

Genome-wide analysis of temporomandibular disorders in FinnGen: cross-population replication and genetic overlap with chronic pain

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Research Article

Keywords: temporomandibular joint disorders, facial pain, chronic pain, genome-wide association study, genetic correlation, single-nucleotide polymorphism

Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11284373/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background. Temporomandibular disorders (TMD) cause more chronic non-dental orofacial pain than any other condition. The recent, larger TMD genetic studies have all relied on FinnGen. Two questions remain open, however: whether genetic liability to TMD is shared across populations, and how it lines up against pain, psychiatric and joint phenotypes. **Methods.** We analysed TMD summary statistics from FinnGen release 13 (23,035 cases, 477,151 controls). Using linkage-disequilibrium score regression, we estimated single-nucleotide polymorphism (SNP) heritability and genetic correlations (rg) with 15 FinnGen traits, osteoarthritis and a non-pain control. The genetic correlation with TMD in Million Veteran Program (MVP) European-ancestry participants was estimated at genome-wide scale, and lead variants were then tested in non-overlapping MVP and UK Biobank participants. Finally, we characterised the loci by fine-mapping, gene-based tests and colocalisation. **Results.** Two loci crossed genome-wide significance: 7p15.3 (rs858236; odds ratio [OR] 0.91, $P = 2.4 \times 10^{-8}$; NUP42/GPNMB/KLHL7) and 12q21.2 (rs75618936; OR 0.90, $P = 7.6 \times 10^{-9}$; SYT1). Liability-scale SNP heritability was 0.049 at 5% prevalence. Genetic correlation between FinnGen and MVP was high (rg 0.86, 95% confidence interval 0.50–1.21), and the 7p15.3 variant showed a concordant nominal association outside Finland (OR 0.93, $P = 0.044$). TMD was genetically correlated with irritable bowel syndrome (rg 0.75), headache (0.62), insomnia (0.61), fibromyalgia (0.54) and depression (0.46). Each of these correlations was stronger than that with rheumatoid arthritis (0.15) or osteoarthritis (0.27) (paired tests, $q < 0.01$). Colocalisation did not support expression-mediated effects. **Conclusions.** Genetic liability to TMD is shared to a large extent between Finnish and US European-ancestry populations, and is closer to chronic pain, insomnia and psychiatric conditions than to joint disease. The SYT1 locus, whose protective allele is sevenfold more common in Finns, awaits replication.

Introduction

Temporomandibular disorders (TMD) span a range of painful and non-painful conditions that affect the temporomandibular joints and the muscles of mastication. They are the commonest cause of chronic non-dental orofacial pain (Smith et al. 2019). Pooled epidemiological work places the prevalence of temporomandibular joint disorder at roughly 31% in adults and older adults (Valesan et al. 2021), and TMD occur about twice as often in women as in men (LeResche 1997). The Diagnostic Criteria for TMD (DC/TMD) provide the standard for diagnosis (Schiffman et al. 2014). Dental occlusion was long suspected of contributing to TMD, but it now appears to play little part in risk (Manfredini et al. 2017). Prospective work from the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) programme instead pointed to comorbid pain conditions, psychological distress, somatic symptoms and worsening sleep quality as the leading predictors of first-onset TMD (Slade et al. 2013; Slade et al. 2016). TMD also occur frequently alongside headache, fibromyalgia, irritable bowel syndrome, low back pain and mood disorders. This cluster is now called chronic overlapping pain conditions, and altered central pain processing has been proposed as a mechanism common to them (Maixner et al. 2016).

That a heritable component underlies TMD is well supported. Candidate-gene work linked COMT haplotypes to pain sensitivity and to TMD onset (Diatchenko et al. 2005), and the OPPERA case-control study reported several associations with candidate pain genes (Smith et al. 2011). The early genome-wide association studies (GWAS) of painful TMD were small, spanning a few hundred to about 1,000 cases, and the loci they reported have not replicated consistently. Examples are SGCA in the Hispanic Community Health Study/Study of Latinos (Sanders et al. 2017) and MRAS in men in OPPERA (Smith et al. 2019). A GWAS of TMD-related pain in Finnish cohorts was likewise underpowered (Leppilahti et al. 2025). Larger GWAS of chronic pain have since shown that pain is polygenic and genetically correlated with psychiatric traits (Johnston et al. 2019), and a multivariate analysis of chronic overlapping pain conditions, TMD among them, identified a shared genetic factor that correlated strongly with multisite chronic pain and less so with rheumatoid arthritis (Johnston et al. 2025).

Larger TMD analyses have become possible with population biobanks. Three studies published in 2026 drew on FinnGen release 12 TMD data (about 20,800 cases): a catalogue of 67 oral diseases that reported a stop-gained variant in GPNMB (Karppinen et al. 2026), a GWAS-by-subtraction that separated anxiety-related from anxiety-independent components of TMD liability (Cao et al. 2026), and a multivariate GWAS of common oral diseases (Ma and Zheng 2026). Karppinen et al. replicated selected lead variants in UK Biobank, the Estonian Biobank and the Million Veteran Program (MVP) (Karppinen et al. 2026). FinnGen TMD summary statistics also underpin Mendelian randomisation studies, for instance of sleep traits and head-and-neck pain (Du et al. 2025; Zhang L et al. 2025). Karppinen et al. additionally estimated genetic correlations between oral diseases, TMD included, and systemic diseases (Karppinen et al. 2026), and Cao et al. reported a genetic correlation of 0.44 between TMD and anxiety (Cao et al. 2026). What has not been reported, as far as we know, is the genome-wide genetic correlation of TMD between independent populations, or a single analysis that sets TMD against a panel of orofacial, visceral, musculoskeletal and widespread pain, headache, sleep and psychiatric phenotypes.

Using public summary statistics alone, we set out to answer three questions. Is TMD genetic liability shared between Finnish and other European-ancestry populations? Is TMD genetically closer to pain, sleep and psychiatric conditions than to joint disease? And which genes underpin the associated loci? To address them, we combined a genome-wide genetic correlation between FinnGen and MVP with replication of lead variants in non-overlapping MVP and UK Biobank participants, and characterised the resulting loci by fine-mapping, gene-based tests,

transcriptome-wide association and colocalisation. Because only summary-level data from publicly described cohorts were used, the study raises no new ethical concerns.

Methods

Study design and ethics. Only publicly released GWAS summary statistics were used, and no individual-level data were accessed. The contributing studies had already obtained ethical approval and informed consent, as described in their original publications (Bycroft et al. 2018; Gaziano et al. 2016; Kurki et al. 2023); no further ethical approval was therefore needed.

Discovery data. Discovery analyses used FinnGen release 13 (R13) summary statistics (GRCh38) for the endpoint TEMPOROMANDIB_INCLAVO. This endpoint is defined by International Classification of Diseases, 10th revision (ICD-10) code K07.6 across hospital discharge, specialist outpatient and primary-care (Avohilmo) registers, and comprises 23,035 cases and 477,151 controls (effective sample size $N_{\text{eff}} = 87,897$). FinnGen genotyping and imputation against a population-specific reference panel have been described elsewhere (Kurki et al. 2023); recent releases use REGENIE for association testing (Karppinen et al. 2026; Mbatchou et al. 2021). We retained single-nucleotide variants with minor allele frequency (MAF) $\geq 1\%$ and complete statistics, and discarded strand-ambiguous A/T and C/G variants with MAF > 0.42 , which left 8,605,283 variants. Chromosome X entered the Manhattan plot and clumping but not the linkage-disequilibrium (LD) score analyses. Inflation was summarised by the genomic-control factor λ_{GC} (Devlin and Roeder 1999). Lead loci were defined by greedy distance clumping (± 500 kb) at $P < 5 \times 10^{-8}$ (genome-wide significance) and $P < 1 \times 10^{-6}$ (suggestive).

