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[1-3]. 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

Clinical Study: 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 with Kellgren-Lawrence grade 2 or 3. 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 radiologic progression from all X-rays (IM).

Genotyping: 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.

Statistics: 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. The exploratory cohort included 220 KOA patients (180 females and 40 males) with a mean age (S.D.) at OA diagnosis of 61.3 (8.6) years. The replication cohort included 62 KOA patients (47 females and 15 males) with a mean age (S.D.) at OA diagnosis of 61.3 (7.7) years **(Table 1).**

714 SNPs verified the quality control and/or inclusion criteria.

23 SNPs and the age at primary KOA diagnosis were significantly associated to KOA severe progression in the exploratory cohort (N=220;p<0.05).

Table 1. Clinical and demographic characteristics of the exploratory and replication KOA cohorts. *p<0.05

	Exploratory cohort			Replication cohort		
Characteristics	**Progressors to severe KOA N=132**	**Non-progressors to severe KOA N=88**	**p-value**	**Progressors to severe KOA N=37**	**Non-progressors to severe KOA N=25**	**p-value**
Gender, males/females	17/71	23/109	0.721	8/29	7/18	0.565
Age at OA diagnosis (years), mean ± SD	65.61 ± 7.7	58.47 ± 8.0	3.85E-10*	61.00 ± 6.75	61.72 ± 9.09	0.721
Patients older than 60 years at OA diagnosis (%)	62 (70%)	50 (38%)	2.19E-06*	21 (56.7%)	14 (56.0%)	0.953
BMI (kg/m^2), mean ± SD	30.81 ± 6.1	29.55 ± 5.6	0.151	29.94 ± 3.84	31.13 ± 6.35	0.415
Patients with OA in the contralateral knee (%)	57 (81%)	93 (77%)	0.129	26 (78.8%)	17 (85.0%)	0.575
Patients with OA in a different joint (%)	32 (78%)	57 (63%)	0.080	13 (81.2%)	12 (75.0%)	0.669

PREDICTIVE MODEL

The predictive accuracy of the clinical variables was limited (AUC=0.66). Combining only genetic variables, a predictive model with a good accuracy was obtained (AUC=0.78). When genetic variables were added to the clinical model (full model-Arthrotest) the prediction of KOA progression was significantly improved (AUC=0.82) **(Figure 1. Table 2).** The predictive ability for KOA progression of the full model was confirmed on the replication cohort (two-sample Z-test;N=62;p=0.190).

