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total variation consisted of Il-2, Il-6, G-CSF, Il-10 and Il-7, the second component explaining 15% of total variation consisted of MCP-1, MIP-1 β and Il-8, the third component, which explained 12% of total variation consisted of Il-7, Il-5 and CRP. CRP was represented negative in the third component, indicating an inverse relation with the cytokines in this component. Genetic analysis revealed that three SNPs in the SELS gene formed 4 common haplotypes, one of which, GAG (frequency 3.5%) showed significant association to the first component ($P=0.019$) and to the third component ($P=0.036$). Furthermore, OA subtype analysis showed that the second component (mainly representing chemokine variation) was significantly associated to hand ROA and disc degeneration ($P=0.029$ and $P=0.010$ respectively) as well as the physical component score (PCS) derived from the SF36 questionnaire ($P=0.042$). Further analysis of these associations showed that the association of hand ROA and the PCS are not independent. The CRP related component also showed a strong association to the PCS ($P=0.007$). The SELS haplotypes showed no association to OA subtypes in the GARP study. The QL analyzed cytokines showed no associations to either OA subtypes or the SELS genetic variation.

Conclusions: Genetic variation in the SELS gene associates to two components, which were revealed by a principal component analysis of 17 cytokines and chemokines and CRP. The CRP containing component also showed association to the physical component score derived from the SF36 questionnaire. A third component was identified which mainly represents chemokine variation. This chemokine representing component showed association to hand OA and disc degeneration as well as the physical component score, indicating chemokines are involved in the etiology of OA.

358 ASSOCIATION OF THE INTERLEUKIN-4/INTERLEUKIN-4 RECEPTOR GENETIC VARIANTS WITH HAND OSTEOARTHRITIS

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Purpose: Primary osteoarthritis (OA) is a common late-onset arthritis that demonstrates a complex mode of transmittance with both joint-site and gender-specific heterogeneity. In OA anti-inflammatory and anabolic cytokines which are usually responsible for the control of cartilage homeostasis are altered or inadequate. Hitherto, functional study had been focused on the interleukin-13 (IL13)/interleukin-4 (Il-4)/Il-4 receptor (Il-4R) system which has a strong chondroprotective role and it is reasonable to speculate that polymorphisms within these genes may be risk factors for OA. We therefore performed a case-control association study to investigate 18 common single polymorphisms (SNPs) in these genes as potential hand OA susceptibility loci.

Methods: Genotyping of the eighteen SNPs (9, 5, 4 mapping respectively to the Il-4R, Il-4 and Il-13 gene), was performed using TaqMan Technology in 413 patients (26 male, 387 female) with hand OA and 326 healthy controls (14 male, 312 female). Statistical analysis: the maximum-likelihood estimates of allele frequencies, Hardy-Weinberg equilibrium, and haplotype frequencies were estimated from the genotype data at 18 SNP loci using Haploview software, which uses the EM (expectation-maximization) algorithm. Pair-wise linkage disequilibrium (LD) between the individual SNPs was calculated using the LD-plot function of this software. Comparisons of the distributions of allele, genotype and haplotype frequencies were performed using the chi-square test.

Results: All eighteen SNPs conformed to Hardy-Weinberg equilibrium in the control group ($p > 0.05$). Analysis on the whole samples showed that only one SNP (rs1805013), mapping to the Il-4R gene, was significantly associated with hand OA ($p=0.0125$). This association was attributable to an increased frequency in the patients of the minor T allele and the association was maintained also when considering only patients who did not develop also hip OA or knee OA. Dividing patients in erosive and non-erosive OA groups according to radiological evidence, this association was remarkably maintained in all the two subgroups and it sharply increased when considering only patients with non-erosive osteoarthritis ($p=0.0077$). Furthermore another SNP rs1805015, showed association with a P -value of 0.0032. In group of patients who developed carpometacarpal OA, this Il-4R SNP (rs1805015) overcome significance threshold ($p=0.0173$). As far as Il-4 gene is concerned, two SNPs

(rs2243250, $p=0.0219$ and rs2243274, $p=0.0121$) showed association in this OA subgroup.