Heritability and genetic correlation. We reimplemented univariate and bivariate LD score regression in Python (Bulik-Sullivan et al. 2015a, b). The implementation used a free intercept, iteratively reweighted least squares with two iterations, exclusion of variants with $\chi^2 > \max(80, 0.001N)$, and a 200-block jackknife for standard errors (SE). The LD reference was the standard European LD scores computed from the 1000 Genomes Project (1000 Genomes Project Consortium. 2015) and restricted to HapMap 3 variants (International HapMap 3 Consortium. 2010) (eur_w_ld_chr; $M = 1,247,656$ autosomal variants with MAF $> 5\%$). Observed-scale SNP heritability was converted to the liability scale using N_{eff} with a sample prevalence of 0.5 (Lee et al. 2011); we assumed a population prevalence (K) of 5%, close to the FinnGen case fraction of 4.6%, and report $K = 2-15\%$ as a sensitivity analysis. The same pipeline, applied to FinnGen body mass index (BMI; $N = 362,216$), served as a check on scaling. Genetic correlations (rg) were estimated with 15 FinnGen R13 endpoints covering orofacial pain, visceral, musculoskeletal and widespread pain, headache, psychiatric, sleep, dental and inflammatory joint phenotypes. Orofacial pain, dental, headache-syndrome, fibromyalgia and reflux endpoints were specified by FinnGen phenocode; the rest were located by name search of the FinnGen R13 endpoint list, taking the matching endpoint with the most cases (codes in Supplementary Table S1). Tension-type headache has no separate endpoint and falls within the headache-syndromes endpoint (ICD-10 G44). Sample overlap within FinnGen inflates the cross-trait intercept but does not bias rg (Bulik-Sullivan et al. 2015a). We also estimated the dentofacial anomalies endpoint (ICD-10 K07) but set it aside from interpretation and from multiple-testing correction, because it contains the TMD code K07.6. P values for the 15 traits were adjusted by the Benjamini-Hochberg false discovery rate (FDR) (Benjamini and Hochberg 1995). In secondary analyses outside this FDR family, we estimated rg with three osteoarthritis endpoints (any site, knee and hip) as degenerative joint comparators, and with senile cataract as a common non-pain control expected to share little genetic liability with TMD. To test whether TMD correlated more strongly with pain, psychiatric and sleep traits than with joint disease, we compared its rg with each of eight such traits (irritable bowel syndrome, headache syndromes, migraine, back pain, fibromyalgia, insomnia, anxiety and depression) and with two orofacial pain traits (trigeminal neuralgia and atypical facial pain) against its rg with rheumatoid arthritis and with each of the three osteoarthritis endpoints. Differences were tested with a paired block jackknife, recomputing both rg estimates in each of the 200 leave-one-block-out samples on a common set of 1,250,954 variants; this accounts for the correlation between the two estimates. P values for the 40 comparisons were FDR-adjusted. To benchmark the implementation, heritability and rg for TMD and six comparators were re-estimated with the `ldsc` function of the GenomicSEM R package (Grotzinger et al. 2019) on the same summary statistics and LD scores.

Replication. Replication used the public FinnGen release 12 $\times$ MVP $\times$ UK Biobank meta-analysis files for the endpoint TEMPOROMANDIB. This endpoint differs from the discovery endpoint TEMPOROMANDIB_INCLAVO, and the MVP and UK Biobank case definitions are those of the public meta-analysis. Since FinnGen release 12 overlaps the discovery sample, only the non-Finnish estimates were used (MVP groups are defined by harmonised ancestry and race/ethnicity):

- MVP European ancestry (EUR): 5,218 cases, 443,293 controls (Gaziano et al. 2016; Verma et al. 2024)
- MVP African ancestry (AFR): 1,741 cases, 116,637 controls (Gaziano et al. 2016; Verma et al. 2024)
- MVP Hispanic (HIS): 909 cases, 48,579 controls (Gaziano et al. 2016; Verma et al. 2024)
- UK Biobank: 281 cases, 408,157 controls (Bycroft et al. 2018)

We also drew on FinnGen's leave-FinnGen-out meta-analysis of these four studies, an inverse-variance-weighted fixed-effect meta-analysis (Willer et al. 2010). Per-study P values had been saddle-point corrected (Zhou et al. 2018) and were therefore inconsistent with the reported

standard errors, so we recomputed $SE = |\beta| / \Phi^{-1}(1 - P/2)$. Inverse-variance meta-analysis with these standard errors reproduced the official leave-FinnGen-out estimates. Replication was assessed by effect direction, by one-sided P values, and by power to detect the discovery effect at two-sided $\alpha = 0.05$. For the genome-wide rg with MVP-EUR, signed z-scores were derived from MVP P values and the sign of β .

Fine-mapping and annotation. For each lead locus (± 500 kb) we computed Wakefield approximate Bayes factors (Wakefield 2009) with a prior standard deviation of 0.2 on the log odds ratio, assuming a single causal variant, and built 95% credible sets from the posterior probabilities (Maller et al. 2012). Only variants with $MAF \geq 1\%$ entered the credible sets. Credible-set variants were annotated with the Ensembl Variant Effect Predictor (VEP; GRCh38) (McLaren et al. 2016). Because approximate Bayes factors ignore LD and allow only one causal variant, we additionally examined FinnGen's public R13 fine-mapping results for the two genome-wide significant loci, obtained with SuSiE (Wang et al. 2020), which uses in-sample LD and permits up to 10 causal variants per 3-Mb region.

Gene-based tests, tissue enrichment and transcriptome-wide association. Gene-level P values were formed by combining the P values of all variants within each GENCODE v44 protein-coding gene ± 10 kb (Frankish et al. 2023) with the aggregated Cauchy association test (ACAT) (Liu et al. 2019). Bonferroni significance was set at 0.05 divided by the number of genes tested (19,013 genes; $P < 2.6 \times 10^{-6}$). For tissue enrichment, gene-level z-scores were regressed on membership in the top 10% most specifically expressed genes of each of 54 Genotype-Tissue Expression (GTEx) v8 tissues (GTEx Consortium. 2020), adjusted for log variant count and log gene length; this gene-level approach is related to, though distinct from, stratified LD score regression of specifically expressed genes (Finucane et al. 2018). The transcriptome-wide association study (TWAS) used S-PrediXcan (Barbeira et al. 2018) with GTEx v8 multivariate adaptive shrinkage (MASHR) expression models (Barbeira et al. 2021) across 10 tissues chosen to span musculoskeletal, neural and control tissues: skeletal muscle, cultured fibroblasts, tibial nerve, whole blood, cervical spinal cord, hypothalamus, cortex, subcutaneous adipose, non-sun-exposed skin and tibial artery. Tissue-level results were combined across tissues by ACAT (Liu et al. 2019), with Bonferroni correction for the number of genes (19,385 genes; $P < 2.6 \times 10^{-6}$).

