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Review

# Genetics of osteoarthritis: Insights from GWAS to therapeutic opportunities


Konstantinos Hatzikotoulas [a], Lorraine Southam [a], Eleftheria Zeggini [a b] *

[a] Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[b] TUM School of Medicine and Health, Technical University of Munich (TUM), TUM University Hospital, Munich, Germany

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ABSTRACT

*Objective:* Osteoarthritis is the most common joint disease and a leading cause of pain and disability worldwide, affecting both weight-bearing and non-weight-bearing joints. Osteoarthritis is a complex polygenic disease shaped by genetic, molecular, and environmental factors.
*Design and results:* Large-scale genome-wide association studies, enabled by global biobanks and international collaboration, have identified hundreds of risk variants implicating pathways involved in skeletal development, extracellular matrix organization, inflammation, metabolism, and neuronal signalling. Integration of genetic findings with multi-omics data in primary tissues has resolved many non-coding risk loci to likely effector genes and core biological processes, such as TGF-β, WNT, and BMP signalling. Emerging approaches linking genetics with imaging phenotypes through artificial intelligence have further refined disease subtypes and mechanisms.
*Conclusions:* Together, these advances in genetics highlight osteoarthritis as a molecularly heterogeneous disease and provide a foundation for improved patient stratification and therapeutic development.


## Introduction

Osteoarthritis is the most prevalent joint disease and a leading cause of pain and disability worldwide [1]. It affects both weight-bearing joints, such as the knee, hip, and spine, and non-weight-bearing joints, including the hand and finger [2]. Globally, more than 595 million people (7.6% of the world's population) are affected by osteoarthritis, representing a 132% increase since 1990, with prevalence projected to approach one billion by 2050 [3]. The disease burden is expected to rise further with increasing life expectancy and obesity rates.

Both genetic and environmental risk factors influence susceptibility to osteoarthritis, including age, female sex, obesity, and joint abnormalities [4]. The genetic contribution to disease risk, or heritability, is estimated to range from 20% to 70% depending on the specific joint affected [5,6]. Despite its high prevalence and substantial impact on quality of life, no disease-modifying treatments are approved, and current management is limited to symptom control and surgical joint replacement.

At the cellular level, osteoarthritis is a whole-joint disorder involving remodelling of subchondral bone [7], osteophyte formation, progressive degeneration of articular cartilage, pathologic changes in ligaments and menisci, hypertrophy of the joint capsule, and synovitis [8]. Additional changes can occur in periarticular muscles, nerves, bursae, and the infrapatellar fat pad, which may further contribute to osteoarthritis pathology and symptom manifestation [9]. The primary cells involved include multiple interacting cell types such as chondrocytes, osteoblasts and osteoclasts, synoviocytes, fibroblasts, and mesenchymal stromal cells [10]. This cellular and tissue heterogeneity underpins the complexity of osteoarthritis pathogenesis and offers an opportunity for detailed mechanistic insight into the disease.

Importantly, drug development programs supported by human genetic evidence are more than twice as likely to succeed compared with those without [11]. Thus, osteoarthritis genetics not only advances mechanistic insight but also provides a foundation for precision medicine and the identification of disease-modifying targets.

* Corresponding author at: Institute of Translational Genomics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, Neuherberg D-85764, Germany.
*E-mail addresses:*
konstantinos.hatzikotoulas@helmholtz-munich.de (K. Hatzikotoulas),
lorraine.southam@helmholtz-munich.de (L. Southam),
eleftheria.zeggini@helmholtz-munich.de (E. Zeggini).

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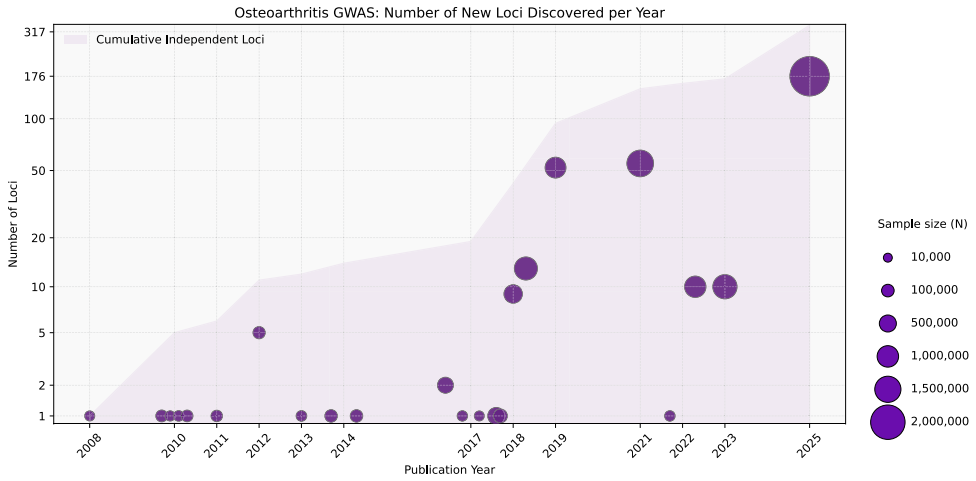


