



Short communication

No genetic association detected with mepolizumab efficacy in severe asthma

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ABSTRACT

Background and objectives: Treatment with mepolizumab, a humanized monoclonal antibody to interleukin-5, reduces the rate of asthma exacerbations and the requirement for systemic glucocorticoids while maintaining asthma control. Treatment decisions are guided by predictors of response, including blood eosinophil thresholds in patients with frequent exacerbations despite intensive anti-inflammatory and controller treatment. Identification of additional predictors of response could aid treatment decisions. We investigated genetic associations that may predict response to mepolizumab-treatment.

Methods: In this post hoc analysis of DREAM and MENSA, association of genetic markers was tested in patients with severe asthma treated with mepolizumab who provided consent for pharmacogenetic research. Association was tested in a tiered approach with alpha spend differing for candidate genetic markers selected for prior history of association with relevant traits or pathways and in a genome-wide analyses ($p < 4.7 \times 10^{-4}$ and $p < 5 \times 10^{-8}$, respectively). Efficacy endpoints included: clinically significant exacerbation rate (tested using a negative binomial model), time to first exacerbation (tested with a Cox proportional hazards model), change in exacerbation rate, change in eosinophil count, and change in IgE level (tested by linear regression).

Results: No genetic marker was significantly associated with the primary endpoint, clinically significant exacerbation rate. One genetic marker was associated with time to first clinically significant exacerbation, but this association was driven by the DREAM data and was not supported in additional sensitivity analyses by treatment regimen/dose.

Conclusion: No genetic effect on mepolizumab-treatment response was identified in this population on intensive asthma treatment, with history of frequent exacerbations and pre-selected for airway eosinophilia.

1. Brief communication

Treatment with mepolizumab, a humanized monoclonal antibody to interleukin-5 (IL-5), reduces the rate of asthma exacerbations and the requirement for systemic glucocorticoids while maintaining asthma control [1–3]. Treatment benefit is guided by predictors of response based on specific phenotypic characteristics. These include blood eosinophil thresholds in patients with frequent exacerbations despite intensive anti-inflammatory and controller treatment. However,

identification of additional predictors of response could aid with treatment decisions. In the Dose Ranging Efficacy and Safety with Mepolizumab (DREAM [1]) study, key phenotypic characteristics were associated with response to mepolizumab. These characteristics guided enrollment in the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA [2]) study. In this post hoc analysis of DREAM and MENSA, we used clinical samples and data from these two studies to investigate potential genetic associations that may predict efficacy response to mepolizumab treatment in patients with severe eosinophilic

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asthma.

The intent-to-treat (ITT) study population included 1192 patients enrolled in two studies: DREAM (NCT01000506), $n = 616$, and MENSA (NCT01691521), $n = 576$. The exploratory pharmacogenetic (PGx) study sample included ITT patients who provided informed consent and blood samples for PGx investigations (DREAM, $n = 589$; MENSA, $n = 464$). To reduce confounding due to genetic admixture, primary PGx analyses were limited to DNA samples and clinical datasets from non-Hispanic white patients (DREAM, $n = 468$; MENSA, $n = 352$).

Efficacy endpoints used for PGx analyses were the clinical study primary endpoint, clinically significant exacerbation rate (CSE; number of asthma exacerbations resulting in emergency room visit, hospitalizations, or at least 3 days of steroid use), time to first CSE, change in CSE rate, change in eosinophil count, and change in immunoglobulin E (IgE) level.

Two analysis approaches were used. Candidate genetic variants (105) from 53 gene regions previously linked to asthma, asthma severity and/or within candidate IL-5 and eosinophil pathway genes (Table E1) were analyzed. Other variants were tested in an exploratory genome-wide association study (GWAS). We selected genetic variants described in asthma or nasal polyp literature and in IL-5/eosinophil literature and reported in IL-5 pathways. This selection used a combination of systematic text mining via the Linguamatics I2E platform (Linguamatics Ltd, Cambridge, UK; www.linguamatics.com [4]) and pathway analysis using QIAGEN's Ingenuity Pathway Analysis (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity) and MetaCore™ from GeneGo (a Thomson Reuters business). DREAM samples were genotyped using the OmniExpressExome BeadChip (Illumina, San Diego, CA, USA), by Expression Analysis (Morrisville, NC, USA) and using KASP assays (LGC Genomics, Hertfordshire, UK). MENSA samples were genotyped using the Axiom Biobank Plus array (Affymetrix, Santa Clara, CA, USA) by BioProcessing Solutions Alliance (Piscataway, NJ, USA). Missing genotypes were imputed [5] using a 1000G project reference panel Phase I data [6].