Colocalisation. For the 7p15.3 genes (GPNMB, KLHL7, IGF2BP3 and NUP42) and SYT1, we tested whether TMD and gene expression share a causal variant with coloc.abf (Giambartolomei et al. 2014) (prior probabilities $p1 = p2 = 10^{-4}$ and $p12 = 10^{-5}$; prior standard deviation 0.2 for TMD log odds ratios and 0.15 for expression effects), using variants within ± 500 kb of each lead variant. GTEx v8 expression quantitative trait locus (eQTL) summary statistics came from the eQTL Catalogue (Kerimov et al. 2021) for 11 tissues: skeletal muscle, cultured fibroblasts, tibial nerve, whole blood, cervical spinal cord, hypothalamus, anterior cingulate cortex (BA24), frontal cortex (BA9), subcutaneous adipose, non-sun-exposed skin and tibial artery. A posterior probability of a shared causal variant (PP.H4) above 0.8 was treated as evidence of colocalisation, and PP.H3 above 0.8 as evidence of distinct causal variants.

Allele frequencies and prior reports. Lead-variant allele frequencies in Finnish and non-Finnish European individuals were taken from gnomAD v4 genomes (Chen S et al. 2024), and those in the replication cohorts from the meta-analysis files. Prior associations were looked up in the GWAS Catalog (Cerezo et al. 2025) and in the public FinnGen release 12 meta-analysis files.

Phenome-wide association (PheWAS). Each lead variant was queried across all FinnGen R13 endpoints through the public FinnGen results browser (Kurki et al. 2023). We report associations passing a Bonferroni threshold for 2,754 endpoints ($P < 1.8 \times 10^{-5}$); associations with endpoints containing the TMD code (K07) were not interpreted.

Software. Analyses were run in Python 3 (pandas, NumPy, SciPy, statsmodels, matplotlib) in Google Colab; the benchmark used R with GenomicSEM (Grotzinger et al. 2019). Analysis code is listed under Code availability.

Results

Two genome-wide significant loci

Quality control left 8,605,283 variants. The GWAS showed modest inflation ($\lambda_{GC} = 1.11$; LD score intercept 1.045, SE 0.008; attenuation ratio 0.33) (Fig. 1). Two loci crossed $P < 5 \times 10^{-8}$, and three more reached $P < 1 \times 10^{-6}$ (Table 1). At four of the five lead variants the minor allele lowered TMD risk; at rs4838340 (9q33.3) the minor allele (G) raised it.

Table 1
Lead TMD loci in FinnGen R13 and replication in independent cohorts (MVP + UK Biobank).

Locus (nearest/implicated gene)	Lead SNP (chr:pos, GRCh38)	EA / OA	EAF	EAF gnomAD FIN / NFE	OR (FinnGen R13)	P (FinnGen R13)	OR (MVP+UKBB) (95% CI)	P (MVP+UKBB)	Direction
12q21.2 (SYT1)	rs75618936 (12:79,130,017)	A / T	0.083	0.0854 / 0.0124	0.902	7.6×10^{-9}	0.914 (0.76–1.10)	0.34	Same
7p15.3 (NUP42 / GPNMB / KLHL7)	rs858236 (7:23,200,148)	T / G	0.103	0.1035 / 0.0490	0.913	2.4×10^{-8}	0.929 (0.86–1.00)	0.044	Same
16q23.1 (ADAMTS18)	rs61580908 (16:77,300,707)	C / T	0.185	0.1917 / 0.1240	0.939	5.2×10^{-7}	0.968 (0.91–1.02)	0.26	Same
9q33.3 (AL589923.1)	rs4838340 (9:126,117,946)	A / G	0.739	0.7387 / 0.7012	0.947	5.7×10^{-7}	0.976 (0.94–1.01)	0.15	Same
16q23.1 (CNTNAP4)	rs189648112 (16:76,320,929)	C / A	0.049	0.0666 / 0.0007	0.892	6.5×10^{-7}	—	—	Not available

Loci are ordered by discovery P value. MVP+UKBB, FinnGen's leave-FinnGen-out inverse-variance meta-analysis of MVP-EUR, MVP-AFR, MVP-HIS and UK Biobank (two-sided P); 95% CIs were derived from P-based standard errors. EA, effect allele; OA, other allele; EAF, effect-allele frequency in FinnGen; FIN / NFE, Finnish / non-Finnish European individuals in gnomAD v4 genomes; OR, odds ratio per effect allele; CI, confidence interval; SNP, single-nucleotide polymorphism; MVP, Million Veteran Program; UKBB, UK Biobank. No MVP or UK Biobank estimate was available for rs189648112. Per-cohort estimates are given in Supplementary Table S2 and allele frequencies in Supplementary Table S3.

Replication across cohorts

All four lead variants present in the replication data carried the same direction of effect as in FinnGen (one-sided sign test $P = 0.0625$, the smallest value attainable with four variants). The 7p15.3 variant was nominally associated (odds ratio [OR] 0.93, $P = 0.044$; one-sided $P = 0.022$), though this did not survive correction for four variants (one-sided $\alpha = 0.0125$); its effect was also nominally significant among MVP African-ancestry participants (OR 0.87, 95% confidence interval [CI] 0.76–1.00, $P = 0.048$). Power to detect the discovery effect sizes at $\alpha = 0.05$ (uncorrected for winner's curse) was 20% for SYT1, 70% for 7p15.3, 58% for ADAMTS18 and 89% for 9q33.3. The SYT1 effect allele was enriched in Finns (gnomAD: 8.5% in Finnish versus 1.2% in non-Finnish European individuals) and sat at 1.0% in MVP-EUR, where the estimate (OR 0.909, 95% CI 0.71–1.16, $P = 0.44$) was too imprecise to confirm or exclude replication. The CNTNAP4 effect allele was almost specific to Finns (6.7% versus 0.07%). The 9q33.3 variant showed no association (OR 0.976, $P = 0.15$) despite an estimated power of 89%.

At the genome-wide level, the genetic correlation of TMD between FinnGen and MVP European-ancestry participants was high ($rg = 0.86$, SE 0.18, 95% CI 0.50–1.21, $P = 2.0 \times 10^{-6}$; 1,216,036 variants). It did not differ significantly from 1 ($P = 0.43$).

SNP-heritability

Observed-scale SNP heritability was 0.058 (SE 0.007), which corresponds to 0.049 (SE 0.006) on the liability scale at $K = 5\%$ (0.038 at $K = 2\%$, 0.061 at $K = 10\%$ and 0.069 at $K = 15\%$). The same pipeline gave an SNP heritability of 0.238 (SE 0.008) with an intercept of 1.48 for BMI. Against GenomicSEM, our implementation produced intercepts within 0.004 and genetic correlations within 0.02 (for example, TMD–MVP rg 0.859 versus 0.856), while observed-scale heritabilities came out 6–17% higher (TMD 0.058 versus 0.055). Standard errors of rg were similar, with one exception: for the TMD–MVP estimate our jackknife SE was larger (0.18 versus 0.13), so the reported cross-cohort confidence interval is conservative (Supplementary Table S4).

