Supplementary Materials:

FCER2 T2206C variant associated with FENO levels in asthmatic children using inhaled corticosteroids: The PACMAN study

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Table S1: Low, medium and high daily doses of inhaled corticosteroids[1]

Drug	Low	Medium	High
12 years and older			
Budesonide Daily dose (mcg)	200-400	>400-800	>800
Younger than 12 years			
Budesonide Daily dose (mcg)	100-200	>200-400	>400

Table S2: Regression coefficients and 95% confidence intervals describing the association between rs28364072 variation of the *FCER2* gene (per copy of the G allele) and the concentration of FENO.

Outcome	n	Effect allele	Crude			Model 1			Model 2		
			β	(95% CI)	P	β	(95% CI)	P	β	(95% CI)	P
FENO*	593	G	-0.16	(-0.27, -0.04)	0.008	-0.12	(-0.23, -0.01)	**0.030**	-0.12	(-0.23, -0.01)	**0.033**
FENO#	593	G	-0.15	(-0.25, -0.04)	0.005	-0.12	(-0.21, -0.02)	**0.019**	-0.12	(-0.22, -0.02)	**0.014**

FENO, Fractional exhaled Nitric Oxide; CI: Confidence Interval.

FENO levels were used as log-transformed (ln).

*The FENO values equals to zero ppb were set at zero ppb.

The FENO values equals to zero ppb were set at 5 ppb.

Crude, Only SNP

Model 1, Adjusted for age and sex

Model 2, Model 1 further adjusted for (adapted) British Thoracic Society (BTS) treatment steps and atopy

Table S3: Functional annotation of rs28364072 using the HaploRegv4.1.

chr	pos (hg38)	LD (r²)	LD (D')	variant	Ref	Alt	EUR freq	Enhancer histone marks	DNAse	Motifs changed	Selected eQTL hits	GENCODE genes / dbSNP func annot
19	7687177	0.82	0.99	rs1078625	A	G	0.32		BLD	11 altered motifs	4 hits	1.6kb 3' of FCER2
19	7689659	0.84	1	rs62110713	C	T	0.25	BLD		EBF		FCER2/ intronic
19	7689705	0.99	1	rs62110714	C	T	0.28	BLD		8 altered motifs		FCER2/ intronic
19	7689743	1	1	rs62110715	T	C	0.28	BLD	BLD	Ik-1,LUN-1		FCER2/ intronic
19	7689790	0.99	1	rs113483829	C	T	0.28	BLD	BLD,BLD	4 altered motifs		FCER2/ intronic
19	7689810	0.99	1	rs111674746	G	C	0.28	BLD	BLD,BLD			FCER2/ intronic
19	7689816	0.99	1	rs113453074	G	T	0.28	BLD	BLD	5 altered motifs		FCER2/ intronic
19	7689819	0.99	1	rs111740138	A	G	0.28	BLD	BLD	4 altered motifs		FCER2/ intronic
19	7689880	1	1	rs35260294	C	T	0.28	BLD	IPSC	NRSF		FCER2/ intronic
19	7689912	1	1	rs34288384	G	A	0.28	BLD	IPSC	ERalpha-a,Hic1,SP1		FCER2/ intronic
19	7690026	0.97	1	rs4996980	G	A	0.29	BLD, HRT		Rad21,Whn		FCER2/ intronic
19	7690031	0.97	1	rs4996979	T	C	0.29	BLD, HRT		4 altered motifs		FCER2/ intronic
19	7690056	0.97	1	rs4996978	A	C	0.29	BLD, HRT		4 altered motifs		FCER2/ intronic
19	7690078	0.97	1	rs4996977	T	C	0.29	BLD, HRT		PU.1		FCER2/ intronic
19	7690082	0.97	1	rs4996976	A	G	0.29	BLD, HRT		4 altered motifs		FCER2/ intronic
19	7690085	0.97	1	rs4996975	C	T	0.29	BLD, HRT	IPSC	AFP1,SIX5		FCER2/ intronic
19	7690170	1	1	rs2228138	G	A	0.28	BLD	ESC	5 altered motifs		FCER2/ synonymous
19	7690273	1	1	rs4996973	A	G	0.28	BLD	4 tissues	7 altered motifs		FCER2/ intronic
19	7690327	1	1	rs4996972	C	T	0.28	BLD, SPLN	4 tissues			FCER2/ intronic
19	7690399	1	1	rs28364072	A	G	0.28	BLD, SPLN		10 altered motifs		FCER2/ intronic
19	7690583	0.99	1	rs2277995	T	C	0.28	BLD, SPLN	BLD,BLD	25 altered motifs		FCER2/ intronic
19	7690586	0.99	1	rs74927160	G	T	0.28	BLD, SPLN	BLD,BLD	16 altered motifs		FCER2/intronic
19	7690599	0.87	1	rs76013233	G	A	0.26	BLD, SPLN	BLD,BLD	AP-2,SP1		FCER2/ intronic
19	7690632	1	1	rs2277994	A	C,G	0.28	BLD, SPLN	BLD,BLD			FCER2/ intronic
19	7690685	1	1	rs2277993	G	A	0.28	BLD, SPLN	BLD,BLD	AP-2		FCER2/ intronic
19	7690696	1	1	rs2277992	A	G	0.28	BLD, SPLN	BLD,BLD,BLD	Smad		FCER2/ intronic

