or *SOX6* in mice leads to a range of abnormalities in the development of spinal structures (39). Although variants in *SOX5* have not been reported in prior GWAS of limb osteoarthritis (knee, hip, or hand) (40-47), the association of *SOX5* with CBP may involve the spinal structures specifically. *SOX5* was also not associated with lumbar intervertebral disc degeneration in the prior two GWAS conducted for intervertebral disc degeneration (48, 49). However, further GWAS of disc-related phenotypes are much needed, as are GWAS of the zygapophyseal ('facet') joint osteoarthritis, the only synovial joints in the spine (50).

The intergenic variants at *CCDC26*/*GSDMC* associated with CBP in the current study were also associated with lumbar microdiscectomy for sciatica in a prior GWAS, with the same direction of effect.(51) These findings are intriguing, given that lumbar disc herniations have long been implicated as a cause of some forms of back pain.(52) Recent studies have concluded that associations between imaging-detected lumbar disc herniation and CBP are of modest magnitude.(10, 11) This might explain the small magnitude association of the top variant at *CCDC26*/*GSDMC* with CBP in the current study (OR 1.08 in discovery), in contrast to the larger magnitude association seen with microdiscectomy of sciatica (OR 1.23). Functional characterization of these intergenic variants indicates the likely involvement of the gene *GSDMC*. *GSDMC* encodes the protein Gasdermin C, part of the *GSDM* family of genes that is expressed in epithelial tissues. Although the specific role of *GSDMC* in lumbar disc herniation and/or sciatica is unclear, *GSDMC* is associated with differential methylation patterns in osteoarthritis-related cartilage and subchondral bone cartilage, (53, 54) consistent with our finding that variants in LD with rs4384683 were located in potential regulatory regions in chondrocytes and osteoblasts. Taken together, these data suggest interconnections between variants at *CCDC26*/*GSDMC* and CBP involving cartilage, osteoarthritis, and/or intervertebral disc degeneration.

The third significant CBP-associated variant in our study was rs2116378, an intronic variant in the gene *DCC* (Deleted in Colorectal Carcinoma), which co-localized with regulatory regions in neural embryonic stem cells. *DCC* encodes a transmembrane protein that is a receptor for netrin-1, an axonal guidance molecule involved in the development of spinal and cortical commissural neurons.(55) Interactions between DCC and netrin-1 are among the best-studied axonal guidance processes, with key roles during development and in

adulthood, and they also affect angiogenesis.(56, 57) Increased expression of netrin-1 and DCC occurs in degenerate human intervertebral discs compared to healthy control discs, and in nucleus pulposus compared to annulus fibrosis.(58) Netrin-1/DCC might therefore mediate neurovascular ingrowth into the intervertebral disc, which has long been implicated as a possible mechanism of chronic discogenic back pain.(58, 59) Netrin-1/DCC interactions also play a role in pain processing in the spinal cord in animal models of mechanical allodynia.(56) Taken together, these findings suggest nociceptive and/or neuropathic mechanisms connecting lumbar intervertebral disc degeneration (including disc herniation) with CBP.

Variants in *CCDC26*/*GSDMC* and *SOX5* associated with greater risk of CBP in our meta-analysis were also reported to be associated with greater height in prior GWAS. Our secondary analyses showed that the association of *SOX5* variants with CBP was independent of height, however, CBP- and height-associated variants in *CCDC26*/*GSDMC* were tightly linked and could not be disentangled in conditional analyses. The association of variants in *CCDC26*/*GSDMC* with both CBP and height might be explained by pleiotropy, causal connections, or other factors. The direction of effects in our study for *CCDC26*/*GSDMC* variants were consistent with epidemiological reports that greater height confers increased risk of back pain (60-62), although a systematic review found no such association.(63) These findings might be viewed as supporting a causal link between height and CBP, but could instead simply reflect shared underlying genetic factors between the two phenotypes. CBP and height have compelling connections to the spine. Prior studies demonstrating the vital role of *SOX5* in normal vertebrate development (34, 36, 39) may hold lessons that apply to other genetic markers including those in *CCDC26*/*GSDMC*: if associations with CBP and height are mediated by the spine and/or vertebral column development, it will be difficult to distinguish pleiotropy and causality using GWAS alone.

SNP-based heritability in the current study (8%) was considerably lower than estimates from twin studies (~40%). This is a common situation with modern methods of estimating heritability using genotype data, since such estimates reflect only one aspect of narrow-sense heritability captured by the additive genetic components of common variants, excluding the contributions of rare variants, non-additive effects, epistasis, or gene-environment interactions.(30) Despite the modest heritability of CBP (and other self-reported traits), we found significant and large magnitude genetic correlations between CBP and other phenotypes that may be risk factors for CBP or consequences of CBP, such as depression and obesity-related factors (but not height). Future GWAS of CBP may benefit from taking these relationships into account, either by accounting for these phenotypes as covariates, or in multivariate GWAS designs.

A distinguishing feature of the current study as compared to many other GWAS is that the CBP phenotype examined represents a symptom, rather than a disease or a biomarker. Although successful

GWAS of self-reported symptoms have been conducted which replicate associations seen with more specific disease phenotypes,(64) our findings highlight potential challenges of GWAS of CBP: despite being one of the largest international studies of CBP ever conducted, our study detected only 3 significant associations with CBP. Still larger sample sizes may be needed in future discovery efforts using this phenotype, or different methods should be used. A consequence of the nonspecific nature of the CBP phenotype is the fact that, unlike other musculoskeletal phenotypes such as osteoarthritis, the tissue correlates optimal for conducting functional follow-up studies of findings from CBP GWAS are unclear. Most animal models for back pain rely on specific mechanisms of inducing pain, such as injuries to the intervertebral disc, zygapophyseal ('facet') joint, dorsal root ganglion, or muscle.(65) However, each of these mechanisms likely explain only a certain portion of back pain cases, and do not encompass the important psychosocial aspects of pain and pain reporting that are relevant in humans. Despite the importance of psychosocial factors, our meta-GWAS findings are a reminder that structural/anatomic factors involving spinal degeneration, such as disc herniations or osteoarthritis of spinal structures (e.g. facet joints), remain potentially important contributors to the CBP. Future GWAS of CBP may benefit from alternative strategies such as CBP endophenotyping (stratification by back pain subtypes), simultaneously studying CBP and spinal degeneration/fracture phenotypes, and allowing for the examination of interactions between genetic markers for spinal degeneration and markers for pain processing or axonal signaling (including *DCC* and netrin-1).

Strengths of our study include its multicohort design and large sample size. A potential limitation of our study was heterogeneity of the CBP phenotype used, a consequence of pooling data from numerous cohorts using different definitions. Although this approach may have helped identify genetic associations shared across CBP subtypes, it might obscure associations pertinent to specific subtypes of back pain. Despite phenotype heterogeneity, which would be expected to bias towards the null, our study successfully identified several associations of statistical significance. Recent efforts to standardize CBP definitions may help to limit phenotype heterogeneity in future meta-GWAS of CBP.(3) Another aspect of the phenotype used in our meta-analysis was that individuals with back pain of less than 3-6 months duration were included as controls. This was done deliberately so as to focus on back pain of chronic duration as the phenotype of interest. That said, GWAS examining back pain of *any* duration, or analyses excluding those with non-chronic back pain, may find different results from ours.

In summary, this meta-analysis of GWAS of CBP identified novel genetic associations with CBP at *SOX5*, *CCDC26*/*GSDMC,* and *DCC.* These findings suggest possible mechanisms involving the spine and/or shared biological pathways involving CBP, cartilage, lumbar disc herniation, height and/or vertebral development.

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REFERENCES

1. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Annals of the rheumatic diseases. 2014;73(6):968-74.
2. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. The Journal of bone and joint surgery. 2006;88 Suppl 2:21-4.
3. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, et al. Report of the NIH Task Force on Research Standards for Chronic Low Back Pain. The spine journal : official journal of the North American Spine Society. 2014;14(8):1375-91.
4. Meucci RD, Fassa AG, Faria NM. Prevalence of chronic low back pain: systematic review. Rev Saude Publica. 2015;49.
5. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat Genet. 2015;47(7):702-9.
6. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, et al. MaTCH (Meta-analysis of Twin Correlations and Heritability) web application. 2017 [cited 2017 May 25]; Available from: http://match.ctglab.nl/ - /specific/plot1
7. Ferreira PH, Beckenkamp P, Maher CG, Hopper JL, Ferreira ML. Nature or nurture in low back pain? Results of a systematic review of studies based on twin samples. Eur J Pain. 2013.
8. Guo TM, Liu M, Zhang YG, Guo WT, Wu SX. Association between Caspase-9 promoter region polymorphisms and discogenic low back pain. Connect Tissue Res. 2011;52(2):133-8.
9. Omair A, Lie BA, Reikeras O, Holden M, Brox JI. Genetic contribution of catechol-O-methyltransferase variants in treatment outcome of low back pain: a prospective genetic association study. BMC Musculoskelet Disord. 2012;13:76.
10. Chou D, Samartzis D, Bellabarba C, Patel A, Luk KD, Kisser JM, et al. Degenerative magnetic resonance imaging changes in patients with chronic low back pain: a systematic review. Spine (Phila Pa 1976). 2011;36(21 Suppl):S43-53.
11. Endean A, Palmer KT, Coggon D. Potential of magnetic resonance imaging findings to refine case definition for mechanical low back pain in epidemiological studies: a systematic review. Spine (Phila Pa 1976). 2011;36(2):160-9.
12. Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. Heritability of low back pain and the role of disc degeneration. Pain. 2007;131(3):272-80.
13. Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Structural brain changes in chronic pain reflect probably neither damage nor atrophy. PLoS One. 2013;8(2):e54475.
14. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci. 2012;15(8):1117-9.
15. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci. 2011;31(20):7540-50.
16. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? Jama. 2010;303(13):1295-302.
17. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet. 2009;2(1):73-80.
18. UK Biobank. Genotype imputation and genetic association studies of UK Biobank Interim Data Release, May 2015; 2015.
19. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68-74.

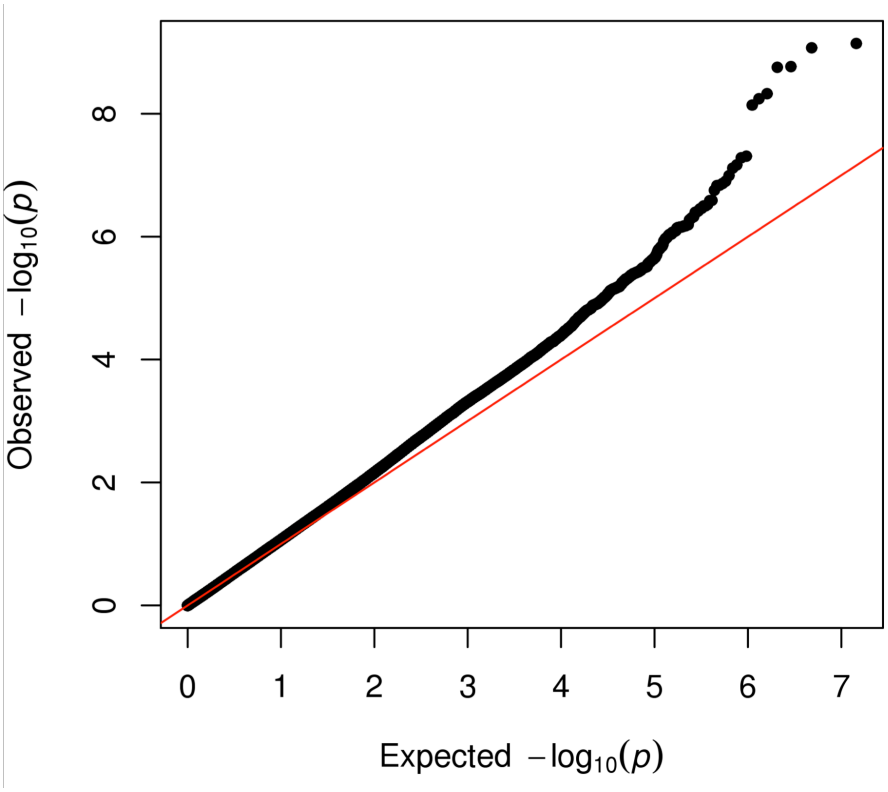
20. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet. 2016;48(10):1279-83.
21. Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Magi R, et al. Quality control and conduct of genome-wide association meta-analyses. Nat Protoc. 2014;9(5):1192-212.
22. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47(3):291-5.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
24. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet. 2014;46(3):310-5.
25. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, et al. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res. 2012;22(9):1790-7.
26. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science. 2015;348(6235):648-60.
27. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun. 2017;8(1):1826.
28. Ernst J, Kellis M. ChromHMM: automating chromatin-state discovery and characterization. Nat Methods. 2012;9(3):215-6.
29. Roadmap Epigenomics C, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, et al. Integrative analysis of 111 reference human epigenomes. Nature. 2015;518(7539):317-30.
30. Zaitlen N, Kraft P. Heritability in the genome-wide association era. Hum Genet. 2012;131(10):1655-64.
31. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015;47(11):1236-41.
32. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;33(2):272-9.
33. Hou L, Srivastava Y, Jauch R. Molecular basis for the genome engagement by Sox proteins. Semin Cell Dev Biol. 2017;63:2-12.
34. Liu CF, Lefebvre V. The transcription factors SOX9 and SOX5/SOX6 cooperate genome-wide through super-enhancers to drive chondrogenesis. Nucleic Acids Res. 2015;43(17):8183-203.
35. Smits P, Li P, Mandel J, Zhang Z, Deng JM, Behringer RR, et al. The transcription factors L-Sox5 and Sox6 are essential for cartilage formation. Dev Cell. 2001;1(2):277-90.
36. Liu CF, Samsa WE, Zhou G, Lefebvre V. Transcriptional control of chondrocyte specification and differentiation. Semin Cell Dev Biol. 2017;62:34-49.
37. Xu J, Kang Y, Liao WM, Yu L. MiR-194 regulates chondrogenic differentiation of human adipose-derived stem cells by targeting Sox5. PLoS One. 2012;7(3):e31861.
38. Budd E, de Andres MC, Sanchez-Elsner T, Oreffo ROC. MiR-146b is down-regulated during the chondrogenic differentiation of human bone marrow derived skeletal stem cells and up-regulated in osteoarthritis. Sci Rep. 2017;7:46704.
39. Smits P, Lefebvre V. Sox5 and Sox6 are required for notochord extracellular matrix sheath formation, notochord cell survival and development of the nucleus pulposus of intervertebral discs. Development. 2003;130(6):1135-48.
40. arc OC, arc OC, Zeggini E, Panoutsopoulou K, Southam L, Rayner NW, et al. Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet. 2012;380(9844):815-23.

41. Elliott KS, Chapman K, Day-Williams A, Panoutsopoulou K, Southam L, Lindgren CM, et al. Evaluation of the genetic overlap between osteoarthritis with body mass index and height using genome-wide association scan data. Annals of the rheumatic diseases. 2013;72(6):935-41.
42. Evangelou E, Kerkhof HJ, Styrkarsdottir U, Ntzani EE, Bos SD, Esko T, et al. A meta-analysis of genome-wide association studies identifies novel variants associated with osteoarthritis of the hip. Annals of the rheumatic diseases. 2014;73(12):2130-6.
43. Evangelou E, Valdes AM, Kerkhof HJ, Styrkarsdottir U, Zhu Y, Meulenbelt I, et al. Meta-analysis of genome-wide association studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22. Annals of the rheumatic diseases. 2011;70(2):349-55.
44. Evans DS, Cailotto F, Parimi N, Valdes AM, Castano-Betancourt MC, Liu Y, et al. Genome-wide association and functional studies identify a role for IGFBP3 in hip osteoarthritis. Annals of the rheumatic diseases. 2015;74(10):1861-7.
45. Hollander WD, Boer CG, Hart DJ, Yau MS, Ramos YFM, Metrustry S, et al. Genome-wide association and functional studies identify a role for matrix Gla protein in osteoarthritis of the hand. Annals of the rheumatic diseases. 2017.
46. Kerkhof HJ, Lories RJ, Meulenbelt I, Jonsdottir I, Valdes AM, Arp P, et al. A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. Arthritis Rheum. 2010;62(2):499-510.
47. Yau MS, Yerges-Armstrong LM, Liu Y, Lewis CE, Duggan DJ, Renner JB, et al. Genome-Wide Association Study of Radiographic Knee Osteoarthritis in North American Caucasians. Arthritis Rheumatol. 2017;69(2):343-51.
48. Williams FM, Bansal AT, van Meurs JB, Bell JT, Meulenbelt I, Suri P, et al. Novel genetic variants associated with lumbar disc degeneration in northern Europeans: a meta-analysis of 4600 subjects. Annals of the rheumatic diseases. 2013;72(7):1141-8.
49. Song YQ, Karasugi T, Cheung KM, Chiba K, Ho DW, Miyake A, et al. Lumbar disc degeneration is linked to a carbohydrate sulfotransferase 3 variant. J Clin Invest. 2013;123(11):4909-17.
50. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol. 2013;9(4):216-24.
51. Bjornsdottir G, Benonisdottir S, Sveinbjornsson G, Styrkarsdottir U, Thorleifsson G, Walters GB, et al. Sequence variant at 8q24.21 associates with sciatica caused by lumbar disc herniation. Nat Commun. 2017;8:14265.
52. Truumees E. A history of lumbar disc herniation from Hippocrates to the 1990s. Clinical orthopaedics and related research. 2015;473(6):1885-95.
53. Zhang Y, Fukui N, Yahata M, Katsuragawa Y, Tashiro T, Ikegawa S, et al. Genome-wide DNA methylation profile implicates potential cartilage regeneration at the late stage of knee osteoarthritis. Osteoarthritis Cartilage. 2016;24(5):835-43.
54. Zhang Y, Fukui N, Yahata M, Katsuragawa Y, Tashiro T, Ikegawa S, et al. Identification of DNA methylation changes associated with disease progression in subchondral bone with site-matched cartilage in knee osteoarthritis. Sci Rep. 2016;6:34460.
55. Finci L, Zhang Y, Meijers R, Wang JH. Signaling mechanism of the netrin-1 receptor DCC in axon guidance. Prog Biophys Mol Biol. 2015;118(3):153-60.
56. Wu CH, Yuan XC, Gao F, Li HP, Cao J, Liu YS, et al. Netrin-1 Contributes to Myelinated Afferent Fiber Sprouting and Neuropathic Pain. Mol Neurobiol. 2016;53(8):5640-51.
57. Dun XP, Parkinson DB. Role of Netrin-1 Signaling in Nerve Regeneration. Int J Mol Sci. 2017;18(3).
58. Bu G, Hou S, Ren D, Wu Y, Shang W, Huang W. Increased expression of netrin-1 and its deleted in colorectal cancer receptor in human diseased lumbar intervertebral disc compared with autopsy control. Spine (Phila Pa 1976). 2012;37(25):2074-81.
59. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet. 1997;350(9072):178-81.

60. Heuch I, Heuch I, Hagen K, Zwart JA. Association between body height and chronic low back pain: a follow-up in the Nord-Trondelag Health Study. BMJ Open. 2015;5(6):e006983.
61. Hershkovich O, Friedlander A, Gordon B, Arzi H, Derazne E, Tzur D, et al. Associations of body mass index and body height with low back pain in 829,791 adolescents. Am J Epidemiol. 2013;178(4):603-9.
62. Smedley J, Egger P, Cooper C, Coggon D. Prospective cohort study of predictors of incident low back pain in nurses. BMJ (Clinical research ed. 1997;314(7089):1225-8.
63. Taylor JB, Goode AP, George SZ, Cook CE. Incidence and risk factors for first-time incident low back pain: a systematic review and meta-analysis. The spine journal : official journal of the North American Spine Society. 2014;14(10):2299-319.
64. Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, et al. Genome-Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci. PLoS Genet. 2016;12(8):e1006125.
65. Shi C, Qiu S, Riester SM, Das V, Zhu B, Wallace AA, et al. Animal models for studying the etiology and treatment of low back pain. J Orthop Res. 2017.

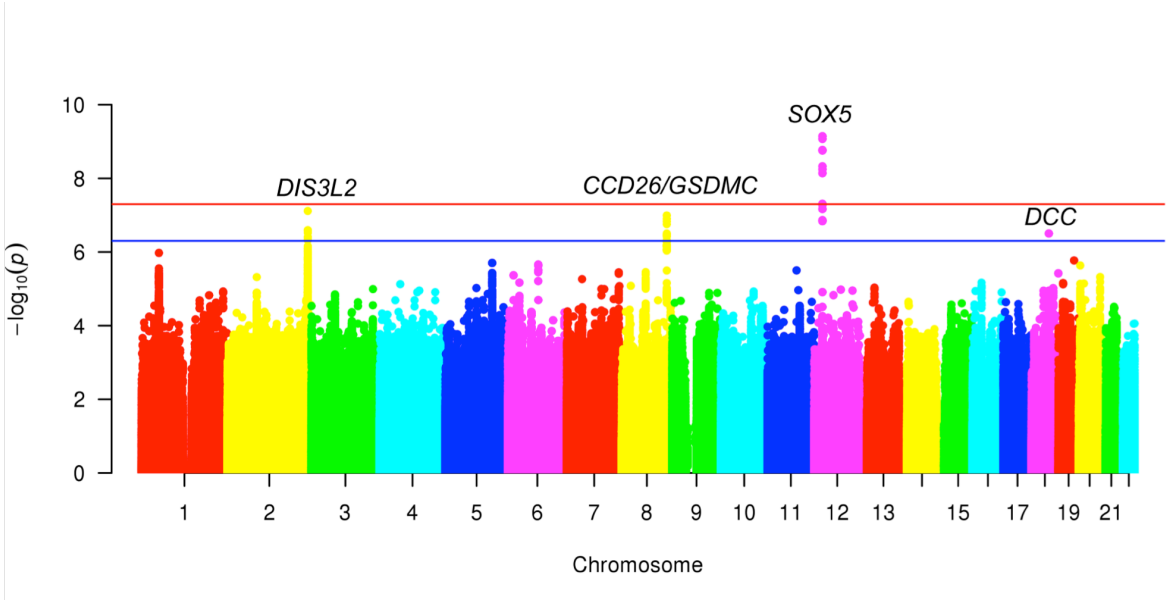
FIGURE LEGENDS

Figure 1. Quantile-quantile plot of p-values from the meta-analysis (discovery) of GWAS of chronic back pain (n=158,025)*



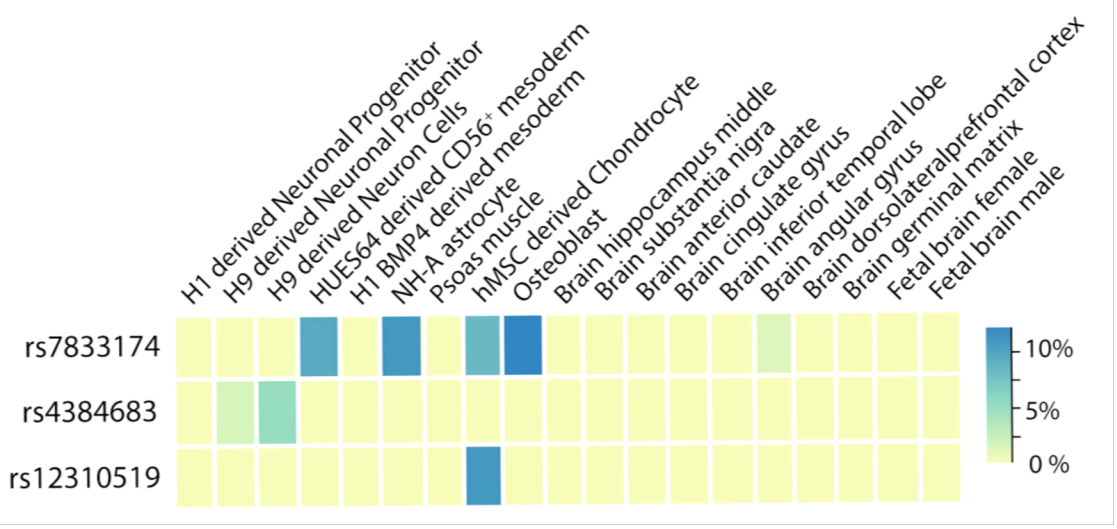
*LD score regression intercept=1.0067
GWAS=genome-wide association study

Figure 2. Manhattan plot for meta-analysis (discovery) of GWAS of chronic back pain (n=158,025)



GWAS=genome-wide association study. Results use the linkage disequilibrium score regression (LDSR) intercept as a correction factor. Red line depicts genome-wide statistical significance ($P < 5\times10^{-8}$). Blue line depicts suggestive significance ($P < 5\times10^{-7}$).

