EXTRACTION REPORT

Genome-wide association and functional studies identify a role for IGFBP3 in hip osteoarthritis

Daniel S Evans,1 Frederic Cailotto,2 Neeta Parimi,1 Ana M Valdes,3 Martha C Castaño-Betancourt,4,5 Youfang Liu,6 Robert C Kaplan,7 Martin Bidlingmaier,8 Ramachandran S Vasan, Alexander Teumer,9,10 Gregory J Tranah,1,11 Michael C Nevitt,11 Steven R Cummings,1 Eric S Orwoll,12 Elizabeth Barrett-Connor,13 Jordan B Renner,14 Joanne M Jordan,6 Michael Doherty,3 Sally A Doherty,3 Andre G Uitterlinden,4,5,15 Joyce B J van Meurs,4 Tim D Spector,16 Rik J Lories,2,17 Nancy E Lane18

OBJECTIVEs
To identify genetic associations with hip osteoarthritis (HOA), we performed a meta-analysis of genome-wide association studies (GWAS) of HOA.

Methods
The GWAS meta-analysis included approximately 2.5 million imputed HapMap single nucleotide polymorphisms (SNPs). HOA cases and controls defined radiographically and by total hip replacement were selected from the Osteoporotic Fractures in Men (MrOS) Study and the Study of Osteoporotic Fractures (SOF) (654 cases and 4697 controls, combined). Replication of genome-wide significant SNP associations (p ≤ 5×10^{-8}) was examined in five studies (3243 cases and 6891 controls, combined). Functional studies were performed using in vitro models of chondrogenesis and osteogenesis.

Results
The A allele of rs788748, located 65 kb upstream of the IGFBP3 gene, was associated with lower HOA odds at the genome-wide significance level in the discovery stage (OR 0.92, p =2×10^{-8}). The association replicated in five studies (OR 0.92, p =0.020), but the joint analysis of discovery and replication results was not genome-wide significant (p =1×10^{-6}). In separate study populations, the rs788748 A allele was also associated with lower circulating IGFBP3 protein levels (p =4×10^{-13}), suggesting that this SNP or a variant in linkage disequilibrium could be an IGFBP3 regulatory variant. Results from functional studies were consistent with association results. Chondrocyte hypertrophy, a deleterious event in OA pathogenesis, was largely prevented upon IGFBP3 knockdown in chondrocytes. Furthermore, IGFBP3 overexpression induced cartilage catabolism and osteogenic differentiation.

Conclusions
Results from GWAS and functional studies provided suggestive links between IGFBP3 and HOA.

INTRODUCTION
Hip osteoarthritis (HOA) is one of the most common forms of arthritis, with nearly 10% of individuals over the age of 70 having this condition.1 The degeneration of the hip joint that occurs with OA is characterised by a loss of articular cartilage, an increase in new bone formation at the margins of the bones, and remodelling of the bone that is adjacent to the joint.2 HOA is associated with pain and disability and often requires total joint replacement.3 Currently, there are no available treatments that can alter the course of this disease.

Genetic and environmental factors contribute to HOA pathogenesis, and the heritability of HOA in women has been reported to be as high as 60%.4 A number of genome-wide significant (GWAS; p ≤ 5×10^{-8}) single nucleotide polymorphism (SNP) associations with HOA and related traits have been identified. Variants at the GDF5 locus and MCF2L locus have been associated with OA of the hip and knee.5–8 DOT1L SNPs have been associated with cartilage thickness and HOA,9,10 and SNPs near the gene NCOA3 have been associated with HOA.11 A recent genome-wide association study (GWAS) of OA that included 24 sub-phenotypes identified five GWAS associations.12

It has been previously noted that the heterogeneity of radiographic HOA classification could hinder the identification of genetic risk factors.13 OA is typically defined using a summary grade score, such as the Kellgren and Lawrence (K/L) score14 or the Croft score,15 but for a given summary grade score, the radiographic features can vary between studies.13 In order to minimise phenotype heterogeneity, we selected 654 HOA cases and 4697 HOA controls from two studies, the Osteoporotic Fractures in Men (MrOS) Study and the Study of Osteoporotic Fractures (SOF), in which the same radiographic scoring methods were applied by a common set of radiograph readers, and we performed a GWAS meta-analysis of HOA. GWS SNP associations were examined for replication in 3243 cases and 6891 controls from five case–control studies. To link HOA-associated SNPs with potential target gene, we examined whether significantly associated SNPs near IGFBP3 were associated with circulating IGFBP3 through a look-up of results from a GWAS meta-analysis of circulating IGFBP3.16