**Fig. 1** Osteoarthritis and Cartilage

Timeline of osteoarthritis risk loci discovery in genome-wide association studies. Each purple circle represents an individual study, with the y-axis showing the number of newly reported genome-wide significantly associated loci across all osteoarthritis phenotypes by year of publication. The light lavender shaded area indicates the cumulative number of independent loci discovered over time. Years with multiple studies have small horizontal offsets to avoid overlap. The size of each circle reflects the proportional sample size of the corresponding study. Definitions of loci vary between publications, typically encompassing a 500 kb to 1 Mb window around the independent GWAS risk variant; for loci with multiple independent variants in close proximity, the window can extend up to 3 Mb.

## Genetic insights into the polygenic architecture of osteoarthritis

Osteoarthritis is a highly polygenic disorder, with genetic susceptibility arising from the combined effects of numerous loci across the genome. Heritability varies by joint site, sex, and ancestry, with classic twin and family studies suggesting that genetic factors explain approximately 39–65% of the variation in radiographic osteoarthritis of the hand and knee in women, around 60% for hip osteoarthritis, and about 70% for spinal osteoarthritis in population-based studies [5]. These findings highlight a substantial genetic contribution to osteoarthritis risk and provide a rationale for genome-wide association studies, which aim to identify the specific loci and variants underlying this polygenic architecture.

Genetic studies have substantially advanced our understanding of osteoarthritis pathogenesis, with early candidate gene studies identifying variants in cartilage- and bone-related genes, including rs143383 in *GDF5* [12,13] and rs12901499 in *SMAD3* [14], associated with both hip and knee osteoarthritis. Subsequent genome-wide association studies (GWAS) have uncovered multiple risk loci and putative effector genes [15–17]. The marked acceleration in locus discovery since 2017, reflects increased sample sizes (Fig. 1), broader ancestral representation (Fig. 2), and advances in analytical methods. This trajectory illustrates the rapid expansion of the osteoarthritis genetics landscape and highlights how growing dataset scale continues to refine the understanding of disease susceptibility. However, it remains unclear when saturation will be reached. The proportion of phenotypic variance explained, and SNP-based heritability captured by current GWAS remain modest, indicating that much of the genetic architecture is unresolved [17]. Evidence from other complex diseases, such as type 2 diabetes, indicates that continued increases in sample size will yield additional loci, with progressively smaller effect sizes [18]. A large-scale GWAS of height including over 5 million individuals reported more than 12,000 associated variants and suggested that common variant discovery may be approaching saturation for this highly polygenic trait [19]. In contrast, for osteoarthritis, further progress is likely to depend on complementary strategies combining increased scale, deeper phenotyping and whole genome sequencing to more fully resolve the allelic architecture of osteoarthritis.

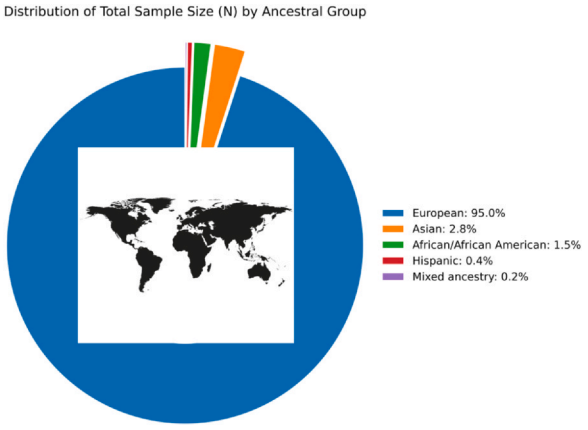


**Fig. 2** Osteoarthritis and Cartilage

Ancestry representation across osteoarthritis GWAS. Donut chart showing the distribution of total sample size (N) by ancestral group across osteoarthritis GWAS. Percentages shown in the legend represent the proportion of the overall combined sample size.