Conclusions: Genetic variants in the coding region of Il-4/Il-4R showed to be associated with hand OA, suggesting a role of this system in hand OA susceptibility. Further functional studies will clarify the role of the SNPs in regulating metabolism, differentiation and survival of chondrocytes, assessing their possible involvement in OA pathogenesis.

359 ASSOCIATION OF REGULATORY POLYMORPHISMS IN MATRIX METALLOPROTEASES WITH OSTEOARTHRITIS RISK

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Purpose: Matrix Metalloproteases (MMP) are a large group of extracellular matrix proteases that play critical roles in cartilage homeostasis and in osteoarthritis (OA) pathogenesis. As they are very redundant and promiscuous in the targets they degrade, it is unclear which of them play a critical role in the different aspects of OA progression. We aimed to explore well-defined regulatory polymorphisms in MMPs to determine their influence in OA susceptibility and gain information on their relevance for OA.

Methods: By bibliographic searches we identified 17 regulatory polymorphisms with experimental support of their effect on MMP levels. They were tested in a preliminary study and 8 of them (MMP1 rs1144393, rs514921 and rs11292517; MMP2 rs243866, rs243865 and rs2285053; and MMP8 rs11225395 and rs1320632) were selected for further analysis. Genotypes were obtained in samples from Spain, the UK and Greece that included patients undergoing total joint replacement of the knee (TKR = 796) or hip (THR = 1412) and OA-free controls (1185). Genotypes were obtained by single-base extension. Combined analysis was done with the Mantel-Haenszel approach.

Results: There was notable heterogeneity in the results across the joint affected, the subject's gender and the sample collection. Three SNPs were associated with TKR, MMP8 rs1320632 (OR=1.36, 95% CI = 1.07-1.71, $P=0.010$), MMP1 rs1144393 (OR=1.13, 95% CI = 1.02-1.34, $P=0.023$), and MMP2 rs2285053 (OR=1.36, 95% CI = 1.10-1.59, $P=0.002$), but the latter showed significant heterogeneity between sample collections. MMP8 rs1320632 and MMP1 rs1144393 were preferentially associated to TKR in women (OR=1.56, 95% CI = 1.16-2.23, $P=0.004$, and OR=1.19, 95% CI = 1.10-1.57, $P=0.003$, respectively), whereas MMP2 rs2285053 was mainly associated in men (OR=1.44, 95% CI = 1.07-2.00, $P=0.02$). This MMP2 SNP was associated to TKR in women from the UK and Greece, but showed an opposed trend in the Spanish. THR patients showed less clear effects. Only the MMP2 rs2285053 SNP showed association with THR in women and it was of an opposite direction to that observed in TKR patients (OR=0.73, 95% CI = 0.57-0.94, $P=0.015$).

Conclusions: We found evidence of a role in knee OA susceptibility for regulatory polymorphisms in two MMP genes, MMP8 and MMP1. The MMP8 associated allele has been shown to increase MMP8 expression levels. This suggests that MMP8 is limiting in the OA process and that increased availability will favor disease development. Interpretation of the MMP1 association is more difficult because there are conflicting reports about its functional effects. Heterogeneity of effects between affected joint, gender and sample collection was present for a regulatory polymorphism in the MMP2 gene and its association to knee or hip OA will require further investigation.

360 ASSOCIATION BETWEEN IL-4 RECEPTOR α AND TGF- β 1 POLYMORPHISMS AND HAND OA

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Purpose: Osteoarthritis (OA) is a common disease characterised by the degeneration of the cartilage of synovial joints such as the hip and knee. Available evidence suggests that genetic factors play a major role in the etiology of OA. The gene product of Il-4 receptor (Il-4R) regulates cartilage chondrocyte differentiation and survival. Transforming growth factor (TGF)-beta, on the other hand, regulates the function of fibroblasts, and has been shown to have a role in the pathogenesis of rheumatoid arthritis. These enzymes may therefore play an important role in development