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GENETICS

Beyond susceptibility—predictors of prognosis and response in RA

The *HLA-DRB1* locus has long been associated with susceptibility to RA (rheumatoid athritis), a link based on variants in the shared epitope at amino acid positions 71–74. New results published by Viatte *et al*. show that the susceptibility variants in *HLA-DRB1* are also associated with radiological severity of disease, mortality and response to anti-TNF agents in several large UK cohorts.

Interestingly, the strongest associations were outside the shared epitope. "Valine at position 11 (Val11) of HLA-DRB1 represents the strongest genetic predictor of radiographic damage (OR 1.75, 95% CI 1.51–2.05; $P = 4.6E{-}13$)," asserts Sebastien Viatte, first author of the study. Longitudinal modelling (which enhances statistical power by integrating multiple records per patient over time) showed that after 5 years, 150 of 315 (48%) Val11 noncarriers, 130 of 213 (61%) heterozygote carriers and 43 of 58 (74%) homozygote carriers had bone erosions. Val11 was also linked with increased all-cause mortality in patients

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with inflammatory polyarthritis (HR 1.16, 95% CI 1.03–1.31, $P = 0.01$; annual mortality 1.9% in noncarriers versus 2.5% in carriers) and with good responses to TNF inhibitors (OR 1.14, 95% CI 1.01–1.30, $P = 0.04$). 439 of 561 (78%) noncarriers versus 698 of 866 (81%) heterozygote carriers and 277 of 322 (86%) homozygote carriers had a moderate or good EULAR response. "Moreover, we found a correlation between genetic risk factors for RA susceptibility, severity and mortality," Viatte adds.

"Our ultimate goal is to assess the usefulness of stratifying patients at diagnosis into different risk and treatment categories, based on a score integrating demographic, clinical, laboratory and genetic data," explains Viatte. "Early and aggressive treatment might not be the best option for every patient, while others might benefit from more-prompt initiation of first-line treatment with biologics," he continues.

Of course, the associations with mortality and treatment response still await replication in independent cohorts. "If the effect on anti-TNF treatment response is confirmed," Viatte notes, "we will test as to whether this effect is restricted to only one class of treatment, or shared with other biologics or non-biologic treatment regimes."

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Original article Viatte, S. *et al.* Association of *HLA-DRB1* haplotypes with rheumatoid arthritis severity, mortality, and treatment response. *JAMA* doi:10.1001/jama.2015.3435