Supplementary Table I.

Checklist for completeness of reprting genetic association studies
(adapted from Little *et al*. PLoS Med. 2009;6(2):e22. PMID: 19192942)

Title and Abstract

1 (a) Indicate the study's design with a commonly used term in the title or the abstract.
The abstract contains a description of the study design, *e.g*. a retrospective case-control analysis.
1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found.
The modified abstract summarises what was done and what was found.

Introduction

2 Explain the scientific background and rationale for the investigation being reported.
Scientific background and rational are explained in the final sentence of the last paragraph of the introduction: "Here, we analysed the contribution of the three candidate genetic markers to clinical and radiographic response to ADA + MTX therapy or MTX monotherapy in the OPTIMA study, taking advantage of a so far unbeknown rather large patient cohort of 894 individuals with homogenous, clinically well-defined, early RA undergoing randomised, standardised treatment with controlled and pre-defined clinical outcome measures."
3 State specific objectives, including any pre-specified hypotheses.
Specific objectives are stated in the last paragraph of the introduction.
State if the study is the first report of a genetic association, a replication effort, or both.
A statement that the study is a replication of previously reported analyses, however, in a so far unbeknown sample size and homogeneity of the study population with regard to disease duration, disease activity, comorbidity, comedication, treatment and clinical assessment, is included in the last paragraph of the introduction.

Methods

4 Present key elements of study design early in the paper.
The key elements of the study design are presented in the abstract, the introduction and the methods section.
5 Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Information regarding setting, locations and relevant dates, including periods of recruitment, exposure, follow-up, and data collection are given in detail in the method section and the clinical manuscript of the OPTIMA trial which is referenced early in the current report.
6 (a) Case-control study – Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls.
The report is on all patients from within the OPTIMA clinical trial who gave written informed consent for genetic analysis. This is stated in the introductory paragraph of the result section.
6 (b) Case-control study – For matched studies, give matching criteria and the number of controls per case.
The analysis was performed on the data from the entire study population from within the randomised controlled clinical trial, OPTIMA. Both, cases and controls, are derived from the same study cohort characterised according to the inclusion criteria of the RCT and randomised for receiving methotrexate or adalimumab + methotrexate treatment.
Give information on the criteria and methods for selection of subsets of participants from a larger study, when relevant.
No selection of subsets was performed and only those patients who did not give written informed consent for genetic analysis were excluded from the analysis reported here.
7 (a) Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
The patient population was treated in an RCT with defined inclusion and exclusion criteria, defined treatment arms and pre-defined clinical assessment. These individual criteria have been published in the manuscript reporting the clinical data of the OPTIMA trial, which is referenced throughout and early in the current manuscript.
7 (b) Clearly define genetic exposures (genetic variants) using a widely-used nomenclature system. Identify variables likely to be associated with population stratification (confounding by ethnic origin).
The genetic variants are introduced in the introduction.
8 (a) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.
The methodology to assess the variables of interest is given in detail in the methods.
8 (b) Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms (including the allele calling algorithm used, and its version), error rates and call rates. State the laboratory/centre where genotyping was done. Describe comparability of laboratory methods if there is more than one group. Specify whether genotypes were assigned using all of the data from the study simultaneously or in smaller batches.
Detailed information with regard to assessment of the genetic data is given in the method section of the manuscript.
9 (a) Describe any efforts to address potential sources of bias.
The data are derived from an RCT. Genetic data were not known to the clinical study team and individual clinical data were not known to the researchers performing the genetic analysis.
9 (b) For quantitative outcome variables, specify if any investigation of potential bias resulting from pharmacotherapy was undertaken. If relevant, describe the nature and magnitude of the potential bias, and explain what approach was used to deal with this.
See response to 9 (a)
10 Explain how the study size was arrived at.
The study size was determined for the RCT based on the hypotheses to be tested in the RCT.
11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.
There were not quantitative variables in the study and no groupings were performed.
If applicable, describe how effects of treatment were dealt with.
Effect of treatment as a function of a genetic value was the primary outcome parameter in the genetic study reported here.
12 (a) Describe all statistical methods, including those used to control for confounding.
All statistical methods are described in the method section. To reduce the potential input of confounding, Cochran-Mantel-Haenszel tests were applied throughout the analysis.
State software version used and options (or settings) chosen.
All statistical analyses were performed with standard software (*e.g*. SPSS) in the most currently available versions.
12 (b) Describe any methods used to examine subgroups and interactions.
There were no subgroups or interactions examined.
12 (c) Explain how missing data were addressed.
There were no missing genetic data. For clinical analysis, non-responder imputation was used with missing responses considered as non-responders. This also was the basis for the definition of responders and non-responders in the analyses of the genetic association reported here.
12 (d) Case-control study – If applicable, explain how matching of cases and controls was addressed.
See above, matching was performed randomly from patients within the same clinically well defined cohort of patients with early RA by randomisation for the treatment arms within the clinical trial.
12 (e) Describe any sensitivity analyses.
All statistical methods are described in the methods section.
12 (f) State whether Hardy-Weinberg equilibrium was considered and, if so, how.
Not applicable to the analysis reported in the current manuscript.
12 (g) Describe any methods used for inferring genotypes or haplotypes.
Not applicable to the analysis reported in the current manuscript.
12 (h) Describe any methods used to assess or address population stratification.
Not applicable to the analysis reported in the current manuscript.
12 (i) Describe any methods used to address multiple comparisons or to control risk of false positive findings.
Bonferroni corrections were performed to address multiple comparisons and the risk of false positive findings.
12 (j) Describe any methods used to address and correct for relatedness among subjects.
There were no actions taken to control for relatedness among subjects. However, the study enrolled 1032 patients in multiple centers globally so that contribution of potentially related subjects was considered to have a minor and statistically neglectable input on the overall results.

