Supplementary note

Sample collections

United Kingdom (UK)

UK samples were recruited from across the UK, all cases were Caucasian of Northern European descent and fulfilled 1987 American College of Rheumatology (ACR) classification criteria modified for genetic studies. All participants gave informed consent and the study was approved by the North West ethics committee (MRC 99/8/84). Serum RF and ACPA antibody titre were measured using commercially available kits [RF-PAIA Immunoturbidimetric Assay for rheumatoid factor, DiastatTM ACPA Kit (Axis-Shield Diagnostics Limited, UK)]. Patients with titres _40 units/ml and _5 units/ml were defined as positive for RF and ACPA antibodies, respectively

Sweden EIRA

Swedish samples were from the Swedish epidemiological and genetic study of RA (EIRA) described elsewhere [1], controls were matched by date of birth, sex and residential area. All rheumatoid arthritis patients met the ACR 1987 revised criteria for rheumatoid arthritis. Blood samples were collected at 19 rheumatology units across Sweden (mainly middle and south of country). Ethics permit was received and informed consent was registered according to the current Swedish law.

Sweden UMEA

Samples were also selected from the Swedish Umea cohort is an inception cohort of RA patients from the four most northern counties of Sweden, controls are randomly selected, matched for age and sex and ethnicity, from the population based Medical Biobank of Northern Sweden. All patients met ACR 1987 criteria. Detection of Anti-Cyclic citrullinated peptide antibodies was analysed using enzyme-linked immunoassays (Euro-Diagnostica, Malmö, Sweden) according to manufacturer's instructions. Cut-off for positivity was 25 AU/ml. The regional Ethics Committee at the University Hospital of UMEA approved this study and all participants gave their written informed consent.

United States (US)

Cases from the US of were selected from three major datasets; The NARAC cases were largely defined from families with RA affected sibling pairs supplemented with singleton subjects whose siblings did not meet criteria for study entry, US singleton RA subjects and subjects from trio families[2, 3]. A second selected group of ACPA+ patients recruited by Dr Fredrick Wolfe in his practice as well as RA patients enrolled in a published inception cohort and patients followed in the

national database for rheumatic diseases directed by Dr Wolfe [4]. A third cohort of subjects were derived from an inception cohort study SONORA as described previously [5].

Spain

Spanish RA patients were recruited across Spain fulfilling 1987 ACR criteria; the controls were obtained from the Spanish DNA bank and were matched by age and gender. Both patients and controls were white of southern European descent. All participants were recruited after providing informed consent.

The Netherlands

Patients were included from Leiden early arthritis clinic (Leiden-EAC) [6], only patients diagnosed with RA according to 1987 ACR criteria within one year after inclusion in the Leiden-EAC were included in this study. The study was approved by the local ethical committee and all patients gave informed consent. Controls were obtained from blood donors.

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