Figure 3. Significant variants are co-localized with potential gene regulatory markers



The heatmap depicts the percentage of variants in gene regulatory regions (associated with enhancers/promotors) in high LD (r^2>0.6) with rs7833174 (*CCDC26/GSDMC*), rs12310519 (*SOX5*), and rs4384683 (*DCC*). We examined epigenetic histone marks in selected cell types/tissues including chondrogenic, bone-related, neuronal and brain cells/tissues; mesodermal cells (related to notochord); and psoas muscle (located proximal to the lumbar spine).

Table 1. Cohorts in Meta-Analysis of Genome-Wide Association Studies of Chronic Back Pain (European Ancestry)

Cohort	**Study setting**	**Country**	**Sample size**	**Chronic back pain definition**	**Prevalence (%)**		**Age** (yr)	**BMI** (kg/m^2)	**Women** (%)
Cardiovascular Health Study (CHS)	Community	USA	2849	≥1 month of back pain in consecutive years	14.2%	Cases (n=404)	72.1 ± 5.1	27.3 ± 5.0	73.3%
						Controls (n=2445)	72.1 ± 5.2	26.1 ± 4.3	59.6%
Framingham Heart Study[14]	Community	USA	2673	≥6 months of back pain	21.0%	Cases (n=561)	67.7 ± 9.3	28.8 ± 5.8	62.2%
						Controls (n=2112)	66.4 ± 9.1	28.0 ± 52	52.9%
Generation Scotland	Population	UK	5071	≥3 months of back pain	26.0%	Cases (n=1322)	54.9 ± 11.8	28.1 ± 5.7	66.7%
						Controls (n=3749)	52.4 ± 12.7	26.4 ± 4.6	55.4%
Johnston County Osteoarthritis Project (JoCo)	Population	USA	480	≥6 months of back pain	38.8%	Cases (n=186)	72.0 ± 8.0	31.4 ± 6.3	65.0%
						Controls (n=294)	73.0 ± 8.0	29.3 ± 5.2	58.4%
Mr. Os Sweden									
Gothenburg	Population	Sweden	920	≥6 months of back pain	14.2%	Cases (n=131)	75.3 ± 3.2	26.7 ± 3.9	0%
						Controls (n=789)	75.3 ± 3.2	26.1 ± 3.4	0%
Malmo	Population	Sweden	948	≥6 months of back pain	10.8%	Cases (n=102)	75.8 ± 3.1	27.2 ± 3.7	0%
						Controls (n=846)	75.6 ± 3.2	26.4 ± 3.6	0%
Mr. Os US	Community	USA	4615	≥6 months of back pain	14.1%	Cases (n=653)	74.6 ± 6.1	28.0 ± 4.1	0%
						Controls (n=3962)	73.9 ± 5.9	27.3 ± 3.8	0%
Osteoarthritis Initiative (OAI)	Community	USA	2474	≥1 month of back pain in consecutive years	13.5%	Cases (n=335)	61.0 ± 9.1	28.9 ± 4.7	57.9%
						Controls (n=2139)	61.7 ± 9.1	28.1 ± 4.5	53.2%
Rotterdam Study (RS)									
RS-1	Community	Netherlands	5965	≥6 months of back pain	14.7%	Cases (n=877)	69.1 ± 9.2	26.7 ± 4.0	72.0%
						Controls (n=5088)	70.0 ± 9.4	26.2 ± 3.7	58.3%
RS-2	Community	Netherlands	1566	≥6 months of back pain	36.7%	Cases (n=574)	65.3 ± 8.0	27.7 ± 4.2	66.7%
						Controls (n=992)	64.6 ± 8.0	27.3 ± 4.1	55.4%
RS-3	Community	Netherlands	3019	≥6 months of back pain	38.2%	Cases (n=1154)	57.4 ± 6.9	28.1 ± 4.8	59.5%
						Controls (n=1865)	56.9 ± 6.7	27.4 ± 4.5	54.3%
Study of Osteoporotic Fractures (SOF)	Community	USA	3615	≥6 months of back pain	16.3%	Cases (n=589)	72.1 ± 5.6	27.6 ± 5.3	100%
						Controls (n=3026)	71.4 ± 5.2	26.6 ± 4.4	100%
10,001 Dalmatians									
Vis	Population	Croatia	251	≥3 months of back pain	22.3%	Cases (n=56)	67.3 ± 13.2	27.8 ± 4.4	69.6%
						Controls (n=195)	63.7 ± 12.1	26.7 ± 4.0	52.8%
Korcula	Population	Croatia	773	≥3 months of back pain	21.2%	Cases (n=164)	64.3 ± 12.9	28.0 ± 4.3	70.7%
						Controls (n=609)	58.0 ± 14.9	27.0 ± 41	64.0%
UK Biobank	Population	United Kingdom	120,024	≥3 months of back pain	18.0%	Cases (n=21,600)	57.3 ± 7.9	28.5 ± 5.4	54.0%
						Controls (n=98,424)	57.0 ± 7.9	27.4 ± 4.8	52.4%
TwinsUK	Population-	United	2782	≥3 months of back pain	29.6%	Cases (n=823)	56.7 ± 12.6	27.4 ± 5.3	90.3%

	based twin registry	Kingdom				Controls (n=1959)	54.3 ± 13.9	26.0 ± 4.9	90.0%
Total of all cohorts	-	-	158,025	-	-	Cases (n=29,531)	-	-	-
						Controls (n=128,494)	-	-	-

Table 2. Association Results for Chronic Back Pain: Meta-analysis (Discovery), Replication, and Joint Meta-analysis*

						Meta-analysis (Discovery)[a]					**Independent Sample (Replication)**[b]		**Joint Meta-Analysis (Discovery-Replication)**[c]	
SNP rsID	Chr:Pos[d]	Nearest Gene	Location	Effect allele	Other allele	EAF	OR	p-value	I^2	Het. p-value	OR	p-value[b]	OR	p-value
rs12310519[e]	12:23975219	*SOX5*	intronic	T	C	0.16	1.08	7.2×10^{-10}	0	0.95	1.06	5.3×10^{-11}	1.07	4.5×10^{-19}
rs1453867	2:232917899	*DIS3L2*	intronic	T	C	0.65	0.95	7.7×10^{-8}	13	0.31	0.98	0.021	0.97	3.9×10^{-7}
rs7833174	8:130718772	*CCDC26/ GSDMC*	intergenic	T	C	0.77	1.06	1.0×10^{-7}	0	0.71	1.04	3.7×10^{-7}	1.05	4.4×10^{-13}
rs4384683	18:50379032	*DCC*	intronic	A	G	0.54	0.95	3.2×10^{-7}	0	0.86	0.97	4.2×10^{-5}	0.97	2.4×10^{-10}

Chr:pos=chromosome-position, EAF=effect allele frequency OR=odds ratio, het.=heterogeneity

*Top variant at each locus meeting suggestive or genome-wide significance level in discovery stage ($p<5.0\times10^{-7}$)

[a]After genomic control using the LD score regression intercept

[b]Replication for rs12310519. The threshold for significance in replication of rs12310519 was $p<0.05$ (0.05/1)

[c]The threshold for genome-wide significance in joint analysis was $p<5\times10^{-8}$

[d]Build GRCh37/hg19

[e]rs115392701 has merged into rs12310519

Supplemental Table S1. Chronic back pain definitions and related question items

Cohort	Chronic back pain definition	Back pain questions for each cohort
Cardiovascular Health Study	≥1 month of back pain in consecutive years	**"*In the past year, have you had pain in your back for more than half the days of any month?*"** "*Yes*" in ≥2 consecutive years (**cases**) vs. other combinations of non-missing responses in consecutive years (**controls**)
Framingham Heart Study	≥6 months of back pain	**"*Have you had back pain in the past 12 months?*"** "*Most of the days*"/"*all days*" **(cases)** vs. "*no*"/"*a few days*"/"*some of the days*" **(controls)**
Generation Scotland	≥3 months of back pain	Question combinations indicating " ***Have you been troubled by pain or discomfort*** [in the back]***, either all the time or on and off…for more than 3 months***?" "*Yes*" (**cases**) vs. "*No*" (**controls**)
Johnston County Osteoarthritis Project	≥6 months of back pain	**"*On MOST days of ANY ONE MONTH in the LAST 12 MONTHS did you have pain, aching, or stiffness in any of the following?*"** "***Lower back (L1 through S1)***" and "***middle back (thoracic)***" locations were specified. ≥6 month duration *"with pain on most days"* **(cases)** vs. other non-missing response options **(controls)**
Mr. Os Sweden		
Gothenburg	≥6 months of back pain	**"*Have you had back pain in the past 12 months?*"** "*Most of the time*"/"*all of the time*" **(cases)** vs. "*no*"/"*never*"/"*rarely*"/"*some of the time*" **(controls)**
Malmo	≥6 months of back pain	**" *Have you had back pain in the past 12 months?*"** "*Most of the time*"/"*all of the time*" **(cases)** vs. "*no*"/"*never*"/"*rarely*"/"*some of the time*" **(controls)**
Mr. Os US	≥6 months of back pain	**"*During the past 12 months have you experienced any back pain?*"** "*Most of the time*"/"*all of the time*" **(cases)** vs. "*no*"/"*never*"/"*rarely*"/"*some of the time*" **(controls)**
Osteoarthritis Initiative	≥1 month of back pain in consecutive years	**"*How often were you bothered by back pain in the past 30 days?*"** "*All of the time*"/"*Most of the time*" in ≥2 consecutive years (**cases**) vs. any other combination of non-missing responses in consecutive years (**controls**)
Rotterdam Study (RS)		
RS-1	≥6 months of back pain	**"*Have you had pain in the low back in the last month?*"** ≥6 month duration of low back pain **(cases)** vs. no back pain or <6 months duration low back pain **(controls)**
RS-2	≥6 months of back pain	**" Do you have pain or stiffness in your back?"** ≥6 month duration **(cases)** vs. no back pain/stiffness or <6 months duration back pain/stiffness **(controls)**
RS-3	≥6 months of back pain	**" Do you have pain or stiffness in your back?"** ≥6 month duration **(cases)** vs. no back pain/stiffness or <6 months duration back pain/stiffness **(controls)**
Study of Osteoporotic Fractures	≥6 months of back pain	**"*During the past 12 months have you experienced any back pain*?"** "*Most of the time*"/"*all of the time*" **(cases)** vs. ""*no*"/"*never*"/"*rarely*"/"*some of the time*" **(controls)**
10,001 Dalmatians		
Vis	≥3 months of back pain	**"*Have you ever had an episode of chronic LBP that lasted for over 3 months?* "** and **"*Do you have low back pain at the moment?*"** "*Yes*" to both questions (**cases**) vs. "*No*" to either question (**controls**)
Korcula	≥3 months of back pain	**"*Have you ever had an episode of chronic LBP that lasted for over 3 months?* "** and **"*Do you have low back pain at the moment?*"** "*Yes*" to both questions (**cases**) vs. "*No*" to either question (**controls**)
TwinsUK	≥3 months of back pain	"***In the past 3 months, have you had pain in your back on most days?"*** or ***"Have you had pain…in this area*** [lumbar or thoracic] ***for at least the past 3 months?"*** "*Yes*" to either question (**cases**) vs. "*No*" to both questions (**controls**)
UK Biobank	≥3 months of back pain	"***In the last month have you experienced any of the following that interfered with your usual activities?*** " (Back pain is a response option) **"*Have you had back pain for more than 3 months?*"** "*Yes*" to both questions (**cases**) vs. "*No*" to the first question or "*Yes*" to the first question and *No*" to the second question (**controls**)

Supplemental Table S2. Genotyping, quality control, and imputation for each cohort

	Genotyping		Quality Control							Imputation			
Cohort	**Platform**	**Genotype calling algorithm/ software**	**Total # of SNPs**	**SNP call rate**	**MAF**	**HWE P-value**	**ID call rate**	**Other sample QC/other exclusions**	**#SNPs that met QC**	**Imputation Software**	**Measure of Imputation Quality**	**Reference panel**	**Total # of SNPs**
Discovery (Meta-analysis)													
Cardiovascular Health Study (CHS)	Illumina 370CNV chip, ITMAT-Broad-CARe Illumina iSELECT chip	Illumina BeadStudio	393,254	≥97%	>0%	≥10-5	> 95%	Participants excluded for presence at baseline of CHD, CHF, peripheral vascular disease, valvular heart disease, stroke, or TIA, or lack of available DNA; genotype discordant with known sex or prior genotyping. SNPs also excluded if >2 duplicate errors or Mendelian inconsistencies, heterozygote frequency = 0, SNP not found in Hapmap.	359,953	MaCH/ Minimac	r2	1000G Phase1 v3 (Nov. 2012)	38,050,714
Framingham Heart Study (FHS)	Affymetrix 500K DualGeneChip+ 50K gene-centered MIP set	BRLMM	549,781	≥97%	≥ 1%	≥10-6	≥ 97%	Excessive heterozygosity, ethnic outliers	412,053	MACH/ Minimac	(O/E) σ2 ratio	1000G Phase1 v3 (Mar. 2012)	36,278,365
Generation Scotland (GS)	Illumina OMNI_Express+Exome	Illumina GenomeStudio	960,919	≥98%	≥ 1%	≥10-6	≥ 97%	Related individuals	630,207	ShapeIt2, IMPUTE2	IMPUTE2 info score	1000G Phase1 v3 (Mar. 2012)	39,321,347
Johnston County Osteoarthritis Project (JoCo)	Illumina Infinium 1M-Duo build 36	Illumina Infinium 1M-Duo build 36	1,199,187	≥98%	≥0.5%	>10-4	≥ 98%	Monomorphic SNPs, SNPs with at least one discordant genotype among duplicate samples were dropped. All subjects that were not reconcilable with the database (by sex and race) were dropped from the analysis	934,056	IMPUTE2	IMPUTE2 info score	1000G Phase 3 (Oct. 2014)	27,547,483
MrOS-Gothenburg	Illumina HumanOmni1_Quad_v1-0 B array	Illumina BeadStudio	1,134,514	≥97%	> 1%	>10-4	≥ 97%	excessive autosomal heterozygozity, first and second degree relatives, genotypic sex mismatch using X and Y chromosome probe intensities and gross chromosome abnormalities	714,543	IMPUTE2	IMPUTE2 info score	1000G Phase 3 and UK10K	35,685,596
MrO- Malmo	HumanOmniExpress-12v1_B build 36	Illumina GenomeStudio	733,202	≥95%	> 1%	>10-6	≥ 97.5%	excessive autosomal heterozygozity, familial relationship (one sample excluded), genotypic sex mismatch, non-caucasians and gross chromosome abnormalities	725,409	IMPUTE2	IMPUTE2 info score	1000G Phase 3 and UK10K	35,653,617
MrOS-US	Illumina HumanOmni1_Quad_v1-0 H	Illumina GenomeStudio	1,140,419	≥97%	≥ 1%	>10-4	≥ 97%	1) Gender mismatches; 2) ethnic outliers; 3) related individuals	740,713	ShapeIt2/ Minimac	MACH r2	1000G Phase 1 v3	27,438,360
Osteoarthritis Initiative (OAI)	Illumina Omni-Quad 2.5M	Illumina BeadStudio	2,440,283	>95%	> 1%	≥10-6	≥ 95%	Mismatches between self-reported and genetically determined gender, large chromosomal abnormalities, cryptic relatedness, ethnic outliers	2,426,302	MACH/ Minimac	(O/E) σ2 ratio	1000G Phase 3	37,426,755
Rotterdam Study 1 (RS1)	Illumina HumanHap 550K V.3 Duo	Illumina BeadStudio	550,000	≥98%	≥ 1%	≥10-6	≥ 97.5%	1) sex mismatch with typed X-linked markers, 2) excess autosomal heterozygosity > 0.336~ FDR > 0.1%, 3) duplicates and/or first or second degree relatives using IBS probabilities > 97% from PLINK, 4) ethnic outliers using IBS distances > 3SD from PLINK	512,349	MACH/ Minimac	(O/E) σ2 ratio	1000G Phase 1 v3	30,072,738
Rotterdam	Illumina	Illumina	550,000	≥98%	≥ 1%	≥10-6	≥	1) sex mismatch with typed X-linked	466,389	MACH/	(O/E) σ2	1000G	30,072,738

Study 2 (RS2)	HumanHap 550K V.3 Duo	BeadStudio					97.5%	markers, 2) excess autosomal heterozygosity > 0.336~ FDR > 0.1%, 3) duplicates and/or first or second degree relatives using IBS probabilities > 97% from PLINK, 4) ethnic outliers using IBS distances > 3SD from PLINK		Minimac	ratio	Phase 1 v3	
Rotterdam Study 3 (RS3)	Illumina HumanHap 610-Quad V1	Illumina BeadStudio	610,901	≥98%	≥ 1%	≥10-6	≥ 97.5%	1) sex mismatch with typed X-linked markers, 2) excess autosomal heterozygosity > 0.336~ FDR > 0.1%, 3) duplicates and/or first or second degree relatives using IBS probabilities > 97% from PLINK, 4) ethnic outliers using IBS distances > 3SD from PLINK	517,658	MACH/ Minimac	(O/E) σ2 ratio	1000G Phase 1 v3	30,072,738
Study of Osteoporotic Fractures (SOF)	Illumina HumanOmni1_Quad_v1-0 H	Illumina GenomeStudio	1,140,420	≥97%	≥ 1%	>10-5	≥ 97%	1) Gender mismatches; 2) ethnic outliers; 3) related individuals	740,714	ShapeIt2/ minimac	MACH r2	1000G Phase 1 v3	27,438,360
10001 Dalmatians-Vis (Vis)	Illumina HumanHap300v1	Illumina GenomeStudio	317,509	≥98%	≥ 1%	≥10-6	> 95%		289,827	pbwt software on the Sanger imputation server	INFO	HRC	11,869,819
10001 Dalmatians-Korcula (Korcula)	Illumina Human370CNV-Quad	Illumina GenomeStudio	346,034	≥98%	≥ 1%	≥10-6	≥ 97%		317,898	pbwt software on the Sanger imputation server	INFO	HRC	11,915,415
UK Biobank (UKB)	Affymetrix UK BiLEVE Axiom array + Affymetrix UK Biobank Axiom® array	Affymetrix Power Tools	820,967	varies per batch	≥ 0.001 %	≥10-12	≥ 95%	Batch effects, plate effects, sex effects, array effects, discordance across control replicates, excess of heterozygosity	805,426	SHAPEIT3	MACH r2	1000G Phase 1 v3 + HRC	72,355,667
TwinsUK	4 different Illumina arrays (HumanHap3001,2, HumanHap610Q, 1M-Duo and 1.2MDuo 1M)	Illumina BeadStudio	317,000; 616,794; 1,192,666; ~1,2 mln. respective-ly	>95%	> 1%	≥10-6	≥ 98%	Mismatch between MZ twins and self-reported sex; non-European ancestry; related individuals	874,733 depending on the dataset (303,940, 553,487, HumanHap 1M and 1.M: 874,733)	IMPUTE2	IMPUTE2 info score	1000G Phase 3	27,445,314
Replication													
UK Biobank (UKB)	Affymetrix UK BiLEVE Axiom array + Affymetrix UK Biobank Axiom® array	Affymetrix Power Tools	820,967	varies per batch*	≥ 0.001 %	≥10-12	≥ 95%	Batch effects, plate effects, sex effects, array effects, discordance across control replicates, excess of heterozygosity	805,426	SHAPEIT3	MACH r2	1000G Phase 1 v3 + HRC	92,693,895

*see http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf

Supplemental Table S3. Details of the GWAS analysis for each cohort and quality control prior to meta-analysis

Cohort	Total # of SNPs post-imputation	Filters		Model used	# SNPs in analysis	Method used to correct for genetic substructure	Software	Following file-level and meta-level quality control (see Supplemental Methods)[a]	
		MAF	Imputation quality					# SNPs in meta-analysis	Genomic Inflation Factor (λ_{GC})
Discovery (Meta-analysis[a])									
Cardiovascular Health Study (CHS)	38,050,714	> 0%	variance on allele dosage ≤0.01	SNP+ age + sex + clinic	9,854,835	NA	R	7,528,846	1.00
Framingham Heart Study (FHS)	36,278,365	> 0%	≥0.3	SNP + age + sex + PC1 + PC2 + PC3 + PC4 + PC5 + kinship	19,344,131	EIGENSTRAT	R/GEE	7,114,199	1.03
Generation Scotland (GS)	39,321,347	> 0%	none	SNP + age + sex (Unrelated individuals only)	39,321,347	Unrelated only	R/ProbABEL	8,934,663	1.01
Johnston County Osteoarthritis Project (JoCo)	27,547,483	> 0%	none	SNP + age + sex + PC1 + PC2 + PC3	27,547,483	EIGENSOFT	PLINK	9,236,276	1.02
MrOS-Gothenburg	35,685,596	> 0%	>0.3	SNP + age	18,648,740	NA	PLINK	9,775,703	1.00
MrO- Malmo	35,653,617	> 0%	>0.3	SNP + age	19,943,738	NA	PLINK	9,764,582	1.00
MrOS-US	27,438,360	none	none	SNP + age + clinic site + PC1 + PC2 + PC3 + PC4	27,438,360	R/GWASTools package	PLINK	8,579,487	1.00
Osteoarthritis Initiative (OAI)	37,426,755	> 0%	>0.3	SNP + age + sex + PC1 + PC2	8,515,357	PLINK-MDS	PLINK	7,552,530	1.01
Rotterdam Study 1 (RS1)	30,072,738	> 0%	none	SNP+ age + sex	30,072,738	NA	MACH/GRIMP	8,017,540	1.01
Rotterdam Study 2 (RS2)	30,072,738	> 0%	none	SNP+ age + sex	30,072,738	NA	MACH/GRIMP	7,987,628	1.00
Rotterdam Study 3 (RS3)	30,072,738	> 0%	none	SNP+ age + sex	30,072,738	NA	MACH/GRIMP	8,055,340	1.02
Study of Osteoporotic Fractures (SOF)	27,438,360	none	none	SNP + age+ clinic site + PC1 + PC2 + PC3 + PC4	27,438,360	R/GWASTools package	PLINK	8,570,668	1.02
10001 Dalmatians-Korcula (Korcula)	11,915,415	> 0%	none	SNP + age + sex + kinship (PC1 + PC2)	11,915,415	GenABEL kinship matrix	RegScan+SNPTEST	7,814,464	1.01
10001 Dalmatians-Vis (Vis)	11,869,819	> 0%	none	SNP + age + sex + kinship (PC1 + PC2)	11,869,819	GenABEL kinship matrix	RegScan+SNPTEST	6,205,227	1.01
UK Biobank (UKB)	92,693,895	>0.001%	none	SNP + age + sex + array + PC1 + … + PC10	72,355,667[b]	UKBB PCs	PLINK	7,852,376	1.07
TwinsUK	27,445,314	> 0%	≥0.3	SNP + age + sex + kinship (Unrelated individuals only)	16,158,721	GenABEL kinship matrix	R/GenABEL	6,902,696	1.01
Replication									
UK Biobank (UKB)	92,693,895	>0.001%	none	SNP + age + sex + array + PC1 + … + PC10	4[bc]	UKBB PCs	PLINK	NA	NA

GWAS=genome-wide association study

[a]Meta-analysis LD score regression (LDSr) intercept was 1.007, indicating no population stratification. The LDSr intercept was used as a correction factor.