Table S3: Functional annotation of rs28364072 using the HaploRegv4.1 (cont'd).

chr	pos (hg38)	LD (r²)	LD (D')	variant	Ref	Alt	EUR freq	Enhancer histone marks	DNAse	Motifs changed	Selected eQTL hits	GENCODE genes / dbSNP func annot
19	7690830	1	1	rs2277991	A	G	0.28	BLD, SPLN	4 tissues	Maf,RREB-1	4 hits	FCER2/ intronic
19	7690859	1	1	rs2277990	A	G	0.28	BLD, SPLN	5 tissues	BCL,ELF1,Ets		FCER2/ intronic
19	7691182	1	1	rs73489945	G	A	0.28	BLD, SPLN	BLD,BLD,BLD	Myb,NRSF,Pax-4		FCER2/ intronic
19	7691202	1	1	rs66508756	T	C	0.28	BLD, SPLN	5 tissues	4 altered motifs		FCER2/ intronic
19	7691237	1	1	rs68063051	T	C	0.28	BLD, SPLN	5 tissues			FCER2/ intronic
19	7691305	1	1	rs67614954	C	T	0.28	BLD, SPLN	4 tissues			FCER2/ intronic
19	7691385	1	1	rs62110718	A	T	0.28	BLD, SPLN	4 tissues			FCER2/ intronic
19	7691425	1	1	rs62110719	C	T	0.28	BLD, SPLN	BLD,BLD,BLD	HNF1,Pbx-1		FCER2/ intronic
19	7691577	1	1	rs72998478	A	G	0.28	BLD	4 tissues	HDAC2,ZBRK1		FCER2/ intronic
19	7691591	1	1	rs66527560	C	G	0.28	BLD	4 tissues	5 altered motifs		FCER2/ intronic
19	7691709	0.93	0.97	rs62110724	G	A	0.28	BLD	4 tissues	LBP-1,Tgif1		FCER2/ intronic
19	7691748	0.96	0.99	rs62110725	A	C	0.29	BLD, OVRY	4 tissues	Ets,Mef2,RREB-1		FCER2/ intronic
19	7691771	0.99	1	rs62110726	T	C	0.28	BLD, OVRY	6 tissues	9 altered motifs		FCER2/ intronic
19	7691820	0.99	1	rs62110727	T	C	0.28	BLD, OVRY	4 tissues	COMP1,Myc		FCER2/ intronic
19	7692781	0.99	1	rs17159834	A	G	0.28	BLD, GI, SPLN	BLD,BLD,BLD	7 altered motifs	4 hits	FCER2/ intronic
19	7692842	0.99	1	rs62110730	C	T	0.28	BLD, GI, SPLN	5 tissues	HIF1		FCER2/ intronic
19	7692867	0.99	1	rs62110731	C	A	0.28	BLD, GI, SPLN	5 tissues	Pou2f2,Pou5f1		FCER2/ intronic
19	7692883	0.99	1	rs62110732	A	G	0.28	BLD, GI, SPLN	6 tissues	Foxp3		FCER2/ intronic
19	7693114	0.99	1	rs17159838	G	A	0.28	4 tissues	5 tissues	RREB-1		FCER2/ intronic
19	7693231	0.98	1	rs34613454	G	C	0.28	ESDR, BLD, GI	BLD,BLD	6 altered motifs		FCER2/ intronic
19	7698025	0.83	1	rs7249360	G	A	0.25	5 tissues	IPSC,BLD	4 altered motifs	4 hits	FCER2/ intronic
19	7698159	0.8	0.99	rs7249320	C	A	0.24	ESC, IPSC, BLD	ESC,IPSC,BLD	10 altered motifs	4 hits	FCER2/ intronic

