

DOS BEST PUBLISHED PAPER 2023

Genome-wide association meta-analysis of knee and hip osteoarthritis uncovers genetic differences between patients treated with joint replacement and patients without joint replacement

Cecilie Henkel, et al.

Clinical Orthopaedic Research Hvidovre (CORH),
Department of Orthopaedic Surgery,
Copenhagen University Hospital Hvidovre, Hvidovre



Med en arvelighed på omkring 50% er det velbeskrevet at risikoen for artrose er påvirket af genetiske faktorer; men det er underbelyst om genetik også påvirker sygdomsprogressionen og dermed risikoen for at få brug for kirurgisk behandling. Netop dette er omdrejningspunktet for artiklen, som præsenterer et af de største genetiske studier af artrose til dato – og det første der eksplicit har undersøgt genetiske forskelle mellem knæ- og hofteartrosepatienter som hhv. har og ikke har gennemgået alloplastikkirurgi. Studiet er baseret på omfattende genetisk kortlægning af >700.000 personer fra Danmark, Island og Storbritannien. Resultaterne viser interessante genetiske forskelle mellem patienter hhv. med og uden tidligere alloplastikkirurgi, og herudover har studiet identificeret 10 nye genvarianter associeret med artrose i knæ- eller hofteled. Ved hjælp af genetisk korrelationsanalyse har studiet yderligere udforsket den komplekse sammenhæng mellem artrose og andre smertetilstande, herunder rygsmærter, fibromyalgi og migræne. Resultaterne kan bane vej for en mere målrettet tilgang til belysning af hvilke biologiske mekanismer der driver sygdommen til slutstadiet med behov for alloplastikkirurgi og kan således bidrage til en dybere forståelse af artrose som sygdom.

Link til artiklen:

doi.org/10.1136/ard-2022-223199
Annals of the Rheumatic Diseases
Impact Factor: 27,4

Osteoarthritis

TRANSLATIONAL SCIENCE

Genome-wide association meta-analysis of knee and hip osteoarthritis uncovers genetic differences between patients treated with joint replacement and patients without joint replacement

Cecilie Henkel¹, Unnur Stykkarsdóttir², Gudmar Thorleifsson², Lilja Stefánsdóttir², Gyda Björnsdóttir², Karina Banasik³, Soren Brunak³, Christian Erikstrup^{4,5}, Khoa Manh Dinh⁴, Thomas Folkmann Hansen^{3,6}, Kaspar René Nielsen⁷, Mie Topholm Bruun⁸, Joseph Dowsett⁹, Thorsten Brodersen¹⁰, DBDS Genomic Consortium, Thorgeir E Thorgeirsson², Kirill Gromov¹¹, Mikael Ploug Boesen^{11,12}, Henrik Ullum¹³, Sisse Rye Ostrowski^{9,14}, Ole Birger Pedersen¹⁵, Kári Stefánsson², Anders Troelsen^{1,11}

Handling editor

Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ard-2022-223199>).

For numbered affiliations see end of article.

Correspondence

Cecilie Henkel, Clinical Orthopaedic Research Hvidovre (CORH), Department of Orthopaedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark; cecilie.henkel@regionhiv.dk

© 2023 ES and AJ contributed equally.

Received 5 August 2022

Accepted 15 October 2022

Published Online first 14 November 2022

Check for updates

© Author(s) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Henkel C, Stykkarsdóttir U, Thorleifsson G, et al. *Ann Rheum Dis* 2023;82:384–392.

384

OBJECTIVES

Osteoarthritis is a common and severe, multifactorial disease with a well-established genetic component. However, little is known about how genetics affect disease progression, and thereby the need for joint replacement. Therefore, we aimed to investigate whether the genetic associations of knee and hip osteoarthritis differ between patients treated with joint replacement and patients without joint replacement.

Methods We included knee and hip osteoarthritis cases along with healthy controls, altogether counting >700 000 individuals. The cases were divided into two groups based on joint replacement status (surgical vs non-surgical) and included in four genome-wide association meta-analyses: surgical knee osteoarthritis (N = 22 525), non-surgical knee osteoarthritis (N = 38 626), surgical hip osteoarthritis (N = 20 221) and non-surgical hip osteoarthritis (N = 17 847). In addition, we tested for genetic correlation between the osteoarthritis groups and the pain phenotypes intervertebral disc disorder, dorsalgia, fibromyalgia, migraine and joint pain.

Results We identified 52 sequence variants associated with knee osteoarthritis (surgical: 17, non-surgical: 3) or hip osteoarthritis (surgical: 24, non-surgical: 1). For the surgical phenotypes, we identified 10 novel variants, including genes involved in autophagy (*rs2447606* in *ATG7*) and mechanotransduction (*rs20212716* in *PIEZO1*). One variant, *rs13107225* in *SLC29A6*, associated more strongly with non-surgical knee osteoarthritis than surgical knee osteoarthritis. For all other variants, significance and effect sizes were higher for the surgical phenotypes. In contrast, genetic correlations with pain phenotypes tended to be stronger in the non-surgical groups.

Conclusions Our results indicate differences in genetic associations between knee and hip osteoarthritis depending on joint replacement status.

INTRODUCTION

Osteoarthritis is a common, chronic disease with a high disease burden that is increasing, especially for

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Some knee and hip osteoarthritis patients only develop mild and tolerable symptoms while other patients will need joint replacement because of severe pain and disability. Knee and hip osteoarthritis have well-established genetic components, but little is known about how genetics affect disease progression to joint replacements.

WHAT THIS STUDY ADDS

► Through treatment-stratified genome-wide association meta-analyses, we have discovered 10 novel variants for knee or hip osteoarthritis treated with joint replacement, including genes involved in autophagy (*ATG7*) and mechanotransduction (*PIEZO1*). We have identified genetic differences between knee and hip osteoarthritis patients with and without joint replacement, counting a higher number of significant sequence variants for the joint replacement groups but a tendency for stronger genetic correlation with pain, other than joint pain, for the non-surgical groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Our results suggest that subgrouping patients in future genome-wide association studies, despite the sacrificing of sample size, may add important information for clinical interpretation.

knee and hip osteoarthritis.¹ Osteoarthritis substantially affects both the health of individual patients, the healthcare system and society at large,² through the costs depend on the severity of the disease. It is well known that some osteoarthritis patients only develop mild and tolerable symptoms while other patients will have symptoms that progress to severe

Henkel C, et al. *Ann Rheum Dis* 2023;82:384–392. doi:10.1136/ard-2022-223199

eular

BMJ