[b]only HRC-imputed SNPs were included in subsequent stages of analysis, including meta-analysis and replication, due to known problems at this time with the second set of imputed SNPs using 1000G + UK10K http://www.ukbiobank.ac.uk/2017/07/important-note-about-imputed-genetics-data/

[c]region-specific analyses were performed, and 4 variants were carried forward into the replication phase

Supplemental Table S4: Association Results for Meta-Analysis of Chronic Back Pain GWAS (all variants with $p<5 \times 10^{-7}$)*

rsID	Chr:pos (hg19)	Effect Allele	Other Allele	EAF	Odds Ratio	95% CI lower bound	95% CI upper bound	p-value	total N	MAC	Mean Imputation quality score	Het. I^2	Het. p-value
rs115392701[a]	**12:23975219**	**t**	**c**	**0.16**	**1.08**	**1.06**	**1.11**	**7.2e-10**	**155961**	**49241**	**0.94**	**0**	**0.95**
rs56290807	12:23972014	a	c	0.17	1.08	1.06	1.1	8.4e-10	152511	50963	0.93	0	0.78
rs7134575	12:23978200	a	g	0.13	1.09	1.06	1.11	1.7e-09	154152	39813	0.94	0	0.91
rs139555077	12:23975953	t	g	0.16	1.08	1.05	1.11	1.8e-09	153145	48325	0.93	0	0.92
rs11831278	12:23960729	t	c	0.16	1.08	1.05	1.1	4.7e-09	153132	47303	0.93	0	0.87
rs9804988	12:23982559	t	c	0.13	1.08	1.06	1.11	5.7e-09	155228	40367	0.94	0	0.92
rs12581539	12:23977474	t	g	0.13	1.08	1.06	1.11	7.2e-09	153854	40269	0.93	0	0.9
rs7977132	12:23936398	a	g	0.16	1.07	1.05	1.1	4.9e-08	150084	47947	0.92	0	0.85
rs34616559	12:23947697	t	c	0.16	1.07	1.05	1.1	5.2e-08	152008	47109	0.92	0	0.85
rs150677659	12:23974404	c	g	0.23	1.06	1.04	1.08	6.8e-08	151984	69856	0.94	0	0.65
rs1453867	**2:232917899**	**t**	**c**	**0.65**	**0.95**	**0.93**	**0.97**	**7.7e-08**	**157283**	**111377**	**1.00**	**12.7**	**0.31**
rs7833174	**8:130718772**	**t**	**c**	**0.77**	**1.06**	**1.04**	**1.08**	**1.0e-07**	**156963**	**71950**	**0.99**	**0**	**0.7**
rs6651255	8:130723792	t	c	0.77	1.06	1.04	1.08	1.3e-07	157561	72663	0.99	0	0.66
rs2955527	12:23973837	t	g	0.77	0.94	0.92	0.96	1.4e-07	152001	70879	0.93	0	0.49
rs2955526	12:23973832	a	c	0.23	1.06	1.04	1.08	1.4e-07	152014	70841	0.93	0	0.49
rs7816342	8:130719623	a	g	0.23	0.94	0.92	0.97	1.5e-07	157509	72350	0.99	0	0.67
rs4130415	8:130718712	t	c	0.77	1.06	1.04	1.08	1.8e-07	157223	72113	0.99	0	0.66
rs2633265	2:233122885	t	c	0.36	1.05	1.03	1.07	2.6e-07	156856	112305	0.99	0.7	0.44
rs3116235	2:232911582	t	c	0.66	0.95	0.93	0.97	2.6e-07	157309	108326	1.00	20.4	0.22
rs1078093	2:233087245	a	g	0.36	1.05	1.03	1.07	3.0e-07	156086	112722	0.98	11.2	0.33
rs7815955	8:130719567	a	t	0.8	1.06	1.04	1.08	3.1e-07	157594	62913	0.99	8.2	0.36
rs4384683	**18:50379032**	**a**	**g**	**0.54**	**0.95**	**0.94**	**0.97**	**3.2e-07**	**156611**	**144334**	**0.99**	**0**	**0.86**
rs10956487	8:130717716	a	g	0.77	1.06	1.04	1.08	3.4e-07	156089	71572	0.99	0	0.73
rs4733724	8:130723728	a	g	0.8	1.06	1.04	1.08	3.5e-07	157797	63316	0.99	9.9	0.34
rs6470764	8:130725665	t	c	0.2	0.94	0.92	0.97	3.8e-07	157964	63305	0.99	6.9	0.38
rs923333	2:233082988	t	c	0.61	0.95	0.93	0.97	4.0e-07	155426	122181	0.97	2.3	0.43
rs3116167	2:232988345	a	g	0.36	1.05	1.03	1.07	4.0e-07	157682	112833	1.00	16.5	0.27

rs6725657	2:232812422	a	g	0.37	1.05	1.03	1.07	4.7e-07	155357	115456	0.96	17.7	0.25
rs7826493	8:130738972	a	g	0.8	1.06	1.04	1.08	4.9e-07	157571	62787	1.00	14.5	0.29

*Meta-analysis results using linkage disequilibrium score regression (LDSR) intercept as a correction factor
The lead SNP in each region is indicated **in bold.** The bold line indicates the threshold for genome-wide significance ($p<5 \times 10^{-8}$)
GWAS=genome-wide association study; chr:pos= chromosome:position, EAF=effect allele frequency (weighted mean across all studies), CI=confidence interval, MAC=minor allele count, Het.=heterogeneity
[a]rs115392701 has merged into rs12310519

Supplemental Table S5. Variants associated with chronic back pain at the suggestive significance level (or proxy variants in LD [r^2>0.6]), and associations with other phenotypes*

rsID	Chr:pos (hg19)	Alleles	Proxy rsID	Proxy Pos (hg19)	Proxy Alleles (Effect/ Other)	r^2	Trait	EAF	Beta	SE	P-value	N	N Studies	Unit	PMID
SOX5															
rs115392701 / rs12310519	**chr12:23975219**	**C/T**	**rs9804988**	**chr12:23982559**	**C/T**	**0.727**	**Height[a]**	**0.90**	**-0.024**	**0.0053**	**9.60E-06**	**236741**	**79**	**Z-score**	**25282103**
CCDC26/GSDMC															
rs7833174	**chr8:130718772**	**C/T**	**rs4733724**	**chr8:130723728**	**G/A**	**0.845**	**Height**	**0.20**	**-0.050**	**0.0037**	**1.00E-41**	**NA**	**NA**	**unit increase**	**25282103**
rs7833174	**chr8:130718772**	**C/T**	**rs4733724**	**chr8:130723728**	**G/A**	**0.845**	**Height**	**0.19**	**-0.050**	**0.0037**	**1.40E-41**	**252637**	**79**	**Z-score**	**25282103**
rs7833174	**chr8:130718772**	**C/T**	**rs7815955**	**chr8:130719567**	**T/A**	**0.845**	**Height**	**0.20**	**-0.050**	**0.0037**	**1.60E-41**	**252535**	**79**	**Z-score**	**25282103**
rs7833174	chr8:130718772	C/T	rs6470764	chr8:130725665	T/C	0.845	Height	0.20	-0.050	0.0037	4.30E-41	252663	79	Z-score	25282103
rs7833174	**chr8:130718772**	**C/T**	**rs4130415**	**chr8:130718712**	**C/T**	**1**	**Height**	**0.19**	**-0.050**	**0.0037**	**5.80E-41**	**252591**	**79**	**Z-score**	**25282103**
rs7833174	**chr8:130718772**	**C/T**	**rs7816342**	**chr8:130719623**	**A/G**	**1**	**Height**	**0.20**	**-0.047**	**0.0036**	**2.00E-39**	**252715**	**79**	**Z-score**	**25282103**
rs7833174	chr8:130718772	C/T	rs2062078	chr8:130734461	T/G	0.835	Height	0.20	-0.047	0.0036	1.20E-38	253131	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6470765	chr8:130736697	C/A	0.835	Height	0.20	-0.047	0.0036	1.40E-38	253054	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6986256	chr8:130728361	A/T	0.835	Height	0.20	-0.047	0.0036	1.70E-38	253160	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6470763	chr8:130720646	C/G	0.737	Height	0.18	-0.049	0.0038	2.90E-38	252464	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs3886937	chr8:130737391	C/T	0.835	Height	0.20	-0.047	0.0036	3.00E-38	253173	79	Z-score	25282103
rs7833174	**chr8:130718772**	**C/T**	**rs7833174**	**chr8:130718772**	**C/T**	**1**	**Height**	**0.23**	**-0.047**	**0.0036**	**4.50E-38**	**251729**	**79**	**Z-score**	**25282103**
rs7833174	chr8:130718772	C/T	rs4733732	chr8:130738457	T/C	0.835	Height	0.20	-0.047	0.0036	4.60E-38	253172	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs1074286	chr8:130737601	T/C	0.835	Height	0.20	-0.047	0.0036	5.10E-38	253173	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs3886938	chr8:130737546	G/T	0.835	Height	0.20	-0.047	0.0036	2.60E-37	252143	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6985118	chr8:130736929	T/A	0.835	Height	0.21	-0.046	0.0037	1.10E-35	245733	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs4128895	chr8:130755205	C/T	0.705	Height	0.18	-0.044	0.0039	4.60E-29	253155	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs4733737	chr8:130754719	T/C	0.71	Height	0.18	-0.044	0.0039	5.00E-29	253204	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs7839339	chr8:130743547	A/T	0.71	Height	0.18	-0.044	0.0039	7.40E-29	253151	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs4236748	chr8:130754887	T/G	0.71	Height	0.18	-0.044	0.0039	8.00E-29	253158	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs1989396	chr8:130756531	A/G	0.71	Height	0.18	-0.044	0.0039	8.10E-29	253078	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6994279	chr8:130740650	C/T	0.71	Height	0.18	-0.044	0.0040	1.30E-28	253160	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs7012249	chr8:130740522	A/G	0.71	Height	0.18	-0.044	0.0040	1.40E-28	253160	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6998296	chr8:130740779	C/T	0.71	Height	0.18	-0.044	0.0040	1.40E-28	253160	79	Z-score	25282103
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height**	**NA**	**NA**	**NA**	**1.70E-28**	**11513**	**NA**	**NA**	**23704328**
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height**	**NA**	**NA**	**NA**	**1.70E-28**	**183727**	**NA**	**NA**	**20881960**
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height**	**NA**	**NA**	**NA**	**1.70E-28**	**94612**	**NA**	**NA**	**21946350**

rs7833174	chr8:130718772	C/T	rs7011557	chr8:130740135	T/G	0.71	Height	0.18	-0.044	0.0040	1.90E-28	253160	79	Z-score	25282103
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height**	**0.20**	**0.050**	**0.0045**	**2.00E-28**	**NA**	**NA**	**unit decrease**	**20881960**
rs7833174	chr8:130718772	C/T	rs6470778	chr8:130759579	T/C	0.71	Height	0.18	-0.043	0.0039	2.60E-28	253090	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6470768	chr8:130739528	A/G	0.71	Height	0.18	-0.044	0.0040	4.70E-28	252174	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6470766	chr8:130736854	G/A	0.706	Height	0.18	-0.044	0.0040	1.30E-27	246945	79	Z-score	25282103
rs7833174	**chr8:130718772**	**C/T**	**rs4733724**	**chr8:130723728**	**G/A**	**0.845**	**Height**	**0.19**	**-0.047**	**0.0053**	**6.57E-19**	**133673**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height**	**0.19**	**-0.047**	**0.0053**	**6.57E-19**	**133673**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs4130415**	**chr8:130718712**	**C/T**	**1**	**Height**	**0.19**	**-0.047**	**0.0053**	**1.60E-18**	**133671**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs7815955**	**chr8:130719567**	**T/A**	**0.845**	**Height**	**0.19**	**-0.047**	**0.0053**	**1.60E-18**	**133673**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs6470765	chr8:130736697	C/A	0.835	Height	0.20	-0.044	0.0051	1.59E-17	133549	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs7833174**	**chr8:130718772**	**C/T**	**1**	**Height**	**0.20**	**-0.043**	**0.0051**	**2.00E-17**	**133668**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs7816342**	**chr8:130719623**	**A/G**	**1**	**Height**	**0.20**	**-0.043**	**0.0051**	**2.00E-17**	**133669**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs6470763	chr8:130720646	C/G	0.737	Height	0.18	-0.046	0.0054	2.25E-17	133683	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6986256	chr8:130728361	A/T	0.835	Height	0.20	-0.044	0.0052	2.85E-17	133668	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs3886937	chr8:130737391	C/T	0.835	Height	0.20	-0.044	0.0052	2.85E-17	133669	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs1074286	chr8:130737601	T/C	0.835	Height	0.20	-0.044	0.0052	2.85E-17	133669	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4733732	chr8:130738457	T/C	0.835	Height	0.20	-0.044	0.0052	2.85E-17	133667	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs2062078	chr8:130734461	T/G	0.835	Height	0.20	-0.043	0.0051	3.89E-17	133605	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs3886938	chr8:130737546	G/T	0.835	Height	0.20	-0.043	0.0051	3.89E-17	133628	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs7815955**	**chr8:130719567**	**T/A**	**0.845**	**Height**	**NA**	**NA**	**NA**	**7.95E-17**	**183727**	**NA**	**NA**	**20881960**
rs7833174	**chr8:130718772**	**C/T**	**rs4733724**	**chr8:130723728**	**G/A**	**0.845**	**Height**	**NA**	**NA**	**NA**	**9.24E-17**	**183727**	**NA**	**NA**	**20881960**
rs7833174	chr8:130718772	C/T	rs6985118	chr8:130736929	T/A	0.835	Height	0.21	-0.043	0.0052	2.44E-16	131884	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs4130415**	**chr8:130718712**	**C/T**	**1**	**Height**	**NA**	**NA**	**NA**	**2.54E-16**	**183727**	**NA**	**NA**	**20881960**
rs7833174	**chr8:130718772**	**C/T**	**rs7816342**	**chr8:130719623**	**A/G**	**1**	**Height**	**NA**	**NA**	**NA**	**1.41E-15**	**183727**	**NA**	**NA**	**20881960**
rs7833174	**chr8:130718772**	**C/T**	**rs7833174**	**chr8:130718772**	**C/T**	**1**	**Height**	**NA**	**NA**	**NA**	**1.64E-15**	**183727**	**NA**	**NA**	**20881960**
rs7833174	chr8:130718772	C/T	rs6470763	chr8:130720646	C/G	0.737	Height	NA	NA	NA	1.64E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6470765	chr8:130736697	C/A	0.835	Height	NA	NA	NA	1.90E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6986256	chr8:130728361	A/T	0.835	Height	NA	NA	NA	2.20E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs3886937	chr8:130737391	C/T	0.835	Height	NA	NA	NA	2.94E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs4733732	chr8:130738457	T/C	0.835	Height	NA	NA	NA	2.94E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs1074286	chr8:130737601	T/C	0.835	Height	NA	NA	NA	4.55E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs2062078	chr8:130734461	T/G	0.835	Height	NA	NA	NA	5.26E-15	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs3886938	chr8:130737546	G/T	0.835	Height	NA	NA	NA	5.26E-15	183727	NA	NA	20881960

rs7833174	chr8:130718772	C/T	rs4559213	chr8:130753742	C/T	0.71	Height	0.18	-0.055	0.0070	8.60E-15	73853	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs4633026	chr8:130752408	C/T	0.71	Height	0.18	-0.055	0.0071	1.00E-14	73853	79	Z-score	25282103
rs7833174	chr8:130718772	C/T	rs6985118	chr8:130736929	T/A	0.835	Height	NA	NA	NA	1.66E-14	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs7839339	chr8:130743547	A/T	0.71	Height	0.18	-0.041	0.0056	1.14E-13	133666	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4733737	chr8:130754719	T/C	0.71	Height	0.18	-0.041	0.0056	1.14E-13	133678	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4236748	chr8:130754887	T/G	0.71	Height	0.18	-0.041	0.0056	1.14E-13	133678	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4128895	chr8:130755205	C/T	0.705	Height	0.18	-0.041	0.0056	1.14E-13	133678	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470768	chr8:130739528	A/G	0.71	Height	0.18	-0.041	0.0056	2.35E-13	133677	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs7011557	chr8:130740135	T/G	0.71	Height	0.18	-0.041	0.0056	2.35E-13	133677	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs7012249	chr8:130740522	A/G	0.71	Height	0.18	-0.041	0.0056	2.35E-13	133676	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6994279	chr8:130740650	C/T	0.71	Height	0.18	-0.041	0.0056	2.35E-13	133676	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6998296	chr8:130740779	C/T	0.71	Height	0.18	-0.041	0.0056	2.35E-13	133677	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs1989396	chr8:130756531	A/G	0.71	Height	0.18	-0.041	0.0056	2.35E-13	133607	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470778	chr8:130759579	T/C	0.71	Height	0.18	-0.040	0.0055	2.71E-13	133621	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470766	chr8:130736854	G/A	0.706	Height	0.18	-0.041	0.0056	2.96E-13	133693	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4733737	chr8:130754719	T/C	0.71	Height	NA	NA	NA	6.92E-12	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs7839339	chr8:130743547	A/T	0.71	Height	NA	NA	NA	7.78E-12	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6470766	chr8:130736854	G/A	0.706	Height	NA	NA	NA	7.78E-12	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6470768	chr8:130739528	A/G	0.71	Height	NA	NA	NA	1.10E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs7011557	chr8:130740135	T/G	0.71	Height	NA	NA	NA	1.10E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs4236748	chr8:130754887	T/G	0.71	Height	NA	NA	NA	1.10E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs4128895	chr8:130755205	C/T	0.705	Height	NA	NA	NA	1.24E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs7012249	chr8:130740522	A/G	0.71	Height	NA	NA	NA	1.39E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs1989396	chr8:130756531	A/G	0.71	Height	NA	NA	NA	1.39E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6994279	chr8:130740650	C/T	0.71	Height	NA	NA	NA	1.56E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6998296	chr8:130740779	C/T	0.71	Height	NA	NA	NA	1.56E-11	183727	NA	NA	20881960
rs7833174	chr8:130718772	C/T	rs6470778	chr8:130759579	T/C	0.71	Height	NA	NA	NA	1.75E-11	183727	NA	NA	20881960
rs7833174	**chr8:130718772**	**C/T**	**rs4733724**	**chr8:130723728**	**G/A**	**0.845**	**Height in females**	**0.19**	**-0.048**	**0.0073**	**5.68E-11**	**73124**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height in females**	**0.19**	**-0.048**	**0.0073**	**7.47E-11**	**73124**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs4130415**	**chr8:130718712**	**C/T**	**1**	**Height in females**	**0.19**	**-0.047**	**0.0073**	**8.96E-11**	**73124**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs7815955**	**chr8:130719567**	**T/A**	**0.845**	**Height in females**	**0.19**	**-0.047**	**0.0073**	**8.96E-11**	**73124**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs6470765	chr8:130736697	C/A	0.835	Height in females	0.20	-0.045	0.0070	9.06E-11	73054	46	Z-score	23754948

rs7833174	chr8:130718772	C/T	rs3886938	chr8:130737546	G/T	0.835	Height in females	0.20	-0.044	0.0070	1.93E-10	73100	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs2062078	chr8:130734461	T/G	0.835	Height in females	0.20	-0.044	0.0070	2.11E-10	73082	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4733732	chr8:130738457	T/C	0.835	Height in females	0.20	-0.045	0.0071	2.82E-10	73122	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6986256	chr8:130728361	A/T	0.835	Height in females	0.20	-0.045	0.0071	3.09E-10	73123	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs3886937	chr8:130737391	C/T	0.835	Height in females	0.20	-0.045	0.0071	3.09E-10	73124	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs1074286	chr8:130737601	T/C	0.835	Height in females	0.20	-0.045	0.0071	3.09E-10	73124	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470763	chr8:130720646	C/G	0.737	Height in females	0.18	-0.046	0.0074	4.09E-10	73129	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs7833174**	**chr8:130718772**	**C/T**	**1**	**Height in females**	**0.20**	**-0.043**	**0.0070**	**6.38E-10**	**73124**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs7816342**	**chr8:130719623**	**A/G**	**1**	**Height in females**	**0.20**	**-0.043**	**0.0070**	**6.38E-10**	**73124**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs4633026	chr8:130752408	C/T	0.71	Height	NA	-0.050	0.0081	9.63E-10	57807	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4559213	chr8:130753742	C/T	0.71	Height	NA	-0.050	0.0081	9.63E-10	57807	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6985118	chr8:130736929	T/A	0.835	Height in females	0.21	-0.043	0.0071	9.91E-10	72209	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470778	chr8:130759579	T/C	0.71	Height in females	0.18	-0.045	0.0075	1.84E-09	73097	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs4130415**	**chr8:130718712**	**C/T**	**1**	**Height in males**	**0.19**	**-0.046**	**0.0077**	**1.95E-09**	**60547**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs7815955**	**chr8:130719567**	**T/A**	**0.845**	**Height in males**	**0.19**	**-0.046**	**0.0077**	**2.11E-09**	**60549**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs4733737	chr8:130754719	T/C	0.71	Height in females	0.18	-0.046	0.0076	2.12E-09	73126	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4236748	chr8:130754887	T/G	0.71	Height in females	0.18	-0.046	0.0076	2.30E-09	73126	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs7839339	chr8:130743547	A/T	0.71	Height in females	0.18	-0.046	0.0076	2.70E-09	73118	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4128895	chr8:130755205	C/T	0.705	Height in females	0.18	-0.046	0.0076	2.70E-09	73126	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Height in males**	**0.19**	**-0.046**	**0.0077**	**2.90E-09**	**60549**	**46**	**Z-score**	**23754948**
rs7833174	**chr8:130718772**	**C/T**	**rs4733724**	**chr8:130723728**	**G/A**	**0.845**	**Height in males**	**0.19**	**-0.046**	**0.0077**	**3.14E-09**	**60549**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs7011557	chr8:130740135	T/G	0.71	Height in females	0.18	-0.045	0.0076	4.01E-09	73124	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs1989396	chr8:130756531	A/G	0.71	Height in females	0.18	-0.045	0.0076	4.01E-09	73088	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470766	chr8:130736854	G/A	0.706	Height in females	0.18	-0.045	0.0076	4.01E-09	73136	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470768	chr8:130739528	A/G	0.71	Height in females	0.18	-0.045	0.0076	4.34E-09	73125	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs7816342**	**chr8:130719623**	**A/G**	**1**	**Height in males**	**0.20**	**-0.044**	**0.0075**	**4.61E-09**	**60545**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs7012249	chr8:130740522	A/G	0.71	Height in females	0.18	-0.045	0.0076	4.70E-09	73124	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6994279	chr8:130740650	C/T	0.71	Height in females	0.18	-0.045	0.0076	4.70E-09	73124	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6998296	chr8:130740779	C/T	0.71	Height in females	0.18	-0.045	0.0076	5.08E-09	73124	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs7833174**	**chr8:130718772**	**C/T**	**1**	**Height in males**	**0.20**	**-0.044**	**0.0075**	**5.42E-09**	**60544**	**46**	**Z-score**	**23754948**
rs7833174	chr8:130718772	C/T	rs6470763	chr8:130720646	C/G	0.737	Height in males	0.18	-0.045	0.0078	8.28E-09	60554	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6986256	chr8:130728361	A/T	0.835	Height in males	0.20	-0.042	0.0075	1.91E-08	60545	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs2062078	chr8:130734461	T/G	0.835	Height in males	0.20	-0.042	0.0075	2.06E-08	60523	46	Z-score	23754948

rs7833174	chr8:130718772	C/T	rs4733732	chr8:130738457	T/C	0.835	Height in males	0.20	-0.042	0.0075	2.06E-08	60545	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs1074286	chr8:130737601	T/C	0.835	Height in males	0.20	-0.042	0.0075	2.23E-08	60545	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs3886937	chr8:130737391	C/T	0.835	Height in males	0.20	-0.042	0.0075	2.40E-08	60545	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs3886938	chr8:130737546	G/T	0.835	Height in males	0.20	-0.042	0.0075	2.40E-08	60528	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470765	chr8:130736697	C/A	0.835	Height in males	0.20	-0.042	0.0075	2.59E-08	60495	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6985118	chr8:130736929	T/A	0.835	Height in males	0.21	-0.042	0.0076	4.14E-08	59676	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4633026	chr8:130752408	C/T	0.71	Height in females	NA	-0.061	0.0120	2.00E-07	28350	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs4559213	chr8:130753742	C/T	0.71	Height in females	NA	-0.061	0.0120	2.00E-07	28350	46	Z-score	23754948
rs7833174	**chr8:130718772**	**C/T**	**rs6470764**	**chr8:130725665**	**T/C**	**0.845**	**Infant length**	**0.20**	**0.054**	**0.0110**	**1.00E-06**	**NA**	**NA**	**unit decrease**	**25281659**
rs7833174	chr8:130718772	C/T	rs4733737	chr8:130754719	T/C	0.71	Height in males	0.18	-0.036	0.0082	8.20E-06	60552	46	Z-score	23754948
rs7833174	chr8:130718772	C/T	rs6470768	chr8:130739528	A/G	0.71	Height in males	0.18	-0.036	0.0082	9.19E-06	60552	46	Z-score	23754948

Bolded lines indicate variants associated with chronic back pain in the discovery stage meta-analysis that were also associated with other phenotypes
Chr:pos=chromosome:position, EAF=effect allele frequency, SE=standard error, Het.= heterogeneity
*Variants associated with back pain at suggestive or genome-wide significance level ($p<5.0x10^{-7}$) in the discovery stage, which achieved genome-wide significance ($p<5.0x10^{-8}$) in the joint meta-analysis (discovery-replication), and which were also associated with any other phenotypes as identified by PhenoScanner, download date 11/22/2017. Associations with other phenotypes listed in this table are limited to those with $p< 5 \times 10^{-5}$. All results are for Europeans.