Pos, position; **LD,** Linkage disequilibrium; **ref,** reference; **Alt,** alternative; **EUR freq**, European frequency; **eQTL**, expression quantitative trait loci; **func annot**, Functional annotation.

Table S4: The effect of rs28364072 on *FCER2* gene expression (using GETX portal, http://www.gtexportal.org/home/).

Gene Symbol	Variant Id	SNP Id	P-Value	Normalized effect size	Tissue
FCER2	19_7755285_A_G_b37	rs28364072	1.30E-05	-0.16	Whole Blood

Figure S1: The genotypes of rs28364072 in GTEx Whole Blood.
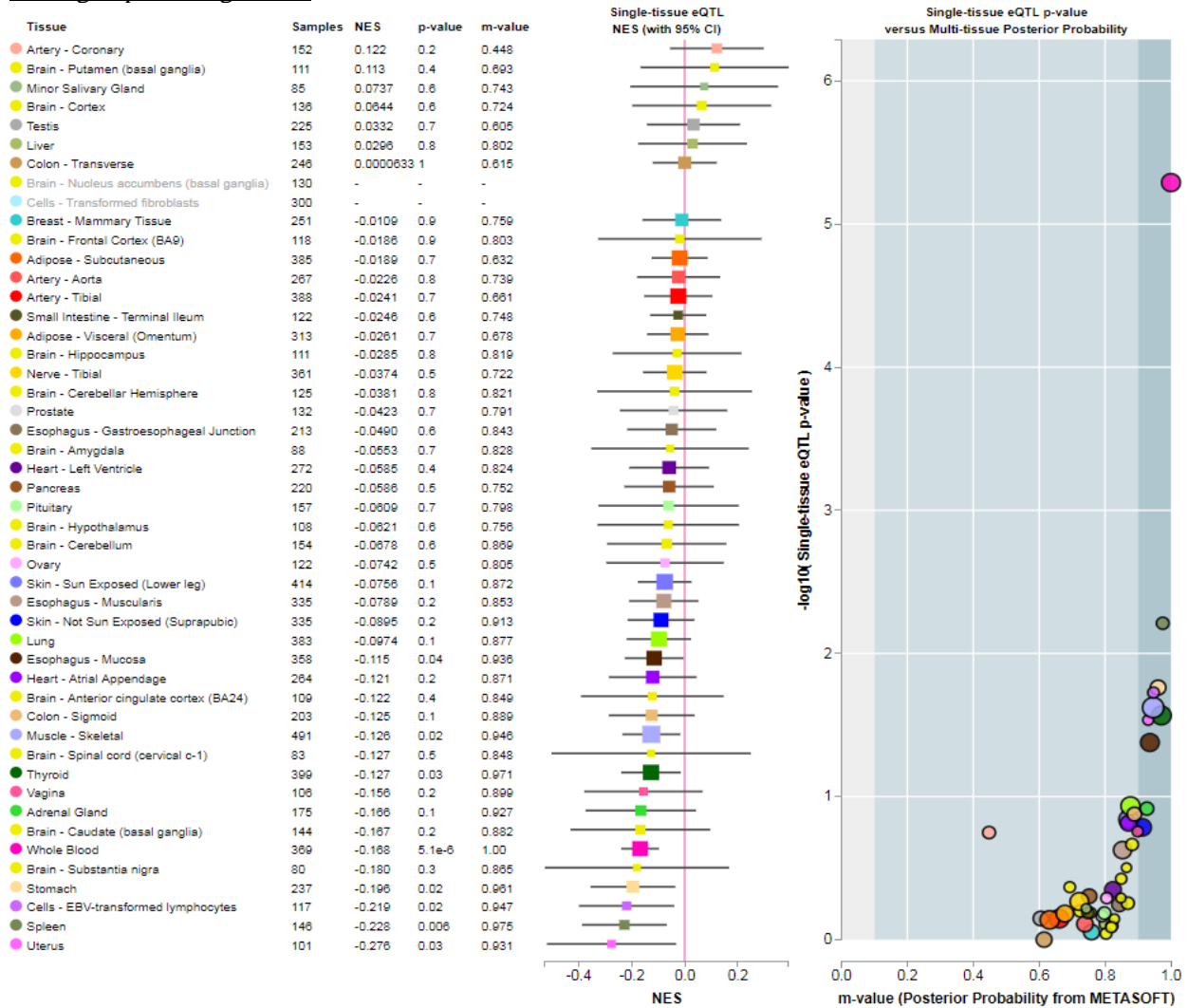 GTEx portal, http://www.gtexportal.org/home/
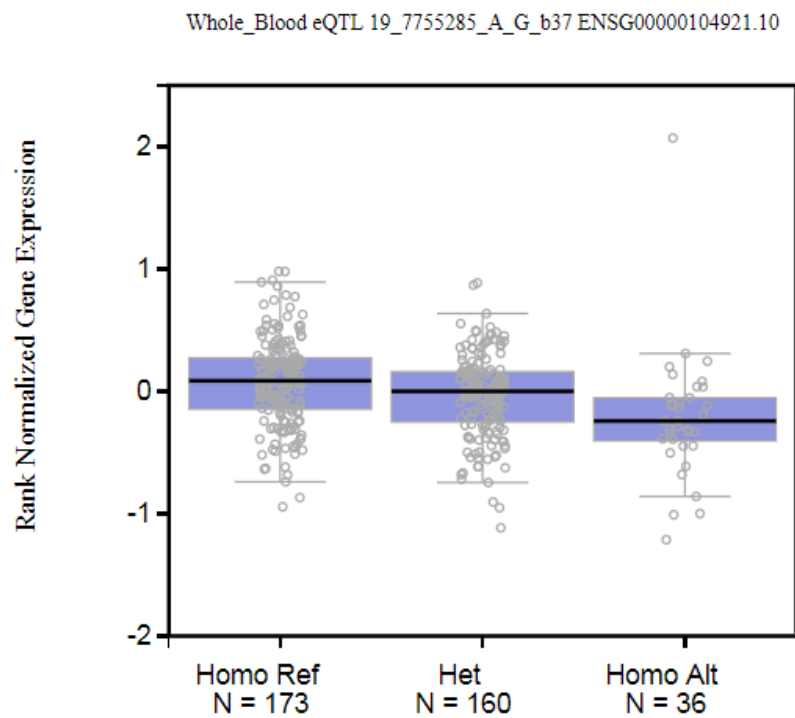
This figure is extracted from the GTEx portal. The legend on the top of the figure includes information on; tissue, analysis, chromosome_position_reference allele_effect allele_build and gene ID (GPR126).