The biological role of the candidate gene IGFBP3 was evaluated through functional studies using model systems of chondrogenesis and osteogenesis.
Clinical and epidemiological research

METHODS

Study populations and case and control definitions

In the MrOS and SOF studies, HOA cases were defined using a modified Croft grade score ≥2 on either hip or total hip replacement (THR).2 HOA controls were those without THR and meeting the following three criteria on both hips: Croft grade ≤1, joint space narrowing ≤1 and osteophytes ≤1. GWS SNP associations were examined for replication using case-control status defined by K/L scores or THR in the Rotterdam study (RS-I and RS-II) and Chingford study, and by THR in the Genetics of Osteoarthritis and Lifestyle (GOAL) study and the Nottingham Study. See online supplementary text S1 for details regarding study descriptions and case-control definitions. All studies were approved by their respective institutional review boards and informed consent was obtained from all participants involved.

Genotyping and statistical analysis

Genome-wide SNPs were genotyped in samples from the MrOS and SOF studies using the Illumina HumanOmni1-Quad array. Quality control procedures for SNPs and samples are described in online supplementary table S1. Principal component analysis was performed to detect evidence for population structure and to generate principal components used to adjust for genetic ancestry.17 Genotypes were imputed using the HapMap phase II release 22 reference panel using MACH.18 SNP associations were estimated using logistic regression models adjusted for the effects of age, sex (if applicable), study site (if applicable) and principal components. Genomic control was applied to results from MrOS and SOF, and fixed-effect meta-analysis with inverse variance weights was performed using METAL.19 The two discovery studies and five replication studies were included in the joint meta-analysis as individual studies. Details regarding genotyping and statistical analysis in discovery and replication studies are presented in online supplementary table S1 and text S1.

Cell culture experiments

 Functional studies of chondrogenesis and osteogenesis were performed using the ATDC5 and MG3T3 cell lines, respectively. The ATDC5 cell line exhibits multi-stage chondrogenic differentiation similar to the process that is observed during chondrogenesis and endochondral bone formation.20 Human articular chondrocytes, isolated from OA patients as previously described,21 were also used in functional studies. Gene knockdown was performed by stable transfection with plasmid overexpressing shmiRNA directed against IGFBP3. Further details are presented in online supplementary text S1.

RESULTS

Characteristics of the study samples

Average age was significantly higher in MrOS participants (100% male) than SOF participants (100% female). Age and minimum joint space width differed by case-control status in MrOS and SOF, but height and body mass index (BMI) did not (see online supplementary table S2).

Locus associated with HOA

A GWS of HOA was performed with 2 459 845 genotyped and imputed SNPs that passed quality control. There was little to no evidence of p value inflation in the individual studies (MrOS λ=1.01, SOF λ=1.01) or the meta-analysis (λ=1.00) (see online supplementary figures S1–S3). GWS SNPs were located at a single locus on chromosome 7 (see online supplementary figure S4). The two GWS SNPs, rs788748 and rs879966, were directly genotyped in both cohorts, and were in moderate linkage disequilibrium (LD) (HapMap CEU r2=0.54), and the effect alleles were associated with decreased odds of HOA (table 1 and figure 1). The nearest gene was IGFBP3 (figure 1). In conditional analysis, the HOA association p values were not significant for rs788748 and rs879966 (p≥0.05), indicating a strong degree of dependence.

Our discovery stage had sufficient power (≥0.8) at α=5×10−8 to detect an OR of 0.68 for SNPs with a minor allele frequency (MAF) of 0.5. As sufficient power was nearly achieved to detect the observed rs788748 OR, the winner’s curse22 adjusted23 rs788748 OR of 0.75 was similar to the observed OR of 0.71.

Genetic variants in components of the growth hormone/insulin-like growth factor (GH/IGF) axis, which includes IGFBP3, have been associated with human height,24 and genetic variation in this gene group is associated with body mass index (BMI) and metabolic syndrome.25 Our findings are consistent with this in that IGFBP3 was associated with HOA, although the relationship was weaker than expected. Further studies are needed to determine whether this association is mediated through height or BMI.