Supplemental Table S6. Variants in *CCDC26*/*GSDMC* associated with chronic back pain at the suggestive significance level ($p<5 \times 10^{-7}$) in the discovery stage meta-analysis, and associations with lumbar discectomy for sciatica in a prior GWAS*

rsID	chr:pos (hg19)	Effect Allele	EAF	Beta reported in Bjornsdottir et al.[1]	Beta for effect allele in *CCDC26*/*GSDMC* (associated with CBP in the current study)	P-value for association with lumbar discectomy for sciatica reported in Bjornsdottir et al.[1]
rs6651255	chr8:129711546	C	0.23	0.81	1.23	5.61E-12
rs7833174	chr8:129706526	C	0.23	0.81	1.23	5.97E-12
rs4130415	chr8:129706466	C	0.23	0.81	1.23	5.99E-12
rs7816342	chr8:129707377	A	0.23	0.82	1.23	7.81E-12
rs7815955	chr8:129707321	T	0.22	0.82	1.23	3.64E-11
rs10956487	chr8:129705470	G	0.23	0.82	1.23	1.38E-11
rs4733724	chr8:129711482	G	0.22	0.82	1.23	3.24E-11
rs6470764	chr8:129713419	T	0.22	0.82	1.23	3.79E-11
rs7826493	chr8:129726726	G	0.22	0.82	1.23	3.48E-11

Chr:pos=chromosome:position, EAF=effect allele frequency
*Bjornsdottir, 2017[1]

Supplemental Table S7: Region-specific secondary analyses accounting for height, conducted in the UKB interim data release sample*

Associations with CBP (for the CBP-associated lead SNPs in SOX5 and *CCDC26/GSDMC* from the discovery stage meta-analysis), with and without adjustment for height as a covariate

						Model 1			Model 2		
rsID	**location/gene**	**chr:pos (hg19)**	**Effect Allele**	**Other Allele**	**EAF**	**N**	**Beta**	**p-value**	**N**	**Beta**	**p-value**
rs12310519	intronic/*SOX5*	12:23975219	T	C	0.16	118108	0.076	1.32E-07	117917	1.11	7.2e-10
rs7833174	intergenic *CCDC26/GSDMC*	8:130718772	T	C	0.77	119007	0.060	2.71E-06	118815	1.10	8.4e-10

Associations with CBP (for the CBP-associated lead SNPs in SOX5 and *CCDC26/GSDMC* from region-specific analyses in UKB interim data release sample), with and without conditioning on the top height-associated variant in the region

						Model 1			Model 3			
rsID	**location/gene**	**chr:pos (hg19)**	**Effect Allele**	**Other Allele**	**EAF**	**N**	**Beta**	**p-value**	**N**	**Beta**	**p-value**	**conditional rsID[a]**
rs7134575	intronic/*SOX5*	12:23978200	A	G	0.13	118947	0.087	2.00E-08	117309	0.087	1.97E-08	rs1498873
rs7833174	intergenic/ *CCDC26/GSDMC*	8:130718772	C	T	0.23	119007	-0.060	2.71E-06	118674	-0.055	0.11	rs3886937

Associations with height (for the CBP-associated lead SNPs in SOX5 and *CCDC26/GSDMC* from region-specific analyses in UKB interim data release sample), with and without conditioning on the top CBP-associated variant in the region

					Model 4			Model 5			
rsID	**location/gene**	**chr:pos (hg19)**	**Effect Allele**	**Other Allele**	**EAF**	**N**	**Beta**	**p-value**	**N**	**Beta**	**p-value**	**conditional rsID[b]**
rs1498873	intronic/*SOX5*	12:24200700	T	G	0.22	118181	0.200	1.38E-10	117125	0.19	4.36E-10	rs7134575
rs3886937	intergenic/ *CCDC26/GSDMC*	8:130737391	C	T	0.20	119479	-0.373	6.79E-31	118482	-0.251	0.0030	rs7833174

UKB= UK biobank, CBP=chronic back pain, chr:pos=chromosome:position, EAF=effect allele frequency

*all results reflect analyses conducted in the UKB interim data release sample only

[a]conditional on the top height-associated SNP in the region

[a]conditional on the top CBP-associated SNP in the region

Model 1: CBP ~ SNP + age + sex + array + PC1 + … + PC10

Model 2: CBP ~ SNP + age + sex + + height+ array + PC1 + … + PC10

Model 3: CBP ~ SNP + age + sex + array + PC1 + … + PC10 (conditional on the top height-associated variant in the region)

Model 4: height ~ SNP + age + sex + array + PC1 + … + PC10

Model 5: height ~ SNP + age + sex + array + PC1 + … + PC10 (conditional on the top CBP-associated variant in the region

Supplemental Table S8. Genetic correlations between CBP and selected phenotypes of conceptual relevance to CBP, using cross-trait LD score regression*

Trait	PMID	r_g [a]	SE	z-score	p-value	observed h^2
Anthropometrics						
Waist circumference	**25673412**	**0.26**	**0.042**	**6.10**	**1.04E-09**	**0.12**
Hip circumference	**25673412**	**0.21**	**0.043**	**4.91**	**8.89E-07**	**0.13**
Obesity class 1	**23563607**	**0.23**	**0.047**	**4.82**	**1.44E-06**	**0.22**
Waist-to-hip ratio	**25673412**	**0.19**	**0.042**	**4.49**	**7.10E-06**	**0.11**
Obesity class 2	**23563607**	**0.26**	**0.059**	**4.33**	**1.46E-05**	**0.19**
Obesity class 3	**23563607**	**0.31**	**0.075**	**4.09**	**4.34E-05**	**0.13**
Body mass index	**20935630**	**0.17**	**0.045**	**3.90**	**9.63E-05**	**0.19**
Overweight	**23563607**	**0.18**	**0.048**	**3.72**	**0.0002**	**0.11**
Extreme bmi	**23563607**	**0.20**	**0.074**	**2.64**	**0.008**	**0.69**
Height_2010	20881960	0.07	0.041	1.66	0.10	0.29
Extreme height	23563607	0.09	0.059	1.59	0.11	1.27
Extreme waist-to-hip ratio	23563607	0.06	0.095	0.66	0.51	0.36
Depression-related phenotypes						
Depressive symptoms	**27089181**	**0.52**	**0.060**	**8.66**	**4.54E-18**	**0.05**
Self-reported depression	**UK biobank**	**0.46**	**0.072**	**6.43**	**1.27E-10**	**0.02**
Major depressive disorder	**22472876**	**0.48**	**0.089**	**5.37**	**7.67E-08**	**0.17**
Arthritis-related phenotypes						
Self-reported osteoarthritis	**UK biobank**	**0.63**	**0.066**	**9.62**	**6.82E-22**	**0.02**
Osteoarthritis of the knee (using ICD10 diagnostic codes)	**UK biobank**	**0.49**	**0.085**	**5.75**	**8.67E-09**	**0.01**
Osteoarthritis of the hip (using ICD10 diagnostic codes)	UK biobank	0.17	0.095	1.77	0.08	0.01
Self-reported arthritis (not otherwise specified)	UK biobank	0.58	0.316	1.84	0.07	0.00
Rheumatoid arthritis	24390342	0.11	0.057	1.96	0.0497	0.16

Nominally significant genetic correlations **in bold**

*All GWAS results in participants of European ancestry; SNPs from the MHC (chr6 26M~34M) region was removed for all traits

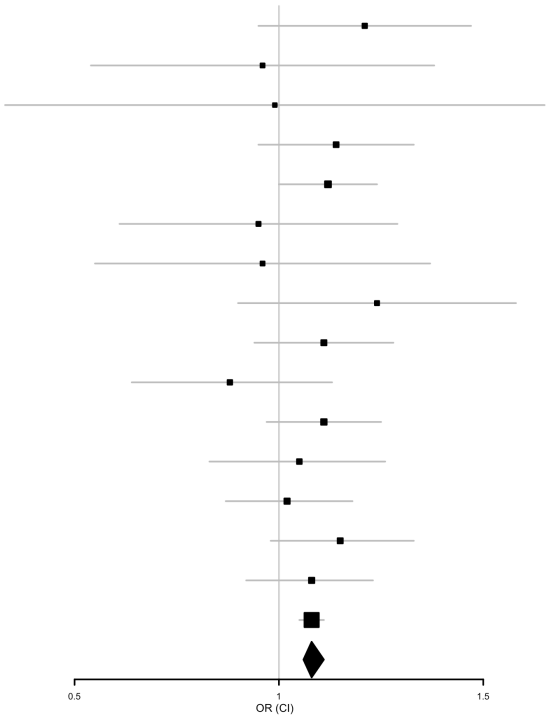
[a]genetic correlations with chronic back pain (results from the discovery stage meta-analysis)

1. Bjornsdottir G, Benonisdottir S, Sveinbjornsson G, et al. Sequence variant at 8q24.21 associates with sciatica caused by lumbar disc herniation. *Nat Commun* 2017;8:14265. doi: 10.1038/ncomms14265

Supplemental Figures

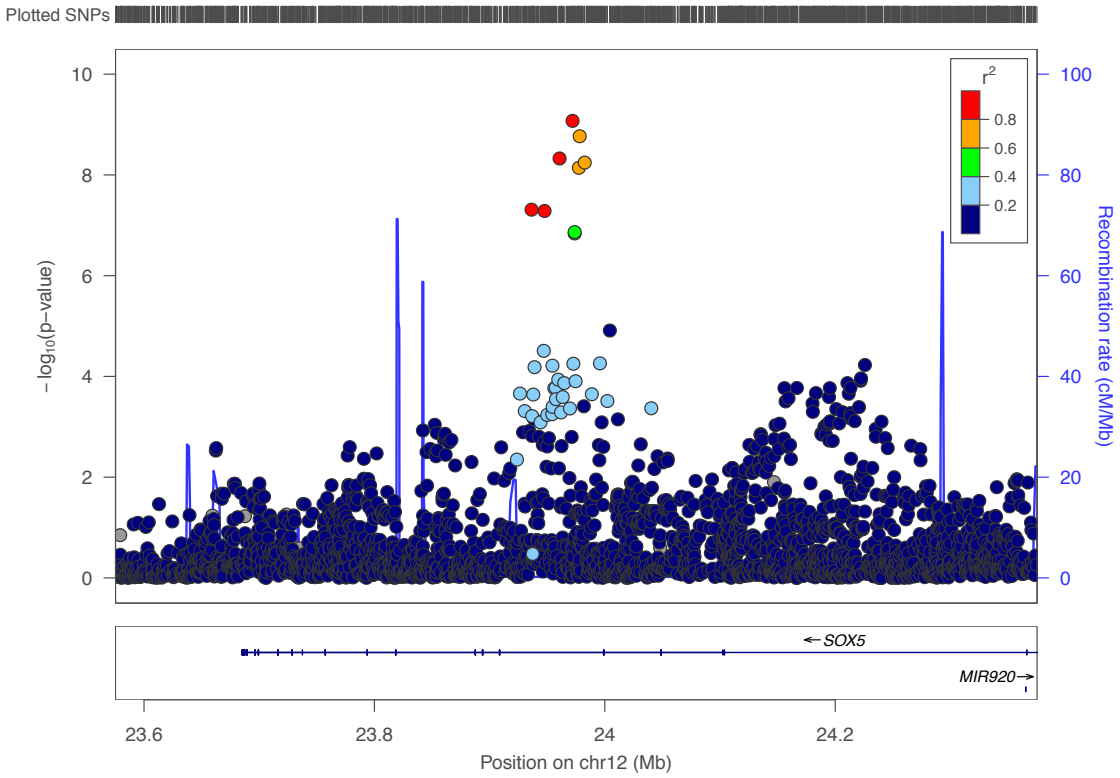
Supplemental Figure S1. Forest plot of rs12310519 (*SOX5*, chr12) association with chronic back pain in the meta-analysis (discovery)

Cohort	OR[CI]	P
CHS	1.21[0.95,1.47]	0.146
Dalmatians-Korcula	0.96[0.54,1.38]	0.856
Dalmatians-Vis	0.99[0.33,1.65]	0.984
FHS	1.14[0.95,1.33]	0.184
GenScot	1.12[1,1.24]	0.0546
JoCo	0.95[0.61,1.29]	0.772
Mr.OS-GBG	0.96[0.55,1.37]	0.847
Mr.OS-Malmo	1.24[0.9,1.58]	0.216
Mr.OS-US	1.11[0.94,1.28]	0.221
OAI	0.88[0.64,1.13]	0.33
RS-1	1.11[0.97,1.25]	0.138
RS-2	1.05[0.83,1.26]	0.674
RS-3	1.02[0.87,1.18]	0.758
SOF	1.15[0.98,1.33]	0.11
TwinsUK	1.08[0.92,1.23]	0.356
UKB	1.08[1.05,1.11]	1.32e-07
Summary	**1.08[1.06,1.11]**	**7.18e-10**



rs115392701 has merged into rs12310519. Point sizes are proportional to inverse variance weights. OR=odds ratio, CI=95% confidence interval, CHS=Cardiovascular Health Study, FHS=Framingham Heart Study, GenScot= Generation Scotland, JoCo= Johnston County Osteoarthritis Project, MrOs-GBG= Mr. Os Sweden (Gothenburg), MrOs-Malmo= Mr. Os Sweden (Malmo), MrOs-US= Mr. Os United States, OAI=Osteoarthritis Initiative, RS=Rotterdam Study, SOF=Study of Osteoporotic Fractures, UK=United Kingdom, UKB=UK biobank (interim data release).

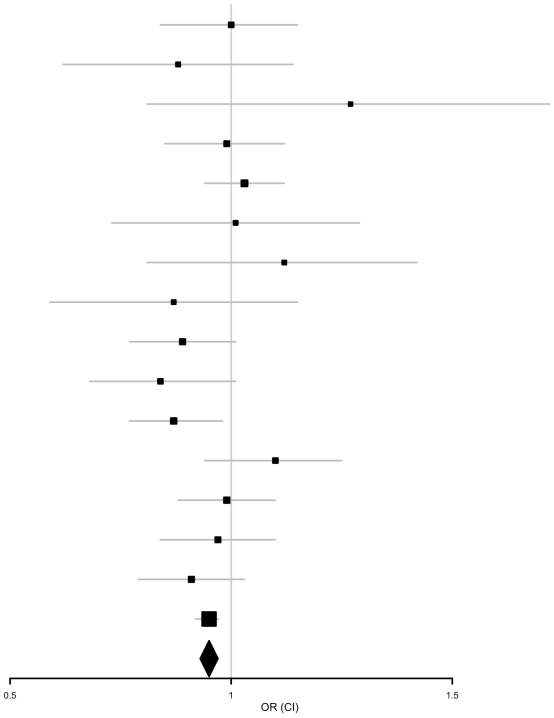
Supplemental Figure S2. Regional association plot of *SOX5* locus



Association p-values are plotted against genomic location. Negative log of the association p-value is represented on the left-hand y-axis, and recombination rate is displayed on the right-hand y-axis. Genomic location is shown on the x-axis, chr:pos. indicated are GRCh38/hg38. RefSeq genes are indicated in the bottom panel. Linkage disequilibrium r^2 relative to the index single nucleotide variant rs115392701 is shown using the colors in the figure legend (rs115392701 has merged into rs12310519).

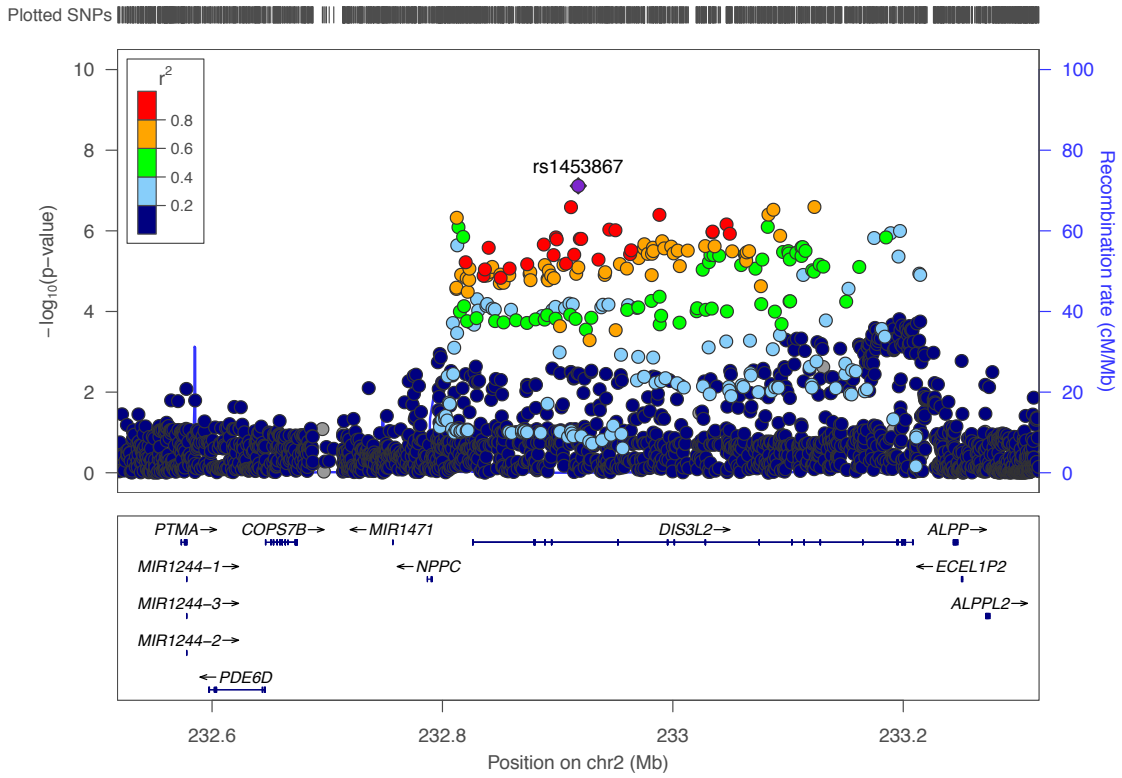
Supplemental Figure S3. Forest plot of rs1453867 (*DIS3L2,* chr2) association with chronic back pain in the meta-analysis (discovery)

Cohort	OR[CI]	P
CHS	1[0.84,1.15]	0.946
Dalmatians-Korcula	0.88[0.62,1.14]	0.323
Dalmatians-Vis	1.27[0.81,1.72]	0.307
FHS	0.99[0.85,1.12]	0.855
GenScot	1.03[0.94,1.12]	0.53
JoCo	1.01[0.73,1.29]	0.932
Mr.OS-GBG	1.12[0.81,1.42]	0.486
Mr.OS-Malmo	0.87[0.59,1.15]	0.327
Mr.OS-US	0.89[0.77,1.01]	0.0565
OAI	0.84[0.68,1.01]	0.0418
RS-1	0.87[0.77,0.98]	0.0111
RS-2	1.1[0.94,1.25]	0.232
RS-3	0.99[0.88,1.1]	0.822
SOF	0.97[0.84,1.1]	0.66
TwinsUK	0.91[0.79,1.03]	0.124
UKB	0.95[0.92,0.97]	8.74e-07
Summary	**0.95[0.93,0.97]**	**7.66e-08**



Point sizes are proportional to inverse variance weights. OR=odds ratio, CI=95% confidence interval, CHS=Cardiovascular Health Study, FHS=Framingham Heart Study, GenScot= Generation Scotland, JoCo= Johnston County Osteoarthritis Project, MrOs-GBG= Mr. Os Sweden (Gothenburg), MrOs-Malmo= Mr. Os Sweden (Malmo), MrOs-US= Mr. Os United States, OAI=Osteoarthritis Initiative, RS=Rotterdam Study, SOF=Study of Osteoporotic Fractures, UK=United Kingdom, UKB=UK biobank (interim data release).

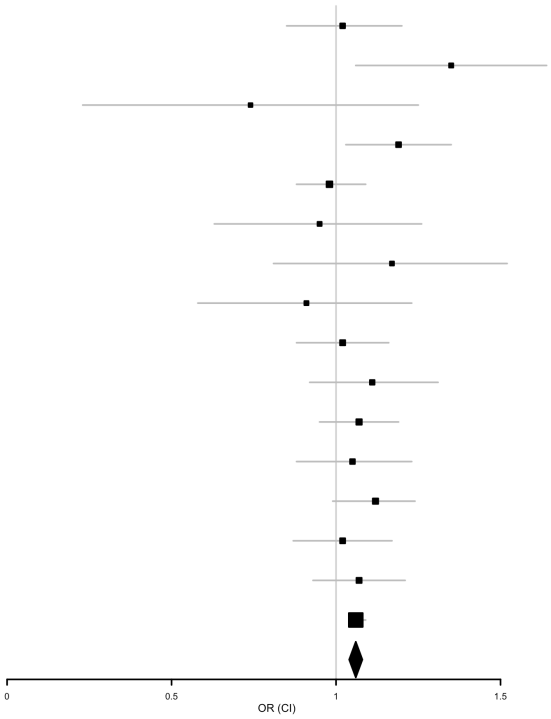
Supplemental Figure S4 Regional association plot of *DIS3L2* locus



Association p-values are plotted against genomic location. Negative log of the association p-value is represented on the left-hand y-axis, and recombination rate is displayed on the right-hand y-axis. Genomic location is shown on the x-axis, chr:pos. indicated are GRCh38/hg38. RefSeq genes are indicated in the bottom panel. Linkage disequilibrium r^2 relative to the index single nucleotide variant rs1453867 is shown using the colors in the figure legend.

