PP43
THE INHERITANCE OF HAND OSTEOARTHRITIS IN ICELAND

Landspitalin University Hospital, Reykjavik, Iceland. *DeCode Genetics, Reykjavik, Iceland

Objective: To investigate the genetic contribution in a large scale study of hand osteoarthritis (HOA) in Iceland using an extensive genealogy database of the Icelandic population.

Patients and methods: As part of an ongoing study, patients with HOA have been actively registered through nationwide clinical and surgical registers, radiology clinics and ergotherpay centers. At present 2917 HOA patients, comprising 1% of the Icelandic population, have been registered through the above channels. The patient phenotypes used are mild and severe interphalangeal (IP) OA and mild and severe thumb base OA (CMC) based on clinical and radiological findings. Two methods were used to investigate the genetic contribution: (1) The average pairwise kinship coefficient (KC) of the patients, and (2) the relative risk (RR) of BOA for relatives. In each case the results were compared with 1000 control sets of similar composition with regard to number, age and sex, generated from the genealogy database.

Results: The KC for patients was significantly higher than for the control sets and increased with increased severity of both IP and CMC involvement. The RR of HOA for sisters of females in the study was 2.0 (p<0.001) while the RR for spouses was not significantly different from controls. The RR increased with severity. Thus, sisters of patients with severe IP had a RR of 5.0 and severe CMC 6.9.

Conclusions: Patients seeking medical services for HOA are more related to each other than matched controls, supporting the role of a genetic component in the disease. The degree of relationship increases with increasing severity of HOA, both of IP and CMC involvement. The relative risks are consistent with an additive model, i.e. negligible dominance.

PP44
STRUCTURE MODIFYING STUDY OF HYALURONAN (500-730 KDa, HYALGAN®) ON OSTEOARTHRITIS OF THE KNEE

Jubb RW1, Piva S2, Beinat L2, Dacre J3, Gishen P4. For the UK Hyalgan Study Group
1 UHB Trust, Birmingham UK; 2Fidia SpA, Abano Terme, Italy; 3UCL, 4Hammersmith Hospital, London UK

Aim: To assess the effect of hyaluronan on joint space narrowing and additional symptom control in patients with osteoarthritus of the knee.

Methods: The study was a 17-center, UK, randomized, placebo-controlled, double-blind study. Patients were assigned to receive three courses of three intra-articular injections of hyaluronan or saline during the 1-year study. The primary end point was the change in joint space width, measured by digital image analysis, over 1 year using weight-bearing, standardized radiographs. Uncontrolled use of analgesics and anti-inflammatory drugs was permitted. Secondary end points were pain changes monitored by pain scales, Lesquesne Index and the SF-36 with LOCF analysis.

Results: In all, 408 patients were enrolled, 319 completed, and there was complete data for 273. The two groups were comparable at entry with a mean age of 64.2 years and 66% were female. Hyaluronan reduced the progression of joint space narrowing in those patients with a greater joint space at entry; hyaluronan mean joint space loss was 0.13mm (sd = 1.1), control group mean joint space loss was 0.55mm (sd = 1.0) [p= 0.021]. Both groups consumed anti-inflammatory drugs for 67% of the time, and 96% were on either analgesics or anti-inflammatory drugs. Despite this, the hyaluronan group showed significant improvement in pain over the control group at 11, 35, 52 weeks by VAS pain on walking [p=0.017, p=0.008, p=0.047] and categorical pain. At all time points the adjusted mean effect size favored the hyaluronan. The blinded assessor's global assessment gave significant improvements for the hyaluronan group over the placebo at 4, 28 and 38 weeks. Tolerability was good.

Conclusions. Repeat cycles of hyaluronan (mw 500-730KDa) give a statistically significant delay in radiological joint space narrowing of the knee, within one year; in osteoarthritic patients with a larger joint space at baseline. During the study significant pain improvement was seen in the hyaluronan group despite most being on unlimited anti-inflammatory drugs and analgesics. The repeated cycles of three hyaluronan injections were safe.

PP45
COLLAGEN II CONTAINING A CYs SUBSTITUTION FOR ARG-a1519: ABNORMAL INTERACTIONS WITH COLLAGEN IX IN VITRO AND ALTERATIONS IN SKELETAL DEVELOPMENT IN TRANSGENIC MICE EXPRESSING THE MUTATED HUMAN GENE

M. Arita 1, E. Adachi 2, S. A. Jimenez* and A. Fertala*
1Department of Dermatology and Cutaneous Biology, Division of Rheumatology, Department of Medicine, 2Department of Pathology, Anatomy and Cell Biology; Thomas Jefferson University ,Philadelphia, USA; *Department of Molecular Morphology, Graduate School of Medical Sciences, Kitasato University, Sagamihara, Japan

Aim: The aim of this study was to analyze the effect of a single amino acid substitution in collagen II found in the patient with an early onset of osteoarthritis on interaction with collagen IX and on a skeletal development of the transgenic mice expressing the mutated gene.

Methods: In this study, we examined molecular interactions between mutant collagen II with a Cys substitution for Arg-a1 - 519 and collagen IX. In addition, we present an analysis of transgenic mice that express human COL2A1 harboring the same mutation.

Results: Binding of collagen IX to recombinant collagen II variants that lack particular D-periods indicate that the C-terminal region of collagen II contains domains with a high affinity for collagen IX. It was also shown that a Cys substitution for Arg-a1-519 changes electrostatic properties of the mutation site, increases the affinity of mutant collagen II for collagen IX, and possibly influences the specificity of the interaction. Study showed that transgenic mice harboring two copies of the mutated human collagen II gene were smaller than their normal littermates and had a cleft palate. Electron microscopy of cartilage revealed a decrease in density of collagen fibrils.

Conclusions: These results suggest that a Cys substitution for Arg-a1-519 in collagen II does not only alter collagen II fibril formation, but also changes the molecular interactions with collagen IX and causes developmental aberrations in transgenic mice that express the mutated gene.