In 2011, a major milestone in osteoarthritis genetics was achieved with the first large-scale collaborative effort of the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) consortium in the United Kingdom, dedicated to uncovering genetic risk factors for the disease [20]. The stage 1 arcOGEN genome-wide association study included

3177 cases and 4894 population-based controls from the UK. Although several association signals were detected, none reached genome-wide significance, underscoring the need for much larger well-powered cohorts and rigorously defined phenotypes to achieve robust discovery. One year later, the expanded Stage 1+2 analysis of 7410 severe osteoarthritis cases and 11,009 controls identified five genome-wide significant loci, which were replicated in an independent set of up to 7473 cases and 42,938 controls, from studies in Iceland, Estonia, the Netherlands, and the UK [21]. The strongest association was observed on chromosome 3 with rs6976, which is in perfect linkage disequilibrium with rs11177 and represents a missense variant in *GNL3*, the gene that encodes nucleostemin. Functional analyses demonstrated increased nucleostemin expression in osteoarthritic chondrocytes, providing direct biological support for a role of this locus in osteoarthritis pathogenesis. Additional significant associations were found near *ASTN2* on chromosome 9, between *FILIP1* and *SENP6* on chromosome 6, and at two loci on chromosome 12 close to *KLHDC5–PTHLH* and *CHST11*, with all risk alleles having common frequency and modest effect sizes. These findings provided new robustly replicated osteoarthritis susceptibility loci and pointed to novel biological pathways potentially amenable to therapeutic targeting.

A major boost to consortium-driven research came from the availability of large, deeply phenotyped biobanks such as the UK Biobank (https://www.ukbiobank.ac.uk), All of Us (https://allofus.nih.gov/), deCODE (http://www.decode.com/), FinnGen (http://www.finngen.fi/en) and the Million Veteran Program (MVP; https://www.mvp.va.gov/), which enabled unprecedented gains in sample size, broadened representation of under-studied ancestries and phenotypes, and provided access to whole-genome sequencing data. Early large-scale efforts focused primarily on individuals of European ancestry, capitalizing on these resources to refine osteoarthritis phenotyping and expand discovery. Zengini and colleagues conducted five genome-wide association analyses across multiple joint sites using the initial UK Biobank release, showing that the larger self-reported dataset offered superior power relative to hospital diagnoses, with high specificity offsetting reduced sensitivity [22]. Around the same time, Styrkarsdottir and collaborators combined Icelandic deCODE data with the UK Biobank to meta-analyse hip and knee osteoarthritis, identifying missense variants in *SMO*, *IL11*, and *COL11A1*, with the first two driven by rare or low-frequency alleles, together with 13 additional new loci [23]. Building further on UK Biobank data together with arcOGEN, Tachmazidou *et al*. reported 52 previously unreported osteoarthritis loci and, for the first time, applied a systematic approach integrating multiple lines of functional evidence to prioritize effector genes, including potential therapeutic targets such as *TGFB1*, *FGF18*, *CTSK*, and *IL11* [24].

Building on these advances from biobank-driven studies, the formation of the Genetics of Osteoarthritis (GO) consortium (http://www.genetics-osteoarthritis.com), enabled broader collaboration and data sharing, greatly expanding sample sizes and culminating in meta-analyses of 11 osteoarthritis phenotypes across both weight-bearing (knee, hip, spine) and non–weight-bearing (hand, finger) joints [15]. Although this GWAS meta-analysis included cohorts from around the world, the vast majority of individuals had European ancestry, with a small fraction (~2.8%) of East Asian ancestry. The study identified 100 independently associated risk variants, 52 of which had not been reported before. Of these, 60 showed associations across multiple joint sites, including rs3771501 (*TGFA*), rs3993110 (*TEAD1/DKK3*), rs72979233 (*CHRDL2*), and rs7967762 (*PFKM/WNT10B*), likely reflecting shared underlying mechanisms in osteoarthritis pathology. Functional evidence linked these loci to TGF-β/BMP and Wnt/β-catenin signalling pathways, whose interaction is implicated in osteoarthritis pathogenesis [25], highlighting these pathways as promising candidates for therapeutic targeting. The remaining 40 variants were specific to weight-bearing joints and 4 were specific to non–weight-bearing joints, demonstrating joint-specific genetic architecture. These findings are further supported by a study showing that hand osteoarthritis exhibited nominal or stronger effects at loci such as *ALDH1A2* and *MGP*, whereas hip and knee loci including *RUNX2*, *COL27A1*, *ASTN2*, *IL11*, and *GDF5* were also associated with hand osteoarthritis, indicating partial overlap in genetic mechanisms across joints [26]. To translate the 100 identified variants into mechanistic insights, analysis of functional genomics data from primary osteoarthritis tissues and complementary computational approaches identified 77 effector genes supported by at least three lines of evidence, including four missense variants, rs2276749 in *VGLL4*, rs3740129 in *CHST3*, rs143083812 in *SMO*, and rs4252548 in *IL11*. To further understand their biological roles in disease processes, additional data were integrated, including analyses of endophenotypes closely related to osteoarthritis, monogenic and rare human disease data, phenome-wide analyses, and other functional genomics datasets. These genes discovered, highlight key pathways in osteoarthritis, including skeletal development, joint degeneration, adipogenesis, muscle function, neuronal processes, and immune and inflammatory responses. Notable examples include structural genes *COL2A1*, *FBN2*, and *CHST3*; signalling regulators *VGLL4*, *TEAD1*, *WNT1*, *PTCH1*, and *WNT10B*; neuronal-associated genes *C2orf40*, *TRIOBP*, *MTMR2*, and *CUX1*; muscle-related *PFKM*; and immune/inflammatory mediators *TLR4*, *NR3C1*, and *TNFSF11*, representing promising candidates for mechanistic studies and therapeutic development. In 2025, the GO Consortium published a landmark follow-up meta-analysis that combined data from up to 489,975 individuals with osteoarthritis and 1,472,094 controls, of whom 12.69% were of non-European ancestry [17]. This large-scale effort identified 962 independent genetic associations, including 513 that had not been previously reported. Integrating single-cell multi-omics data revealed significant enrichment of genetic signals in pathways related to embryonic skeletal development. By incorporating 24 orthogonal lines of evidence, spanning transcriptomic, proteomic, and epigenomic profiles from primary joint tissues, the study implicated approximately 700 effector genes. Among these, the consortium identified rare coding-variant burden associations with consistently larger effect sizes than those observed for common variants. The implicated genes converged on eight key biological processes, including the circadian clock, glial-cell-related pathways, and several signalling pathways already known to be involved in osteoarthritis pathogenesis, such as TGFβ, FGF, WNT, BMP, and retinoic acid signalling, as well as extracellular matrix organization. Together, these findings represent a major advance in elucidating the genetic architecture of osteoarthritis and provide an extensive catalogue of potential therapeutic targets.

