

## EXTENDED REPORT

# Estimation of heritability of different outcomes for genetic studies of TNFi response in patients with rheumatoid arthritis

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## ABSTRACT

**Objectives** Pharmacogenetic studies of tumour necrosis factor inhibitors (TNFi) response in patients with rheumatoid arthritis (RA) have largely relied on the changes in complex disease scores, such as disease activity score 28 (DAS28), as a measure of treatment response. It is expected that genetic architecture of such complex score is heterogeneous and not very suitable for pharmacogenetic studies. We aimed to select the most optimal phenotype for TNFi response using heritability estimates.

**Methods** Using two linear mixed-modelling approaches (Bayz and GCTA), we estimated heritability, together with genomic and environmental correlations for the TNFi drug-response phenotype  $\Delta$ DAS28 and its separate components:  $\Delta$  swollen joint count (SJC),  $\Delta$  tender joint count (TJC),  $\Delta$  erythrocyte sedimentation rate (ESR) and  $\Delta$  visual-analogue scale of general health (VAS-GH). For this, we used genome-wide single nucleotide polymorphism (SNP) data from 878 TNFi-treated Dutch patients with RA. Furthermore, a multivariate genome-wide association study (GWAS) approach was implemented, analysing separate DAS28 components simultaneously.

**Results** The highest heritability estimates were found for  $\Delta$ SJC ( $h^2_{\text{gbayz}}=0.76$  and  $h^2_{\text{gGCTA}}=0.87$ ) and  $\Delta$ TJC ( $h^2_{\text{gbayz}}=0.62$  and  $h^2_{\text{gGCTA}}=0.82$ ); lower heritability was found for  $\Delta$ DAS28 ( $h^2_{\text{gbayz}}=0.59$  and  $h^2_{\text{gGCTA}}=0.71$ ) while estimates for  $\Delta$ ESR and  $\Delta$ VASGH were near or equal to zero. The highest genomic correlations were observed for  $\Delta$ SJC and  $\Delta$ TJC (0.49), and the highest environmental correlation was seen between  $\Delta$ TJC and  $\Delta$ VASGH (0.62). The multivariate GWAS did not generate excess of low p values as compared with a univariate analysis of  $\Delta$ DAS28.

**Conclusions** Our results indicate that multiple SNPs together explain a substantial portion of the variation in change in joint counts in TNFi-treated patients with RA. In conclusion, of the outcomes studied, the joint counts are most suitable for TNFi pharmacogenetics in RA.

## INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) have improved the outcome for many patients with rheumatoid arthritis (RA), with marked clinical and radiographic benefits.<sup>1 2</sup> Unfortunately, these

medications are not effective in all patients with RA, with up to one-third of the patients failing to display significant clinical improvement.<sup>3 4</sup> Currently, the mechanism of non-response to TNFi is unclear, and there remains a pressing need for reliable biomarkers to achieve optimal therapeutic response at earlier stages of RA. Results of pharmacogenetic research into biomarkers for response to TNFi therapy in RA are, however, somewhat disappointing. Five genome-wide association studies (GWAS) have been performed, with the largest study including 2706 samples, but only loci with suggestive evidence of association have been reported.<sup>5–9</sup>

All five GWASs used the change in disease activity score 28 (DAS28) as a measure for therapy response. DAS28 is one of the two major scoring systems for evaluating disease activity in RA. It is widely used in both clinical trials and clinical practice.<sup>10–12</sup> The DAS28 formula incorporates information from four individually weighted components: swollen joint count (SJC), tender joint count (TJC), a self-determined assessment of patients' general health on a visual analogue scale (VAS-GH) and acute phase response. Although the DAS28 score is very powerful in measuring treatment response in the clinical setting, it is unclear if the composite measurement is the most suitable measure for genetic analyses. The genetic effects influencing this complex assemblage of separate disease measurements, reflecting the patients' subjective assessments of well-being, biological markers of inflammation and joint counts, are likely to be individually modest. The separate components of DAS28 are probably closer to the biological mechanisms underlying treatment response and, therefore, less heterogeneous and potentially more heritable. Given the potential limitation of using DAS28 in genetic studies for TNFi response, we sought to refine the outcome paradigm by studying separate components of DAS28 individually.

