Published in final edited form as:
Pain. 2019 June ; 160(6): 1361–1373. doi:10.1097/j.pain.0000000000001514.

Insight into the genetic architecture of back pain and its risk factors from a study of 509,000 individuals

Maxim B Freidin[1,*], **Yakov A Tsepilov**[2,3,4,*], **Melody Palmer**[5], **Lennart C Karssen**[4], **CHARGE Musculoskeletal Working Group**, **Pradeep Suri**[6,7,8], **Yurii S Aulchenko**[4], **Frances MK Williams**[1,#]

[1]Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, London, UK [2]Novosibirsk State University, Faculty of Natural Sciences, Novosibirsk, Russia [3]Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia [4]PolyOmica, 's-Hertogenbosch, The Netherlands [5]Department of Medical Genetics, University of Washington, Seattle, USA [6]Seattle Epidemiologic Research and Information Center (ERIC), Veterans Affairs Office of Research and Development, Seattle, USA [7]Rehabilitation Care Services, VA Puget Sound Healthcare System, Seattle, USA [8]Department of Rehabilitation Medicine, University of Washington, Seattle, USA

Abstract

Back pain (BP) is a common condition of major social importance and poorly understood pathogenesis. Combining data from the UK Biobank and CHARGE consortium cohorts allowed us to perform a very large GWAS (total N = 509,070) and examine the genetic correlation and pleiotropy between BP and its clinical and psychosocial risk factors. We identified and replicated three BP associated loci, including one novel region implicating *SPOCK2*/*CHST3* genes. We provide evidence for pleiotropic effects of genetic factors underlying BP, height, and intervertebral disc problems. We also identified independent genetic correlations between BP and depression symptoms, neuroticism, sleep disturbance, overweight, and smoking. A significant enrichment for genes involved in central nervous system and skeletal tissue development was observed. The study of pleiotropy and genetic correlations, supported by the pathway analysis, suggests at least two strong molecular axes of BP genesis, one related to structural/anatomic factors such as intervertebral disk problems and anthropometrics; and another related to the psychological

[#]Corresponding author.
[*]These authors contributed equally to this work.

AUTHOR CONTRIBUTIONS

MF and YT contributed to the design of the study, carried out statistical analysis, produced the figures, and first draft of the manuscript; LC provided statistical and computational support; MP and PS analysed CHARGE dataset and contributed to interpretation of the results; YA and FW conceived and oversaw the study, contributed to the design and interpretation of the results; all co-authors contributed to the final manuscript revision.

COMPETING FINANCIAL INTERESTS

YSA and LCK are owners of Maatschap PolyOmica, a private organization, providing services, research and development in the field of computational and statistical (gen)omics. Other authors declare no conflicts of interest.

DATA AVAILABILITY

Summary statistics from our GWAS discovery and meta-analysis are available for interactive exploration at the GWAS archive (http://gwasarchive.org). The data set was also deposited at Zenodo (https://doi.org/10.5281/zenodo.1319332). The data generated in the secondary analyses of this study are included with this article in the supplementary tables.

component of pain perception and pain processing. These findings corroborate the current biopsychosocial model as a paradigm for BP. Overall, the results demonstrate BP to have an extremely complex genetic architecture that overlaps with the genetic predisposition to its biopsychosocial risk factors. The work sheds light on pathways of relevance in the prevention and management of LBP.

Keywords

back pain; genome-wide association study; CHARGE; UK Biobank; pleiotropy

INTRODUCTION

Back pain (BP) is a common debilitating condition with a lifetime prevalence of 40% and a very important socioeconomic impact [26; 37]. According to the Global Burden of Disease 2016 study, it leads the list of disabling conditions in many parts of the world [8]. Known clinical risk factors for BP include age, female gender and raised body mass index [56]. The greatest risk for episodes of severe BP in population based studies is thought to be attributable to intervertebral lumbar disc degeneration (LDD) [75], though its predictive and diagnostic impact remains debated [62]. In the majority of episodes of BP the symptoms are transient; however, about 10% of those experiencing acute BP develop a chronic condition [37] which places a great socioeconomic burden on society [16; 25; 38].

There is a clear genetic predisposition to BP with estimates of heritability in the range of 30%−68% [3; 28; 33; 43]. Similar or higher heritability estimates for LDD have been obtained [4; 29]. Importantly, not only is there a phenotypic association between LDD and LBP but a genetic correlation between the two has been reported in twin studies (11%−13%) [3; 31], suggestive of shared genetic background. Twin studies have demonstrated that BP also shares an underlying genetic predisposition with several of its risk factors including depression and anxiety [49], educational attainment [73], obesity [9] as well as with other pain conditions such as chronic widespread musculoskeletal pain [36].

We recently performed a genome-wide association study (GWAS) for chronic BP (BP lasting longer than 3 months) from the interim release of the UK Biobank [54] and from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Musculoskeletal Working Group [55] (total N = 158,000 individuals). Despite a large sample size and relatively well-defined phenotype, the study identified and replicated only three loci associated with chronic BP. This suggests that the genetic architecture of BP is extremely complex and far larger samples are required to make progress in the field.

In the present study we sought to expand the BP GWAS and explore the genetic associations with many of the biopsychosocial risk factors for BP. In brief, we examined 350,000 individuals of European ancestry from the UK Biobank in the discovery phase (91,100 cases and 258,900 controls) followed by a replication phase combining the UK Biobank participants of European, African and Asian ancestry not included in the discovery set, and data from the CHARGE cohorts (total N = 157,752). Post-GWAS analyses included the analysis of pleiotropy, genetic correlations and pathway analyses (Figure 1).

MATERIAL AND METHODS

Phenotype definition

The study was based on data from the UK Biobank Resource [54] and cohorts from CHARGE Consortium Musculoskeletal Working Group. For UK Biobank cases of BP were defined as those who reported “Back pain” in the response to the question: “Pain type(s) experienced in last month”. Controls were defined as those who did not report BP in response to this question. Individuals who did not reply or replied: “Prefer not to answer” or “Pain all over the body” were excluded.

For CHARGE Consortium cases were defined as those reporting BP present for at least 3 months, while the controls were defined as those who reported no BP or BP with shorter duration [55]. Thus, the definition of BP in these cohorts corresponded to chronic BP.

Sample

The available sample from UK Biobank included 487,409 individuals with imputed data. We split the UK Biobank into discovery and replication subsets to be able to achieve at least 80% statistical power for replication based on our preliminary analysis of the interim release of the UK Biobank dataset. For the discovery set we selected at random 350,000 British individuals of European ancestry (EA) according to the genetic principal components provided by the UK Biobank (Supplementary Table 1).

For replication, we used a combination of the UK Biobank participants not included in the discovery set, and from the CHARGE Consortium [55]. Replication cohorts from the UK Biobank comprised rest of EA individuals (n = 103,862), individuals of African ancestry (AA, n = 7,259), individuals of South Asian ancestry (Indian, Pakistani, and Bangladeshi; n = 7,159), and Chinese individuals (n = 1,485). The CHARGE Consortium provided data for EA individuals from 15 cohorts (total n = 35,205–37,987). To reduce the risk of bias due to population stratification, all these groups were analysed separately followed by a meta-analysis. Total resulting sample size for replication was 154,970–157,752 individuals (Supplementary Table 1).

Statistical analysis

Genome-wide association testing—PLINK 2.0 was used to carry out the genome-wide association analysis in the UK Biobank discovery and replication samples. Imputed genotypes provided by the UK Biobank were used [54] and only SNPs imputed using the Haplotype Reference Consortium panel (http://www.haplotype-reference-consortium.org/site) were analysed due to the reported issue with SNPs imputed using 1000 Genomes panel (http://www.ukbiobank.ac.uk/2017/07/important-note-about-imputed-genetics-data/; Additional results file). Logistic regression was used to evaluate additive genetic effects of the SNPs for BP as a binary trait adjusting for age, sex, genotyping array type, and 10 genetic principal components provided by the UK Biobank.

The following filters were applied: minor allele count ≥100; deviation from Hardy-Weinberg equilibrium p-value ≥1e-6; genotyping call rate ≥0.98%; individual call rate ≥0.98%; and

imputation quality score ≥0.7 (MACH r2 calculated by PLINK 2.0). Only biallelic autosomal markers were used and SNPs that had the same rsID in different genomic locations were excluded.

Conditional and joint multi-SNP analysis—Conditional and joint analysis (COJO) as implemented in the program GCTA [72] was used to find SNPs independently associated with the phenotype. As the input, this method uses summary statistics and a reference sample to estimate LD. We performed the analyses using $p = 5\times10^{-8}$ and $p = 1\times10^{-5}$ as the genome-wide significance and suggestive significance thresholds respectively. For the LD reference, we used a sample of 10,000 British EA individuals randomly selected from 350,000 people used in the GWAS discovery phase.

Replication and meta-analysis—Replication was performed by meta-analysis of all replication cohorts for loci selected at the discovery phase. Replication significance threshold was set as p-value<0.01 (Bonferroni corrected 0.05/5). Subsequent analyses of heritability, genetic correlation, and functional investigation used the results of meta-analysis of the discovery cohort and replication cohort of EA individuals from UK Biobank (N=453,862). METAL software [68] was used for inverse-variance-weighted meta-analysis.

LD hub [76] and ldsc [7] tools were used to calculate genetic correlations. Summary statistics files were filtered using ldsc software with default options (r2>0.9, MAF>0.01 and the overlap with “high quality SNPs” – a total of 1,215,001 common HapMap3 SNPs with high imputation quality). The HLA region on chromosome 6 was excluded. These SNPs were used for the further analysis of genetic correlations as well as to estimate genomic control inflation factor lambda (intercept) [11]. SNP-based heritability was calculated using the genome wide restricted multiple likelihood (GREML) algorithm [71] as implemented in BOLT-LMM software [32].

Genetic correlation analyses

Genetic correlations were estimated using the BP meta-analysis results (N=453,862), not including the CHARGE cohorts. Two sets of traits were analyzed. The first set included a total of 225 traits out of 235 available on LD-hub after removing duplicates via using only the most recent study for each trait as indicated by the largest PMID number. Another set comprised 17 traits considered by us as risk factors for BP: self-reported osteoarthritis, self-reported intervertebral disc problems, self-reported osteoporosis, scoliosis, smoking status, standing height, BMI, happiness, fluid intelligence score, years of education, anxiety/panic attacks, depression and Big Five personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism). Genetic correlations between BP and 225 traits were considered statistically significant at p-value $\leq 4.4\times10^{-5}$ (Bonferroni corrected, 0.01/225). To visualize the results, we focused on genetic correlations of greatest magnitude and selected only the traits with absolute values of genetic correlation with BP >0.25. This filtering led to a total of 23 traits (excluding BP). Clustering and visualization were carried out using “corrplot” package for R and basic “hclust” function. For clustering, we estimated squared Euclidean distances by subtracting absolute values of genetic correlation from 1 and used Ward’s clustering method.

To obtain genetic correlations that were independent from each other, we estimated partial genetic correlations with BP for a subset of traits using the inverse of the correlation matrix followed by the correlation estimate using the equation $\rho_{ij} = -\frac{p_{ij}}{\sqrt{p_{ii} * p_{jj}}}$, where p_{ij} is the {*i*,*j*} element of the inverted matrix. To avoid collinearity, from the 23 traits most strongly correlated with BP we selected 8 traits representing subclusters (having the highest absolute value of genetic correlation with BP) of the correlation dendrogram using distance threshold of 0.5.

In silico functional analysis

VEP, RegulomeDB and credible set—Functional annotation of SNPs was carried out using variant effect predictor (VEP) software [40] with GRCH37 genomic reference and RegulomeDB database [6]. For each studied locus, we selected the 'credible set' of SNPs that had strong associations with BP and was thought likely to have causal influences on genes within the associated loci, using the PAINTOR method [30]. To apply PAINTOR, we used the same reference set of individuals as described above (n = 10,000; the same subset as used in the COJO and DEPICT analyses) to generate a clumped set of SNPs followed by the estimate of pair-wise correlation matrices for all SNPs in each region using PLINK1.9 (we did not apply PLINK2 for these procedures as it doesn't have this functionality). The PAINTOR software was run using its default parameters. In the next step, for all selected SNPs we added LD-proxies with r^2>0.8 in the EUR population according to 1000G v3 data. All output results were aggregated into one file and SNPs marked by PAINTOR as the 99% credible set (a list of SNPs that, with a 99% probability, would include the functional variants) were chosen for further functional annotation using VEP and RegulomeDB.

