Investigation of genetically-regulated gene expression and response to treatment in rheumatoid arthritis highlights an association between *IL18RAP* expression and treatment response

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ABSTRACT

Objectives

In this study, we sought to investigate whether there was any association between genetically-regulated gene expression (as predicted using various reference panels) and anti-TNF treatment response (change in erythrocyte sedimentation rate, ESR) using 3,158 European ancestry rheumatoid arthritis patients.

Methods

The genetically-regulated portion of gene expression was estimated in the full cohort of 3,158 subjects (as well as within a sub-cohort consisting of 1,575 UK patients) using the PrediXcan software package with three different reference panels. Estimated expression was tested for association with anti-TNF treatment response. As a replication/validation experiment, we also investigated the correlation between change in ESR with measured gene expression at the *Interleukin 18 Receptor Accessory Protein* (*IL18RAP*) gene in whole blood and synovial tissue, using an independent replication data set of patients receiving conventional synthetic disease modifying anti-rheumatic drugs, with directly measured (via RNA sequencing) gene expression.

Results

We found that predicted expression of *IL18RAP* showed a consistent signal of association with treatment response across the reference panels. In our independent replication data set, *IL18RAP* expression in whole blood showed correlation with the change in ESR between baseline and follow-up ($r = -0.35$, $p = 0.0091$). Change in ESR was also correlated with the expression of *IL18RAP* in synovial tissue ($r = -0.28$, $p = 0.02$).

Conclusion

Our results suggest that *IL18RAP* expression is worthy of further investigation as a potential predictor of treatment response in rheumatoid arthritis that is not specific to a particular drug type.

Keywords: Rheumatoid Arthritis, Treatment, Pharmacogenetics

INTRODUCTION

Tumour necrosis factor α inhibitors (anti-TNFs) are the most commonly-prescribed second-line drugs for conventional synthetic Disease Modifying Anti-Rheumatic Drug (csDMARD)-resistant rheumatoid arthritis (RA) patients. However, patients show a significant non-response rate to anti-TNF treatment[1, 2]. With recent advances in microarray and RNA sequencing (RNA-Seq) technologies, it is hypothesised that gene expression profiling might inform our understanding of the heterogeneity of responses to treatment in RA[3]. Indeed, Tanino et al.[4] identified ten genes predictive of response to the anti-TNF antibody Infliximab, based on a transcriptome analysis of white blood cells from RA patients, while Julià et al.[5] identified an eight-gene predictor model from microarray gene expression analysis on whole blood RNA samples from RA patients. Previously, using a microarray analysis of mononuclear cell RNAs, Lequerré et al.[6] was able to perfectly separate responders to Infliximab from non-responders.

However, when studying a large number of patients, measuring gene expression at a genome-wide scale might not be financially feasible, as RNA-seq remains more expensive than genome-wide genotyping approaches. The PrediXcan method/software package[7] is a cost-effective approach for estimating the genetically-regulated portion of gene expression at each gene from a genome-wide set of genes. PrediXcan estimates the component of a gene's expression determined by an individual's SNP genotypes (at SNPs in the vicinity of the gene), and then tests for association between the predicted expression and the phenotype. The estimation of gene expression is performed using whole-genome tissue-dependent prediction models trained with reference panels that have both SNP and gene expression data. Here, we applied PrediXcan to data on RA patients receiving anti-TNF treatment from the MAximising Therapeutic Utility for Rheumatoid Arthritis (MATURA) consortium[8], focussing on testing the association between the change in erythrocyte sedimentation rate (ESR) and predicted gene expression. We elected to focus on change in ESR as an objective measure of response that has been shown to have higher heritability than other measures of response[9].

METHODS

UK data set

The UK data set was comprised of imputed genome-wide SNP genotype data (9,084,265 SNPs) for up to 1583 patients receiving anti-TNF treatment from the MATURA consortium; this corresponds to the "anti-TNF, ESR data set" previously described by Cherlin et al.[10] Quality control (QC) on the imputed SNP data was performed using standard procedures outlined by Anderson et al.[11] Individuals were excluded if the reported sex did not match the sex assessed by genotype, and samples with elevated missingness rate, outlying heterozygosity rate, outlying ethnicity and relatedness were also excluded. SNPs were excluded if they had a post-imputation INFO score < 0.8. Genotype hard calls were set to missing if the posterior probability was < 0.9. The data was filtered by minor allele frequency (MAF > 0.01), Hardy-Weinberg disequilibrium (p > 0.000001) and missing genotype rate (<0.05). The SNP genotypes were encoded according to the number of copies of the minor allele possessed. The phenotype was defined as the difference between the follow-up ESR measure (measured at 6 months, or 3 months if this was not available) and the baseline ESR measure on the log scale, that is, $\log(ESR_{fu}) - \log(ESR_{bl})$. This difference was then adjusted (by taking as the final phenotype the standardised residuals from a linear regression, carried out in the statistical software package R) for baseline ESR, drug type (a 5-level categorical variable indicating Adalimumab, Etanercept, Infliximab, Certolizumab pegol and Golimumab), a separate binary indication of whether or not patients received another DMARD in addition to the anti-TNF treatment, gender and the first ten principal components (PCs) of the SNP genotypes. The final post-QC data set was comprised of 1,575 individuals and 4,542,023 SNPs.

Expanded European ancestry data set

An expanded European ancestry data set was constructed, consisting of imputed genotype data at 4,498,586 genome-wide SNPs for 3158 patients. This expanded data set consisted of a combination of the original (1,575 patient) UK data set and a separate independent data set of 1,583 US and EU patients, corresponding to a subset (to which we were granted access) of the

patients from a pre-existing international collaboration formed to study the genetics of response to TNFi agents[12]. The same QC procedures were performed separately on the 1,583 US/EU patients, and their post-QC SNP genotype data were merged with the data for the 1,575 UK patients. In this combined European ancestry data set, the phenotype, defined as the difference between the follow-up ESR measure and the baseline ESR measure on the log scale, was adjusted for the baseline ESR measure on the log scale ($\log(ESR_{bl})$) and the first three PCs (which was found sufficient to produce no inflation in the genome-wide set of test statistics for association between SNPs and phenotype) and subsequently adjusted for gender; other covariates were not available. The standardised residuals after all adjustments were then taken as the final phenotype.