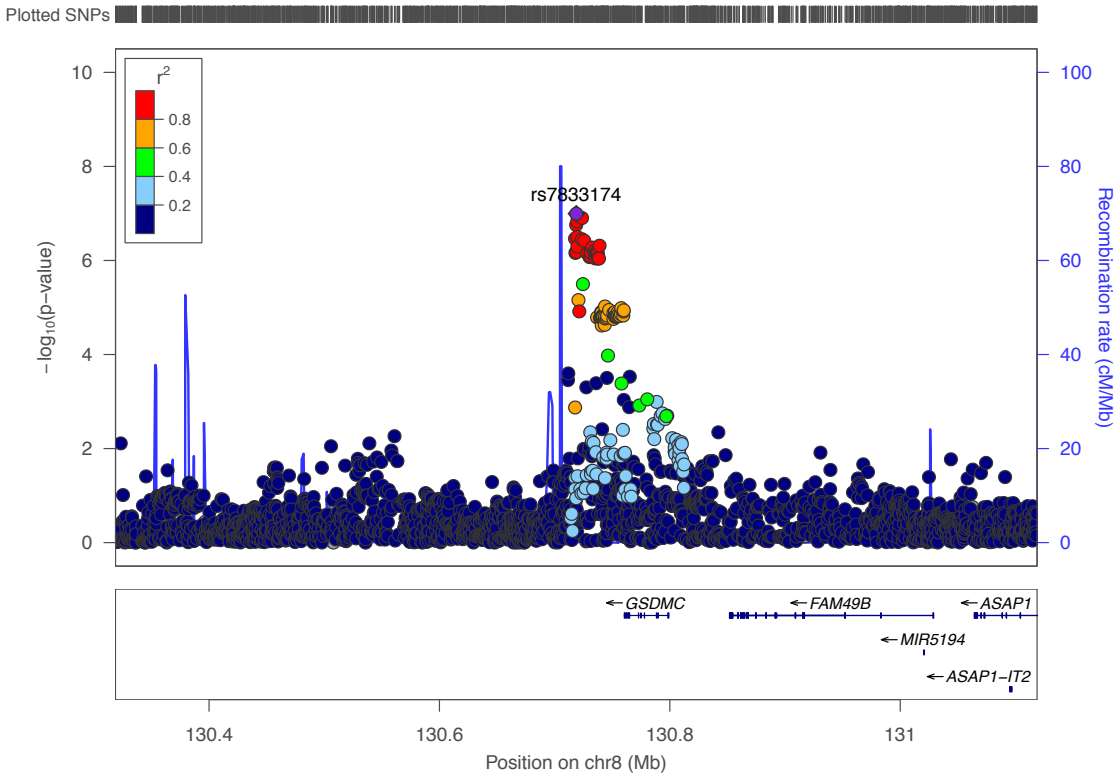
Supplemental Figure S5. Forest plot of rs7833174 (*CCDC26/GSDMC,* chr8) association with chronic back pain in the meta-analysis (discovery)

Cohort	OR[CI]	P
CHS	1.02[0.85,1.2]	0.796
Dalmatians-Korcula	1.35[1.06,1.64]	0.0427
Dalmatians-Vis	0.74[0.23,1.25]	0.253
FHS	1.19[1.03,1.35]	0.0288
GenScot	0.98[0.88,1.09]	0.77
JoCo	0.95[0.63,1.26]	0.746
Mr.OS-GBG	1.17[0.81,1.52]	0.393
Mr.OS-Malmo	0.91[0.58,1.23]	0.559
Mr.OS-US	1.02[0.88,1.16]	0.752
OAI	1.11[0.92,1.31]	0.291
RS-1	1.07[0.95,1.19]	0.274
RS-2	1.05[0.88,1.23]	0.562
RS-3	1.12[0.99,1.24]	0.0776
SOF	1.02[0.87,1.17]	0.79
TwinsUK	1.07[0.93,1.21]	0.343
UKB	1.06[1.04,1.09]	2.7e-06
Summary	**1.06[1.04,1.08]**	**1.01e-07**



Point sizes are proportional to inverse variance weights. OR=odds ratio, CI=95% confidence interval, CHS=Cardiovascular Health Study, FHS=Framingham Heart Study, GenScot= Generation Scotland, JoCo= Johnston County Osteoarthritis Project, MrOs-GBG= Mr. Os Sweden (Gothenburg), MrOs-Malmo= Mr. Os Sweden (Malmo), MrOs-US= Mr. Os United States, OAI=Osteoarthritis Initiative, RS=Rotterdam Study, SOF=Study of Osteoporotic Fractures, UK=United Kingdom, UKB=UK biobank (interim data release).

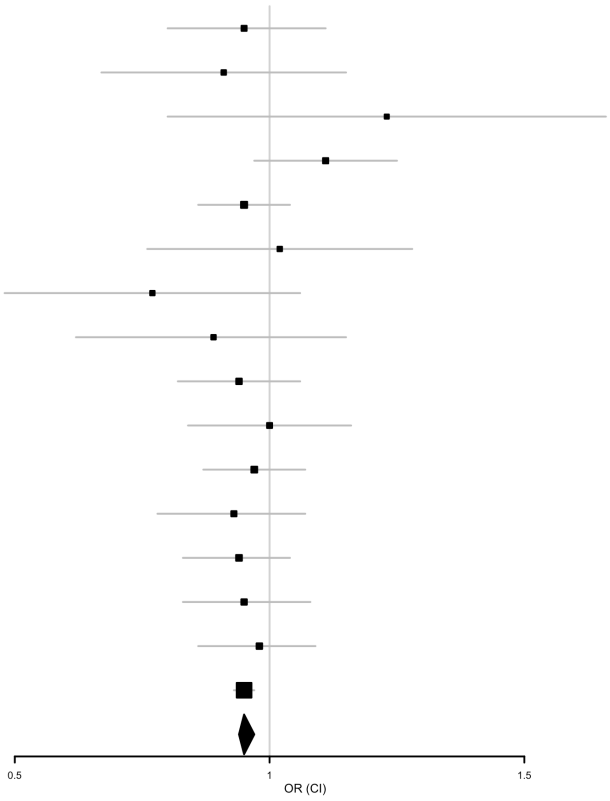
Supplemental Figure S6 Regional association plot of *CCDC26/GSDMC* locus



Association p-values are plotted against genomic location. Negative log of the association p-value is represented on the left-hand y-axis, and recombination rate is displayed on the right-hand y-axis. Genomic location is shown on the x-axis, chr:pos. indicated are GRCh38/hg38. RefSeq genes are indicated in the bottom panel. Linkage disequilibrium r^2 relative to the index single nucleotide variant rs7833174 is shown using the colors in the figure legend.

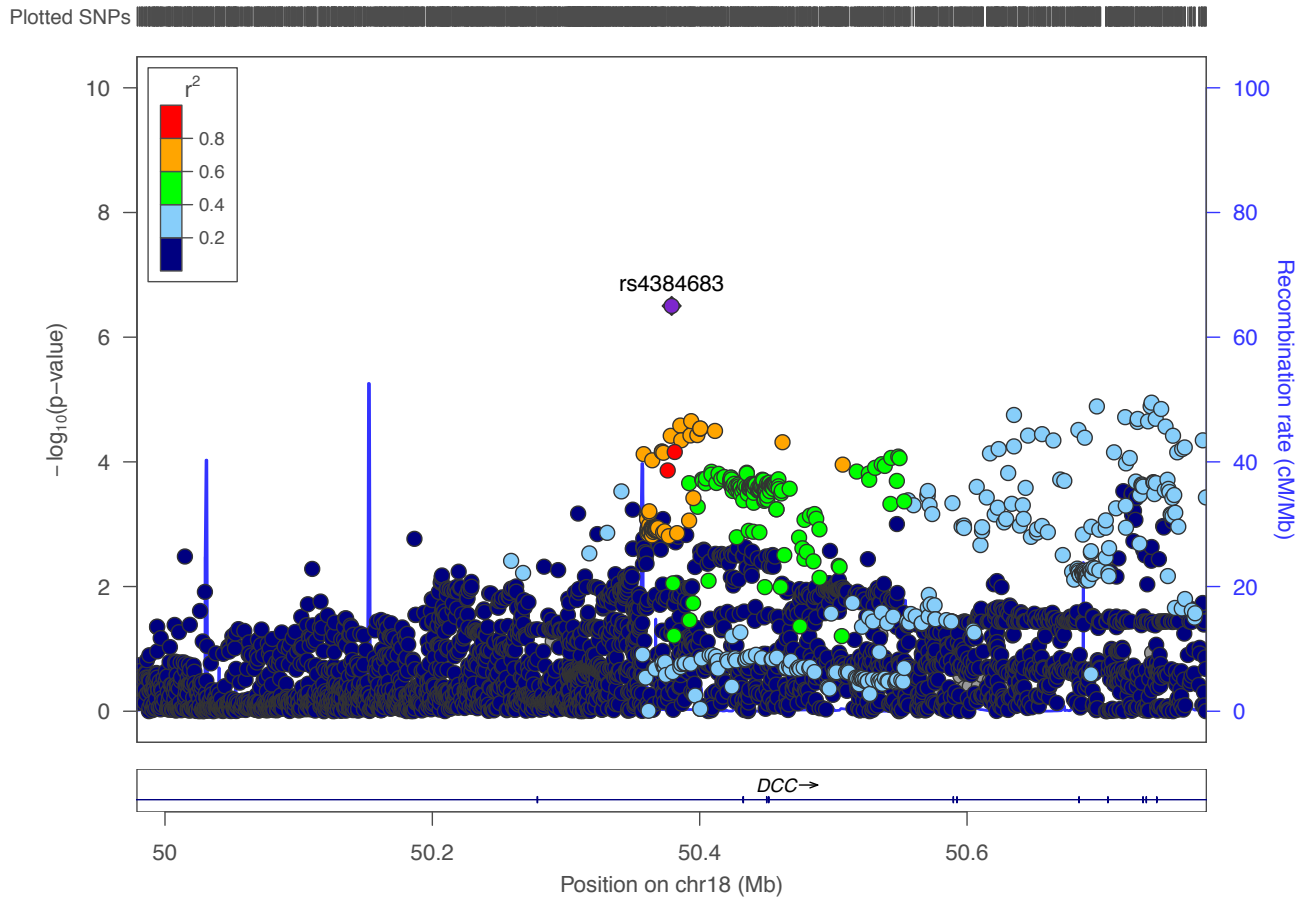
Supplemental Figure S7. Forest plot of rs4384683 (*DCC,* chr18) association with chronic back pain in the meta-analysis (discovery)

Cohort	OR[CI]	P
CHS	0.95[0.8,1.11]	0.548
Dalmatians-Korcula	0.91[0.67,1.15]	0.448
Dalmatians-Vis	1.23[0.8,1.66]	0.351
FHS	1.11[0.97,1.25]	0.155
GenScot	0.95[0.86,1.04]	0.218
JoCo	1.02[0.76,1.28]	0.884
Mr.OS-GBG	0.77[0.48,1.06]	0.0808
Mr.OS-Malmo	0.89[0.62,1.15]	0.378
Mr.OS-US	0.94[0.82,1.06]	0.341
OAI	1[0.84,1.16]	0.968
RS-1	0.97[0.87,1.07]	0.618
RS-2	0.93[0.78,1.07]	0.318
RS-3	0.94[0.83,1.04]	0.212
SOF	0.95[0.83,1.08]	0.448
TwinsUK	0.98[0.86,1.09]	0.701
UKB	0.95[0.93,0.97]	2.67e-06
Summary	**0.95[0.94,0.97]**	**3.15e-07**



Point sizes are proportional to inverse variance weights. OR=odds ratio, CI=95% confidence interval, CHS=Cardiovascular Health Study, FHS=Framingham Heart Study, GenScot= Generation Scotland, JoCo= Johnston County Osteoarthritis Project, MrOs-GBG= Mr. Os Sweden (Gothenburg), MrOs-Malmo= Mr. Os Sweden (Malmo), MrOs-US= Mr. Os United States, OAI=Osteoarthritis Initiative, RS=Rotterdam Study, SOF=Study of Osteoporotic Fractures, UK=United Kingdom, UKB=UK biobank (interim data release).

Supplemental Figure S8 Regional association plot of *DCC* locus



Association p-values are plotted against genomic location. Negative log of the association p-value is represented on the left-hand y-axis, and recombination rate is displayed on the right-hand y-axis. Genomic location is shown on the x-axis, chr:pos. indicated are GRCh38/hg38. RefSeq genes are indicated in the bottom panel. Linkage disequilibrium r^2 relative to the index single nucleotide variant rs4384683 is shown using the colors in the figure legend.

Supplemental Methods

Cohort Descriptions and Cohort-Specific Phenotype Descriptions

See Supplemental Table S2 for further details of chronic back pain phenotype definitions for each cohort.

Cardiovascular Health Study (CHS)- CHS is a community-based observational study of risk factors for cardiovascular disease in ambulatory adults 65 years or older.[1] Participants were recruited from Medicare enrollment lists in four U.S. communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Starting in 1989, 5201 participants underwent extensive annual clinical examinations. An additional predominantly African-American cohort of 687 individuals was enrolled in 1992-1993. Study measures included traditional cardiovascular risk factors such as blood pressure and lipids as well as objective measures of subclinical disease, including echocardiography of the heart, carotid ultrasound, and cranial magnetic-resonance imaging. African-Americans were not included in the current study due to the meta-analysis' focus on individuals of European ancestry only. All participants gave informed consent to use genetic data for analyses. A variety of self-report measures were also collected. Back pain questions began during the 2nd examination, and included the question "In the past year, have you had pain in your back for more than half the days of any month?".

Framingham Heart Study (FHS)- FHS began in 1948 as a longitudinal population-based cohort study of the causes of heart disease.[2] The Original cohort was comprised of 5,209 men and women from the town of Framingham, Massachusetts. In 1971, 5,124 offspring of the original Framingham cohort and their spouses were entered in the Offspring cohort.[3] Examination 8 of the Framingham Offspring cohort study began in 2005 and concluded in 2008. Participants were asked "Have you had back pain in the past 12 months?", with response options including "no", "a few days", "some days", "most of the days", and "all days".

Generation Scotland (GS)- GS is a family-based genetic epidemiology study with genetic, sociodemographic, and clinical data from approximately 24,000 volunteers across Scotland aged 18–98 years.[4] Participants were recruited through a variety of methods from February 2006 to March 2011. Biological samples and anonymized data form a resource for research on the genetics of health, disease and quantitative traits of current and projected public health importance. A 'broad' form of consent was acquired from participants to use their data and samples for a wide range of medical research, including re-contact for the potential collection of other data or samples, or for participation in related studies.[4] Participants reporting any musculoskeletal pain were asked whether specific areas of pain or discomfort had been going on for more than 3 months. Participants specified 'yes' or 'no' for back pain of duration > 3 months.

Johnston County Osteoarthritis Project (JoCo)- JoCo is an ongoing, population-based prospective cohort begun in 1990 to fill knowledge gaps about prevalence, incidence, and progression of OA, and its risk factors, in Caucasian and African-American men and women in North Carolina.[5] Participants were recruited from six townships and surrounding rural areas, and eligible individuals completed two home interviews and clinic examinations. The sample has been followed approximately every 5 years since inception with repeated surveys, radiographic, and clinical assessments, and other diagnostic testing. Beginning in 2012, participants were asked a series of questions about areas of pain

experienced in the last 12 months, including middle back (thoracic) and/or lower back (L1 through S1) pain that they had experienced on most days of any one month in the last year. Those who reported pain in the middle back or lower back were then asked the number of months in the past year during which they had had pain in this location on most days of the month.

MrOs Sweden- MrOs Sweden is a population-based cohort study of community-living Swedish men aged 69–81, part of a multi-national collaboration including the MrOs US study and MrOs Hong Kong.[6] MrOs Sweden includes 3,014 men recruited from 3 study centers, including Gothenburg, Malmo, and Uppsala. Participants were randomly selected from the Swedish national population register. At the study baseline, participants answered a questionnaire including fracture history, lifestyle, and clinical symptoms.[6] Participants were asked "Have you had back pain in the past 12 months?". Response options included "no", "never", "rarely", "some of the time", "most of the time", and "all of the time". Only participants from the Gothenburg and Malmo sites who had available genetic and back pain data were included in the current study.

MrOs US (The Osteoporotic Fractures in Men) - MrOs US is a prospective, population-based cohort study of older men recruited from the geographic regions surrounding Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland, and San Diego. The study was designed to determine the extent to which fracture risk is related to bone mass and geometry, lifestyle, anthropometric, and neuromuscular measures, as well as to determine how fractures affect quality of life in older men.[7] MrOs US is part of a multi-national collaboration including the MrOs Sweden study and MrOs Hong Kong. At baseline, MrOs participants completed questionnaires regarding medical history, medications, physical activity, diet, alcohol intake, and cigarette smoking. Objective measures of anthropometric, neuromuscular, vision, strength, and cognitive variables were also obtained. MrOs participants were asked the question "During the past 12 months have you experienced any back pain?", with response options including "no", "never", "rarely", "some of the time", "most of the time", and "all of the time".

Osteoarthritis Initiative (OAI)- The OAI is a multicenter, longitudinal, prospective observational study of knee osteoarthritis. It is a public-private partnership between the NIH and private industry that seeks to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression.[8] OAI includes 4,796 participants age 45-79 recruited from clinical centers in Maryland, Ohio, Pennsylvania, and Rhode Island. Participants completed serial assessments and examinations annually since study inception, with a smaller subset seen more frequently for analysis of change over shorter intervals. At each annual assessment, participants were asked the question ""How often were you bothered by back pain in the past 30 days?", with response options including "no", "rarely", "some of the time", "most of the time", and "all of the time".

Rotterdam Study (RS)- Rotterdam Study is a prospective population-based cohort study on the determinants of chronic disabling diseases, ongoing since 1990.[9] The first Rotterdam cohort (RS-1) included 7,983 persons ≥55 years of age living in the Ommoord district in the city of Rotterdam, in the Netherlands. In 2000, 3011 additional participants ≥55 years of age were added to the cohort (RS-2). In 2006, a further extension of the cohort was initiated in which 3,932 subjects living in the Ommoord district were included, aged 45–54 years (RS-3)[9]. Back pain was assessed at several of the RS examinations. In RS-1, back pain was assessed with the question, "Have you had pain in the low back in the last month?", with further questions as to the duration of pain in the low back. In RS-2 and RS-3, back pain was

assessed with the question, “Do you have pain or stiffness in your back?”, with further questions as to the duration of pain in the back.

Study of Osteoporotic Fractures (SOF)- SOF is a community-based multi-center prospective observational study of a cohort of 10,366 women ≥55 years of age who were recruited from four metropolitan areas in the US: Minneapolis, Pittsburgh, Portland, and Baltimore. The primary purpose of SOF was to describe the risk factors for osteoporotic fractures in women.[10] Participants were initially recruited from mailings to age-eligible women identified from community-based listings, such as memberships of large health maintenance organizations. SOF is funded by NIA. SOF participants were asked the question “During the past 12 months have you experienced any back pain?”, with response options including “no”, ”never”, ”rarely”, ”some of the time”, “most of the time”, and ”all of the time, constantly”.

10,001 Dalmatians- This study aims to identify genetic and environmental determinants of health and disease in genetic-isolate island populations from Dalmatia, Croatia. The Vis and Korcula cohorts included unselected Croatians who were recruited from villages on the Dalmatian islands of Vis and Korcula. Participants completed questionnaires regarding lifestyle and environmental exposures, biochemical and physiological measurements, and genotyping. Participants were asked the questions “Have you ever had an episode of chronic LBP that lasted for over 3 months? ” and “Do you have low back pain at the moment?”, and participants who responded yes to both questions were considered to have chronic back pain of duration > 3 months.

TwinsUK- TwinsUK is a British adult twin registry originally assembled to study the heritability and genetics of age-related diseases[11]. The registry was started in 1992 and consists of approximately 13,000 monozygotic and dizygotic adult Northern European twins aged 16 to 85 years from all over the UK, as well as some parents and siblings. Individuals were recruited from the general population through national media campaigns throughout the UK. TwinsUK is generally representative of singletons and the United Kingdom population. TwinsUK participants were asked the question “In the past 3 months, have you had pain in your back on most days?”. Further questions inquired about back pain in specific locations while referencing a mannekin showing locations of the pain in the thoracic and lumbar regions, and whether any such pain had persisted for at least the past 3 months.

UK Biobank (UKB)- The UK (United Kingdom) Biobank is a population-based prospective study involving more than 500,000 participants, established to allow detailed studies of the genetic and nongenetic determinants of the diseases of middle age and old age.[12] UKB aims to combine extensive assessment of exposures with comprehensive follow-up and characterization of many different diseases and health-related outcomes, as well as to promote innovative science by maximizing access to the resource. The study thus far has collected and continues to collect longitudinal data and extensive phenotypic and genotypic detail about its participants, including data from questionnaires, physical measures, diagnostic imaging, and genotyping. Participants reported locations (including back pain) where they had experienced pain in the last month that interfered with usual activities. Participants reporting back pain specified ‘yes’ or ‘no’ for back pain of duration > 3 months.

Statistical Analysis (Detailed Description)

Discovery meta-analysis included adults of European ancestry from these 16 population- and community-based cohorts listed above. Replication was conducted in an independent sample of UKB European

ancestry participants not included in the UKB interim data release that was used for discovery, and a joint (discovery-replication) meta-analysis was performed

For the discovery stage, we conducted genome-wide association analyses in each of the 16 cohorts, and subsequent meta-analysis of autosomal SNPs to combine results from all cohorts. Each site conducted GWAS using logistic regression models with additive genetic effects to test for associations between each variant and chronic back pain as a binary trait. These models adjusted for age, sex, and study-specific covariates such as study site, clinic site, or array. (Supplemental Table S3) Each cohort evaluated population substructure and adjusted for principle components where indicated (Supplemental Table S3). Height and body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, were not included as covariates in site-specific GWAS, since these traits might lie along the causal pathway or (in the case of BMI) reflect a consequence of CBP. Harmonization and quality control for GWAS results from each cohort were conducted using the EasyQC software package in the R statistical environment (v3.2.2), using methods described previously.[13] After removal of SNPs with low minor allele frequencies (<0.005 for UKB, <0.03 for Vis, <0.01 for other cohorts) or imputation quality (<0.7 for UKB, <0.6 for other cohorts), deviation from Hardy-Weinberg equilibrium (p < 1 x 10-6), low number of cases (<15) or controls (<15), large absolute values of beta coefficients (≥10), and low minor allele count (≤10), call rates <0.95, the range of SNPs included in the meta-analysis was between 6,205,227 (Croatia-Vis) and 9,775,703 (MrOs-Gothenburg) (Supplemental Table S3). Fixed-effect inverse-variance weighted meta-analysis was performed using METAL (http://csg.sph.umich.edu/abecasis/metal/). Quality control and meta-analysis were conducted twice, independently of each other, by researchers at the University of Washington (MP and PS) and PainOmics (YA, LCK, and YT). The results from the two centers were compared to ensure accuracy. We used linkage disequilibrium (LD) score regression (LDsr) to examine potential confounding.[14] The genome-wide significance level was defined as $p<5\times10^{-8}$, and suggestive significance level was defined as $p<5\times10^{-7}$, after using the LDsr intercept as a correction factor. Q-Q and Manhattan plots were generated in R. Effect heterogenity across studies was quantified using the I^2 metric (range 0-100%).[15] Between-study heterogeneity was tested using the Cochran Q statistic which was considered significant at p<0.1. We used LocusZoom (http://csg.sph.umich.edu/locuszoom/) to evaluate regional association plots at regions of interest, and conducted Genome-Wide Complex Trait Analysis conditional and joint analyses (http://cnsgenomics.com/software/gcta/#About) for variants in each locus exceeding the suggestive significance level, conditional on the most significant variant at each locus.

