genotype ($p < 0.05$). In radiological features, no changes was observed in vitamin D group whereas in placebo group decreased Medial-JSW and increased Osteophyte was observed in Tt and tt genotype in comparion to TT genotype of TaqI polymorphism. These changes were of borderline significance. No similar effect was observed for ApaI polymorphism.
Conclusions: VDR gene polymorphism (TaqI) influences the clinico-radiological response to vitamin D supplementation in Osteoarthritis knee with insufficient 25-OHD levels. If these results are confirmed by the larger studies, this would justify tailoring vitamin D supplementation using VDR genotyping in vitamin D insufficient KOA patients.

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TOWARDS A MOLECULAR DESCRIPTION OF DISEASE; A SYSTEMS BIOLOGY APPROACH IN OSTEOARTHRITIS

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Purpose: Osteoarthritis represents an increasing threat worldwide, affects people of all ages, inducing premature disability and economic impairment. Bioinformatics, computational and systems biology are used for defining molecular profile of diseases by integrating available information. This approach requires knowledge about details as well as overview about predictable interconnections. Bioinformatics is proposed as a tool in organizing existent knowledge aiming introduction of the discovery science principles in handling clinical and experimental data. Computational biology is used to detect possible correlations and links in molecular pathways and further pointed as one useful method to design focused systematic research.
Methods: Genes and proteins involved in the process specific to Homo sapiens have been extracted using data available in Gene Cards, Uniprot, pubmed cited literature and gene ontology (GO) databases. Interactions network analysis was build using Gene Regulatory Network (GRN) and Gene Set Enrichment Analysis (GSEA) considering the following factors; down and up regulation, co expression, predicted protein interaction, Transcription Factor (TF) regulation. ChIP-seq data sets were aligned usin to build version version hg19 of the human genome. Enhancers were defined as regions of ChIP-seq enrichment for H3K27ac in human cells.
Results: Several sets of genes previously associated with chondrocyte metabolism and inflamation were identified. Gene expression not previously associated with OA have been identified. OA-associated SNPs appear in super-enhancers of chondroprogenitor cells.
Conclusion: systems biology approach in disease characterization has the potential in defining the pathological mechanisms, in offering biomarker and therapeutical targets. Our approach is acontribution in this respect towards a definition of osteoarthritis.

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IMPROVED PREDICTION OF KNEE OSTEOARTHRITIS PROGRESSION BY GENETIC POLYMORPHISMS. ARTHROTEST STUDY RESULTS

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Purpose: Single Nucleotide Polymorphisms (SNPs) are inherited genetic variations that can predispose or protect individuals against clinical events. Osteoarthritis (OA) has a multifactorial etiology with a strong genetic component. Genetic factors influence not only knee OA onset, but also disease progression. The aim of this study was to develop a genetic prognostic tool to predict radiologic progression towards severe disease in primary knee OA (KOA) patients.
Methods: Cross-sectional, retrospective, multicentric, association study with Spanish KOA patients. 595 patients from 31 sites were selected. Inclusion criteria: Caucasian patients aged ≥40 years at the time of diagnosis of primary KOA, for whom two anteroposterior X-rays were available, one corresponding to the time of OA diagnosis with Kellgren–Lawrence grade 2 or 3 and the other to the end of the follow-up period. Patients who progressed to KL score 4 or were referred for total knee replacement in ≤ 8 years since the diagnosis were classified as progressors to severe disease. A unique expert viewer measured the radiologic progression from all X-rays. A candidate gene study analyzing 774 SNPs was conducted. SNP genotyping was performed with Illumina Golden gate technology or KASPar chemistry. Clinical variables of the initial stages of the disease (gender, BMI, age at diagnosis, OA in the contralateral knee and OA in other joints) were registered as potential predictors. Univariate analysis was done to identify associations between the baseline clinical variables or SNPs and KOA progression. SNPs and clinical variables with an association of $p < 0.05$ were included on the multivariate analysis using forward logistic regression.
Results: 282 patients fulfilled DNA and X-ray quality control criteria (220 in the exploratory cohort and 62 in the validation cohort). The univariate association analysis showed that one of the clinical variables and 23 SNPs were significantly associated to KOA severe progression in the exploratory cohort ($p < 0.05$). The predictive accuracy of the clinical variable was limited, as indicated by the area under the ROC curve (AUC = 0.66). When genetic variables were added to the clinical model (full model) the prediction of KOA progression was improved and the AUC increased to 0.82. Combining only genetic variables, a predictive model with a good accuracy (AUC = 0.78) was also obtained. The predictive ability for KOA progression of the full model was confirmed on the validation cohort (two-sample Z-test $p = 0.190$).
Conclusions: Genetic polymorphisms predict radiologic progression more accurately than clinical variables. An accurate prognostic tool to predict primary KOA progression has been developed, based on genetic and clinical information from OA patients. This model could help clinicians optimize patients' preventive and therapeutic care, according to their OA progression rate, and personalize disease management.

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FUNCTIONAL ANALYSIS OF THE OSTEOARTHRITIS SUSCEPTIBILITY LOCUS MARKED BY THE POLYMORPHISM rs10492367

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Purpose: The arcOGEN genome-wide association study, published in 2012, reported that the rs10492367 G to T single nucleotide polymorphism (SNP) marks a region on chromosome 12p that is associated with hip osteoarthritis (OA) in Europeans, with an odds ratio (OR) of 1.14 and a p-value of 1.48×10^{-8}. rs10492367 is an intergenic SNP located 59 kb downstream of kelch domain-containing protein 5 (KLHDC5) and 96 kb downstream of parathyroid hormone-like hormone (PTHLH). While there is sparse published data for KLHDC5, PTHLH has been widely studied, with its protein having a crucial role in endochondral ossification. As rs10492367 is not in high linkage disequilibrium (LD) with any common non-synonymous transcript polymorphisms, it is unlikely that the OA association is due to a change in the coding sequence of either of these two nearby genes. Instead, rs10492367 could function as a cis-acting polymorphism, influencing PTHLH or KLHDC5 gene transcription, resulting in allelic expression imbalance (AEI). Furthermore, as rs10492367 resides in a region predicted to have enhancer activity based on the ENCODE dataset, identification of functional variants within this region that affect such activity will prove vital in dissecting the OA signal. Thus, the aims of this study are to assess whether rs10492367 marks AEI in either PTHLH or KLHDC5, and to determine if any intergenic SNPs in high LD (≥0.8) with rs10492367 are functionally active in regulating enhancer activity of this OA associated region.
Methods: Cartilage was obtained from the hip or knee of OA patients who had undergone elective total joint replacement, and from non-OA patients who had undergone total joint replacement as a result of a neck-of-femur fracture (NOF). Using quantitative real-time polymerase chain reaction (qPCR), overall expression of PTHLH and KLHDC5 was measured in cDNA synthesised from cartilage RNA and stratified by rs10492367 genotype. Allelic expression imbalance analysis was performed using pyrosequencing. Since rs10492367 is intergenic, the transcript SNPs rs6253 in PTHLH and rs9029 in KLHDC5 were used as markers to measure allelic imbalance in 29 and 21 heterozygous OA patients, respectively. The data was stratified by rs10492367 genotype to evaluate whether any allelic differences corresponded to the presence of either of the association SNP alleles. Eight SNPs were in an LD of ≥0.8 with the association SNP; thus, 18 pGL3 promoter vector constructs were generated, each of which contained one of the alleles from