Replication data set

The replication dataset consisted of 90 treatment-naive early rheumatoid arthritis patients fulfilling the 2010 ACR/EULAR RA Classification Criteria from the Pathobiology of Early Arthritis Cohort (PEAC), in whom ultrasound-guided synovial biopsies (n=87 post-QC) and whole blood samples (n=67) were subject to RNA-sequencing as previously described[13]. Notably both synovial biopsies and blood samples were taken prior to patients receiving any disease modifying treatment such as corticosteroids. 1μg of total RNA was used as an input material for library preparation using TruSeq RNA Sample Preparation Kit v2 (Illumina). Generated libraries were amplified with 10 cycles of PCR. Size of the libraries was confirmed using 2200 TapeStation and High Sensitivity D1K screen tape (Agilent Technologies) and concentration was determined by qPCR based method using Library quantification kit (KAPA). Multiplexed libraries (five per lane) were sequenced on Illumina HiSeq2500 to generate 50 million paired-end 75 base pair reads. Transcript abundance was derived using Kallisto v0.43.0 and tximport 1.4.0 using GENCODE v24/GRCh38 as reference, and transformed to regularised log expression (RLE) using DESeq2 1.14.1. RNA-Seq data have been deposited in ArrayExpress under Accession code E-MTAB-6141. Genotyping and QC was performed using the same methodology as for the UK data set as described above. Expression quantitative trait locus (eQTL) analysis on PEAC blood RNA-seq samples was performed using the matrix eQTL package in R[14] using 4 principal components to adjust for ancestry and 4 probabilistic estimation of expression residuals (PEER) calculated as per Stegle et al.[15] as model covariates.

Discovery analysis based on predicted gene expression

PrediXcan was applied to both the UK data set and the expanded European ancestry data set. In PrediXcan, an elastic net prediction model is built using a reference panel containing SNP and gene expression data. This model is then used to predict expression levels in the analysis cohort on the basis of the measured genotypes, and the resulting predicted expression levels are tested for association with the outcome of interest. We applied PrediXcan using three reference panels: (i) a MATURA reference panel comprising 210 MATURA samples (a subset of the UK samples used later for testing), for which SNP and gene expression data were available[8]); (ii) a GTEx reference panel for which PrediXcan provides pre-calculated models; this panel comprises 338 samples from the Genotype- Tissue Expression Consortium[16]; (iii) a DGN reference panel for which PrediXcan provides pre- calculated models; this panel comprises 922 samples from the Depression Genes and Networks Consortium[17].

To construct the MATURA reference panel, we used 33,170 QC-ed and batch-adjusted[18] gene expression probes from the Illumina HT-12 Gene Expression Beadchip, measured in whole-blood at baseline in 210 patients, together with QC-ed imputed genotype data at 3,978,972 genome-wide SNPs in the same patients. Probes that corresponded to different genes (according to the GENCODE version 19[19]) were removed, and probes that corresponded to the same gene were combined as specified[20]. The final gene expression data set consisted of 17,008 probes. We note that the SNPs used for constructing the MATURA reference panel corresponded to a subset of the SNPs present within the UK data set, however, they did not correspond to an exact subset of SNPs present in the expanded European ancestry data set owing to different SNPs remaining post-QC. We used default PrediXcan parameters to build the elastic net model (α = 0.4, window size = 1 Mbp, false discovery rate threshold = 0.05). The final MATURA reference panel included 1,573 genes. Models based on whole-blood GTEx and DGN reference panels were provided as part of the PrediXcan software (downloaded from http://predictdb.org/), and included 6,057 and 9,836 genes, respectively.

Replication analysis based on measured gene expression

Clinical parameters including DAS28 score and subcomponents, ESR, CRP, rheumatoid factor

(RF) and anti-citrullinated peptide antibody (ACPA) positivity/titre were collected at baseline and every 3 months. Patients were treated with methotrexate-based combination DMARDs (81%), methotrexate alone (6.8%), hydroxychloroquine alone (5.9%) or sulfasalazine alone (3.4%) or no DMARDs (2.5%). Clinical response was assessed by change in clinical parameters at 6 months and correlated with *IL18RAP* transcript levels measured by RNA-seq in baseline synovial biopsy or whole blood.

RESULTS

Discovery analysis based on predicted gene expression

The results for the UK and expanded European ancestry data sets are shown in figures 1 and 2, respectively. Although no genes pass experiment-wide significance, for the UK data set (figure 1), the most significant gene identified using the MATURA reference panel (*IL18RAP* on chromosome 2) achieved close to experiment-wide significance ($p = 4.3 \times 10^{-5}$), and this was also the top gene when using the DGN reference panel ($p = 6.7 \times 10^{-5}$). When using the GTEx reference panel, *IL18RAP* was the fourth top gene ($p = 1.5 \times 10^{-3}$).

For the expanded European ancestry data set (figure 2), *IL18RAP* was again the top gene when using the MATURA reference panel ($p = 1.4 \times 10^{-4}$). With the DGN reference panel, this gene was the fifth top gene ($p = 2.3 \times 10^{-4}$), and with the GTeX reference panel, it was the fourth top gene ($p = 4.0 \times 10^{-4}$). Online supplementary table 1 shows the significance levels and effect estimates achieved at *IL18RAP* when using either the full 3158-person expanded European ancestry cohort or when it is divided into its constituent UK or US/EU sub-cohorts. (Note that the results for the UK sub-cohort differ slightly from those obtained in the original analysis of the UK data set on account of (a) the different phenotypic adjustments made when using the full expanded European ancestry data set and (b) slightly different SNPs being available for prediction of expression, see below). The signal is seen to be predominantly driven by the results from the UK sub-cohort, with the US/EU sub-cohort showing the same direction of effect, but with the effect size considerably attenuated.

The PrediXcan models for predicting the expression of *IL18RAP* involved 77, 46 and 86 SNPs when using the MATURA, GTEx and DGN reference panels, respectively (online supplementary table 2). All 77 SNPs from the MATURA reference panel appeared in the

expanded European ancestry data set, while 37 out of 46 SNPs from the GTEx reference panel and 82 out of 86 SNPs from the DGN reference panel appeared. Density estimates for the resulting predicted expression values are shown in online supplementary figure 1; their relationship with phenotype is shown in online supplementary figure 2. The prediction R^2 statistic for *IL18RAP* (based on PrediXcan's internal tenfold cross-validation procedure using the relevant reference panel) was 0.32 ($p = 1.9 \times 10^{-19}$) with the MATURA reference panel, 0.30 ($p = 4.4 \times 10^{-247}$) with the GTEx reference panel and 0.71 ($p = 2.8 \times 10^{-28}$) with the DGN reference panel, suggesting reasonable predictive ability for expression at this gene across all panels. As expected (given the association between SNPs contributing to the prediction models and expression, and between predicted expression and response), a number of SNPs also showed direct associations with response (online supplementary table S2), although as noted previously[10] these do not meet genome-wide significance levels.

