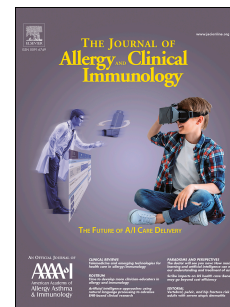


# Journal Pre-proof

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# Inversed association of FCER1A allergy variant in monocytes and plasmacytoid dendritic cells

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The authors have no conflict of interest to declare.

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## Keywords

Allergy, asthma, FCER1A, GWAS, IgE, monocytes, plasmacytoid dendritic cells, SNP, rs2427837, Singapore

**Capsule Summary**

We show that a SNP in the high-affinity IgE FC-receptor *FCER1A* differentially affects monocytes and pDCs and correlates with allergic disease status. *FCER1A* might be a suitable target for patients with asthma or atopy.

## To the Editor,

Numerous GWAS, including one published in *JACI* by *Ferreria et al.*, have reported an association between rs2427837 and allergic disease status (1). This SNP is located within the first intron of the high affinity IgE FC-receptor (*FCER1A*). However, the candidate gene that seems to strongly correlate with this SNP is *OR10J5* — an olfactory receptor located ~250 kb upstream of the polymorphism (1). Here, we present evidence to support that rs2427837 instead correlates with *FCER1A* mRNA levels in whole blood and protein levels on monocytes and plasmacytoid dendritic cells (pDCs).

We first analyzed mRNA data from 31,430 whole blood samples constituting 35 different cohorts collected by the eQTLgen consortium. We consistently detected a strong correlation ( $p = 5.8E-152$ ) between rs2427837 and *FCER1A* (**Figure 1A**). The expression levels of only two other genes also significantly correlated with this SNP: *DARC* ( $p = 4.9E-54$ ) and *AIM2* ( $p = 4.2E-08$ ). Notably, we did not detect a significant correlation with *OR10J5* (**Table E1**). Furthermore, and consistent with data from the GTEX consortium (<https://www.gtexportal.org/home/gene/ENSG00000184155>), we did not detect *OR10J5* in our blood samples. To identify the cell subsets affected by rs2427837, we analyzed *FCER1A* protein levels in whole blood subsets by flow cytometry. A previous study reported a correlation between rs2427837 and *FCER1A* levels at nominal significance in basophils(2). However, when we analyzed 135 samples from a functional cohort of Singapore Chinese participants, we found no impact of this SNP on *FCER1A* levels in these cells (**Figure 1B**). Rather, we found a strong correlation between rs2427837 and *FCER1A* protein levels on monocytes ( $p < 0.001$ ) but not to other allergy-relevant subsets, namely eosinophils or neutrophils (**Figure 1C, D, E**). This discrepancy in basophils could be due to cell-treatment effects: the previous study treated the cells with lactic acid to strip IgE from the surface receptor. IgE has a stabilizing effect on *FCER1A* surface expression, which on basophils is further enhanced by the cell-type-specific Fc receptor alpha-chain *MS4A2* (4). Another recent analysis of *FCER1A* levels in peripheral blood mononuclear cell (PBMC) fractions also found no association between *FCER1A*<sup>+</sup> basophil subsets and atopy or asthma (3). However, the rs2427837 SNP was not considered in this work.

We validated our findings in additional samples using a comprehensive flow cytometry panel, gating out the four major *FCER1A*-expressing immune-cell subsets: monocytes, pDCs, myeloid DCs (mDCs) and basophils (**Figure E1, E2**). We found an allele-dependent increase in the *FCER1A*<sup>+</sup> positive subset, with the AA genotype conferring the highest frequency (**Figure E2**). The impact of this increase was evident only on classical CD16<sup>+</sup> monocytes, as non-classical CD16<sup>+</sup> monocytes do not express *FCER1A* and are thus unaffected by the polymorphism (**Figure E2**). We then replicated this correlation between *FCER1A* expression in classical monocytes and the rs2427837 SNP in individuals with AG and GG genotypes, as the AA genotype is rare in East Asians (**Figure 2A**). Further analysis in a validation cohort revealed a strong correlation between rs2427837 and *FCER1A* levels in classical monocytes ( $p = 6.04E-04$ ) (**Figure 2C**). We also observed increased *FCER1A* mRNA levels in classical monocytes in individuals with the AA genotype compared to AG and GG when analyzing eQTL data obtained by the DICE project for various immune populations (**Figure E3**). Staining with anti-IgE further confirmed that this increase in *FCER1A* levels also translates into increased IgE surface expression on monocytes (**Figure 2B**).

Besides classical monocytes, rs2427837 correlated with FCER1A levels in pDCs. Here, we found that individuals with the G allele expressed high FCER1A levels (**Figure 2D**). Although this correlation opposes what we saw with monocytes, it is concordant with the reported effects on stripped basophils (2). We found no correlation for any other subsets, including untreated basophils and mDCs (**Figure 2D, E and Figure E4**). The rs2427837 SNP has been associated with asthma and total IgE levels in asthmatics, where the major G allele results in higher IgE production and an elevated disease risk. However, the region has multiple SNPs which could have combined effect on the functional consequence of *FCER1A* (4). Furthermore, when we analyzed whole blood gene expression data we saw a significantly higher level of *FCER1A* mRNA expression in individuals with a history of asthma from N=166 (42 asthma cases and 124 controls) subjects from the SSIC cohort and N=256 (98 asthma cases and 158 controls) from the BAMSE birth cohort (***P*=0.045, and *P*=0.0086** respectively). Although basophils have been associated with the clinical manifestations of this SNP, the lack of any detectable genotype effect on untreated cells makes it unlikely that they mediate the genetic effect. Our findings showing increased FCER1A levels in pDCs, however, is in line with previous reports showing higher FCER1A levels on pDCs in asthmatic patients (5).