Results

13 (a) Report the numbers of individuals at each stage of the study – *e.g.* numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.
All numbers are given in the results.
13 (b) Give reasons for non-participation at each stage.
The only single reason for non-participation of an individual from the clinical trial in the genetic analysis is missing written informed-consent for genetic analysis.
13 (c) Consider use of a flow diagram.
As there is little information above the statement given as response to 13 (b), we opted for not using a flow diagram.
Report numbers of individuals in whom genotyping was attempted and numbers of individuals in whom genotyping was successful.
These numbers are given in the manuscript.
14 (a) Give characteristics of study participants (*e.g.* demographic, clinical, social) and information on exposures and potential confounders.
All this information is given in the text, the tables and the clinical manuscript referenced early and throughout the study.
14 (b) Indicate the number of participants with missing data for each variable of interest.
Beyond missing data on genetic analyses due to missing informed consent, no additional dropouts from the study population occurred for any of the individual variables of interest.
15 Case-control study – Report numbers in each exposure category, or summary measures of exposure.
All these data are given in the manuscript.
Report numbers in each genotype category.
These numbers are indicated in the manuscript.
16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence intervals). Make clear which confounders were adjusted for and why they were included.
As the genetic association to treatment response was analysed in two cohorts randomly assigned from the same population to one of the two treatment arms, the risk of confounding is rather low. Also, Cochran-Mantel-Haenszel tests were applied to reduce the risk of unknown confounding parameters.
16 (b) Report category boundaries when continuous variables were categorised.
The boundaries for the definition of the clinical efficacy of treatment are defined by validated clinical disease activity scores as stated in the manuscript.
16 (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
Not relevant to the analysis reported in the current manuscript.
16 (d) Report results of any adjustments for multiple comparisons.
Bonferroni corrections were applied for all statistical analyses to control for multiple comparisons and potentially false positive results. Only the corrected data are given in the manuscript.
17 (a) Report other analyses done – *e.g.* analyses of subgroups and interactions, and sensitivity analyses.
No other analyses were performed, subgroups were not created and interactions were not assessed.
17 (b) If numerous genetic exposures (genetic variants) were examined, summarise results from all analyses undertaken.
Not applicable to the analysis reported in the current manuscript.
17 (c) If detailed results are available elsewhere, state how they can be accessed.
Not applicable to the analysis reported in the current manuscript.

Discussion

(18) Summarise key results with reference to study objectives.
The key results are summarised and discussed in the text with reference to the study objectives.
(19) Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.
Limitations of the study are discussed at the end of the discussion: Limitations of this genetic analysis include relatively modest sample size, lack of statistical power, and lack of primary and confirmatory groups. Although a significant association between HLA-DRB1 SE copy number and treatment response was demonstrated in the current analysis, given the prevalence of the SE in RA, some association with treatment response, lack of response, or toxicity is not unexpected. In this analysis, statistically significant association between I50V IL4R variant and radiographic progression was detected. Yet, relatively short follow-up time and low overall radiographic progression may have masked the stronger correlation observed in previous studies. Similar frequencies of AEs were observed across different genetic variants except association of I50V IL4R variant with nausea, upper respiratory tract infection, and nasopharyngitis in the ADA + MTX group. In the OPTIMA study, frequencies of AEs were comparable between treatment arms through week 26 [2]. However, a greater number of serious infections and deaths occurred in the ADA + MTX group, possibly due to increased age and comorbidities.
(20) Discuss the generalisability (external validity) of the study results.
See comment to item (19).