Random effect models have recently been introduced as an approach for analysing GWASs, which allow estimation of overall heritability of the traits without explicitly identifying the genetic loci responsible. In this study, we applied a Bayesian hierarchical method<sup>13</sup> and frequentist linear mixed models<sup>14</sup> to existing GWAS data.<sup>7 15</sup> These

methods provide two related but alternative statistical approaches to estimate the additive genetic contribution (ie, the heritability) to variation in the DAS28 score and its components. In essence, these methods exploit differences in relatedness between individuals as estimated from all single nucleotide polymorphisms (SNPs) to partition phenotypic variance into a genetic component and an environmental component. Furthermore, we used these methods to estimate the contribution of genetic and environmental factors to correlations between TNFi-induced changes in components of DAS28 (for instance, the genetic and environmental contribution to the phenotypic correlation between the change in SJC and TJC). We also estimated genomic and environmental correlations of TNFi-induced change in DAS28 with each of its separate components to measure how strongly each of the separate components contributes to the genetic 'make-up' of  $\Delta$ DAS28. Finally, we implemented a multivariate approach in which the separate DAS28 components are studied simultaneously to see if taking cross-trait variance into account would be more informative when compared with univariate analyses of  $\Delta$ DAS28 and its separate components.

## MATERIALS AND METHODS

### Samples and GWAS data

DNA samples of 984 Dutch patients with RA were collected through a collaborative effort, in which 669 patients were recruited as part of the Dutch Rheumatoid Arthritis Monitoring registry (<http://www.dreamregistry.nl>) and 315 patients with RA were included through ApotheekZork database, which mediates the distribution of adalimumab in the Netherlands. All patients were diagnosed with RA according to the 1987 revisited American College of Rheumatology criteria and treated with TNFi medication in accordance with the indications in the Netherlands.<sup>13</sup> Data were collected at baseline and after 14 weeks of the treatment. The following measures are included in this study: 28-joint counts for swelling and tenderness (SJC, TJC); Westergren erythrocyte sedimentation rate (ESR) and patients' self-assessment of general health on 100 mm visual analogue scale (0=best possible, 100=worst possible). DAS28 values were also calculated for these time points. Patients who discontinued treatment within 14 weeks after treatment initiation were excluded from the study. Written informed consent was obtained from all patients, and the study was approved by the institutional ethics committee of each participating hospital.

Genotypes were obtained using the Illumina's HumanHap 550-Duo BeadChip and Human 660W-Quad arrays. Quality control (QC) procedures were applied using the whole genome association analysis toolset PLINK.<sup>16</sup> We selected biallelic autosomal markers based on the following criteria: call rate <0.01, minor allele frequency >0.01 and Hardy-Weinberg equilibrium ( $p < 10^{-6}$ ). This resulted in 488 254 SNP markers eligible for analysis. Furthermore, subjects with gender mismatch with phenotypic data, call rate <99% and cryptic relatedness (PI-HAT >0.125) were excluded. Finally, principal components were computed to adjust for population stratification using the EIGENSTRAT package,<sup>17</sup> and individuals were removed as outliers based on the EIGENSTRAT default filter. This resulted in 878 individuals available for analysis.

Available clinical variables (age, sex, methotrexate comedication and baseline DAS28, SJC, TJC, ESR and VASGH) were inspected for association with the phenotypes analysed in this study ( $\Delta$ DAS28,  $\Delta$ SJC,  $\Delta$ TJC,  $\Delta$ ESR and  $\Delta$ VASGH). The only significantly associated variables were the baseline values of the phenotypes assessed. To include baseline covariates in our

model, we computed standardised residuals derived from regressing  $\Delta$ DAS28 and its individual components on relevant baseline covariates. These standardised residuals were used in all subsequent analyses.