Various studies have implicated FCER1A and pDC recruitment to the lungs in asthma and allergic airway diseases. In particular, a study in school-aged children found that FCER1A<sup>+</sup> pDC subsets could differentiate asthmatic from non-asthmatic atopic children (3). In addition, pDCs expressing CD123 (IL3-receptor alpha) are recruited to the lungs during inflammation and migrate to the draining lymph nodes to augment Th2 responses in a mouse model of allergic airway disease (6). These pDCs exhibit an activated inflammatory phenotype in the nasal mucosa upon stimulation with TNF-alpha: here, they favor a Th2 polarizing profile and can markedly increase in number to trigger airway allergy. Thus, not surprisingly, they associate with a higher risk of experiencing asthma attacks and a severe form of the disease. Using data from the GTEx portal, we also found an eQTL association for rs2427837 in lung tissue for *FCER1A* gene (<https://www.ncbi.nlm.nih.gov/gene/?term=2205>) (**Figure E5**). Similar to the effect on pDCs, the AA genotype correlated with the highest *FCER1A* mRNA levels. It is noteworthy that a functional genotype-dependent FCER1A expression has been previously described for the SNP rs2251746 in basophils and mast cells (7).

In monocytes, we found that the AG genotype was associated with increased FCER1A levels and conferred a lower risk for IgE production and allergic disease. This effect could be because serum IgE is cleared via FCER1A capture and internalization by monocytes and mDCs (8). Importantly, the particularly strong correlation between the AG genotype and IgE surface expression on these cells suggests that the contribution of monocytes to allergy control might be underappreciated. A recent review highlighted that FCER1A engagement in monocytes induces indoleamine 2,3-dioxygenase upregulation, which inhibits T-cell proliferation and enhances regulatory T-cell function by depleting tryptophan (9). Moreover, FCER1A cross-linking in monocytes induces IL-10, an anti-inflammatory mediator that might attenuate basophil and DC activation and monocyte phagocytic activity.

Taken together, we propose a model of FCER1A regulation in monocytes and pDCs based on the rs2427837 genotype that is associated with allergic disease risk (7) (**Figure E6**). Certain limitations to our study should be acknowledged. First, we did not evaluate the correlation between rs2427837 and *FCER1A* gene expression in allergic cases versus healthy

controls. Second, the associations that we made between *FCER1A* gene expression and asthma in the SSIC and BAMSE cohorts derive from whole blood samples, not individual immune-cell subsets. Further studies that combine genetic and immune characterizations of *FCER1A* in immune-cell subsets will help to elucidate the contribution of each factor to asthma and allergic disease. Importantly, we confirm that the association of allergy relevant SNP rs2427837 with *FCER1A* and consider that targeting *FCER1A* in monocytes and pDCs might constitute a novel option to reduce allergen-specific responses.

