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Genetically proxied IL-1 receptor antagonism and risk of polymyalgia rheumatica

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Key message: IL-1 receptor antagonism is associated with reduced risk of polymyalgia rheumatica

Dear Editor,

Polymyalgia rheumatica (PMR) is a symmetrical, glucocorticoid-sensitive inflammatory disorder of extracapsular structures [1]. PMR affects chronically mechanically-stressed fibrocartilage-containing structures such as sternoclavicular joints, pubic symphysis, entheses and interspinous ligaments. IL-1 generated by activation of the NLRP3 inflammasome, from autoinflammatory stimuli such as calcium pyrophosphate crystals that are commonly found in fibrocartilage, might then be amplified locally by IL-6 and spread contralaterally [2]. Compared to glucocorticoids, disadvantages of IL-6 inhibition as a therapeutic strategy for PMR include slow onset of benefit and long half-life for washout in the case of adverse effects. An alternative strategy for PMR relapse prevention might be to inhibit IL-1.

The potential efficacy of pharmacologically targeting a protein can be investigated by leveraging naturally occurring genetic variation that mimics its perturbation. Drugs supported by human genetic data are over twice as likely to receive regulatory approval and this approach correctly predicted clinical trial success of IL-6 receptor inhibition for PMR [3]. We examined the potential effect of genetically proxied IL-1 receptor antagonist (IL-1Ra) on risk of PMR.

IL-1Ra is a naturally occurring competitive inhibitor of IL-1; anakinra - a recombinant IL-1Ra - is approved for another immune-mediated inflammatory disease, rheumatoid arthritis (RA). We proxied IL-1Ra using two complementary approaches. First, we selected weakly correlated (r^2<0.1 using the 1000 genomes project as reference panel) single-nucleotide polymorphisms (SNPs) within or ± 50kilobases from *IL1RN* that were associated with circulating CRP (natural-log transformed mg/L) at genome-wide significance ($p<5x10^{-8}$) from a genome-wide association study (GWAS) of 204,402 individuals of European ancestry [4]. We selected CRP as the biomarker because IL-1 inhibition reduces CRP concentrations [5]. Second, we applied the same instrument selection process to genetic data for circulating IL-1Ra (i.e., cis-protein quantitative trait loci), from a GWAS meta-analysis of 55,792 individuals of European ancestry [6]. We evaluated instrument strength by calculating F-statistics estimated using $beta^2$/$standard\ error^2$ (F >10 suggest low likelihood of weak instrument bias). Genetic data for PMR were obtained from a GWAS of 4,285 cases and 17,140 controls of self-reported White British ancestry in the UK Biobank [3]. We included rheumatoid arthritis (22,350 cases; 74,823 controls [7]) as a positive control outcome to examine instrument validity. We used the inverse-variance weighted method and accounted for weak linkage disequilibrium. Pair-wise conditional colocalization was performed to investigate potential genetic confounding through linkage disequilibrium. We used a curated genotype-phenotype database PhenoScanner to search for associations between variants used to instrument each drug target and

other traits that may represent pleiotropic pathways. Further information on methodological approaches employed are provided in supplementary materials.

Using CRP as the biomarker, three SNPs were selected to proxy IL-1Ra signalling (median F statistic 69) (supplementary Table S1). Genetically proxied IL-1Ra was associated with a reduced risk of PMR (OR 0.40 per log(mg/L) reduction in CRP; 95%CI 0.16-0.97; p=0.04). Results were concordant when using nine variants (median F statistic 81) to instrument circulating IL-1Ra (OR 0.79 per standard deviation increase in IL-1Ra; 95%CI 0.63-1.00; p=0.051). Results across both analyses were not driven by any single SNP (supplementary Figure S1). Colocalization analysis was underpowered but showed low posterior probabilities of both genetic confounding and the presence of causal variants in *IL1RN* (supplementary Figure S2 and Table S2). IL-1Ra was associated with reduced risk of RA (Figure 1). We found no evidence that the genetic instruments used to proxy IL-1Ra were associated with expression of other cytokines that may represent pleiotropic pathways.

This study provides genetic evidence that IL-1Ra is causally associated with reduced risk of PMR, which was consistent across two approaches to proxy the drug target. These findings are consistent with a small candidate gene study (n=139) that suggested a potential role for *IL1RN* in PMR susceptibility [8], and supports the role of IL-1 signalling in PMR pathogenesis. Long-term glucocorticoids remain the cornerstone of PMR treatment, which can lead to significant additional morbidity in typically elderly and often comorbid individuals. Steroid-sparing treatment options are limited. These results support IL-1Ra, such as anakinra, as a potential therapeutic candidate. However, MR estimates may not be directly comparable to pharmacological inhibition because life-long drug target perturbation proxied by germline genetic variants differs from shorter duration of clinical interventions. Our findings relate to risk rather than treatment of PMR, although these are likely to coincide as is the case for IL-6 inhibition and PMR. Clinical studies are needed to test IL-1 inhibition as a therapeutic strategy for PMR.

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Data availability statement: UK Biobank data are available to all bona fide researchers for use in health-related research that is in the public interest. The application procedure is described at www.ukbiobank.ac.uk.

Patient consent for publication: Participant consent was obtained by the UK Biobank study.

Ethics approval: Ethical approval was obtained by the UK Biobank study. The current analysis was performed under application number 72723.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Conflicts of Interest: SLM: Consultancy on behalf of institution to: Roche/Chugai, Sanofi, AbbVie, AstraZeneca. Investigator on industry-sponsored clinical trials for: GSK, Sanofi, Sparrow. Attendance at EULAR2019 supported by Roche. Virtual attendance at ACR21 supported by Pfizer. Co-applicant on research grants from Vifor and Roche. Patron of the charity PMRGCAuk. The other authors declare no conflicts of interest.

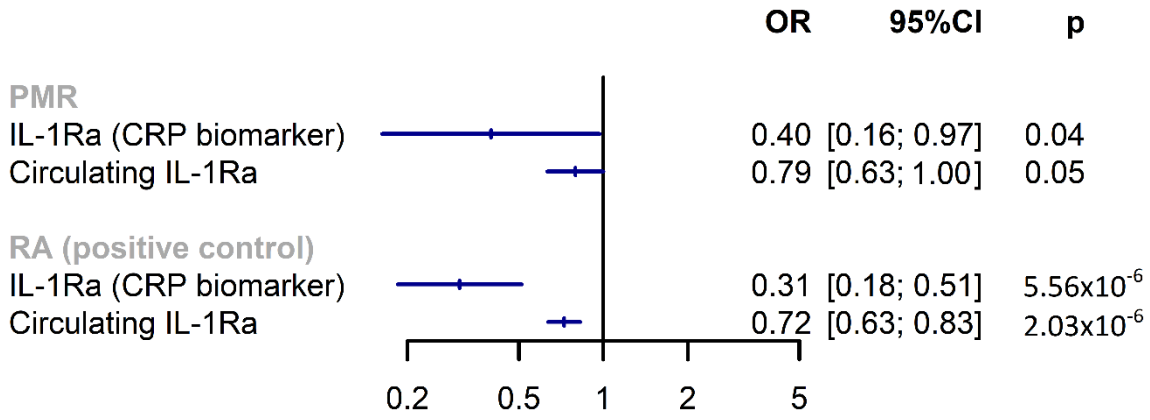

Figure 1. Genetically proxied IL-1 receptor antagonism using CRP as downstream biomarker and circulating IL-1Ra levels. Estimates are scaled to per unit reduction in natural-log-transformed mg/L and per standard deviation increase in circulating IL-1Ra level.

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