The most significant gene overall using the expanded European ancestry data set was *ARV1* on chromosome 1, which appeared both when using the DGN reference panel ($p = 9.1 \times 10^{-5}$) and the GTEx reference panel ($p = 6.4 \times 10^{-5}$). This gene was absent on the MATURA reference panel because the PrediXcan software failed to predict its expression value. In the original analysis of the UK data set, the signals for the *ARV1* gene were generally weaker than, or similar to, those seen at *IL18RAP* (figure 1). Additionally, the prediction accuracy for *ARV1* in the expanded European ancestry data set, as measured by the R^2 statistic, was very low ($R^2 = 9.6 \times 10^{-3}$; $p = 0.072$) with the GTEx reference panel, and relatively lower ($R^2 = 0.18$; $p = 2.1 \times 10^{-41}$) than that seen for *IL18RAP* with the DGN reference panel, suggesting that these results at *ARV1* should be interpreted with caution.

Replication analysis based on measured gene expression

In the replication data set, we observed a significant expression quantitative trait locus (eQTL) association ($P = 5.8 \times 10^{-11}$) between multiple SNPs across the *IL18RAP* locus and *IL18RAP* expression measured by RNA-Seq of whole blood samples in patients with early RA (figure 3a, b), thus confirming that *IL18RAP* genetic polymorphisms regulate expression of *IL18RAP* in peripheral blood in early RA patients. The expression of *IL18RAP* measured in whole blood showed correlation with the change in ESR between baseline and 6-month follow-up ($r = -0.35$; $p = 0.0091$) in RA patients treated with MTX-based combination DMARD therapy (figure 3c); specifically

each unit increase in *IL18RAP* regularised log expression resulted in a 13.4 mm/hour decrease in ESR between baseline and 6 months. Also, a correlation was observed between the expression of *IL18RAP* in synovial tissue and the change in ESR ($r = -0.28$; $p = 0.02$) (figure 3d); specifically each unit increase in regularised log expression resulted in a 11.8 mm/hour decrease in change in ESR over 6 months. Thus, our replication experiment based on actual measured gene expression (in an independent set of patients) validates the association between predicted *IL18RAP* expression and treatment response seen in the discovery cohort.

DISCUSSION

In this study, we investigated the association between the genetically-regulated portion of gene expression and change in the ESR in a large cohort of RA patients from the MATURA consortium. We found that predicted expression of *IL18RAP* showed a consistent signal across data sets analysed using different reference panels, while achieving a reasonable level of prediction accuracy as measured by the prediction R^2. Despite the consistency of the results for *IL18RAP*, some differences in the strength of the signal were observed for different data sets and reference panels. These differences require further investigation, however they can be partly explained by the different sample sizes (and SNPs available to inform prediction) in the different reference panels. In an independent replication data set of patients treated with csDMARDs with measured gene expression, the asso- ciation between expression of *IL18RAP* and change in the ESR was confirmed both in whole-blood and synovial tissue, highlighting *IL18RAP* as a gene worthy of further investigation for prediction of treatment response in RA that is not treatment-specific. No other expressed genes were consistently associated with response, providing confidence that it is the *IL18RAP* gene that is driving the association rather than serving as a proxy for another gene.

The protein encoded by *IL18RAP* enhances the IL-18 binding activity of the IL-18 receptor and plays a role in signaling by IL-18 [21]. IL-18 plays an inflammatory role in RA[22, 23] and has previously been identified as a potential therapeutic target in the treatment of RA[24, 25]. It has been suggested that IL-18 plays some part in the degradation of articular cartilage in arthritis[26]. Additionally, Rooney et al.[27] showed that synovial tissue IL-18 production measured by immunohistochemistry was correlated with serum C reactive protein in inflammatory arthritis, while

Joosten et al.[28] found a correlation between the level of IL-18 in the synovial tissue of the RA patients and ESR.

Previous studies have reported a potential association between *IL18RAP* and treatment response in RA. Analysis of CAGE sequencing data from the FANTOM5 consortium showed that *IL18RAP* is highly expressed in neutrophils, gamma delta T cells, eosinophils and NK cells[29]. Analysis of the BioGPS database (http://biogps.org/) confirms that *IL18RAP* is highly expressed in NK cells. *IL18RAP* expression is upregulated in NK and T cells in response to IFN-alpha and IL-12[30]. *IL18RAP* was found to be significantly upregulated (adjusted $P = 5.5 \times 10^{-78}$) in NK cells in single cell RNA-seq RA synovium data from Stephenson et al.[31]. Similarly in a second single cell RNA-seq study of RA synovium[32], *IL18RAP* shows increased expression in synovial tissue T cell populations. In RA synovium, the baseline expression of the S1 module (NK cell surface signature) from Li et al.[33] which includes *IL18RAP* as one of its 45 genes, correlates significantly with change in ESR. Additionally, the synovial baseline expression for another NK cell module (M7.2) which includes *IL18RAP* is also significant for the change in ESR.

Our own investigation of the relationship between measured expression of *IL18RAP* and change in the ESR in whole-blood and synovial tissue in our replication data set was motivated by our initial identification of a relationship between change in the ESR and predicted expression of *IL18RAP* in our discovery data sets, using the PrediXcan method/software. Other methods/software packages for performing transcriptome-wide association studies exist, but as shown by Fryett et al[34], they tend to perform very similarly to one another. These methods are dependent on the underlying eQTL data used to build the prediction models, and therefore would generally be expected to give very similar results. Given that the external datasets used to inform the prediction were derived from population studies and would unlikely to have been enriched for patients with RA, the risk of the association detected with ESR being spurious is low.

We elected to focus on change in ESR as an objective measure of response that has been shown to have higher heritability than other measures of response[9]. Other clinical outcomes relating to anti-TNF treatment response, such as joint destruction scores or CRP, could certainly be assessed using similar approaches. However, joint destruction scores were not available in our discovery data set, and there were many missing values for CRP, making this a less attractive

option in this instance.

Overall, our results, combined with the existing evidence, suggest that the expression of *IL18RAP* in whole blood might have utility for predicting response to treatment in RA. However, the effect observed in our replication samples (11.8-13.4 mm/hour decrease in change in ESR over 6 months) is, by itself, probably too small to be clinically useful, and the small to moderate correlations seen between *IL18RAP* expression and change in ESR (figure 3c, d) suggest that the actual predictive ability of *IL18RAP* expression alone may be limited. This approach shows the value of integrating genetic and expression data to identify factors correlated with response which could be incorporated into a multi-omic predictive model in the future. Further investigation of the relationship between *IL18RAP* expression and varying measures of treatment response in additional patient cohorts is thus warranted.

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Contributors

Substantial contributions to conception or design of the study: SC, PM, JHB, CP, AB, HJC. Substantial contributions to drafting the manuscript: SC, MJL, HJC. Substantial contributions to data acquisition: CP, AB. Substantial contributions to data analysis or interpretation: SC, MJL, DP, NN, KG, ET, MRB. All authors contributed to revising the manuscript critically for important intellectual content and approved the final manuscript. The funding agencies had no part in writing or reviewing the manuscript. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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Competing Interests

The authors declare no competing interests.