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## Figure legends

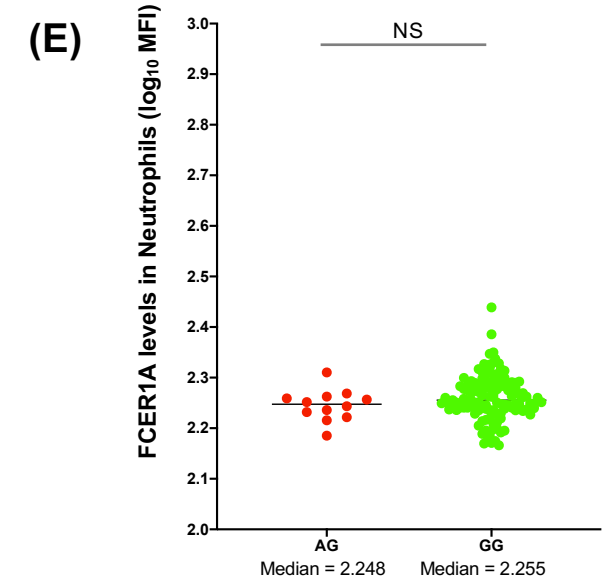
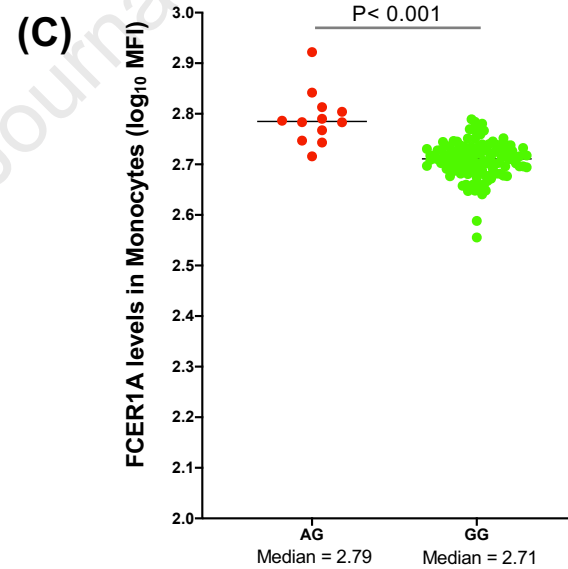
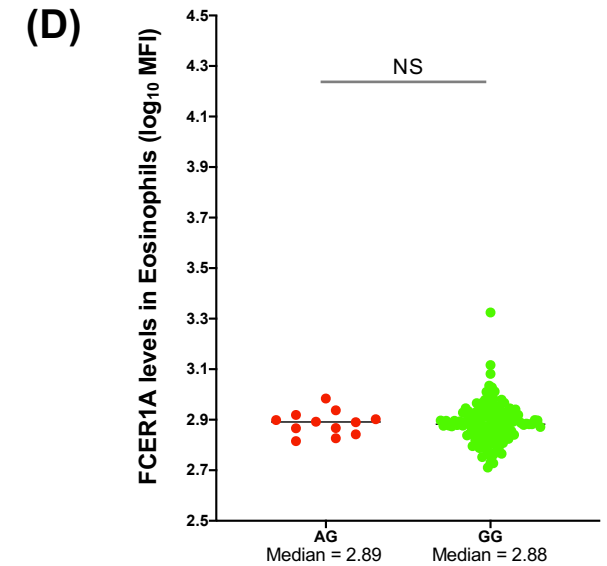
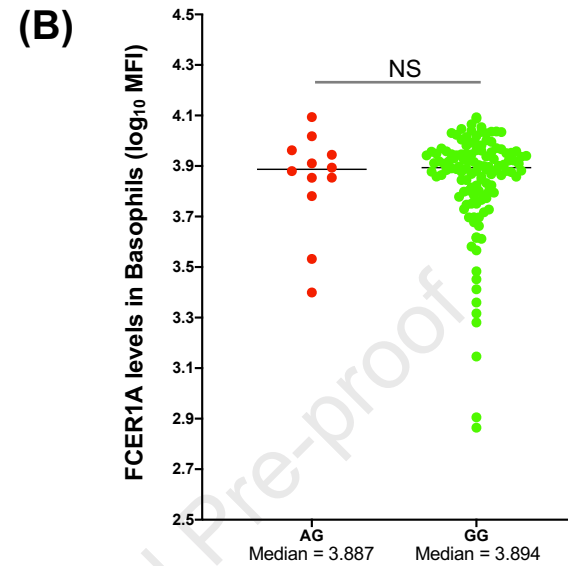
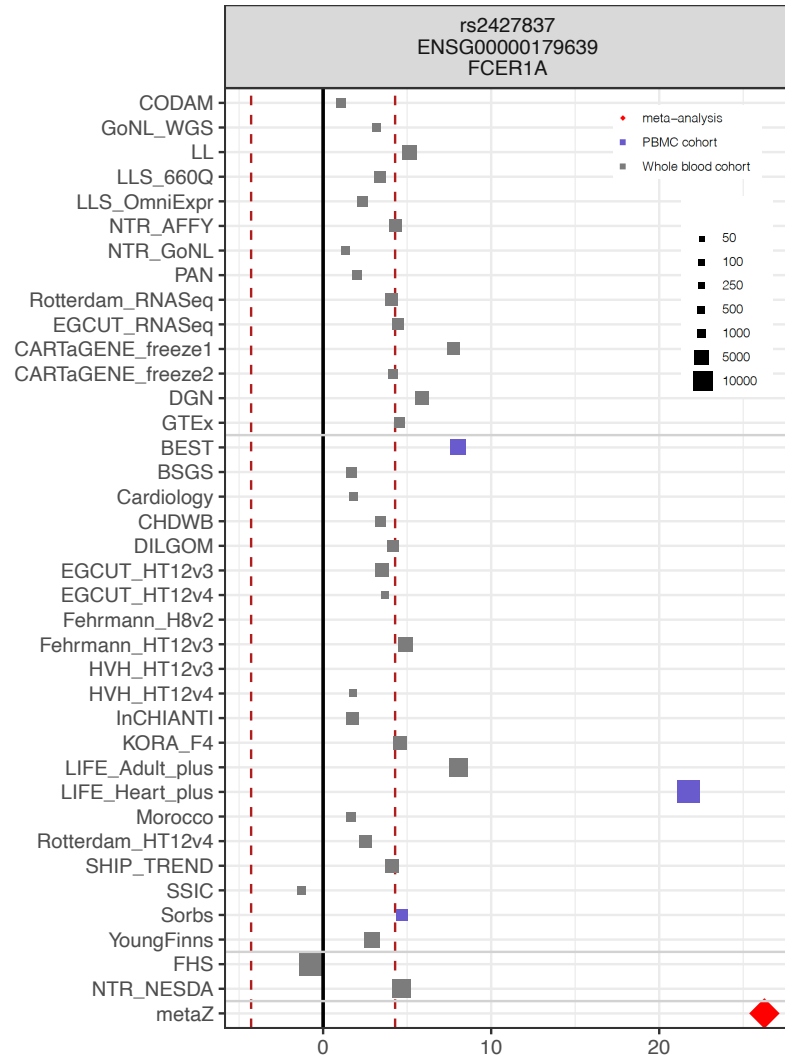
### Figure 1: Association of rs2427837 to *FCER1A* gene and protein levels