### Genomic heritability and correlation estimation using a Bayesian mixed model

In this analysis, estimation of genomic heritability and correlation was based on phenotype (separate components of  $\Delta$ DAS28) and SNP data. The variance components were estimated with a Bayesian mixed model with a random regression version of SNP Best Linear Unbiased Predictors model using the software, Bayz.<sup>13 18</sup> In matrix notation, the general mixed model can be described as:  $y = \mu + Zu + e$ , where  $y$  are the phenotypes,  $\mu$  is a mean,  $u$  is a vector with SNP effects taken as regression coefficients for allele substitution for each SNP in the study and  $Z$  is a covariate matrix for the random effects (SNP markers) containing centred SNP covariates. Residuals are denoted as  $e$ . Residuals here are also referred to as 'environment' from the common quantitative genetic paradigm to split a phenotype in genetic and environmental factors. The approach for estimating parameters in Bayz is based on a Markov chain Monte Carlo, and a total of 100 000 iterations were applied. A univariate Bayesian mixed model was applied to estimate the heritability of each individual separate DAS28 component and DAS28, itself; and bivariate Bayesian mixed models were run estimating environmental and genomic covariances using a hierarchical latent variable model, as in.<sup>18</sup> Both estimates were retrieved from postanalyses made with the tool, gbayz, implemented in the Bayz software. Heritability was calculated as:  $h^2 = \sigma_a^2 / (\sigma_a^2 + \sigma_e^2)$ , where  $\sigma_a^2$  is the additive genomic variance and  $\sigma_e^2$  is the residual variance.

### Genomic heritability estimation using GCTA

Software developed by Yang *et al*<sup>14</sup> (GCTA) was also applied for univariate modelling of SNP-explained variances as a validation of the Bayesian model. Briefly, this method uses the estimates of genetic relationships from genome-wide SNP information and incorporates these into a regression model to provide an estimate of the genetic variance of a given phenotype. Since this method can be highly sensitive to uneven linkage disequilibrium (LD) between SNPs, we calculated a modified kinship matrix in which SNPs are weighted according to local LD using LDAK software (<http://dougsped.com/download/>).<sup>19</sup> All further analyses of genomic heritability in GCTA were adjusted for the first three principal components, with the selected genetic relationship matrix cut-off of 0.025.

### Univariate and multivariate GWAS

The additive genetic effect of each SNP allele on change in DAS28 and each of the DAS28 components (SJC, TJC, VASGH and ESR) after 14 weeks of TNFi treatment was estimated using linear regression analysis with adjustment for first three principal components. These analyses were performed using PLINK software.<sup>16</sup> Multivariate test of association (MQFAM) (downloaded from <http://genepi.qimr.edu.au/staff/manuelf/multivariate/main.html>), implemented in PLINK, was also applied. Using this approach, the components that constitute DAS28, that is, SJC, TJC, VASGH and ESR, were submitted to a canonical correlation analysis (CCA) in which the linear combination of traits that explain the largest proportion of the covariation between the marker and all traits is extracted.<sup>20</sup> The results of the univariate and multivariate GWASs were compared by visual inspection of Quantile-Quantile (Q-Q) plots. To quantify the inflation seen in GWAS for  $\Delta$ SJC we used

permutation analysis based on 1000 replicates to test whether the number of SNPs with p value below 0.0001 was significantly different from the null expectation.

## RESULTS

Table 1 shows an overview of the demographics and outcomes for the patient population studied.

### Heritability

SNP-based estimates of the heritability and posterior SDs from the Bayz approach as well as heritability estimates and SDs generated with GCTA are presented in table 2. Although there are differences in the absolute estimates generated by these two approaches, they show similar trends. The highest heritability was estimated for  $\Delta$ SJC ( $h^2_{\text{Bayz}}=0.76$  and  $h^2_{\text{GCTA}}=0.87$ ), indicating that most of the variation seen in this trait can be attributed to common SNPs. Estimated heritability for  $\Delta$ TJC is also high ( $h^2_{\text{Bayz}}=0.62$  and  $h^2_{\text{GCTA}}=0.82$ ). A somewhat lower heritability is found for  $\Delta$ DAS28 ( $h^2_{\text{Bayz}}=0.59$  and  $h^2_{\text{GCTA}}=0.71$ ). Heritability estimates for  $\Delta$ ESR and  $\Delta$ VASGH generated with GCTA are equal to zero, while the Bayesian approach indicates low to moderate heritability ( $h^2_{\text{Bayz}}=0.18$  and  $h^2_{\text{Bayz}}=0.29$ , respectively). In the last two estimates, the highest posterior density, a Bayesian CI, included zero.