Patient and public involvement statement

This study was conducted as part of the programme of work undertaken by the MATURA Consortium (http://www.matura.whri.qmul.ac.uk/). A patient advisory group was established in 2014 when the MATURA project commenced. The group meets regularly to: ensure MATURA strategy is maintaining relevance, accountability and direction by embedding patients and members of the public within the decision making processes; determine what level of confidence in tests, and what type of tests, would be acceptable to patients for treatment decisions; maximise patient recruitment to research studies by increasing awareness through patient groups; readily obtain patients perspective on grant applications related to stratified medicines for RA; facilitate the dissemination of the results from MATURA research, for instance by producing lay summaries of papers in conjunction with the researchers (http://www.matura.whri.qmul.ac.uk/news.php).

Patient consent for publication

Not required.

Ethics approval

This study used anonymised data for human subjects from an international collaboration of 13 studies originally published in PLOS Genetics 2013;9:e1003394. All participants provided informed consent and institutional review board and ethics approvals were in place for each of the studies and described in the original publication. Approval for additional data pre- sented in this manuscript was provided by the North West 6 Central Manchester South Ethics Committee (COREC 04/Q1403/37) and the London–Dulwich Research Ethics Committee (REC 05/Q0703/198).

Data sharing statement

Data are available upon reasonable request.

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Figure Legends

Figure 1: Manhattan plots of P -values from tests of association between genetically-regulated gene expression and the change in ESR for the 1575-person UK data set. The genetically-regulated gene expression was estimated with (a) the MATURA reference panel, (b) the GTEx reference panel, and (c) the DGN reference panel. On each panel, the red dashed line represents the experiment-wide significance level computed using a Bonferroni correction for the number of tests performed. The black diamond represents the *IL18RAP* gene. The white diamond represents the *ARV1* gene.

Figure 2: Manhattan plots of P-values from tests of association between genetically-regulated gene expression and the change in ESR for the 3158-person expanded European ancestry data set. The genetically-regulated gene expression was estimated with (a) the MATURA reference panel, (b) the GTEx reference panel, and (c) the DGN reference panel. On each panel, the red dashed line represents the experiment-wide significance level computed using a Bonferroni correction for the number of tests performed. The black diamond represents the *IL18RAP* gene. The white diamond represents the *ARV1* gene.

Figure 3: Confirmation of the *IL18RAP* expression quantitative trait locus and clinical consequences in rheumatoid arthritis. (a) Manhattan plot showing expression quantitative trait locus analysis comparing influence of SNPs at the *IL18RAP* locus on *IL18RAP* expression in blood measured by RNA-seq. (b) Scatter plot of SNP rs10439410 in the 5' upstream region of *IL18RAP* and *IL18RAP* expression in whole blood. (c & d) Correlation between the change in ESR between baseline and 6 months of combination DMARD therapy and *IL18RAP* expression measured by RNA-seq in whole blood (c) and synovial tissue (d).

Key messages

What is already known about this subject?

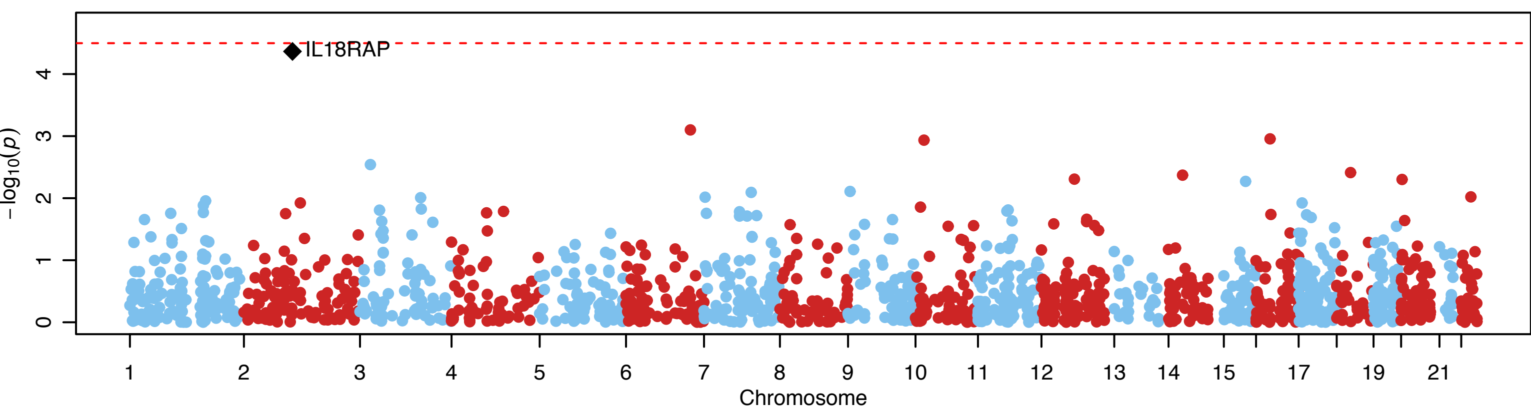
- IL-18 plays an inflammatory role in rheumatoid arthritis and has previously been identified as a potential therapeutic target.
- The protein encoded by the gene *IL18RAP* enhances the IL-18-binding activity of the IL-18 receptor and plays a role in IL-18 signaling.

What does this study add?

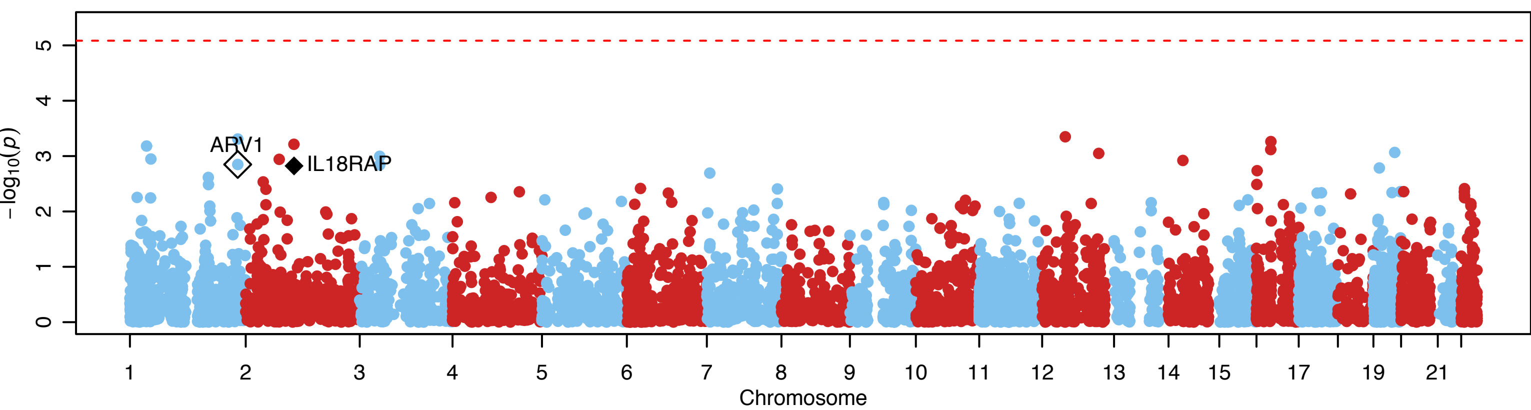
- We demonstrate a robust association between *IL18RAP* gene expression (both in whole-blood and synovial tissue) and treatment response in rheumatoid arthritis.
- The association between *IL18RAP* expression and treatment response is not specific to a particular drug type but is observed across different treatments.

