SUPPLEMENTAL MATERIAL

Ho JE et al: Common Genetic Variation at the *IL1RL1* Locus Regulates IL-33/ST2 Signaling

Supplemental Methods

Study Sample

Of 3,532 participants, 735 participants were excluded due to the following reasons: missing biomarker measurements (n=82), prevalent heart failure (n=38), left ventricular (LV) systolic dysfunction (LV fractional shortening <0.30, or mild or greater LV systolic dysfunction by visual assessment on echocardiography) (n=302), missing covariates (n=60), or missing genotype (n=253).

Clinical Assessment

Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, or the use of insulin or oral hypoglycemic medications. LV hypertrophy was defined using previously reported ECG criteria (1). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (2). High-sensitivity CRP and B-type natriuretic peptide (BNP) were measured as previously described (3). Total and high-density lipoprotein cholesterol were measured by standard enzymatic methods using an Abbott Diagnostics ABA-200 analyzer (4).

Expression SNP analysis

We identified alias rsIDs (n=10) for significant sST2 loci using SNAP (5). Further proxy SNPs in high linkage disequilibrium (r^2>0.9) were identified with SNAP. Current and alias rsIDs were searched for primary SNPs and LD proxies against a collected database of expression SNP (eSNP) results including the following tissues: fresh lymphocytes (6), fresh leukocytes (7),

leukocyte samples in individuals with Celiac disease (8), lymphoblastoid cell lines (LCL) derived from asthmatic children (9), HapMap LCL from 3 populations (10), a separate study on HapMap CEU LCL (11), peripheral blood monocytes (12, 13), omental and subcutaneous adipose (14, 15), stomach (15), and whole blood samples (16), endometrial carcinomas (17), brain cortex(12, 18), 3 large studies of brain regions including prefrontal cortex, visual cortex and cerebellum, respectively (Emilsson, personal communication), liver (15, 19, 20), osteoblasts (21), skin (22), and additional fibroblast, T cell and LCL samples (23). The collected eSNP results met criteria for statistical significance for association with gene transcript levels as described in the original papers.

Cell Culture Studies

Cell Culture And Reagents

Human KU812, a basophil cell line, was kindly provided by Dr. David Frank (Dana-Faber Cancer Institute, Boston, MA) and maintained in RPMI 1640 (Invitrogen) containing 10% FBS. HEK293 cells were cultured in DMEM (Invitrogen) containing 10% FBS. IL-33 (Peprotech), anti-ST2 mAb (R&D), PD98059 (Invivogen), SP600125 (Invivogen), Rapamycin (Invivogen), wortmannin (Invivogen), Bay11-7082 (Invivogen), SR 11302 (Tocris Bioscience), Phorbol 12-myristate 13-acetate (PMA, Sigma Aldrich) were commercially available and were used in this study.

Cloning And Plasmids

Full-length wild type human ST2L was obtained via Reverse Transcription-PCR from KU812 cells cDNA by using forward primer (5'-CTGGAGTAATCTCAACAACG-3') and reverse

primer (5'-CGAGTTACCAATACTTGCTC-3'). pCR-Blunt II Topo vector (Invitrogen) was used as intermediate vector. Mutations were introduced by using PCR-based mutagenesis. Full-length ST2L cDNA were then subcloned into pCDH-EF1-MCS-T2A-Puro lentiviral vector (System Biosciences) by using the forward primer (5'-AGCGCTAGCATGGGGTTTTGGATCTTAGC- 3') and the reverse primer containing a His-taq before the stop codon (5'-GCTGGATCCCTAATGATGATGATGATGATGTTGCTTCT GGGCAGCCAAG-3') for cell line creation. All constructs were verified by DNA sequencing.

Lentivirus Preparation And Cell Line Creation

Lentiviral constructs were introduced with psPAX and pMD2.G packaging and envelope vectors into 293TN cells using PureFection reagent per manufacturer's protocol as previous described (24). 72 h later, culture media were harvested and lentiviral particles concentrated by ultracentrifugation (if destined for in vivo delivery) or Peg-IT reagent (if destined for cell line creation). Stable cell lines were created by transducing KU812 cells with concentrated lentivirus and subjected to subsequent puromycin selection. Expression was confirmed via Western blotting for ST2 and/or His-taq as appropriate. Membrane and cytosol fractions of the cell lysates were prepared by using Mem-PER Eukaryotic Membrane Protein Extraction Reagent Kit (Thermal Scientific) according to manufacturer's instruction.

ST2 Promoter Constructs And Promoter Assay

We used PCR with specific primers to amplify the different regions upstream of exon 1a (distal) and exon 1b (proximal) of the human *IL1RL1* gene from the DNA of the BAC clone (RP11-315O22). ST2 proximal and distal promoters fragments containing different lengths of

sequences were inserted between the SacI and NheI sites of the pGL3-basic vector (Promega) containing the entire coding sequences of firefly luciferase with specific primers.

The distal promoter fragments were constructed by using the primers:

hST2-exon1a/-697F: 5'-ATCGGGATCCGAGCTCAGATAGGCCATCTCGGGCAT-3'

hST2-exon1a/+741R: 5'-ATATGCTAGCACCAAAACACAATTAAACTCCT-3'

The proximal promoter fragments were constructed by using the primers:

hST2-exon1b/-1745F: 5'-ATCGGGATCCGAGCTC TGTAAATCACTTAGACTGTG-3'

hST2-exon1b/+200R: 5'-ATATGCTAGCTGCTGTGGAATACATGAGAA-3'

For reporter assay, KU812 cells expressing ST2L variants were plated in 12-well plates (1×10^6 cells/well, n=6 per treatments) and maintained in RPMI serum free medium before transfection. Cells were transfected by using the Purefection (System Biosciences) with 500 ng of reporter plasmids. All cells were also transfected with a SEAP control plasmid for normalizing transfection efficiencies. After transfection, cells were maintained in RPMI serum free medium overnight (18 h). For signal inhibitor treatment study, cells were incubated with signal inhibitors for additional 24 h. After 24 h incubation, cells were harvested in lysis buffer and assayed for luciferase activity per the manufacturer's protocol.

Realtime-PCR

Total RNA was isolated using Trizol reagent per manufacturer's instructions (Invitrogen). cDNA was synthesized from 1 μg of total RNA and random hexamers using the TaqMan Reverse Transcription kit (Applied Biosystems). 1 μl diluted cDNA was used per 20 μl reaction

from an initial input of 1 μg total RNA diluted to a final volume of 600 μl following cDNA reverse transcription. Real time PCR was performed in a 7300 Realtime PCR system (Applied Biosystems), with 40 cycles of: 95°C x 15 sec, 60°C x 1 min. All reactions were performed in duplicate. Relative amount of sST2 or ST2L mRNA was normalized to HPRT.

The following primers specific for sST2, ST2L, and HPRT were used in this study:

hST2-RT (CDS)-F: 5'-CTGTCTGGCCCTGAATTTGC-3';

hST2-RT (CDS)-R: 5'-AGCAGAGTGGCCTCAATCCA-3';

hST2-RT(3'-UTR)-F: 5'-TTATAGTGTGACGGCGACCA-3';

hST2-RT(3'-UTR)-R: 5'-TCTAGACAAGCCAGCCCATT-3';

hssT2-RT-F: 5'-CTGTCTGGCCCTGAATTTGC-3';

hssT2-RT-R: 5'-TGGAACCACACTCCATTCTGC-3';

hIL-33-RT-F: 5'-GGAGTGCTTTGCCTTTGGTA-3';

hIL-33-RT-R: 5'-TCATTTGAGGGGTGTTGAGA-3';

hIL-1B-RT-F:5'-CAGCCAATCTTCATTGCTCA-3';

hIL-1B-RT-R:5'-GCATCTTCCTCAGCTTGTCC-3';

hHPRT-F297: 5'-GCTATAAATTCTTTGCTGACCTGCTG-3';

hHPRT-R436: 5'-AATTACTTTTATGTCCCCTGTTGACTGG -3';

For the qRT-PCR analysis of sST2 mRNA expression, KU812 cells (1 x 10^6/well, n=2 per treatments) were treated with DMSO or IL-33 (20ng/ml) with and without signal inhibitors as indicated. Cells were pretreated with Wortmannin (5μM), LY294002 (5μM), Rapamycin (5μM), PD98059 (10 μM), SP60125 (10 μM), BAY11-7082 (10 μM), or SR11302 (10 μM) for 30 minutes, and then incubated with IL-33 (20 ng/ml) for 8 h. RNA was then isolated for qRT

PCR analysis. For anti-ST2 mAb inhibition experiments, cells were pre-incubated with PBS, Rapamycin (5mM), anti-ST2 mAb (1μg/ml), IL-33 (20 ng/ml), IL-33 (20 ng/ml) plus anti-ST2 (1μg/ml), IL-33 (20 ng/ml) plus Rapamycin (5μM), IL-33 (20 ng/ml) plus Rapamycin (1μg/ml) plus anti-ST2 mAb (1μg/ml) or Rapamycin (1μg/ml) plus anti-ST2 (1μg/ml). Cells were treated for 8 h for qRT-PCR analysis, and 24 h for ELISA analysis.

ELISA

For basal sST2 protein expression level analysis, KU812, U937, Jurkat T, or A549 cells (1 x 10^6/well, n=3 per treatments) expressing wild type (WT) or *IL1RL1* variants (A78E, A433T, Q501K, Q501R, T549I, L551S) are cultured in serum free RPMI 1640 medium for 24 h. The media were collected for ELISA analysis for sST2 (Presage^{TM} ST2; Critical Diagnostics, San Diego, CA, USA), IL-1β (R&D System), and IL-33 (R&D System). For signal activation analysis, cells were subjected to serum starvation for 8 h, then treated with PBS or IL-33 for 30min. Cell lysates were then used for ELISA detection of phospho-NF-κB p65 (Ser536), phospho-c-Jun (Ser63), phospho-AKT (Thr308), and phospho-STAT3 (Tyr705) according to manufacturer's instructions (Cell Signal).

Co-Immunoprecipitation

HEK293 cells expressing *IL1RL1* variants were plated in 6-well plates (1 x 10^6 cells/well, n=6 per treatments) and maintained in DMEM serum free medium before transfection. Cells were transfected by using the Purefection (System Biosciences) with 500 ng of pcDNA3.1-PI3K-p85alpha-FLAG (kindly provided by Dr. Umut Ozcan, Children's Hospital Boston), pCDNA3.1-Mal-c-myc, and pcDNA3.1-MYD88-HA (kindly provided by Prof. Alexander N. R. Weber,

German Cancer Research Centre (DKFZ), Germany. After 24 hour transfection, the cells were harvested and lysates were immunoprecipitated by anti-FLAG for PI3K-p85 subunit, anti-c-myc for Mal, anti-HA for MYD88, or anti-His for ST2L variant protein. Precipitates and whole cell lysates were analyzed by immunoblot.

Statistical analysis

Clinical Correlates of sST2 concentrations

Age and sex were forced into the model; eligible covariates included systolic blood pressure, diabetes mellitus, body mass index, cigarette smoking, total and high-density lipoprotein cholesterol, hypertension treatment, LV hypertrophy, atrial fibrillation, and eGFR.

Heritability

In secondary analyses, we adjusted for duration of hypertension and diabetes, defined as the time from earliest study visit when diagnosis was confirmed to the sixth examination cycle. We further adjusted for potential inflammatory conditions, including the current use of glucocorticoids, history of asthma or use of bronchodilators, cardiovascular disease, self-reported history of cancer or tumor, C-reactive protein concentration, and the use of non-steroidal anti-inflammatory medications.

Cell Culture Studies

All data are expressed as means ± s.e. For two sample comparisons, a two-tailed t test was employed. *P* values less than 0.05 were considered significant.

Supplemental Table 1. Characteristics of 2,991 participants

	Men (n=1,241)	Women (n=1,556)
Age, years	58 (10)	59 (10)
Systolic blood pressure, mmHg	129 (17)	127 (20)
Diastolic blood pressure, mmHg	78 (9)	74 (9)
Body-mass index, kg/m^2	28 (4)	27 (6)
Diabetes mellitus, %	12	9
Anti-hypertensive treatment, %	28	25
Smoker, %	15	16
Atrial fibrillation, %	2	1
Left ventricular hypertrophy, %	1	0
Total cholesterol, mg/dl	200 (40)	212 (38)
HDL cholesterol, mg/dl	44 (12)	58 (16)
eGFR, $ml/min/1.73m^2$	91 (44)	89 (43)
sST2, ng/ml, median (25%ile-75%ile)	23.4 (19.1-28.8)	18.7 (15.3-23.2)

Values are mean (standard deviation) unless otherwise indicated.