SMR/HEIDI analysis—Potential pleiotropic effects of genetic variants on BP and other traits were tested using summary data-based Mendelian randomization (SMR) analysis and heterogeneity in dependent instruments (HEIDI) method [77]. SMR-HEIDI is analogous to conventional Mendelian randomization and may be conducted using summary level GWAS data. In short, the SMR tests for association between the traits of interest mediated by a locus, and HEIDI identifies whether the traits are affected by the same underlying causal variant. This analysis was carried out for SNPs associated with BP in the current study. Briefly, starting with an index SNP, we screened for traits which may be affected by genetic variation in the same region, and then performed a pleiotropy vs linkage disequilibrium test. In the screening stage, we used a limited list of traits including 19 traits considered as risk factors for BP (Supplementary table 2A). To perform HEIDI analysis, regional summary level GWAS results are required, including regression coefficients and respective standard errors. Such data were available for seventeen traits: self-reported osteoarthritis, self-reported intervertebral disc problems, self-reported osteoporosis, scoliosis, smoking status, standing height, BMI, happiness, fluid intelligence score, years of education, anxiety/panic attacks, depression and Big Five personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism).

We also examined for overlap between the SNPs associated with BP and eQTLs in blood [67] and 44 tissues provided by the GTEx database [17] (Supplementary tables 2B) using a

similar procedure: we examined if a SNP was established as an eQTL for a specific gene in the region of interest and, if positive, the HEIDI test was performed as above.

Following Bonferroni procedure, the results of the SMR test were considered statistically significant at $p < 3\times10^{-5}$ (0.05/1685, where 1685 is the number of genes available in blood eQTL data and GTEx data for three studied loci) for eQTLs; and $p<9.8\times10^{-4}$ (0.05/(17×3) accounting for 3 studied loci and 17 complex traits) for complex traits.

For the HEIDI test, a hypothesis of pleiotropy was rejected at $p < 0.01$; the hypothesis was accepted at $p>0.01$.

Gene prioritization, pathway and tissue enrichment analysis—To prioritize genes in associated regions, gene set enrichment and tissue/cell type enrichment analyses were carried out using DEPICT software v. 1 rel. 194 [47]. For this analysis we chose independent variants (identified by COJO) found in the BP meta-analysis results (N=453,862) with $p<5\times10^{-8}$ (23 SNPs) and $p<1\times10^{-5}$ (227 SNPs). We used a random subset of 10,000 individuals from the UK Biobank for calculation of LD (the same subsets as used for COJO analysis).

We also conducted gene analysis and gene-set analysis using MAGMA v1.6 included in FUMA web tool [66] using the default options.

RESULTS

Novel genomic loci associated with back pain

The discovery sample of white British individuals (as defined by genetic principal components; N = 350,000) comprised 91,100 BP cases and 258,900 controls, giving a prevalence of BP of 26%. Cases and controls did not differ significantly by age (mean age 57.05 years) or sex (54% female) (Supplementary Table 1). SNP-based heritability estimated by the GREML algorithm was 6.8±0.2% on the observed scale and 12.2±0.4% on the liability scale. LD-score regression estimated the genomic inflation factor to be 1.29 with an intercept of 1.032±0.009 and an estimate of the standardized genomic control inflation factor of λ_{1000}=1.00024 [1]); this suggests that most of the inflation was introduced by polygenic effects and that the influence of confounding by population structure and cryptic relatedness was minimal (QQ-plot in Supplementary Figure 1).

After adjusting the results of the discovery GWAS for genomic control factor of 1.032, a total of 183 SNPs positioned over 5 loci remained statistically significant at genome-wide significance level of $p\leq5\times10^{-8}$ (Figure 2; Table 1). COJO confirmed that the 5 regions were independent of one another (Supplementary Table 3A). Using meta-analysis of the UK Biobank replication cohorts and the CHARGE Consortium cohorts (total N = 154,970–157,752), three associations were replicated ($p<0.01$) (Supplementary Table 3B): rs12310519 ($p = 5.00\times10^{-5}$), rs7814941 ($p = 5.32\times10^{-5}$), and rs3180 ($p = 6.59\times10^{-3}$).

Of the three replicated loci, two have been reported previously as associated with other BP phenotypes: the chromosome 12 lead SNP rs12310519 located in the intron of the *SOX5* gene was associated with chronic BP in the recent GWAS by the CHARGE and PainOMICS

consortia [55]. The region on chromosome 8 (lead SNP rs7814941), located in an intergenic site of *GSDMC* and *CCDC26* was identified in a study of sciatica [5] and was among the loci associated with chronic BP at $p<5\times10^{-8}$ in the GWAS by the CHARGE and PainOMICS consortia [55] but not previously replicated.

The novel replicated locus on chromosome 10 (rs3180 SNP) lies in the region between the 3'-UTR of *SPOCK2* and downstream of the *CHST3* gene. This region was previously shown to be associated with LDD with the leading SNP rs4148941 reported as a functional variant influencing *CHST3* gene expression level in intervertebral disc tissue [53]. The gene encodes an enzyme which catalyzes sulfation of chondroitin, a component of proteoglycans crucially important in cartilage tissue function and hydration. Rare mutations in *CHST3* that disrupt its enzymatic activity have been reported in patients with recessive skeletal abnormalities, including spondyloepiphyseal dysplasia Omani type, Larsen syndrome, humero-spinal dysostosis, and chondrodysplasia with multiple dislocation [22; 57–60]. Another gene in the region, *SPOCK2*, was previously reported as the positional candidate for bronchopulmonary dysplasia [18], chromosome 16q carcinogenic deletion (along with *CHST3*) [42], and age of smoking initiation [10]. The gene encodes a proteoglycan SPARC/Osteonectin (Cwcv And Kazal Like Domains Proteoglycan 2) involved in extracellular matrix formation and is highly expressed in the central nervous system (CNS) [61]. Using available *in-silico* instruments we did not find sufficient evidence to determine whether *SPOCK2* or *CHST3* was the most likely gene associated with BP on chromosome 10 (See Additional results file).

We also sought to determine whether the three replicated loci hold known functional variants using variant effect predictor (VEP) analysis [40] and the RegulomeDB database [6]. For each locus we selected sets of SNPs that would most likely include a functional variant (the so-called 99% 'credible set'; see Material and Methods). In total, we selected 203 SNPs (Supplementary Table 4A). According to the results of the VEP annotation, there were no missense variants or variants with strongly predicted regulatory function in terms of influence protein activity (Supplementary Table 4B). However, according to RegulomeDB, a number of SNPs in the chromosome 8 and chromosome 10 loci were found likely to influence binding of transcription factors (Supplementary Table 4C). In particular, 8 SNPs on chromosome 8 had RegulomeDB score 2b ("Likely to affect binding"). On chromosome 10, 8 SNPs had RegulomeDB scores 1b,d,f ("Likely to affect binding and linked to expression of a gene target") and 6 SNPs had scores 2a,b ("Likely to affect binding"). Importantly, the lead SNPs from these two loci, rs7814941 and rs3180, did not appear to be functional. Also, none of the SNPs from the credible set on chromosome 12 was predicted to be functional according to RegulomeDB. These results suggest that genetic variation in the chromosome 8 and 10 loci likely influence back pain via gene expression rather than protein function. At present no conclusion can be drawn for chromosome 12 region.

To achieve higher statistical power for the subsequent study of pleiotropic effects and genetic correlations, a meta-analysis of discovery (EA British N = 350,000) and replication sets (other EA N = 103,862) was performed, yielding a total sample size of 453,862. The SNP-based heritability estimate from this meta-GWAS was 6.9±0.2% on the observed scale and 12.3±0.4% on the liability scale. LD-score regression estimated the genomic inflation

factor to be 1.37 with intercept of 1.036±0.009 (standardized genomic control inflation factor of λ_{1000}=1.00021). A total of 651 SNPs in 23 loci achieved genome-wide significance threshold of $p<5\times10^{-8}$ (Supplementary Figure 2, Supplementary Tables 5). COJO analysis confirmed that significant loci were independent of one another. Subsequently, we refer to the results of this meta-analysis as BP_{ma} to contrast with the discovery GWAS.

Causal and pleiotropic effects of genetic factors underlying back pain and its risk factors

Identifying causal genes via a study of gene expression—For replicated regions we aimed to identify genes whose expression might mediate the association between SNP and BP. We performed a summary-data based Mendelian randomization (SMR) analysis followed by heterogeneity in dependent instruments (HEIDI) analysis [77] using eQTL data from a range of tissues including blood [67] and 44 tissues provided in the GTEx v. 6p database [17] (Supplementary table 2A). In short, SMR tests the association between gene expression in a particular tissue and a trait using the most highly associated SNP as a genetic instrument. A significant SMR test indicates that a given functional variant determines both gene expression and the trait of interest via causality or pleiotropy, but it may also suggest that functional variants underlying gene expression are in linkage disequilibrium with those controlling the trait. Whether a functional variant mediates both BP and gene expression was inferred from the HEIDI test: $p_{HEIDI} \geq 0.01$ (likely shared causal SNP) and $p_{HEIDI} < 0.01$ (sharing of a causal SNP is unlikely). Results are presented in Supplementary Table 2C.

We observed a statistically significant SMR ($p<3\times10^{-5}$) and no difference in association patterns for the rs3180 locus and *SPOCK2* in blood ($\beta_{SMR} = 5.9$; $p_{SMR} = 1.0\times10^{-8}$) and in adrenal gland ($\beta_{SMR} = -20.6$; $p_{SMR} = 1.3\times10^{-6}$). Moreover, for this locus we detected three suggestively significant SMR coefficient and $p_{HEIDI} >0.01$: two for the *CHST3* gene in testis ($\beta_{SMR} = 6.3$; $p_{SMR} = 5.5\times10^{-5}$) and in EBV-transformed lymphocytes ($\beta_{SMR} = -17.1$; $p_{SMR} = 1.7\times10^{-4}$); and one for the *SPOCK2* gene in muscle skeletal tissue ($\beta_{SMR} = -9.6$; $p_{SMR} = 8.7\times10^{-5}$). The results suggest that either *SPOCK2* or *CHST3* or both are causal genes for BP in the region tagged by rs3180. It is worth noting though that some of the tissues with significant findings in this analysis (testis, EBV-transformed lymphocytes, adrenal gland) do not seem relevant to BP in an anatomical or functional sense. Nevertheless, a BP-associated variation in the *SPOCK2*/*CHST3* region was linked with *CHST3* expression in intervertebral disc tissue in an *in vitro* functional study previously [53].

For the locus tagged by rs7814941 we detected two statistically significant SMR coefficients for the *GSDMC* gene. However, in all cases there was a significant ($p_{HEIDI} <2\times10^{-7}$) difference in association patterns between the SNP and the gene expression and BP. This suggests that the association between this region and BP is unlikely driven by variation in *GSDMC* gene expression.

Pleiotropic effects of genetic variants associated with BP and other complex traits—Using the SMR/HEIDI approach, we also tested for potential pleiotropy of effects of three BP loci on seventeen known risk factors or related conditions for which data were available in public databases: osteoarthritis, self-reported intervertebral disc problems, osteoporosis, scoliosis, smoking status, standing height, BMI, well-being (happiness), fluid

intelligence score, educational attainment (years of education), anxiety/panic attacks, depression and the 'Big Five' personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism) (Supplementary Table 2B; Supplementary methods).

Results are presented in Supplementary Table 2D. Statistically significant ($p<9.8\times10^{-4}$) SMR coefficients were revealed for height with variants rs7814941 and rs3180 (p_{SMR} = 3.60×10^{-13} and 4.35×10^{-5}, respectively). Locus rs7814941 showed significant heterogeneity in association patterns with height ($p_{HEIDI} = 5.58\times10^{-12}$) suggesting the presence of different functional variants for height and BP at this locus. Locus rs3180 showed no heterogeneity in association patterns between BP and height in HEIDI ($p_{HEIDI} = 0.79$), thus suggesting pleiotropy – the same functional variant(s) was influencing both traits. All three loci demonstrated significant SMR results with intervertebral disc problems (p_{SMR} = 3.30×10^{-7}, 3.75×10^{-7}, and 3.17×10^{-5}, for rs3180, rs12310519, and rs7814941, respectively; Table 2); with all three showing no heterogeneity in association patterns between BP and intervertebral disc problems (all $p_{HEIDI} > 0.01$); and in all cases SMR coefficient was positive, suggesting that the same causal genetic factors attributable to these loci increase the risk of both BP and self-reported intervertebral disc problems.

