Genetic association analysis of LRCH-1 for knee osteoarthritis

Sirs,

Osteoarthritis (OA) is the most common cause of musculoskeletal disability related to aging and it is characterised by late-onset degeneration of the articular cartilage (1). As the results of several studies have indicated, genetic factors comprise an essential component of the etiology of OA (2-4). In the study by Spector *et al*. (5) study, rs912428, a C/T polymorphism in intron 1 of leucine rich repeats and calponin homology containing 1 (LRCH1) was a risk factor for knee OA. In contrast, Snelling *et al*. did not detect an association with either knee OA (6). In addition, there was no association of LRCH1 with the knee OA susceptibility in a Greek population and two East Asian populations (Chinese, Japanese) (7). Therefore, the objective of our study was to assess whether the candidate SNP was associated with knee OA susceptibility in our Korean cohort.

Two thousand, four hundred sixty-two subjects aged 50 years and older were assessed for OA at the knee. The radiographs were read by two examiners who were blinded to the clinical information, and they used an atlas of radiographic features to obtain a global Kellgren/Lawrence (K/L) score (0–4 scale). Of those, 725 subjects had radiographic OA (defined as a K/L score of ≥2). Inflammatory arthritis was excluded, as was post-traumatic or post-septic arthritis. Height and weight were measured to calculate the body mass index (BMI). Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). The SNP of LRCH1 gene was genotyped. Genotyping was performed using High Resolution Melt (HRM) or the Taq-Man allelic discrimination assay, and using the Rotor-Gene 6000 (Corbett Research, Sydney, Australia). The genotyping accuracy was 99.0%, as determined from the genotype concordance between duplicate samples. The genotype frequencies of the SNP were in Hardy-Weinberg equilibrium. Associations were tested by calculating the ORs and 95% confidence intervals (95% CIs), using multivariate logistic regression analysis with adjustments for age, sex, weight, and the body mass index (BMI). All the analyses were performed using SPSS software (version 16; SPSS, Chicago, IL).

In total, 2462 subjects were genotyped (725 patients with OA and 1737 healthy controls) for SNP; 76.4% of the OA patients were female. The mean age of the OA patients was older than that of the controls (67.4 *vs*. 62.7 years, respectively, $p<0.001$). The mean (SD) BMI of the patients and controls was 25.3 (3.0) and 24.1 (2.8) kg/m^2, respectively. Table I lists the genotype and allele frequencies of the SNP in the whole study population. The genotype and allele frequencies of the SNP rs912428 in our study are not comparable with those of the UK studies (5, 6). For example, we observed a T-allele frequency of 9.0% in our controls, compared with the T-allele frequencies of 14.0–19% in the UK controls. When we stratified the population by gender, none of the genotypes or allele frequencies significantly differed between the groups when adjusted for age, gender, and BMI.

In this present study, we did not observe any association either when the cases were studied as a whole or when they were subjected to stratification by gender. The susceptibility to various diseases does vary according to race and ethnicity, and in complex diseases, reports of linkage to specific genetic regions are only rarely replicated in different racial and ethnic groups (8). To more fully test the potential of this gene highlighted by this current research, a follow up study that explores the role of haplotypes on the genetic susceptibility to OA might be desirable.

Table I. Association between rs912428 and the risk of osteoarthritis.

SNP	rs number	Genotype/ Allele	Normal (n=1737)	Osteoarthritis (n=725)	*p*-value	OR* (95% CI)
LRCH1	rs912428	CC	1439 (82.8)	604 (83.3)		1.00
		CT	284 (16.4)	118 (16.3)	0.27	0.94 (0.73–1.22)
		TT	14 (0.8)	3 (0.4)	0.41	0.40 (0.10–1.62)
		C	3162 (91.0)	1326 (91.4)		1
		T	312 (9.0)	124 (8.6)	0.37	0.90 (0.70–1.14)

*ORs and 95% CIs were estimated using multiple logistic regression analyses and adjusted for age, gender and BMI.

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