### Multivariate versus univariate GWAS

SNPs numbering 488 254 were tested for association with  $\Delta$ DAS28,  $\Delta$ SJC,  $\Delta$ TJC,  $\Delta$ ESR and  $\Delta$ VASGH as outcomes in univariate GWAS analysis. A multivariate GWAS on change in separate DAS28 components was also conducted. Q–Q plots of GWASs are presented in figure 1. Visual inspection of inflation of the observed versus expected association signals indicated that the multivariate approach (CCA) did not lead to an excess of low p values as compared with a univariate analysis of

$\Delta$ DAS28. The biggest inflation of p values was observed for the  $\Delta$ SJC univariate GWAS; however, permutation analysis indicated that this inflation is not significantly different from the null expectation ( $p=0.09$ ).

## DISCUSSION

Pharmacogenetic studies of TNFi response in patients with RA have relied on composite measures, such as DAS28, as outcome of the TNFi therapy.<sup>21</sup> In this study, we analysed the genetic properties of changes in the separate components of DAS28 after 14 weeks of TNFi therapy individually, comparing them with change in DAS28 and a multivariate approach that jointly analysed changes in separate components. Furthermore, we presented the estimates of heritability using genome-wide SNP data as well as estimates of correlation of the different outcomes of TNFi therapy in patients with RA, of Dutch descent. Accurate measures of heritability will give us more insight to the genetic basis of drug treatment response, besides, the results presented in this study might serve as a basis for other researchers to optimise designs of future genetic studies by using the most heritable traits to identify genes contributing to TNFi.

The SNP-heritability was estimated using two different approaches that use the linear mixed-effect model framework.<sup>13 14</sup> Both approaches generated similar patterns and comparable results for the heritability estimates of single traits. We found that a large proportion of variation in change in joint counts can be attributed to common SNPs ( $h^2_{\text{Bayz}}=0.76$  and  $h^2_{\text{GCTA}}=0.87$  for  $\Delta$ SJC and  $h^2_{\text{Bayz}}=0.62$  and  $h^2_{\text{GCTA}}=0.82$  for  $\Delta$ TJC). On the other hand, our results suggest that common SNPs have little (if any) effect on the variation seen in the  $\Delta$ ESR and  $\Delta$ VASGH. For  $\Delta$ DAS28, the estimated proportion of the variation explained by common SNPs is in between those seen for joint counts and  $\Delta$ ESR and  $\Delta$ VASGH. This is not surprising given the fact that DAS28 is composed of these individual measurements. In a recent publication, Plant and colleagues also reported heritability analysis of responses to TNF inhibition.<sup>22</sup> Results of their analysis on a group of 1140 RA patients treated with TNFi are indicating different patterns of heritability among traits. The reported heritability estimates were smaller for most traits, with marked exception of  $\Delta$ ESR. However, the heritability estimates based on the smaller subgroup of patients treated with monoclonal antibodies to TNF are more similar to those reported here, with the highest heritability estimate calculated for  $\Delta$ SJC ( $h_g=0.60$ ).<sup>22</sup>

We also conducted univariate GWASs using change in both DAS28 and each of its separate components as outcomes and compared these results with those yielded with a multivariate approach including all the DAS28 separate components. Considering that heritability estimates for changes in joint counts were high, the negative results of the association study