Back pain shares genetic components with psychiatric, sociodemographic and anthropometric traits

To establish shared genetic components between BP and other complex traits, we carried out an agnostic analysis of 225 complex traits available in LD-hub. We observed a significant genetic correlation ($p<4.4\times10^{-5}$) between BP_{ma} and 33 traits (Supplementary Table 6, Supplementary Figure 3), with the strongest positive correlations ($\rho_g>0.35$) found with BP and neuroticism [45] ($\rho_g=0.49$), insomnia [19] ($\rho_g=0.46$), depressive symptoms [45] ($\rho_g=0.53$) and major depressive disorder [35] ($\rho_g=0.39$). The strongest negative correlations ($\rho_g<-0.35$) were between BP_{ma} and age of first birth [2] ($\rho_g=-0.49$), years of schooling [46] ($\rho_g=-0.47$), mothers age at death [48] ($\rho_g=-0.43$), parents age at death [48] ($\rho_g=-0.38$) and college completion [51] ($\rho_g=-0.51$). The traits exhibiting strong genetic correlation with BP fell into several distinct clusters (Figure 3): 1) the cluster of obesity-related traits, 2) the cluster related to mood and sleep, and 3) the cluster related to sociodemographic factors (including education) and smoking.

To identify which pair-wise genetic correlations were conditionally independent of each other, we calculated partial genetic correlations for BP_{ma} and 8 traits selected from each subcluster (using a distance threshold of 0.5 on a hierarchical clustering dendrogram) of the genetic correlation matrix (Figure 4, Supplementary Figure 4). In short, partial correlation is the measure of association between two variables while controlling for the effect of one or more additional variables. This analysis found such traits as "mother age of death", "lung cancer", and "former vs current smoking", and "age of first birth" to not be independently correlated with BP. Partial correlations for depressive symptoms and sleep duration were similar to the pair-wise correlations. Finally, partial correlations with BP for "waist circumference" and "college completion" were much smaller than the pair-wise correlations but remained statistically significant ($p<4.4\times10^{-5}$).

In addition to an agnostic analysis of all complex traits from LD-hub, we also carried out a focused analysis of genetic correlations between BP and 17 complex traits considered as risk factors for BP: self-reported osteoarthritis, self-reported intervertebral disc problems, self-reported osteoporosis, scoliosis, smoking status, standing height, BMI, happiness, fluid intelligence score, years of education, anxiety/panic attacks, depression and Big Five traits (Supplementary Table 2B). The strongest positive correlations were found for self-reported intervertebral disc problems ($\rho_g = 0.77$, $p = 6.7\times10^{-24}$); self-reported osteoarthritis ($\rho_g = 0.55$, $p = 7.5\times10^{-41}$); and depression ($\rho_g = 0.44$, $p = 1.3\times10^{-23}$). The strongest negative correlation was found for education attainment ($\rho_g = -0.47$, $p = 7.1\times10^{-101}$). Scoliosis, smoking status and BMI had moderate positive genetic correlation with BP_{ma} ($\rho_g = 0.35$, 0.35 and 0.33 respectively, with p=0.001, 7.3×10^{-42} and 2.0×10^{-56} respectively). Overall, the results of the analysis of the risk factors were consistent with the analysis of 225 traits.

Genetic factors underlying back pain are involved in neurological pathways

We used DEPICT with all independent variants (as identified by COJO analysis) from BP_{ma} with p < 1e-5 (227 SNPs in total) and identified potential enrichment of gene sets (FDR<0.2) related to nervous system development and skeletal muscle development (Supplementary Table 7A–C). We did not identify a significant enrichment of expression across any tissues and cell types (FDR > 0.2), although we observed a trend towards enrichment of components of CNS (Supplementary Table 7A–C). Similar results were observed when analyzing enrichment of expression of genes located around 23 BP_{ma} independent genome-wide significant variants (Supplementary Table 7D–F).

Analysis by MAGMA [66] revealed three significant gene sets (Supplementary Table 8): M12307 (“Nikolsky breast cancer 16q24 amplicon”, FDR=0.02; copy number amplicons of 53 genes enriched with major tumorigenic pathways and breast cancer-causative genes [41]), GO:0051590 (positive regulation of neurotransmitter transport, FDR=0.02) and GO:0021952 (central nervous system projection neuron axonogenesis, FDR=0.02). Tissue expression analysis for 30 general tissue types revealed significant enrichment of expression in brain (FDR=0.01).

DISCUSSION

The current study is the largest genetic association study to date for BP and included more than 500,000 individuals. The results provide insights into the genetic composition of predisposition to BP, one of the leading causes of disability worldwide. We quadrupled the number of genome-wide significantly associated BP loci (from five [55] to 23), and increased the number of replicated BP loci from one to three. Our work has implicated two new positional candidate genes: *SPOCK2* and *CHST3*. The region where these genes reside has previously been described as associated with LDD in Chinese individuals, and an *in vitro* functional study suggested a mechanism linking variation in this locus (specifically, rs4148941) and expression of *CHST3*, a functionally highly plausible gene [53]. Our *in silico* functional analysis, however, suggests that the closely adjacent *SPOCK2* gene may be another candidate in the region. In particular, we provide evidence of relationships between both *SPOCK2* and *CHST3* gene expression and the risk of BP. At the same time, using

available *in-silico* instruments, we couldn't provide enough evidence in favor of *SPOCK2* or *CHST3* as the most likely gene associated with BP on the locus on chromosome 10 (see Additional results file).

We found evidence of pleiotropic effects for the genetic factors underlying BP, height, and intervertebral disc problems. From epidemiological studies, both height and LDD are known to be associated with BP and have been proposed to have causal effects on BP [24; 75]. The genetic pleiotropy identified in the current study provides insight into the molecular background underlying these associations. Importantly, while only one of the three loci (rs3180) exhibited pleiotropic effects for BP and height, all three demonstrated pleiotropy for BP and self-reported intervertebral disk problems. In addition, the observed genetic correlation between height and BP was small and statistically insignificant (ρ_g=0.05, p=0.07), while the genetic correlation between intervertebral disc problems and BP was high and strongly statistically significant (ρ_g = 0.77, p = 6.7×10^{-24}). These results strongly suggest shared underlying genetic factors between intervertebral disk degeneration and BP, as compared to height and BP, and are in keeping with the epidemiological evidence of strong association of BP with disc degeneration [31; 34] and a weaker association with height [56]. An alternative explanation for our observation that loci influencing BP also affect intervertebral disc problems might be an overlap between individuals reporting both BP and intervertebral disc problems in UK Biobank. Indeed, 66% of people in the UK Biobank who reported intervertebral disc problems also reported BP. Yet only 5% people who reported BP also reported intervertebral disc problems: the correlation between the two phenotypes was small (r = 0.13), although significant (p<2.2e-16). In support of a shared genetic basis for BP and intervertebral disc problems, we found that the lead SNPs tagging regions near *SOX5* (rs12310519) and *GSDMC/CCDC26* (rs7814941 via proxy rs4733724) had nominally significant associations (p = 1.1×10^{-4} and p = 0.023, respectively) with MRI-proven LDD in a meta-analysis of 4600 individuals who were independent from the current study sample and not selected by BP status [69].

To our knowledge, this is the first study to use contemporary quantitative genetic methods to replicate the results of twin studies examining shared genetic influences on BP with other traits, including putative BP risk factors [3; 13; 20; 23; 27; 31; 34; 52]. In so doing, we took the broadest approach to date and examined a wide range of complex traits and known risk factors, revealing three clusters sharing significant genetic correlations with BP: the obesity-related traits, the mood and sleep related traits, and the sociodemographic factors (including education) and smoking. Moreover, we identified mutually independent genetic correlations between BP and depression, sleep disturbance, waist circumference and college completion. The magnitude and direction of many of the observed genetic correlations in the current study follow from the results of classic epidemiology and genetic epidemiology studies of BP suggesting, perhaps, that the environmental components to these risk factors have been overstated or at least themselves have a genetic basis, at least in part. For instance, we observed strong positive genetic correlations between BP and depression related phenotypes, and between BP and obesity-related traits. These traits are known to co-occur with BP and twin studies have suggested that they share underlying genetic factors [49], with similar genetic correlations also seen for other pain phenotypes [15; 39; 44]. Our results confirm a recent twin report of genetic correlation of sleep disturbance with BP [50]. Overall, the

analysis of genetic correlations provides evidence for shared molecular pathways underlying BP and traits considered as BP risk factors, thus providing the basis for identification of causal links between them.

Our pathway analysis revealed the importance of genetic factors in CNS and skeletal muscle in BP. While the CNS has long been recognized as the key component in the pathogenesis of chronic pain [21], the role of skeletal muscle is still not well defined [64; 65]. Altogether, these data provide a starting point for further functional analyses of mechanisms underlying BP (Figure 5). The study of pleiotropy and genetic correlations, supported by the pathway analysis, suggests at least two strong molecular axes of BP genesis, one related to structural/anatomic factors such as intervertebral disk problems and anthropometrics; and another related to the psychological component of pain perception and pain processing. These two axes correspond roughly to the different “biomedical” and “biopsychosocial” viewpoints that have dominated BP research and clinical care for the past several decades [14]. Pathway analysis also produced an unexpected enrichment for genes involved in “Nikolsky breast cancer 16q24 amplicon” gene set. This gene set includes 53 genes and represents one of 30 genomic regions with copy number gain found in the analysis of 191 breast tumours [41]. It is not known to be enriched for pain-related or other relevant pathways; therefore, its relationship with BP needs to be explored further.

Despite the study of close to half a million people, we identified and replicated only 3 loci. Also, in keeping with other common complex traits, the SNP-based heritability was rather low (12% on the liability scale). These estimates are lower than those observed in twin studies [3; 28; 33; 43]. This situation is not uncommon, because in GWAS only a subset of common genetic variants that are captured by SNPs presented on major genotyping microarrays is examined, while heritability attributed to rarer variants and other variation (e.g. indels and copy number variants) is omitted [74]. The low SNP-based heritability suggests that BP is genetically a very complex, highly polygenic phenotype. This is also supported by the small effect sizes observed in our study (e.g. $\beta = -0.056 \pm 0.007$, corresponding to odds ratio of 0.95 with 95% CI 0.93–0.96). In part, this can also be explained by the heterogeneity of the phenotype itself, as BP arises from many triggers having different underlying molecular pathologies [63]. Our approach used a standard definition of “any back pain” in the discovery stage, but permitted some heterogeneity with respect to BP duration among cohorts included in the replication stage (any BP in the UK Biobank sub-cohorts vs chronic BP in the CHARGE cohorts). In our prior study [55], we focused on chronic back pain (duration > 3 months) and it was our intention for the current study to see if the phenotype of “current back pain” might yield different results from chronic back pain. This turned out not to be the case, as the results of both GWAS are broadly similar. Future progress of genetic studies of BP would benefit from more consistent phenotyping. Our experience to date of working with back pain consortia – with no more than 3 cohorts having closely comparable back pain definitions and question items – has shown that it is extremely difficult to bring together cohorts of comparable size having uniform phenotype definition. This reflects the current state of BP research, where there is no universally accepted gold standard for defining BP [55]. Recently established consensus guidelines for core BP definitions may facilitate future efforts to harmonize definitions between cohorts [12]. Our study results may also have been affected by the definition of

controls used, as many people who did not report having BP did in fact experience pain in other sites (e.g. knee, hip, neck, shoulder). Given that there is an overlap between the genetic components of different pain locations [70], this may bias the study towards the null and towards the variants that are specific for BP only. In any case, the selection of controls in our study likely led to conservative result estimates, and makes false positive findings very unlikely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This study was supported by the European Community's Seventh Framework Programme funded project PainOmics (Grant agreement # 602736). The research has been conducted using the UK Biobank Resource (project # 18219). We are grateful to the UK Biobank participants for making such research possible.

The development of software implementing SMR/HEIDI test and database for GWAS results was supported by the Russian Ministry of Science and Education under the 5–100 Excellence Program".

Dr. Suri's time for this work was supported by VA Career Development Award # 1IK2RX001515 from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service. Dr. Suri is a Staff Physician at the VA Puget Sound Health Care System. The contents of this work do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Dr. Tsepilov's time for this work was supported by the Federal Agency of Scientific Organizations via the Institute of Cytology and Genetics (project 0324–2019-0040) and by the Russian Foundation for Basic Research (project 19–015-00151).

We thank Eugene Pakhomov for developing software and database for eQTL-related analyses and Dr Sodbo Sharapov for assistance with data submission.

Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Musculoskeletal Working Group: We acknowledge the following individuals from the CHARGE Musculoskeletal Working Group as non-author contributors involved in the meta-analysis of data from CHARGE cohorts : Cindy G. Boer, Michelle S. Yau, Daniel S. Evans, Andrea Gelemanovic, Traci M. Bartz, Maria Nethander, Liubov Arbeeva, Tuhina Neogi, Archie Campbell, Dan Mellstrom, Claes Ohlsson, Lynn M. Marshall, Eric Orwoll, Andre Uitterlinden, Jerome I. Rotter, Gordan Lauc, Bruce M. Psaty, Magnus K Karlsson, Nancy E. Lane, Gail Jarvik, Ozren Polasek, Marc Hochberg, Joanne M. Jordan, Joyce B. J. Van Meurs, Rebecca Jackson, Carrie M. Nielson, Braxton D. Mitchell, Blair H. Smith, Caroline Hayward, and Nicholas L. Smith.

REFERENCES

[1]. Aulchenko YS. Effects of Population Structure in Genome-wide Association Studies In: Zeggini E, Morris A, editors. Analysis of Complex Disease Association Studies: A Practical Guide: Academic Press, 2011 pp. 123–156.

[2]. Barban N, Jansen R, de Vlaming R, Vaez A, Mandemakers JJ, Tropf FC, Shen X, Wilson JF, Chasman DI, Nolte IM, Tragante V, van der Laan SW, Perry JR, Kong A, Consortium B, Ahluwalia TS, Albrecht E, Yerges-Armstrong L, Atzmon G, Auro K, Ayers K, Bakshi A, Ben-Avraham D, Berger K, Bergman A, Bertram L, Bielak LF, Bjornsdottir G, Bonder MJ, Broer L, Bui M, Barbieri C, Cavadino A, Chavarro JE, Turman C, Concas MP, Cordell HJ, Davies G, Eibich P, Eriksson N, Esko T, Eriksson J, Falahi F, Felix JF, Fontana MA, Franke L, Gandin I, Gaskins AJ, Gieger C, Gunderson EP, Guo X, Hayward C, He C, Hofer E, Huang H, Joshi PK, Kanoni S, Karlsson R, Kiechl S, Kifley A, Kluttig A, Kraft P, Lagou V, Lecoeur C, Lahti J, Li-Gao R, Lind PA, Liu T, Makalic E, Mamasoula C, Matteson L, Mbarek H, McArdle PF, McMahon G, Meddens SF, Mihailov E, Miller M, Missmer SA, Monnereau C, van der Most PJ, Myhre R, Nalls MA, Nutile T, Kalafati IP, Porcu E, Prokopenko I, Rajan KB, Rich-Edwards J, Rietveld CA, Robino A, Rose LM, Rueedi R, Ryan KA, Saba Y, Schmidt D, Smith JA, Stolk L,

Streeten E, Tonjes A, Thorleifsson G, Ulivi S, Wedenoja J, Wellmann J, Willeit P, Yao J, Yengo L, Zhao JH, Zhao W, Zhernakova DV, Amin N, Andrews H, Balkau B, Barzilai N, Bergmann S, Biino G, Bisgaard H, Bonnelykke K, Boomsma DI, Buring JE, Campbell H, Cappellani S, Ciullo M, Cox SR, Cucca F, Toniolo D, Davey-Smith G, Deary IJ, Dedoussis G, Deloukas P, van Duijn CM, de Geus EJ, Eriksson JG, Evans DA, Faul JD, Sala CF, Froguel P, Gasparini P, Girotto G, Grabe HJ, Greiser KH, Groenen PJ, de Haan HG, Haerting J, Harris TB, Heath AC, Heikkila K, Hofman A, Homuth G, Holliday EG, Hopper J, Hypponen E, Jacobsson B, Jaddoe VW, Johannesson M, Jugessur A, Kahonen M, Kajantie E, Kardia SL, Keavney B, Kolcic I, Koponen P, Kovacs P, Kronenberg F, Kutalik Z, La Bianca M, Lachance G, Iacono WG, Lai S, Lehtimaki T, Liewald DC, LifeLines Cohort S, Lindgren CM, Liu Y, Luben R, Lucht M, Luoto R, Magnus P, Magnusson PK, Martin NG, McGue M, McQuillan R, Medland SE, Meisinger C, Mellstrom D, Metspalu A, Traglia M, Milani L, Mitchell P, Montgomery GW, Mook-Kanamori D, de Mutsert R, Nohr EA, Ohlsson C, Olsen J, Ong KK, Paternoster L, Pattie A, Penninx BW, Perola M, Peyser PA, Pirastu M, Polasek O, Power C, Kaprio J, Raffel LJ, Raikkonen K, Raitakari O, Ridker PM, Ring SM, Roll K, Rudan I, Ruggiero D, Rujescu D, Salomaa V, Schlessinger D, Schmidt H, Schmidt R, Schupf N, Smit J, Sorice R, Spector TD, Starr JM, Stockl D, Strauch K, Stumvoll M, Swertz MA, Thorsteinsdottir U, Thurik AR, Timpson NJ, Tung JY, Uitterlinden AG, Vaccargiu S, Viikari J, Vitart V, Volzke H, Vollenweider P, Vuckovic D, Waage J, Wagner GG, Wang JJ, Wareham NJ, Weir DR, Willemsen G, Willeit J, Wright AF, Zondervan KT, Stefansson K, Krueger RF, Lee JJ, Benjamin DJ, Cesarini D, Koellinger PD, den Hoed M, Snieder H, Mills MC. Genome-wide analysis identifies 12 loci influencing human reproductive behavior. Nat Genet 2016;48(12):1462–1472. [PubMed: 27798627]

[3]. 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):272–280. [PubMed: 17335977]

[4]. Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. Genetic and environmental effects on disc degeneration by phenotype and spinal level: a multivariate twin study. Spine (Phila Pa 1976) 2008;33(25):2801–2808. [PubMed: 19050586]

[5]. Bjornsdottir G, Benonisdottir S, Sveinbjornsson G, Styrkarsdottir U, Thorleifsson G, Walters GB, Bjornsson A, Olafsson IH, Ulfarsson E, Vikingsson A, Hansdottir R, Karlsson KO, Rafnar T, Jonsdottir I, Frigge ML, Kong A, Oddsson A, Masson G, Magnusson OT, Gudbjartsson T, Stefansson H, Sulem P, Gudbjartsson D, Thorsteinsdottir U, Thorgeirsson TE, Stefansson K. Sequence variant at 8q24.21 associates with sciatica caused by lumbar disc herniation. Nat Commun 2017;8:14265. [PubMed: 28223688]

[6]. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, Karczewski KJ, Park J, Hitz BC, Weng S, Cherry JM, Snyder M. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res 2012;22(9):1790–1797. [PubMed: 22955989]

[7]. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, ReproGen C, Psychiatric Genomics C, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control C, Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015;47(11):1236–1241. [PubMed: 26414676]

[8]. Collaborators GDaIIaP. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390(10100):1211–1259. [PubMed: 28919117]

[9]. Dario AB, Ferreira ML, Refshauge KM, Lima TS, Ordonana JR, Ferreira PH. The relationship between obesity, low back pain, and lumbar disc degeneration when genetics and the environment are considered: a systematic review of twin studies. Spine J 2015;15(5):1106–1117. [PubMed: 25661432]

[10]. David SP, Hamidovic A, Chen GK, Bergen AW, Wessel J, Kasberger JL, Brown WM, Petruzella S, Thacker EL, Kim Y, Nalls MA, Tranah GJ, Sung YJ, Ambrosone CB, Arnett D, Bandera EV, Becker DM, Becker L, Berndt SI, Bernstein L, Blot WJ, Broeckel U, Buxbaum SG, Caporaso N, Casey G, Chanock SJ, Deming SL, Diver WR, Eaton CB, Evans DS, Evans MK, Fornage M, Franceschini N, Harris TB, Henderson BE, Hernandez DG, Hitsman B, Hu JJ, Hunt SC, Ingles SA, John EM, Kittles R, Kolb S, Kolonel LN, Le Marchand L, Liu Y, Lohman KK, McKnight B, Millikan RC, Murphy A, Neslund-Dudas C, Nyante S, Press M, Psaty BM, Rao DC, Redline S,

Rodriguez-Gil JL, Rybicki BA, Signorello LB, Singleton AB, Smoller J, Snively B, Spring B, Stanford JL, Strom SS, Swan GE, Taylor KD, Thun MJ, Wilson AF, Witte JS, Yamamura Y, Yanek LR, Yu K, Zheng W, Ziegler RG, Zonderman AB, Jorgenson E, Haiman CA, Furberg H. Genome-wide meta-analyses of smoking behaviors in African Americans. Transl Psychiatry 2012;2:e119.

[11]. Devlin B, Roeder K. Genomic control for association studies. Biometrics 1999;55(4):997–1004. [PubMed: 11315092]

[12]. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, Carrino JA, Chou R, Cook K, DeLitto A, Goertz C, Khalsa P, Loeser J, Mackey S, Panagis J, Rainville J, Tosteson T, Turk D, Von Korff M, Weiner DK. 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):1375–1391. [PubMed: 24950669]

[13]. 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.

[14]. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, Ferreira PH, Fritz JM, Koes BW, Peul W, Turner JA, Maher CG, Lancet Low Back Pain Series Working G. Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet 2018.

[15]. Gasperi M, Herbert M, Schur E, Buchwald D, Afari N. Genetic and Environmental Influences on Sleep, Pain, and Depression Symptoms in a Community Sample of Twins. Psychosom Med 2017;79(6):646–654. [PubMed: 28658193]

[16]. Gore M, Sadosky A, Stacey BR, Tai KS, Leslie D. The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. Spine (Phila Pa 1976) 2012;37(11):E668–677. [PubMed: 22146287]

[17]. GTEx_Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 2015;348(6235):648–660. [PubMed: 25954001]

[18]. Hadchouel A, Durrmeyer X, Bouzigon E, Incitti R, Huusko J, Jarreau PH, Lenclen R, Demenais F, Franco-Montoya ML, Layouni I, Patkai J, Bourbon J, Hallman M, Danan C, Delacourt C. Identification of SPOCK2 as a susceptibility gene for bronchopulmonary dysplasia. Am J Respir Crit Care Med 2011;184(10):1164–1170. [PubMed: 21836138]

[19]. Hammerschlag AR, Stringer S, de Leeuw CA, Sniekers S, Taskesen E, Watanabe K, Blanken TF, Dekker K, Te Lindert BHW, Wassing R, Jonsdottir I, Thorleifsson G, Stefansson H, Gislason T, Berger K, Schormair B, Wellmann J, Winkelmann J, Stefansson K, Oexle K, Van Someren EJW, Posthuma D. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. Nat Genet 2017;49(11):1584–1592. [PubMed: 28604731]

[20]. Hartvigsen J, Nielsen J, Kyvik KO, Fejer R, Vach W, Iachine I, Leboeuf-Yde C. Heritability of spinal pain and consequences of spinal pain: a comprehensive genetic epidemiologic analysis using a population-based sample of 15,328 twins ages 20–71 years. Arthritis and rheumatism 2009;61(10):1343–1351. [PubMed: 19790135]

[21]. Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: a review. PM R 2011;3(12):1116–1125. [PubMed: 22192321]

[22]. Hermanns P, Unger S, Rossi A, Perez-Aytes A, Cortina H, Bonafe L, Boccone L, Setzu V, Dutoit M, Sangiorgi L, Pecora F, Reicherter K, Nishimura G, Spranger J, Zabel B, Superti-Furga A. Congenital joint dislocations caused by carbohydrate sulfotransferase 3 deficiency in recessive Larsen syndrome and humero-spinal dysostosis. Am J Hum Genet 2008;82(6):1368–1374. [PubMed: 18513679]

[23]. Hestbaek L, Iachine IA, Leboeuf-Yde C, Kyvik KO, Manniche C. Heredity of low back pain in a young population: a classical twin study. Twin Res 2004;7(1):16–26. [PubMed: 15053850]

[24]. 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.