Supplemental Table 2. Genome-wide significant SNPs associated with sST2 concentrations

Chr	SNP	Position (NCBI 36.3)	Nearest gene	Major allele	Minor allele	MAF	beta	se	*P*
2	rs950880	102298994	*IL1RL1*	C	A	0.39	-0.18	0.01	7.11E-94
2	rs13001325	102305468	*IL1RL1*	C	T	0.39	-0.18	0.01	8.64E-94
2	rs12479210	102315593	*IL1RL1*	C	T	0.39	-0.18	0.01	9.42E-94
2	rs13019081	102317254	*IL1RL1*	A	C	0.39	-0.18	0.01	9.47E-94
2	rs1420101	102324148	*IL1RL1*	C	T	0.39	-0.18	0.01	4.33E-92
2	rs12712142	102327016	*IL1RL1*	C	A	0.40	-0.17	0.01	1.68E-84
2	rs6543119	102329504	*IL1RL1*	A	T	0.40	-0.17	0.01	3.55E-84
2	rs13017455	102331174	*IL1RL1*	C	T	0.40	-0.17	0.01	6.92E-84
2	rs11123923	102334276	*IL1RL1*	C	A	0.40	-0.16	0.01	4.89E-81
2	rs2287037	102345460	*IL18R1*	C	T	0.40	-0.16	0.01	1.26E-80
2	rs12998521	102340849	*IL18R1*	G	T	0.40	-0.16	0.01	1.27E-80
2	rs953934	102298725	*IL1RL1*	C	T	0.56	-0.15	0.01	2.56E-70
2	rs12712135	102297380	*IL1RL1*	A	G	0.56	-0.15	0.01	2.70E-70
2	rs11123918	102301669	*IL1RL1*	T	C	0.55	-0.15	0.01	8.88E-68
2	rs10182639	102302237	*IL1RL1*	C	A	0.55	-0.15	0.01	8.99E-68
2	rs11690443	102302563	*IL1RL1*	T	A	0.55	-0.15	0.01	9.18E-68
2	rs4142132	102303914	*IL1RL1*	G	A	0.55	-0.15	0.01	9.43E-68
2	rs974389	102303413	*IL1RL1*	G	A	0.55	-0.15	0.01	9.44E-68
2	rs11123920	102306265	*IL1RL1*	C	T	0.55	-0.15	0.01	9.44E-68
2	rs12996772	102313633	*IL1RL1*	A	T	0.55	-0.15	0.01	9.44E-68
2	rs6706844	102306844	*IL1RL1*	T	C	0.55	-0.15	0.01	9.44E-68
2	rs1420102	102315251	*IL1RL1*	C	T	0.55	-0.15	0.01	9.44E-68
2	rs12466380	102315371	*IL1RL1*	A	G	0.55	-0.15	0.01	9.45E-68
2	rs1420088	102305866	*IL1RL1*	T	C	0.55	-0.15	0.01	9.45E-68
2	rs10189711	102297313	*IL1RL1*	A	G	0.55	-0.15	0.01	9.68E-68
2	rs1558622	102296579	*IL1RL1*	G	A	0.55	-0.15	0.01	9.75E-68
2	rs4090473	102289419	*IL1RL1*	C	G	0.55	-0.15	0.01	9.95E-68
2	rs4399750	102284220	*IL1RL1*	T	C	0.55	-0.15	0.01	1.04E-67
2	rs1997467	102317505	*IL1RL1*	A	G	0.55	-0.15	0.01	1.06E-67
2	rs1997466	102317899	*IL1RL1*	C	G	0.55	-0.15	0.01	1.21E-67
2	rs1362350	102318230	*IL1RL1*	G	C	0.55	-0.15	0.01	1.43E-67
2	rs1362349	102318404	*IL1RL1*	G	C	0.55	-0.15	0.01	9.54E-67
2	rs12712141	102319499	*IL1RL1*	T	C	0.55	-0.15	0.01	1.06E-66
2	rs11685424	102293413	*IL1RL1*	G	A	0.55	-0.15	0.01	4.15E-66
2	rs12469506	102332303	*IL1RL1*	C	T	0.30	-0.13	0.01	1.05E-41
2	rs17026974	102318792	*IL1RL1*	G	A	0.28	-0.13	0.01	3.26E-40
2	rs873022	102322115	*IL1RL1*	G	T	0.28	-0.13	0.01	5.40E-40
2	rs3771177	102322292	*IL1RL1*	G	T	0.28	-0.13	0.01	5.55E-40
2	rs3732129	102323964	*IL1RL1*	T	C	0.28	-0.13	0.01	6.35E-40
2	rs12905	102326439	*IL1RL1*	G	A	0.28	-0.13	0.01	1.04E-39

2	rs11694360	102427579	*IL18RAP*	G	A	0.35	-0.13	0.01	1.40E-39
2	rs11123928	102427718	*IL18RAP*	G	A	0.35	-0.13	0.01	1.40E-39
2	rs7597017	102428548	*IL18RAP*	A	G	0.35	-0.13	0.01	1.41E-39
2	rs13029918	102323723	*IL1RL1*	A	G	0.05	-0.29	0.02	1.54E-39
2	rs11465730	102433290	*IL18RAP*	A	G	0.48	-0.12	0.01	5.13E-38
2	rs6705385	102443001	*IL18RAP*	A	C	0.48	-0.12	0.01	6.48E-38
2	rs6705498	102443102	*IL18RAP*	A	G	0.48	-0.12	0.01	6.52E-38
2	rs6719196	102443320	*IL18RAP*	G	T	0.48	-0.12	0.01	6.59E-38
2	rs3821204	102326713	*IL1RL1*	C	G	0.28	-0.13	0.01	8.01E-38
2	rs13024003	102274193	*IL1RL1*	G	C	0.05	-0.29	0.02	1.17E-37
2	rs13017541	102272608	*IL1RL1*	C	T	0.05	-0.29	0.02	1.25E-37
2	rs13407644	102271783	*IL1RL1*	A	G	0.05	-0.29	0.02	1.97E-37
2	rs13024772	102268605	*IL1RL1*	G	A	0.05	-0.29	0.02	2.59E-37
2	rs12463588	102451689	*SLC9A4*	C	G	0.48	-0.11	0.01	3.21E-37
2	rs2310302	102452481	*SLC9A4*	G	C	0.48	-0.11	0.01	3.62E-37
2	rs12469887	102453190	*SLC9A4*	T	C	0.48	-0.11	0.01	4.08E-37
2	rs12989419	102267186	*IL1RL1*	A	C	0.05	-0.29	0.02	4.72E-37
2	rs4140786	102454608	*SLC9A4*	G	T	0.48	-0.11	0.01	5.70E-37
2	rs10201184	102455510	*SLC9A4*	G	C	0.48	-0.11	0.01	7.08E-37
2	rs17027006	102331764	*IL1RL1*	G	C	0.28	-0.12	0.01	1.36E-36
2	rs1420103	102315064	*IL1RL1*	C	A	0.23	0.13	0.01	1.01E-35
2	rs2310220	102318283	*IL1RL1*	A	G	0.23	0.13	0.01	1.13E-35
2	rs3771172	102352244	*IL18R1*	C	T	0.28	-0.12	0.01	1.27E-35
2	rs3771171	102352382	*IL18R1*	T	C	0.28	-0.12	0.01	1.28E-35
2	rs2160202	102352586	*IL18R1*	G	A	0.28	-0.12	0.01	1.29E-35
2	rs4851005	102377984	*IL18R1*	C	T	0.36	-0.11	0.01	2.30E-35
2	rs2058622	102351856	*IL18R1*	G	A	0.23	0.13	0.01	2.88E-35
2	rs3771170	102352412	*IL18R1*	A	T	0.23	0.13	0.01	2.91E-35
2	rs2058623	102352602	*IL18R1*	T	C	0.23	0.13	0.01	2.95E-35
2	rs1465321	102353050	*IL18R1*	C	T	0.23	0.13	0.01	3.03E-35
2	rs2287034	102377020	*IL18R1*	C	A	0.28	-0.12	0.01	2.22E-34
2	rs3849365	102510823	*SLC9A4*	A	G	0.37	0.11	0.01	2.61E-34
2	rs13009757	102278606	*IL1RL1*	C	T	0.05	-0.27	0.02	2.67E-34
2	rs17027037	102361316	*IL18R1*	A	G	0.28	-0.12	0.01	7.14E-34
2	rs2080289	102361452	*IL18R1*	G	A	0.28	-0.12	0.01	7.36E-34
2	rs11683700	102363237	*IL18R1*	C	T	0.28	-0.12	0.01	8.58E-34
2	rs1035130	102367834	*IL18R1*	C	T	0.28	-0.12	0.01	1.15E-33
2	rs4851582	102417990	*IL18RAP*	T	C	0.28	-0.12	0.01	1.25E-33
2	rs11681718	102417576	*IL18RAP*	A	G	0.28	-0.12	0.01	1.26E-33
2	rs17027166	102421852	*IL18RAP*	G	A	0.28	-0.12	0.01	1.28E-33
2	rs10490204	102422966	*IL18RAP*	A	C	0.28	-0.12	0.01	1.28E-33
2	rs17027179	102423591	*IL18RAP*	C	T	0.28	-0.12	0.01	1.29E-33
2	rs10490203	102425669	*IL18RAP*	T	G	0.28	-0.12	0.01	1.30E-33

2	rs3771150	102427283	*IL18RAP*	G	A	0.28	-0.12	0.01	1.31E-33
2	rs4851570	102372819	*IL18R1*	A	G	0.28	-0.12	0.01	1.44E-33
2	rs1135354	102380734	*IL18R1*	T	G	0.28	-0.12	0.01	1.93E-33
2	rs1014286	102515532	*SLC9A4*	A	G	0.35	0.11	0.01	2.61E-33
2	rs2008159	102515594	*SLC9A4*	G	A	0.35	0.11	0.01	2.61E-33
2	rs2008157	102515614	*SLC9A4*	G	A	0.35	0.11	0.01	2.61E-33
2	rs741285	102514601	*SLC9A4*	T	C	0.35	0.11	0.01	2.61E-33
2	rs1005043	102511858	*SLC9A4*	G	A	0.35	0.11	0.01	2.62E-33
2	rs4851018	102513047	*SLC9A4*	T	C	0.35	0.11	0.01	2.62E-33
2	rs17027230	102445762	*IL18RAP*	C	T	0.28	-0.12	0.01	2.85E-33
2	rs1005042	102511791	*SLC9A4*	G	A	0.35	0.11	0.01	2.88E-33
2	rs1829849	102516130	*SLC9A4*	C	A	0.35	0.11	0.01	2.89E-33
2	rs6737119	102517541	*SLC9A4*	A	G	0.35	0.11	0.01	3.05E-33
2	rs6709284	102517596	*SLC9A4*	G	C	0.35	0.11	0.01	3.22E-33
2	rs2177317	102517751	*SLC9A4*	G	A	0.36	0.11	0.01	3.73E-33
2	rs11693955	102395597	*IL18RAP*	A	T	0.28	-0.12	0.01	4.38E-33
2	rs13015714	102338297	*IL1RL1*	T	G	0.22	0.13	0.01	4.47E-33
2	rs3771156	102403109	*IL18RAP*	C	T	0.28	-0.12	0.01	4.56E-33
2	rs3849364	102510674	*SLC9A4*	C	T	0.36	0.11	0.01	4.85E-33
2	rs3732123	102384509	*IL18R1*	C	G	0.28	-0.12	0.01	4.92E-33
2	rs12712156	102510452	*SLC9A4*	C	A	0.36	0.11	0.01	5.42E-33
2	rs4851617	102518492	*SLC9A4*	T	C	0.35	0.11	0.01	6.62E-33
2	rs17027087	102382350	*IL18R1*	C	T	0.28	-0.12	0.01	8.44E-33
2	rs4241211	102509591	*SLC9A4*	G	T	0.36	0.11	0.01	9.24E-33
2	rs4851011	102456110	*SLC9A4*	C	T	0.28	-0.12	0.01	1.23E-32
2	rs17027255	102456559	*SLC9A4*	C	T	0.28	-0.12	0.01	1.24E-32
2	rs4292112	102520212	*SLC9A4*	A	G	0.36	0.11	0.01	1.24E-32
2	rs17027258	102457972	*SLC9A4*	A	G	0.28	-0.12	0.01	1.31E-32
2	rs2015478	102507879	*SLC9A4*	G	A	0.36	0.11	0.01	1.35E-32
2	rs1357471	102506904	*SLC9A4*	T	C	0.36	0.11	0.01	2.02E-32
2	rs4851614	102506830	*SLC9A4*	T	C	0.36	0.11	0.01	2.49E-32
2	rs10490202	102527264	*SLC9A4*	G	C	0.36	0.11	0.01	5.15E-32
2	rs1362347	102286017	*IL1RL1*	C	T	0.11	-0.17	0.01	1.14E-31
2	rs2270297	102359107	*IL18R1*	C	T	0.22	0.12	0.01	1.45E-31
2	rs12987782	102304398	*IL1RL1*	G	A	0.11	-0.17	0.01	1.47E-31
2	rs13001301	102305430	*IL1RL1*	C	T	0.11	-0.17	0.01	1.49E-31
2	rs6753717	102359593	*IL18R1*	C	A	0.22	0.12	0.01	1.49E-31
2	rs6750020	102361146	*IL18R1*	A	G	0.22	0.12	0.01	1.51E-31
2	rs3771179	102320324	*IL1RL1*	T	G	0.11	-0.17	0.01	1.51E-31
2	rs3755278	102318649	*IL1RL1*	T	C	0.11	-0.17	0.01	1.52E-31
2	rs13016771	102325512	*IL1RL1*	G	A	0.11	-0.17	0.01	1.53E-31
2	rs17695648	102314613	*IL1RL1*	A	G	0.11	-0.17	0.01	1.59E-31
2	rs2110734	102418638	*IL18RAP*	T	C	0.22	0.12	0.01	2.52E-31