Table 1 SNP association results in discovery and replication studies

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chr: Position</th>
<th>Minor allele</th>
<th>Major allele</th>
<th>p Value</th>
<th>Minor allele</th>
<th>Major allele</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs788748</td>
<td>Chr 7: 45 992 706*</td>
<td>A (0.49)</td>
<td>G (0.51)</td>
<td>7×10⁻⁷</td>
<td>A (0.49)</td>
<td>G (0.51)</td>
<td>6×10⁻⁷</td>
</tr>
<tr>
<td>rs879966</td>
<td>Chr 7: 46 015 992*</td>
<td>A (0.39)</td>
<td>G (0.61)</td>
<td>5×10⁻³</td>
<td>A (0.39)</td>
<td>G (0.61)</td>
<td>4×10⁻³</td>
</tr>
</tbody>
</table>

*NCBI build 36 chromosome and position.†Effect allele (effect allele frequency).

GOAL, Genetics of Osteoarthritis and Lifestyle Study; MrOS, Osteoporotic Fractures in Men Study; ND, not determined; RS, Rotterdam Study; SNP, single nucleotide polymorphism; SOF, Study of Osteoporotic Fractures.


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associations are shared between OA and height.\textsuperscript{25} Rs788748 and rs879966 were in low LD (1000 Genomes phase 1 CEU $r^2=0.09$ and 0.16, respectively) with a functional IGFBP3 promoter polymorphism ($−202\ A/C$, rs2854744)\textsuperscript{26} associated with GH-dependent growth,\textsuperscript{27} and adjustment for height or BMI had a minimal effect on rs788748 and rs879966 HOA associations (see online supplementary table S3), indicating that height is unlikely to mediate the SNP associations.

The two GWS SNP associations were examined for replication in five HOA case–control studies (see online supplementary tables S4 and S5). In the meta-analysis of replication results, the rs788748 HOA association was significant and in the same direction as the discovery stage ($p=0.020$), with little evidence for heterogeneity ($Q$ test $p=0.20$, $I^2=36.67$) (table 1, figure 2). The rs879966 genotyping assay failed in the two largest replication studies, GOAL and Nottingham, and not surprisingly, it was not significantly associated with HOA among the replication studies (table 1). In a joint meta-analysis of discovery and replication stage results, the rs788748 OR (95% CI) was 0.86 (0.81 to 0.91) and the $p$ value was $1 \times 10^{-6}$.

Previously reported SNP associations with OA at rs11177/ rs6976 near GNL3/GLT8D1,\textsuperscript{12} rs10948172 near SUPT3H and RUNX2,\textsuperscript{12} rs11842874 in MCF2L,\textsuperscript{8} rs12982744 in DOT1L,\textsuperscript{9,10} and rs6094710 near NCOA3\textsuperscript{11} were significantly associated ($p<0.05$) with HOA in study-specific or meta-analysis results, but the direction of effect did not replicate for rs11842874 or rs6094710 (see online supplementary table S6).

**Characterisation of associated SNPs**

ENCODE project data indicated that histone modifications typically associated with enhancers (histone-3 lysine-4 monomethylation and histone-3 lysine-27 acetylation)\textsuperscript{18} were located near rs788748 and rs879966. In addition, DNase I hypersensitivity sites and transcription factor binding sites identified using ChIP-Seq were located near rs788748 (see online supplementary figure S5).

A GWAS meta-analysis of circulating IGFBP3 and IGF-I levels reported an association region that spanned rs788748 and rs879966, but the association estimates for these two SNPs were not reported.\textsuperscript{16} A look-up of the associations for these SNPs revealed that the rs788748 and rs879966 alleles associated with lower odds of HOA were significantly associated with lower circulating IGFBP3 and IGF-I levels.
circulating IGFBP3 but not circulating IGF-1 (R Kaplan, personal communication) (table 2). The two reported independent SNPs most significantly associated with circulating IGFBP3 (rs11977526 and rs700752)\(^16\) were not significantly associated with HOA (see online supplementary table S7). Based on HapMap CEU genotypes, rs788748 was in low LD with rs11977526 (\(r^2=0.05\)), rs700752 (\(r^2=0.04\)) and a potentially causal SNP related to IGFBP3 levels, rs2854746 (\(r^2=0.05\)).\(^28\)\(^29\)

**Functional studies of IGFBP3**

The function of IGFBP3 was explored in the ATDC5 chondrogenesis model system. Hypertrophic differentiation of chondrocytes, a process related to cartilage loss, is associated with decreased expression of type II collagen and aggrecan, matrix calcification, and increased expression of the Runx2 transcription factor.\(^1O\) Runx2, together with MEF2C, increases the expression of type X collagen, matrix metalloproteinases (MMPs) and Indian Hedgehog (Ihh).

