VALIDATION OF A DISTINCT PSORIATIC ARTHRITIS RISK VARIANT AT IL23R

Ashley Budu-Aggrey1,2, John Bowes3, Sabine Loehr3, Steffen Uebe3, Maria I. Zervou5, Philip Hellis7, Anthony W. Ryan6, David Kane7, Eleanor Korendowych8, Emiliano Giardina9, Jonathan Packham10, Ross McManus6, Oliver FitzGerald11, Neil McHugh8, Frank Behrens12, Harald Burkhardt12, Ulrike Huffmeier9, Pauline Ho1,13, Javier Martin14, Santos Castaneda15, George Goulielmos4, Andre Reis3 and Anne Barton1,2,13

1Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, 2NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust and University of Manchester, Manchester Academy of Health Sciences, UK, 3Human Genetics, Friedrich-Alexander-Universitaet Erlangen-Nuernberg, Erlangen, Germany, 4Molecular Medicine and Human Genetics and Internal Medicine, University of Crete, Heraklion, Greece, 5NIHR-Leeds Musculoskeletal Biomedical Research Unit Leeds Institute of Rheumatic and Musculoskeletal Medicine University of Leeds, UK, 6Clinical Medicine, Molecular Medicine, Adelaide, Meath Hospital and Trinity College Dublin, Ireland, 7Royal National Hospital for Rheumatic Diseases and Pharmacy and Pharmacology, University of Bath, UK, 8Biomedicine and Prevention, University of Rome ‘Tor Vergata’ and Laboratory of Molecular Genetics UILDM, Fondazione Santa Lucia IRCCS, Rome, Italy, 9Rheumatology, Haywood Hospital, Health Services Research Unit, Science and Technology in Medicine, Keele University, 10Rheumatology, St. Vincent’s University Hospital, UCD School of Medicine and Medical Sciences and Conway Institute of Biomedical and Biomedical Research, University College Dublin, Ireland, 11Rheumatology and Fraunhofer IME-Project-Group Translational Medicine and Pharmacology, Goethe University, Frankfurt, Germany, 12The Kellogg Centre for Rheumatology, Central Manchester Foundation Trust, NIHR Manchester Biomedical Research Centre, Manchester UK, 13Parasitologia y Biomedicina Lopez-Neyra, CSIC, Granada, Spain and 14Rheumatology, Hospital La Princesa, IIS-Princesa, Madrid, Spain

Background: PsA is an inflammatory arthritis that is associated with psoriasis and is estimated to present in ~14% of psoriasis patients in the UK. PsA is a complex disease that is influenced by both genetic and environmental factors. Genetic studies have aided the discovery of PsA risk loci, the majority of which also confer a risk for psoriasis. We have recently reported evidence of specific loci that confer a risk for PsA and not psoriasis, including a variant at IL23R that was also found to be independent of a psoriasis variant reported at the same locus.

Methods: In this study we attempted to identify additional PsA-specific risk variants by genotyping 32 single nucleotide polymorphisms (SNPs), which included those found to have nominal significance in our recent Immunochip study (P < 10^-9). These were analysed in 914 PsA cases and 6945 controls from the UK, Crete, Spain and Germany, which were independent from those genotyped as part of the Immunochip study. Genotyping was performed using the Life Technologies QuantStudio genotyping platform and association testing was carried out using PLINK. Genotype data were also available from the psoriasis WTCCC2 study (excluding known PsA, n = 1784). Multinomial logistic regression was carried out in Stata to compare effect estimates in PsA and psoriasis using PsA Immunochip data (n = 1962). A direct comparison of PsA and psoriasis genotypes was also performed.

Results: We found a significant association for the SNP rs12044149 mapping to IL23R (P = 4.03 × 10^-6). A weak association was found with the psoriasis risk variant rs9986642, which has been reported at the same
locus ($P = 0.04$). The association with rs12044149 remained significant when conditioning upon rs9988642 ($P_{\text{cond}} = 4.86 \times 10^{-3}$). Likewise, rs9988642 remained significantly associated with psoriasis when conditioning upon rs12044149 ($P = 1.0 \times 10^{-3}$ vs $P_{\text{cond}} 1.63 \times 10^{-3}$), indicating that they represent independent effects. Effect estimates for rs12044149 were significantly different between PsA and psoriasis ($P = 2.0 \times 10^{-3}$). When genotypes for rs12044149 were directly compared between PsA and psoriasis, the risk allele was significantly increased in PsA ($P = 1.91 \times 10^{-3}$; odds ratio = 1.2).

**Conclusion:** For the first time we have been able to successfully validate a PsA-specific (associated with PsA but not psoriasis) risk variant at the IL23R locus in an independent cohort, confirming rs12044149 to be independent of rs9988642 ($r^2 = 0.01$). This now gives a total of four PsA-specific associations that have been identified. Such variants could potentially provide markers to identify psoriasis patients who are prone to developing PsA. IL-23 is a target for the psoriasis drug ustekinumab, which has also shown efficacy in PsA during clinical trials. Therefore it would be interesting to explore the role of disease-specific risk variants in treatment response.

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