In 2022, McDonald *et al.* [16] leveraged the MVP and UK Biobank to perform the largest multi-ancestry genetic study of osteoarthritis to date, including 484,374 participants with 14.7% of non-European ancestry. The analysis identified 27 independent risk loci, 10 of which were newly reported in this study. Notably, four of these newly discovered loci, mapping to regions containing *EFEMP1* (chromosome 2), *SCN11A/WDR48/GORASP1/TTC21A* (chromosome 3), *GML/CYP11B1/CYP11B2* (chromosome 8), and *TMEM263/MTERF2/CRY1* (chromosome 12), were first detected in the European-ancestry–-stratified results and also replicated in the multi-ancestry meta-analysis, suggesting that their effects are likely shared across populations.

Large biobanks and international consortia have enabled more refined investigation of clinically well-defined osteoarthritis phenotypes, including end-stage disease requiring joint replacement. A meta-analysis by Henkel *et al.* [27] involving more than 700,000 individuals of Northern European ancestry dissected genetic

differences between surgical and nonsurgical hip and knee osteoarthritis, identifying ten variants specific to the surgical phenotype, including signals at genes implicated in autophagy (rs2447606 in *ATG7*) and mechanotransduction (rs202127176 in *PIEZO1*). Similarly, Kulm *et al.* [28] used total hip arthroplasty as a proxy for end-stage hip osteoarthritis in a GWAS of 15,353 cases and 374,193 controls, uncovering five new loci associated with end-stage hip osteoarthritis.

Compared with weight-bearing joints, the genetics of hand osteoarthritis has been less extensively studied. Initial genome-wide studies identified associated variants in the *ALDH1A2* gene and rare variants at 1p31 in severe hand osteoarthritis [29]. Subsequent work identified an association near *MGP*, where reduced gene expression may increase disease burden by diminishing inhibition of cartilage calcification [30]. Radiographic analyses further identified two additional loci, including a robust chromosome 1 association pointing to *WNT9A* as the likely causal gene in thumb osteoarthritis, highlighting the value of phenotype-stratified approaches in uncovering joint-specific genetic mechanisms [26]. The most recent meta-analysis of erosive hand osteoarthritis confirmed *ALDH1A2* and *MGP* as risk loci and identified two further loci related to bone biology, *BMP6* and *SPP1*|*MEPE* [31]. Moreover, genome-wide studies of minimum joint space width as a proxy for cartilage thickness [32] and of hip shape using alpha angle measurements have identified multiple risk loci, highlighting growth-related mechanisms in hip osteoarthritis and demonstrating a moderate genetic correlation, with evidence supporting a causal relationship between altered hip morphology and osteoarthritis development. In the largest DXA-image–based hip-shape genome-wide association study to date [33], many novel loci were identified, including signals overlapping with hip osteoarthritis and hip fracture. Mendelian-randomization analyses indicated that hip shape itself may not causally drive hip osteoarthritis but does appear to influence hip fracture risk, suggesting that interventions aimed at modifying hip shape to prevent osteoarthritis in older adults may have limited therapeutic value. These studies illustrate how richly phenotyped biobanks can capture several manifestations of osteoarthritis that are rarely accessible in traditional cohorts.