Associations with each genetic variant were analyzed using regression models, assuming an additive genetic model. Generalized linear regression, assuming a negative binomial outcome with log-link function, was used for CSE, Cox regression was used for time to first CSE, and normal linear regression was used for change in CSE, eosinophil count, and IgE. Three GWAS principal components, corticosteroid use and number of exacerbations prior to commencement of treatment were included in each regression model to account for population ancestry and clinical heterogeneity. Subject level data was analyzed separately for the two studies, then meta-analyzed.

The false-positive rates were set to 5%, with statistical significance declared at $p < 4.7 \times 10^{-4}$ for candidate genetic variant and $p < 5.0 \times 10^{-8}$ for GWAS analysis, respectively [7]. No further adjustments were made for the number of phenotypes analyzed.

Power (assuming an additive genetic model) was evaluated for changes in exacerbation rate ratio, ranging from 1.1 to 2.5, with variant frequencies between 10% and 50%. The candidate variant analysis had 80% power to identify differences in exacerbation rate ratios of ≥ 1.6 , for common genetic variants with minor allele frequency $> 20\%$ (power to detect smaller genetic effects and/or lower frequency alleles is limited). The power for this PGx study was estimated assuming an effect equivalent to or higher than the clinical study effect size for each trial (Fig. E1).

Key covariates and demographic factors such as age, sex, baseline eosinophil count, baseline oral corticosteroid use, or baseline exacerbation count in the 12 months prior to study enrollment are summarized for the ITT and PGx analysis samples, and by placebo- and mepolizumab-treated subgroups, for DREAM (Table E2A) and MENSA (Table E2B). These summaries suggest that the PGx cohort is representative of the ITT population in each study.

After multiple test adjustment in either candidate gene variant or GWAS analyses (Fig. E2), no variant was significantly associated with

the primary endpoint, CSE.

However, genomic regions with association evidence just below the GWAS threshold for statistical significance ($5 \times 10^{-8} < p\text{-value} \leq 10^{-6}$) were evaluated. Four variants in chromosome 6 and two variants mapping to chromosome 9 met this criterion. The four variants in chromosome 6 (rs114633080, rs137893217, rs78517277 and rs117220641) are in complete Linkage Disequilibrium (LD) so indistinguishable in effect. These variants are all intergenic. The nearest genes to these variant location include *UTRN* (which encodes a cytoskeleton protein, utrophin) and *EPH2A* (which encodes a phosphatase, laforin), but there is no clear biologic justification for involvement of either of these genes with asthma or mepolizumab response. The two variants on chromosome 9 also meeting this criterion (rs10811516 and rs10811517) are in complete LD, and map to an intergenic region flanked by type I interferon genes including *IFNA14* and a pseudogene of unknown function, *IFNA22P*. Type I interferons are cytokines with antiviral, antiproliferative, and immunomodulatory properties. Group 2 innate lymphoid cells (ILC2) are involved in respiratory virus-associated pulmonary type 2 immunopathology. Although a specific role for interferon alpha 14 has not been defined in infection associated immune responses, other type I interferons directly regulate the activation of ILC2. In the recent publication of Duerr et al., 2016 [8], cultures of ILC2 cells produced less IL-5 when treated with a different type 1 interferon, Interferon β . Although this result is intriguing, a role for interferon alpha 14 in ILC2 cell activation is yet to be established.