Figure S2: *FCER2* expression by rs28364072 in different tissues (using GTEx portal).
www.gtexportal.org/home/

Tissue	Samples	NES	p-value	m-value
Artery - Coronary	152	0.122	0.2	0.448
Brain - Putamen (basal ganglia)	111	0.113	0.4	0.693
Minor Salivary Gland	85	0.0737	0.6	0.743
Brain - Cortex	136	0.0644	0.6	0.724
Testis	225	0.0332	0.7	0.605
Liver	153	0.0296	0.8	0.802
Colon - Transverse	246	0.0000633	1	0.615
Brain - Nucleus accumbens (basal ganglia)	130	-	-	-
Cells - Transformed fibroblasts	300	-	-	-
Breast - Mammary Tissue	251	-0.0109	0.9	0.759
Brain - Frontal Cortex (BA9)	118	-0.0186	0.9	0.803
Adipose - Subcutaneous	385	-0.0189	0.7	0.632
Artery - Aorta	267	-0.0226	0.8	0.739
Artery - Tibial	388	-0.0241	0.7	0.661
Small Intestine - Terminal Ileum	122	-0.0246	0.6	0.748
Adipose - Visceral (Omentum)	313	-0.0261	0.7	0.678
Brain - Hippocampus	111	-0.0285	0.8	0.819
Nerve - Tibial	361	-0.0374	0.5	0.722
Brain - Cerebellar Hemisphere	125	-0.0381	0.8	0.821
Prostate	132	-0.0423	0.7	0.791
Esophagus - Gastroesophageal Junction	213	-0.0490	0.6	0.843
Brain - Amygdala	88	-0.0553	0.7	0.828
Heart - Left Ventricle	272	-0.0585	0.4	0.824
Pancreas	220	-0.0586	0.5	0.752
Pituitary	157	-0.0609	0.7	0.798
Brain - Hypothalamus	108	-0.0621	0.6	0.756
Brain - Cerebellum	154	-0.0678	0.6	0.869
Ovary	122	-0.0742	0.5	0.805
Skin - Sun Exposed (Lower leg)	414	-0.0756	0.1	0.872
Esophagus - Muscularis	335	-0.0789	0.2	0.853
Skin - Not Sun Exposed (Suprapubic)	335	-0.0895	0.2	0.913
Lung	383	-0.0974	0.1	0.877
Esophagus - Mucosa	358	-0.115	0.04	0.936
Heart - Atrial Appendage	264	-0.121	0.2	0.871
Brain - Anterior cingulate cortex (BA24)	109	-0.122	0.4	0.849
Colon - Sigmoid	203	-0.125	0.1	0.889
Muscle - Skeletal	491	-0.126	0.02	0.946
Brain - Spinal cord (cervical c-1)	83	-0.127	0.5	0.848
Thyroid	399	-0.127	0.03	0.971
Vagina	106	-0.156	0.2	0.899
Adrenal Gland	175	-0.166	0.1	0.927
Brain - Caudate (basal ganglia)	144	-0.167	0.2	0.882
Whole Blood	369	-0.168	5.1e-6	1.00
Brain - Substantia nigra	80	-0.180	0.3	0.865
Stomach	237	-0.196	0.02	0.961
Cells - EBV-transformed lymphocytes	117	-0.219	0.02	0.947
Spleen	146	-0.228	0.006	0.975
Uterus	101	-0.276	0.03	0.931

ENSG00000104921.10 *FCER2* and 19_7755159_A_G_b37 eQTL (Meta - Analysis RE2 P-Value: 1.91618e-11)

NOTE: using GTEx portal, http://www.gtexportal.org/home/

"**NES** :The slope of the linear regression of normalized expression data versus the three genotype categories using single-tissue eQTL analysis, representing eQTL effect size. The normalized expression values are based on quantile normalization within each tissue, followed by inverse quantile normalization for each gene across samples.
**p-value**: From a t-test that compares observed beta from single-tissue eQTL analysis to a null beta of 0.
m-value: The posterior probability that an eQTL effect exists in each tissue tested in the cross-tissue meta-analysis. The m-value ranges between 0 and 1 (Han and Eskin, PLoS Genetics 8(3): e1002555, 2012),
m-value interpretation:
Small m-value (e.g. <0.1); The tissue is predicted to NOT have an eQTL effect. Large m-value (e.g. >0.9); The tissue is predicted to HAVE an eQTL effect. Otherwise; The prediction of the existence of an eQTL effect is ambiguous." [2]