GWAS have predominantly relied on SNP arrays combined with imputation to reference panels, capturing mainly common variants (minor allele frequency (MAF) > 5%) and, to a lesser extent, low-frequency variants (MAF > 1% to ≤5%). Advances in sequencing technologies, particularly whole-exome sequencing and whole-genome sequencing, together with the emergence of large-scale sequencing biobanks comprising millions of participants, have substantially expanded the ability to interrogate rare genetic variation. Resources such as the UK Biobank, All of Us, and the Trans-Omics for Precision Medicine program (https://topmed.nhlbi.nih.gov/), now enable comprehensive detection of both common and rare variants, including structural variants and non-coding regulatory variation. In osteoarthritis, rare variant studies have identified high-impact alleles with large effect sizes, including a missense variant in *COMP*, c.1141G > C (allelic frequency = 0.026%, odds ratio (OR) = 16.7), and a frameshift mutation in *CHADL*, rs532464664, which associates through a recessive mode of inheritance in the Icelandic population (homozygote frequency = 0.15%, OR = 7.71) [34]. Similarly, hand osteoarthritis has been linked to rare variants at 1p31, in addition to common variants in *ALDH1A2*, highlighting the contribution of rare, or ancestry-specific alleles to disease susceptibility [29]. Furthermore, a large meta-analysis across hundreds of thousands of individuals identified six rare variant associations (MAF 0.03–0.11%) with large effect sizes (OR range = 3.03–9.52), primarily driven by a large extended family in Iceland [15], illustrating how rare variation can substantially contribute to osteoarthritis risk and offering a plausible explanation for part of the missing heritability [35].

## From genetic loci to mechanisms: molecular quantitative trait loci in osteoarthritis tissues

Over 90% of osteoarthritis risk variants identified through GWAS fall outside protein-coding regions [17]. Uncovering the effector genes and regulatory mechanisms they perturb, requires functional genomic approaches. Recent years have seen a rapid expansion of multi-omics studies that, when integrated with genetic findings, deepen our understanding of the molecular mechanisms underlying osteoarthritis. Reviews of this growing literature highlight the power of combining genomics, transcriptomics, proteomics, metabolomics, epigenomics, single-cell and spatial omics to generate a comprehensive molecular map of osteoarthritic joints [36–38]. Here, we review genetically-driven findings from such approaches that inform osteoarthritis risk and biology.

The integration of genetic data with molecular profiles facilitates the discovery of molecular quantitative trait loci (molQTLs), such as DNA methylation QTLs (mQTLs), protein QTLs (pQTLs), and expression QTLs (eQTLs), linking genetic variants to downstream molecular phenotypes. Steinberg *et al.* [39] generated tissue- and disease-stage-specific cis-eQTL and cis-pQTL maps from intact and degraded cartilage and synovial tissue of 115 osteoarthritis patients, identifying regulatory variants for 1891 genes and prioritizing five GWAS-linked genes, *ALDH1A2*, *NPC1*, *SMAD3*, *FAM53A*, and *SLC44A2* through genetic colocalization. Expanding on this work, Kreitmaier *et al.* [40] generated genome-wide cis-mQTL maps, identifying tens of thousands of significant mQTLs, sex-specific regulatory effects, and 19 methylation sites with putative causal effects on knee osteoarthritis, including *COLGALT2*, *MFHAS1*, and *WWP2*. More recently, the same group further expanded the molQTL framework by generating matched genome-wide mQTL and expression quantitative trait methylation (eQTM) maps across multiple primary osteoarthritis tissues, including low- and high-grade cartilage and synovium, as well as synovium, infrapatellar fat pad, and blood, from 314 patients undergoing total knee replacement [41]. Integration of these epigenomic maps with GWAS through tissue-specific colocalisation analyses identified DNA methylation sites with putative causal roles in osteoarthritis and resolved genetic risk signals to 50 likely effector genes, highlighting novel candidates that substantially extend the functional interpretation of noncoding GWAS loci. These include *CDK10*, which encodes a component of the CDK10/Cyclin M kinase complex regulating actin cytoskeleton organization [42]; *EXOSC6*, a subunit of the RNA exosome complex involved in RNA processing, cytokine production, and cellular homeostasis, with depletion linked to cell senescence [43–45]; and *GDNF*, a neurotrophic factor implicated in osteoarthritis-related skeletal pain through activation and sensitization of nonpeptidergic neurons via the GDNF/GFRα1 pathway in preclinical models [46].