Genetic correlation with orofacial, pain, psychiatric and sleep traits

TMD was genetically correlated with all 15 traits after FDR correction ($q < 0.05$; Table 2; Fig. 2; Supplementary Table S5). The largest point estimate was for atypical facial pain (rg 1.20, SE 0.39), which also had the widest confidence interval. Among the more precisely estimated traits, the strongest correlations were with irritable bowel syndrome (0.75), headache syndromes (0.62), insomnia (0.61) and migraine (0.57). The weakest among the 15 primary traits was with rheumatoid arthritis (0.15, 95% CI 0.01–0.29).

Table 2
Genetic correlation of TMD with FinnGen R13 traits (LD score regression).

Trait	Group	Cases	rg (SE)	95% CI	P	FDR q
Atypical facial pain	Orofacial pain	2,010	1.20 (0.39)*	0.43–1.97	2.2×10^{-3}	2.5×10^{-3}
Irritable bowel syndrome	Visceral	13,914	0.75 (0.08)	0.59–0.91	4.4×10^{-21}	1.6×10^{-20}
Trigeminal neuralgia	Orofacial pain	2,356	0.66 (0.24)	0.19–1.13	6.4×10^{-3}	6.9×10^{-3}
Headache syndromes	Headache	22,497	0.62 (0.06)	0.50–0.75	3.3×10^{-22}	2.4×10^{-21}
Insomnia	Sleep	51,643	0.61 (0.07)	0.48–0.74	5.9×10^{-21}	1.8×10^{-20}
Migraine	Headache	28,504	0.57 (0.06)	0.45–0.69	8.3×10^{-22}	4.2×10^{-21}
Dorsalgia / back pain	Musculoskeletal pain	88,320	0.54 (0.05)	0.44–0.65	6.5×10^{-24}	9.8×10^{-23}
Gastro-oesophageal reflux	Visceral	37,811	0.54 (0.06)	0.42–0.66	7.2×10^{-18}	1.4×10^{-17}
Fibromyalgia	Widespread pain	4,005	0.54 (0.09)	0.36–0.72	3.8×10^{-9}	6.2×10^{-9}
Anxiety	Psychiatric	26,248	0.51 (0.06)	0.40–0.63	1.2×10^{-18}	2.9×10^{-18}
Depression	Psychiatric	61,203	0.46 (0.05)	0.35–0.56	3.6×10^{-18}	7.7×10^{-18}
Dental caries	Dental	233,767	0.36 (0.06)	0.24–0.49	2.3×10^{-8}	3.1×10^{-8}
Chronic apical periodontitis	Dental	83,192	0.35 (0.07)	0.21–0.48	1.0×10^{-6}	1.3×10^{-6}
Sleep apnoea	Sleep	69,677	0.30 (0.05)	0.20–0.40	4.1×10^{-9}	6.2×10^{-9}
Rheumatoid arthritis	Inflammatory joint	16,775	0.15 (0.07)	0.01–0.29	0.039	0.039
Secondary analyses						
Osteoarthritis, any site	Degenerative joint	106,674	0.27 (0.04)	0.19–0.36	2.7×10^{-10}	—
Knee osteoarthritis	Degenerative joint	64,535	0.21 (0.04)	0.13–0.29	7.9×10^{-7}	—
Hip osteoarthritis	Degenerative joint	32,962	0.22 (0.05)	0.12–0.31	1.6×10^{-5}	—
Senile cataract	Non-pain control	91,611	0.11 (0.06)	–0.01 to 0.22	0.064	—

*Unconstrained estimate; values above 1 can arise from sampling error when SE is large. The dentofacial anomalies endpoint (K07) is not shown because it contains the TMD code K07.6 (case overlap); it was excluded from the FDR correction ($m = 15$). Osteoarthritis and senile cataract were added as secondary comparators and were not part of the FDR family. Headache syndromes, FinnGen endpoint "Other headache syndromes" (ICD-10 G44); anxiety, "Other anxiety disorders" (ICD-10 F41). CI, confidence interval; FDR, Benjamini–Hochberg false discovery rate. Endpoint codes are given in Supplementary Table S1, and comparator heritabilities and cross-trait intercepts in Supplementary Table S5.

Secondary analyses placed the correlation of TMD with osteoarthritis at 0.27 (95% CI 0.19–0.36) for any site, 0.21 (0.13–0.29) for the knee and 0.22 (0.12–0.31) for the hip; the correlation with the non-pain control, senile cataract, was weak and not significant (0.11, –0.01 to 0.22; $P = 0.064$) (Table 2). In paired tests, the rg of TMD with each of irritable bowel syndrome, headache syndromes, migraine, back pain, fibromyalgia, insomnia, anxiety and depression exceeded its rg with rheumatoid arthritis and with each osteoarthritis endpoint (32 comparisons; all $q \leq 0.0051$) (Supplementary Table S6). The rg with atypical facial pain likewise exceeded those with all four joint traits ($q \leq 0.02$), whereas the rg with trigeminal neuralgia differed significantly only from that with rheumatoid arthritis ($q = 0.036$).

Fine-mapping, gene-based tests and TWAS

The 7p15.3 95% credible set (168 variants) contained protein-altering and splice variants (Supplementary Table S7): the lead variant rs858236 and rs1637215 are missense variants in NUP42, rs11537976 is a stop-gained variant in GPNMB (effect-allele frequency 0.067), and rs77982996 is a splice-donor variant in KLHL7, with further splice-region variants in GPNMB and NUP42. None stood out individually (posterior probability ≤ 0.013 each). The SYT1 credible set (42 variants) held no coding variants (Fig. 3). Credible sets at the suggestive loci contained 181 (ADAMTS18), 62 (CNTNAP4) and 9 (9q33.3) variants. FinnGen's SuSiE fine-mapping, which uses in-sample LD, likewise identified a single credible set at each locus (Supplementary Table S8): 188 variants with a maximum posterior inclusion probability (PIP) of 0.014 at 7p15.3, containing all of the coding variants above, and 45 variants within SYT1 (all annotated variants intronic) with a maximum PIP of 0.022 at 12q21.2. Gene-based tests placed GPNMB, KLHL7, NUP42 (all at 7p15.3) and SYT1 past Bonferroni correction (Supplementary

Table S9). The TWAS identified KLHL7, IGF2BP3 and the long non-coding RNA AC005082.12 (all at 7p15.3) after Bonferroni correction (Supplementary Table S10). For these three genes, higher predicted expression went with lower TMD risk: KLHL7 in cortex and cervical spinal cord ($Z = -5.5$), IGF2BP3 in tibial nerve ($Z = -5.4$) and AC005082.12 in six tissues ($Z = -4.7$ to -5.2). Only KLHL7 and IGF2BP3 cleared the Bonferroni threshold when tissues were taken one at a time, whereas AC005082.12 did so in two of the nine tissues in which it was modelled (Supplementary Table S10). Most of these expression models relied on only one or two variants. No GTEx tissue showed significant enrichment at FDR 5%.