Of the 105 candidate genetic variants, only 8 variants had weak evidence of association ($p < 0.05$, Fig. 1). No suggestive associations were found with change in eosinophils or IgE in either GWAS or candidate gene analyses. However, the intronic variant, rs1021621 (A > G), in *POU2F1*, was significantly associated with time to first CSE ($p = 2 \times 10^{-5}$) when both studies were meta-analyzed, with a 20% reduction in CSE rate in patients treated with mepolizumab ($p = 0.007$, not statistically significant). This *POU2F1* variant was further tested in patient subsets by dose. This association was driven mainly by the DREAM data ($p = 1.5 \times 10^{-4}$) over the MENSA data ($p = 0.037$), and in particular, a small subset of patients who were treated with 750 mg (intravenously), the highest experimental dose ($p = 0.002$, $n = 119$). Given the small number of samples, this suggestive association will require replication in larger sample sets.

In summary, we conducted a PGx efficacy analysis for mepolizumab-treatment response in patients with severe eosinophilic asthma with a history of frequent exacerbations. The available sample size, though the largest reported to date, only had statistical power to identify large and common genetic effects; this study was therefore not powered to detect small genetic effects or effects from rare variants. No PGx effects on mepolizumab-treatment response were identified. However, given that we had 80% power to detect common genetic effects (minor allele frequency $> 20\%$) in non-Hispanic white patients, similar in size to the overall treatment effect, it is possible that less common and/or small genetic effects on mepolizumab-treatment response will be missed.

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Author contributions

LC, MC, HO, NB, SY and SG were involved in the concept and design of the study. EH was involved in the acquisition of the data. All authors were involved in data analysis and interpretation, preparation and review of the manuscript and approved the final version to be submitted.

Conflict of interest

MC, NB, SY, and SG are employees of GlaxoSmithKline (GSK) and

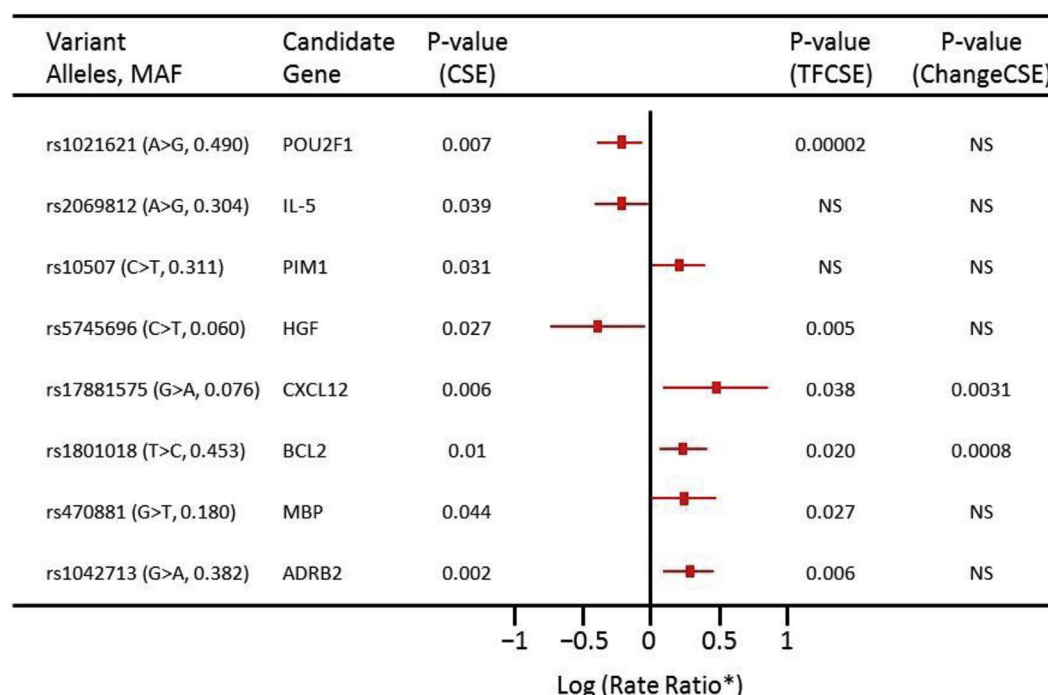


Fig. 1. Candidate Variant/Gene Association Results – with $p < 0.05$ on the primary endpoint (CSE) with corresponding data on secondary endpoints.