Earlier integrative genomic analyses combining GWAS with mQTL and in silico functional annotation have shown that many osteoarthritis risk variants map to regulatory elements influencing cartilage biology, and in silico prioritization highlighted *COLGALT2*, *COL11A2*, and *WWP2* as compelling effector gene candidates through their regulatory relationships with osteoarthritis associated variants [47]. Multi-tissue epigenetic profiling at an osteoarthritis susceptibility locus demonstrated that osteoarthritis associated genetic variation correlates with differential methylation and allelic expression imbalance of the cytoskeletal gene *PLEC* across cartilage, synovium, and fat pad, with more pronounced effects in joint tissues and downstream impacts on pathways including Wnt signalling, immune regulation and glycosaminoglycan biosynthesis [48]. More recently, locus-level functional dissection of the *COLGALT2* osteoarthritis risk locus demonstrated that a single risk allele can exert opposing effects on DNA methylation and gene expression across different joint tissues, revealing tissue-specific pleiotropy [49]. These

findings highlight the complexity of regulatory risk mechanisms and caution that genetically targeted therapies may have divergent effects across joint tissues.

The combination of genetic colocalization between mQTLs and osteoarthritis with eQTL data from Steinberg *et al.* [39] enabled the identification of seven prioritized genes. Complementing these findings, the same group profiled DNA methylation in infrapatellar fat pad tissue from 70 osteoarthritis patients and integrated these data with matched genotypes to construct a genome-wide cis-mQTL map, identifying 37 putative causal methylation sites colocalizing with knee osteoarthritis GWAS signals and implicating both established (e.g., *WWP2*, *COL27A1*, *ALDH1A2*) and novel (*USP8*, *TSKU*, *FER1L4*) osteoarthritis effector genes [50]. More recently, integrated analysis of response eQTLs, chromatin accessibility, and three-dimensional chromatin structure in human osteoarthritis chondrocytes revealed how regulatory genetic variation influences gene expression and disease risk mechanisms by linking osteoarthritis associated variants to their target genes through 3D genomic architecture [51].

Together, these studies demonstrate that osteoarthritis is driven by interconnected genetic, epigenetic, transcriptional, and metabolic networks acting across multiple cell types and spatial niches within the joint. By simultaneously capturing molecular depth, cellular heterogeneity, and regulatory architecture, integrative multi-omics approaches provide a powerful framework for refining disease subtypes, identifying robust biomarkers, and uncovering therapeutic targets, thereby accelerating progress toward precision medicine in osteoarthritis.

## Translational implications in osteoarthritis

### *Patient stratification*

Osteoarthritis is a highly heterogeneous disease, and patient stratification is increasingly recognized as critical for both clinical management and clinical trial design [52,53]. Reviews and consensus frameworks now distinguish phenotypes (clinical presentation), endotypes (dominant molecular mechanisms), and theratypes (treatment-responsive subgroups), emphasizing that matching therapies to mechanistic endotypes is critical for improving clinical trial success [52]. The osteoarthritis literature most consistently describes several phenotypic categories including metabolic syndrome, inflammatory, bone and/or cartilage, and mechanical overload or injury phenotypes [54]. Additional proposed phenotypes include minimal joint disease [55], hormonal or menopause-related [56], ageing-related [57], chronic pain–dominant [58] and muscle-/obesity-/depression-/psychological distress associated phenotypes [54,55].

High-throughput omics studies have demonstrated the potential to define biologically meaningful endotypes [36,37]. However, stratification based on genetics alone is unlikely to capture the full complexity of osteoarthritis, due to the modest effect sizes of most risk alleles, the predominantly non-coding nature of GWAS signals, and strong tissue-specific and environmental influences. Consequently, a genetics-only stratification framework may miss critical molecular and clinical heterogeneity necessary for personalized therapeutic strategies.

Nevertheless, genetic information can contribute to patient stratification in several important ways. In clinical trial design, the pervasive carriage of osteoarthritis risk alleles across patients for multiple biological pathways, including retinoic acid, TGFB, BMP, Wnt, FGF, ECM assembly, circadian rhythm, and glial cell–related pathways, offers an opportunity to enrich trial cohorts for individuals most likely to progress or respond to pathway-targeted interventions [17]. For mechanistic stratification, variants in genes associated with cartilage degradation (e.g. *GDF5*, *COL2A1*, *CHST3*), bone remodelling (e.g. *TGFB1*, *WNT1*, *FBN2*), matrix composition (e.g. *COL2A1*, *ACAN*, *HSPG2*), or pain pathways (*APOE*, *NR3C1*, *ESR1*) can define biologically meaningful endotypes, enabling therapies to be targeted toward the dominant underlying disease mechanisms [15,17].

