

# *IL1* Polymorphisms May Predispose Distal Interphalangeal Joints of the Hands to Effects of Mechanical Overload

The increasing impact of osteoarthritis (OA) on individuals, families, and society is considerable. For example, the prevalence of OA has increased in the United States to nearly 27 million, the third most prevalent condition causing work disability<sup>1</sup>. As expected, increasingly sophisticated studies are being undertaken in an effort to better define the etiology and pathogenesis of OA<sup>2-4</sup>. The overall objectives of such studies are to develop novel strategies for prevention and early treatment of OA. Genotype, age, sex, body mass index (BMI) and joint load are the main known risk factors for the development and progression of primary OA<sup>1</sup>.

Many studies have shown familial aggregation for the occurrence and progression of primary OA after adjusting for age, sex, and BMI. For example, findings in the Genetics, Arthrosis, and Progression study from the Netherlands showed that familial aggregation of OA is most striking in the hand and hip, and that changes in joint space narrowing are significantly correlated between siblings<sup>5</sup>. The latter studies, however, do not quantify the relative contributions of genetic and environmental factors in family members with OA. The relative contributions of the latter factors have been determined in twin sets after adjustment for the known risk factors. Comparisons of identical and nonidentical twins show that the contribution of genetic factors to radiographic OA of the hand, hip and knee in women is between 39% and 60%<sup>6</sup>.

Characterization of the genetic variants responsible for the heritability of OA has evolved through several stages. Many of the early studies focused on genes encoding extracellular matrix macromolecules of articular cartilage<sup>7</sup>. These studies were a natural extension of rapid progress being made in characterizing genetic variants that produced various chondrodysplasias and early-onset OA. For example, mutations of genes encoding the protein chains of type II, IX and XI collagens as well as matrilin 3 and cartilage oligomeric matrix protein were identified in patients with various types of spondyloepiphyseal dysplasia, multiple epiphyseal dysplasia, and pseudoachondroplasia<sup>7</sup>. Most of the mutations of these genes, and of other genes producing chondrodysplasias, resulted in a major reduction in the production of a protein or in abnormal structure and function of

a protein. Chondrocyte biology was often seriously impaired because of the retention of unfolded mutant protein within the secretory system<sup>7</sup>. The magnitude of these various metabolic changes indicates that the genetic variants identified in patients with chondrodysplasias and early-onset OA had large gene effect sizes. In contrast, different variants of many of the same genes have been associated with the occurrence and progression of late-onset primary OA<sup>1</sup>. However, the gene variant effect sizes were small and varied considerably between genders, joint groups, and ethnicity<sup>1</sup>. Because of these generally disappointing results, more recent studies have focused on general genome approaches to identifying genes of potential importance in late-onset primary OA<sup>3,4</sup>.

Genome-wide linkage scans of families containing multiple members with primary OA revealed linked regions on 12 chromosomes<sup>1</sup>. However, the contribution of each linked region to the OA phenotype was small and variable between countries, genders, and types of OA. For example, a meta-analysis of genome-wide scans from 893 families containing 3000 affected individuals from Iceland, United Kingdom, and United States showed that OA susceptibility genes in these populations were most likely to reside in regions 7q34-7q36.3, 11p12-11q13.4, 6p21.1-6q15, 2q31.1-2q34, and 15q21.3-15q26.1<sup>8</sup>. Genes that may play a role in OA have been identified using association studies of variants of candidate genes selected from the various linked regions, as well as from more recent large scale genome-wide association studies. The associated genes can be grouped into categories such as inflammation (*IL1*, *ILAR*, *COX2*, *IL6*, *IL10*, *PTGS2*, and *HLA*), cartilage matrix molecules (*ASPN*, *MATN3*, *COL2A1*, *COMP*, and *CILP*), Wnt signaling (*FRZB* and *LRP5*), bone morphogenetic proteins (*BMP2*, *BMP5*, and *GDF5*), proteases or their inhibitors (*ADAM12*, *TNA*, and *AACT*), and modulators of chondrocytes, osteocytes or osteoclasts (*ESR1*, *VDR1*, *CALM1*, *LRCH1* and *OPG*)<sup>1</sup>.

The association of genes involved in inflammation with primary OA is consistent with the observation that low-grade synovitis is frequent in symptomatic OA<sup>9,10</sup>. Synovitis also appears to be important in the progression of

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OA. For example, the progression of knee OA was greater in patients with synovitis at baseline than in patients without synovitis<sup>11</sup>. The synovitis in OA appears to be driven by cytokines, such as interleukin-1 (IL-1), although the synovial levels of proinflammatory cytokines are lower than in rheumatoid arthritis<sup>10</sup>.

Single locus polymorphisms and extended haplotypes within the *IL1* gene cluster have been variably associated with hip, knee, and hand OA<sup>1</sup>. The reasons for the discordant results are unclear but may include differences in *IL1* genotype distributions and differences in environmental modulation of the *IL1* cluster effects on the risk of OA. The article by Solovieva and colleagues in this issue of *The Journal* provides evidence that joint load may be an important modulator of the effects of the *IL1* gene cluster on the risk of OA<sup>12</sup>. In previous studies, they showed that stereotyped repetitive tasks for prolonged periods of time increased the risk of OA in joints of the thumb, index, and middle fingers among Finnish dentists<sup>13</sup>. In another Finnish study, evidence of genetic linkage was found between distal interphalangeal (DIP) OA of the hand and chromosomal region 2q12-q14, which harbors the *IL1* gene cluster<sup>14</sup>. Consequently, Solovieva and colleagues evaluated whether the association of DIP OA with *IL1* gene cluster polymorphisms varies with differential use of the hands. The study groups included Finnish women, between 45 and 63 years of age, who were either dentists with high hand loads or teachers with low hand loads. They found that the minor alleles of 2 *IL1β* polymorphisms and 2 *IL1β-IL1RN* extended haplotypes were associated with increased risk of bilateral DIP OA of the hands in middle-aged and well educated Finnish women. This aspect of the study confirmed previously published findings of a significant association between *IL1* gene cluster variants and DIP OA in Finnish women<sup>14</sup>. The risk haplotype identified by Solovieva and colleagues includes alleles that have been shown by others to increase the production of IL-1β, a proinflammatory cytokine, and to decrease the production of IL-1Ra, an antiinflammatory cytokine<sup>15</sup>. Solovieva and colleagues also observed stronger associations between the *IL1* gene cluster polymorphisms and hand OA in the dentists than in the teachers. This aspect of their study provided support for their proposal that IL-1, and particularly IL-1β, may be a key mediator in hand OA associated with joint overload.

The results presented by Solovieva and colleagues indicate the need to include joint loading with other environmental factors in future studies of the genetic and environmental aspects of OA. While the other environmental risk factors — age, gender and BMI — are easily recorded, joint loading is likely to be difficult to quantify in patients. Further work will be needed to develop standardized protocols for recording the type and duration of loading of various joints that occur during various occupational, recreational, and other activities.

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