*Association results for the primary endpoint (CSE, $n = 584$); threshold for declaring statistical significance, $p < 4.7 \times 10^{-4}$. ADRB2, adrenoceptor beta 2; BCL2, B-cell CLL/lymphoma 2; ChangeCSE, difference in on-treatment CSE and the year prior; CSE, clinically significant asthma exacerbation rate; CXCL12, C-X-C motif chemokine ligand 12; HGF, hepatocyte growth factor; IL-5, interleukin 5; MAF, minor allele frequency; MBP, myelin basic protein; NS, not significant; PIM1, Pim-1 proto-oncogene, serine/threonine kinase; POU2F1, POU class 2 homeobox 1; TFCSE, time to first CSE.

own stock/stock options in GSK. LC and EH are former employees of GSK and own stock/stock options in GSK. HO is a former employee of GSK. ERB has received grants from AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Cephalon/Teva, Forest, Genentech, GSK, Johnson & Johnson (Jansen), Novartis, Sanofi, and Regeneron. He has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GSK, Forest, Novartis, Regeneron, and Sanofi. MH has received grants from GSK and Sanofi, and has received personal fees for consultancy/advisory boards from GSK, AstraZeneca, Novartis, Roche, and Sanofi. PJT has received consultancy fees from GSK, Novartis, CSL Behring, Boehringer Ingelheim, and AstraZeneca. PG has received grants and personal speaker's fees from GSK, Novartis, and AstraZeneca.

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Appendix A. Supplementary data

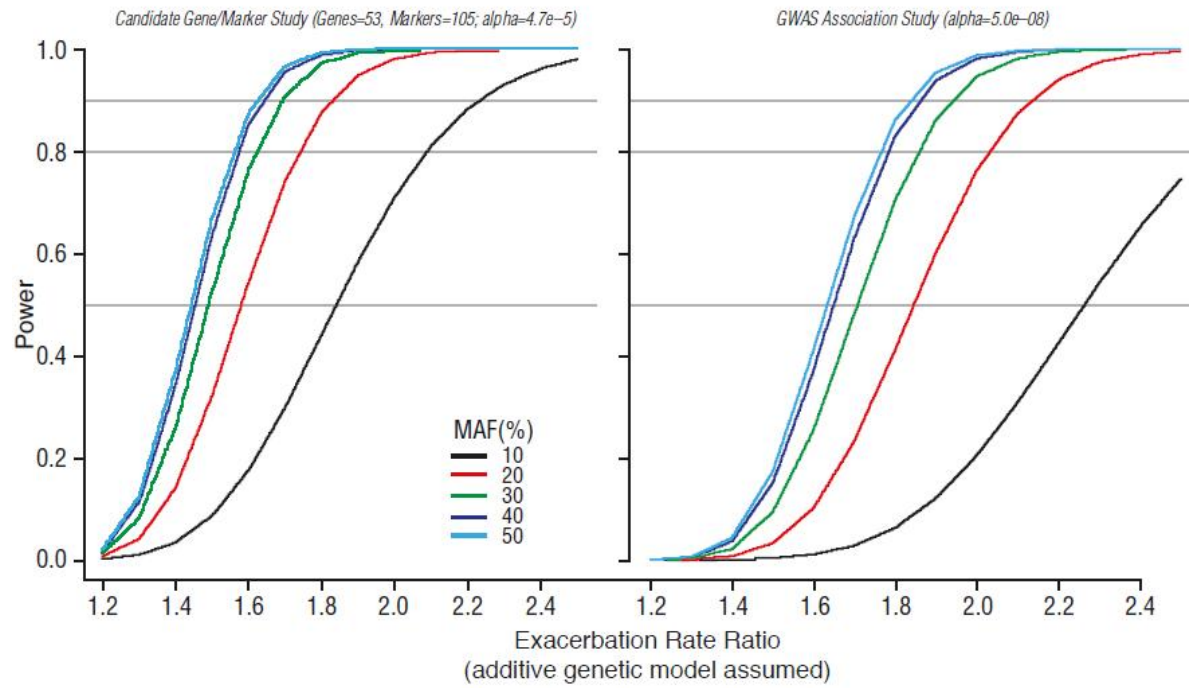
Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2017.10.019>.