**Table 1** Study population characteristics

Number	878
Female (%)	68.6
TNFi drug	
Infliximab	246 (22.9)
Adalimumab	675 (62.7)
Etanercept	132 (12.3)
MTX comedication (%)	N (73.4)
DAS28	
Baseline	5.5±1.2
$\Delta$ DAS28, 14 weeks	3.6±1.3
SJC	
Baseline	10.17±5.49
$\Delta$ SJC, 14 weeks	5.52±5.44
TJC	
Baseline	10.04±7.40
$\Delta$ TJC, 14 weeks	6.37±7.11
ESR (mm/h)	
Baseline	28.32±22.05
$\Delta$ ESR, 14 weeks	10.25±16.60
VASGH	
Baseline	62.54±22.03
$\Delta$ VASGH, 14 weeks	28.61±27.90

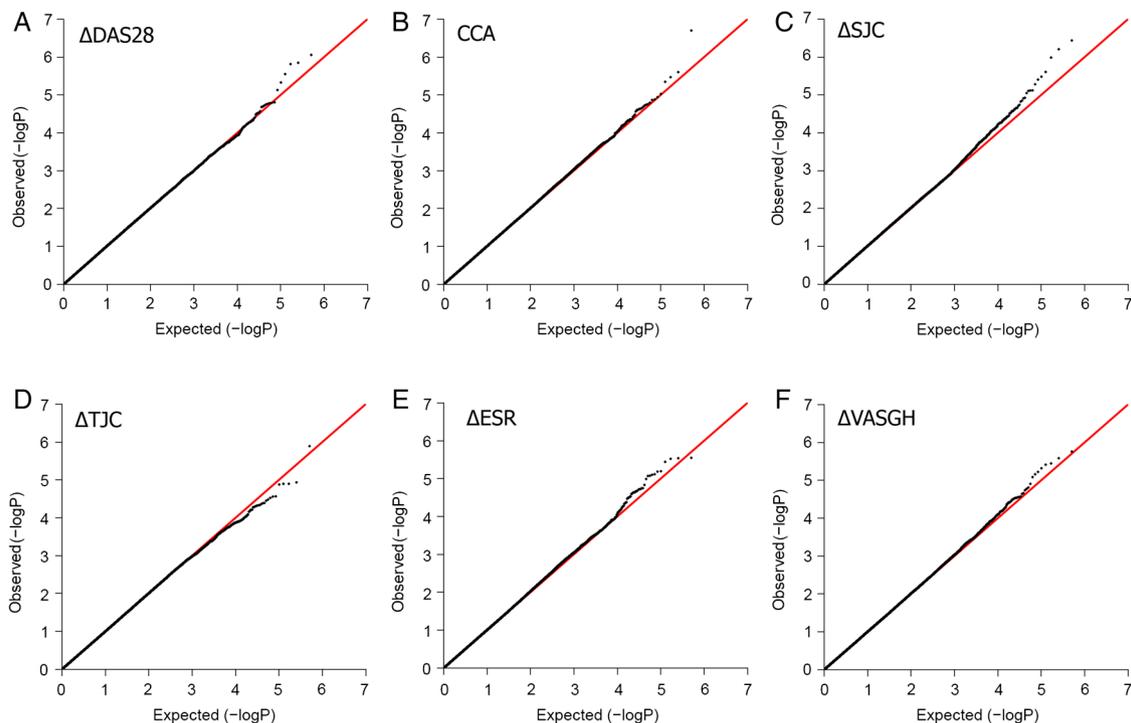
Numbers are depicted as n (%) or mean±SD.

TNFi, tumour necrosis factor inhibitors; MTX, methotrexate; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; SJC, swollen joint count; TJC, tender joint count; VASGH, visual-analogue scale of general health.

**Table 2** Heritability estimates

	Bayz		GCTA	
	$h^2_G$	HPDint	$h^2_G$	SE
$\Delta$ SJC	0.76	0.44–0.97	0.87	0.07
$\Delta$ TJC	0.62	0.17–0.96	0.82	0.12
$\Delta$ ESR	0.18	0.00–0.44	0.00	0.33
$\Delta$ VASGH	0.29	0.00–0.66	0.00	0.38
$\Delta$ DAS28	0.59	0.17–0.93	0.71	0.18

DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate;  $h^2_G$ , genomic heritability; HPD, highest posterior density; HPDint, Bayesian CI; SJC, swollen joint count; TJC, tender joint count; VASGH, visual-analogue scale of general health.