Phenome-wide associations of lead variants

Once endpoints containing K07 were excluded, four lead variants were associated with other FinnGen endpoints at the Bonferroni threshold (Supplementary Table S12). rs75618936 (SYT1) was associated with excessive vomiting in pregnancy ($P = 2.2 \times 10^{-6}$), rs4838340 (9q33.3) with abdominal wall hernia ($P = 3.7 \times 10^{-6}$), rs61580908 (ADAMTS18) with sciatica with lumbago ($P = 8.3 \times 10^{-6}$) and rs189648112 (CNTNAP4) with current and ever smoking ($P = 1.5 \times 10^{-5}$ and 1.6×10^{-5} ; the effect allele lowered the odds of smoking). The associations of rs858236 and rs4838340 with dentofacial anomalies mirror the K07/K07.6 case overlap and are not reported as independent findings. In the GWAS Catalog, rs75618936 had no listed association, and rs858236 was listed for a telomere-length trait ($P = 2 \times 10^{-9}$).

Discussion

The genetic correlation between FinnGen and MVP ($rg = 0.86$, 95% CI 0.50–1.21) points to a large shared component of genetic liability to TMD in Finnish and US veteran populations. Earlier FinnGen-based studies replicated selected lead variants, but none reported a genome-wide genetic correlation between independent populations (Cao et al. 2026; Karppinen et al. 2026; Ma and Zheng 2026). The two cohorts differ in health-care system, in how cases are ascertained (national registry diagnoses that include primary care versus veteran health records) and in sex composition: TMD occur about twice as often in women as in men (LeResche 1997), whereas MVP participants are predominantly male (Gaziano et al. 2016). That the correlation stayed high across these differences suggests that diagnosis-code definitions in registry (FinnGen) and electronic health record (MVP) data capture largely the same underlying liability. The wide confidence interval nonetheless leaves room for incomplete sharing.

TMD was genetically closer to chronic pain, insomnia and psychiatric traits than to inflammatory or degenerative joint disease, and paired tests upheld the difference for all eight such traits tested. The correlations spanned visceral (irritable bowel syndrome, 0.75), headache (0.57–0.62), musculoskeletal (back pain, 0.54) and widespread pain (fibromyalgia, 0.54) phenotypes, together with insomnia, anxiety and depression. The anxiety estimate (0.51) is close to the 0.44 that Cao et al. reported in FinnGen release 12 (Cao et al. 2026). This profile fits the clinical concept of chronic overlapping pain conditions (Maixner et al. 2016) and the OPPERA finding that comorbid pain, psychological distress and poor sleep predict TMD onset (Slade et al. 2013; Slade et al. 2016). It also agrees with several earlier results: the multivariate factor for chronic overlapping pain conditions lay closer to multisite chronic pain than to rheumatoid arthritis (Johnston et al. 2025); multisite chronic pain overlaps genetically with psychiatric traits (Johnston et al. 2019); and fibromyalgia shows strong genetic correlations with low back pain and irritable bowel syndrome (Kerrebijn et al. 2026). Probable sleep bruxism in FinnGen follows a similar pattern of genetic correlation with pain diagnoses, sleep apnoea and reflux disease (Strausz et al. 2023). The modest positive rg with rheumatoid arthritis is consistent with Mendelian randomisation studies that report a causal effect of rheumatoid arthritis on TMD (odds ratios 1.08–1.35) (Chen X et al. 2024; Li et al. 2025; Zhang Y et al. 2025). Because temporomandibular joint pathology is mainly degenerative rather than autoimmune, osteoarthritis is the more relevant joint comparator. Its genetic correlation with TMD (0.21–0.27) was numerically larger than that of rheumatoid arthritis, yet significantly smaller than those of the eight pain, insomnia and psychiatric traits. This fits a modest degenerative contribution to TMD liability alongside a larger pain-related component, though shared pain reporting or health-care use may also feed into the osteoarthritis correlation. The weak, non-significant correlation with senile cataract argues against shared health-care use or general morbidity as the sole explanation for the broad correlation profile, although such effects cannot be ruled out. The correlations with dental caries (0.36) and chronic apical periodontitis (0.35) may partly reflect shared dental-care use, since TMD are often diagnosed in dental settings. A multivariate study using high-definition likelihood reported a near-zero rg between TMD and caries (Ma and Zheng 2026); the discrepancy may stem from different caries endpoints and estimators.

Of the single loci, 7p15.3 has the strongest support. It reached genome-wide significance and kept the same direction of effect in the non-Finnish meta-analysis, with nominal significance overall and among MVP African-ancestry participants. Gene-based tests (GPNMB, KLHL7, NUP42) and the TWAS (KLHL7, IGF2BP3) also pointed to this region, but these signals reflect the same LD block rather than independent lines of evidence. Colocalisation gave no support to a shared causal variant for any gene tested (maximum PP.H4 0.26) and favoured distinct causal variants for several gene–tissue pairs. Some gaps in that analysis are worth flagging: the GTEx cortex sample carrying the KLHL7 TWAS signal was not among the colocalisation datasets (anterior cingulate and frontal cortex were tested instead), the KLHL7 result in cervical spinal cord was inconclusive (PP.H4 0.26), IGF2BP3 could be tested only in fibroblasts and not in tibial nerve, and AC005082.12 was

not tested at all. Expression mediation can therefore be neither confirmed nor excluded. GPNMB (osteoactivin) is a transmembrane glycoprotein expressed by osteoblasts, macrophages and microglia; it promotes osteogenesis and angiogenesis and acts largely anti-inflammatory (Bianco and Kratky 2023; Hu et al. 2013; Satoh et al. 2019). GPNMB and KLHL7 were recently assigned to an anxiety-independent component of TMD liability, and that study also reported a TWAS association for KLHL7 (Cao et al. 2026). Biallelic KLHL7 variants cause a recessive syndrome that overlaps Crisponi/cold-induced sweating syndrome (Kanthi et al. 2019), but no role in pain has been described. The credible set holds coding variants in three genes: missense variants in NUP42 (including the lead variant), a stop-gained variant in GPNMB that was already reported in FinnGen release 12 (Karppinen et al. 2026), and a splice-donor variant in KLHL7. Neither our credible set nor SuSiE fine-mapping with in-sample LD prioritised any of them (posterior probability ≤ 0.013 and PIP ≤ 0.012 each), and SuSiE found a single signal.

The absence of colocalisation is compatible with a coding mechanism, but the effector gene at 7p15.3 still cannot be assigned.