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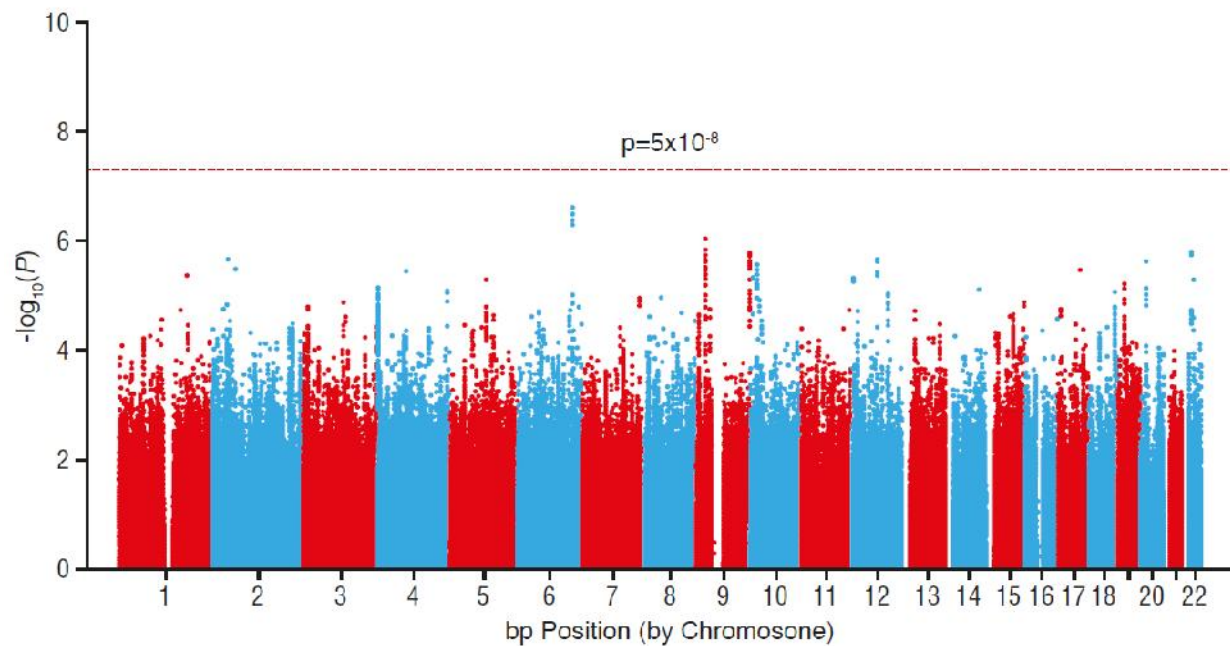
Online repository materials

Figure E1. Power of analysis of the 584 mepolizumab-treated subjects in the combined study sample.



GWAS, genome-wide association study; MAF, minor allele frequency.

Figure E2. Genome-wide association results for the primary endpoint, CSE. No variants were significantly associated with CSE.



CSE, clinically significant asthma exacerbation rate.

Table E1. Candidate polymorphisms.