2	rs6746271	102419427	*IL18RAP*	C	G	0.22	0.12	0.01	2.52E-31
2	rs2058660	102420881	*IL18RAP*	A	G	0.22	0.12	0.01	2.52E-31
2	rs2058658	102421235	*IL18RAP*	C	T	0.22	0.12	0.01	2.52E-31
2	rs4851009	102422076	*IL18RAP*	A	G	0.22	0.12	0.01	2.53E-31
2	rs1558650	102426456	*IL18RAP*	A	T	0.22	0.12	0.01	2.53E-31
2	rs6734736	102429312	*IL18RAP*	T	C	0.22	0.12	0.01	2.53E-31
2	rs6708413	102429801	*IL18RAP*	A	G	0.22	0.12	0.01	2.53E-31
2	rs917996	102448705	*SLC9A4*	A	C	0.22	0.12	0.01	2.91E-31
2	rs6717915	102446051	*SLC9A4*	C	A	0.22	0.12	0.01	2.92E-31
2	rs6718157	102446246	*SLC9A4*	T	A	0.22	0.12	0.01	2.92E-31
2	rs6720564	102445729	*IL18RAP*	C	T	0.22	0.12	0.01	2.95E-31
2	rs4241210	102445172	*IL18RAP*	A	G	0.22	0.12	0.01	2.97E-31
2	rs2272128	102406361	*IL18RAP*	A	G	0.22	0.12	0.01	3.00E-31
2	rs6543141	102442783	*IL18RAP*	A	G	0.22	0.12	0.01	3.06E-31
2	rs6705001	102442642	*IL18RAP*	G	A	0.22	0.12	0.01	3.08E-31
2	rs6761825	102441993	*IL18RAP*	C	T	0.22	0.12	0.01	3.11E-31
2	rs1468791	102458453	*SLC9A4*	G	A	0.22	0.12	0.01	3.11E-31
2	rs4070554	102440925	*IL18RAP*	G	A	0.22	0.12	0.01	3.16E-31
2	rs917997	102437000	*IL18RAP*	C	T	0.22	0.12	0.01	3.36E-31
2	rs7559479	102435219	*IL18RAP*	A	G	0.22	0.12	0.01	3.42E-31
2	rs3817465	102406016	*IL18RAP*	T	A	0.22	0.12	0.01	3.42E-31
2	rs7597819	102459338	*SLC9A4*	G	A	0.22	0.12	0.01	3.51E-31
2	rs6737668	102459513	*SLC9A4*	T	C	0.22	0.12	0.01	3.56E-31
2	rs1420106	102401476	*IL18RAP*	G	A	0.22	0.12	0.01	4.04E-31
2	rs3755268	102404959	*IL18RAP*	G	C	0.22	0.12	0.01	4.04E-31
2	rs3755267	102405019	*IL18RAP*	G	T	0.22	0.12	0.01	4.04E-31
2	rs1807782	102399579	*IL18RAP*	T	C	0.22	0.12	0.01	4.08E-31
2	rs11694658	102411452	*IL18RAP*	G	A	0.22	0.12	0.01	4.18E-31
2	rs2160232	102413312	*IL18RAP*	A	G	0.22	0.12	0.01	4.27E-31
2	rs6716784	102414899	*IL18RAP*	G	T	0.22	0.12	0.01	4.42E-31
2	rs6543134	102416890	*IL18RAP*	G	T	0.22	0.12	0.01	4.54E-31
2	rs2041756	102416342	*IL18RAP*	G	A	0.22	0.12	0.01	4.54E-31
2	rs2110735	102417357	*IL18RAP*	G	A	0.22	0.12	0.01	4.54E-31
2	rs990171	102453202	*SLC9A4*	C	A	0.22	0.12	0.01	5.02E-31
2	rs4851575	102391635	*IL18R1*	A	G	0.22	0.12	0.01	5.15E-31
2	rs4851007	102391245	*IL18R1*	G	T	0.22	0.12	0.01	5.63E-31
2	rs1035127	102386351	*IL18R1*	G	A	0.22	0.12	0.01	5.65E-31
2	rs1921622	102332499	*IL1RL1*	A	G	0.47	0.10	0.01	6.06E-31
2	rs7581853	102534156	*SLC9A4*	T	C	0.36	0.11	0.01	6.23E-31
2	rs10193009	102535409	*SLC9A4*	T	C	0.36	0.11	0.01	6.23E-31
2	rs11123937	102536114	*SLC9A4*	A	G	0.36	0.11	0.01	6.52E-31
2	rs887971	102407599	*IL18RAP*	T	C	0.30	-0.11	0.01	7.00E-31
2	rs12712159	102536414	*SLC9A4*	A	G	0.36	0.11	0.01	7.02E-31

2	rs887972	102407377	*IL18RAP*	G	A	0.30	-0.11	0.01	7.31E-31
2	rs997056	102537351	*SLC9A4*	G	A	0.36	0.11	0.01	8.39E-31
2	rs2110737	102538695	*SLC9A4*	A	T	0.36	0.11	0.01	1.09E-30
2	rs17639215	102319876	*IL1RL1*	G	A	0.13	0.15	0.01	1.71E-30
2	rs10210658	102542181	*SLC9A4*	G	T	0.36	0.11	0.01	1.86E-30
2	rs10469840	102459675	*SLC9A4*	C	T	0.23	0.12	0.01	2.34E-29
2	rs985523	102320808	*IL1RL1*	G	A	0.13	0.14	0.01	6.56E-28
2	rs6719130	102324668	*IL1RL1*	C	T	0.13	0.14	0.01	1.07E-27
2	rs12999542	102331824	*IL1RL1*	A	C	0.11	-0.15	0.01	2.08E-27
2	rs12996097	102330060	*IL1RL1*	G	A	0.11	-0.15	0.01	2.17E-27
2	rs13028993	102330381	*IL1RL1*	T	C	0.11	-0.15	0.01	2.17E-27
2	rs12989197	102329171	*IL1RL1*	G	A	0.11	-0.15	0.01	2.20E-27
2	rs1946131	102328361	*IL1RL1*	C	T	0.11	-0.15	0.01	2.21E-27
2	rs12999517	102325692	*IL1RL1*	T	C	0.11	-0.15	0.01	3.12E-27
2	rs10515921	102347450	*IL18R1*	T	G	0.13	0.14	0.01	1.85E-25
2	rs10208293	102332742	*IL1RL1*	G	A	0.29	0.10	0.01	2.28E-24
2	rs2241116	102369697	*IL18R1*	C	A	0.22	-0.11	0.01	2.38E-24
2	rs11465596	102353525	*IL18R1*	C	A	0.13	0.14	0.01	2.70E-24
2	rs951774	102279096	*IL1RL1*	C	A	0.14	0.13	0.01	3.78E-24
2	rs11465597	102353645	*IL18R1*	A	G	0.11	-0.15	0.01	6.02E-24
2	rs2293225	102402321	*IL18RAP*	C	T	0.22	-0.11	0.01	8.02E-24
2	rs9308855	102257227	*IL1RL2*	G	A	0.25	0.11	0.01	1.09E-23
2	rs1882511	102250153	*IL1RL2*	A	G	0.25	0.11	0.01	1.29E-23
2	rs1922288	102254997	*IL1RL2*	C	T	0.23	0.12	0.01	2.04E-23
2	rs3771167	102352620	*IL18R1*	A	G	0.12	0.14	0.01	6.07E-23
2	rs6728945	102352903	*IL18R1*	T	C	0.12	0.14	0.01	6.86E-23
2	rs12469892	102262216	*IL1RL1*	G	A	0.13	0.13	0.01	7.05E-23
2	rs6747153	102270259	*IL1RL1*	G	A	0.28	0.10	0.01	8.03E-23
2	rs11690532	102442858	*IL18RAP*	C	T	0.19	-0.11	0.01	9.03E-23
2	rs1882510	102250050	*IL1RL2*	C	T	0.13	0.13	0.01	9.03E-23
2	rs2192669	102617986	*SLC9A2*	C	T	0.31	0.09	0.01	1.91E-22
2	rs13015695	102254873	*IL1RL2*	C	A	0.06	-0.20	0.02	2.17E-22
2	rs12995644	102246459	*IL1RL2*	C	A	0.06	-0.19	0.02	3.97E-22
2	rs6724109	102491450	*SLC9A4*	G	C	0.23	0.10	0.01	4.05E-22
2	rs6751949	102491570	*SLC9A4*	A	G	0.23	0.10	0.01	4.08E-22
2	rs6724322	102491614	*SLC9A4*	T	C	0.23	0.10	0.01	4.13E-22
2	rs4851607	102492064	*SLC9A4*	T	C	0.23	0.10	0.01	4.16E-22
2	rs10195948	102492168	*SLC9A4*	C	T	0.23	0.10	0.01	4.19E-22
2	rs4851616	102518294	*SLC9A4*	T	C	0.23	0.10	0.01	6.30E-22
2	rs6724213	102517651	*SLC9A4*	C	A	0.23	0.10	0.01	6.41E-22
2	rs4851615	102513431	*SLC9A4*	T	G	0.43	0.09	0.01	8.39E-22
2	rs6708949	102490397	*SLC9A4*	C	G	0.23	0.10	0.01	9.36E-22
2	rs9989749	102490074	*SLC9A4*	A	G	0.23	0.10	0.01	9.57E-22