How might this impact on clinical practice or future developments?

- Measurements of *IL18RAP* expression could potentially be incorporated into a multi-omic predictive model for treatment response in rheumatoid arthritis in the future.



(a)



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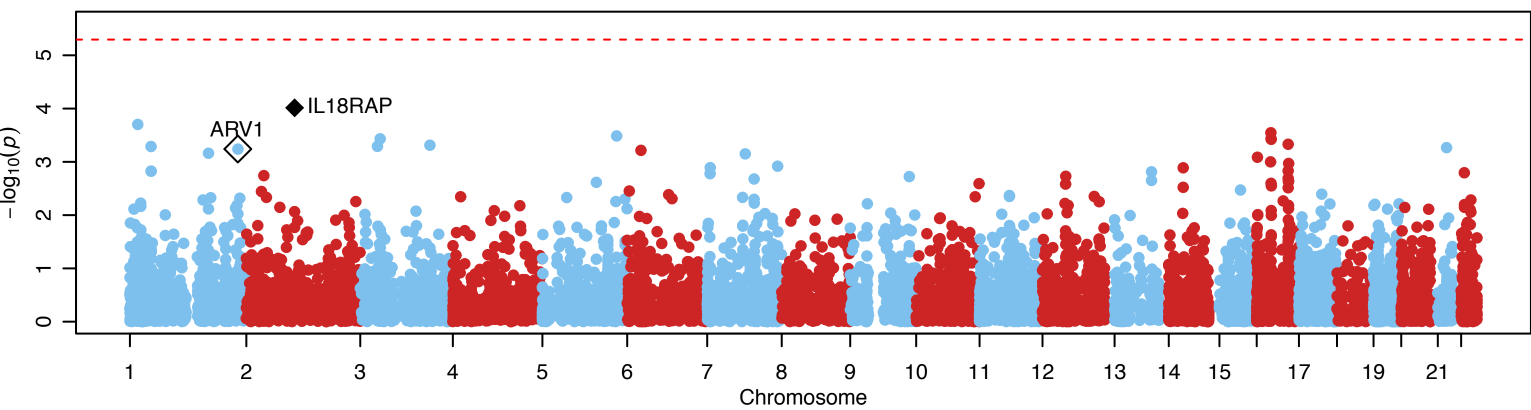

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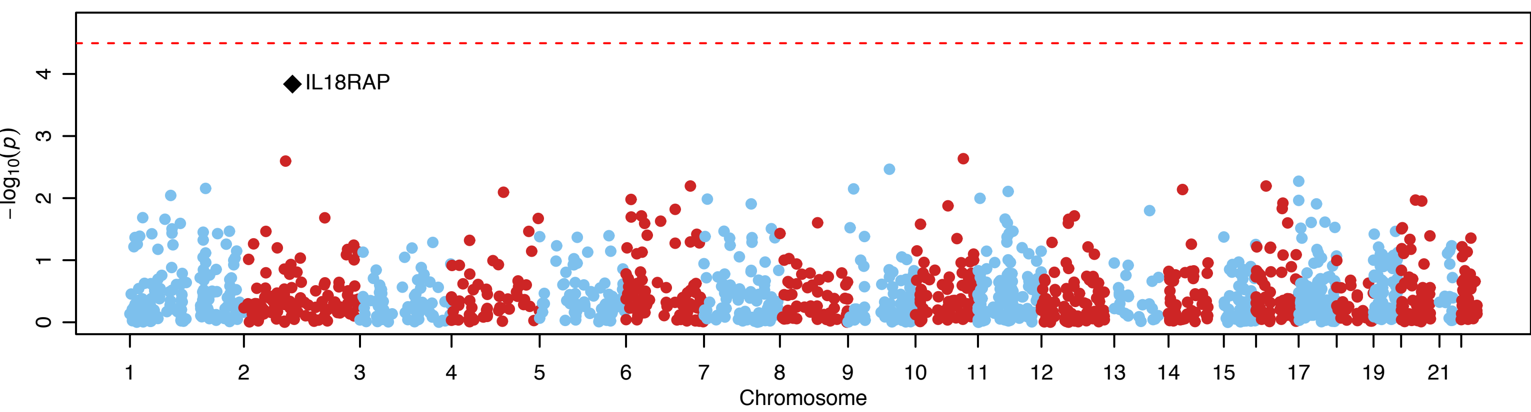

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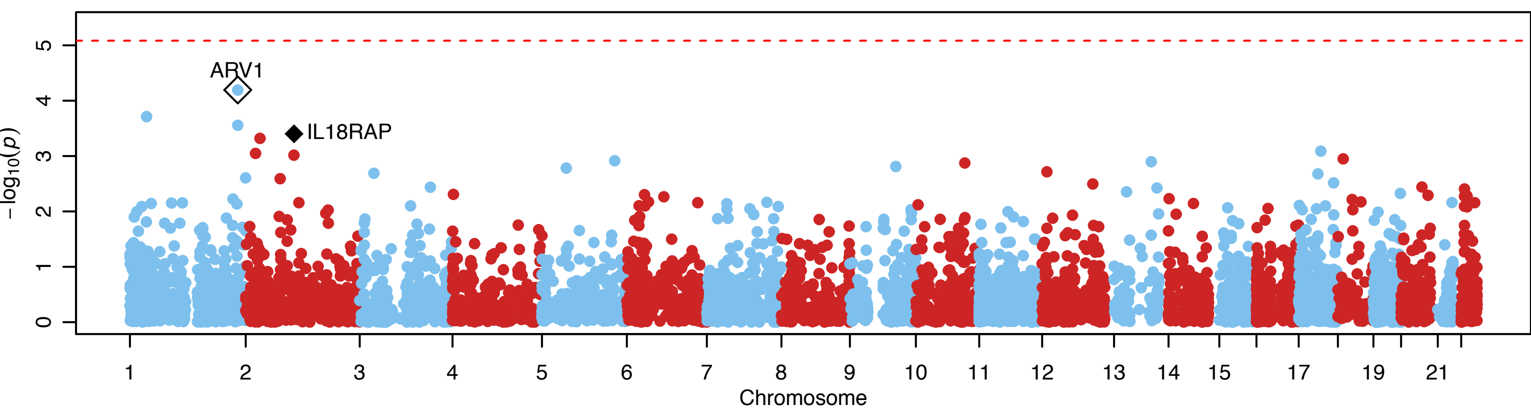