Polymorphism	Chr	Candidate gene	Functional consequence*	Polymorphism	Chr	Candidate gene	Functional consequence*
rs4950928	1	<i>CHI3L1</i>	utr variant 5'	rs2302009	7	<i>CCL26</i>	utr variant 3'
rs4950930	1	intergenic near <i>CHI3L1</i>	intergenic variant (1000 Genomes)	rs6967330	7	<i>CDHR3</i>	intron variant, missense, nc transcript variant
rs10399931	1	<i>CHI3L1</i>	upstream variant 2KB,utr variant 5'	rs5745696	7	<i>HGF</i>	intron variant
rs10920579	1	<i>CHI3L1</i>	upstream gene variant (1000 Genomes)	rs1364612	9	<i>IFNB1</i>	downstream variant 500B
rs1021621	1	<i>POU2F1</i>	intron variant	rs1342326	9	intergenic near <i>IL33</i>	intergenic variant (1000 Genomes)
rs10496476	2	<i>DPP10</i>	intron variant	rs3939286	9	intergenic near <i>IL33</i>	intergenic variant (1000 Genomes)
rs12619285	2	<i>IKZF2</i>	intron variant	rs10512202	9	<i>SYK</i>	intron variant
rs3771166	2	<i>IL18R1</i>	intron variant	rs17881575	10	<i>CXCL12</i>	intron variant, utr variant 3'
rs11685480	2	<i>IL1RL1</i>	upstream variant 2KB	rs545659	11	<i>GPR44</i>	utr variant 3'
rs1041973	2	<i>IL1RL1</i>	missense,nc transcript variant,utr variant 5'	rs3184504	12	<i>SH2B3</i>	missense, synonymous codon, utr variant 5'
rs1420101	2	<i>IL1RL1</i>	intron variant,nc transcript variant	rs167769	12	<i>STAT6</i>	intron variant, utr variant 5 prime
rs17748980	2	<i>STAT1</i>	intron variant (1000 Genomes)	rs2233859	14	<i>LOC100507513</i> , <i>RNASE3</i>	intron variant
rs9853223	3	<i>CCR3</i>	intron variant	rs2073342	14	<i>LOC100507513</i> , <i>RNASE3</i>	intron variant, missense
rs3091250	3	<i>CCR3</i>	intron variant	rs2233860	14	<i>LOC100507513</i> , <i>RNASE3</i>	intron variant, utr variant 3'
rs3091311	3	<i>CCR3</i>	intron variant	rs744910	15	<i>SMAD3</i>	intron variant

rs4987053	3	<i>CCR3</i>	synonymous codon	rs223819	16	<i>CCL22</i>	intron variant
rs6550178	3	<i>CCR4</i>	intron variant	rs1805010	16	<i>IL4R</i>	missense, synonymous codon, utr variant 5'
rs4857855	3	<i>3q21 (near GATA2)</i>	downstream gene variant (1000 Genomes)	rs1805011	16	<i>IL4R</i>	Missense
rs4328821	3	intergenic near <i>GATA2</i>	regulatory region variant (1000 Genomes)	rs1805015	16	<i>IL4R</i>	missense
rs4054760	3	<i>IL5RA</i>	intron variant,utr variant 5 prime	rs1801275	16	<i>IL4R</i>	missense
rs2290608	3	<i>IL5RA</i>	utr variant 5'	rs2872507	17	<i>ZBP2-GSDMB</i>	intergenic variant (1000 Genomes)
rs11735550	4	<i>KIT</i>	intron variant	rs7216389	17	<i>GSDMB</i>	intron variant
rs1598861	4	<i>LOC101929401, NFKB1</i>	intron variant	rs4065275	17	<i>ORMDL3</i>	intron variant
rs1020759	4	<i>NFKB1</i>	intron variant	rs12603332	17	<i>LRRC3C, ORMDL3</i>	intron variant, upstream variant 2KB
rs17813652	5	<i>ADCY2</i>	intron variant	rs8079416	17	<i>LRRC3C</i>	intron variant
rs10063916	5	<i>ADCY2</i>	intron variant	rs2305480	17	<i>GSDMB</i>	downstream variant 500B, missense, nc transcript variant
rs4701786	5	<i>ADCY2</i>	intron variant	rs4987869	18	<i>BCL2</i>	utr variant 3'
rs326171	5	<i>ADCY2</i>	intron variant	rs4987797	18	<i>BCL2</i>	intron variant
rs326173	5	<i>ADCY2</i>	utr variant 3'	rs720321	18	<i>BCL2</i>	intron variant
rs1042713	5	<i>ADRB2</i>	missense	rs954954	18	<i>BCL2</i>	intron variant
rs25882	5	<i>CSF2</i>	missense	rs4987752	18	<i>BCL2</i>	intron variant
rs1881457	5	<i>IL13, TH2LCRR</i>	upstream variant 2KB	rs7242402	18	<i>BCL2</i>	intron variant
rs1800925	5	<i>IL13, TH2LCRR</i>	upstream variant 2KB	rs2850761	18	<i>BCL2</i>	intron variant