Recent advances in artificial intelligence (AI) and machine learning, have enabled the extraction of quantitative imaging-derived phenotypes from medical images, providing a powerful complement to traditional case/control definitions for genetic studies. For example, Flynn *et al.* [59] trained deep learning models on knee DXA scans to classify osteoarthritis cases and measure joint space width, a quantitative trait reflecting disease severity, which substantially increased the number of genome-wide significant loci discovered compared with binary phenotypes. Similarly, Faber *et al.* [60] derived continuous structural osteoarthritis imaging phenotypes from UK Biobank imaging data using machine learning and then performed genome-wide association analyses on these traits. Their findings demonstrate that these imaging-derived phenotypes exhibit distinct genetic architectures, providing evidence for genetically defined endotypes within osteoarthritis. Together, these studies illustrate how AI- and machine learning driven imaging phenotyping can refine osteoarthritis genetic studies, uncovering loci and pathways not captured by conventional clinical definitions.

Genetically informed endotypes refine patient stratification and, when combined with polygenic approaches, enhance prediction of risk and mechanistic subtypes in osteoarthritis.

### *Polygenic risk scores (PRS)*

PRS derived from genome-wide association studies have emerged as promising tools for predicting disease susceptibility and related health outcomes [61,62]. However, despite the appeal of genetic risk prediction, these promises have not yet translated into routine clinical practice. PRS calculation has become increasingly popular, but for many complex traits, including osteoarthritis, predictive performance has generally been modest [63]. One explanation is that genetic factors account for only a limited proportion of osteoarthritis risk, while current PRS largely capture common variants identified through genome-wide association studies and fail to encompass the full spectrum of genetic contributions, such as rare variants [64]. In addition, the predictive performance of PRS is constrained by the phenotypic definitions used in the underlying GWAS. The vast majority of large-scale osteoarthritis GWAS have relied on prevalent disease and, in some cases, on imperfect proxies of disease progression, such as total joint replacement. As a result, PRS derived from these studies may reflect a mixture of susceptibility and progression signals, potentially limiting their ability to accurately predict incident disease. Future improvements in PRS performance will likely depend on the development of GWAS based on well-characterised incident and progressive osteoarthritis phenotypes, although such studies are challenging due to the need for longitudinal data and large sample sizes.

Early conceptual frameworks of osteoarthritis emphasized its multifactorial and systems-level nature [15,65–67]. Although recent large-scale analyses have demonstrated PRS constructed from hundreds of osteoarthritis risk loci, their predictive accuracy remains limited [17]. In independent datasets, no osteoarthritis phenotype achieved an area under the receiver operating characteristic curve (AUC) above 80%, with the best performance observed for hip osteoarthritis (AUC 58.6%), improving to 66% when body mass index was included in the model. Similar findings have been reported in other recent studies, where the authors suggested that a healthier lifestyle is consistently associated with a lower risk of osteoarthritis, regardless of genetic risks [68]. Persistent challenges, including

suboptimal precision, limited transferability across ancestrally diverse populations and low familiarity with PRS among patients and healthcare providers, must be addressed before widespread clinical adoption [69]. Importantly, integrating PRS with complementary modalities such as proteomics, metabolomics, imaging and longitudinal electronic health record data may substantially enhance osteoarthritis risk prediction, inform screening strategies and enable earlier interventions to reduce disease burden.

*From genetic insights to therapeutics: novel targets and repurposed drugs*

Genetic and functional genomics studies have substantially expanded the repertoire of candidate drug targets for osteoarthritis. Large-scale genome-wide association studies, integrated with expression, protein, and epigenetic quantitative trait loci, have linked non-coding risk variants to effector genes involved in key biological pathways such as TGF-β, WNT, FGF signalling, extracellular matrix organization, and inflammatory regulation [17,52]. Importantly, many genetically supported targets encode proteins that are pharmacologically tractable, providing a rational foundation for therapeutic development. These findings help prioritize targets with higher likelihood of clinical success and lower risk of late-stage trial failure.

Drug repurposing offers an efficient strategy to accelerate therapeutic translation in osteoarthritis by leveraging existing drugs with established safety profiles. Integrative genomic and network-based analyses have identified multiple approved drugs whose targets overlap with osteoarthritis risk genes or disease-relevant pathways, including agents used for metabolic, cardiovascular, and inflammatory conditions [17,52,70]. Although observational and preclinical evidence supports potential benefits for some of these compounds, rigorous randomized clinical trials are required to establish disease-modifying effects. Genetically informed repurposing strategies provide a systematic approach to prioritizing candidates with higher probabilities of success.