The most highly associated at genome-wide significant loci were subjected to replication in the independent sample of UKB participants. Analysis in the independent sample used logistic regression with additive genetic effects, adjusting for age, sex, array, and 10 principal components (Supplemental Table S3); significant replication was defined using a Bonferroni-corrected threshold of p<0.05 divided by the number of genome-wide significant loci (0.05/1). The most highly-associated variants at loci with suggestive significance were selected for a joint (discovery-replication) meta-analysis using p<5×10–8 to define genome-wide significance.

For genome-wide significant variants and those in LD (r^2 >0.6) we examined previously reported GWAS associations with other phenotypes using PhenoScanner v1.1 (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner), and conducted functional annotation using FUMA (http://fuma.ctglab.nl). FUMA draws upon multiple publicly available databases, annotating variants for functional consequences on gene functions using the combined annotation dependent depletion (CADD) score,[16] potential regulatory functions (RegulomeDB score),[17] and effects on gene expression

using expression quantitative trait loci (eQTLs) of different tissue types (GTExv6 and other databases for eQTLs)[18,19] (Supplemental File). The CADD score is computed based on 63 annotations; the higher the score, the more potentially deleterious the variant is. A CADD score of ≥10 indicates a variant predicted to be among the 10% most deleterious substitutions involving the human genome, a score of ≥20 indicates the 1% most deleterious, and soforth. We used data from the Roadmap Epigenomics Project to evaluate whether the lead variants at each locus reside in enhancer regions for tissue types of interest by comparing CHIP-seq signals for chromatin state markers in selected tissues with possible conceptual connections to back pain via roles involving chondrogenesis, vertebral development, muscle, and the central nervous system.[20,21]

Because genome-wide significant variants at *SOX5* and *CCDC26/GSDMC* were found to be associated with height in prior published GWAS, we conducted *post hoc* region-specific GWAS secondary analyses accounting for possible interrelationships with height. Model 1 (CBP ~ SNP + age + sex + array + PC1 + … + PC10) examined associations between SNPs and CBP using logistic regression, among UKB participants from the interim data release. Model 2 (CBP ~ SNP + age + sex + + height+ array + PC1 + … + PC10) used similar methods, but also adjusted for height. Models 1 and 2 were compared descriptively with respect to the lead SNPs in *SOX5* and *CCDC26/GSDMC* that were identified in the discovery stage meta-analysis, to assess whether these SNP-CBP associations differed when including height as a covariate. Model 3 (CBP ~ SNP + age + sex + array + PC1 + … + PC10) was the same as Model 1, but analysis was conditional on the top height-associated variant in the region. Models 1 and 3 were compared descriptively with respect to the lead SNPs from region-specific analyses among participants from the UKB interim data release, to assess whether results for the lead SNPs differed when conditional on the top height-associated variant in the region. Model 4 was a linear regression model with additive genetic effects to examine for associations between each variant and height (height ~ SNP + age + sex + array + PC1 + … + PC10). Model 5 was the same as Model 4 (height ~ SNP + age + sex + array + PC1 + … + PC10), but analysis was conditional on the top CBP-associated variant in the region. Models 4 and 5 were compared descriptively with respect to the lead SNPs from region-specific analyses among participants from the UKB interim data release, to assess whether results for the lead SNPs differed when conditional on the top CBP-associated variant in the region (Supplemental Table S7).

Last, we used LDsr of summary-level GWAS results from the discovery stage to estimate heritability due to common autosomal SNPs and genetic correlations.[14] We transformed the observed SNP heritability to the liability scale, in order to make heritability estimates for CBP comparable with traditional heritability estimates from twin studies.[22] We used cross-trait LDsr and publicly available meta-GWAS results from LDhub to examine genetic correlations with a limited list of traits with strong conceptual links to CBP, including anthropometrics (adult height, infant/childhood height, waist/hip circumference, BMI, and overweight/obesity), depression and depressive symptoms, osteoarthritis and rheumatoid arthritis.[23,24]

1. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263-76.
2. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health 1951;41:279-81.
3. Suri P, Katz JN, Rainville J, Kalichman L, Guermazi A, Hunter DJ. Vascular disease is associated with facet joint osteoarthritis. Osteoarthritis Cartilage 2010;18:1127-32.
4. Smith BH, Campbell A, Linksted P, et al. Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. Int J Epidemiol 2013;42:689-700.
5. Jordan JM. An Ongoing Assessment of Osteoarthritis in African Americans and Caucasians in North Carolina: The Johnston County Osteoarthritis Project. Trans Am Clin Climatol Assoc 2015;126:77-86.
6. Kherad M, Rosengren BE, Hasserius R, et al. Low clinical relevance of a prevalent vertebral fracture in elderly men--the MrOs Sweden study. The spine journal : official journal of the North American Spine Society 2015;15:281-9.
7. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. Contemp Clin Trials 2005;26:569-85.
8. Lester G. The Osteoarthritis Initiative: A NIH Public-Private Partnership. HSS J 2012;8:62-3.
9. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. Eur J Epidemiol 2015;30:661-708.
10. The Study of Osteoporotic Fractures (SOF): A Brief Introduction. (Accessed 10/07/2017, at https://sofonline.epi-ucsf.org/docs/Study_Overview.pdf.)
11. Spector TD, Williams FM. The UK Adult Twin Registry (TwinsUK). Twin Res Hum Genet 2006;9:899-906.
12. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
13. Winkler TW, Day FR, Croteau-Chonka DC, et al. Quality control and conduct of genome-wide association meta-analyses. Nat Protoc 2014;9:1192-212.
14. Bulik-Sullivan BK, Loh PR, Finucane HK, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015;47:291-5.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
16. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 2014;46:310-5.
17. Boyle AP, Hong EL, Hariharan M, et al. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res 2012;22:1790-7.
18. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 2015;348:648-60.
19. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 2017;8:1826.
20. Ernst J, Kellis M. ChromHMM: automating chromatin-state discovery and characterization. Nat Methods 2012;9:215-6.
21. Roadmap Epigenomics C, Kundaje A, Meuleman W, et al. Integrative analysis of 111 reference human epigenomes. Nature 2015;518:317-30.
22. Zaitlen N, Kraft P. Heritability in the genome-wide association era. Hum Genet 2012;131:1655-64.

23. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015;47:1236-41.
24. Zheng J, Erzurumluoglu AM, Elsworth BL, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics 2017;33:272-9.

List of data repositories and tools used in FUMA in the current study

Category	Name	Description	Link
Reference Variants	dbSNP 146	Map rsID of input files to dbSNP build 146	ftp://ftp.ncbi.nlm.nih.gov/snp/organisms/human_9606_b146_grch137p13/database/organism_data/RsMergeArch.bcp.gz
Reference Genome	1000 Genomes Project Phas	Compute MAF and r2 for each available population	ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/
Functional annotations of SNPs	CADD v1.3	Deleteriousness score of variants	http://cadd.gs.washington.edu/download
	RegulomeDB	Score of regulatory variants	http://www.regulomedb.org/downloads
	15-core chromatin state	Chromatin states of genomic region in 127 tissue/cell types	http://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/
eQTLs	GTEx v6	cis-eQTLs of 44 tissue types	http://www.gtexportal.org/home/
	BIOS QTL Browser		http://genenetwork.nl/biosqtlbrowser/
Gene expression	GTEx v6	Normalized gene expression (RPKM: Read Per Kilo base per Million) for 53 tissue types	http://www.gtexportal.org/home/

Table.1 Summary of FUMA results

							LD r2 >0.6		Lead SNP		Scores SNP >0.6				Exonic SNP >0.6		GTEX eQTL		BIOS EQTL	
rsID*	**Chr**	**pos**	**MarkerName**	**A1**	**A2**	**p**	**nSNPs**	**nGWASSNPs**	**CADD****	**RDB****	**CADD****		**RDB****		**SNP**	**Gene**	**Tissue**	**Gene**	**Tissue**	Gene
rs7833174	8	130718772	8:130718772	**C**	T	1.01E-07	80	71	2.216	7	rs6470778	18.75	Multiple	2B	-	-	Skeletal Muscle, Heart Left Ventricle, Thyroid, Esophagus Mucosa, Skin (sun exposed)	GSDMC	-	-
rs12310519	**12**	23975219	12:23975219	**C**	T	7.18E-10	10	9	10.52	7	rs12310519	10.52	Multiple	6	-	-	-	-	-	-
rs4384683	18	50379032	18:50379032	A	G	3.15E-07	62	58	2.159	7	rs2116378	11.21	Multiple	5	-	-	-	-	-	-

nSNPs= number of SNPs in LD (r2>0.6) with the lead SNP in the region

nGWASSNPs= number of SNPs in LD (r2>0.6) with the lead SNP in the region associated with CBP at level of suggestive significance (p<5 x 10-7)

**** Scores:**

CADD : CADD score which is computed based on 63 annotations. The higher score, the more deleterious the SNP is. A CADD score of greater of equal 10 indicates that these are predicted to be the 10% most deleterious substitutions that you can do to the human genome, a score of greater or equal 20 indicates the 1% most deleterious and so on. Kircher et al., A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 2014;46(3):310-5.

RDB : RegulomeDB score which is the categorical score (from 1a to 7). 1a is the highest score that the SNP has the most biological evidence to be regulatory element.

nSNPs= number of SNPs in LD (r2>0.6) with the lead SNP in the region

nGWASSNPs= number of SNPs in LD (r2>0.6) with the lead SNP in the region associated with CBP at level of suggestive significance (p<5 x 10-7)

Table2. Lead SNPs

No	GenomicLocus	uniqID	rsID	chr	pos	p	nIndSigSNPs	IndSigSNPs
1	1	8:130718772:C:T	rs7833174	8	#########	1.01E-07	1	rs7833174
2	2	12:23975219:C:T	rs12310519	12	23975219	7.18E-10	2	rs12310519;rs12308843
3	3	18:50379032:A:G	rs4384683	18	50379032	3.15E-07	1	rs4384683

nIndSignSNPs= number of 'independent' significant SNPs (independent SNPs refers to those not in LD with the lead SNP; it does not refer to independence conditional on the lead SNV using GCTA COJO analyses, as described in the manuscript).

Table3. Independent SNPs (r2 >0.6)*

No	GenomicLocus	uniqID	rsID	chr	pos	p	nSNPs	nGWASSNPs
1	1	8:130718772:C:T	rs7833174	8	130718772	1.01E-07	80	71
2	2	12:23975219:C:T	rs12310519	12	23975219	7.18E-10	10	9
3	3	18:50379032:A:G	rs4384683	18	50379032	3.15E-07	62	58

*Independent SNPs here refers to those not LD with the lead SNP (it does not refer to independence conditional on the lead SNV using GCTA COJO analyses, as described in the manuscript). See 5.All SNPs for information about all independent SNPs

Table4. SNPs in FUMA Analysis, including Lead SNPs and those in LD (r2>0.6)