rs20541	5	<i>IL13</i>	missense	rs949037	18	<i>BCL2</i>	intron variant
rs2243204	5	<i>IL13</i>	intron variant (1000 Genomes)	rs1801018	18	<i>BCL2</i>	nc transcript variant, synonymous codon
rs40401	5	<i>IL3, LOC105379174</i>	intron variant, missense	rs7236477	18	<i>DSG1</i>	intron variant
rs2243250	5	<i>IL4</i>	upstream variant 2KB	rs470881	18	<i>MBP</i>	intron variant
rs4143832	5	<i>IL5</i>	regulatory region variant (1000 Genomes)	rs2228138	19	<i>FCER2</i>	synonymous codon
rs2069812	5	<i>IL5</i>	intron variant, upstream variant 2KB	rs28364072	19	<i>FCER2</i>	intron variant
rs3212430	5	<i>ITGA2</i>	intron variant	rs7249320	19	<i>FCER2</i>	intron variant
rs3756537	5	<i>ITGA2</i>	intron variant	rs2228137	19	<i>FCER2</i>	missense
rs988557	5	<i>ITGA2</i>	intron variant	rs2787094	20	<i>ADAM33</i>	downstream variant 500B,nc transcript variant, utr variant 3'
rs2112290	5	<i>ITGA2</i>	intron variant	rs2280090	20	<i>ADAM33</i>	intron variant, missense, nc transcript variant
rs3212578	5	<i>ITGA2</i>	intron variant	rs2280091	20	<i>ADAM33</i>	intron variant, missense, nc transcript variant
rs2244012	5	<i>RAD50</i>	intron variant	rs3918402	20	<i>ADAM33</i>	intron variant
rs3806932	5	<i>TSLP</i>	upstream variant 2KB	rs511898	20	<i>ADAM33</i>	intron variant
rs10062929	5	<i>TSLP</i>	intron variant, upstream variant 2KB	rs487377	20	<i>ADAM33</i>	intron variant
rs7723819	5	<i>WDR36</i>	upstream variant 2KB	rs3918241	20	<i>MMP9</i>	upstream variant 2KB
rs1043828	5	<i>WDR36</i>	utr variant 3'	rs3918256	20	<i>MMP9</i>	intron variant
rs9373124	6	<i>HBS1L</i>	intron variant (1000 Genomes)	rs3787268	20	<i>MMP9</i>	intron variant
rs9494145	6	<i>HBS1L-MYB</i>	intergenic variant	rs17577	20	<i>MMP9</i>	missense

			(1000 Genomes)				
rs10507	6	<i>PIM1</i>	utr variant 3'	rs2284033	22	<i>IL2RB</i>	intron variant
rs2269426	6	<i>TNXB</i> (MHC domain)	intron variant				

*Functional consequence for each polymorphism is assigned by the National Center for Biotechnology Information (NCBI;dbSNP Build 147).

If this was not assigned by NCBI, then a secondary assignment was sought through 1000 Genomes (Ensembl; GRCh37), as noted.

Table E2A. Baseline characteristics of DREAM patients.