[25]. Hong J, Reed C, Novick D, Happich M. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. Spine (Phila Pa 1976) 2013;38(1):75–82. [PubMed: 23038621]

[26]. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, Williams G, Smith E, Vos T, Barendregt J, Murray C, Burstein R, Buchbinder R. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73(6):968–974. [PubMed: 24665116]

[27]. Junqueira DR, Ferreira ML, Refshauge K, Maher CG, Hopper JL, Hancock M, Carvalho MG, Ferreira PH. Heritability and lifestyle factors in chronic low back pain: results of the Australian twin low back pain study (The AUTBACK study). European journal of pain 2014;18(10):1410–1418. [PubMed: 24733726]

[28]. Junqueira DR, Ferreira ML, Refshauge K, Maher CG, Hopper JL, Hancock M, Carvalho MG, Ferreira PH. Heritability and lifestyle factors in chronic low back pain: results of the Australian twin low back pain study (The AUTBACK study). Eur J Pain 2014;18(10):1410–1418. [PubMed: 24733726]

[29]. Kalichman L, Hunter DJ. The genetics of intervertebral disc degeneration. Familial predisposition and heritability estimation. Joint Bone Spine 2008;75(4):383–387. [PubMed: 18448379]

[30]. Kichaev G, Yang WY, Lindstrom S, Hormozdiari F, Eskin E, Price AL, Kraft P, Pasaniuc B. Integrating functional data to prioritize causal variants in statistical fine-mapping studies. PLoS Genet 2014;10(10):e1004722. [PubMed: 25357204]

[31]. Livshits G, Popham M, Malkin I, Sambrook PN, Macgregor AJ, Spector T, Williams FM. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. Ann Rheum Dis 2011;70(10):1740–1745. [PubMed: 21646416]

[32]. Loh PR, Kichaev G, Gazal S, Schoech AP, Price AL. Mixed-model association for biobank-scale datasets. Nat Genet 2018;50(7):906–908. [PubMed: 29892013]

[33]. MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. Arthritis Rheum 2004;51(2):160–167. [PubMed: 15077255]

[34]. MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. Arthritis and rheumatism 2004;51(2):160–167. [PubMed: 15077255]

[35]. Major Depressive Disorder Working Group of the Psychiatric GC, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Muller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Volzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013;18(4):497–511. [PubMed: 22472876]

[36]. Malkin I, Williams FM, LaChance G, Spector T, MacGregor AJ, Livshits G. Low back and common widespread pain share common genetic determinants. Ann Hum Genet 2014;78(5):357–366. [PubMed: 24962672]

[37]. Manchikanti L, Singh V, Falco FJ, Benyamin RM, Hirsch JA. Epidemiology of low back pain in adults. Neuromodulation 2014;17 Suppl 2:3–10. [PubMed: 25395111]

[38]. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000;84(1):95–103. [PubMed: 10601677]

[39]. McIntosh AM, Hall LS, Zeng Y, Adams MJ, Gibson J, Wigmore E, Hagenaars SP, Davies G, Fernandez-Pujals AM, Campbell AI, Clarke TK, Hayward C, Haley CS, Porteous DJ, Deary IJ, Smith DJ, Nicholl BI, Hinds DA, Jones AV, Scollen S, Meng W, Smith BH, Hocking LJ. Genetic and Environmental Risk for Chronic Pain and the Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-Model Analysis. PLoS Med 2016;13(8):e1002090. [PubMed: 27529168]

[40]. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, Flicek P, Cunningham F. The Ensembl Variant Effect Predictor. Genome Biol 2016;17(1):122. [PubMed: 27268795]

[41]. Nikolsky Y, Sviridov E, Yao J, Dosymbekov D, Ustyansky V, Kaznacheev V, Dezso Z, Mulvey L, Macconaill LE, Winckler W, Serebryiskaya T, Nikolskaya T, Polyak K. Genome-wide functional synergy between amplified and mutated genes in human breast cancer. Cancer Res 2008;68(22):9532–9540. [PubMed: 19010930]

[42]. Nordgard SH, Johansen FE, Alnaes GI, Bucher E, Syvanen AC, Naume B, Borresen-Dale AL, Kristensen VN. Genome-wide analysis identifies 16q deletion associated with survival, molecular subtypes, mRNA expression, and germline haplotypes in breast cancer patients. Genes Chromosomes Cancer 2008;47(8):680–696. [PubMed: 18398821]

[43]. Nyman T, Mulder M, Iliadou A, Svartengren M, Wiktorin C. High heritability for concurrent low back and neck-shoulder pain: a study of twins. Spine (Phila Pa 1976) 2011;36(22):E1469–1476. [PubMed: 21192295]

[44]. Ogata S, Williams F, Burri A. Genetic Factors Explain the Association Between Pain Catastrophizing and Chronic Widespread Pain. J Pain 2017;18(9):1111–1116. [PubMed: 28506778]

[45]. Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, Meddens SF, Linner RK, Rietveld CA, Derringer J, Gratten J, Lee JJ, Liu JZ, de Vlaming R, Ahluwalia TS, Buchwald J, Cavadino A, Frazier-Wood AC, Furlotte NA, Garfield V, Geisel MH, Gonzalez JR, Haitjema S, Karlsson R, van der Laan SW, Ladwig KH, Lahti J, van der Lee SJ, Lind PA, Liu T, Matteson L, Mihailov E, Miller MB, Minica CC, Nolte IM, Mook-Kanamori D, van der Most PJ, Oldmeadow C, Qian Y, Raitakari O, Rawal R, Realo A, Rueedi R, Schmidt B, Smith AV, Stergiakouli E, Tanaka T, Taylor K, Wedenoja J, Wellmann J, Westra HJ, Willems SM, Zhao W, LifeLines Cohort S, Amin N, Bakshi A, Boyle PA, Cherney S, Cox SR, Davies G, Davis OS, Ding J, Direk N, Eibich P, Emeny RT, Fatemifar G, Faul JD, Ferrucci L, Forstner A, Gieger C, Gupta R, Harris TB, Harris JM, Holliday EG, Hottenga JJ, De Jager PL, Kaakinen MA, Kajantie E, Karhunen V, Kolcic I, Kumari M, Launer LJ, Franke L, Li-Gao R, Koini M, Loukola A, Marques-Vidal P, Montgomery GW, Mosing MA, Paternoster L, Pattie A, Petrovic KE, Pulkki-Raback L, Quaye L, Raikkonen K, Rudan I, Scott RJ, Smith JA, Sutin AR, Trzaskowski M, Vinkhuyzen AE, Yu L, Zabaneh D, Attia JR, Bennett DA, Berger K, Bertram L, Boomsma DI, Snieder H, Chang SC, Cucca F, Deary IJ, van Duijn CM, Eriksson JG, Bultmann U, de Geus EJ, Groenen PJ, Gudnason V, Hansen T, Hartman CA, Haworth CM, Hayward C, Heath AC, Hinds DA, Hypponen E, Iacono WG, Jarvelin MR, Jockel KH, Kaprio J, Kardia SL, Keltikangas-Jarvinen L, Kraft P, Kubzansky LD, Lehtimaki T, Magnusson PK, Martin NG, McGue M, Metspalu A, Mills M, de Mutsert R, Oldehinkel AJ, Pasterkamp G, Pedersen NL, Plomin R, Polasek O, Power C, Rich SS, Rosendaal FR, den Ruijter HM, Schlessinger D, Schmidt H, Svento R, Schmidt R, Alizadeh BZ, Sorensen TI, Spector TD, Steptoe A, Terracciano A, Thurik AR, Timpson NJ, Tiemeier H, Uitterlinden AG, Vollenweider P, Wagner GG, Weir DR, Yang J, Conley DC, Smith GD, Hofman A, Johannesson M, Laibson DI, Medland SE, Meyer MN, Pickrell JK, Esko T, Krueger RF, Beauchamp JP, Koellinger PD, Benjamin DJ, Bartels M, Cesarini D. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet 2016;48(6):624–633. [PubMed: 27089181]

[46]. Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, Turley P, Chen GB, Emilsson V, Meddens SF, Oskarsson S, Pickrell JK, Thom K, Timshel P, de Vlaming R, Abdellaoui A, Ahluwalia TS, Bacelis J, Baumbach C, Bjornsdottir G, Brandsma JH, Pina Concas M, Derringer J, Furlotte NA, Galesloot TE, Girotto G, Gupta R, Hall LM, Harris SE, Hofer E, Horikoshi M, Huffman JE, Kaasik K, Kalafati IP, Karlsson R, Kong A, Lahti J, van der Lee SJ, deLeeuw C, Lind PA, Lindgren KO, Liu T, Mangino M, Marten J, Mihailov E, Miller MB, van der Most PJ, Oldmeadow C, Payton A, Pervjakova N, Peyrot WJ, Qian Y, Raitakari O, Rueedi R, Salvi E, Schmidt B, Schraut KE, Shi J, Smith AV, Poot RA, St Pourcain B, Teumer A,

Thorleifsson G, Verweij N, Vuckovic D, Wellmann J, Westra HJ, Yang J, Zhao W, Zhu Z, Alizadeh BZ, Amin N, Bakshi A, Baumeister SE, Biino G, Bonnelykke K, Boyle PA, Campbell H, Cappuccio FP, Davies G, De Neve JE, Deloukas P, Demuth I, Ding J, Eibich P, Eisele L, Eklund N, Evans DM, Faul JD, Feitosa MF, Forstner AJ, Gandin I, Gunnarsson B, Halldorsson BV, Harris TB, Heath AC, Hocking LJ, Holliday EG, Homuth G, Horan MA, Hottenga JJ, de Jager PL, Joshi PK, Jugessur A, Kaakinen MA, Kahonen M, Kanoni S, Keltigangas-Jarvinen L, Kiemeney LA, Kolcic I, Koskinen S, Kraja AT, Kroh M, Kutalik Z, Latvala A, Launer LJ, Lebreton MP, Levinson DF, Lichtenstein P, Lichtner P, Liewald DC, LifeLines Cohort S, Loukola A, Madden PA, Magi R, Maki-Opas T, Marioni RE, Marques-Vidal P, Meddens GA, McMahon G, Meisinger C, Meitinger T, Milaneschi Y, Milani L, Montgomery GW, Myhre R, Nelson CP, Nyholt DR, Ollier WE, Palotie A, Paternoster L, Pedersen NL, Petrovic KE, Porteous DJ, Raikkonen K, Ring SM, Robino A, Rostapshova O, Rudan I, Rustichini A, Salomaa V, Sanders AR, Sarin AP, Schmidt H, Scott RJ, Smith BH, Smith JA, Staessen JA, Steinhagen-Thiessen E, Strauch K, Terracciano A, Tobin MD, Ulivi S, Vaccargiu S, Quaye L, van Rooij FJ, Venturini C, Vinkhuyzen AA, Volker U, Volzke H, Vonk JM, Vozzi D, Waage J, Ware EB, Willemsen G, Attia JR, Bennett DA, Berger K, Bertram L, Bisgaard H, Boomsma DI, Borecki IB, Bultmann U, Chabris CF, Cucca F, Cusi D, Deary IJ, Dedoussis GV, van Duijn CM, Eriksson JG, Franke B, Franke L, Gasparini P, Gejman PV, Gieger C, Grabe HJ, Gratten J, Groenen PJ, Gudnason V, van der Harst P, Hayward C, Hinds DA, Hoffmann W, Hypponen E, Iacono WG, Jacobsson B, Jarvelin MR, Jockel KH, Kaprio J, Kardia SL, Lehtimaki T, Lehrer SF, Magnusson PK, Martin NG, McGue M, Metspalu A, Pendleton N, Penninx BW, Perola M, Pirastu N, Pirastu M, Polasek O, Posthuma D, Power C, Province MA, Samani NJ, Schlessinger D, Schmidt R, Sorensen TI, Spector TD, Stefansson K, Thorsteinsdottir U, Thurik AR, Timpson NJ, Tiemeier H, Tung JY, Uitterlinden AG, Vitart V, Vollenweider P, Weir DR, Wilson JF, Wright AF, Conley DC, Krueger RF, Davey Smith G, Hofman A, Laibson DI, Medland SE, Meyer MN, Yang J, Johannesson M, Visscher PM, Esko T, Koellinger PD, Cesarini D, Benjamin DJ. Genome-wide association study identifies 74 loci associated with educational attainment. Nature 2016;533(7604):539–542. [PubMed: 27225129]

[47]. Pers TH, Karjalainen JM, Chan Y, Westra HJ, Wood AR, Yang J, Lui JC, Vedantam S, Gustafsson S, Esko T, Frayling T, Speliotes EK, Genetic Investigation of ATC, Boehnke M, Raychaudhuri S, Fehrmann RS, Hirschhorn JN, Franke L. Biological interpretation of genome-wide association studies using predicted gene functions. Nat Commun 2015;6:5890. [PubMed: 25597830]

[48]. Pilling LC, Atkins JL, Bowman K, Jones SE, Tyrrell J, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Wood AR, Freathy RM, Murray A, Weedon MN, Xue L, Lunetta K, Murabito JM, Harries LW, Robine JM, Brayne C, Kuchel GA, Ferrucci L, Frayling TM, Melzer D. Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. Aging (Albany NY) 2016;8(3):547–560. [PubMed: 27015805]