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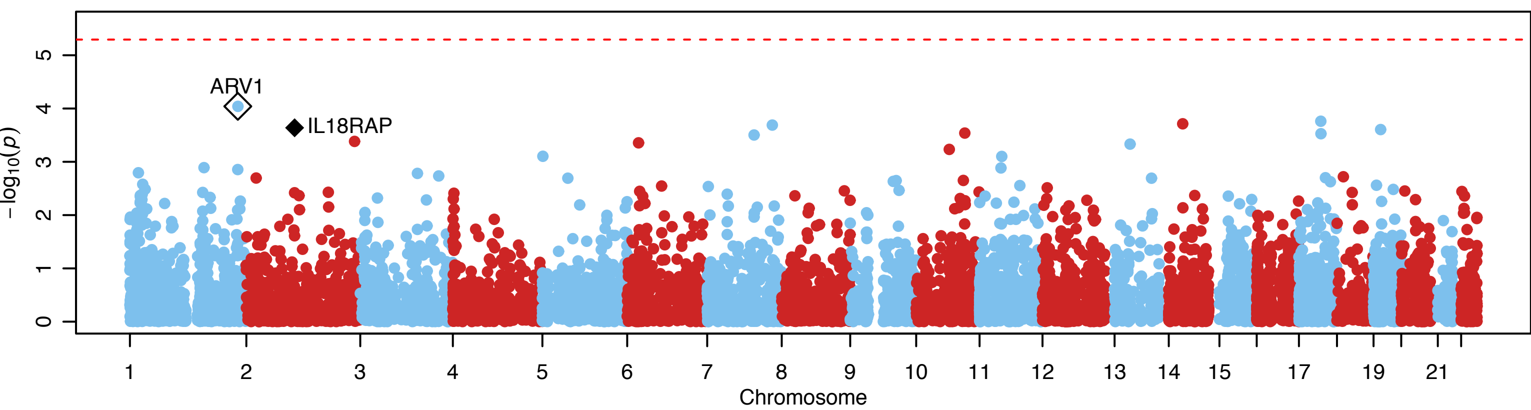

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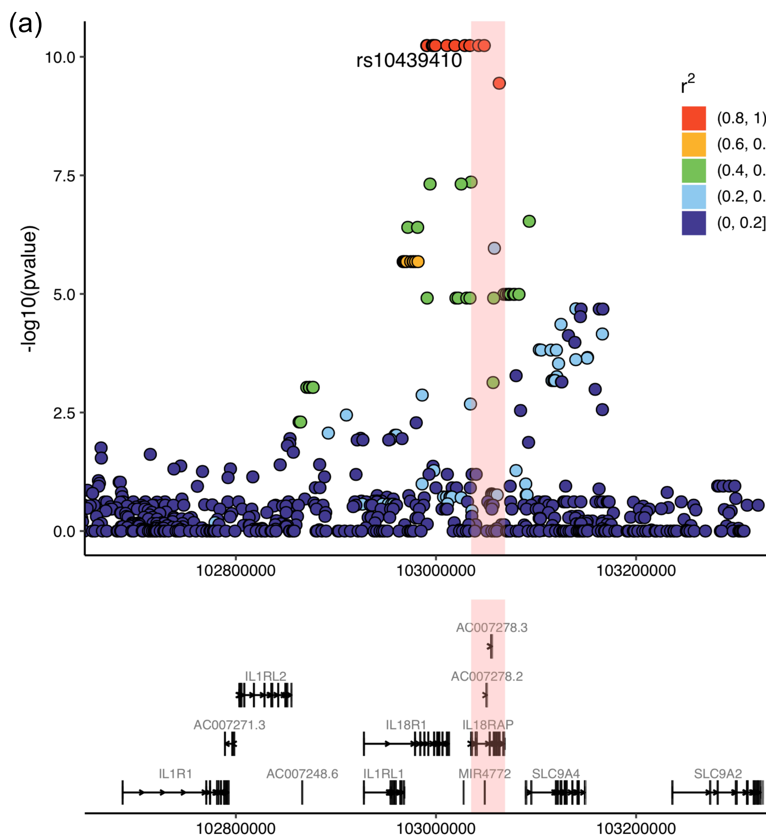
(a)
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7.5
5.0
2.5
0.0
102800000
103000000
103200000
r2
(0.8, 1)
(0.6, 0.8]
(0.4, 0.6]
(0.2, 0.4]
(0, 0.2]
AC007278.3
AC007278.2
IL1RL2
AC007271.3
IL18R1
IL18RAP
IL1R1
AC007248.6
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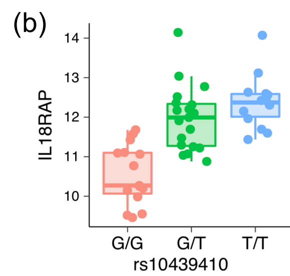
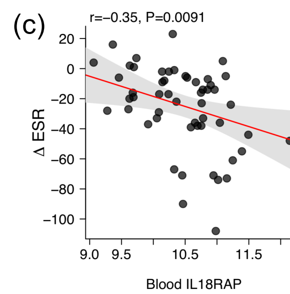
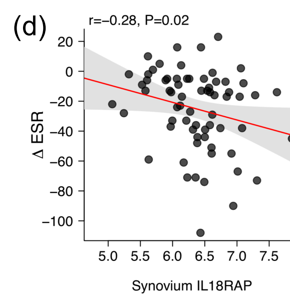
SLC9A2


(b)
IL18RAP
G/G
G/T
T/T
rs10439410


(c)
r=−0.35, P=0.0091
Δ ESR
Blood IL18RAP


(d)
r=−0.28, P=0.02
Δ ESR
Synovium IL18RAP

Investigation of genetically-regulated gene expression and response to treatment in rheumatoid arthritis highlights an association between *IL18RAP* expression and treatment response

Online Supplementary Material

Table S1. Effect sizes and significance levels achieved at *IL18RAP* when using either the full 3158-person expanded European ancestry cohort or when it is divided into its constituent UK (1575 people) and US/EU (1583 people) sub-cohorts.