Efficient knockdown of IGFBP3 was achieved in ATDC5 cells (figure 3A). By day 21, matrix calcification (Alizarin Red staining), sulfated proteoglycan synthesis (Alcian Blue and Safranin O staining) and collagen content (Sirius red staining) were reduced (See online supplementary figure S6) indicating that IGFBP3 knockdown impairs mineralisation and the early phase of chondrogenesis.

IGFBP3 knockdown in ATDC5 cells resulted in a lack of expression of type X collagen and lower expression levels of Runx2 and Ihh, indicating that hypertrophy was largely prevented (figure 3C, D, F). Expression of type II collagen was also reduced, but to a lesser extent (figure 3B). WNT signalling is known to activate Runx2 expression and stimulate hypertrophy.\(^1O\) Consistent with prevention of hypertrophy, IGFBP3 knockdown resulted in lower levels of Tcf1, a marker of active WNT signalling (figure 3E).

The effect of IGFBP3 overexpression was examined in articular cartilage isolated from patients who underwent knee replacement for OA (figure 3G, H). Overexpression of IGFBP3 in human articular cartilage pellets resulted in lower expression levels of aggrecan (figure 3G) and increased expression of MMP-13 (figure 3H), consistent with increased cartilage catabolism.

HOA is a disease of both cartilage and bone, with a significant component involving bone remodelling.\(^3I\) The role of IGFBP3 in osteogenic differentiation was examined using the MC3T3-E1 cell-based model, a cell line that exhibits temporal gene expression comparable to the in vivo differentiation process.\(^32\) Knockdown experiments were not performed because IGFBP3 is not expressed in the MC3T3-E1 cell line.\(^33\) IGFBP3 overexpression strongly enhanced extracellular matrix mineralisation assayed by Alizarin Red staining and alkaline phosphatase activity (see online supplementary figure S7a, b). Expression levels of Osteocalcin and Osteopontin were 2.5- and 22.3-fold higher, respectively, in IGFBP3-overexpressing cells at day 21 (see online supplementary figure S7c, d). At the first day of induced IGFBP3 overexpression, before osteoblastogenesis was induced, Osterix mRNA levels were already 50-fold higher, and they remained 14-fold more expressed at day 21 (see online supplementary figure S7e).

**DISCUSSION**

In this study, we identified a novel GWS HOA locus near the gene IGFBP3. The genetic variant allele associated with lower odds of HOA was also associated with lower levels of circulating IGFBP3, and experimental knockdown of IGFBP3 prevented chondrocyte hypertrophic differentiation, a deleterious event in OA pathogenesis that results in cartilage loss. Moreover, IGFBP3 overexpression in articular cartilage from OA patients increased expression of genes associated with cartilage catabolism, and IGFBP3 overexpression in a cellular model of osteogenic differentiation resulted in an increase in matrix mineralisation, consistent with an activation of osteoblastic differentiation. Our results from GWAS and functional studies indicate that IGFBP3 levels in cartilage are related to cartilage maintenance and HOA.

Understanding molecular mechanisms underlying genetic associations requires the identification of genes affected by associated genetic variants.\(^4I\) Our integration of a GWAS meta-analysis of circulating IGFBP3\(^16\) with our GWAS of HOA revealed that the HOA-associated SNPs rs788748 and rs879966 were significantly associated with circulating IGFBP3, which indicated that these SNPs or variants in LD could be regulatory variants associated with IGFBP3 expression. Circulating IGFBP3 reflects IGFBP3 gene activity from multiple tissues, and associated SNPs could be regulatory variants associated with IGFBP3 expression in at least one tissue, which is then reflected in circulating protein levels. These results cannot be used to determine the tissue in which associated variants might regulate IGFBP3, but the direction of effect for SNP alleles can be inferred, namely, that the rs788748 A allele associated with lower odds of HOA is also associated with lower levels of IGFBP3 expression in at least one tissue. It is also important to note that even though the SNPs near IGFBP3 previously reported to be the most significantly associated with circulating IGFBP3\(^16\) are not significantly associated with HOA, these SNPs explain a small percentage of the variance in IGFBP3 levels, thus preventing meaningful interpretation of the relationship between circulating IGFBP3 and HOA.