[49]. Pinheiro MB, Ferreira ML, Refshauge K, Colodro-Conde L, Carrillo E, Hopper JL, Ordonana JR, Ferreira PH. Genetics and the environment affect the relationship between depression and low back pain: a co-twin control study of Spanish twins. Pain 2015;156(3):496–503. [PubMed: 25679471]

[50]. Pinheiro MB, Morosoli JJ, Ferreira ML, Madrid-Valero JJ, Refshauge K, Ferreira PH, Ordonana JR. Genetic and Environmental Contributions to Sleep Quality and Low Back Pain: A Population-Based Twin Study. Psychosom Med 2018;80(3):263–270. [PubMed: 29240646]

[51]. Rietveld CA, Medland SE, Derringer J, Yang J, Esko T, Martin NW, Westra HJ, Shakhbazov K, Abdellaoui A, Agrawal A, Albrecht E, Alizadeh BZ, Amin N, Barnard J, Baumeister SE, Benke KS, Bielak LF, Boatman JA, Boyle PA, Davies G, de Leeuw C, Eklund N, Evans DS, Ferhmann R, Fischer K, Gieger C, Gjessing HK, Hagg S, Harris JR, Hayward C, Holzapfel C, Ibrahim-Verbaas CA, Ingelsson E, Jacobsson B, Joshi PK, Jugessur A, Kaakinen M, Kanoni S, Karjalainen J, Kolcic I, Kristiansson K, Kutalik Z, Lahti J, Lee SH, Lin P, Lind PA, Liu Y, Lohman K, Loitfelder M, McMahon G, Vidal PM, Meirelles O, Milani L, Myhre R, Nuotio ML, Oldmeadow CJ, Petrovic KE, Peyrot WJ, Polasek O, Quaye L, Reinmaa E, Rice JP, Rizzi TS, Schmidt H, Schmidt R, Smith AV, Smith JA, Tanaka T, Terracciano A, van der Loos MJ, Vitart V, Volzke H, Wellmann J, Yu L, Zhao W, Allik J, Attia JR, Bandinelli S, Bastardot F, Beauchamp J, Bennett DA, Berger K, Bierut LJ, Boomsma DI, Bultmann U, Campbell H, Chabris CF, Cherkas

L, Chung MK, Cucca F, de Andrade M, De Jager PL, De Neve JE, Deary IJ, Dedoussis GV, Deloukas P, Dimitriou M, Eiriksdottir G, Elderson MF, Eriksson JG, Evans DM, Faul JD, Ferrucci L, Garcia ME, Gronberg H, Guethnason V, Hall P, Harris JM, Harris TB, Hastie ND, Heath AC, Hernandez DG, Hoffmann W, Hofman A, Holle R, Holliday EG, Hottenga JJ, Iacono WG, Illig T, Jarvelin MR, Kahonen M, Kaprio J, Kirkpatrick RM, Kowgier M, Latvala A, Launer LJ, Lawlor DA, Lehtimaki T, Li J, Lichtenstein P, Lichtner P, Liewald DC, Madden PA, Magnusson PK, Makinen TE, Masala M, McGue M, Metspalu A, Mielck A, Miller MB, Montgomery GW, Mukherjee S, Nyholt DR, Oostra BA, Palmer LJ, Palotie A, Penninx BW, Perola M, Peyser PA, Preisig M, Raikkonen K, Raitakari OT, Realo A, Ring SM, Ripatti S, Rivadeneira F, Rudan I, Rustichini A, Salomaa V, Sarin AP, Schlessinger D, Scott RJ, Snieder H, St Pourcain B, Starr JM, Sul JH, Surakka I, Svento R, Teumer A, LifeLines Cohort S, Tiemeier H, van Rooij FJ, Van Wagoner DR, Vartiainen E, Viikari J, Vollenweider P, Vonk JM, Waeber G, Weir DR, Wichmann HE, Widen E, Willemsen G, Wilson JF, Wright AF, Conley D, Davey-Smith G, Franke L, Groenen PJ, Hofman A, Johannesson M, Kardia SL, Krueger RF, Laibson D, Martin NG, Meyer MN, Posthuma D, Thurik AR, Timpson NJ, Uitterlinden AG, van Duijn CM, Visscher PM, Benjamin DJ, Cesarini D, Koellinger PD. GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. Science 2013;340(6139):1467–1471. [PubMed: 23722424]

[52]. Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. Arthritis Rheum 1999;42(2):366–372. [PubMed: 10025932]

[53]. Song YQ, Karasugi T, Cheung KM, Chiba K, Ho DW, Miyake A, Kao PY, Sze KL, Yee A, Takahashi A, Kawaguchi Y, Mikami Y, Matsumoto M, Togawa D, Kanayama M, Shi D, Dai J, Jiang Q, Wu C, Tian W, Wang N, Leong JC, Luk KD, Yip SP, Cherny SS, Wang J, Mundlos S, Kelempisioti A, Eskola PJ, Mannikko M, Makela P, Karppinen J, Jarvelin MR, O'Reilly PF, Kubo M, Kimura T, Kubo T, Toyama Y, Mizuta H, Cheah KS, Tsunoda T, Sham PC, Ikegawa S, Chan D. Lumbar disc degeneration is linked to a carbohydrate sulfotransferase 3 variant. J Clin Invest 2013;123(11):4909–4917. [PubMed: 24216480]

[54]. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. 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(3):e1001779. [PubMed: 25826379]

[55]. Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, Evans DS, Gelemanovic A, Bartz TM, Nethander M, Arbeeva L, Karssen L, Neogi T, Campbell A, Mellstrom D, Ohlsson C, Marshall LM, Orwoll E, Uitterlinden A, Rotter JI, Lauc G, Psaty BM, Karlsson MK, Lane NE, Jarvik GP, Polasek O, Hochberg M, Jordan JM, Van Meurs JBJ, Jackson R, Nielson CM, Mitchell BD, Smith BH, Hayward C, Smith NL, Aulchenko YS, Williams FMK. Genome-wide Meta-analysis of 158,000 Individuals of European Ancestry Identifies Three Loci Associated with Chronic Back Pain. 2018.

[56]. 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. Spine J 2014;14(10):2299–2319. [PubMed: 24462537]

[57]. Thiele H, Sakano M, Kitagawa H, Sugahara K, Rajab A, Hohne W, Ritter H, Leschik G, Nurnberg P, Mundlos S. Loss of chondroitin 6-O-sulfotransferase-1 function results in severe human chondrodysplasia with progressive spinal involvement. Proc Natl Acad Sci U S A 2004;101(27):10155–10160. [PubMed: 15215498]

[58]. Tuysuz B, Mizumoto S, Sugahara K, Celebi A, Mundlos S, Turkmen S. Omani-type spondyloepiphyseal dysplasia with cardiac involvement caused by a missense mutation in CHST3. Clin Genet 2009;75(4):375–383. [PubMed: 19320654]

[59]. Unger S, Lausch E, Rossi A, Megarbane A, Sillence D, Alcausin M, Aytes A, Mendoza-Londono R, Nampoothiri S, Afroze B, Hall B, Lo IF, Lam ST, Hoefele J, Rost I, Wakeling E, Mangold E, Godbole K, Vatanavicharn N, Franco LM, Chandler K, Hollander S, Velten T, Reicherter K, Spranger J, Robertson S, Bonafe L, Zabel B, Superti-Furga A. Phenotypic features of carbohydrate sulfotransferase 3 (CHST3) deficiency in 24 patients: congenital dislocations and vertebral changes as principal diagnostic features. Am J Med Genet A 2010;152A(10):2543–2549. [PubMed: 20830804]

[60]. van Roij MH, Mizumoto S, Yamada S, Morgan T, Tan-Sindhunata MB, Meijers-Heijboer H, Verbeke JI, Markie D, Sugahara K, Robertson SP. Spondyloepiphyseal dysplasia, Omani type: further definition of the phenotype. Am J Med Genet A 2008;146A(18):2376–2384. [PubMed: 18698629]

[61]. Vannahme C, Schubel S, Herud M, Gosling S, Hulsmann H, Paulsson M, Hartmann U, Maurer P. Molecular cloning of testican-2: defining a novel calcium-binding proteoglycan family expressed in brain. J Neurochem 1999;73(1):12–20. [PubMed: 10386950]

[62]. Videman T, Battie MC, Gibbons LE, Maravilla K, Manninen H, Kaprio J. Associations between back pain history and lumbar MRI findings. Spine (Phila Pa 1976) 2003;28(6):582–588. [PubMed: 12642766]

[63]. Vlaeyen JWS, Maher CG, Wiech K, Van Zundert J, Meloto CB, Diatchenko L, Battie MC, Goossens M, Koes B, Linton SJ. Low back pain. Nat Rev Dis Primers 2018;4(1):52. [PubMed: 30546064]

[64]. Ward SR, Kim CW, Eng CM, Gottschalk LJt, Tomiya A, Garfin SR, Lieber. Architectural analysis and intraoperative measurements demonstrate the unique design of the multifidus muscle for lumbar spine stability. J Bone Joint Surg Am 2009;91(1):176–185. [PubMed: 19122093]

[65]. Ward SR, Tomiya A, Regev GJ, Thacker BE, Benzl RC, Kim CW, Lieber RL. Passive mechanical properties of the lumbar multifidus muscle support its role as a stabilizer. J Biomech 2009;42(10):1384–1389. [PubMed: 19457491]

[66]. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 2017;8(1):1826. [PubMed: 29184056]

[67]. Westra HJ, Peters MJ, Esko T, Yaghootkar H, Schurmann C, Kettunen J, Christiansen MW, Fairfax BP, Schramm K, Powell JE, Zhernakova A, Zhernakova DV, Veldink JH, Van den Berg LH, Karjalainen J, Withoff S, Uitterlinden AG, Hofman A, Rivadeneira F, Hoen PAC, Reinmaa E, Fischer K, Nelis M, Milani L, Melzer D, Ferrucci L, Singleton AB, Hernandez DG, Nalls MA, Homuth G, Nauck M, Radke D, Volker U, Perola M, Salomaa V, Brody J, Suchy-Dicey A, Gharib SA, Enquobahrie DA, Lumley T, Montgomery GW, Makino S, Prokisch H, Herder C, Roden M, Grallert H, Meitinger T, Strauch K, Li Y, Jansen RC, Visscher PM, Knight JC, Psaty BM, Ripatti S, Teumer A, Frayling TM, Metspalu A, van Meurs JBJ, Franke L. Systematic identification of trans eQTLs as putative drivers of known disease associations. Nat Genet 2013;45(10):1238–1243. [PubMed: 24013639]

[68]. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26(17):2190–2191. [PubMed: 20616382]

[69]. Williams FM, Bansal AT, van Meurs JB, Bell JT, Meulenbelt I, Suri P, Rivadeneira F, Sambrook PN, Hofman A, Bierma-Zeinstra S, Menni C, Kloppenburg M, Slagboom PE, Hunter DJ, MacGregor AJ, Uitterlinden AG, Spector TD. Novel genetic variants associated with lumbar disc degeneration in northern Europeans: a meta-analysis of 4600 subjects. Ann Rheum Dis 2013;72(7):1141–1148. [PubMed: 22993228]

[70]. Williams FM, Spector TD, MacGregor AJ. Pain reporting at different body sites is explained by a single underlying genetic factor. Rheumatology (Oxford) 2010;49(9):1753–1755. [PubMed: 20525736]

[71]. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large proportion of the heritability for human height. Nat Genet 2010;42(7):565–569. [PubMed: 20562875]

[72]. Yang J, Ferreira T, Morris AP, Medland SE, Genetic Investigation of ATC, Replication DIG, Meta-analysis C, Madden PA, Heath AC, Martin NG, Montgomery GW, Weedon MN, Loos RJ, Frayling TM, McCarthy MI, Hirschhorn JN, Goddard ME, Visscher PM. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet 2012;44(4):369–375, S361–363. [PubMed: 22426310]

[73]. Zadro JR, Shirley D, Pinheiro MB, Sanchez-Romera JF, Perez-Riquelme F, Ordonana JR, Ferreira PH. Does educational attainment increase the risk of low back pain when genetics are considered? A population-based study of Spanish twins. Spine J 2017;17(4):518–530. [PubMed: 27989723]

[74]. Zaitlen N, Kraft P. Heritability in the genome-wide association era. Hum Genet 2012;131(10):1655–1664. [PubMed: 22821350]

[75]. Zheng CJ, Chen J. Disc degeneration implies low back pain. Theor Biol Med Model 2015;12:24. [PubMed: 26552736]