Figure S3: CD23 and NO production.[3]
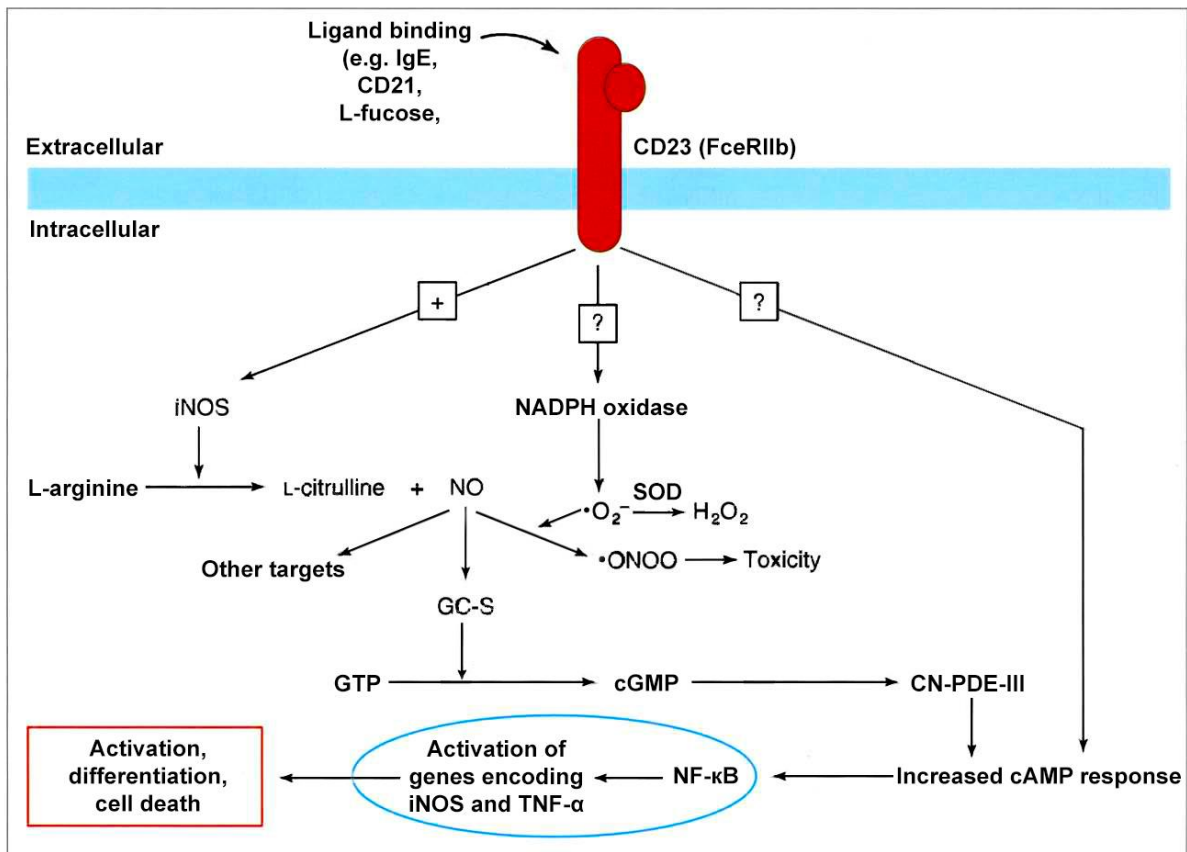
Note: "Proposed sequence of events following the ligation of CD23 at the surface of monocytes. CD23 engagement, elicited through interaction with one of its multiple ligands, induces stimulation of the NOS and NADPH oxidase pathways".[3]

Supplemental references:

1. Global Initiative for Asthma (GINA) for Asthma Management and Prevention, 2018. *Available from: http://www.ginasthma.org/. 2018.*

2. GTEx portal. *www.gtexportal.org/home/.*

3. Dugas B, Mossalayi MD, Damais C, Kolb JP. Nitric oxide production by human monocytes: evidence for a role of CD23. *Immunology today.* 1995; 16: 574-580.