IGFBP3 is one of six insulin-like growth factor binding proteins (IGFBPs) in humans.\(^7I\) IGFBPs modulate IGF signalling by

### Table 2

<table>
<thead>
<tr>
<th>SNP</th>
<th>EA (freq)</th>
<th>IGFB3</th>
<th>I2</th>
<th>IGF-1</th>
<th>I2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>Effect direction</td>
<td></td>
<td>p Value</td>
<td>Effect direction</td>
</tr>
<tr>
<td>rs788748</td>
<td>A (0.49)</td>
<td>6x10^-13</td>
<td>-</td>
<td>61.3</td>
<td>0.82</td>
</tr>
<tr>
<td>rs879966</td>
<td>G (0.40)</td>
<td>4x10^-13</td>
<td>-</td>
<td>56.2</td>
<td>0.80</td>
</tr>
</tbody>
</table>

rs788748 was genotyped in CHS, KORA and SHIP and imputed in FHS (imputation accuracy=1.0). rs879966 was genotyped in CHS and imputed in FHS, KORA and SHIP (imputation accuracy=0.98, 0.99 and 0.99, respectively).

* Study order: KORA, FHS, SHIP and CHS.

EA, effect allele; SNP, single nucleotide polymorphism.

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binding to the two ligands (IGF-I and IGF-II) that primarily signal through the type I IGF-I receptor (IGF-IR). In articular cartilage from individuals without OA, IGF-I activates anabolic processes and inhibits catabolism of cartilage. In OA cartilage, IGF-I’s anabolic activity is greatly diminished, despite the presence of its receptor (IGF-IR). Higher levels of IGFBPs, in particular IGFBP3, have been observed in OA cartilage, leading to the notion that IGFBPs could decrease IGF-I’s bioavailability and could at least be partially responsible for the reduced responsiveness of OA cartilage to IGF-I. Consistent with this notion, an IGFBP-insensitive IGF-I analogue exhibited a stronger anabolic effect on cartilage than IGF-I alone, and a small molecule that inhibits the binding of IGFBPs to IGF-I restored the anabolic effect of IGF-I on OA chondrocytes. Our experimental results also suggest that lower levels of IGFBP3 could promote cartilage maintenance. Further studies are needed to determine whether the HOA association with rs788748 is mediated through a potential alteration in the role of IGFBP3 in cartilage homeostasis during developmental growth to determine joint morphology or perhaps through a subtle impact on IGFBP3 throughout life to affect the threshold for developing HOA. Furthermore, whether IGFBP3’s

Figure 3 Impact of IGFBP3 knockdown and overexpression on markers of cartilage homeostasis. ATDC5 cells stably transfected with a transgene expressing siRNA directed against IGFBP3 are marked in red, and control cells in blue (A–F). IGFBP3 overexpression (grey bars) and control cells (white bars) in articular cartilage (G and H). Gene expression levels quantified by RT-PCR were IGFBP3 (A), type II collagen/Col2A1 (B), type X collagen/Col10A1 (C), Runx2 (D), Tcf1 (E), Ihh (F), aggrecan (G) and MMP13 (H). *p ≤ 0.05 difference with day 1 levels. #p ≤ 0.05 difference with control at each day.

effect on cartilage homeostasis depends on IGF-I will need to be explored in future studies, as IGFBP3 possesses a nuclear localisation sequence, it has been found to localise to the nucleus in cartilage, and it has been proposed to have IGF-independent effects in other biological processes.\textsuperscript{35, 47}

The nearly complete elimination of IGFBP3 expression in our knockdown experiments had strong effects on the prevention of chondrocyte hypertrophy, but subtle effects on cartilage maintenance were also observed, arguing for a minimum required level of IGFBP3. The HOA-associated variants rs788748 and rs879966 were associated with a reduction, but not elimination, of circulating IGFBP3. We also observed that chondrocyte hypertrophy was stimulated by overexpression of IGFBP3 in OA cartilage, which is already in a diseased state, leaving it unknown whether this same effect would be observed in healthy cartilage. With this caveat in mind, higher levels of IGFBP3 could contribute to cartilage loss in diseased cartilage. Taken together, our cell-based experiments argue for a certain range of IGFBP3 in cartilage that supports healthy cartilage homeostasis. In order for IGFBP3-targeted HOA treatments to potentially be effective, this proposed healthy IGFBP3 range will need to be carefully characterised. Furthermore, IGFBP3-targeted therapies must consider the potential impacts on cancer and other IGFBP3-associated diseases.\textsuperscript{35}