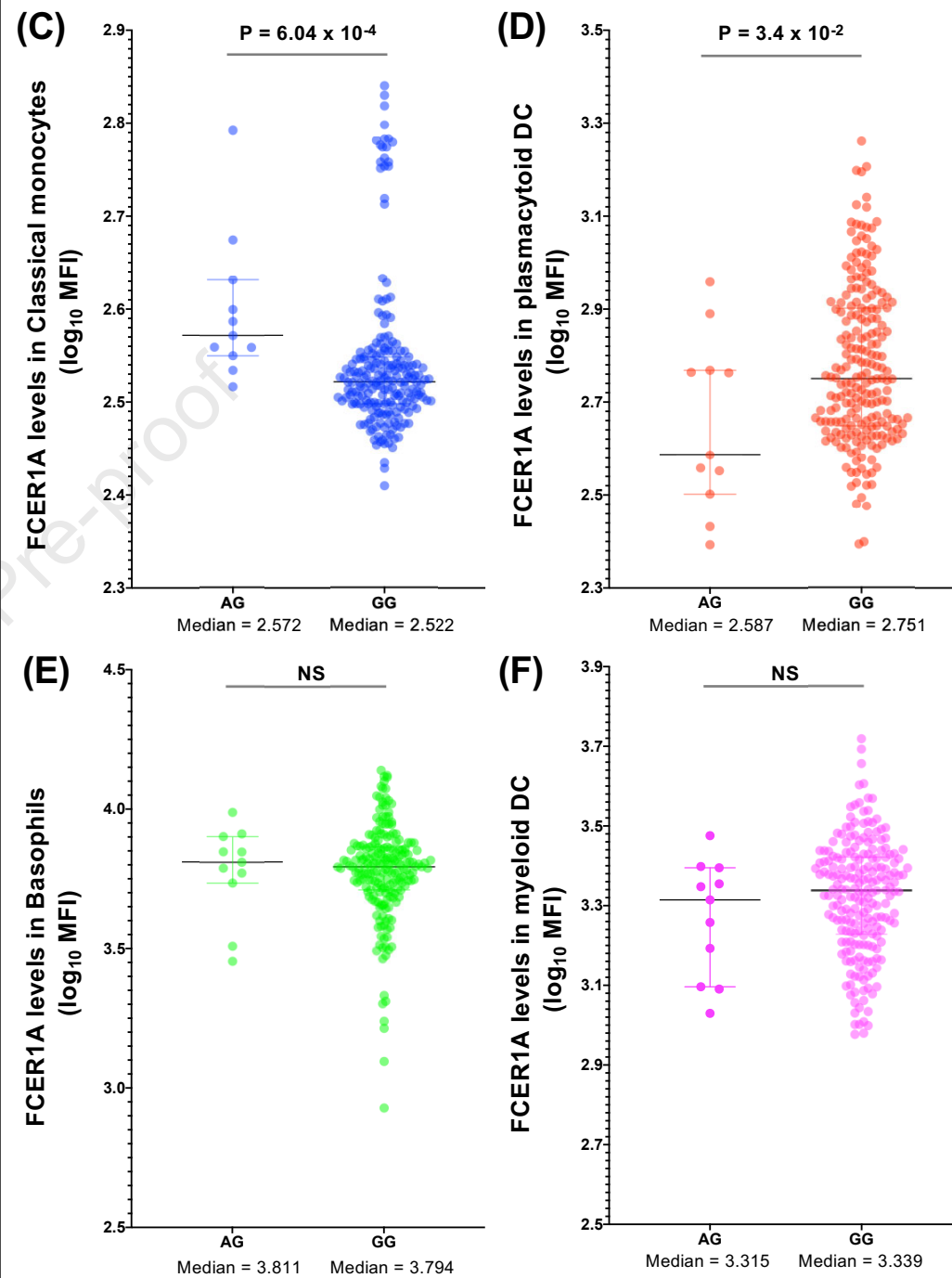
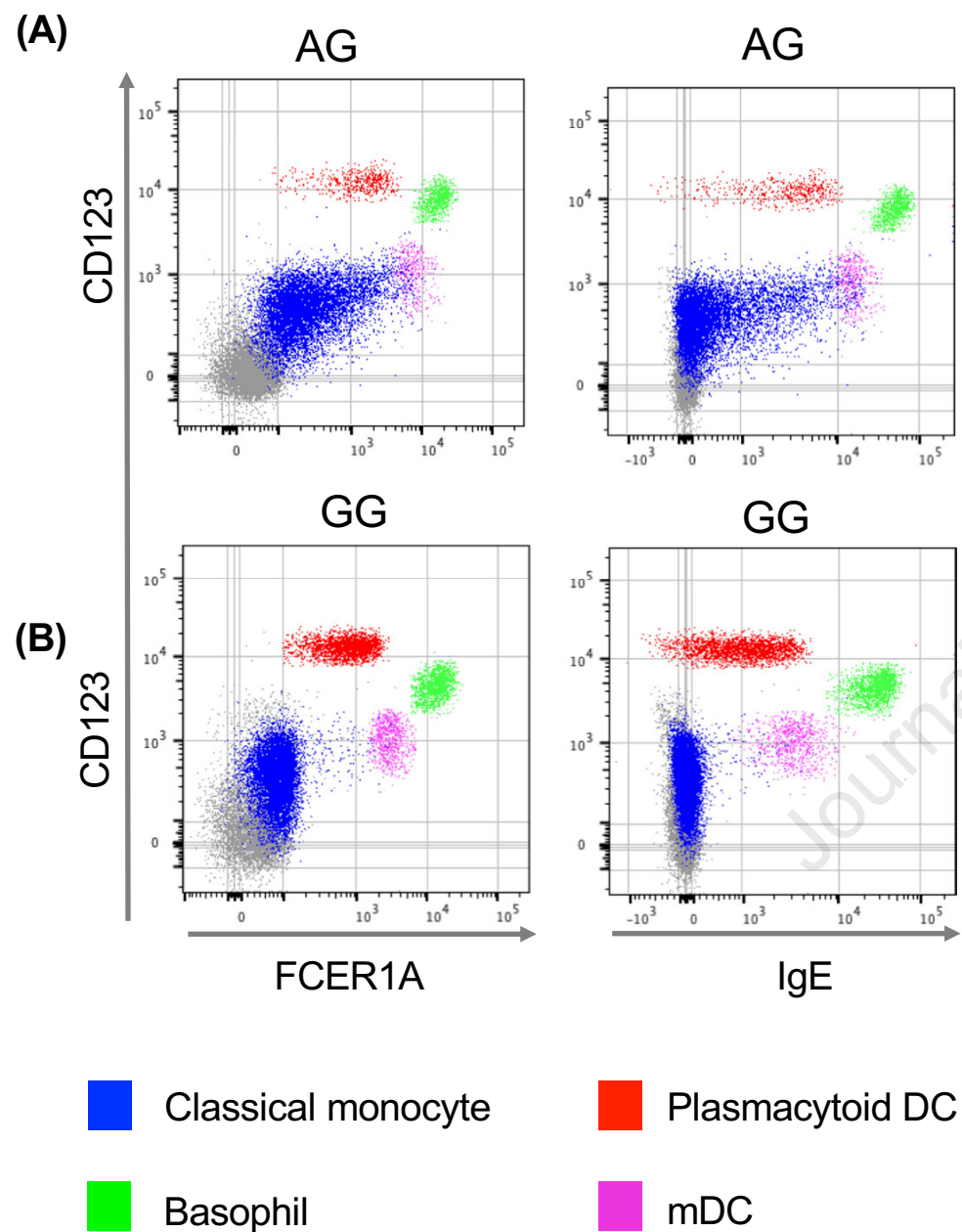
(A) Individual cohort association between rs2427837 and *FCER1A* gene expression, and meta-analysis data. (B) Correlation between rs2427837 genotypes and *FCER1A* protein expression in basophils and monocytes. P-values, Mann-Whitney test.