2	rs13019784	102489733	*SLC9A4*	G	A	0.23	0.10	0.01	9.84E-22
2	rs1024798	102508083	*SLC9A4*	C	G	0.23	0.10	0.01	1.14E-21
2	rs10172553	102519407	*SLC9A4*	T	C	0.43	0.08	0.01	1.54E-21
2	rs11123935	102506183	*SLC9A4*	G	A	0.23	0.10	0.01	1.64E-21
2	rs12712155	102494395	*SLC9A4*	T	A	0.23	0.10	0.01	1.71E-21
2	rs4851609	102495298	*SLC9A4*	C	T	0.23	0.10	0.01	1.72E-21
2	rs10193407	102505730	*SLC9A4*	T	C	0.23	0.10	0.01	1.73E-21
2	rs6761291	102521501	*SLC9A4*	T	C	0.43	0.08	0.01	1.75E-21
2	rs11676371	102496124	*SLC9A4*	C	G	0.23	0.10	0.01	1.75E-21
2	rs4851608	102492416	*SLC9A4*	T	C	0.43	0.09	0.01	1.79E-21
2	rs2058656	102503458	*SLC9A4*	G	T	0.43	0.08	0.01	1.80E-21
2	rs4851612	102504312	*SLC9A4*	G	C	0.43	0.08	0.01	1.80E-21
2	rs2192758	102498701	*SLC9A4*	G	C	0.23	0.10	0.01	1.81E-21
2	rs2192757	102498810	*SLC9A4*	T	C	0.23	0.10	0.01	1.84E-21
2	rs1476999	102498111	*SLC9A4*	A	G	0.43	0.09	0.01	1.86E-21
2	rs2216000	102499072	*SLC9A4*	C	G	0.43	0.09	0.01	1.90E-21
2	rs1523204	102502069	*SLC9A4*	A	G	0.43	0.09	0.01	1.94E-21
2	rs1523203	102502191	*SLC9A4*	G	A	0.23	0.10	0.01	1.99E-21
2	rs4851611	102502370	*SLC9A4*	T	A	0.23	0.10	0.01	2.02E-21
2	rs6750971	102505257	*SLC9A4*	G	A	0.23	0.10	0.01	2.04E-21
2	rs1403551	102502878	*SLC9A4*	G	T	0.23	0.10	0.01	2.04E-21
2	rs1403550	102502741	*SLC9A4*	C	T	0.23	0.10	0.01	2.04E-21
2	rs4851613	102504422	*SLC9A4*	C	T	0.23	0.10	0.01	2.12E-21
2	rs6750851	102505193	*SLC9A4*	G	A	0.23	0.10	0.01	2.14E-21
2	rs2215998	102532475	*SLC9A4*	G	A	0.43	0.08	0.01	2.95E-21
2	rs10194822	102531936	*SLC9A4*	G	T	0.43	0.08	0.01	3.05E-21
2	rs11685483	102525525	*SLC9A4*	C	A	0.23	0.10	0.01	3.18E-21
2	rs10196579	102536613	*SLC9A4*	T	C	0.43	0.08	0.01	3.48E-21
2	rs2310295	102537498	*SLC9A4*	A	G	0.43	0.08	0.01	4.21E-21
2	rs759381	102460755	*SLC9A4*	T	A	0.24	0.10	0.01	4.62E-21
2	rs6739426	102526875	*SLC9A4*	G	A	0.23	0.10	0.01	4.64E-21
2	rs2871474	102517873	*SLC9A4*	A	G	0.21	0.11	0.01	5.95E-21
2	rs4851019	102543997	*SLC9A4*	A	T	0.43	0.08	0.01	7.61E-21
2	rs10202404	102543846	*SLC9A4*	T	C	0.43	0.08	0.01	7.61E-21
2	rs11899041	102527485	*SLC9A4*	A	T	0.23	0.10	0.01	7.64E-21
2	rs9989842	102490065	*SLC9A4*	G	C	0.21	0.11	0.01	1.11E-20
2	rs6714379	102499742	*SLC9A4*	G	A	0.20	0.11	0.01	1.73E-20
2	rs7600901	102282003	*IL1RL1*	A	G	0.14	0.13	0.01	2.74E-20
2	rs12997225	102231180	*IL1RL2*	A	C	0.06	-0.18	0.02	2.82E-20
2	rs13018912	102230742	*IL1RL2*	G	T	0.06	-0.18	0.02	2.86E-20
2	rs1303960	102532264	*SLC9A4*	A	G	0.23	0.10	0.01	5.17E-20
2	rs759382	102460645	*SLC9A4*	T	G	0.23	0.10	0.01	5.35E-20
2	rs12712157	102531561	*SLC9A4*	C	T	0.23	0.10	0.01	5.59E-20

2	rs13019803	102142634	*IL1R1*	C	T	0.12	-0.14	0.02	5.95E-20
2	rs2005881	102539491	*SLC9A4*	A	G	0.23	0.10	0.01	1.05E-19
2	rs6761871	102543229	*SLC9A4*	C	A	0.23	0.10	0.01	1.51E-19
2	rs4851619	102542843	*SLC9A4*	T	C	0.23	0.10	0.01	1.67E-19
2	rs12993937	102222263	*IL1RL2*	G	T	0.06	-0.18	0.02	3.33E-19
2	rs6543146	102463127	*SLC9A4*	G	T	0.42	0.08	0.01	8.53E-18
2	rs12995229	102213339	*IL1RL2*	A	G	0.06	-0.17	0.02	9.24E-18
2	rs1030026	102464610	*SLC9A4*	C	A	0.42	0.08	0.01	1.27E-17
2	rs2140316	102465108	*SLC9A4*	A	T	0.42	0.08	0.01	1.94E-17
2	rs1861245	102333338	*IL1RL1*	C	T	0.39	0.08	0.01	2.94E-17
2	rs6759588	102406591	*IL18RAP*	A	G	0.13	0.12	0.01	3.00E-17
2	rs13424006	102333668	*IL1RL1*	T	C	0.39	0.08	0.01	3.25E-17
2	rs6751967	102333845	*IL1RL1*	T	C	0.39	0.08	0.01	3.39E-17
2	rs6749114	102334019	*IL1RL1*	A	C	0.39	0.08	0.01	3.54E-17
2	rs4988956	102334439	*IL1RL1*	G	A	0.39	0.08	0.01	3.66E-17
2	rs4988957	102334507	*IL1RL1*	T	C	0.39	0.08	0.01	3.66E-17
2	rs10204137	102334644	*IL1RL1*	A	G	0.39	0.08	0.01	3.66E-17
2	rs4988955	102334360	*IL1RL1*	A	G	0.39	0.08	0.01	3.67E-17
2	rs4988958	102334717	*IL1RL1*	T	C	0.39	0.08	0.01	3.84E-17
2	rs10192157	102334788	*IL1RL1*	C	T	0.39	0.08	0.01	4.06E-17
2	rs1362348	102351056	*IL18R1*	C	G	0.39	0.08	0.01	4.11E-17
2	rs10206753	102334794	*IL1RL1*	T	C	0.39	0.08	0.01	4.33E-17
2	rs3755276	102344891	*IL18R1*	C	T	0.39	0.08	0.01	4.88E-17
2	rs10176664	102342604	*IL18R1*	G	A	0.39	0.08	0.01	5.15E-17
2	rs7603730	102340803	*IL18R1*	A	C	0.39	0.08	0.01	6.09E-17
2	rs13017475	102219640	*IL1RL2*	C	T	0.06	-0.17	0.02	7.83E-17
2	rs4851602	102482737	*SLC9A4*	A	G	0.42	0.08	0.01	8.97E-17
2	rs13002972	102218293	*IL1RL2*	G	A	0.06	-0.17	0.02	9.30E-17
2	rs10170583	102341196	*IL18R1*	G	A	0.39	0.08	0.01	1.13E-16
2	rs12987900	102215780	*IL1RL2*	G	A	0.06	-0.17	0.02	1.30E-16
2	rs1997502	102210681	*IL1RL2*	G	A	0.34	0.08	0.01	2.92E-16
2	rs7600961	102401887	*IL18RAP*	G	A	0.13	0.11	0.01	3.25E-16
2	rs11465670	102400872	*IL18RAP*	T	C	0.13	0.11	0.01	3.37E-16
2	rs3771166	102352654	*IL18R1*	G	A	0.38	0.08	0.01	3.43E-16
2	rs1974675	102352807	*IL18R1*	G	A	0.38	0.08	0.01	3.52E-16
2	rs1558648	102176600	*IL1RL2*	T	G	0.13	-0.13	0.02	3.94E-16
2	rs13014084	102221197	*IL1RL2*	A	G	0.07	-0.15	0.02	4.09E-16
2	rs13033782	102210265	*IL1RL2*	G	A	0.06	-0.16	0.02	5.31E-16
2	rs11465698	102421009	*IL18RAP*	T	C	0.13	0.11	0.01	6.65E-16
2	rs12992518	102204030	*IL1RL2*	C	T	0.06	-0.16	0.02	7.06E-16
2	rs6741230	102436063	*IL18RAP*	C	T	0.13	0.11	0.01	7.55E-16
2	rs13028635	102198716	*IL1RL2*	C	T	0.06	-0.16	0.02	7.65E-16
2	rs13002813	102197712	*IL1RL2*	T	C	0.06	-0.16	0.02	7.74E-16

2	rs12989930	102196254	*IL1RL2*	T	C	0.06	-0.16	0.02	7.87E-16
2	rs10490570	102194171	*IL1RL2*	C	T	0.06	-0.16	0.02	8.15E-16
2	rs13021607	102191158	*IL1RL2*	G	A	0.06	-0.16	0.02	8.86E-16
2	rs7605606	102487968	*SLC9A4*	A	G	0.36	0.08	0.01	1.08E-15
2	rs3917254	102142950	*IL1R1*	G	A	0.11	-0.12	0.02	1.14E-15
2	rs12987222	102180548	*IL1RL2*	G	T	0.06	-0.16	0.02	1.19E-15
2	rs6754776	102131210	*IL1R1*	C	G	0.13	-0.11	0.01	2.16E-15
2	rs2241132	102170467	*IL1RL2*	C	A	0.11	-0.13	0.02	2.68E-15
2	rs3917291	102148598	*IL1R1*	G	A	0.06	-0.16	0.02	1.20E-14
2	rs3917314	102157295	*IL1R1*	A	C	0.06	-0.15	0.02	1.98E-14
2	rs3917320	102159307	*IL1R1*	A	C	0.06	-0.15	0.02	2.13E-14
2	rs3917328	102160973	*IL1R1*	C	T	0.06	-0.15	0.02	2.21E-14
2	rs3917325	102160339	*IL1R1*	T	G	0.06	-0.15	0.02	2.21E-14
2	rs1016160	102611457	*SLC9A2*	G	A	0.16	0.09	0.01	4.68E-14
2	rs2310187	102116860	*IL1R1*	G	T	0.13	-0.10	0.01	5.61E-14
2	rs6752379	102113137	*IL1R1*	G	A	0.13	-0.10	0.01	6.58E-14
2	rs13035227	102130269	*IL1R1*	T	C	0.15	-0.11	0.01	1.72E-13
2	rs10208542	102098747	*IL1R1*	G	C	0.12	-0.10	0.01	1.80E-13
2	rs871195	102101269	*IL1R1*	C	A	0.12	-0.10	0.01	2.07E-13
2	rs13029169	102102173	*IL1R1*	G	A	0.12	-0.10	0.01	2.19E-13
2	rs13012334	102102452	*IL1R1*	A	G	0.12	-0.10	0.01	2.23E-13
2	rs7557377	102103020	*IL1R1*	C	T	0.12	-0.10	0.01	2.25E-13
2	rs12470623	102110447	*IL1R1*	A	T	0.12	-0.10	0.01	2.26E-13
2	rs6712813	102104458	*IL1R1*	C	T	0.12	-0.10	0.01	2.36E-13
2	rs6727859	102104596	*IL1R1*	A	G	0.12	-0.10	0.01	2.38E-13
2	rs6727985	102104707	*IL1R1*	A	G	0.12	-0.10	0.01	2.38E-13
2	rs2310186	102109612	*IL1R1*	T	G	0.12	-0.10	0.01	2.38E-13
2	rs1468790	102458873	*SLC9A4*	C	G	0.45	0.07	0.01	6.78E-13
2	rs1468788	102458945	*SLC9A4*	T	C	0.45	0.07	0.01	6.80E-13
2	rs1115281	102257539	*IL1RL2*	G	C	0.33	0.07	0.01	6.95E-13
2	rs10469856	102255261	*IL1RL2*	T	A	0.33	0.07	0.01	8.87E-13
2	rs3755285	102210452	*IL1RL2*	T	C	0.26	-0.07	0.01	1.20E-12
2	rs12996377	102196910	*IL1RL2*	T	A	0.13	-0.10	0.01	1.32E-12
2	rs10200945	102251189	*IL1RL2*	T	A	0.33	0.07	0.01	1.60E-12
2	rs11123915	102247255	*IL1RL2*	T	G	0.33	0.07	0.01	1.76E-12
2	rs11692304	102461836	*SLC9A4*	G	A	0.50	-0.06	0.01	2.20E-12
2	rs17775170	102618359	*SLC9A2*	G	A	0.21	-0.08	0.01	3.50E-12
2	rs4851610	102501084	*SLC9A4*	G	C	0.17	0.08	0.01	4.23E-12
2	rs3917296	102151265	*IL1R1*	A	G	0.09	0.12	0.02	7.15E-12
2	rs11123913	102191911	*IL1RL2*	T	C	0.24	-0.07	0.01	1.07E-11
2	rs11123912	102182968	*IL1RL2*	G	A	0.24	-0.07	0.01	1.13E-11
2	rs2302621	102208556	*IL1RL2*	T	G	0.40	0.06	0.01	1.48E-11
2	rs917994	102203846	*IL1RL2*	A	G	0.40	0.06	0.01	1.52E-11