Other information

(21) Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.
Funding of the study is indicated in the acknowledgement paragraph of the manuscript.

Supplementary Table II. Allele distribution by treatment arm at baseline.*

Genotype	ADA + MTX (n=443)	PBO + MTX (n=451)	Total (n=894)	*p*-value†
HLA-DRB1 SE				0.27
0 copies	145 (33)	167 (37)	312 (35)	
1 copy‡	216 (49)	215 (48)	431 (48)	
2 copies‡	82 (19)	69 (15)	151 (17)	
I50V IL4R				0.38
AA (I50/I50)	145 (33)	130 (29)	275 (31)	
AG (I50/V50)‡	210 (47)	233 (52)	443 (50)	
GG (V50/V50)‡	88 (20)	88 (20)	176 (20)	
I232T Fc_RIIb				0.03
TT (I232/I232)	360 (81)	333 (74)	693 (78)	
TC (I232/T232)‡	77 (17)	111 (25)	188 (21)	
CC (T232/T232)‡	6 (1)	7 (2)	13 (1)	

*All values are n (%) unless otherwise noted. †*p*-values from chi-square or Fisher's exact test.
‡The risk alleles are "shared epitope", "G", and "C" for HLA-DRB1, IL4R and FcgRIIb, respectively
ADA: adalimumab; Fc_RIIb: Fc gamma receptor IIb; HLA-DRB1 SE: human leukocyte antigen DRB1 SE; IL4R: interleukin-4 receptor; MTX: methotrexate; PBO: placebo; SE: shared epitope.

Supplementary Table III. Baseline race distribution in ADA+MTX and PBO+MTX groups.

Genotype	ADA + MTX (n=443)	PBO + MTX (n=451)	Total (n=894)	*p*-value†
HLA-DRB1 SE				
0 copies	n=145	n=167	n=312	0.867
White	120 (83)	137 (82)	257 (82)	
Black	12 (8)	14 (8)	26 (8)	
Asian	4 (3)	7 (4)	11 (4)	
Other	9 (6)	9 (5)	18 (6)	
1 copy	n=216	n=215	n=431	0.596
White	198 (92)	200 (93)	398 (92)	
Black	4 (2)	7 (3)	11 (3)	
Asian	8 (4)	2 (1)	10 (2)	
Other	6 (3)	6 (3)	12 (3)	
2 copies	n=82	n=69	n=151	0.037
White	77 (94)	69 (100)	146 (97)	
Black	3 (4)	0	3 (2)	
Asian	0	0	0	
Other	2 (2)	0	2 (1)	
I50V IL4R				
AA (I50/I50)	n=145	n=130	n=275	0.731
White	131 (90)	119 (92)	250 (91)	
Black	7 (5)	3 (2)	10 (4)	
Asian	5 (3)	2 (2)	7 (3)	
Other	2 (1)	6 (5)	8 (3)	
AG (I50/V50)	n=210	n=233	n=443	0.703
White	186 (89)	209 (90)	395 (89)	
Black	8 (4)	13 (6)	21 (5)	
Asian	5 (2)	4 (2)	9 (2)	
Other	11 (5)	7 (3)	18 (4)	
GG (V50/V50)	n=88	n=88	n=176	1.000
White	78 (89)	78 (89)	156 (89)	
Black	4 (5)	5 (6)	9 (5)	
Asian	2 (2)	3 (3)	5 (3)	
Other	4 (5)	2 (2)	6 (3)	
I232T Fc_RIIb				
TT(I232/I232)	n=360	n=333	n=693	0.956
White	328 (91)	303 (91)	631 (91)	
Black	10 (3)	10 (3)	20 (3)	
Asian	9 (3)	7 (2)	16 (2)	
Other	13 (4)	13 (4)	26 (4)	
TC (I232/T232)	n=77	n=111	n=188	0.292
White	63 (82)	97 (87)	160 (85)	
Black	9 (12)	10 (9)	19 (10)	
Asian	3 (4)	2 (2)	5 (3)	
Other	2 (3)	2 (2)	4 (2)	
CC (T232/T232)	n=6	n=7	n=13	0.416
White	4 (67)	6 (86)	10 (77)	
Black	0	1 (14)	1 (8)	
Asian	0	0	0	
Other	2 (33)	0	2 (15)	

*All values are n (%) unless otherwise noted. †*p*-values from chi-square test.
ADA: adalimumab; FcγRIIb: Fc gamma receptor IIb; HLA-DRB1 SE: human leukocyte antigen DRB1 SE; IL4R: interleukin-4 receptor; MTX: methotrexate; PBO: placebo; SE: shared epitope.