### Figure 2: Flow cytometry determined protein expression of *FCER1A* in immune subsets in the SSIC cohort

(A-B) *FCER1A* expression in immune subsets stratified by the rs2427837 genotype. The color indicates the various subsets gated on CD123 and *FCER1* $\alpha$  (A) and IgE (B). (C-D) Association between *FCER1A* ( $\log_{10}$ ) MFI in classical monocytes (C) and plasmacytoid dendritic cells (pDC) (D) and the rs2427837 genotype.

**(A) eQTLGen Figure**  
(35 cohorts, N = 31430)





## Materials and methods

### *Flow cytometry staining and characterization of FCER1A protein levels in immune subsets*

The relevant details for the discovery and validation cohorts from the Singapore Chinese cohort have been previously described (1). For the discovery cohort, whole blood samples were lysed with lysis buffer and stained with anti-FcεRI-FITC (AER37, eBioscience), anti-IgE-APC (MB10-5C4, Miltenyi Biotec), and anti-CD123-PerCP-Cy5.5 (6H6, eBioscience) antibodies. For the validation cohort, another four antibodies were included to identify various immune cell populations: anti-CD14 (61D3, eBioscience), anti-CD16 (3G8, Biolegend), anti-CD1c (L161, Biolegend) and anti-HLA-DR (L243, BD Bioscience). In some experiments, staining was performed using the same validation antibody panels on peripheral blood mononuclear cells (PBMCs). A LiveDead exclusion dye was included to discriminate the viable cells. The samples were analysed on a BD FACS CantoII or a BD LSRFortessa flow cytometer. Data analysis and visualisation was performed using Flowjo version 9.9.6 or 10.6.2 software.

### *Genotyping data from the Singapore Chinese cohort*

The Singapore Chinese cohort genotyping data were obtained from Illumina Infinium chips containing SNPs covering the whole genome. DNA extraction and genotyping was performed as previously described (2). Genotyping data for SNPs in the FCER1A locus (rs2427837 and rs2251746) were extracted and the correlation with FCER1A protein expression was determined by performing non-parametric tests.

### *eQTLgen consortium data*

eQTL data for the rs2427837 SNP from whole blood and PBMCs were obtained from the eQTLGen consortium (<https://www.eqtlgen.org>) (3). A meta-analysis of the data from the various cohorts was performed using the Z-score, and a p-value was calculated for a meta p-value and combined Z-score(4).

#### ***GTEx data***

Gene expression plots and eQTL data from lung tissue were downloaded from the GTEx consortium webpage. Data for this consortium were published previously (5).

#### ***Gene expression data from BAMSE cohort***

*FCER1A* gene expression in whole blood and phenotype information for asthma from the BAMSE cohort was extracted from a previously reported dataset (6). Associations of gene expression with the clinical phenotype were determined by performing non-parametric tests. A p-value <0.05 was considered statistically significant.

#### ***Gene expression data from SSIC cohort***

Gene expression data for the Chinese samples were obtained from participants of the Singapore Systems Immunology cohort (SSIC). This cohort constitutes part of an unpublished study that aimed to identify differentially expressed genes for allergic diseases. RNA was isolated from tempus blood tubes using a Qiagen blood kit and then the RNA quality was determined using a Bioanalyzer. An Illumina Human HT-12 gene expression chip was used to determine the mRNA levels. The *FCER1A* mRNA levels extracted for the analysis are presented in this manuscript. The asthma phenotype was determined from the participants answers to a self-report questionnaire and a positive skin prick test result to the house dust mite allergen. Associations between gene expression and the clinical phenotype

were determined by performing non-parametric tests. A  $p < 0.05$  was considered statistically significant.

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## Online Figure legends

### Figure E1: Gating strategy to identify immune populations by flow cytometry

Live cells were first gated using the live/dead (L/D) marker before size stratification using forward (FSC) and side scatters (SSC). Monocytes were gated using the lineage markers CD14 and CD16, while dendritic cells and basophils were gated using CD123, HLA-DR and CD1c.

### Figure E2: FCER1A expression in monocytes stratified by rs2427837.

(A) Two donors per genotype are presented for each of the GG, AG and AA genotype. (B) The percentage of FCER1A-positive monocytes increasing with allele dosage of “A” in classical monocytes.

### Figure E3: Correlation between the rs2427837 genotype and *FCER1A* gene expression in monocytes from the DICE project.

(A-B) An eQTL association plot in (A) classical monocytes (B) non-classical monocytes

### Figure E4: Association of rs2427837 to different immune subsets.

(A-D) Data were obtained from (A) non-classical monocytes (B) T-lymphocytes (C) B-lymphocytes and (D) Natural Killer (NK) cells in the Singapore Chinese cohort (AG= 11, GG=210). The subjects reported here are the same samples reported in Figure 2C-F. Protein levels of FCER1A reported as log<sub>10</sub>MFI

### Figure E5: Association between SNPs at the FCER1A locus and *FCER1A* expression in lung tissue from GTEX portal.

(A) Manhattan plot of the chromosome 1 locus containing *FCER1A* SNPs and their association with gene expression. (B) eQTL plot in lung tissue stratified by the rs2427837 genotype.

### Figure E6: Possible implications of the FCER1A polymorphism rs2427837.

The impact of the rs2427837 genotype on the FCER1A-positive subsets in monocytes and pDCs. A potential balance between these subsets might influence immune regulation associated with allergic phenotypes.