2	rs6743219	102198143	*IL1RL2*	C	T	0.40	0.06	0.01	1.54E-11
2	rs1922291	102195249	*IL1RL2*	G	A	0.40	0.06	0.01	1.57E-11
2	rs1922302	102185481	*IL1RL2*	G	T	0.40	0.06	0.01	1.58E-11
2	rs12474258	102183127	*IL1RL2*	T	C	0.40	0.06	0.01	1.65E-11
2	rs2302612	102218140	*IL1RL2*	T	C	0.18	-0.08	0.01	2.08E-11
2	rs6754556	102217356	*IL1RL2*	A	T	0.18	-0.08	0.01	2.22E-11
2	rs6709635	102216871	*IL1RL2*	G	A	0.18	-0.08	0.01	2.30E-11
2	rs13007967	102099210	*IL1R1*	A	G	0.14	-0.09	0.01	3.34E-11
2	rs12712129	102100017	*IL1R1*	G	A	0.14	-0.09	0.01	3.39E-11
2	rs955754	102215513	*IL1RL2*	T	C	0.18	-0.08	0.01	3.58E-11
2	rs6758443	102214494	*IL1RL2*	G	T	0.18	-0.08	0.01	5.82E-11
2	rs11693697	102282094	*IL1RL1*	T	C	0.21	-0.08	0.01	6.81E-11
2	rs10207579	102469721	*SLC9A4*	T	C	0.48	0.06	0.01	6.87E-11
2	rs4851604	102485313	*SLC9A4*	A	G	0.48	0.06	0.01	9.85E-11
2	rs4851606	102487321	*SLC9A4*	A	G	0.30	0.06	0.01	1.10E-10
2	rs4851605	102487300	*SLC9A4*	G	A	0.30	0.06	0.01	1.11E-10
2	rs7558013	102359238	*IL18R1*	G	T	0.21	0.07	0.01	2.81E-09
2	rs10515922	102281086	*IL1RL1*	A	G	0.09	-0.09	0.02	5.12E-09
2	rs17027173	102423475	*IL18RAP*	G	A	0.22	0.07	0.01	6.88E-09
2	rs6543135	102428838	*IL18RAP*	C	T	0.27	0.06	0.01	9.89E-09
2	rs10167431	102219234	*IL1RL2*	C	T	0.48	0.05	0.01	1.04E-08
2	rs1558625	102228596	*IL1RL2*	G	A	0.34	0.06	0.01	1.40E-08
2	rs4851017	102487201	*SLC9A4*	A	C	0.29	0.06	0.01	1.55E-08
2	rs7567885	102475284	*SLC9A4*	G	T	0.29	0.06	0.01	1.56E-08
2	rs1403548	102476807	*SLC9A4*	T	C	0.29	0.06	0.01	1.56E-08
2	rs12712153	102478193	*SLC9A4*	T	C	0.29	0.06	0.01	1.56E-08
2	rs11687071	102478352	*SLC9A4*	A	G	0.29	0.06	0.01	1.56E-08
2	rs7566063	102478997	*SLC9A4*	A	C	0.29	0.06	0.01	1.56E-08
2	rs7591872	102479073	*SLC9A4*	C	G	0.29	0.06	0.01	1.56E-08
2	rs7591878	102479090	*SLC9A4*	A	G	0.29	0.06	0.01	1.56E-08
2	rs4851016	102486832	*SLC9A4*	T	C	0.29	0.06	0.01	1.60E-08
2	rs2075187	102486743	*SLC9A4*	A	G	0.29	0.06	0.01	1.62E-08
2	rs11465699	102421199	*IL18RAP*	G	A	0.04	0.14	0.02	1.64E-08
2	rs11690932	102485461	*SLC9A4*	A	G	0.29	0.06	0.01	1.73E-08
2	rs2075190	102484991	*SLC9A4*	T	A	0.29	0.06	0.01	1.76E-08
2	rs2075191	102484731	*SLC9A4*	T	G	0.29	0.06	0.01	1.77E-08
2	rs2075192	102484660	*SLC9A4*	G	A	0.29	0.06	0.01	1.77E-08
2	rs2075193	102484459	*SLC9A4*	A	G	0.29	0.06	0.01	1.78E-08
2	rs6728288	102483700	*SLC9A4*	T	A	0.29	0.06	0.01	1.80E-08
2	rs12995030	102482898	*SLC9A4*	G	C	0.29	0.06	0.01	1.81E-08
2	rs12987295	102482270	*SLC9A4*	A	G	0.29	0.06	0.01	1.82E-08
2	rs4851012	102482347	*SLC9A4*	T	C	0.29	0.06	0.01	1.83E-08
2	rs4851600	102482655	*SLC9A4*	G	C	0.29	0.06	0.01	1.83E-08

2	rs4851014	102482708	*SLC9A4*	T	C	0.29	0.06	0.01	1.83E-08
2	rs10175045	102469664	*SLC9A4*	C	T	0.29	0.06	0.01	2.16E-08
2	rs1523198	102464906	*SLC9A4*	T	C	0.29	0.06	0.01	2.17E-08
2	rs6725806	102582604	*SLC9A2*	G	T	0.26	0.06	0.01	3.21E-08

Supplemental Table 3. Suggestive loci associated with sST2 ($P<1 \times 10^{-6}$)

Chr	SNP	Position (NCBI 36.3)	Nearest gene (s)	Location	Allele (major/minor)	MAF	P-value
1	rs1775453	195895965	*DENND1B*	intronic	T/C	0.26	2.34E-07
1	rs10923038	88424359	*PKN2*	intergenic	A/C	0.34	4.17E-07
18	rs206548	10372883	*APCDD1*	intergenic	C/T	0.48	8.57E-07

Supplemental Table 4. Association of top 10 sST2 SNPs and clinical phenotypes (p-values[A])

Trait	rs950880	rs13029918	rs1420103	rs1014286	rs17639215	rs12999542	rs13019803	rs1558648	rs2302612	rs11693697
Clinical Disease Phenotypes										
CVD (25)	0.52	0.23	0.39	0.38	0.39	0.35	**0.04**	0.69	0.11	0.24
Mortality (26)	0.91	0.36	0.72	0.83	0.78	0.51	**0.03**	**0.003**	0.36	0.54
Heart failure (27)	0.38	0.46	0.35	0.63	0.43	0.33	0.69	0.34	0.71	0.34
Asthma (28)	NA	NA	NA	0.24	NA	NA	NA	NA	0.02	0.94
Clinical Traits										
Systolic BP (29)	0.50	0.80	0.40	0.43	0.86	0.75	0.81	0.39	0.92	0.76
Diastolic BP (29)	0.51	0.37	0.69	0.44	0.85	0.87	0.77	0.24	0.65	0.57
BMI (30)	0.80	0.35	0.87	0.53	0.89	0.33	0.11	0.62	0.13	0.50
Fasting glucose (31)	0.13	0.29	0.11	0.04	0.28	**0.01**	0.93	0.27	0.20	0.55
HOMA-IR (31)	0.80	0.52	0.57	0.39	0.37	0.80	0.35	0.48	0.80	0.79
HDL (32)	0.40	0.99	0.86	0.85	0.52	0.32	0.50	0.23	0.96	0.24
LDL (32)	0.25	0.74	0.84	0.51	0.61	0.61	0.74	0.73	0.28	0.30
Total cholesterol (32)	0.41	0.59	0.96	0.38	0.56	0.65	0.80	0.94	0.11	0.84
Triglycerides (32)	0.30	0.62	0.10	0.22	0.41	0.66	0.46	0.35	0.32	0.37
Biomarker traits										
BNP (FHS)	0.18	0.63	1.00	0.64	0.97	0.67	0.66	0.11	0.58	0.66
NT-proBNP (FHS)	0.06	0.13	0.31	0.79	**0.03**	**0.03**	0.16	0.97	0.11	0.21
CRP (33)	**0.02**	**0.01**	**0.0004**	**0.01**	1.00	0.66	**0.01**	**0.003**	**0.03**	**0.05**
Echocardiographic traits										
LV diast. dim. (34)	0.85	0.31	0.59	**0.02**	0.16	0.25	0.16	0.35	0.45	0.65
LV mass (34)	0.32	0.65	0.69	**0.02**	**0.02**	0.68	0.16	0.34	0.28	0.61
LA dimension (34)	0.31	0.68	0.04	0.08	0.71	0.91	0.96	0.84	0.90	0.92

[A]Bonferroni-corrected P-value threshold = 0.005

Supplemental Table 5. sST2 concentrations according to genotype for missense variants

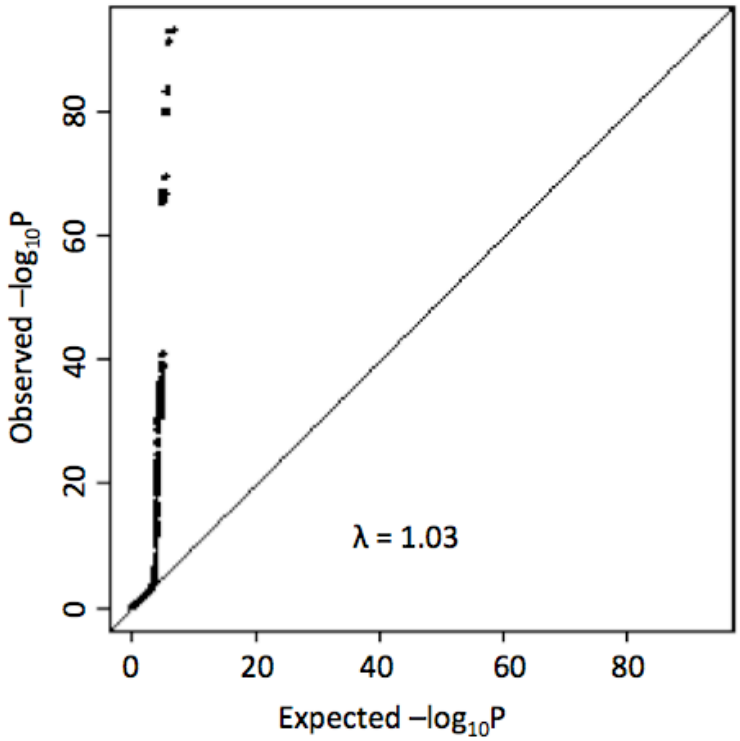
Variant	Major/minor Allele	sST2 concentration, ng/ml (SD)		
		Major homozygote	Heterozygote	Minor homozygote
rs6749114* (Q501K)	A/C	20.9 (8.2)	22.4 (8.2)	24.1 (9.6)
rs4988956 (A433T)	G/A	20.9 (8.2)	22.4 (8.2)	24.1 (9.6)
rs10204137 (Q501R)	A/G	20.9 (8.2)	22.4 (8.2)	24.1 (9.6)
rs10192157 (T549I)	C/T	20.9 (8.2)	22.4 (8.2)	24.1 (9.6)
rs10206753 (L551S)	T/C	20.9 (8.2)	22.4 (8.2)	24.1 (9.6)
rs1041973 (A78E)	C/A	22.6 (8.4)	21.6 (8.6)	20.4 (7.7)

*perfect proxy for nSNP 10192036 in 1000 Genomes Pilot 1 dataset

Supplemental Table 6. Association of sST2 genetic variants with previously reported immune and inflammatory conditions