We found no report of SYT1 as a TMD locus in the published FinnGen release 12 analyses (Cao et al. 2026; Karppinen et al. 2026; Ma and Zheng 2026). SYT1 encodes synaptotagmin-1, the principal calcium sensor for fast synchronous neurotransmitter release (Geppert et al. 1994; Südhof 2013), and pathogenic SYT1 variants cause a neurodevelopmental disorder (Baker et al. 2018). Synaptotagmin-1 could therefore plausibly shape nociceptive transmission. The credible set is non-coding, and SuSiE identified a single signal of 45 variants within SYT1; this is compatible with a regulatory mechanism, but SYT1 itself remains unconfirmed as the effector gene. The lead allele is about seven times more frequent in Finns than in other Europeans, which helps to explain the low replication power. Colocalisation with GTEx eQTLs, measured mostly in non-Finnish individuals, showed no shared variant (maximum PP.H4 0.23) and favoured distinct variants in subcutaneous adipose tissue and tibial artery. In the public FinnGen release 12 files, the strongest association of the variant was $P = 2.2 \times 10^{-7}$, short of genome-wide significance and consistent with its absence from earlier reports, and the GWAS Catalog listed no association. The PheWAS association of the SYT1 variant with excessive vomiting in pregnancy is hypothesis-generating. The most severe form of this condition, hyperemesis gravidarum, has placental and appetite-related genetic components, including fetal GDF15 acting on the maternal brainstem (Fejzo et al. 2024; Fejzo et al. 2018). Among the suggestive loci, CNTNAP4, whose lead allele is almost specific to Finns, encodes Caspr4, a neuronal member of the neurexin superfamily that regulates GABAergic and dopaminergic synaptic transmission (Karayannis et al. 2014; Spiegel et al. 2002). ADAMTS18 encodes a secreted extracellular-matrix protease (Nie and Zhang 2023), and its lead variant was also associated with sciatica, which may point to a connective-tissue contribution. The CNTNAP4 lead allele also lowered the odds of smoking, which could reflect pleiotropy or confounding of the TMD association by smoking. These suggestive loci need confirmation.

Taken at population level, these results place TMD alongside other chronic pain, sleep and mood disorders in terms of shared genetic liability. Genetic correlations say nothing about clinical interventions, but they do supply a biological rationale for the assessment of comorbid pain, sleep and psychological problems that is already recommended for patients with TMD (Maixner et al. 2016; Slade et al. 2016).

Strengths and limitations. The main strengths are the large discovery sample, a genome-wide genetic correlation with a non-overlapping cohort, lead-variant estimates from three MVP population groups, and a panel of 15 comparison traits analysed on a common scale. Osteoarthritis and non-pain control comparators, formal tests of differences between genetic correlations and benchmarking of our LD score implementation against GenomicSEM lend further weight to the cross-trait results. The study also has limitations. First, cases were defined by registry ICD-10 codes (K07.6) rather than DC/TMD examination (Schiffman et al. 2014); painful and intra-articular subtypes cannot be separated, and misclassification between TMD, atypical facial pain and trigeminal neuralgia could inflate the orofacial correlations. Second, the discovery data overlap FinnGen release 12, on which the 2026 publications rest (Cao et al. 2026; Karppinen et al. 2026; Ma and Zheng 2026), and Karppinen et al. already replicated selected TMD lead variants outside Finland (Karppinen et al. 2026); the new contributions are therefore the genome-wide cross-population genetic correlation, the ancestry-specific lead-variant estimates, the cross-trait panel and the SYT1 locus. Third, lead-variant replication had limited power, particularly for the Finnish-enriched SYT1 allele (20%). The 9q33.3 variant did not replicate despite an estimated 89% power, although that estimate is probably inflated by winner's curse. UK Biobank contributes only 281 cases, the replication endpoint (TEMPOROMANDIB) differs from the discovery endpoint, and genome-wide genetic correlations with MVP African- and Hispanic-ancestry participants were not estimated. Fourth, the 1000 Genomes European LD reference (1000 Genomes Project Consortium. 2015) differs from Finnish LD, which may contribute to the elevated intercepts (TMD 1.045; BMI 1.48); absolute heritability and intercepts should therefore be read with caution. Because the same reference enters the numerator and denominator of r_g , genetic correlations should be less affected (Bulik-Sullivan et al. 2015a). Our Python LD score regression agreed closely with GenomicSEM for intercepts and genetic correlations but returned 6–17% higher heritabilities, a further reason for caution with absolute heritability. Fifth, liability-scale heritability depends on the assumed prevalence (Lee et al. 2011) (0.038–0.069 for $K = 2$ –15%). Sixth, our fine-mapping assumed one causal variant per locus, and approximate Bayes factors do not use LD; SuSiE with in-sample LD supported a single signal at each genome-wide significant locus, but the wide credible sets of both methods reflect modest association strength. The two 16q23.1 loci, about 980 kb apart, were separated only by distance and may not be independent. Colocalisation also assumed a single causal variant, consistent with the SuSiE results, and used bulk GTEx tissues of modest size that do not include the temporomandibular joint, masticatory muscles or trigeminal ganglion. Seventh, although the senile cataract control argues against a purely non-specific explanation, the broad correlation

profile may partly reflect shared health-care use or general morbidity in registry phenotypes. Finally, analyses were not sex-stratified, and chromosome X was not included in LD score analyses.

In conclusion, genetic liability to TMD is largely shared between Finnish and US European-ancestry populations, and overlaps more with chronic pain, insomnia and psychiatric conditions than with rheumatoid arthritis and osteoarthritis. The 7p15.3 (NUP42/GPNMB/KLHL7) locus had the same direction of effect in the non-Finnish meta-analysis, yet did not colocalise with the expression of nearby genes in up to 11 GTEx tissues. The Finnish-enriched SYT1 locus at 12q21.2 remains a candidate that requires replication.

Declarations

Supplementary material

The supplementary workbook contains:

Ethics approval

Ethical approval was not required for this study, because only publicly available, de-identified summary statistics were analysed. Each contributing study obtained ethical approval and informed consent from its participants, as described in the original publications.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Use of artificial intelligence tools

During the preparation of this work, the authors used Claude (Anthropic) to assist with analysis code and language editing. The authors reviewed and edited all output and take full responsibility for the content of the publication.

Funding

This work received no specific funding.

Author Contribution

• S.E. and C.Y. conceived and designed the study. • S.E. and T.A. carried out the analyses. • S.E., M.H., H.G. and E.E. contributed to the interpretation of the results and to the preparation of figures and tables. • S.E. and C.Y. wrote the first draft of the manuscript. • All authors critically revised the manuscript and read and approved the final version.

Acknowledgement

We are grateful to the participants and investigators of FinnGen, the Million Veteran Program and UK Biobank. This research used MVP and UK Biobank data as released through the FinnGen public meta-analysis.

Data Availability

All analyses in this study were based on publicly released GWAS summary statistics and open reference resources; no new data were generated. Discovery summary statistics for the FinnGen data freeze 13 (R13) endpoint TEMPOROMANDIB_INCLAVO and for all comparator endpoints can be downloaded from the FinnGen Google Cloud Storage bucket (gs://finngen-public-data-r13/summary_stats/). The file manifest is at storage.googleapis.com/finngen-public-data-r13/summary_stats/finngen_R13_manifest.tsv, and access instructions are at finngen.gitbook.io/documentation/data-download. FinnGen endpoint definitions, including K11_DENTOFACIAL_ANOMALIES, are documented in the Risteys portal (risteys.finnngen.fi). Variant-level associations for the phenome-wide scan were retrieved from the FinnGen R13 results browser (r13.finnngen.fi). SuSiE fine-mapping results released by FinnGen are available at <gs://finngen-public-data-r13/finemap/>. Replication estimates were taken from the public FinnGen release 12 × Million Veteran Program (MVP) × UK Biobank meta-analysis of the TEMPOROMANDIB endpoint (gs://finngen-public-data-r12/meta_analysis/mvp_ukbb/summary_stats/); only estimates independent of FinnGen were used (MVP European, African and Hispanic groups and UK Biobank). Reference and annotation resources were the European LD scores from the 1000 Genomes Project restricted to HapMap 3 variants (Zenodo record 8182036, zenodo.org/records/8182036), GTEx v8 expression data and MASHR prediction models (gtexportal.org; predictdb.org), GTEx v8 eQTL summary statistics from the eQTL Catalogue (<ftp.ebi.ac.uk/pub/databases/spot/eQTL/sumstats/>), GENCODE release 44 ([encodeproject.org](https://www.encodeproject.org)), gnomAD v4 (gnomad.broadinstitute.org), the NHGRI-EBI GWAS Catalog ([ebi.ac.uk/gwas](https://www.ebi.ac.uk/gwas)) and the Ensembl Variant Effect Predictor REST service (rest.ensembl.org). All results derived in this study are provided in Supplementary Tables S1–S12.