**Table E1: The meta-analysis association results of rs2427837 in the eQTLgen cohort**

| ID        | Pos (hg19) | ID              | Symbol        | p-value   | Z-score | Assessed | Other | No. cohorts | No. samples | FDR        |
|-----------|------------|-----------------|---------------|-----------|---------|----------|-------|-------------|-------------|------------|
| rs2427837 | 159258545  | ENSG00000179639 | <i>FCER1A</i> | 5.79E-152 | 26.2582 | A        | G     | 35          | 31430       | 0          |
| rs2427837 | 159258545  | ENSG00000213088 | <i>DARC</i>   | 4.93E-54  | 15.4776 | A        | G     | 36          | 26609       | 0          |
| rs2427837 | 159258545  | ENSG00000163568 | <i>AIM2</i>   | 4.23E-08  | 5.4811  | A        | G     | 36          | 31644       | 0.00015849 |

Association statistics are shown in the table. The p-value and Z-score were calculated for the combined meta-analysis of the statistics of all the cohorts described in the eQTLgen consortium. More details on the analysis are provided in *Vosa et al.* <sup>7</sup>

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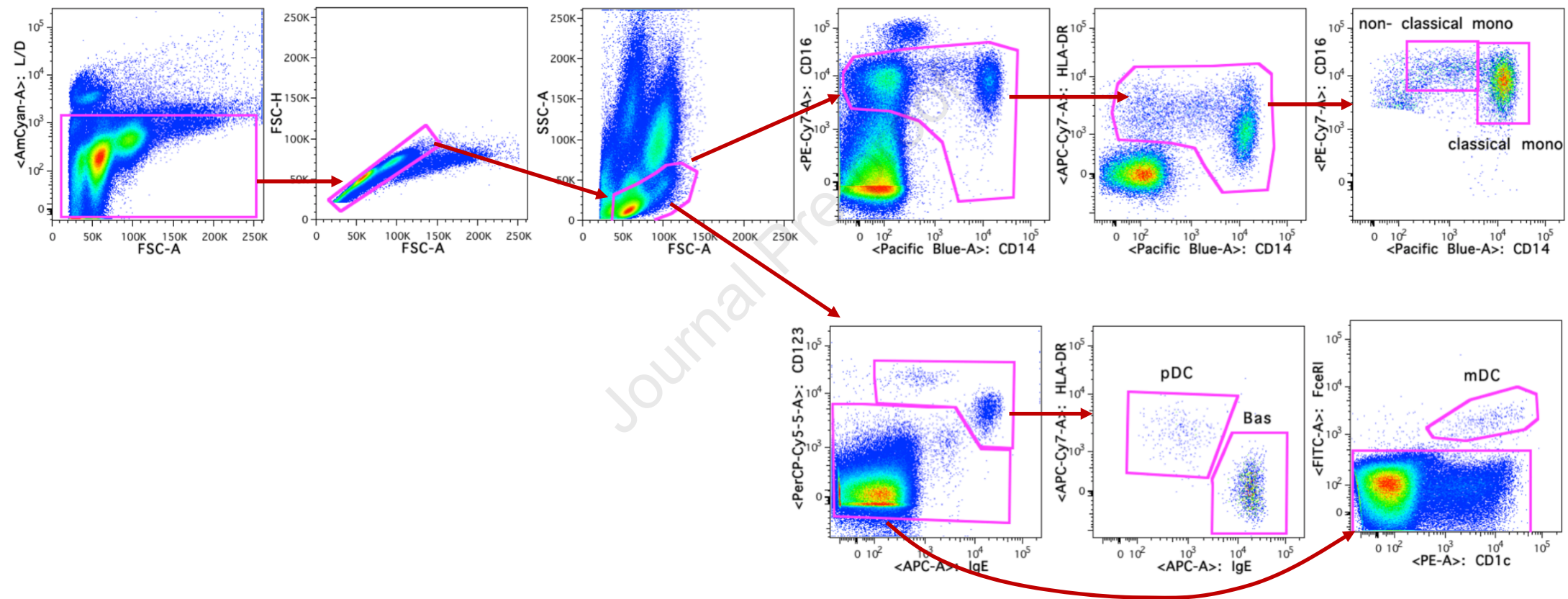
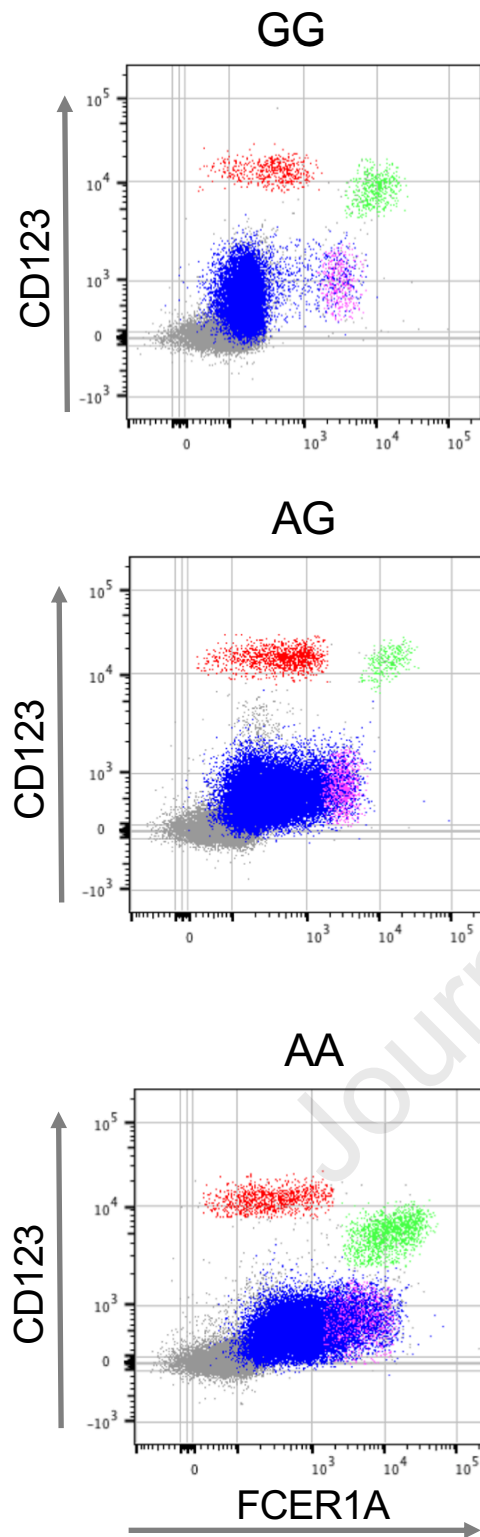
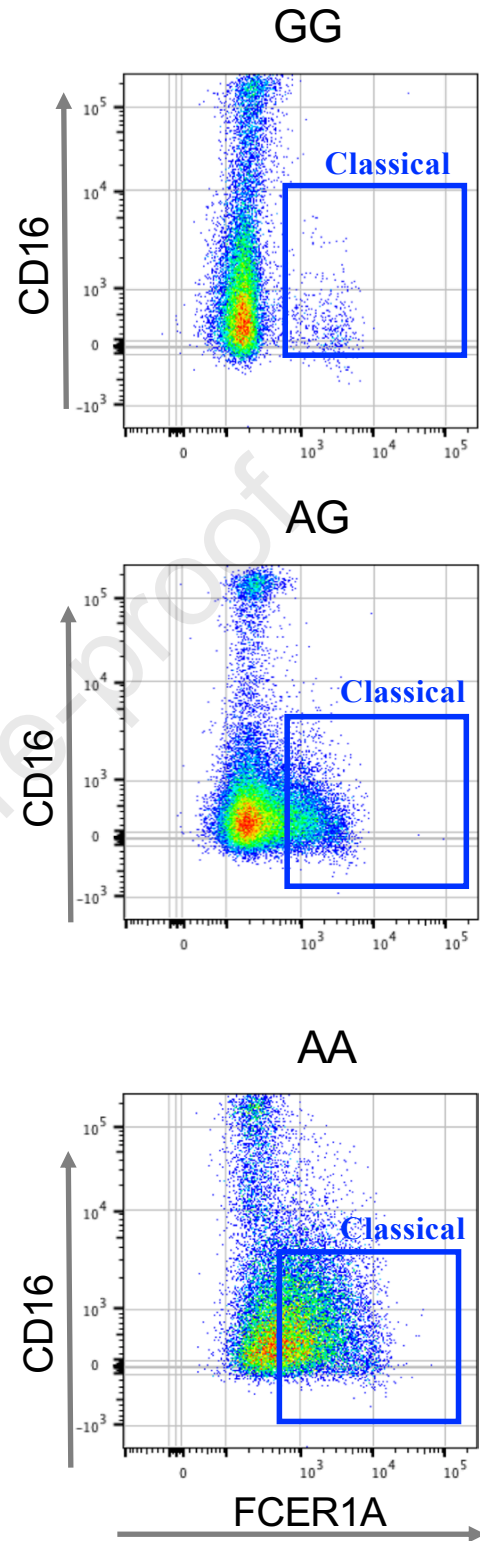