Reference panel	Gene	UK		US/EU		Full	
		Effect size	*P*-value	Effect size	*P*-value	Effect size	*P*-value
MATURA	*IL18RAP*	-0.210	0.00021	-0.054	0.17344	-0.131	0.00014
GTEx	*IL18RAP*	-0.235	0.00105	-0.076	0.11999	-0.152	0.00040
DGN	*IL18RAP*	-0.128	0.00025	-0.030	0.21817	-0.079	0.00023

Table S2. The columns "Effect MATURA", "Effect GTEx" and "Effect DGN" represent the effects of the SNPs in the prediction models when using the MATURA (77 SNPs), GTEx (46 SNPs) and DGN (86 SNPs) reference panels. The columns "Coeff" and "*P*-value" represent the coefficient and the *P*-value from the association between the SNPs and the phenotype in the UK data set.

SNP	BP	Effect MATURA	Effect GTEx	Effect DGN	Coeff	*P*-value
rs13413645	-	-	-0.040	-	-	-
rs6759556	-	-	0.216	-	-	-
rs2310220	-	-	0.094	-	-	-
rs11465677	-	-	-0.003	-	-	-
rs17775170	-	-	0.009	-	-	-
rs10178585	-	-	-0.028	-	-	-
rs10185170	-	-	0.068	-	-	-
rs12328682	-	-	0.004	-	-	-
rs7599071	-	-	-0.010	-	-	-
rs1093515	-	-	-	0.015	-	-
rs13427957	-	-	-	-0.015	-	-
rs266064	-	-	-	-0.004	-	-
rs4319952	-	-	-	-0.021	-	-
rs7589943	102038936	-	0.055	-	0.006	0.96600
rs290772	102126220	-	-	0.007	-0.065	0.34800
rs75094400	102142042	0.080	-	-	-0.236	0.02390
rs17201799	102179247	-	0.054	-	-0.038	0.37600
rs12990046	102543479	0.039	-	-	-0.007	0.85600
rs11678842	102674806	-0.010	-	-	0.074	0.08400
rs13388182	102722402	-	-	-0.020	0.032	0.38700
rs13029804	102723017	-	-	0.014	-0.072	0.11000
rs1812326	102860411	-0.031	-	-	0.069	0.05930
rs10186746	102866377	-0.026	-	-	0.065	0.07800
rs62151694	102899464	0.049	-	-	-0.072	0.25500
rs13007174	102960487	0.006	-	-	-0.081	0.17300
rs13014044	102961366	0.005	-	-	-0.087	0.14800
rs1946131	102961929	0.005	-	-	-0.077	0.19600
rs1054096	102962350	0.005	-	-	-0.079	0.18600
rs12989197	102962739	0.004	-	-	-0.075	0.21100
rs12996097	102963628	0.004	-	-	-0.081	0.17400
rs13028993	102963949	0.004	-	-	-0.076	0.20100
rs12999542	102965392	-	-	0.017	-0.083	0.16300
rs13014644	102971363	0.015	-	-	-0.079	0.18500
rs13015714	102971865	-	0.018	-	0.111	0.00955
rs11465567	102978400	0.006	-	-	-0.072	0.22800

rs11465572	102980223	0.001	-	-	-0.071	0.23200
rs4134504	102982223	0.005	-	-	-0.081	0.17000
rs2058622	102985424	-	-	0.016	0.112	0.00945
rs2058623	102986170	-	-	0.015	0.113	0.00863
rs1465321	102986618	-	-	0.002	0.113	0.00863
rs11465597	102987213	-	-	0.006	-0.057	0.33600
rs10439410	102990788	0.007	-	0.031	-0.143	0.00005
rs6731157	102991191	0.006	-	-	-0.143	0.00005
rs6745614	102991213	0.007	-	-	-0.143	0.00005
rs6758936	102991369	0.007	-	0.016	-0.143	0.00005
rs2270297	102992675	-	0.011	0.050	0.115	0.00729
rs11465623	102993039	-	0.058	0.019	-0.020	0.76900
rs6753717	102993161	-	0.012	0.048	0.115	0.00729
rs2041739	102994333	0.012	-	0.018	-0.143	0.00006
rs6750020	102994714	-	0.013	0.046	0.114	0.00807
rs10208196	102996345	0.007	-	0.019	-0.143	0.00005
rs7556917	102997720	0.008	-	-	-0.143	0.00005
rs7584093	102997721	0.008	-	-	-0.143	0.00006
rs3213733	102997884	-	-	0.001	-0.102	0.03120
rs3213732	102998279	0.008	-	0.021	-0.144	0.00005
rs10204757	102998974	0.008	-	-	-0.143	0.00005
rs6760621	102999952	0.008	-	0.021	-0.143	0.00005
rs11465641	103000868	0.009	-	-	-0.143	0.00005
rs17651485	103001650	-	0.057	0.086	-0.027	0.68000
rs3771161	103003961	-	-	0.001	-0.099	0.03470
rs3771159	103004958	0.009	-	-	-0.143	0.00005
rs11903946	103005330	0.009	-	-	-0.143	0.00005
rs6706002	103006104	0.009	-	0.023	-0.143	0.00005
rs6749014	103006448	0.009	-	0.022	-0.144	0.00005
rs12712146	103008714	0.006	-	-	-0.156	0.00002
rs4851004	103009537	0.009	-	0.023	-0.144	0.00005
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rs1420094	103015687	0.011	-	0.023	-0.143	0.00005
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rs3732124	103018052	-	-	0.022	-0.143	0.00005
rs4851571	103019000	-	-	0.022	-0.144	0.00005
rs4851572	103019031	0.009	-	0.022	-0.144	0.00005
rs10202813	103019740	-	-	0.014	-0.099	0.03460

