# Gene signatures and biomarkers predict onset of rheumatoid arthritis in at-risk individuals

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The results of two studies presented today at the Annual European Congress of Rheumatology (EULAR 2018) provide insight into molecular changes prior to the onset of arthritis which could inform future novel diagnostics and early therapeutic interventions.

Rheumatoid arthritis (RA) is characterised by joint inflammation leading to destruction of bone and cartilage. Since structural joint damage is irreversible, early recognition and treatment is a key focus in an effort to halt the progression of the disease. There is a phase before any evidence of RA where specific autoantibodies are present in the body. Individuals who have these antibodies are referred to as RA-risk, however only a subset of these will develop active disease in the short term.

"These studies may help us better understand and potentially identify which individuals classified as at-risk will go on to develop RA," said Professor Robert Landewé, Chairperson of the Scientific Programme Committee, EULAR. "This is important because it will contribute to the development of early preventative strategies including potential pharmacological treatment to prevent the onset of disease."

## Study reveals synovial tissue gene signatures associated with development of disease in RA-risk individuals

Samples of synovial tissue were taken from the knee joint of 67 RA-risk individuals who were then followed to see if they went on to develop RA. An explorative genome-wide transcriptional profile study was carried out in 13 individuals to identify gene transcripts with a significant association with arthritis development. These 'gene signatures' were then validated using quantitative real-time PCR† to measure changes in specific genes.

"Our results clearly show molecular changes appearing in the synovial tissue before the onset of arthritis," said Dr. Lisa van Baarsen, Principal Investigator at the Amsterdam Rheumatology and Immunology Center | Academic Medical Center, the Netherlands. "The characterisation of these gene signatures will enable us to better understand the pathophysiology of the pre-clinical phase of the disease and potentially identify novel drug targets for preventive intervention."

An explorative genome-wide transcriptional profiling study in 13 individuals demonstrated that an increased expression of 3,151 transcripts was associated with a higher risk of arthritis development, and 2,437 transcripts with a lower risk. Further analysis revealed that individuals who developed RA had a higher expression of genes involved in several immune response-related pathways (e.g. T-cell and B-cell receptor pathways, cytokine and chemokine signalling and antigen processing and presentation) and lower expression of genes involved in extracellular matrix receptor interaction, Wnt-mediated signal transduction and lipid metabolism.

Investigators chose 27 differentially expressed genes for validation in the whole study cohort using quantitative real-time PCR. This analysis classified the RA-risk individuals into two groups, where most individuals who developed RA were grouped together ($p=0.03$).

Immunohistochemistry analyses ($n=54$) of the samples taken at inclusion

showed that most individuals already had an abundant expression of chemokine CXCL12 and its receptor CXCR4 which are known to accumulate in the synovium of rheumatoid arthritis patients. They also showed that RA-risk individuals that developed arthritis were more likely to show a positive gp38 staining and lower lipid staining.

## BCR clones predict imminent onset of rheumatoid arthritis in at-risk patients

Another cohort study in 129 RA-risk individuals validated recent findings8 that dominant B-cell receptor (BCR) clones in peripheral blood, can accurately predict imminent onset of arthritis in RA-risk individuals.

"Our data support a new biomarker that demonstrates better predictive power compared with other available biomarkers evaluated so far," said Ms. Anne Musters, MD, Amsterdam Rheumatology and Immunology Center | Academic Medical Center, the Netherlands. "We think that peripheral BCR clones can be used to identify RA-risk individuals that will go on to develop arthritis, which will support the evaluation of early interventions to prevent the onset of disease."

Results of the study showed that the number of dominant BCR clones was significantly increased in RA-risk individuals who developed arthritis within three years (p

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