were challenged by in vivo collagenase treatment, increased staining of the chondrocytes was seen.

**Conclusions:** We identified a genetic variant on chromosome 19 to be associated with cartilage thickness and hip OA. The variant is located in a gene showing an expression pattern that supports a role in chondrogenetic differentiation. GWAS for underlying endophenotypes might be a prolific route to identify risk loci for complex diseases such as OA.

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GLOBAL DNA METHYLATION ANALYSIS IN OSTEOARTHRITIS SYNOVIAL FIBROBLASTS

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**Purpose:** Aberrant transcription profiling in osteoarthritis (OA) synovial fibroblasts (SFs) lacking consistent specific genetic mutations suggests that epigenetic mechanisms along with the environmental factors may be involved in its pathogenesis. Compared to those from normal or rheumatoid arthritis (RA) SFs, over-activated OASFs have an important role in the destruction of normal joint architecture, and the imprinted, phenotypical aggressiveness could be determined by epigenetic mechanism. To investigate a global DNA methylation of human OASFs using methylated DNA isolation assay (MeDIA)-CpG promoter microarray, and compared it with SFs of RA patients or healthy controls in Korea population.

**Methods:** Human synovial tissue samples obtained during undergoing total knee joint replacement surgery in 2 OA and 3 RA patients. Normal synovium was collected by arthroscopic or open knee surgery of traumatic ligament injury of healthy populations. Total DNA extracted from SFs using the QIAamp DNA mini and blood kit protocol (Qiagen, Hilden, Germany). To discover novel hypo- or hypermethylated genes in OA by genome-wide search, we introduce a MeDIA-coupled CpG microarray method for directly identifying differentially methylated regions of the genomes in each pooled synovial cells between OA and RA patients. The methylation status of promising candidates was validated by quantitative pyrosequencing assay in each synovial cells.

**Results:** In two CpG microarray, 4 genes were screened as 5 fold hypomethylated targets among 1,714 porbes. Through stepwise subtraction processes, we finally selected four candidate targets. Among of these targets, two genes, APEX1 gene (ggt-OA1) and TGFB1 gene (ggt-OA2) have shown so far a significant decrease in the methylation frequency in OA when compared in independent groups of synovial DNA samples from OA patients with from RA and normal controls.

**Conclusions:** APEX1 and TGFB1 gene promoter is hypomethylated in OA SFs than OA and healthy controls. Pathophysiologic correlation and their role as a diagnostic or prognostic marker should be investigated in a larger number of patients group hereafter.

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HFE C282Y HOMOZYGOSITY IS ASSOCIATED WITH AN INCREASED RISK OF TOTAL HIP REPLACEMENT FOR OSTEOARTHRITIS IN MEN BUT NOT WOMEN

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**Purpose:** The evidence for an association between mutations in HFE gene related to hemochromatosis and risk of hip or knee osteoarthritis is inconsistent. Total joint replacement is considered a surrogate measure for symptomatic end-stage osteoarthritis. This study aimed to examine the relationship between HFE gene mutations and risk of total hip and knee replacement in a population-based cohort.

**Methods:** The Melbourne Collaborative Cohort Study is a prospective cohort study that commenced recruitment in 1990. Participants born in Australia, New Zealand, the United Kingdom, or Ireland (n = 27,848) were genotyped for the HFE C282Y variant. Total hip and knee replacements for osteoarthritis were ascertained from the Australian Orthopaedic Association National Joint Replacement Registry. Hazard ratios (HRs) and confidence intervals (CIs) were obtained from Cox regression.

**Results:** Compared to those with no C282Y variant, C282Y homozygotes were at increased risk of total hip replacement (HR 1.94, 95% CI 1.04–3.62). The association was stronger for men (HR 3.34, 95% CI 1.48–7.52) than for women (HR 1.22, 95% CI 0.46–3.27) (p for interaction = 0.21). Only 3 C282Y homozygotes had total knee replacements; the HR was 0.51 (95% CI 0.16–1.57). C282Y/H63D compound heterozygosity was not related to the risk of total hip or knee replacement.

**Conclusions:** HFE C282Y homozygosity was associated with increased risk of total hip replacement for osteoarthritis for men but not for women. The mechanism for this is unknown and the findings need to be confirmed in future studies.

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THE mtDNA HAPLOGROUPS INFLUENCE THE PROGRESSION OF OSTEOARTHRITIS (OA)

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**Purpose:** To analyze the influence of the mtDNA haplogroups in the progression of the osteoarthritis (OA) disease.

**Methods:** The DNA of 282 knee and/or hip OA samples from Hospital Universitario A Coruña was isolated to obtain their mtDNA haplogroups. Knee and/or hip radiographs from all these samples were obtained at two stages of the OA disease of at least 36 months between them, and evaluated according to the K/L scale from grade 0 to IV. Statistical analyses included Kaplan-Meier survival curves for each haplogroup or cluster tested, as well as Cox regression models taking into account another variables such as gender, haplogroup (or cluster) and body mass index (BMI).

**Results:** For this study, two types of progression were established: OA progression and severity progression. We considered OA progression when a patient evolved from K/L grade 0-I to K/L grade II-III or K/L grade IV, and from K/L grade II-III to K/L grade IV, in at least one of the joints analyzed. The results obtained showed that the OA progression varies significantly according to the mtDNA haplogroups (p = 0.030), and the main differences were detected when compared patients that belonged to the cluster TJ (better progressors) with patients of the cluster KU (worse progressors) (p = 0.083) (Figure 1). On the other hand, we considered severity progression when a patient evolved to knee or hip prosthesis from an initial K/L grade III or less. In this case, the results obtained showed that patients carrying the most common mtDNA haplogroup H had a worse severity progression than non-H patients (p = 0.035) (Figure 2). The Cox regression model also showed that males evolved worse than females (p = 0.028).

**Conclusions:** The mtDNA haplogroups influence the progression of OA; these results strength the role of the mitochondria in the OA disease.

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Fig. 1. Kaplan–Meier survival curve showing the different OA progression between clusters KU and TJ.