OA-pain intensity is strongly associated with loss of function and quality of life. To date, it is unclear if NP alone, as a recovery of bone and cartilage associated with loss of joint specific phenotypic pain and quality of life in patients with hip or knee OA. The primary aim of this study is to investigate if NP is associated with loss of joint specific patient-centered functional outcomes and Health Related Quality of life (HRQOL). The secondary aim is to investigate the relationship between NP and centrally mediated symptoms (mood, fatigue, sleep quality) and symptoms associated with CS (widespread pain, illness burden, pain intensity at rest).

Methods: 259 adult primary OA-patients (139 hip-OA, 160 knee-OA) completed a questionnaire survey by mail. All patients answered questions about demographic characteristics, OA-pain duration, previous joint surgery, widespread pain and comorbidities. Subsequently, the modified-painDETECT questionnaire (mPDQ; to measure NP), the Knee or Hip Injury and Osteoarthritis Outcome Score (KOOS/HOOS; to measure joint pain) and Body Present Detection Questionnaire (mPDQ; to measure MPN), the Knee or Hip Injury and Osteoarthritis Outcome Score (KOOS/HOOS; to measure joint specific patient-centered functional outcomes), the Short Form-36 (SF-36; to measure HRQOL), a joint pain Numeric Rating Scale, a Visual Analogue Scale for joint pain at rest and the Pittsburgh Sleep Quality Index were administered. Patients were grouped based on their mPDQ-score, the first group (n=184) involved patients with a nociceptive pain phenotype (mPDQ score <12), the second group (n=115) represented a possible or likely neuropathic pain phenotype (hip-OA: 34.5%; knee-OA: 41.9%). The NP-group scored significantly higher on body mass index (BMI), pain intensity, duration and pain medication usage. None of the patients used non-conventional centrally acting pain medication. No significant differences were observed based on the presence of previous joint surgery. After adjusting for relevant covariates like sex, age, BMI, pain intensity and pain duration: possible or likely NP was significantly associated with loss of joint specific outcomes on all 5 subscales of the KOOS/HOOS (mean difference 9.8 points). This goes along with significant loss of HRQOL on the SF-36 dimensions “Physical Functioning” and “Bodily Pain”. Furthermore, the NP phenotype was to a large extend significantly associated (adjusted for sex, age, BMI) with centrally mediated symptoms (mood, p<0.05; fatigue, p<0.05; sleep quality, p=0.062) and features associated with CS (widespread pain, p=0.001; illness burden, p=0.075; pain at rest, p=0.001).

Conclusions: The results indicate that NP-independent from pain intensity and pain duration- is mainly associated with clinical relevant loss of joint specific patient-centered functional aspects of HRQOL due to the high prevalence of NP in OA-patients and the found association with centrally mediated symptoms and possible CS; it seems to be justified to treat NP-patients more specifically with non-conventional centrally acting pain medication.

81 GENETIC VARIANTS IN THE SUPT3H-RUNX2 LOCUS CONFER SUSCEPTIBILITY FOR BONE AND CARTILAGE RELATED DISORDERS VIA LONG-RANGE REGULATION OF RUNX2


Purpose: Genome-wide association studies (GWAS) have identified in total 6 independent SNPs within the 5’ region of the RUNX2 gene to be associated to cartilage and bone related phenotypes. We hypothesize that these SNPs may regulate RUNX2 expression in a time- and differentiation dependent manner. In this way, these SNPs might regulate cartilage and bone differentiation, which result in the multitude of associations found in this region. Therefore we aim to elucidate the effect of the identified SNPs on the regulation and expression of RUNX2 and how these confer susceptibility to cartilage and bone related disorders, such as osteoarthritis and bone mineral density.

Methods: Independent GWAS signals were identified with linkage disequilibrium (LD) from the HapMap project and GCTA conditional joint analysis. SNPs in LD with the GWAS loci were identified with the SNAP tool and HaploReg (V2.2, Broad Institute). GWAS SNPs and SNPs in high LD were analyzed for enrichment in genomic regulatory regions, and co-location with DNA binding proteins using data from the ENCODE Project, Roadmap epigenetics project, Vista enhancer browser and the FANTOM5 database. GWAS SNPs and SNPs in another, but one of the signals for mJSW was in high LD with that of hip OA mJSW (r^2>0.8). Next we analysed all GWAS signals for enrichment in genome regulatory regions. All independent GWAS signals co-localized to regions with enrichment of active enhancer markers, H3K4me1, H3K27ac and DNase1 hypersensitivity enrichment and bi-directional CAGE reads, in osteoblast and chondrogenic cells. CTCF (CCCTC-binding factor or 11-zinc finger protein) is essential for chromatin organization and gene regulation, its functions include transcription initiation and the formation of long-range chromatin interactions. The BMD associated SNPs were situated in an area that is involved in CTCF-binding in osteoblasts. These SNPs are located ~700 kb away from the RUNX2 promoter, yet they do have a significant effect (p<0.05) on RUNX2 gene expression in human cartilage (as quantified by RNAseq in 96 samples). In addition, we observed that when we stimulated RUNX2 expression in human chondrocytes by TGFβ stimulation, there is also an increase in CTCF binding near the RUNX2 promoter. These results suggest that CTCF binding may play a role in the regulation of RUNX2 gene expression.

Conclusions: We have shown that variants in the SUPT3H-RUNX2 locus associated to cartilage and bone phenotypes are located in potential gene regulatory regions, and effect RUNX2 gene expression. We hypothesize that the SNPs are localized in long-range enhancers which, mediated by a CTCF chromatin-loop to the RUNX2 promoters, regulate RUNX2 gene expression in a time- and differentiation dependent manner during cartilage and bone development. Future studies will further investigate the chomatin architecture of the SUPT3H-RUNX2 locus.

Figure 1. SNPs found in GWAS located in the SUPT3H-RUNX2 locus are associated to bone and cartilage phenotypes.

82 METHYLATION OF CARTILAGE DNA IS A MEDIATOR OF GENETIC RISK AT SEVERAL OA SUSCEPTIBILITY LOCI

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Purpose: Replicated OA genetic risk loci are now emerging through the use of powerful case-control association studies. The analysis of the epigenetics of OA has also received considerable attention in the last few years, particularly CpG methylation in cartilage chondrocyte genomic DNA. The vast majority of OA risk loci reported to date do not contain amino-acid substitution polymorphisms that can account for the association signal, implying that OA risk alleles act by modulating gene expression rather than by changing protein sequence. DNA methylation is a specific mechanism used by the cell to regulate gene expression. DNA methylation is known to mediate genetic risk in several diseases including rheumatoid arthritis. In this study we assessed whether DNA methylation is an intermediary of OA genetic risk by correlating genotype at OA risk loci with cartilage DNA CpG methylation.

Methods: In the discovery analysis, DNA was collected from the cartilage of 110 elderly individuals. Seventy one of these were OA knee patients, 20...