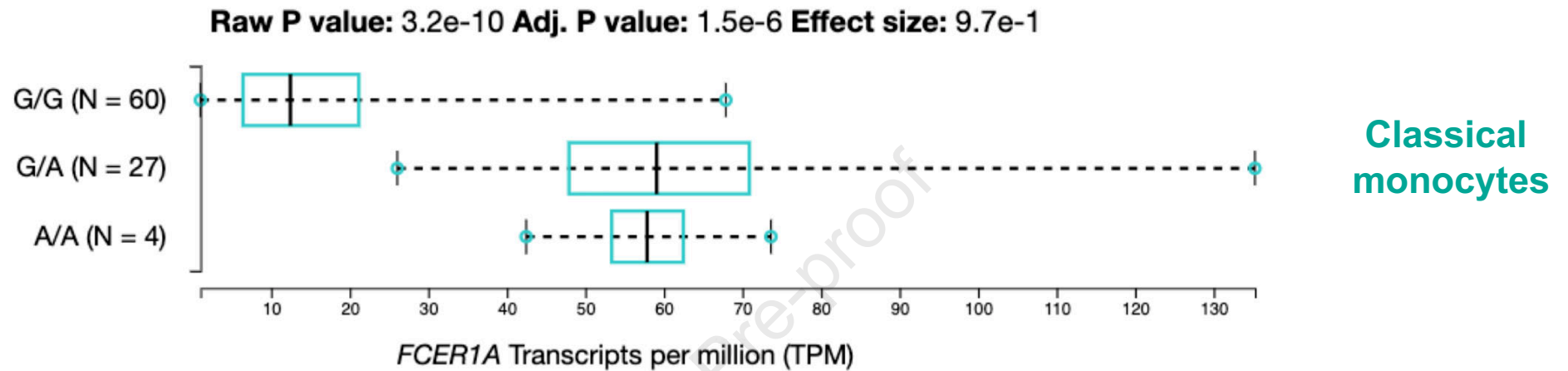
Figure E1

**(A) rs2427837 genotype****(B) rs2427837 genotype**

- Classical monocyte
- Plasmacytoid DC
- Myeloid DC
- Basophil

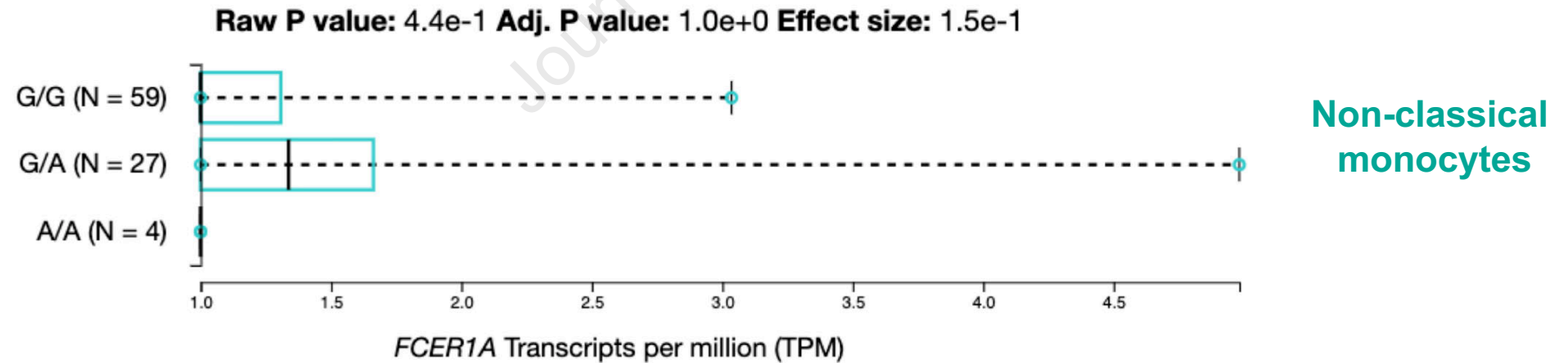
(A)