Several disease-modifying and symptom-modifying therapies are currently being evaluated in osteoarthritis clinical trials, targeting pathways implicated by genetic and molecular studies. These include growth factor-based approaches (e.g., FGF18 analogs), anti-inflammatory agents, inhibitors of cartilage catabolism, and compounds targeting subchondral bone remodelling. A structured overview of these agents, including their molecular targets, trial phase, and clinical outcomes, highlights how translational genomics is increasingly informing therapeutic pipelines and guiding rational trial design. Looking forward, a key challenge is how to intersect genetic discoveries with clinical research to accelerate benefits for patients. In osteoarthritis, enriching clinical trials with individuals who are more likely to progress with or without the intervention, may increase the ability to detect treatment effects with smaller sample sizes and reduce heterogeneity. In this context, polygenic risk scores may help identify individuals at higher risk of progression for trial recruitment, while proteomic and other molecular measures could define disease subtypes most likely to respond to specific interventions. Such approaches support a vision of clinical trials recruiting with omics in mind, enabling more targeted and efficient evaluation of emerging therapies.

## Conclusions and future directions

Over the past decade, advances in human genetics and functional genomics have fundamentally reshaped the understanding of osteoarthritis, transforming it from a largely mechanically driven disorder into a complex, polygenic disease underpinned by diverse molecular pathways. Large-scale genome-wide association studies, enabled by global biobanks and international consortia, have uncovered hundreds of risk loci spanning developmental, metabolic, inflammatory, neuronal, and circadian processes. These discoveries have clarified that osteoarthritis susceptibility reflects the cumulative effects of many common variants of modest effect, complemented by rarer variants with substantially larger impact, operating across multiple joint tissues and disease stages.

A major driver of recent progress in human genetic studies of osteoarthritis has been the dramatic increase in sample sizes and phenotypic resolution. The transition from underpowered candidate gene studies to biobank-scale analyses has markedly improved statistical power, enabling robust locus discovery, cross-joint comparisons, and systematic prioritization of effector genes. Importantly, recent efforts have begun to address the historical bias toward European ancestry populations. Increasing inclusion of individuals from diverse ancestries not only improves generalizability and equity but also enhances fine-mapping resolution and facilitates the discovery of ancestry-specific and low-frequency variants. Expanding diversity in both genetic and functional genomic datasets will be essential for avoiding biased biological inference and ensuring that future therapeutic insights benefit global populations.

Rare variant studies represent another critical frontier in osteoarthritis genetics. While common variants explain a substantial proportion of population-level risk, rare coding variants often exhibit much larger effect sizes and can directly implicate causal genes and pathways. The identification of high-impact alleles in genes such as *COMP*, *CHADL* and *IL11* underscores the value of whole-exome and whole-genome sequencing approaches for uncovering biologically actionable mechanisms. As sequencing resources continue to scale, integrating rare variant burden analyses with common variant GWAS will be essential to more fully resolve the genetic architecture of osteoarthritis and address components of missing heritability.

Beyond single-trait analyses, cross-phenotype and cross-disease GWAS (C-GWAS) approaches offer powerful opportunities to dissect shared genetic architecture across related traits, such as joint shape, cartilage thickness, pain sensitivity, metabolic traits, and inflammatory phenotypes. These methods can reveal pleiotropic loci, clarify causal relationships through Mendelian randomization, and identify pathways that contribute to multiple disease manifestations. In osteoarthritis, such integrative approaches are particularly valuable given the disease's strong overlap with skeletal development, obesity, pain processing, and ageing-related pathways.

Crucially, genetic discoveries alone are insufficient without functional interpretation. The integration of GWAS with molecular quantitative trait loci, single-cell and spatial omics, chromatin conformation data, and AI-derived imaging phenotypes has begun to bridge the gap from association to mechanism. These multi-layered approaches are converging on a core set of biological processes, including TGF-β, WNT, FGF, BMP, extracellular matrix organization, and neuronal signalling, that operate across tissues and disease stages. This convergence strengthens confidence in these pathways as key biological drivers of osteoarthritis and highlights them as priority targets for therapeutic development.

Looking ahead, the future of osteoarthritis genetics lies in the deep integration of diverse datasets across scales, populations, and modalities. Combining large, ancestrally diverse cohorts with rich longitudinal phenotyping, multi-omics profiling, imaging-derived traits, and clinical outcomes will enable more precise disease subtyping and mechanistic stratification. Such efforts will be essential for translating genetic insights into clinically meaningful advances, including improved risk prediction, patient stratification, and the rational prioritization of disease-modifying therapies. As genetics continues to inform both biological understanding and therapeutic strategy, it is poised to play a central role in accelerating progress toward precision medicine in osteoarthritis.

## Author contributions

All authors contributed to the preparation and critical revision of the manuscript and approved the final version for submission.

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The funder had no involvement in the study design, interpretation of data, writing of the manuscript, and decision to publish.

## Declaration of Competing Interest

The authors declare no conflicts of interest related to this manuscript.

## Declaration of Generative AI and AI-assisted technologies in the writing process

No generative AI was used in the writing of the manuscript.

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