Purpose: In our studies, consisting of affected sibpairs with OA at multiple joint sites and a random population based cohort of twin families, we focus on identification of loci involved in the inflammatory response.

Methods: A 10 cM genome scan comprising 400 microsatellite markers taken from the Human Linkage Set v2.5 MD10 (Applied Biosystems) was finished in a generalised OA sibpair study (GARP) and in the twin sample (Zaterdag samples) using an ABI3700 (Applied Biosystems). The GARP study consists of 382 probands (aged 40-70 years) and their siblings of Dutch ancestry with predominantly symptomatic familial OA at multiple joint sites of the hand or in two or more of the following joints sites (hand, spine, knee or hip). The Zaterdag sample consists of 139 families comprising 309 subjects which were included in a twin study with no further inclusion criteria.

LPS stimulated cytokine profiles of sibling pairs were available for TNF-alpha, IL-1 beta, IL1 receptor antagonist and IL-10 in both studies.

Results: By use of Merlin-regress and a grid based analysis of the data both studies was performed for the phenotypes indicated. A meta analysis was performed using the output from the initial analysis. Based on LOD scores in the individual studies as well as LOD scores obtained by use of the meta analysis a selection of 5 peaks was made for follow up. These 5 peaks were finemapped by additional microsatellite markers upon which analyses were repeated for the regions finemapped. 2 peaks appeared to be robust upon finemapping, resulting in a maximum LOD score in the unaffected study group of 4.52 for IL-10 in a region in which other cytokines also showed evidence for linkage and a linkage peak resulting from the meta analysis of both studies on chromosome 4 with a LOD score of 1.5.

TagSNPs and possible functional variants for the genetic regions under linkage will be selected by use of online genetic databases, to further elucidate the genetic regions or genes which cause the linkage signals.

Conclusions: Our studies suggest that the studied COL2A1 gene polymorphisms may play a role in the etiology of polyarticular hand OA.