[76]. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, Hemani G, Tansey K, Laurin C, Early G, Lifecourse Epidemiology Eczema C, Pourcain BS, Warrington NM, Finucane HK, Price AL, Bulik-Sullivan BK, Anttila V, Paternoster L, Gaunt TR, Evans DM, Neale BM. 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):272–279. [PubMed: 27663502]

[77]. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, Montgomery GW, Goddard ME, Wray NR, Visscher PM, Yang J. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet 2016;48(5):481–487. [PubMed: 27019110]

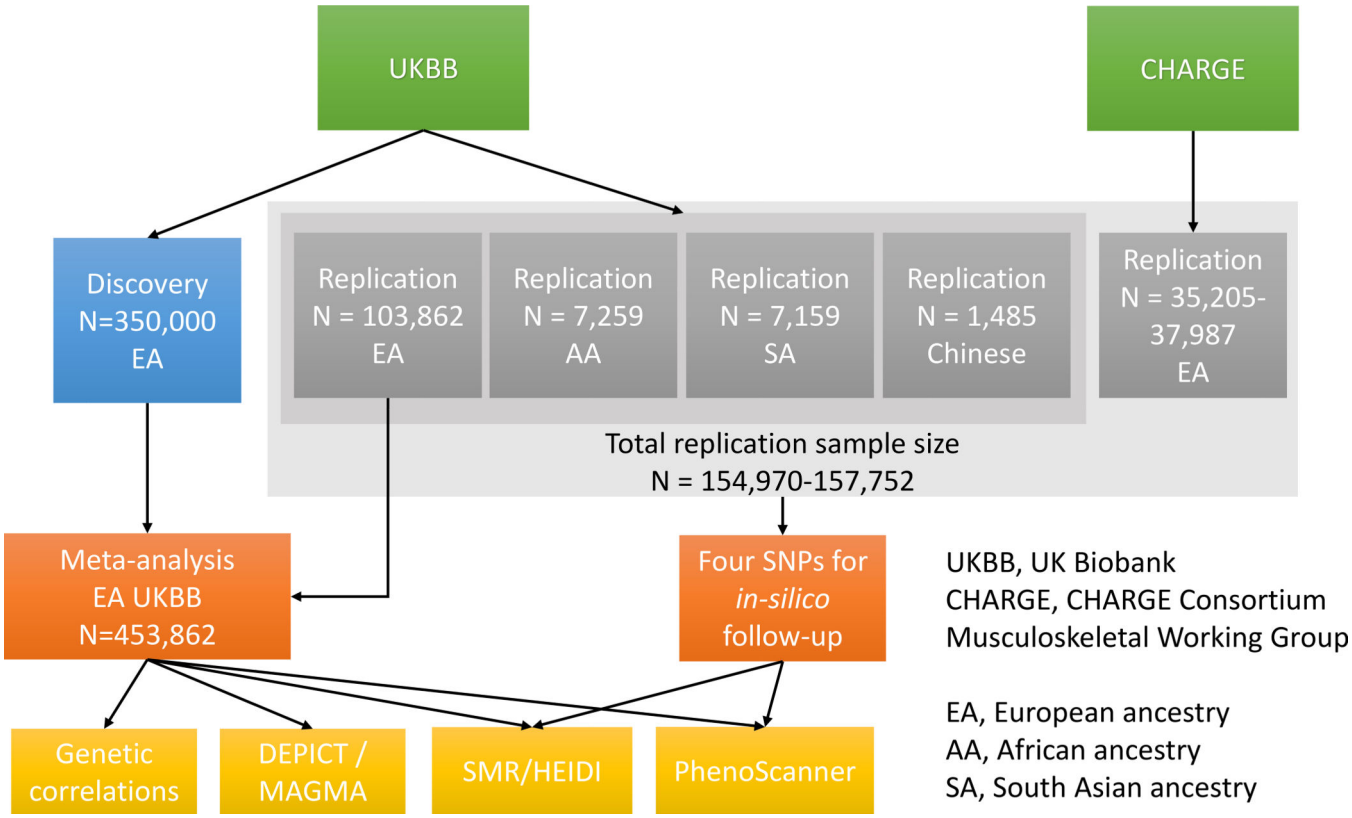

Figure 1. Overview of the study.

GWAS for back pain used a combination of UK Biobank and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium cohorts. Discovery was performed using 350,000 individuals of European ancestry from the UK Biobank. Replication cohorts included individuals of European (EA), African (AA) and South Asian (SA) ancestry and Chinese individuals from the UK Biobank and CHARGE cohorts (N = 154,970–157,752). Meta-analysis was carried out using the discovery cohort and other individuals of European ancestry from the UK Biobank (N = 453,862) and the results used to estimate genetic correlations with risk factors, establish causal or pleiotropic relationships using summary-data based Mendelian randomization (SMR) followed by heterogeneity in dependent instruments (HEIDI) analysis, and to perform DEPICT and MAGMA analyses to reveal functional relevance.

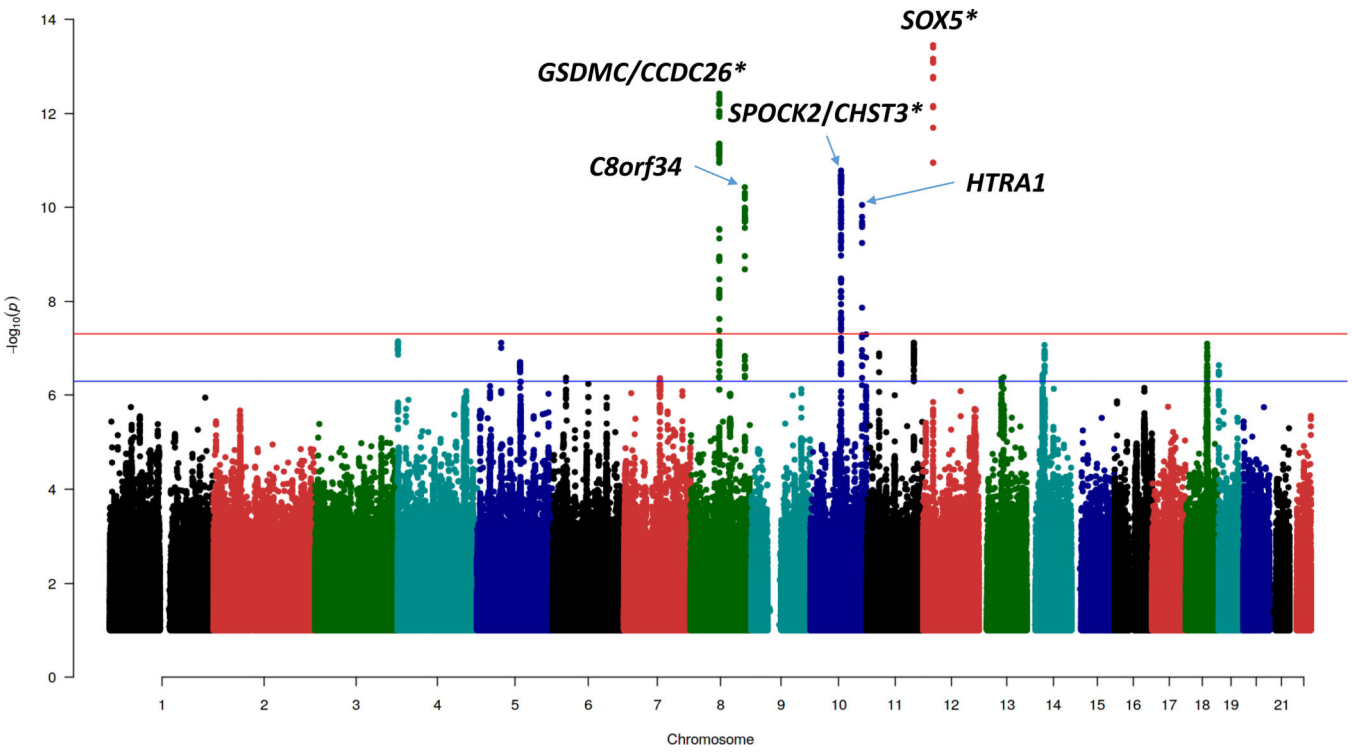

Figure 2. Manhattan plot of discovery GWAS for back pain.

Correction was made for genomic control (1.032). The red line corresponds to genome-wide significance threshold of 5×10^{-8}, while the blue line corresponds to a suggestive association threshold of 5×10^{-7}. Only SNPs with p<0.1 are presented. Asterisks depict replicated loci.

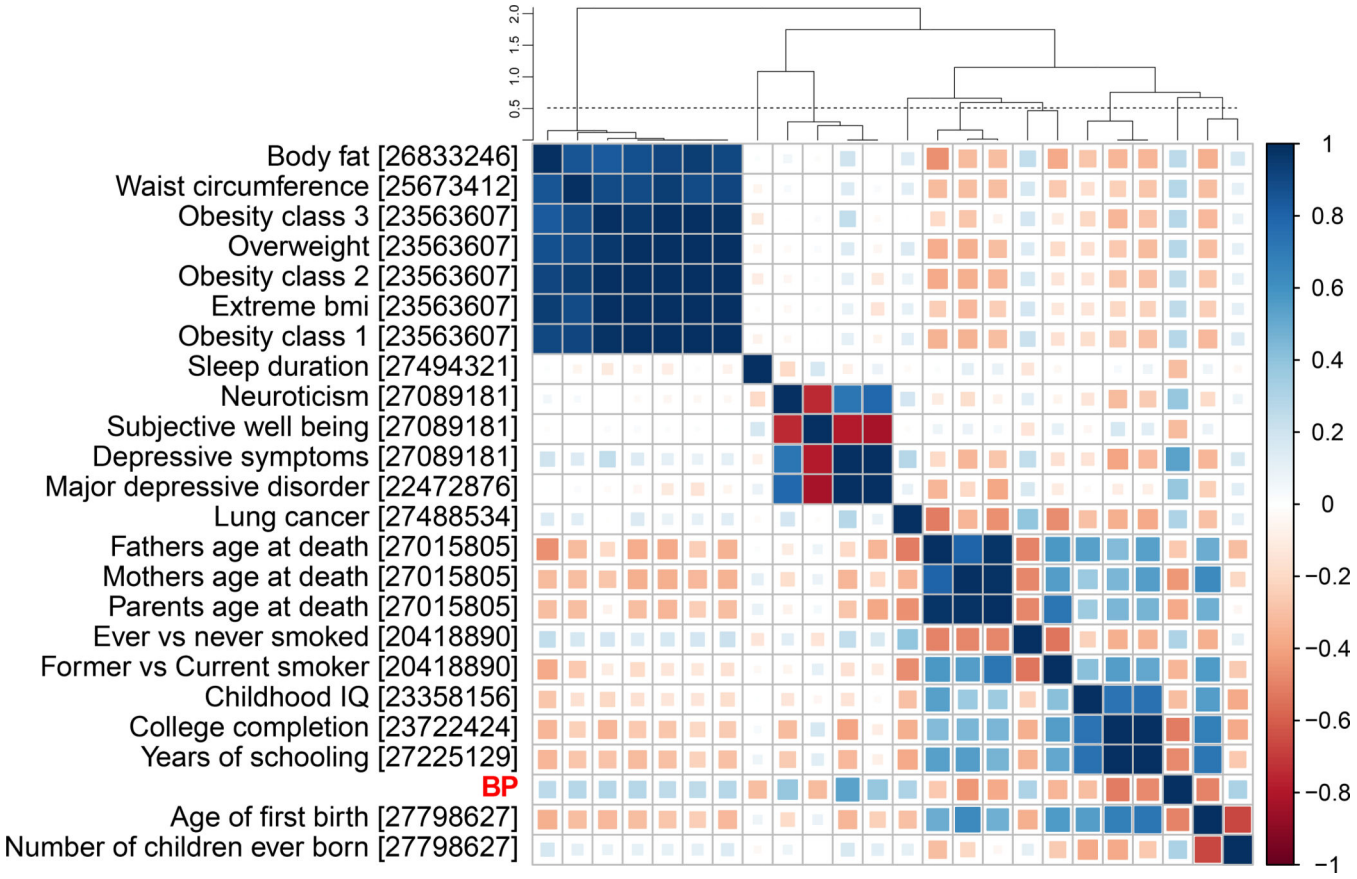

Figure 3. Heatmap for 23 traits with strongest statistically significant genetic correlations with back pain (absolute $\rho_g \geq 0.25$; $p \leq 4.4 \times 10^{-5}$).

