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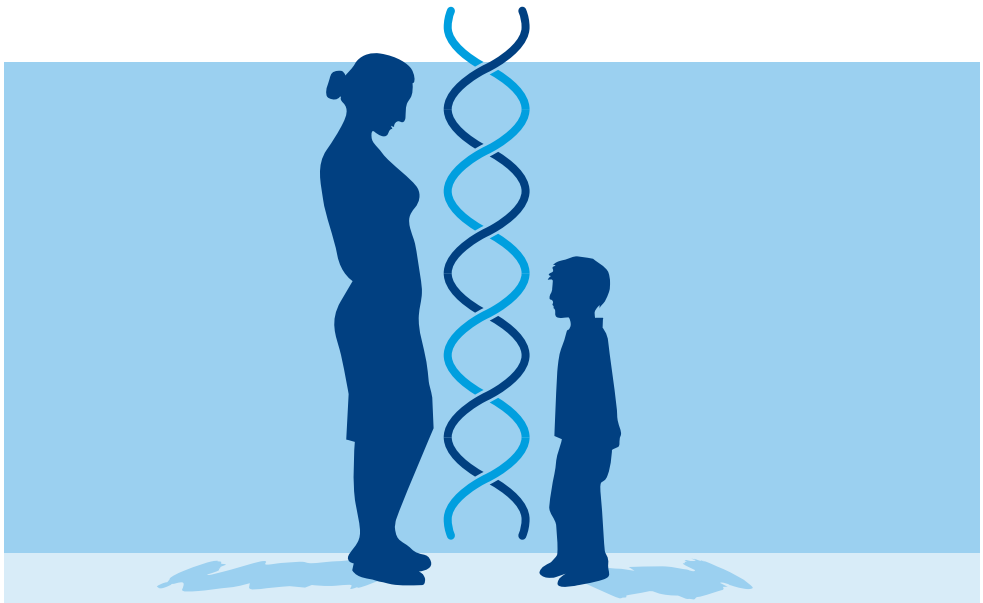

GENETICS

# Subtype of JIA is genetically similar to adult RA

Rheumatoid factor (RF)-positive polyarticular juvenile idiopathic arthritis (JIA) phenotypically resembles adult rheumatoid arthritis (RA) but, to date, investigations into the genetic factors underlying this rare form of JIA have been limited, primarily by a lack of sufficiently sized cohorts. The multinational JIA Consortium for Immunochip (JACI) was formed to overcome this limitation, and has now published a study revealing that RF-positive polyarticular JIA is genetically more similar to adult RA than to the two most common types of JIA, oligoarticular JIA and RF-negative polyarticular JIA.

Previous genetic studies of RF-positive polyarticular JIA were performed in small cohorts and focused on a few candidate genes. To more fully understand the genetics of RF-positive polyarticular JIA in comparison with other forms of JIA and adult RA, JACI used an Immunochip array to genotype a total of 340 individuals with RF-positive polyarticular JIA and 14,412 controls from populations in the USA, UK, Germany, Norway and Canada.

> “The findings of the [JIA Consortium for Immunochip] study are consistent with clinical observations”

Using a logistic regression model, the investigators discovered several single nucleotide polymorphisms (SNPs) that were associated with RF-positive polyarticular JIA. Unsurprisingly, the strongest association was with a SNP in the HLA region, rs3129769 ($P = 5.51 \times 10^{-31}$). Notably, this variant is in strong linkage disequilibrium with an HLA SNP associated with adult RA (rs660895). By contrast, no association was found with the HLA SNP most strongly associated with oligoarticular JIA and RF-negative polyarticular JIA (rs7775055).

Six of 27 non-HLA SNPs associated with risk of oligoarticular or RF-negative polyarticular JIA and 19 of 44 non-HLA SNPs associated with risk of RA also showed evidence of an association with RF-positive polyarticular JIA ($P < 0.05$); the difference between the two proportions was not statistically significant ($P = 0.0676$).

The investigators also found that a weighted genetic risk score (wGRS) generated using RA-associated SNPs better predicted RF-positive polyarticular JIA cases than did a wGRS generated using JIA-associated SNPs (area under the curve (AUC) = 0.71 versus AUC = 0.58; $P = 8.26 \times 10^{-33}$). Notably, the genetic profile of RF-positive polyarticular JIA seemed to be more similar to early-onset RA (age at onset 16–29 years) than late-onset RA (age at onset ≥70 years), as the wGRS for RA was similarly effective in predicting cases of RF-positive polyarticular JIA or early-onset RA, but less effective in predicting cases of late-onset RA.

The findings of the JACI study are consistent with clinical observations and support the view that RF-positive polyarticular JIA is a childhood-onset presentation of seropositive RA. “Our research confirms that young children with RF-positive JIA are genetically similar to adults with RA,” reports corresponding author Sampath Prahalad. “This provides a rationale for translating therapies of successful pharmacological agents from adult RA to RF-positive polyarticular JIA and vice versa.”

“Although our multinational cohort is the largest of its kind, it is still very modest in terms of genetic studies,” cautions Prahalad. “We plan to continue analysing children with RF-positive polyarticular JIA to replicate and extend these findings. We also plan to further investigate the factors that lead to the development of disease in these children at a young age.”

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