rs2427837 genotype



(B)

rs2427837 genotype



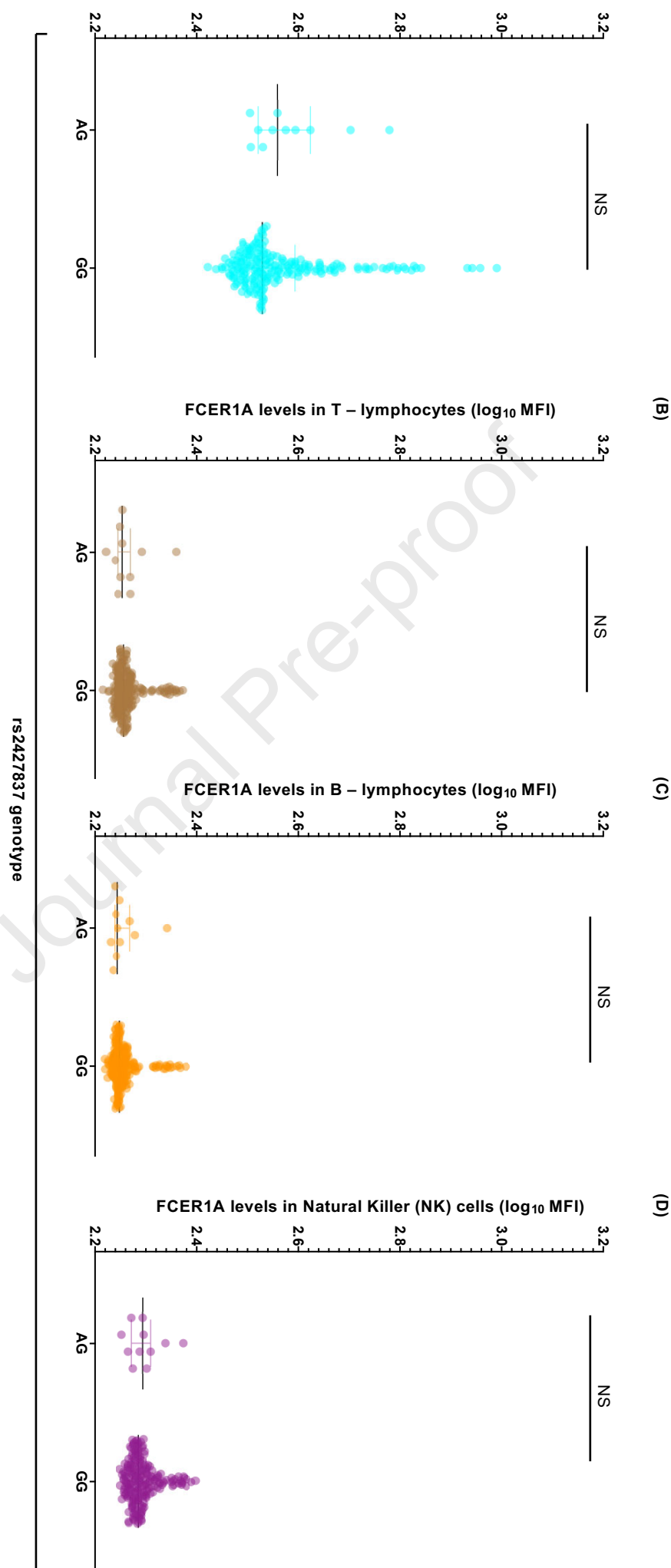
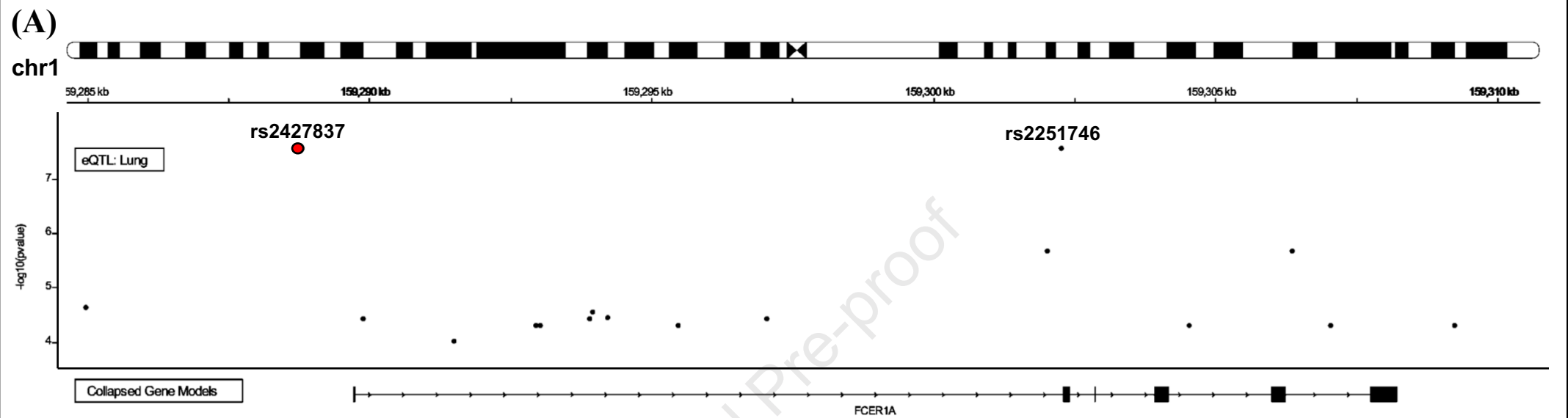


Figure E4



**(B)**