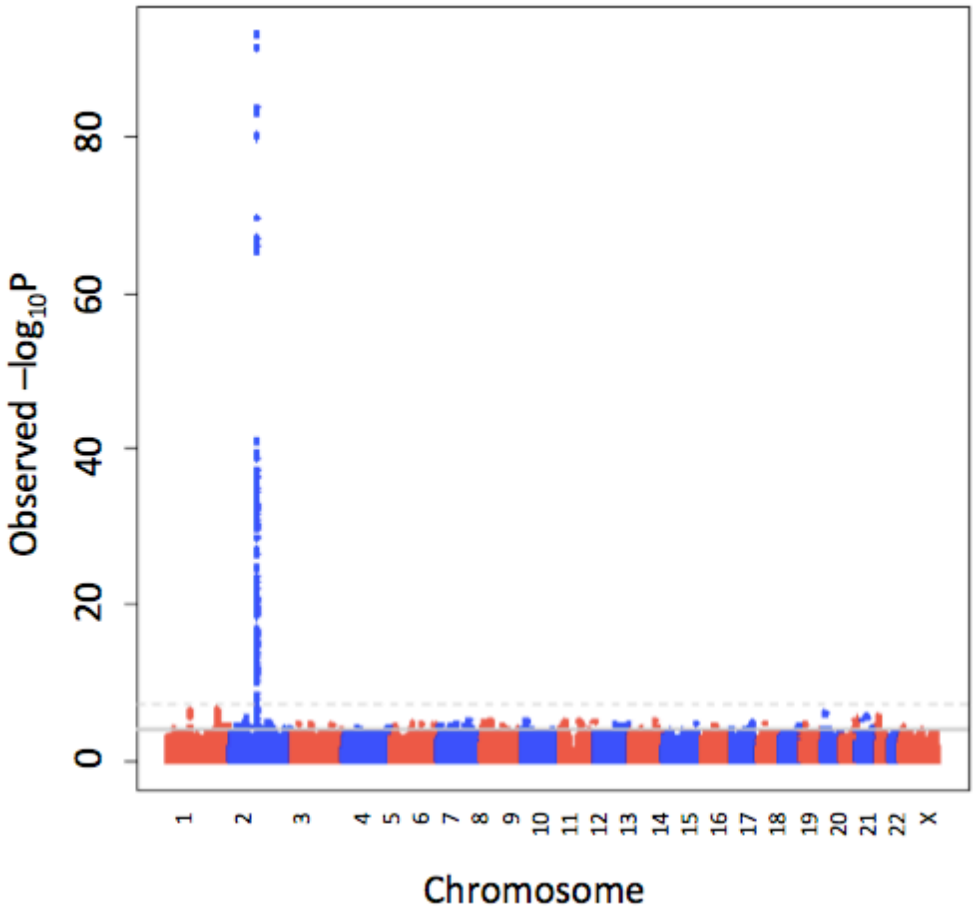
rsID	sST2 *P*	Previous disease	Previous disease *P*	Reference
rs1420101	4.33×10^{-92}	Eosinophil count Asthma	5.3×10^{-14} 5.5×10^{-12}	Gudbjartsson DF, *Nat Genet*, 2009 (35)
rs13015714	4.47×10^{-33}	Celiac disease	4.4×10^{-9}	Hunt K, *Nat Genet*, 2008(36)
rs917997	3.36×10^{-31}	Crohn's disease	2.2×10^{-6}	Wang K, *Hum Mol Genet*, 2010 (37)
rs917997	3.36×10^{-31}	Inflammatory bowel disease	1.9×10^{-8}	Zhernakova A, *Am J Hum Genet*, 2008 (38)
rs917997	3.36×10^{-31}	Celiac disease	8.5×10^{-10}	Hunt K, *Nat Genet*, 2008 (36)
rs917997	3.36×10^{-31}	Type 1 diabetes	8.0×10^{-5}	Smyth DJ, *N Engl J Med*, 2008 (39)
rs1035127	5.65×10^{-31}	Crohn's Disease	1.2×10^{-4}	Barrett JC, *Nat Genet*, 2008 (40)
rs1974675	3.52×10^{-16}	Asthma	5.0×10^{-5}	Zhu G, *Eur J Hum Genet*, 2008 (41)

Supplemental Figure 1



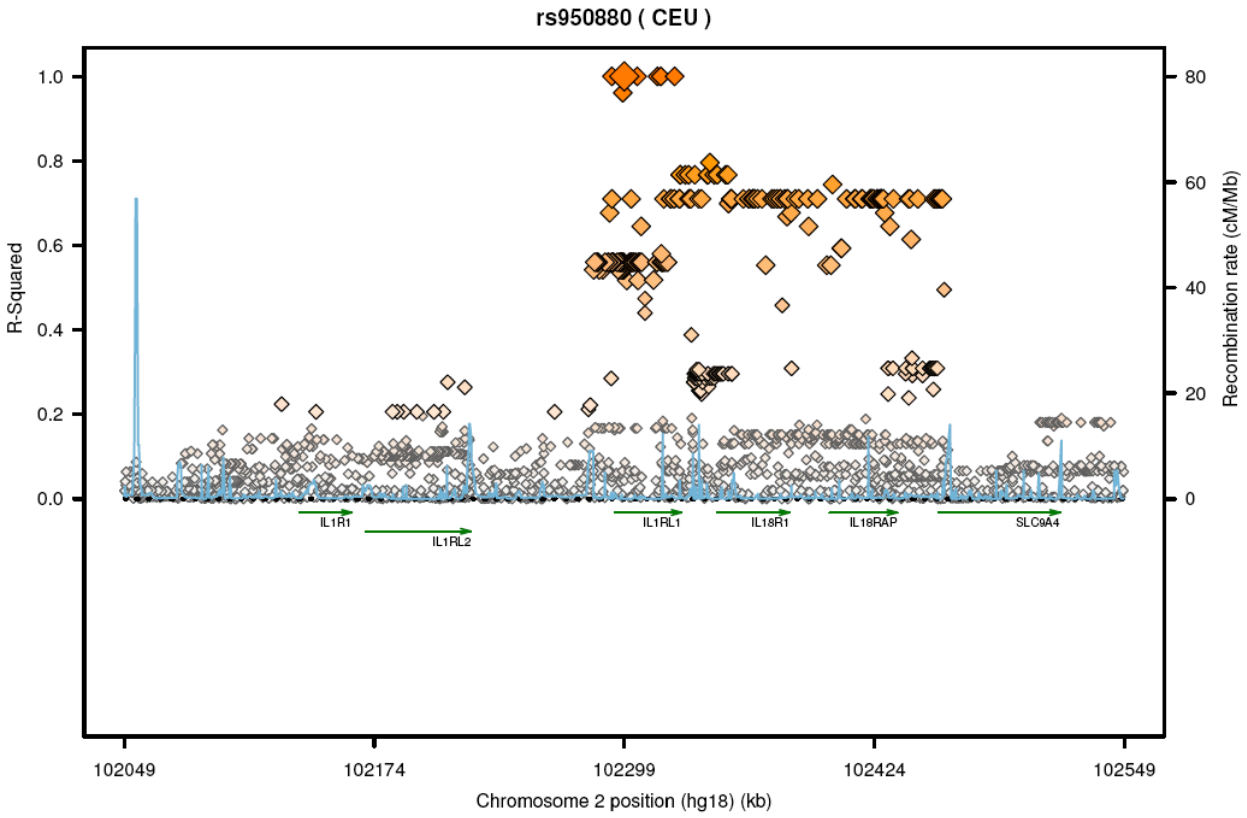
Quantile-quantile plot of sST2 genome-wide association study

Supplemental Figure 2



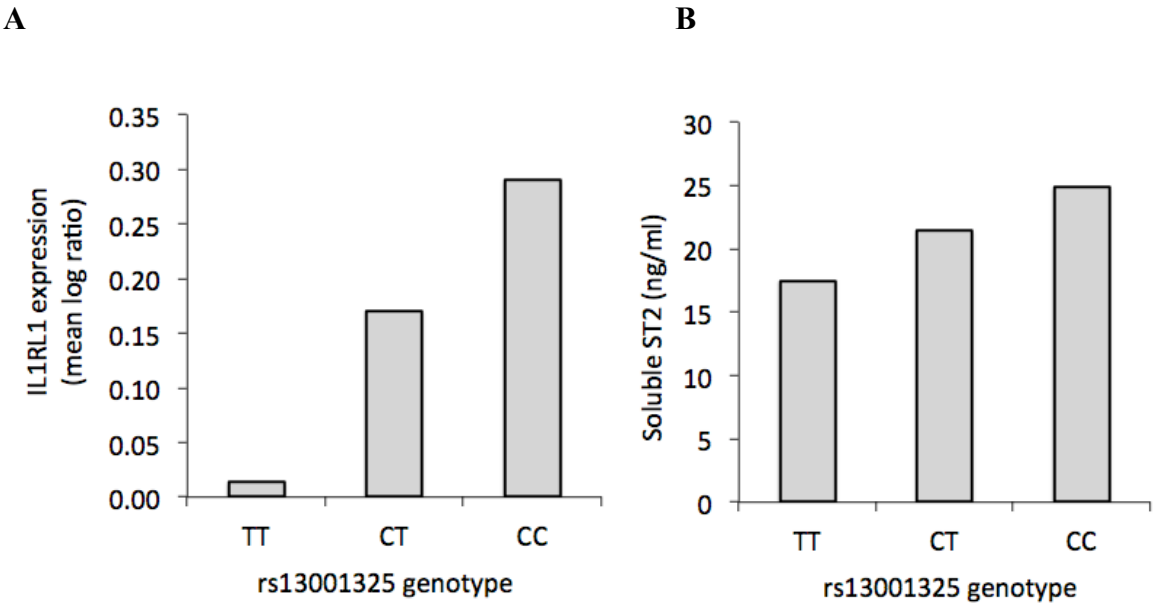
Manhattan plot of sST2 genome-wide association study

Supplemental Figure 3



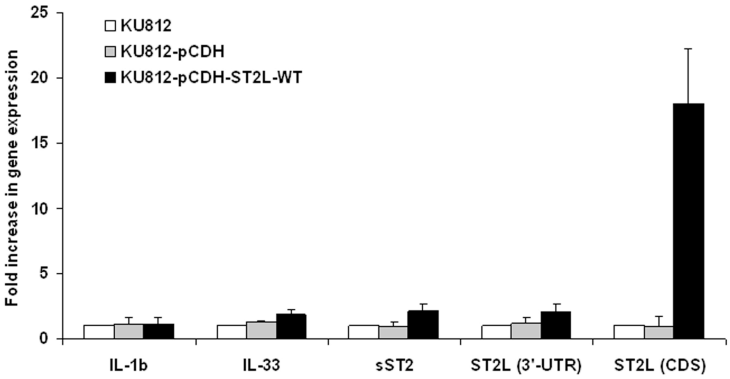
Regional linkage disequilibrium plot displaying genetic loci within the same region as *IL1RL1*

Supplemental Figure 4



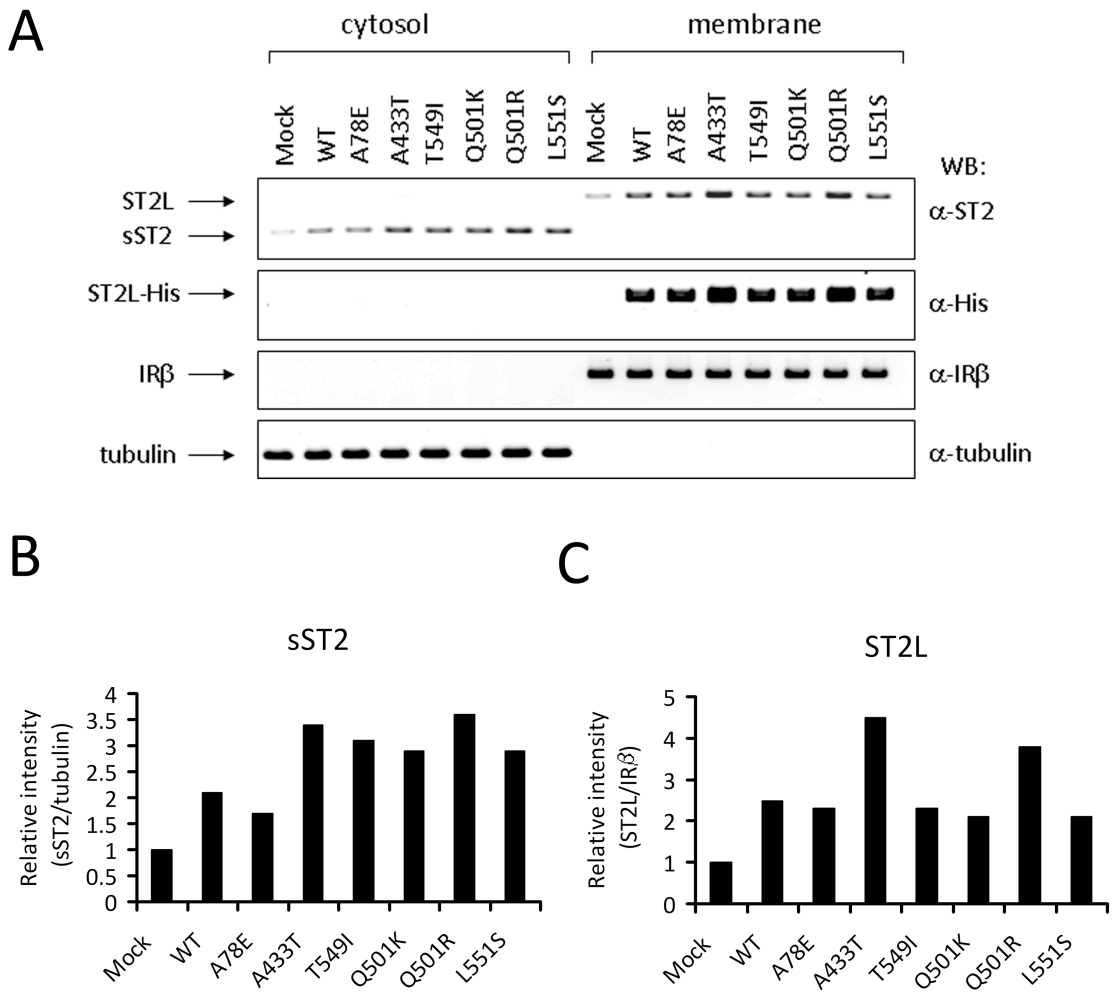
Gene expression levels of IL1RL1 and circulating sST2 levels by rs13001325 genotype. In panel A, there was a 1.9 fold higher expression level of IL1RL1 in pre-frontal cortex tissue of major homozygotes (CC) compared with minor homozygotes (TT) for rs13001325. Expression levels are expressed in mean log ratio of the intensity measurements between IL1RL1 gene expression and reference channels.(42) In panel B, sST2 concentrations are associated with rs13001325 genotype with the same directionality as gene expression. Standard errors by genotype are 0.42 ng/ml (CC), 0.22 (CT), and 0.22 (TT).