uniqID	rsID	chr	pos	non_effect_allele	effect_allele	MAF	gwasP	beta	se	r2	IndSigSNP	GenomicLocus	nearestGene	dist	func	CADD	RDB	minChrState	commonChrState	posMapFilt	eqtlMapFilt	ciMapFilt
8:130717716:A:G	rs10956487	8	130717716	G	A	0.2565	3.44E-07	0.0569	0.0112	1	rs7833174	1	ENSG00000254223	21791	intergenic	4.277	7	5	15	0	1	1
8:130717755:A:G	rs10956488	8	130717755	G	A	0.174	0.001339	0.042	0.0131	0.605537	rs7833174	1	ENSG00000254223	21830	intergenic	2.716	7	5	15	0	1	1
8:130718020:A:G	rs10808583	8	130718020	G	A	0.2256	6.90E-07	-0.0583	0.0118	0.857833	rs7833174	1	ENSG00000254223	22095	intergenic	0.86	7	5	15	0	1	1
8:130718712:C:T	rs4130415	8	130718712	C	T	0.2565	1.75E-07	0.0581	0.0111	1	rs7833174	1	ENSG00000224110	22278	intergenic	2.743	7	5	15	0	1	1
8:130718772:C:T	rs7833174	8	130718772	C	T	0.2565	1.01E-07	0.0593	0.0111	1	rs7833174	1	ENSG00000224110	22218	intergenic	2.216	7	5	15	0	1	1
8:130718859:A:G	rs7814941	8	130718859	G	A	0.2256	6.63E-07	0.0585	0.0118	0.857833	rs7833174	1	ENSG00000224110	22131	intergenic	3.483	6	5	15	0	1	1
8:130719443:A:G	rs79164994	8	130719443	A	G	0.2435	NA	NA	NA	0.794698	rs7833174	1	ENSG00000224110	21547	intergenic	1.387	5	2	15	0	0	1
8:130719567:A:T	rs7815955	8	130719567	T	A	0.2256	3.15E-07	0.0598	0.0117	0.857833	rs7833174	1	ENSG00000224110	21423	intergenic	1.255	2b	2	15	0	1	1
8:130719623:A:G	rs7816342	8	130719623	G	A	0.2565	1.47E-07	-0.0584	0.0111	1	rs7833174	1	ENSG00000224110	21367	intergenic	2.521	5	2	15	0	1	1
8:130719718:A:T	rs7816131	8	130719718	T	A	0.2247	5.08E-07	0.0587	0.0117	0.853646	rs7833174	1	ENSG00000224110	21272	intergenic	1.131	3a	2	15	0	1	1
8:130720646:C:G	rs6470763	8	130720646	G	C	0.2028	6.96E-06	-0.054	0.012	0.765569	rs7833174	1	ENSG00000224110	20344	intergenic	1.543	4	2	15	0	1	1
8:130721420:C:T	rs10087031	8	130721420	T	C	0.2197	NA	NA	NA	0.833099	rs7833174	1	ENSG00000224110	19570	intergenic	0.119	2b	2	15	0	0	1
8:130721421:C:T	rs116662391	8	130721421	T	C	0.2256	NA	NA	NA	0.857833	rs7833174	1	ENSG00000224110	19569	intergenic	0.281	2b	2	15	0	0	1
8:130723728:A:G	rs4733724	8	130723728	G	A	0.2256	3.53E-07	0.0594	0.0117	0.857833	rs7833174	1	ENSG00000224110	17262	intergenic	1.198	7	2	15	0	1	1
8:130723792:C:T	rs6651255	8	130723792	C	T	0.2565	1.25E-07	0.0586	0.0111	1	rs7833174	1	ENSG00000224110	17198	intergenic	3.647	7	2	15	0	1	1
8:130725665:C:T	rs6470764	8	130725665	C	T	0.2256	3.81E-07	-0.0593	0.0117	0.857833	rs7833174	1	ENSG00000224110	15325	intergenic	16.12	5	5	15	0	1	1
8:130728361:A:T	rs6986256	8	130728361	T	A	0.2237	7.07E-07	-0.0581	0.0117	0.849484	rs7833174	1	ENSG00000224110	12629	intergenic	0.324	3a	5	15	0	1	1
8:130729518:G:T	rs4368942	8	130729518	T	G	0.2187	NA	NA	NA	0.828105	rs7833174	1	ENSG00000224110	11472	intergenic	2.068	6	5	15	0	0	1
8:130730280:A:C	rs11984666	8	130730280	C	A	0.2237	8.46E-07	-0.0576	0.0117	0.849484	rs7833174	1	ENSG00000224110	10710	intergenic	1.744	7	5	15	0	1	1
8:130731244:A:C	rs10956490	8	130731244	C	A	0.2237	6.40E-07	0.0583	0.0117	0.849484	rs7833174	1	ENSG00000224110	9746	intergenic	1.195	7	5	15	0	1	1
8:130731376:C:T	rs4733725	8	130731376	C	T	0.2237	8.21E-07	-0.0579	0.0117	0.849484	rs7833174	1	ENSG00000224110	9614	intergenic	2.012	7	5	15	0	1	1
8:130731402:C:T	rs4733726	8	130731402	C	T	0.2237	6.70E-07	-0.058	0.0117	0.849484	rs7833174	1	ENSG00000224110	9588	intergenic	0.02	6	5	15	0	1	1
8:130732739:C:T	rs7815298	8	130732739	C	T	0.2237	5.31E-07	0.0595	0.0119	0.849484	rs7833174	1	ENSG00000224110	8251	intergenic	4.377	6	5	15	0	1	1
8:130734461:G:T	rs2062078	8	130734461	G	T	0.2237	6.37E-07	-0.0581	0.0117	0.849484	rs7833174	1	ENSG00000224110	6529	intergenic	0.191	NA	5	15	0	1	1
8:130735330:A:C	rs7841981	8	130735330	C	A	0.2247	9.05E-07	-0.0574	0.0117	0.844489	rs7833174	1	ENSG00000224110	5660	intergenic	4.743	4	5	15	0	1	1
8:130735460:C:T	rs60228607	8	130735460	C	T	0.2237	7.03E-07	-0.0579	0.0117	0.849484	rs7833174	1	ENSG00000224110	5530	intergenic	1.676	2b	5	15	0	1	1
8:130735662:C:T	rs28743107	8	130735662	C	T	0.2326	NA	NA	NA	0.82127	rs7833174	1	ENSG00000224110	5328	intergenic	1.845	6	5	15	0	0	1
8:130736697:A:C	rs6470765	8	130736697	C	A	0.2237	6.96E-07	0.0579	0.0117	0.849484	rs7833174	1	ENSG00000224110	4293	intergenic	0.821	6	5	15	0	1	1
8:130736854:A:G	rs6470766	8	130736854	G	A	0.1958	1.63E-05	0.054	0.0125	0.730421	rs7833174	1	ENSG00000224110	4136	intergenic	10.24	5	5	15	0	1	1
8:130736929:A:T	rs6985118	8	130736929	T	A	0.2237	6.65E-07	0.0581	0.0117	0.849484	rs7833174	1	ENSG00000224110	4061	intergenic	0.217	6	5	15	0	1	1
8:130737391:C:T	rs3886937	8	130737391	C	T	0.2237	8.49E-07	0.0576	0.0117	0.849484	rs7833174	1	ENSG00000224110	3599	intergenic	4.835	5	5	15	0	1	1
8:130737546:G:T	rs3886938	8	130737546	G	T	0.2237	7.23E-07	0.0579	0.0117	0.849484	rs7833174	1	ENSG00000224110	3444	intergenic	5.27	5	5	15	0	1	1
8:130737601:C:T	rs1074286	8	130737601	C	T	0.2237	9.08E-07	-0.0574	0.0117	0.849484	rs7833174	1	ENSG00000224110	3389	intergenic	0.805	5	5	15	0	1	1
8:130738457:C:T	rs4733732	8	130738457	C	T	0.2237	9.11E-07	-0.0577	0.0117	0.849484	rs7833174	1	ENSG00000224110	2533	intergenic	4.355	4	5	15	0	1	1
8:130738972:A:G	rs7826493	8	130738972	G	A	0.2237	4.85E-07	0.0589	0.0117	0.849484	rs7833174	1	ENSG00000224110	2018	intergenic	0.984	4	5	15	0	1	1
8:130739528:A:G	rs6470768	8	130739528	G	A	0.1968	1.63E-05	-0.0538	0.0125	0.734573	rs7833174	1	ENSG00000224110	1462	intergenic	1.288	6	5	15	0	1	1
8:130739657:C:T	rs6470769	8	130739657	C	T	0.1968	1.77E-05	-0.0537	0.0125	0.734573	rs7833174	1	ENSG00000224110	1333	intergenic	0.771	7	5	15	0	1	1
8:130740135:G:T	rs7011557	8	130740135	G	T	0.1968	1.62E-05	-0.054	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	upstream	0.15	5	5	15	0	1	1
8:130740400:G:T	rs7012062	8	130740400	G	T	0.1968	1.25E-05	-0.0545	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	upstream	1.584	5	5	15	0	1	1
8:130740522:A:G	rs7012249	8	130740522	G	A	0.1968	1.63E-05	-0.054	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	upstream	0.328	5	4	15	0	1	1
8:130740650:C:T	rs6994279	8	130740650	C	T	0.1968	1.29E-05	0.0546	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	upstream	1.274	5	4	15	0	1	1
8:130740779:C:T	rs6998296	8	130740779	C	T	0.1968	1.91E-05	0.0537	0.0126	0.734573	rs7833174	1	ENSG00000224110	0	upstream	0.239	4	4	15	0	1	1
8:130740859:C:T	rs7016313	8	130740859	C	T	0.1968	1.56E-05	-0.054	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	upstream	10.09	2b	4	15	0	1	1
8:130740898:C:T	rs6998472	8	130740898	C	T	0.1968	2.42E-05	0.0528	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	upstream	1.298	2b	4	15	0	1	1
8:130741042:A:G	rs10109335	8	130741042	G	A	0.1968	1.55E-05	-0.054	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	ncRNA_exonic	3.732	4	4	15	0	1	1
8:130741139:A:G	rs10956491	8	130741139	G	A	0.1968	1.62E-05	0.0539	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	ncRNA_exonic	2.716	4	4	15	0	1	1
8:130741183:G:T	rs7017052	8	130741183	G	T	0.1968	1.56E-05	-0.0539	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	ncRNA_exonic	1.943	4	4	15	0	1	1
8:130741320:C:G	rs7017235	8	130741320	G	C	0.1968	1.71E-05	-0.0538	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	ncRNA_exonic	4.97	5	5	15	0	1	1
8:130741938:G:T	rs6470770	8	130741938	G	T	0.1968	1.67E-05	0.0538	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	ncRNA_intronic	6.311	5	5	15	0	1	1
8:130742257:A:G	rs6984575	8	130742257	G	A	0.1968	1.57E-05	-0.0539	0.0125	0.734573	rs7833174	1	ENSG00000224110	0	ncRNA_exonic	10.56	4	2	15	0	1	1
8:130743547:A:T	rs7839339	8	130743547	T	A	0.1968	2.33E-05	-0.0534	0.0126	0.734573	rs7833174	1	ENSG00000224110	0	downstream	7.075	4	2	15	0	1	1
8:130743726:A:C	rs6470771	8	130743726	C	A	0.1948	9.52E-06	0.0556	0.0126	0.726887	rs7833174	1	ENSG00000224110	1035	intergenic	6.716	5	5	15	0	1	1
8:130743745:C:G	rs6470772	8	130743745	G	C	0.1958	1.71E-05	0.0538	0.0125	0.731032	rs7833174	1	ENSG00000224110	1054	intergenic	4.16	5	5	15	0	1	1
8:130743801:C:G	rs6470773	8	130743801	G	C	0.1968	1.55E-05	-0.0539	0.0125	0.734573	rs7833174	1	ENSG00000224110	1110	intergenic	0.052	5	5	15	0	1	1
8:130745178:C:G	rs4613961	8	130745178	G	C	0.1968	1.62E-05	0.0538	0.0125	0.734573	rs7833174	1	ENSG00000224110	2487	intergenic	9.441	6	4	15	0	1	1
8:130745576:C:T	rs6983071	8	130745576	C	T	0.1968	1.48E-05	0.0541	0.0125	0.734573	rs7833174	1	ENSG00000224110	2885	intergenic	0.694	7	4	15	0	1	1
8:130746029:C:G	rs117091376	8	130746029	G	C	0.1968	NA	NA	NA	0.734573	rs7833174	1	ENSG00000224110	3338	intergenic	0.247	6	5	15	0	0	1
8:130746030:C:G	rs118087346	8	130746030	G	C	0.1968	NA	NA	NA	0.734573	rs7833174	1	ENSG00000224110	3339	intergenic	0.17	6	5	15	0	0	1
8:130746035:C:G	rs140880131	8	130746035	G	C	0.1968	NA	NA	NA	0.734573	rs7833174	1	ENSG00000224110	3344	intergenic	0.167	7	5	15	0	0	1
8:130747251:A:C	rs4733733	8	130747251	C	A	0.1968	1.13E-05	-0.0552	0.0126	0.734573	rs7833174	1	ENSG00000224110	4560	intergenic	2.672	7	5	15	0	1	1
8:130747520:A:C	rs9694838	8	130747520	C	A	0.1968	1.53E-05	0.054	0.0125	0.734573	rs7833174	1	ENSG00000224110	4829	intergenic	0.333	7	5	15	0	1	1
8:130749240:A:T	rs9750611	8	130749240	T	A	0.1968	1.90E-05	-0.0534	0.0125	0.734573	rs7833174	1	ENSG00000224110	6549	intergenic	2.613	7	5	15	0	1	1
8:130749290:C:T	rs9957867	8	130749290	C	T	0.1968	1.81E-05	-0.0535	0.0125	0.734573	rs7833174	1	ENSG00000224110	6599	intergenic	0.957	7	5	15	0	1	1
8:130749375:C:T	rs189933136	8	130749375	T	C	0.1968	NA	NA	NA	0.734573	rs7833174	1	ENSG00000224110	6684	intergenic	0.803	7	5	15	0	1	1
8:130751015:C:T	rs4360262	8	130751015	C	T	0.1968	1.32E-05	-0.0546	0.0125	0.734573	rs7833174	1	ENSG00000224110	8324	intergenic	6.982	7	5	15	1	1	1
8:130751025:G:T	rs4584118	8	130751025	G	T	0.1968	1.75E-05	0.0539	0.0126	0.734573	rs7833174	1	ENSG00000224110	8334	intergenic	7.238	7	5	15	1	1	1
8:130752372:A:C	rs4366050	8	130752372	C	A	0.1968	1.25E-05	-0.0546	0.0125	0.734573	rs7833174	1	GSDMC	8070	intergenic	0.242	7	5	15	1	1	1
8:130752408:C:T	rs4633026	8	130752408	C	T	0.1968	1.57E-05	0.0539	0.0125	0.734573	rs7833174	1	GSDMC	8034	intergenic	3.738	6	5	15	1	1	1
8:130752725:C:T	rs4367506	8	130752725	C	T	0.1968	1.50E-05	-0.054	0.0125	0.734573	rs7833174	1	GSDMC	7717	intergenic	2.747	7	5	15	1	1	1
8:130753603:A:G	rs7844275	8	130753603	G	A	0.1968	1.56E-05	-0.0539	0.0125	0.734573	rs7833174	1	GSDMC	6839	intergenic	0.062	6	5	15	1	1	1
8:130753742:C:T	rs4559213	8	130753742	C	T	0.1968	1.54E-05	0.054	0.0125	0.734573	rs7833174	1	GSDMC	6700	intergenic	3.766	6	5	15	1	1	1
8:130754719:C:T	rs4733737	8	130754719	C	T	0.1968	1.28E-05	-0.0545	0.0125	0.734573	rs7833174	1	GSDMC	5723	intergenic	9.136	7	4	15	1	1	1
8:130754887:G:T	rs4236748	8	130754887	G	T	0.1968	1.54E-05	-0.054	0.0125	0.734573	rs7833174	1	GSDMC	5555	intergenic	7.164	6	4	15	1	1	1
8:130755205:C:T	rs4128895	8	130755205	C	T	0.1978	1.44E-05	0.0542	0.0125	0.729665	rs7833174	1	GSDMC	5237	intergenic	0.056	NA	4	15	1	1	1
8:130756531:A:G	rs1989396	8	130756531	G	A	0.1968	1.50E-05	-0.054	0.0125	0.734573	rs7833174	1	GSDMC	3911	intergenic	0.587	5	4	15	1	1	1
8:130757584:C:T	rs4509279	8	130757584	C	T	0.1968	1.39E-05	-0.0542	0.0125	0.734573	rs7833174	1	GSDMC	2858	intergenic	5.525	7	4	15	1	1	1
8:130757820:A:G	rs61199848	8	130757820	G	A	0.1968	1.03E-05	0.0551	0.0125	0.734573	rs7833174	1	GSDMC	2622	intergenic	2.656	7	4	15	1	1	1
8:130759579:C:T	rs6470778	8	130759579	C	T	0.1968	1.48E-05	-0.0542	0.0125	0.734573	rs7833174	1	GSDMC	0	downstream	18.75	6	4	15	1	1	1
8:130759766:A:G	rs61503621	8	130759766	G	A	0.1968	1.22E-05	0.0547	0.0125	0.734573	rs7833174	1	GSDMC	0	downstream	0.33	5	4	15	1	1	1
8:130759999:A:G	rs4733738	8	130759999	G	A	0.1968	1.15E-05	-0.0548	0.0125	0.734573	rs7833174	1	GSDMC	0	downstream	5.668	5	4	15	1	1	1
12:23936398:A:G	rs7977132	12	23936398	G	A	0.1561	4.89E-08	0.0702	0.0129	0.929776	rs12310519	2	SOX5	0	intronic	0.724	7	5	15	1	0	1
12:23947697:C:T	rs34616559	12	23947697	C	T	0.1551	5.19E-08	0.0705	0.013	0.923239	rs12310519	2	SOX5	0	intronic	2.833	6	5	15	1	0	1
12:23960729:C:T	rs11831278	12	23960729	C	T	0.1501	4.71E-09	0.0756	0.0129	0.985336	rs12310519	2	SOX5	0	intronic	0.714	6	5	15	1	0	0
12:23972014:A:C	rs56290807	12	23972014	C	A	0.163	8.44E-10	0.0767	0.0125	0.871374	rs12310519	2	SOX5	0	intronic	4.222	6	5	15	1	0	0
12:23974911:C:G	rs7303462	12	23974911	C	G	0.1481	NA	NA	NA	1	rs12310519	2	SOX5	0	intronic	0.167	6	5	15	1	0	0
12:23975219:C:T	rs12310519	12	23975219	C	T	0.1481	7.18E-10	0.0777	0.0126	1	rs12310519	2	SOX5	0	intronic	10.52	7	5	15	1	0	0
12:23975953:G:T	rs11834194	12	23975953	G	T	0.1481	1.75E-09	0.0769	0.0128	0.985225	rs12310519	2	SOX5	0	intronic	0.42	7	5	15	1	0	0
12:23977474:G:T	rs12581539	12	23977474	G	T	0.1213	7.22E-09	0.0795	0.0137	0.796142	rs12310519	2	SOX5	0	intronic	1.483	7	4	15	1	0	0
12:23978200:A:G	rs7134575	12	23978200	G	A	0.1173	1.71E-09	0.0831	0.0138	0.75587	rs12310519	2	SOX5	0	intronic	0.52	7	4	15	1	0	0
12:23982559:C:T	rs9804988	12	23982559	C	T	0.1163	5.68E-09	0.0798	0.0137	0.735329	rs12310519	2	SOX5	0	intronic	1.146	7	1	15	1	0	0
8:50358109:C:T	rs62083314	18	50358109	C	T	0.4076	7.51E-05	0.0377	0.0095	0.797406	rs4384683	3	DCC	0	intronic	4.511	6	9	15	1	0	0
8:50358345:A:T	rs2018174	18	50358345	T	A	0.4563	NA	NA	NA	0.6673	rs4384683	3	DCC	0	intronic	7.411	6	9	15	1	0	0
8:50360650:C:T	rs8094747	18	50360650	C	T	0.4563	0.0007337	0.0321	0.0095	0.660509	rs4384683	3	DCC	0	intronic	0.915	7	9	15	1	0	1
8:50360651:C:T	rs8094748	18	50360651	C	T	0.4563	0.0008346	0.0318	0.0095	0.660509	rs4384683	3	DCC	0	intronic	1.884	7	9	15	1	0	1
8:50360919:C:T	rs2116381	18	50360919	C	T	0.4563	0.001367	0.0299	0.0093	0.660509	rs4384683	3	DCC	0	intronic	1.049	NA	9	15	1	0	1
8:50360995:A:G	rs2116380	18	50360995	G	A	0.4563	0.001193	0.0303	0.0093	0.660509	rs4384683	3	DCC	0	intronic	0.983	NA	9	15	1	0	1
8:50361036:A:G	rs2156285	18	50361036	G	A	0.4563	0.001269	-0.0301	0.0094	0.660509	rs4384683	3	DCC	0	intronic	2.675	NA	9	15	1	0	1
8:50361058:A:G	rs2116379	18	50361058	G	A	0.4563	0.001196	0.0299	0.0093	0.660509	rs4384683	3	DCC	0	intronic	4.932	NA	9	15	1	0	1
8:50361432:A:G	rs2187221	18	50361432	G	A	0.4563	0.001229	0.0302	0.0093	0.660509	rs4384683	3	DCC	0	intronic	4.504	NA	9	15	1	0	1
8:50361584:C:T	rs2116378	18	50361584	C	T	0.4563	0.001435	-0.0297	0.0093	0.660509	rs4384683	3	DCC	0	intronic	11.21	7	9	15	1	0	1
8:50362131:A:C	rs28703132	18	50362131	C	A	0.4553	0.001324	0.0299	0.0093	0.652115	rs4384683	3	DCC	0	intronic	10.66	6	9	15	1	0	1
8:50362203:G:T	rs28630913	18	50362203	G	T	0.4553	0.001034	-0.0306	0.0093	0.652115	rs4384683	3	DCC	0	intronic	0.829	7	9	15	1	0	1
8:50362308:A:G	rs28459539	18	50362308	G	A	0.4553	0.0006617	0.0319	0.0094	0.652115	rs4384683	3	DCC	0	intronic	1.613	7	9	15	1	0	1
8:50362311:C:T	rs28678524	18	50362311	C	T	0.4553	0.0006196	-0.0321	0.0094	0.652115	rs4384683	3	DCC	0	intronic	0.296	7	9	15	1	0	1
8:50362783:A:C	rs9964377	18	50362783	C	A	0.4563	0.00132	-0.03	0.0093	0.660509	rs4384683	3	DCC	0	intronic	1.39	7	9	15	1	0	1
8:50363895:G:T	rs8083955	18	50363895	G	T	0.4563	0.001134	0.0304	0.0093	0.660509	rs4384683	3	DCC	0	intronic	6.464	6	9	15	1	0	1
8:50363934:C:T	rs34305227	18	50363934	C	T	0.4553	0.001248	0.0301	0.0093	0.652115	rs4384683	3	DCC	0	intronic	1.382	7	9	15	1	0	1
8:50364137:A:G	rs12957268	18	50364137	G	A	0.4563	0.001175	0.0302	0.0093	0.660509	rs4384683	3	DCC	0	intronic	1.975	6	9	15	1	0	1
8:50364321:A:G	rs55775712	18	50364321	G	A	0.4573	0.001512	0.0296	0.0093	0.656655	rs4384683	3	DCC	0	intronic	1.607	7	9	15	1	0	1
8:50364452:A:C	rs55678240	18	50364452	C	A	0.4573	0.001238	0.0301	0.0093	0.656655	rs4384683	3	DCC	0	intronic	0.963	6	9	15	1	0	1
8:50364508:C:T	rs34486623	18	50364508	C	T	0.4056	9.43E-05	0.0368	0.0094	0.784195	rs4384683	3	DCC	0	intronic	1.248	7	9	15	1	0	1
8:50364871:C:T	rs13313672	18	50364871	C	T	0.4573	0.001215	0.0301	0.0093	0.656655	rs4384683	3	DCC	0	intronic	1.233	6	9	15	1	0	1
8:50365357:G:T	rs9962954	18	50365357	G	T	0.4563	0.001329	0.0299	0.0093	0.660509	rs4384683	3	DCC	0	intronic	6.339	5	9	15	1	0	1
8:50365388:A:G	rs9950718	18	50365388	G	A	0.4563	0.001189	0.0302	0.0093	0.660509	rs4384683	3	DCC	0	intronic	2.298	5	9	15	1	0	1
8:50366291:A:C	rs10853623	18	50366291	C	A	0.4563	0.001225	0.0301	0.0093	0.660509	rs4384683	3	DCC	0	intronic	0.483	6	9	15	1	0	1
8:50366637:C:T	rs10853624	18	50366637	C	T	0.4553	0.001231	-0.0301	0.0093	0.652115	rs4384683	3	DCC	0	intronic	2.068	7	9	15	1	0	1
8:50366840:C:T	rs10502951	18	50366840	C	T	0.4563	0.00127	0.03	0.0093	0.660509	rs4384683	3	DCC	0	intronic	5.628	6	9	15	1	0	1
8:50366941:A:G	rs10502952	18	50366941	G	A	0.4553	0.001118	0.0306	0.0094	0.652115	rs4384683	3	DCC	0	intronic	3.23	7	9	15	1	0	1
8:50367134:A:T	rs1006262	18	50367134	T	A	0.4563	0.001144	0.0303	0.0093	0.660509	rs4384683	3	DCC	0	intronic	0.924	6	9	15	1	0	1
8:50367297:A:T	rs1006263	18	50367297	T	A	0.4563	0.001209	-0.0302	0.0093	0.660509	rs4384683	3	DCC	0	intronic	8.032	6	9	15	1	0	1
8:50367369:G:T	rs1006264	18	50367369	G	T	0.4563	0.00125	-0.0301	0.0093	0.660509	rs4384683	3	DCC	0	intronic	2.256	5	9	15	1	0	1
8:50367412:C:T	rs1573411	18	50367412	C	T	0.4563	0.001175	-0.0302	0.0093	0.660509	rs4384683	3	DCC	0	intronic	3.686	NA	9	15	1	0	1
8:50367527:A:G	rs9783901	18	50367527	G	A	0.4583	0.001246	0.0301	0.0093	0.666322	rs4384683	3	DCC	0	intronic	8.384	6	9	15	1	0	1
8:50367700:G:T	rs4998815	18	50367700	G	T	0.4563	0.001246	0.0301	0.0093	0.660509	rs4384683	3	DCC	0	intronic	6.241	6	9	15	1	0	1
8:50368768:A:G	rs1573410	18	50368768	G	A	0.4543	0.001234	0.0301	0.0

Table5.eQTLresults (SNPs, LD r2>0.6)

uniqID	db	tissue	gene	testedAllele	p	tz	FDR	RiskIncAllele	alignedDirection	chr	pos	symbol	eqtlMapFilt
8:130718712:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	9.17E-14	8.000471738	0.000312239	C	+	8	130718712	GSDMC	1
8:130718772:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	9.17E-14	8.000471738	0.000312239	C	+	8	130718772	GSDMC	1
8:130723792:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	9.17E-14	8.000471738	0.000312239	C	+	8	130723792	GSDMC	1
8:130719623:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	1.37E-13	7.93485435	0.000312239	G	-	8	130719623	GSDMC	1
8:130717716:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	1.49E-13	7.921621487	0.000312239	G	+	8	130717716	GSDMC	1
8:130759999:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.99E-12	7.377352707	0.000312239	G	-	8	130759999	GSDMC	1
8:130759579:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	4.05E-12	7.374966689	0.000312239	C	-	8	130759579	GSDMC	1
8:130759766:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	4.05E-12	7.374966689	0.000312239	G	+	8	130759766	GSDMC	1
8:130740400:G:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	1.24E-11	7.185241579	0.000312239	G	-	8	130740400	GSDMC	1
8:130745178:C:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	1.59E-11	7.142416556	0.000312239	G	+	8	130745178	GSDMC	1
8:130751015:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	2.08E-11	7.096279106	0.000312239	C	-	8	130751015	GSDMC	1
8:130749240:A:T	GTEx	Esophagus_Mucosa	ENSG00000147697	A	2.74E-11	7.048554645	0.000312239	T	-	8	130749240	GSDMC	1
8:130741938:G:T	GTEx	Esophagus_Mucosa	ENSG00000147697	G	3.11E-11	7.026490499	0.000312239	G	+	8	130741938	GSDMC	1
8:130739528:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	G	-	8	130739528	GSDMC	1
8:130739657:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	C	-	8	130739657	GSDMC	1
8:130740135:G:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	G	-	8	130740135	GSDMC	1
8:130740522:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	G	-	8	130740522	GSDMC	1
8:130740650:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	C	+	8	130740650	GSDMC	1
8:130740859:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	C	-	8	130740859	GSDMC	1
8:130740898:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	C	+	8	130740898	GSDMC	1
8:130741042:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	G	-	8	130741042	GSDMC	1
8:130741139:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	3.28E-11	7.016963612	0.000312239	G	+	8	130741139	GSDMC	1
8:130741183:G:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	G	-	8	130741183	GSDMC	1
8:130741320:C:G	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	G	-	8	130741320	GSDMC	1
8:130742257:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	G	-	8	130742257	GSDMC	1
8:130743547:A:T	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	T	-	8	130743547	GSDMC	1
8:130743745:C:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	3.28E-11	7.016963612	0.000312239	G	+	8	130743745	GSDMC	1
8:130743801:C:G	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	G	-	8	130743801	GSDMC	1
8:130745576:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	C	+	8	130745576	GSDMC	1
8:130749290:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	C	-	8	130749290	GSDMC	1
8:130752372:A:C	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	C	-	8	130752372	GSDMC	1
8:130752725:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	C	-	8	130752725	GSDMC	1
8:130753603:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	G	-	8	130753603	GSDMC	1
8:130753742:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	C	+	8	130753742	GSDMC	1
8:130754719:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	C	-	8	130754719	GSDMC	1
8:130754887:G:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	G	-	8	130754887	GSDMC	1
8:130755205:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.28E-11	7.016963612	0.000312239	C	+	8	130755205	GSDMC	1
8:130756531:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	3.28E-11	7.016963612	0.000312239	G	-	8	130756531	GSDMC	1
8:130757584:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	3.28E-11	7.016963612	0.000312239	C	-	8	130757584	GSDMC	1
8:130757820:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	3.28E-11	7.016963612	0.000312239	G	+	8	130757820	GSDMC	1
8:130752408:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.37E-11	7.012292638	0.000312239	C	+	8	130752408	GSDMC	1
8:130747520:A:C	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.37E-11	7.01222104	0.000312239	C	+	8	130747520	GSDMC	1
8:130740779:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	3.41E-11	7.010305627	0.000312239	C	+	8	130740779	GSDMC	1
8:130751025:G:T	GTEx	Esophagus_Mucosa	ENSG00000147697	G	3.60E-11	7.000915808	0.000312239	G	+	8	130751025	GSDMC	1
8:130749375:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	C	1.35E-10	6.768626054	0.000312239	NA	NA	8	130749375	GSDMC	1
8:130751025:G:T	GTEx	Muscle_Skeletal	ENSG00000147697	G	2.37E-10	6.54513282	0.00030405	G	+	8	130751025	GSDMC	1
8:130751015:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	2.40E-10	6.543342454	0.00030405	C	-	8	130751015	GSDMC	1
8:130740779:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	2.51E-10	6.535319012	0.00030405	C	+	8	130740779	GSDMC	1
8:130745178:C:G	GTEx	Muscle_Skeletal	ENSG00000147697	G	2.93E-10	6.509461008	0.00030405	G	+	8	130745178	GSDMC	1
8:130752408:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	2.93E-10	6.508976802	0.00030405	C	+	8	130752408	GSDMC	1
8:130738972:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	3.66E-10	6.59077005	0.000312239	G	+	8	130738972	GSDMC	1
8:130747520:A:C	GTEx	Muscle_Skeletal	ENSG00000147697	C	3.89E-10	6.460602082	0.00030405	C	+	8	130747520	GSDMC	1
8:130749240:A:T	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.05E-10	6.453932301	0.00030405	T	-	8	130749240	GSDMC	1
8:130741938:G:T	GTEx	Muscle_Skeletal	ENSG00000147697	G	4.29E-10	6.444004421	0.00030405	G	+	8	130741938	GSDMC	1
8:130757584:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439892963	0.00030405	C	-	8	130757584	GSDMC	1
8:130757820:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	G	4.40E-10	6.439892963	0.00030405	G	+	8	130757820	GSDMC	1
8:130739528:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	G	-	8	130739528	GSDMC	1
8:130739657:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	C	-	8	130739657	GSDMC	1
8:130740135:G:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	G	-	8	130740135	GSDMC	1
8:130740522:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	G	-	8	130740522	GSDMC	1
8:130740650:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	C	+	8	130740650	GSDMC	1
8:130740859:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	C	-	8	130740859	GSDMC	1
8:130740898:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	C	+	8	130740898	GSDMC	1
8:130741042:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	G	-	8	130741042	GSDMC	1
8:130741139:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	G	4.40E-10	6.439738219	0.00030405	G	+	8	130741139	GSDMC	1
8:130741183:G:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	G	-	8	130741183	GSDMC	1
8:130741320:C:G	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	G	-	8	130741320	GSDMC	1
8:130742257:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	G	-	8	130742257	GSDMC	1
8:130743547:A:T	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	T	-	8	130743547	GSDMC	1
8:130743745:C:G	GTEx	Muscle_Skeletal	ENSG00000147697	G	4.40E-10	6.439738219	0.00030405	G	+	8	130743745	GSDMC	1
8:130743801:C:G	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	G	-	8	130743801	GSDMC	1
8:130745576:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	C	+	8	130745576	GSDMC	1
8:130749290:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	C	-	8	130749290	GSDMC	1
8:130752372:A:C	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	C	-	8	130752372	GSDMC	1
8:130752725:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	C	-	8	130752725	GSDMC	1
8:130753603:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	G	-	8	130753603	GSDMC	1
8:130753742:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	C	+	8	130753742	GSDMC	1
8:130754719:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	C	-	8	130754719	GSDMC	1
8:130754887:G:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.40E-10	6.439738219	0.00030405	G	-	8	130754887	GSDMC	1
8:130755205:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	C	4.40E-10	6.439738219	0.00030405	C	+	8	130755205	GSDMC	1
8:130756531:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	4.40E-10	6.439738219	0.00030405	G	-	8	130756531	GSDMC	1
8:130740400:G:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	4.46E-10	6.437337815	0.00030405	G	-	8	130740400	GSDMC	1
8:130718712:C:T	GTEx	Skin_Sun_Exposed_Lower_leg	ENSG00000147697	C	4.48E-10	6.483644967	0.00028813	C	+	8	130718712	GSDMC	1
8:130718772:C:T	GTEx	Skin_Sun_Exposed_Lower_leg	ENSG00000147697	C	4.48E-10	6.483644967	0.00028813	C	+	8	130718772	GSDMC	1
8:130723792:C:T	GTEx	Skin_Sun_Exposed_Lower_leg	ENSG00000147697	C	4.48E-10	6.483644967	0.00028813	C	+	8	130723792	GSDMC	1
8:130719623:A:G	GTEx	Skin_Sun_Exposed_Lower_leg	ENSG00000147697	A	4.87E-10	6.468871767	0.00028813	G	-	8	130719623	GSDMC	1
8:130738457:C:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	5.05E-10	6.532724846	0.000312239	C	-	8	130738457	GSDMC	1
8:130717716:A:G	GTEx	Skin_Sun_Exposed_Lower_leg	ENSG00000147697	G	6.51E-10	6.417913494	0.00028813	G	+	8	130717716	GSDMC	1
8:130759579:C:T	GTEx	Muscle_Skeletal	ENSG00000147697	T	6.82E-10	6.364111521	0.00030405	C	-	8	130759579	GSDMC	1
8:130759766:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	G	6.82E-10	6.364111521	0.00030405	G	+	8	130759766	GSDMC	1
8:130747251:A:C	GTEx	Esophagus_Mucosa	ENSG00000147697	A	8.77E-10	6.432266938	0.000312239	C	-	8	130747251	GSDMC	1
8:130736854:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	9.35E-10	6.420593881	0.000312239	G	+	8	130736854	GSDMC	1
8:130759999:A:G	GTEx	Muscle_Skeletal	ENSG00000147697	A	1.18E-09	6.268850779	0.00030405	G	-	8	130759999	GSDMC	1
8:130743726:A:C	GTEx	Esophagus_Mucosa	ENSG00000147697	C	1.99E-09	6.281607177	0.000312239	C	+	8	130743726	GSDMC	1
8:130718020:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	A	4.74E-09	6.118925744	0.000312239	G	-	8	130718020	GSDMC	1
8:130718859:A:G	GTEx	Esophagus_Mucosa	ENSG00000147697	G	4.83E-09	6.115536819	0.000312239	G	+	8	130718859	GSDMC	1
8:130719567:A:T	GTEx	Esophagus_Mucosa	ENSG00000147697	T	4.83E-09	6.115536819	0.000312239	T	+	8	130719567	GSDMC	1

