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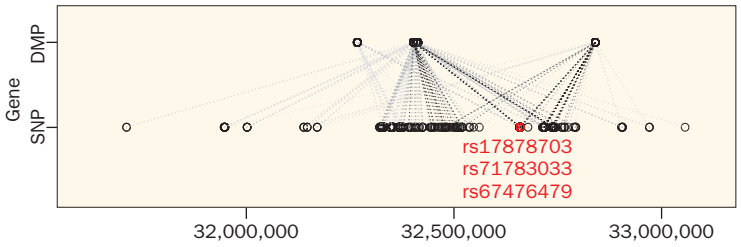
RHEUMATOID ARTHRITIS

Cell sorting to sort cause from effect in RA epigenetics

"A new mechanism is described whereby epigenetic changes—methylation—may indicate the effects of genetic variability on disease phenotype," says Tomas Ekström, describing a new paper published in *Nature Biotechnology* in which rheumatoid arthritis (RA) was used as a model for a new approach in epigenetic analysis. Importantly, the method adjusts for cell-type heterogeneity. Using it (and with the assumption that blood is the key tissue in RA pathogenesis) the investigators identified ten positions that are potentially differentially-methylated in patients with RA.

With a background in cancer epigenetics, Ekström teamed up with his Karolinska Institutet colleague Lars Klareskog, who has longstanding interest in enviromental influences on RA pathogenesis. In a cross-Atlantic collaboration with Andy Feinberg, of Johns Hopkins University, and Martin Ayree at Massachusetts General Hospital, both of whom are developing new ways to study the relationships between genotype, epigenetics and phenotype, these investigators and colleagues analysed samples from 354 patients with anti-citrullinated protein antibody-positive RA and 337 control individuals.



Association between candidate genetic risk-mediating differentially-methylated positions and genotype within a section of the MHC. In red are 3 previously identified rheumatoid arthritis-associated genetic variants. Reproduced from Liu, Y. *et al. Nat. Biotech.* doi:10.1038/nbt.2487. © NPG

Methodology used in genotype analyses cannot simply be applied in epigenetic research; DNA methylation patterns differ by cell type, and the cause–effect relationship of disease-associated epigenetic markers is usually unclear. "We applied methods developed by others to address both problems," explains Ekström, "but also, and critically, felt it important to replicate the results in flow-sorted cells."

Soumya Raychaudhuri, an independent expert in genetic influences in RA, concurs with this emphasis; "A real strength of this study was the effort to address the cell-specific nature of these effects, and to address the issue of causal versus correlated methylation states." He notes that nine of the ten key sites identified were within the MHC, which "could represent interesting novel biological phenomena, or might represent residual confounding, given the strength of the genetic associations in that region." The findings, he adds, "should motivate us to identify the critical immune cell-types, sort them from blood of cases and controls, and then test the reproducibility of the epigenetic differences."

Crucial next steps are to amass functional evidence of what these epigenetic changes do, as well as how they relate to environmental influences and genetic variation.

Emma Leah

Original article Liu, Y. *et al.* Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis. *Nat. Biotech.* doi:10.1038/nbt.2487

Further reading Viatte, S. *et al.* Genetics and epigenetics of rheumatoid arthritis. *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2012.237