Supplemental Figure 5



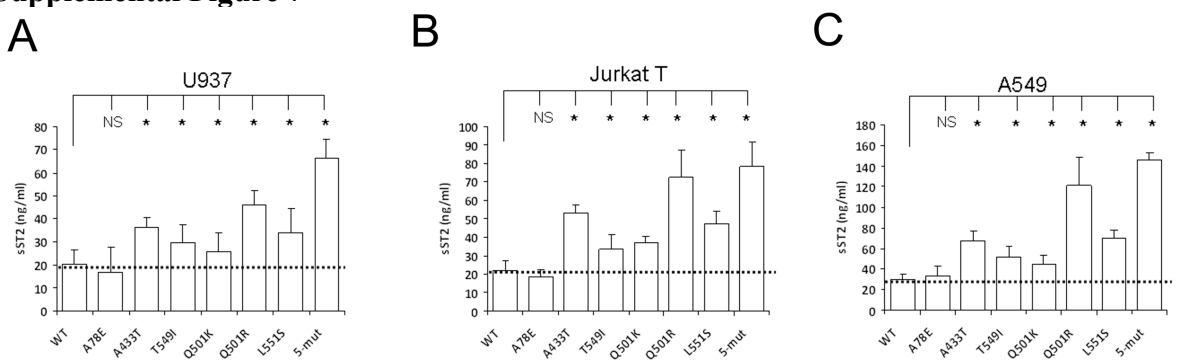
Basal mRNA expression of IL-33, IL-1β, sST2, and ST2L in KU812 cells and stable cells expressing wildtype ST2L. mRNA expression in KU812 cells expressing the wildtype ST2L and the uninfected control KU812 were analyzed by realtime RT-PCR. Primers targeting the 3'-UTR or coding sequences (CDS) of ST2L were used to detect endogenous or exogenous ST2L expression, respectively.

Supplemental Figure 6



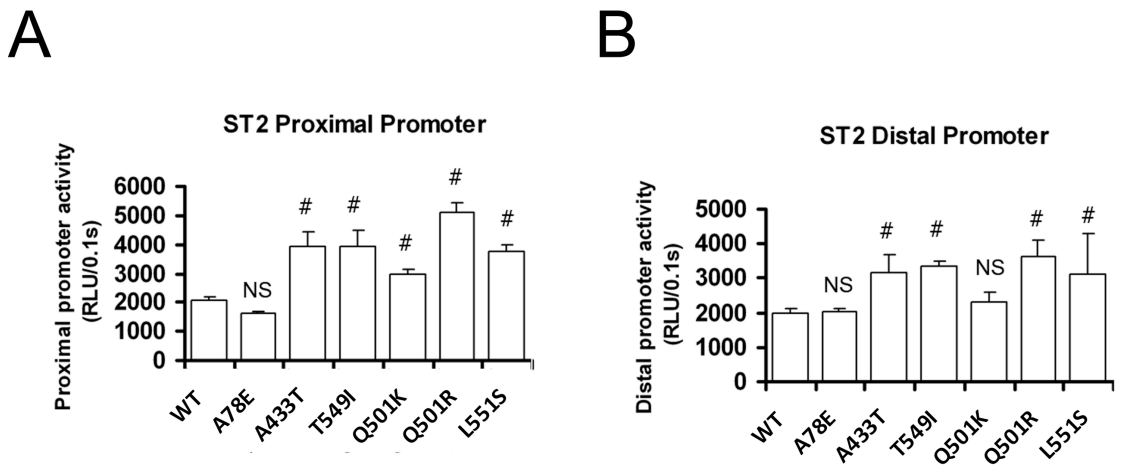
Expression of ST2 protein in cells expressing *IL1RL1* variants. (A) Membrane and cytosol fractions subtracted from whole cell lysates were analyzed by immunoblotting with anti-ST2 mAb (for both ST2L and sST2), anti-His (for exogenous ST2L-His), anti-Insulin receptor b (IRb, for quality control of membrane fraction), or anti-tubulin (for quality control of cytosol fraction). Protein levels of sST2 (B) and ST2L (C) were quantified by relative intensity. Data are representative of 2 independent experiments.

Supplemental Figure 7



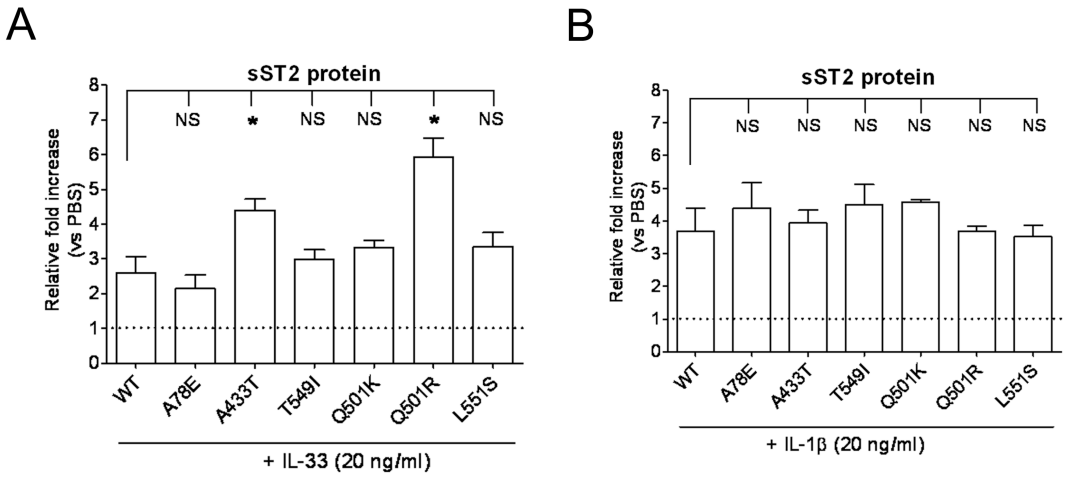
***IL1RL1* intracellular missense variants induce sST2 and IL-33 in U937, Jurkat T and A549 cells.** (A) U937, (B) Jurkat T, and (C) A549 cells (three stable cell lines per group) expressing wild type (WT) and IL1RL1 missense variants were cultured in serum free RPMI 1640 medium for 24 h. Media were collected for ELISA analysis of sST2 levels. **P* <0.05 compare to WT group. Error bars represent mean ± s.e. from two independent experiments.

Supplemental Figure 8



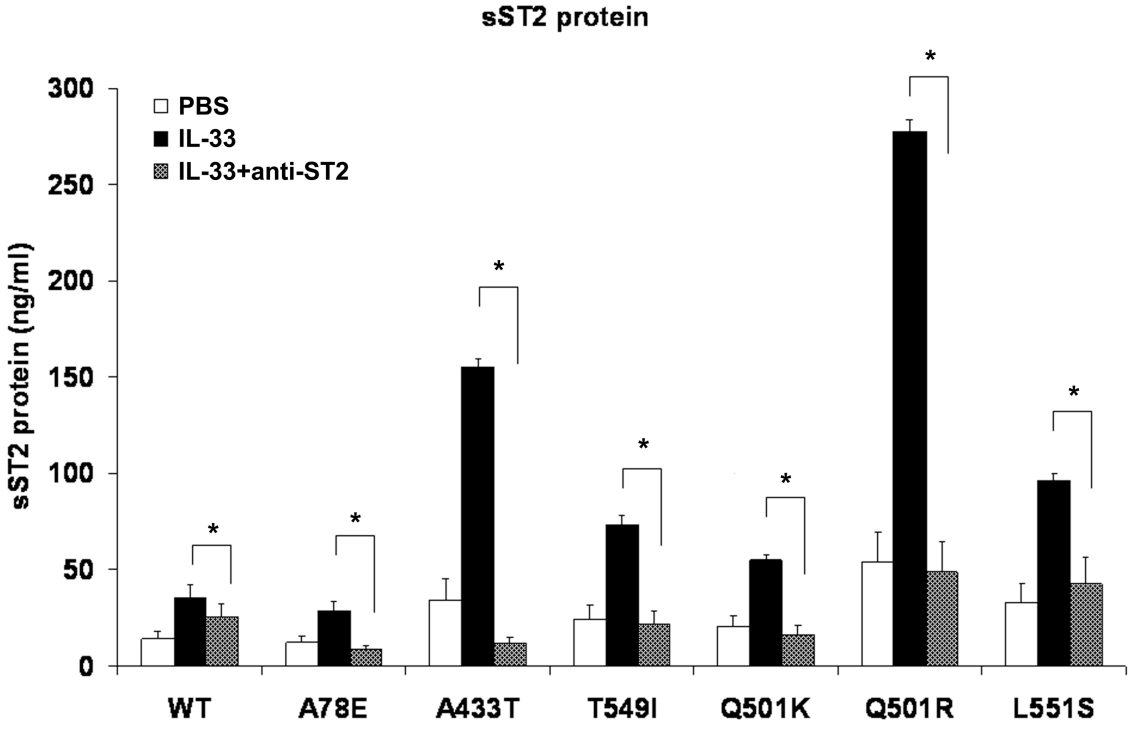
IL1RL1 **missense variants upregulated both proximal and distal ST2 promoter activities.** KU812 cells (1 x 10^6/well) expressing WT or ST2 variants were transfected with (a) proximal ST2 promoter construct (-1745/+200) or (b) distal ST2 promoter construct (-697/+741) for 18 h and then medium was changed to serum free RPMI-1640 and cells were cultured for additional 24 h. Cell lysates were then analyzed using a luciferase assay. #P<0.05 vs WT. Error bars represent mean ± s.e from two independent experiments.