Code availability

The analysis was carried out with Python scripts covering:

- data acquisition and quality control
- LD score regression, including the paired test of differences between genetic correlations
- replication, fine-mapping, gene-based tests, transcriptome-wide association and colocalisation
- allele-frequency and phenome-wide look-ups
- figure generation

The benchmark against GenomicSEM was run in R with the GenomicSEM package (github.com/GenomicSEM/GenomicSEM). The scripts are available from the corresponding authors on reasonable request and will be released in a public repository upon publication. They can be made available to editors and reviewers during peer review.

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Figures

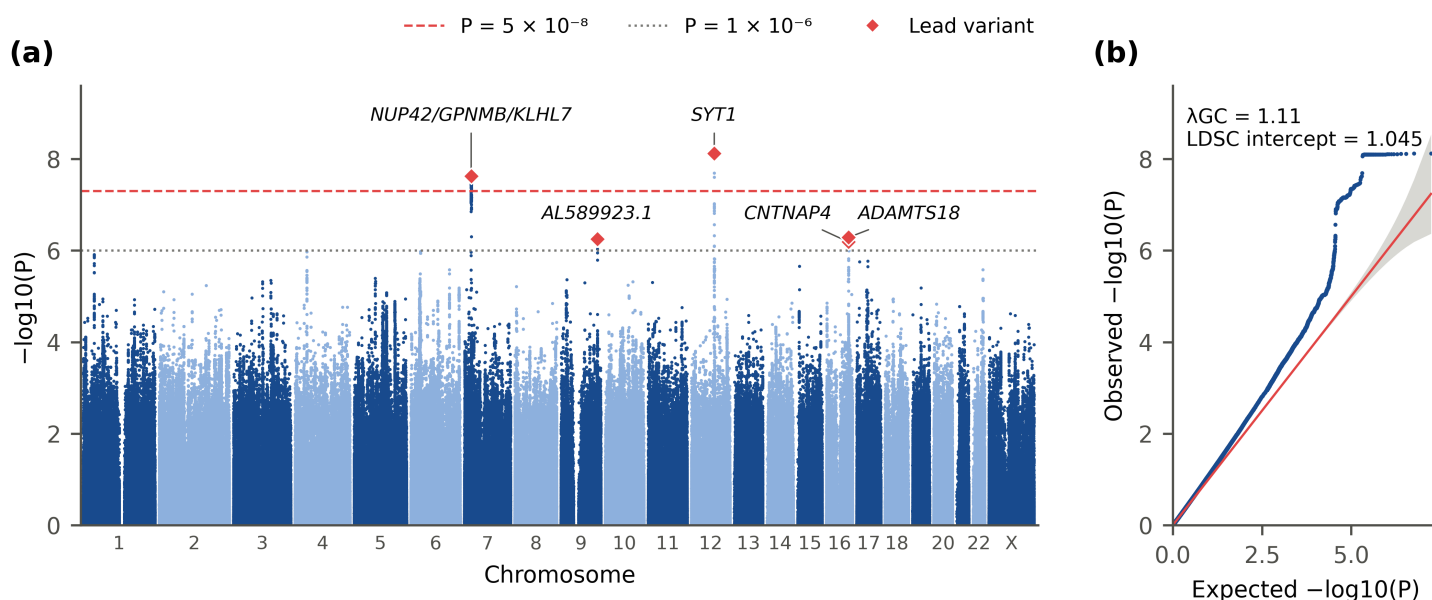


Figure 1

Genome-wide association results for TMD in FinnGen release 13. (a) Manhattan plot of $-\log_{10}(P)$ for 8,605,283 variants against genomic position (GRCh38). The red dashed line marks genome-wide significance ($P = 5 \times 10^{-8}$) and the grey dotted line the suggestive threshold ($P = 1 \times 10^{-6}$); red diamonds mark the five lead variants, labelled with the nearest or implicated gene (Table 1). Non-significant points are thinned for display (all variants with $P < 0.01$ are shown). (b) Quantile–quantile plot of observed against expected $-\log_{10}(P)$, with the 95% confidence band in grey ($\lambda_{GC} = 1.11$; LD score intercept 1.045). $n = 23,035$ cases and 477,151 controls.