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rs4851575	103025203	-0.045	0.171	0.046	0.113	0.00811
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rs1420106	103035044	-0.043	0.022	0.045	0.113	0.00857
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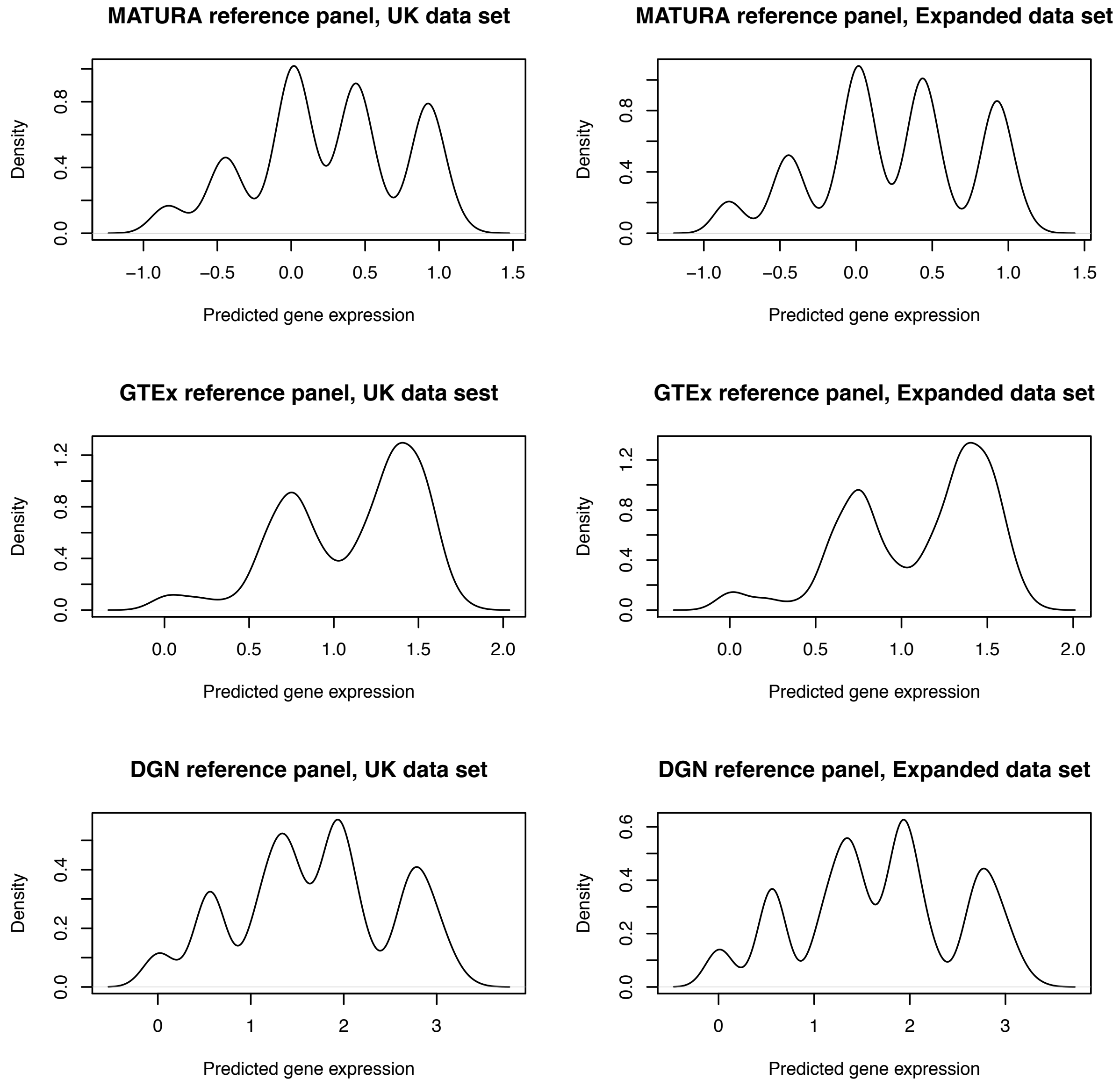

Figure S1. Density estimates (calculated using the density() function in R) of the predicted genetically-regulated gene expression at *IL18RAP* in the UK and expanded European ancestry cohorts.

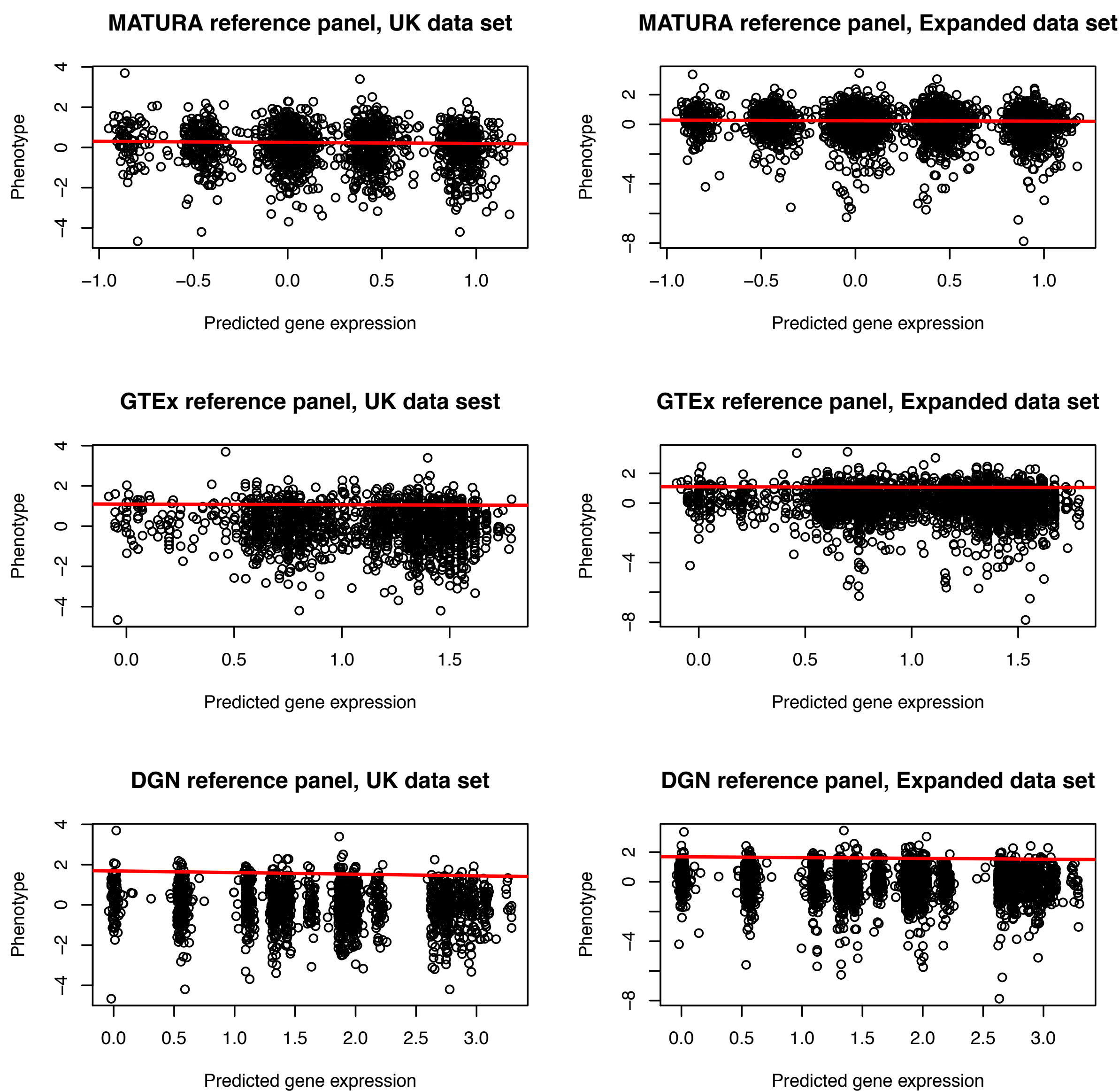

Figure S2. Plots of the linear regressions that are being fitted at *IL18RAP* in the UK and expanded European ancestry cohorts. Estimated regression lines are shown in red.