**Figure 1** Quantile–Quantile (Q–Q) plots for the genome-wide association studies (GWASs). Q–Q plots for the GWAS of (A) change in disease activity score 28 (DAS28), (B) multivariate analysis (canonical correlation analysis, CCA) of change in swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR) and visual-analogue scale of general health (VASGH) after 14 weeks of treatment, (C) change in SJC, (D) change in TJC, (E) change in ESR, (F) change in VASGH after 14 weeks of tumour necrosis factor inhibitors (TNFi) therapy.

might indicate that genetic architecture of these outcomes is highly polygenic, with large numbers of loci of small effect controlling the trait. Detecting such genetic loci would require larger sample size than that achieved in this study. The results of the multivariate approach were comparable with the univariate analysis of  $\Delta$ DAS28 in that no genome-wide significant associations were identified.

Additionally, we analysed environmental and genomic correlations between changes in DAS28 and changes in its components (see online supplementary table S1). It should be emphasised that the uncertainty was large for all reported estimates, and that larger sample sizes would be required to improve on the precision of these estimates (in replication samples). We found positive genetic correlations between changes in all individual components of DAS28, ranging from 0.23 (between  $\Delta$ TJC and  $\Delta$ VASGH) to 0.49 (between  $\Delta$ SJC and  $\Delta$ TJC). The estimates for environmental correlations between all the DAS28 components were found to be positive with values similar or smaller than those seen in estimates of genomic correlations for most of the traits. The estimate for the environmental correlation of  $\Delta$ TJC and  $\Delta$ VASGH ( $0.60 \pm 0.24$ ) was relatively high;  $\Delta$ TJC and  $\Delta$ VASGH are subjective measurements of pain, and the observed environmental correlation may be a consequence of non-genetic factors, such as use of analgesic drugs.

The findings presented in this study, may serve a useful purpose in the future design of pharmacogenetic studies of TNFi response in patients with RA. The composite indices, such as DAS28, are clearly efficient in monitoring the effects of the treatment in patients with RA in a clinical setting as they give a comprehensive view of the patients' response.<sup>21</sup> However, our results suggest that disease activity score may not be the most suitable outcome for the genetic association studies, as  $\Delta$ DAS28 is not as heritable as  $\Delta$ SJC and  $\Delta$ TJC. This is not surprising as DAS28 is a conglomerate of

several components and its genetic aetiology is expected to be more complex and heterogeneous. For the development of clinically useful biomarkers, it is essential to have a clinically relevant endpoint. The goal of treatment is certainly better captured by DAS28 for a clinical setting as it also includes the measure of patients' well-being. However, our results suggest that variation seen in ESR and VASGH cannot be attributed to SNPs, whereas, most of the variation seen in changes in joint counts can be attributed to common SNPs. This can still have a substantial influence on clinical decision making as the number of SJCs and TJCs is regarded as the most specific measure of patient assessment in standard clinical care<sup>23</sup> and the most important measure for RA clinical trials to distinguish active from control trials.<sup>24</sup> Identification of genetic markers that could predict the change in joint counts following TNFi therapy could help to tailor the treatment to the individual patient and better understand the mechanisms underlying the effects of TNFi therapy on pathophysiological changes in joints of patients with RA.

In summary, to our knowledge, this is the first study to report measures of heritability of both  $\Delta$ DAS28 and changes in its separate components, together with estimates of their genomic and environmental correlations. In this report, we used different methodological strategies to define the most suitable outcome of the pharmacogenetic studies of TNFi treatment in patients with RA. We provided evidence that common SNPs explain a large proportion of the phenotypic variation seen in change in joint counts due to TNFi therapy. Future studies with greater power will provide better accuracy for the estimates presented here, and a further validation of our findings in an independent cohort is required.

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