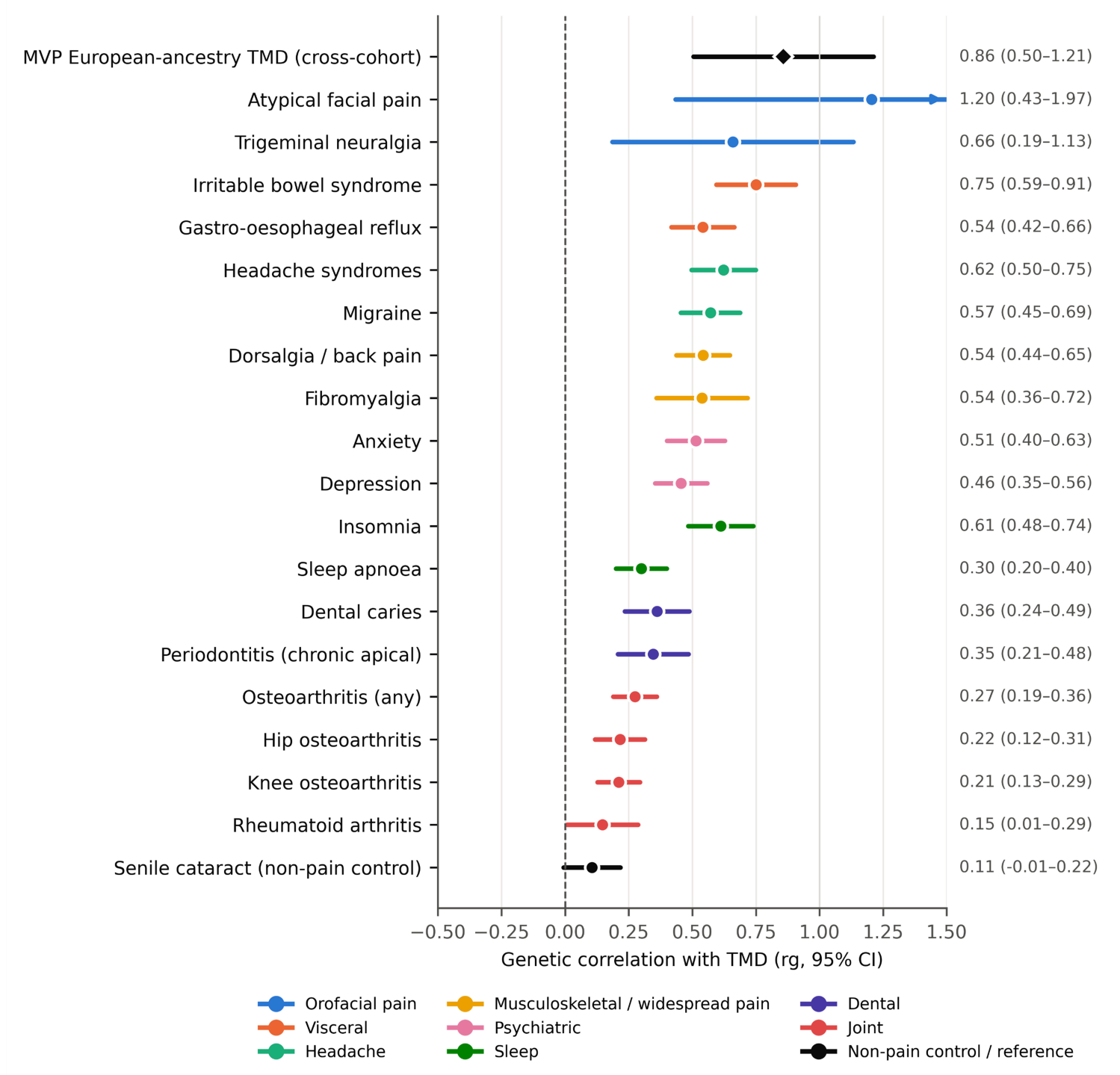


Figure 2

Genetic correlations of TMD with FinnGen traits. Points show LD score regression rg estimates between TMD (FinnGen R13) and the 15 primary endpoints (orofacial pain, visceral, musculoskeletal and widespread pain, headache, psychiatric, sleep, dental and inflammatory joint), the three osteoarthritis endpoints (any site, knee and hip) and the non-pain control (senile cataract), with horizontal bars for 95% confidence intervals, grouped and coloured by trait category. The estimate for MVP European-ancestry TMD (rg 0.86) is shown at the top as the cross-cohort reference. The dashed vertical line marks rg = 0. The axis is truncated at 1.5; the atypical facial pain interval (0.43–1.97) extends beyond it and is marked with an arrow.

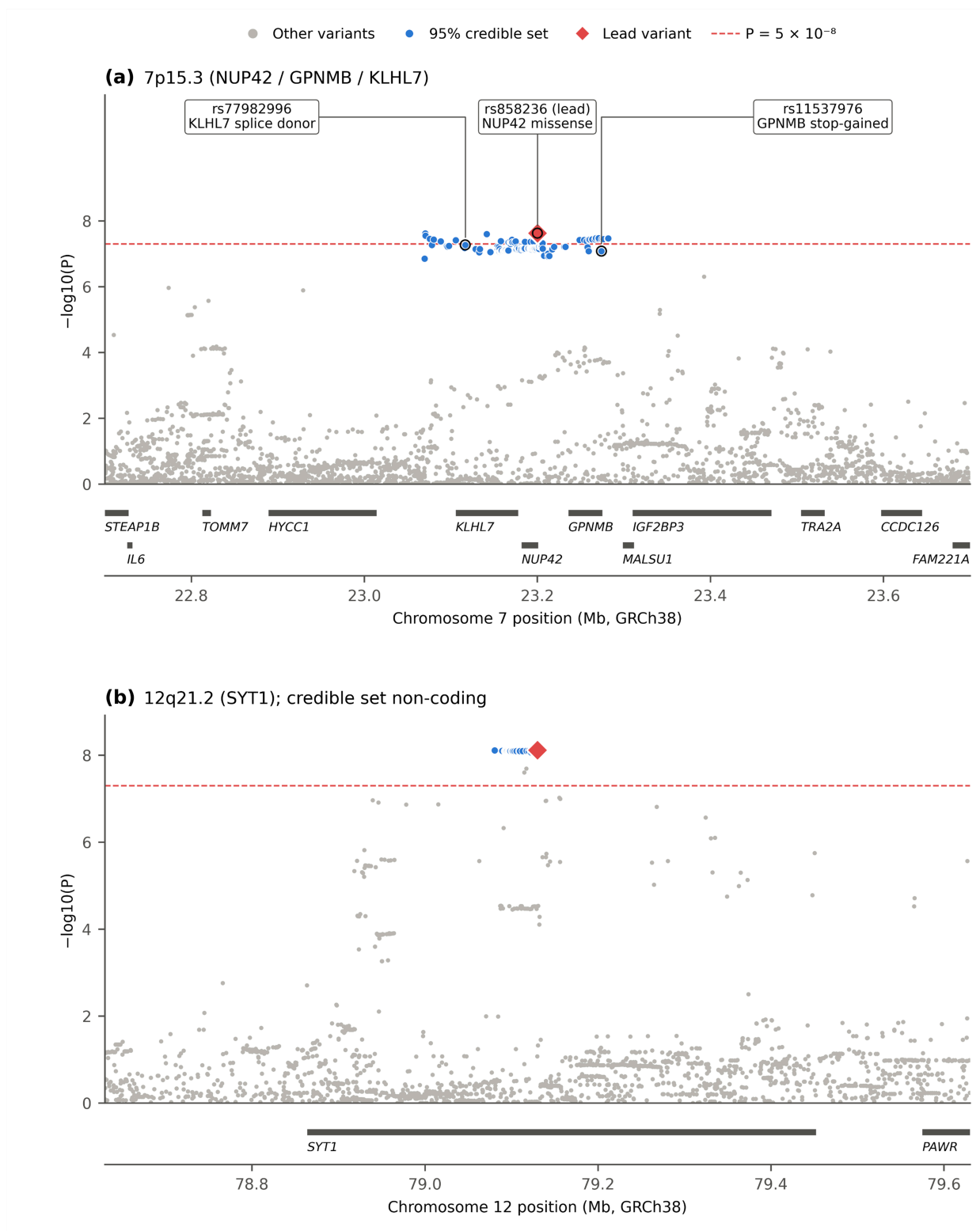


Figure 3

Fine-mapping of the two genome-wide significant loci. Regional association plots for (a) 7p15.3 (NUP42/GPNMB/KLHL7; lead variant rs858236) and (b) 12q21.2 (SYT1; lead variant rs75618936) in FinnGen R13, showing $-\log_{10}(P)$ against GRCh38 position within ± 500 kb of the lead variant. Blue points are variants in the 95% credible set (Wakefield approximate Bayes factors, single-causal-variant model), grey points other variants, and the red diamond the lead variant; the dashed line marks $P = 5 \times 10^{-8}$. In (a), three coding credible-set variants annotated by VEP are labelled: rs858236 (NUP42 missense, lead), rs11537976 (GPNMB stop-gained) and rs77982996 (KLHL7 splice donor). The credible set in (b) contains no coding variants. Protein-coding gene tracks are from GENCODE v44.

Supplementary Files

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- [SupplementaryTablesTMD.xlsx](#)