		ITT population (N=616)			PGx population (N=589)		
		Placebo	Mepolizumab	Total	Placebo	Mepolizumab	Total
Baseline measures or covariates		(n=155)	(n=461)	(n=616)	(n=148)	(n=441)	(n=589)
Age (years)	Mean	46.39	49.37	48.62	46.60	49.37	48.68
	Min	20.00	15.00	15.00	20.00	15.00	15.00
	Max	68.00	74.00	74.00	68.00	74.00	74.00
Age group	<35	24 (15)	52 (11)	76 (12)	22 (15)	51 (12)	73 (12)
	≥35	131 (85)	409 (89)	540 (88)	126 (85)	390 (88)	516 (88)
Eosinophils (cells/uL)	<150	38 (24)	123 (27)	161 (26)	38 (26)	118 (27)	156 (27)
	150<300	32 (21)	129 (28)	161 (26)	28 (19)	126 (29)	154 (26)
	300<500	37 (24)	98 (21)	135 (22)	37 (25)	94 (21)	131 (22)
	≥500	48 (31)	111 (24)	159 (26)	45 (30)	103 (23)	148 (25)
Sex	Female	97 (63)	290 (63)	389 (63)	94 (64)	277 (63)	371 (63)
	Male	58 (37)	171 (37)	229 (37)	54 (36)	164 (37)	218 (37)
Race	White (EU ancestry)*	120 (77)	366 (79)	486 (79)	115 (78)	353 (80)**	468 (79)
	Asian	8 (5)	26 (6)	34 (5)	8 (5)	25 (6)	33 (6)
	Black	6 (4)	17 (4)	23 (4)	4 (3)	13 (3)	17 (3)
	Other	21 (14)	52 (11)	73 (12)	21 (14)	50 (11)	71 (12)
OCS daily use	No	110 (71)	318 (69)	428 (69)	105 (71)	304 (69)	409 (69)
	Yes	45 (29)	143 (31)	188 (31)	43 (29)	137 (31)	180 (31)
Exacerbations	2	66 (43)	220 (48)	286 (46)	64 (43)	212 (48)	276 (47)
	3	52 (33)	102 (22)	154 (25)	48 (32)	97 (22)	145(25)
	≥4	37 (24)	139 (30)	176 (29)	36 (25)	132 (30)	168(28)

*Only non-Hispanic white (EU ancestry) subjects were included in PGx analyses.

**One subject was excluded from the analysis due to cryptic relatedness.

ITT, intent-to-treat; PGx, pharmacogenetics; OCS, oral corticosteroids.

Table E2B: Baseline characteristics of MENSA patients.

Baseline measures or covariates		ITT population (N=576)			PGx population (N=464)		
		Placebo (n=191)	Mepolizumab (n=385)	Total (n=576)	Placebo (n=154)	Mepolizumab (n=310)	Total (n=464)
Age (years)	Mean	49.18	50.58	50.12	49.23	50.00	49.93
	Min	12.00	12.00	12.00	12.00	12.00	12.00
	Max	76.00	82.00	82.00	76.00	81.00	81.00
Age group (%)	<35	28 (15)	47 (12)	75 (13)	22 (14)	37 (12)	59 (13)
	≥35	163 (85)	338 (88)	501 (87)	132 (86)	273 (88)	405 (87)
Eosinophils (cells/uL)	<150	34 (18)	89 (23)	123 (21)	28 (18)	70 (22)	98 (21)
	150<300	51 (27)	94 (25)	145 (25)	40 (26)	80 (26)	120 (26)
	300<500	40 (21)	78 (20)	118 (21)	32 (21)	71 (23)	103 (22)
	≥500	66 (34)	124 (32)	190 (33)	54 (35)	89 (29)	143 (31)
Sex (%)	Female	107 (56)	222 (58)	329 (57)	85 (55)	178 (57)	263 (57)
	Male	84 (44)	163 (42)	247 (43)	69 (45)	132 (43)	201 (43)
Race (%)	White (EU ancestry)*	134 (70)	269 (70)	403 (70)	117 (76)	235 (76)**	352 (76)
	Asian	38 (20)	67 (17)	105 (18)	20 (13)	31 (10)	51 (11)
	Black	3 (2)	13 (3)	16 (3)	3 (2)	12 (4)	15 (3)
	Other	16 (8)	36 (10)	52 (9)	14 (9)	32 (10)	46 (10)
OCS daily use	No	147 (77)	285 (74)	432 (75)	116 (75)	232 (75)	348 (75)
	Yes	44 (23)	100 (26)	144 (25)	38 (25)	78 (25)	116 (25)
Exacerbations	2	90 (47)	156 (40)	246 (43)	77 (50)	131 (42)	208 (45)
	3	46 (24)	95 (25)	141 (24)	33 (21)	75 (24)	108 (23)
	4+	55 (29)	134 (35)	189 (33)	44 (29)	104 (34)	148 (32)

*Only non-Hispanic white (EU ancestry) subjects were included in PGx analyses.

**Three subjects were excluded from association analysis due to cryptic relatedness.

ITT, intent-to-treat; PGx, pharmacogenetics; OCS, oral corticosteroid.