A number of factors that regulate IGFBP3 expression have been identified, but IGFBP3 transcriptional enhancers that function in chondrocytes are not well characterised.\textsuperscript{35} HMGAI binds to several sites 2 kb upstream of the IGFBP3 promoter and is required for IGFBP3 expression in chondrocytes,\textsuperscript{48} but DNA near rs788748 and rs879966 has not been experimentally tested for enhancer activity. HMGAI binding data was not included in the ENCODE project, but there is evidence that C/EBPβ, HMGAI’s binding partner, binds DNA near rs788748 (see online supplementary figure S5). Functional studies of this genomic region could help to elucidate the dynamic role IGFBP3 plays in OA development.

Despite a directionally consistent and significant association in the replication studies, the joint analysis p value (combined discovery and replication) was less significant than the discovery stage p value, which is not surprising given that the replication stage sample size was larger and the replication stage effect size was closer to the null, indicating a possible winner’s curse effect\textsuperscript{32} even though a correction for this effect had little impact on the discovery stage OR.\textsuperscript{23} While joint analysis provides greater power in two-stage designs than replication analysis to identify GWS associations, even greater power is achieved in one-stage designs where genome-wide SNPs are genotyped in all samples.\textsuperscript{49} We performed a one-stage design in the MrOS and SOF cohorts to identify GWS SNP associations, followed by a standard replication analysis of the two GWS associations in independent studies. As genome-wide SNPs were tested in the discovery stage, the significance threshold accounting for the multiple testing burden should only be applied to discovery stage results. Furthermore, given our allocation of studies in discovery and replication, a replication stage two-tailed p value of $1 \times 10^{-3}$ is required to achieve genome-wide significance in a joint analysis (see online supplementary text S1), a threshold that exceeds typical significance thresholds for replication. Moreover, the practice of combining discovery and replication stage results to achieve genome-wide significance has been noted to present multiple testing problems.\textsuperscript{50}

In summary, our results from GWAS and functional studies support the role of IGFBP3 in HOA. Further work is needed to determine whether IGFBP3’s effect on cartilage homeostasis requires its interaction with IGF-I. If the IGFBP3 and IGF-I interaction plays a role in HOA, consideration of this interaction could enhance HOA therapies that target the anabolic effect of IGF-I.

Author affiliations

1. California Pacific Medical Center Research Institute, San Francisco, California, USA

2. Laboratory of Tissue Homeostasis and Disease, Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, KU Leuven, Leuven, Belgium

3. Department of Academic Rheumatology, University of Nottingham, Nottingham City Hospital, Nottingham, UK

4. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

5. The Netherlands Genomics Initiative-sponsored Netherlands Consortium for Healthy Aging (NGI-NCHA), Rotterdam/Leiden, The Netherlands

6. Departments of Medicine and Orthopedics, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

7. Albert Einstein College of Medicine, Bronx, New York, USA

8. Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität München, Munich, Germany

9. Section of Preventive Medicine and Epidemiology, Boston University School of Medicine, Boston, Massachusetts, USA

10. Institute of Functional Genomics, Emst Moritz Arndt University, Greifswald, Greifswald, Germany

11. Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA

12. School of Medicine, Oregon Health & Science University, Portland, Oregon, USA

13. Division of Epidemiology, Departments of Family and Preventive Medicine and Medicine, University of California San Diego, La Jolla, California, USA

14. Departments of Medicine and Radiology, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

15. Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

16. Department of Twin Research and Genetic Epidemiology Unit, King’s College London, London, UK

17. Division of Rheumatology, University Hospitals Leuven, Leuven, Belgium

18. University of California at Davis, Sacramento, California, USA

Contributors

DSE, FC, MCN, RJL and NEL: conceived and designed the study; DSE, FC and NEL: wrote the revised paper. DSE, MCN, RJL and NEL: performed the data analysis; DSE, FC, NP, AMV, MCC-B and YL: analysed the data; DSE, FC and NEL: conceived and designed the study; DSE, FC, MCN, RJL and NEL: wrote the revised paper.

Ethics approval

None.

Provenance and peer review

All studies participating in the GWAS meta-analysis were approved by their respective institutional review boards.

Competing interests

None.

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