TableLeqTL results (SNPs, LD r2>0.6)

uniqID	db	tissue	gene	testedAllele	p	tz	FDR	RiskincAllele	alignedDirection	chr	pos	symbol	eqtlMapMin
8:130738712:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	9.17E-14	8.000471738	0.000112238	C	+	8	130738712	GSDMC	1
8:130738772:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	9.17E-14	8.000471738	0.000112238	C	+	8	130738772	GSDMC	1
8:130738792:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	A	9.17E-14	8.000471738	0.000112238	C	+	8	130738792	GSDMC	1
8:130739623:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	1.37E-13	7.93485435	0.000112238	G	-	8	130739623	GSDMC	1
8:130739716:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	1.49E-13	7.921621487	0.000112238	G	+	8	130739716	GSDMC	1
8:130739999:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.99E-12	7.37552707	0.000112238	G	-	8	130739999	GSDMC	1
8:130740579:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	4.05E-12	7.374966489	0.000112238	C	+	8	130740579	GSDMC	1
8:130739766:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	4.05E-12	7.374966489	0.000112238	G	+	8	130739766	GSDMC	1
8:130740400:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	G	1.24E-11	7.181241579	0.000112238	G	-	8	130740400	GSDMC	1
8:130741578:CG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	1.59E-11	7.142416556	0.000112238	G	+	8	130741578	GSDMC	1
8:130741015:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	2.08E-11	7.094279106	0.000112238	C	-	8	130741015	GSDMC	1
8:130740240:AT	GTEx	Esophagus_Mucosa	ENSG00000014707	A	2.74E-11	7.068154645	0.000112238	T	-	8	130740240	GSDMC	1
8:130741938:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	G	3.11E-11	7.026490499	0.000112238	G	+	8	130741938	GSDMC	1
8:130739528:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130739528	GSDMC	1
8:130739617:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	C	-	8	130739617	GSDMC	1
8:130740135:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	G	-	8	130740135	GSDMC	1
8:130740522:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130740522	GSDMC	1
8:130740650:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	C	+	8	130740650	GSDMC	1
8:130740659:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	C	-	8	130740659	GSDMC	1
8:130740898:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	C	+	8	130740898	GSDMC	1
8:130741042:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130741042	GSDMC	1
8:130741139:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	3.28E-11	7.016963612	0.000112238	G	+	8	130741139	GSDMC	1
8:130741183:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	G	-	8	130741183	GSDMC	1
8:130741320:CG	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	G	-	8	130741320	GSDMC	1
8:130742257:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130742257	GSDMC	1
8:130741547:AT	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	T	-	8	130741547	GSDMC	1
8:130741745:CG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	3.28E-11	7.016963612	0.000112238	G	-	8	130741745	GSDMC	1
8:130743801:CG	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	G	-	8	130743801	GSDMC	1
8:130745576:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	C	-	8	130745576	GSDMC	1
8:130746260:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	C	-	8	130746260	GSDMC	1
8:130752372:AC	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	C	-	8	130752372	GSDMC	1
8:130752725:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	C	-	8	130752725	GSDMC	1
8:130753603:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130753603	GSDMC	1
8:130753742:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	C	+	8	130753742	GSDMC	1
8:130754719:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	C	-	8	130754719	GSDMC	1
8:130754887:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	G	-	8	130754887	GSDMC	1
8:130755205:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.28E-11	7.016963612	0.000112238	C	+	8	130755205	GSDMC	1
8:130756531:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130756531	GSDMC	1
8:130756584:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	C	-	8	130756584	GSDMC	1
8:130757824:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	T	3.28E-11	7.016963612	0.000112238	G	-	8	130757824	GSDMC	1
8:130757826:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	3.28E-11	7.016963612	0.000112238	G	+	8	130757826	GSDMC	1
8:130758428:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	A	3.28E-11	7.016963612	0.000112238	G	-	8	130758428	GSDMC	1
8:130759120:AC	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.37E-11	7.0122104	0.000112238	C	+	8	130759120	GSDMC	1
8:130760779:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	3.41E-11	7.010265627	0.000112238	C	+	8	130760779	GSDMC	1
8:130761025:GT	GTEx	Esophagus_Mucosa	ENSG00000014707	G	3.60E-11	7.000915808	0.000112238	G	-	8	130761025	GSDMC	1
8:130760975:CT	GTEx	Esophagus_Mucosa	ENSG00000014707	C	1.15E-10	6.768626054	0.000112238	NA	NA	8	130760975	GSDMC	1
8:130761025:GT	GTEx	Muscle_Skeletal	ENSG00000014707	G	2.37E-10	6.54513282	0.00034655	G	+	8	130761025	GSDMC	1
8:130761015:CT	GTEx	Muscle_Skeletal	ENSG00000014707	T	2.40E-10	6.541642454	0.00034655	C	-	8	130761015	GSDMC	1
8:130760779:CT	GTEx	Muscle_Skeletal	ENSG00000014707	C	2.51E-10	6.535139012	0.00034655	C	+	8	130760779	GSDMC	1
8:130761578:CG	GTEx	Muscle_Skeletal	ENSG00000014707	G	2.93E-10	6.509461608	0.00034655	G	+	8	130761578	GSDMC	1
8:130742408:CT	GTEx	Muscle_Skeletal	ENSG00000014707	C	2.93E-10	6.508976802	0.00034655	C	+	8	130742408	GSDMC	1
8:130738972:AG	GTEx	Esophagus_Mucosa	ENSG00000014707	G	3.64E-10	6.19677005	0.000112238	G	-	8	130738972	GSDMC	1
8:130747520:AC	GTEx	Muscle_Skeletal	ENSG00000014707	C	3.89E-10	6.46062082	0.00034655	C	+	8	130747520	GSDMC	1
8:130746040:AT	GTEx	Muscle_Skeletal	ENSG00000014707	A	4.05E-10	6.453632301	0.00034655	T	-	8	130746040	GSDMC	1
8:130741938:GT	GTEx	Muscle_Skeletal	ENSG00000014707	G	4.29E-10	6.444004421	0.00034655	G	+	8	130741938	GSDMC	1
8:130757584:CT	GTEx	Muscle_Skeletal	ENSG00000014707	T	4.40E-10	6.439892963	0.00034655	C	-	8	130757584	GSDMC	1
8:130757824:AG	GTEx	Muscle_Skeletal	ENSG00000014707	G	4.40E-10	6.439892963	0.00034655	G	+	8	130757824	GSDMC	1
8:130758428:AG	GTEx	Muscle_Skeletal	ENSG00000014707	A	4.40E-10	6.439892963	0.00034655	G	-	8	130758428	GSDMC	1
8:130759120:AC	GTEx	Muscle_Skeletal	ENSG00000014707	C	4.40E-10	6.439892963	0.00034655	C	-	8	130759120	GSDMC	1
8:130760779:CT	GTEx	Muscle_Skeletal	ENSG00000014707	T	4.40E-10	6.439892963	0.00034655	C	-	8	130760779	GSDMC	1
8:130761025:GT	GTEx	Muscle_Skeletal	ENSG00000014707	G	4.40E-10	6.439892963	0.00034655	G	-	8	130761025	GSDMC	1
8:130760975:CT	GTEx	Muscle_Skeletal	ENSG00000014707	C	4.40E-10	6.439892963	0.00034655	C	-	8	130760975	GSDMC	1
8:130742408:CT	GTEx	Muscle_Skeletal	ENSG00000014707	T	4.40E-10	6.439892963	0.00034655	C	-	8	130742408	GSDMC	1
8:130738972:AG	GTEx	Muscle_Skeletal	ENSG00000014707	A	4.40E-10	6.439892963	0.00034655	G	-	8	130738972	GSDMC	1
8:130747520:AC	GTEx	Muscle_Skeletal	ENSG00000014707	A	4.40E-10	6.439892963	0.00034655	C	-	8	130747520	GSDMC	1
8:130746040:AT	GTEx	Muscle_Skeletal	ENSG00000014707	A	4.40E-10	6.439892963	0.00034655	T	-	8	130746040	GSDMC	1
8:130741938:GT	GTEx	Muscle_Skeletal	ENSG00000014707	G	4.40E-10	6.439892963	0.00034655	G	-	8	130741938	GSDMC	1
8:130757584:CT	GTEx	Muscle_Skeletal	ENSG00000014707	T	4.40E-10	6.439892963	0.00034655	C	-	8	130757584	GSDMC	1
8:130757824:AG	GTEx	Muscle_Skeletal	ENSG00000014707	G	4.40E-10	6.439892963	0.00034655	G	-

Table 1. Tumor characteristics (GEO, n = 57, n = 1,000,000 simulations)

| sample | TMB | HLA1 | HLA2 | HLA3 | HLA4 | HLA5 | HLA6 | HLA7 | HLA8 | HLA9 | HLA10 | HLA11 | HLA12 | HLA13 | HLA14 | HLA15 | HLA16 | HLA17 | HLA18 | HLA19 | HLA20 | HLA21 | HLA22 | HLA23 | HLA24 | HLA25 | HLA26 | HLA27 | HLA28 | HLA29 | HLA30 | HLA31 | HLA32 | HLA33 | HLA34 | HLA35 | HLA36 | HLA37 | HLA38 | HLA39 | HLA40 | HLA41 | HLA42 | HLA43 | HLA44 | HLA45 | HLA46 | HLA47 | HLA48 | HLA49 | HLA50 | HLA51 | HLA52 | HLA53 | HLA54 | HLA55 | HLA56 | HLA57 | HLA58 | HLA59 | HLA60 | HLA61 | HLA62 | HLA63 | HLA64 | HLA65 | HLA66 | HLA67 | HLA68 | HLA69 | HLA70 | HLA71 | HLA72 | HLA73 | HLA74 | HLA75 | HLA76 | HLA77 | HLA78 | HLA79 | HLA80 | HLA81 | HLA82 | HLA83 | HLA84 | HLA85 | HLA86 | HLA87 | HLA88 | HLA89 | HLA90 | HLA91 | HLA92 | HLA93 | HLA94 | HLA95 | HLA96 | HLA97 | HLA98 | HLA99 | HLA100 | HLA101 | HLA102 | HLA103 | HLA104 | HLA105 | HLA106 | HLA107 | HLA108 | HLA109 | HLA110 | HLA111 | HLA112 | HLA113 | HLA114 | HLA115 | HLA116 | HLA117 | HLA118 | HLA119 | HLA120 | HLA121 | HLA122 | HLA123 | HLA124 | HLA125 | HLA126 | HLA127 | HLA128 | HLA129 | HLA130 | HLA131 | HLA132 | HLA133 | HLA134 | HLA135 | HLA136 | HLA137 | HLA138 | HLA139 | HLA140 | HLA141 | HLA142 | HLA143 | HLA144 | HLA145 | HLA146 | HLA147 | HLA148 | HLA149 | HLA150 | HLA151 | HLA152 | HLA153 | HLA154 | HLA155 | HLA156 | HLA157 | HLA158 | HLA159 | HLA160 | HLA161 | HLA162 | HLA163 | HLA164 | HLA165 | HLA166 | HLA167 | HLA168 | HLA169 | HLA170 | HLA171 | HLA172 | HLA173 | HLA174 | HLA175 | HLA176 | HLA177 | HLA178 | HLA179 | HLA180 | HLA181 | HLA182 | HLA183 | HLA184 | HLA185 | HLA186 | HLA187 | HLA188 | HLA189 | HLA190 | HLA191 | HLA192 | HLA193 | HLA194 | HLA195 | HLA196 | HLA197 | HLA198 | HLA199 | HLA200 | HLA201 | HLA202 | HLA203 | HLA204 | HLA205 | HLA206 | HLA207 | HLA208 | HLA209 | HLA210 | HLA211 | HLA212 | HLA213 | HLA214 | HLA215 | HLA216 | HLA217 | HLA218 | HLA219 | HLA220 | HLA221 | HLA222 | HLA223 | HLA224 | HLA225 | HLA226 | HLA227 | HLA228 | HLA229 | HLA230 | HLA231 | HLA232 | HLA233 | HLA234 | HLA235 | HLA236 | HLA237 | HLA238 | HLA239 | HLA240 | HLA241 | HLA242 | HLA243 | HLA244 | HLA245 | HLA246 | HLA247 | HLA248 | HLA249 | HLA250 | HLA251 | HLA252 | HLA253 | HLA254 | HLA255 | HLA256 | HLA257 | HLA258 | HLA259 | HLA260 | HLA261 | HLA262 | HLA263 | HLA264 | HLA265 | HLA266 | HLA267 | HLA268 | HLA269 | HLA270 | HLA271 | HLA272 | HLA273 | HLA274 | HLA275 | HLA276 | HLA277 | HLA278 | HLA279 | HLA280 | HLA281 | HLA282 | HLA283 | HLA284 | HLA285 | HLA286 | HLA287 | HLA288 | HLA289 | HLA290 | HLA291 | HLA292 | HLA293 | HLA294 | HLA295 | HLA296 | HLA297 | HLA298 | HLA299 | HLA300 | HLA301 | HLA302 | HLA303 | HLA304 | HLA305 | HLA306 | HLA307 | HLA308 | HLA309 | HLA310 | HLA311 | HLA312 | HLA313 | HLA314 | HLA315 | HLA316 | HLA317 | HLA318 | HLA319 | HLA320 | HLA321 | HLA322 | HLA323 | HLA324 | HLA325 | HLA326 | HLA327 | HLA328 | HLA329 | HLA330 | HLA331 | HLA332 | HLA333 | HLA334 | HLA335 | HLA336 | HLA337 | HLA338 | HLA339 | HLA340 | HLA341 | HLA342 | HLA343 | HLA344 | HLA345 | HLA346 | HLA347 | HLA348 | HLA349 | HLA350 | HLA351 | HLA352 | HLA353 | HLA354 | HLA355 | HLA356 | HLA357 | HLA358 | HLA359 | HLA360 | HLA361 | HLA362 | HLA363 | HLA364 | HLA365 | HLA366 | HLA367 | HLA368 | HLA369 | HLA370 | HLA371 | HLA372 | HLA373 | HLA374 | HLA375 | HLA376 | HLA377 | HLA378 | HLA379 | HLA380 | HLA381 | HLA382 | HLA383 | HLA384 | HLA385 | HLA386 | HLA387 | HLA388 | HLA389 | HLA390 | HLA391 | HLA392 | HLA393 | HLA394 | HLA395 | HLA396 | HLA397 | HLA398 | HLA399 | HLA400 | HLA401 | HLA402 | HLA403 | HLA404 | HLA405 | HLA406 | HLA407 | HLA408 | HLA409 | HLA410 | HLA411 | HLA412 | HLA413 | HLA414 | HLA415 | HLA416 | HLA417 | HLA418 | HLA419 | HLA420 | HLA421 | HLA422 | HLA423 | HLA424 | HLA425 | HLA426 | HLA427 | HLA428 | HLA429 | HLA430 | HLA431 | HLA432 | HLA433 | HLA434 | HLA435 | HLA436 | HLA437 | HLA438 | HLA439 | HLA440 | HLA441 | HLA442 | HLA443 | HLA444 | HLA445 | HLA446 | HLA447 | HLA448 | HLA449 | HLA450 | HLA451 | HLA452 | HLA453 | HLA454 | HLA455 | HLA456 | HLA457 | HLA458 | HLA459 | HLA460 | HLA461 | HLA462 | HLA463 | HLA464 | HLA465 | HLA466 | HLA467 | HLA468 | HLA469 | HLA470 | HLA471 | HLA472 | HLA473 | HLA474 | HLA475 | HLA476 | HLA477 | HLA478 | HLA479 | HLA480 | HLA481 | HLA482 | HLA483 | HLA484 | HLA485 | HLA486 | HLA487 | HLA488 | HLA489 | HLA490 | HLA491 | HLA492 | HLA493 | HLA494 | HLA495 | HLA496 | HLA497 | HLA498 | HLA499 | HLA500 | HLA501 | HLA502 | HLA503 | HLA504 | HLA505 | HLA506 | HLA507 | HLA508 | HLA509 | HLA510 | HLA511 | HLA512 | HLA513 | HLA514 | HLA515 | HLA516 | HLA517 | HLA518 | HLA519 | HLA520 | HLA521 | HLA522 | HLA523 | HLA524 | HLA525 | HLA526 | HLA527 | HLA528 | HLA529 | HLA530 | HLA531 | HLA532 | HLA533 | HLA534 | HLA535 | HLA536 | HLA537 | HLA538 | HLA539 | HLA540 | HLA541 | HLA542 | HLA543 | HLA544 | HLA545 | HLA546 | HLA547 | HLA548 | HLA549 | HLA550 | HLA551 | HLA552 | HLA553 | HLA554 | HLA555 | HLA556 | HLA557 | HLA558 | HLA559 | HLA560 | HLA561 | HLA562 | HLA563 | HLA564 | HLA565 | HLA566 | HLA567 | HLA568 | HLA569 | HLA570 | HLA571 | HLA572 | HLA573 | HLA574 | HLA575 | HLA576 | HLA577 | HLA578 | HLA579 | HLA580 | HLA581 | HLA582 | HLA583 | HLA584 | HLA585 | HLA586 | HLA587 | HLA588 | HLA589 | HLA590 | HLA591 | HLA592 | HLA593 | HLA594 | HLA595 | HLA596 | HLA597 | HLA598 | HLA599 | HLA600 | HLA601 | HLA602 | HLA603 | HLA604 | HLA605 | HLA606 | HLA607 | HLA608 | HLA609 | HLA610 | HLA611 | HLA612 | HLA613 | HLA614 | HLA615 | HLA616 | HLA617 | HLA618 | HLA619 | HLA620 | HLA621 | HLA622 | HLA623 | HLA624 | HLA625 | HLA626 | HLA627 | HLA628 | HLA629 | HLA630 | HLA631 | HLA632 | HLA633 | HLA634 | HLA635 | HLA636 | HLA637 | HLA638 | HLA639 | HLA640 | HLA641 | HLA642 | HLA643 | HLA644 | HLA645 | HLA646 | HLA647 | HLA648 | HLA649 | HLA650 | HLA651 | HLA652 | HLA653 | HLA654 | HLA655 | HLA656 | HLA657 | HLA658 | HLA659 | HLA660 | HLA661 | HLA662 | HLA663 | HLA664 | HLA665 | HLA666 | HLA667 | HLA668 | HLA669 | HLA670 | HLA671 | HLA672 | HLA673 | HLA674 | HLA675 | HLA676 | HLA677 | HLA678 | HLA679 | HLA680 | HLA681 | HLA682 | HLA683 | HLA684 | HLA685 | HLA686 | HLA687 | HLA688 | HLA689 | HLA690 | HLA691 | HLA692 | HLA693 | HLA694 | HLA695 | HLA696 | HLA697 | HLA698 | HLA699 | HLA700 | HLA701 | HLA702 | HLA703 | HLA704 | HLA705 | HLA706 | HLA707 | HLA708 | HLA709 | HLA710 | HLA711 | HLA712 | HLA713 | HLA714 | HLA715 | HLA716 | HLA717 | HLA718 | HLA719 | HLA720 | HLA721 | HLA722 | HLA723 | HLA724 | HLA725 | HLA726 | HLA727 | HLA728 | HLA729 | HLA730 | HLA731 | HLA732 | HLA733 | HLA734 | HLA735 | HLA736 | HLA737 | HLA738 | HLA739 | HLA740 | HLA741 | HLA742 | HLA743 | HLA744 | HLA745 | HLA746 | HLA747 | HLA748 | HLA749 | HLA750 | HLA751 | HLA752 | HLA753 | HLA754 | HLA755 | HLA756 | HLA757 | HLA758 | HLA759 | HLA760 | HLA761 | HLA762 | HLA763 | HLA764 | HLA765 | HLA766 | HLA767 | HLA768 | HLA769 | HLA770 | HLA771 | HLA772 | HLA773 | HLA774 | HLA775 | HLA776 | HLA777 | HLA778 | HLA779 | HLA780 | HLA781 | HLA782 | HLA783 | HLA784 | HLA785 | HLA786 | HLA787 | HLA788 | HLA789 | HLA790 | HLA791 | HLA792 | HLA793 | HLA794 | HLA795 | HLA796 | HLA797 | HLA798 | HLA799 | HLA800 | HLA801 | HLA802 | HLA803 | HLA804 | HLA805 | HLA806 | HLA807 | HLA808 | HLA809 | HLA810 | HLA811 | HLA812 | HLA813 | HLA814 | HLA815 | HLA816 | HLA817 | HLA818 | HLA819 | HLA820 | HLA821 | HLA822 | HLA823 | HLA824 | HLA825 | HLA826 | HLA827 | HLA828 | HLA829 | HLA830 | HLA831 | HLA832 | HLA833 | HLA834 | HLA835 | HLA836 | HLA837 | HLA838 | HLA839 | HLA840 | HLA841 | HLA842 | HLA843 | HLA844 | HLA845 | HLA846 | HLA847 | HLA848 | HLA849 | HLA850 | HLA851 | HLA852 | HLA853 | HLA854 | HLA855 | HLA856 | HLA857 | HLA858 | HLA859 | HLA860 | HLA861 | HLA862 | HLA863 | HLA864 | HLA865 | HLA866 | HLA867 | HLA868 | HLA869 | HLA870 | HLA871 | HLA872 | HLA873 | HLA874 | HLA875 | HLA876 | HLA877 | HLA878 | HLA879 | HLA880 | HLA881 | HLA882 | HLA883 | HLA884 | HLA885 | HLA886 | HLA887 | HLA888 | HLA889 | HLA890 | HLA891 | HLA892 | HLA893 | HLA894 | HLA895 | HLA896 | HLA897 | HLA898 | HLA899 | HLA900 | HLA901 | HLA902 | HLA903 | HLA904 | HLA905 | HLA906 | HLA907 | HLA908 | HLA909 | HLA910 | HLA911 | HLA912 | HLA913 | HLA914 | HLA915 | HLA916 | HLA917 | HLA918 | HLA919 | HLA920 | HLA921 | HLA922 | HLA923 | HLA924 | HLA925 | HLA926 | HLA927 | HLA928 | HLA929 | HLA930 | HLA931 | HLA932 | HLA933 | HLA934 | HLA935 | HLA936 | HLA937 | HLA938 | HLA939 | HLA940 | HLA941 | HLA942 | HLA943 | HLA944 | HLA945 | HLA946 | HLA947 | HLA948 | HLA949 | HLA950 | HLA951 | HLA952 | HLA953 | HLA954 | HLA955 | HLA956 | HLA957 | HLA958 | HLA959 | HLA960 | HLA961 | HLA962 | HLA963 | HLA964 | HLA965 | HLA966 | HLA967 | HLA968 | HLA969 | HLA970 | HLA971 | HLA972 | HLA973 | HLA974 | HLA975 | HLA976 | HLA977 | HLA978 | HLA979 | HLA980 | HLA981 | HLA982 | HLA983 | HLA984 | HLA985 | HLA986 | HLA987 | HLA988 | HLA989 | HLA990 | HLA991 | HLA992 | HLA993 | HLA994 | HLA995 | HLA996 | HLA997 | HLA998 | HLA999 | HLA1000 |
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