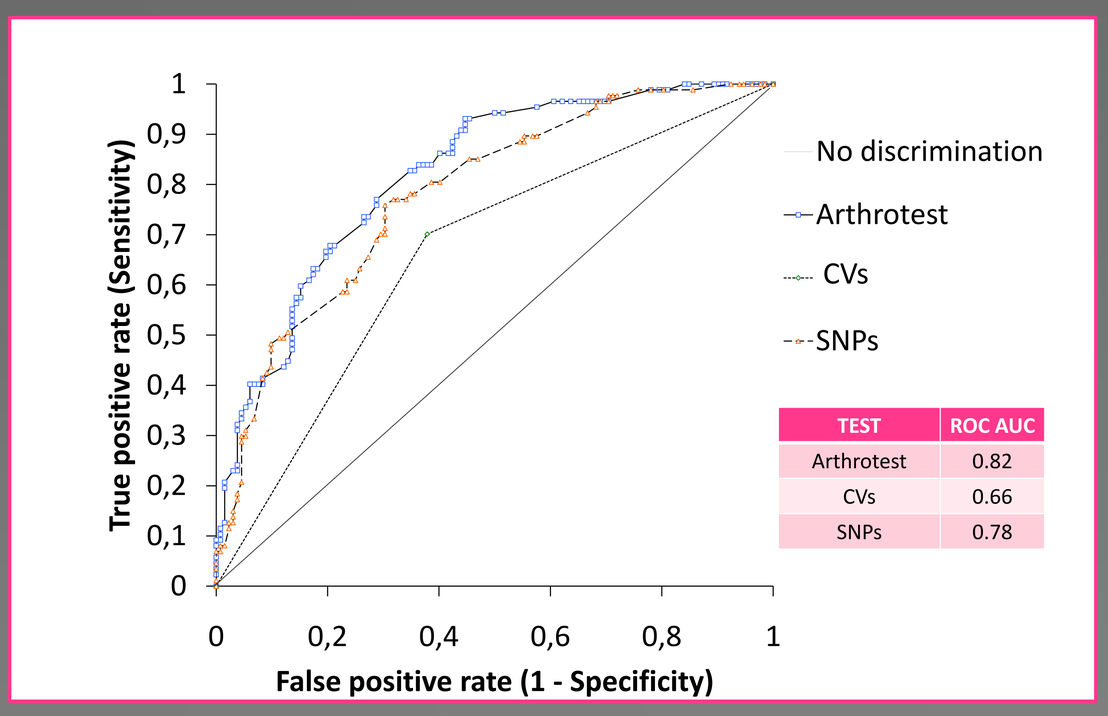

Figure 1. Multivariate models (ROC curves) to predict knee OA progression. The full model (Arthrotest) combining SNPs and clinical variables and the reduced models combining only clinical variables (CV) or SNPs are shown.

Table 2. Comparison between the predictive value of the full model (Arthrotest) and the models based only in clinical variables (CV) or SNPs alone. AUC: Area Under the ROC Curve.

Contrast	AUC Difference	95% CI		SE	Z	p
Arthrotest vs CVs	0.16	0.10	to 0.22	0.030	5.36	<0.0001
Arthrotest vs SNPs	0.04	0.00	to 0.07	0.019	2.01	0.0444
CVs vs SNPs	-0.12	-0.21	to -0.03	0.044	-2.74	0.0061

The model obtained combines the clinical variable and 8 SNPs, namely **rs2073508, rs10845493, rs2206593, rs10519263, rs874692, rs7342880, rs780094 and rs12009**. SNPs contribute 78% to the predictive strength of the full model, the remaining 22% being explained by the age at disease diagnosis. The SNP rs2073508 in the *TGFB1* gene, and the SNP rs12009 in the gene *GRP78 (HSPA5)* were the SNPs with a highest contribution to the predictive power of the model, 17% and 11%, respectively **(Figure 2).**

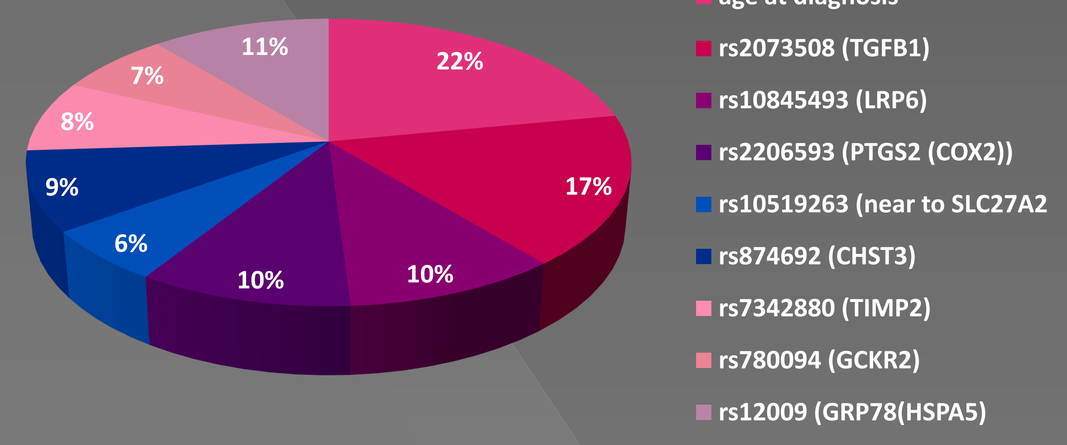

Figure 2. Relative contribution to the explained variability of the data by the variants included in the model.

Conclusions

- ❑ **An accurate prognostic tool to predict primary KOA progression has been developed, based on genetic and clinical information from OA patients.**
- ❑ **Genetic polymorphisms predict radiologic progression more accurately than clinical variables.**
- ❑ **This model could help clinicians optimize patients' preventive and therapeutic care, according to their OA progression rate, and personalize disease management.**

References: (1) Valdes, AM et al. *Best Pract Res Clin Rheumatol* 2010(a);24:3-14; (2) Valdes AM et al. *Arthritis Rheum* 2004;50(8):2497-507; (3) Zhai G et al. *Osteoarthritis Cartilage* 2007;15(2):222–5.

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