Hierarchical clustering was carried out based on genetic correlations between all pairs of traits. PMID references are placed in square brackets. The dashed line on the cluster dendrogram refers to the threshold of 0.5, depicting 9 subclusters (including BP).

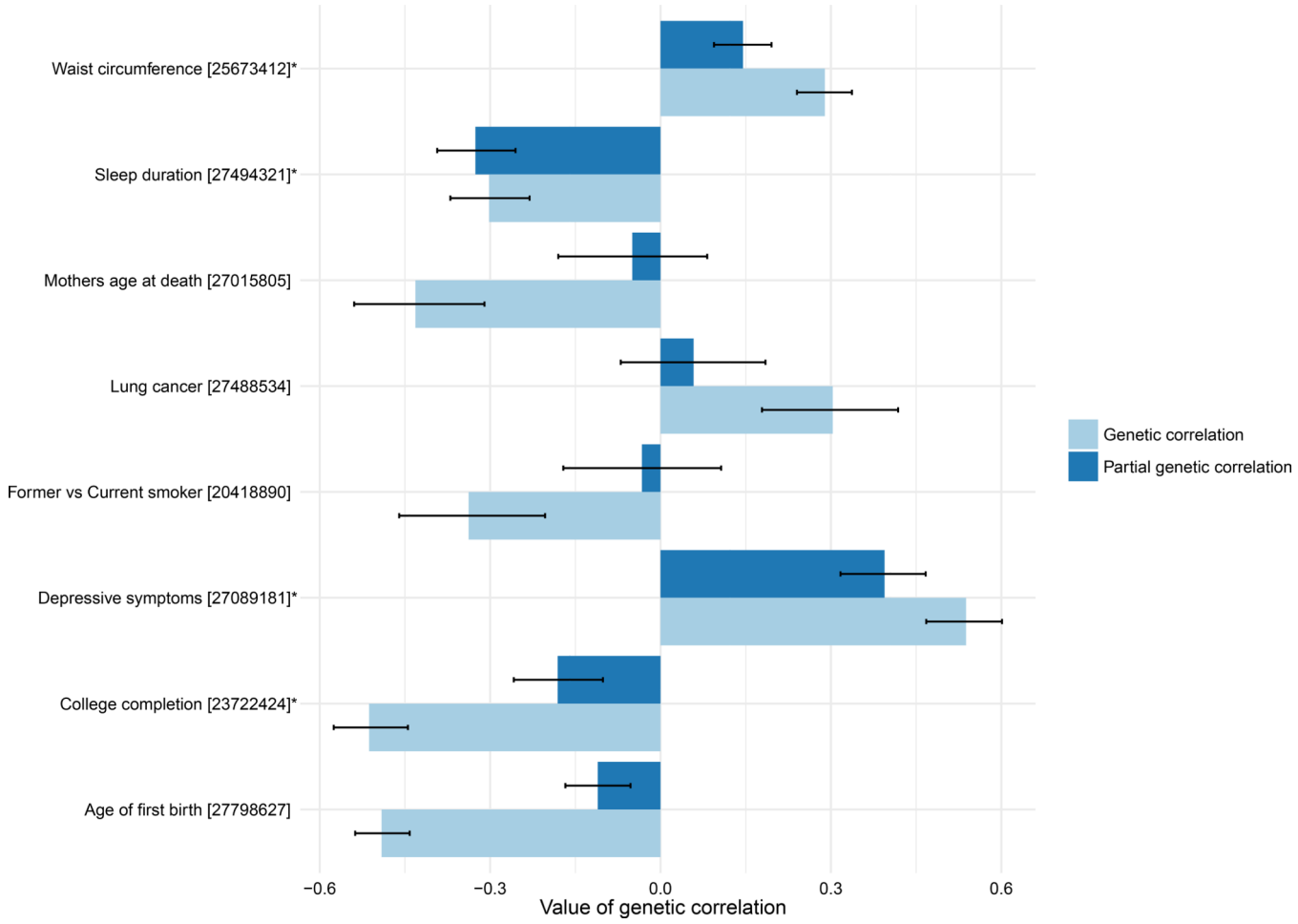

Figure 4. Partial genetic correlation and pair-wise genetic correlation barplots for 8 traits (one trait from each subcluster with threshold of 0.5 on hierarchical clustering dendrogram of genetic correlation matrix).

Error bars correspond to 95% confidence intervals. Asterisks depict traits in which partial correlation with BP is significant ($p<4.4\times10^{-5}$).

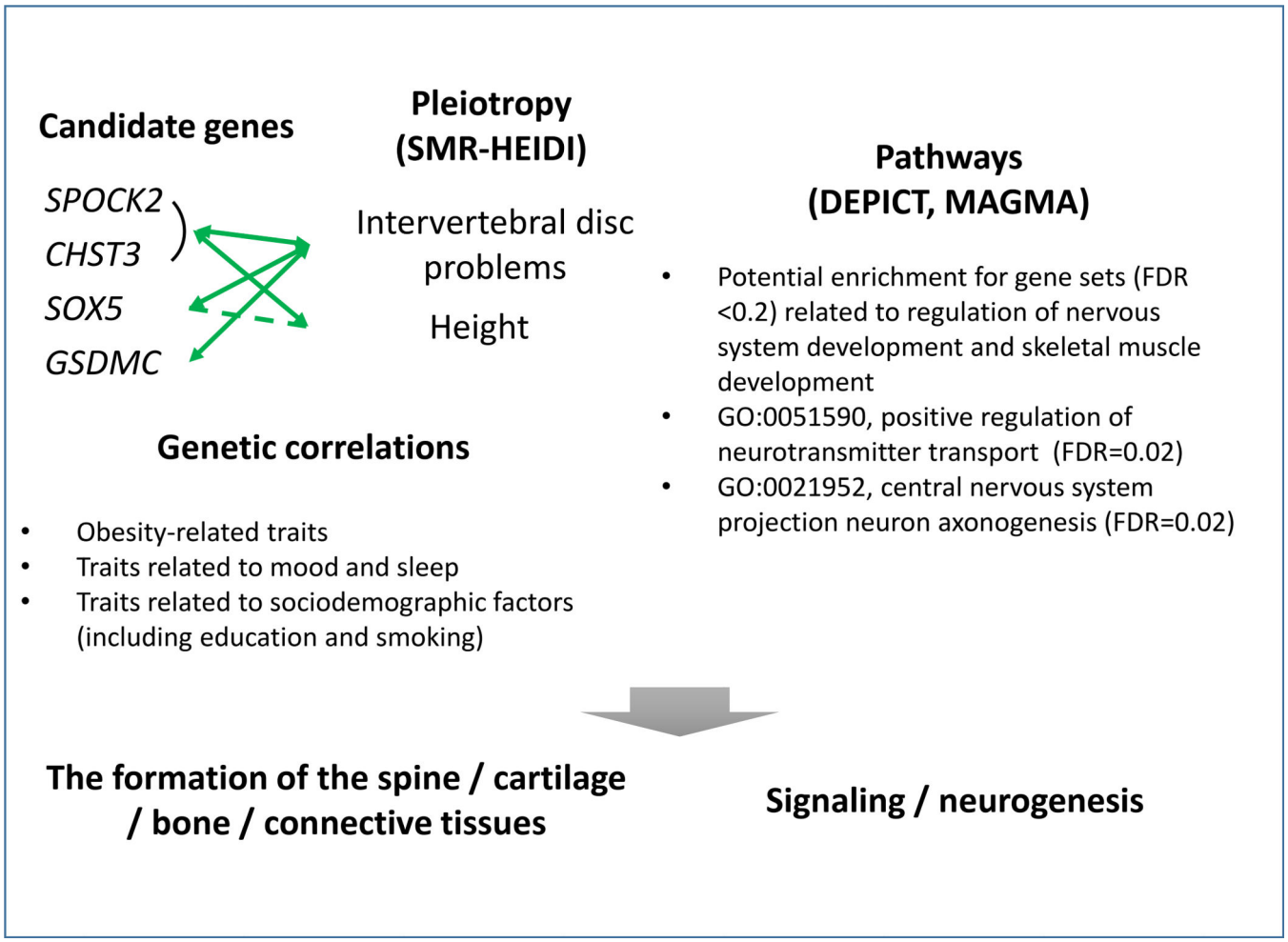

Figure 5. Summary of genes and pathways in back pain.

Left part of the figure summarizes information about positional candidate genes and genetic correlations. Green arrows depict pleiotropy by SMR/HEIDI method. Dashed green lines depict suggested pleiotropy by SMR/HEIDI. Left part of the figure summarizes the results of pathway analyses.

Table 1.

Results of discovery and replication GWAS of BP.

			DISCOVERY					REPLICATION		
SNP	**Nearby gene**	**Chr:Pos**	**Eff/Ref Allele**	**EAF**	**BETA (SE)**	**P before GC**	**P after GC**	**BETA(SE)**	**P**	**N**
rs12310519	***SOX5***	**12:23975219**	**C/T**	**0.84**	**−0.056 (0.007)**	**1.38×10^{-14}**	**3.52×10^{-14}**	**−0.05 (0.011)**	**5.00×10^{-5}**	**157618**
rs1865442	*C8orf34*	8:69574165	C/T	0.82	−0.052 (0.007)	1.60×10^{-13}	3.79×10^{-13}	−0.03 (0.011)	1.05×10^{-2}	157724
rs3180	***SPOCK2/CHST3***	**10:73820622**	**A/G**	**0.44**	**−0.037 (0.006)**	**7.83×10^{-12}**	**1.65×10^{-11}**	**−0.02 (0.008)**	**6.59×10^{-3}**	**157731**
rs7814941	***GSDMC/CCDC26***	**8:130718859**	**A/G**	**0.80**	**0.046 (0.007)**	**1.81×10^{-11}**	**3.71×10^{-11}**	**0.04 (0.010)**	**5.32×10^{-5}**	**157728**
rs2672596	*HTRA1*	10:124226793	G/A	0.74	0.041 (0.006)	4.46×10^{-11}	8.89×10^{-11}	0.02 (0.010)	3.98×10^{-2}	157735
rs10870267	*DPYSL4*	10:133968063	C/T	0.44	0.030 (0.006)	3.09×10^{-8}	5.05×10^{-8}	–	–	–
rs4974563	*SPON2*	4:1138153	C/T	0.30	−0.032 (0.006)	4.39×10^{-8}	7.10×10^{-8}	–	–	–
rs2910576	*PLK2*	5:57532748	A/T	0.19	0.038 (0.007)	4.71×10^{-8}	7.60×10^{-8}	–	–	–
rs7105462	*NCAM1*	11:112912048	G/A	0.41	0.030 (0.006)	4.72×10^{-8}	7.62×10^{-8}	–	–	–
rs10502966	*DCC*	18:50748499	A/G	0.58	−0.030 (0.006)	4.94×10^{-8}	7.96×10^{-8}	–	–	–

Chr:Pos – physical position of the SNP; Eff/Ref Allele – Effect and Reference alleles; EAF – effect allele frequency; BETA (SE) – effect of the SNP and standard error; P before GC – p-value before genomic control; P after GC – p-value after genomic control; N – sample size of replication. Bold font indicates the SNPs that passed the thresholds for statistical significance (5×10^{-8} for the discovery and 0.01 for replication phases, respectively).

Table 2.

Results of summary-level Mendelian randomization and pleiotropy analysis of SNPs associated with BP

Trait	Statistics	SNP (Gene)		
		rs3180 (*SPOCK2/CHST3*)	**rs12310519 (*SOX5*)**	**rs7814941 (*GSDMC/CCDC26*)**
Height	β_{SMR}	−1.677	0.800	6.013
	p_{SMR}	4.3×10^{-5}	7.4×10^{-3}	3.6×10^{-13}
	p_{HEIDI}	0.79	–	5.6×10^{-12}
Intervertebral disc problems	β_{SMR}	0.068	0.050	0.040
	p_{SMR}	3.3×10^{-7}	3.8×10^{-7}	3.2×10^{-5}
	p_{HEIDI}	0.75	0.12	0.50

Results of SMR/HEIDI tests using data from GeneAtlas. For the HEIDI tests, a hypothesis of pleiotropy was rejected at $p < 0.01$; with $p > 0.01$, we considered pleiotropy as a likely explanation. Two traits (height and intervertebral disc problems) with at least one significant SMR coefficient ($p<9.8\times10^{-4}$) among three loci are presented. β_{SMR} is SMR coefficient; p_{SMR} is p-value for SMR test; p_{HEIDI} is p-value for HEIDI test (not calculated if p_{SMR} was insignificant, "–").