Supplemental Figure 9



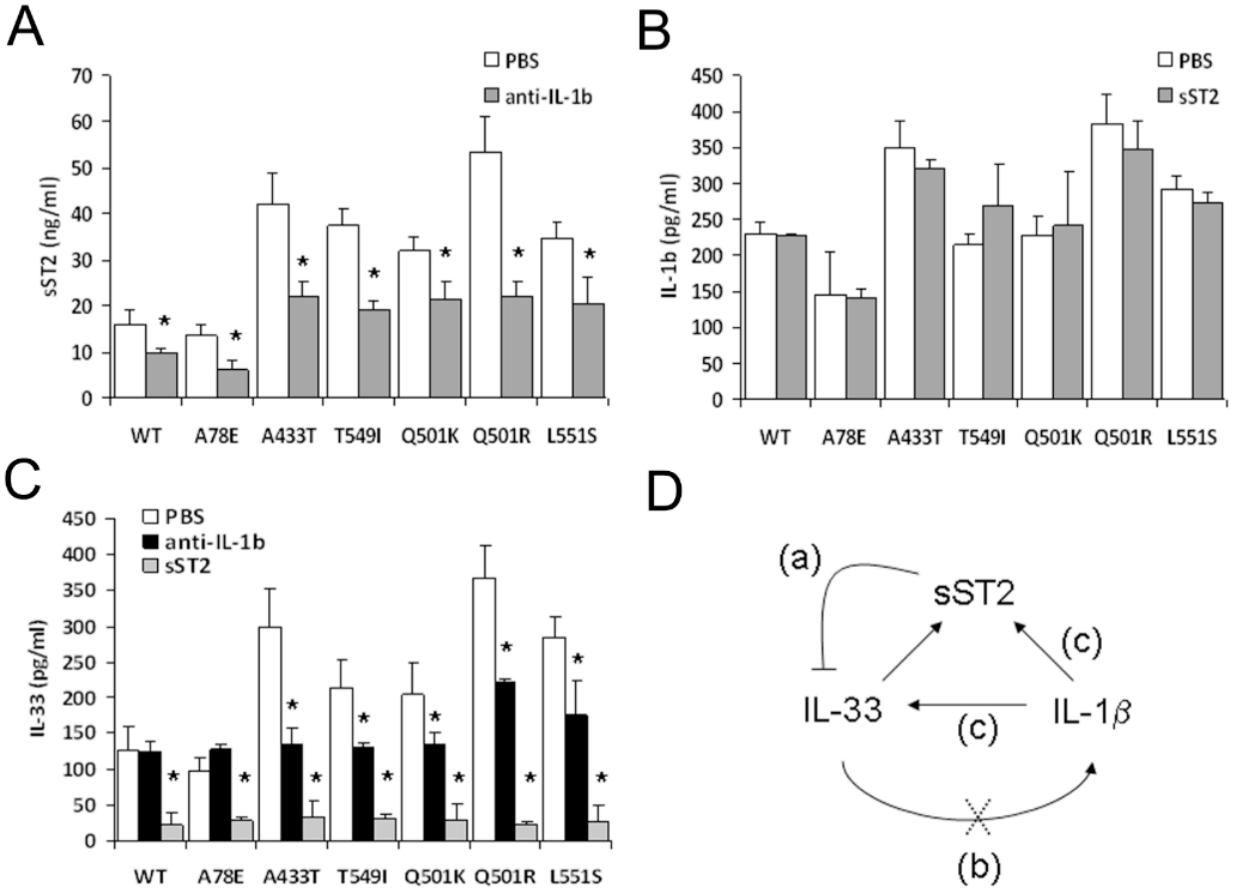
Correlation between sST2 and IL-1β in cells expressing *IL1RL1* missense variants. KU812 cells ($5x10^5$/well) expressing WT or ST2L variants were cultured in serum free RPMI-1640 medium for 24 hours. Media were then collected for ELISA analysis for sST2 and IL-1β. Effect of (A) IL-33 or (B) IL-1β on sST2 expression in cells expressing *IL1RL1* variants. Dashed line indicates PBS treated cells as referent group. Data are mean ± s.e. from two independent experiments. Eight different stable cell lines in each group were used in this experiment. **P*<0.05 vs WT

Supplemental Figure 10



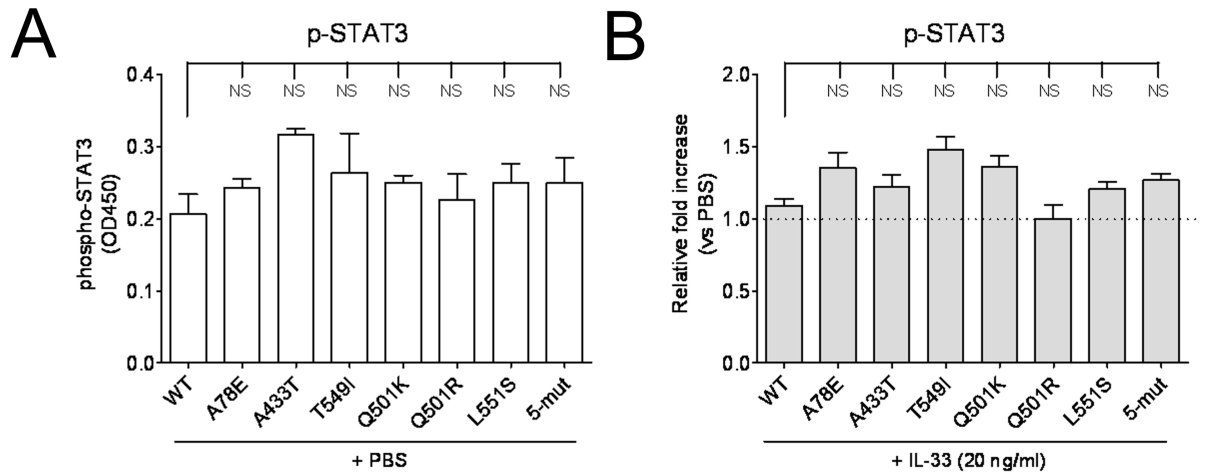
IL-33 induced sST2 expression through an ST2-dependent pathway. KU812 cells ($5x10^5$/well, three different stable cell lines in each group) expressing WT or *IL1RL1* variants were treated with PBS, IL-33, or IL-33 + anti-ST2, for 24 hours. Media were then collected for ELISA analysis for sST2. Error bars represent mean ± s.e from two independent experiments. **P*<0.05 for IL-33 vs IL33+anti-ST2.

Supplemental Figure 11



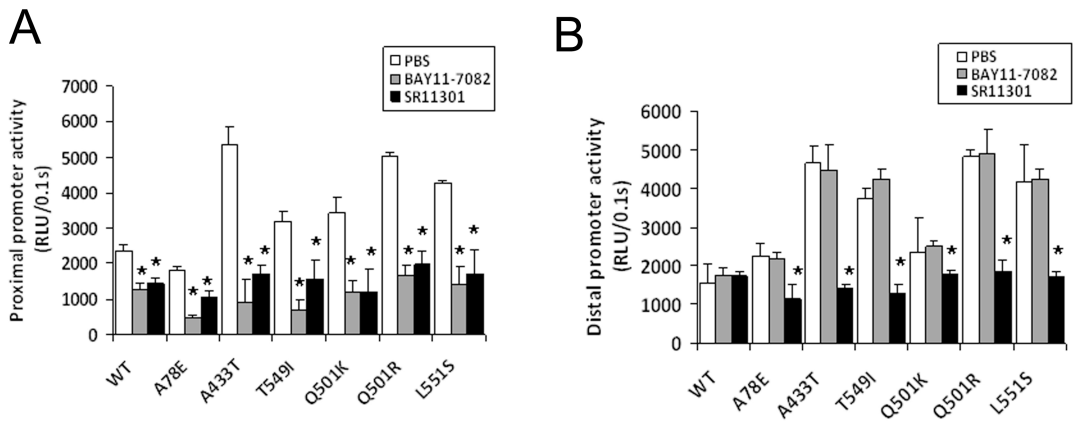
Interaction between IL-33, sST2 and IL-1β. (A) Incubation of anti-IL-1β mAb reduced the basal sST2 expression in KU812 cells expressing the *IL1RL1* variants. (B) Blocking of IL-33 by addition of sST2 did not affect basal IL-1β levels. (C) Basal IL-33 levels were reduced by anti-IL-1β and sST2. (D) Schematic model depicting the interaction between IL-33, sST2, and IL-1β. (a) IL-33 itself upregulates sST2, which in turn feeds back to inhibit IL-33 levels. (b) IL-33 has limited effect on basal IL-1β expression in these conditions. (c) IL-1β acts as an inducer of IL-33 and sST2. * $p<0.05$ compare to PBS treated group. Three stable cell lines were analyzed in each group. Error bars represent mean ± s.e. from two independent experiments.

Supplemental Figure 12



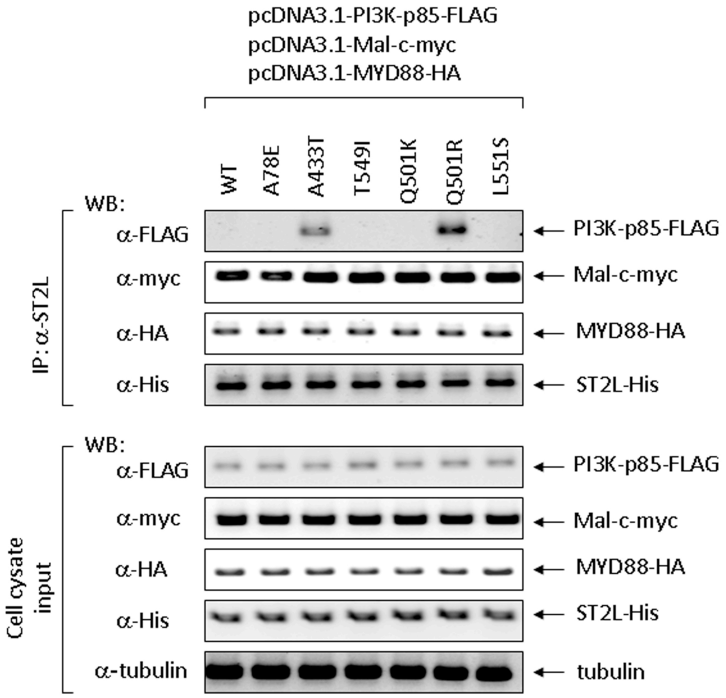
***IL1RL1* missense variants did not affect STAT3 activation.** KU812 cells ($5x10^5$/well, three different stable cell line in each group) expressing WT or ST2L variants were treated with PBS or IL-33 (20ng/ml) for 30 minutes. Phosphor-STAT3 was analyzed using ELISA-based phosphor-protein assay. (a) Basal phosphor-STAT3 level. (b) Relative fold increase in phosphor-STAT3 level with IL-33. Error bars represent mean ± s.e. from two independent experiments.

Supplemental Figure 13



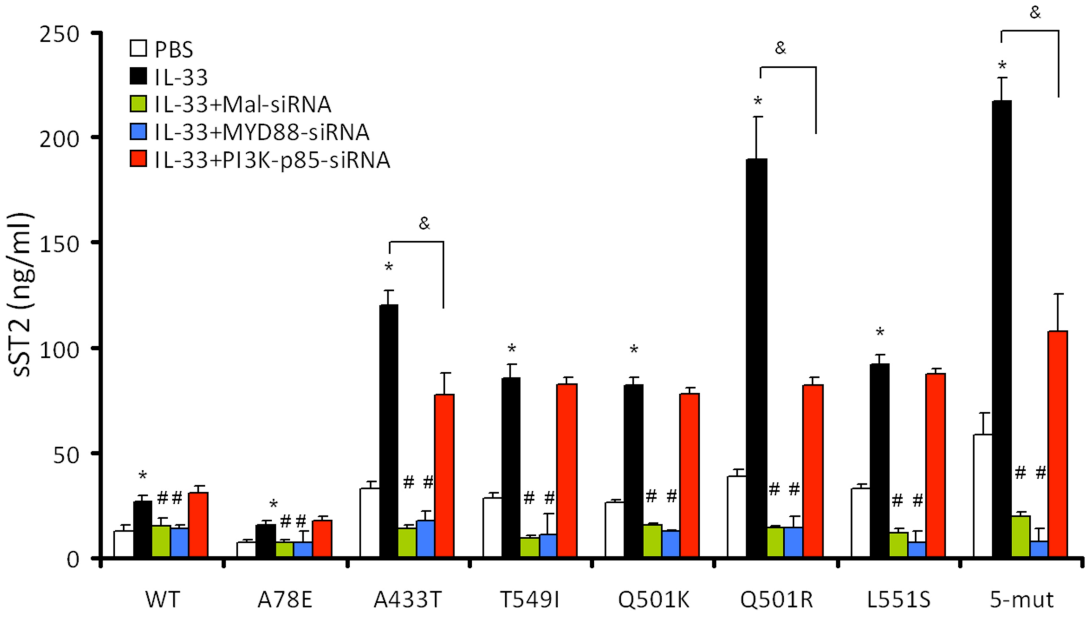
Regulation of the proximal and distal *IL1RL1* promoters by *IL1RL1* variants. (A) Proximal promoter activity and (B) distal promoter activity were analyzed in cells expressing IL1RL1 variants treated with BAY11-7082 (10 μM) or SR11301 (10 μM). * $p<0.05$ compare to PBS treated group. Three stable cell lines were analyzed in each group. Error bars represent mean ± s.e. from two independent experiments.

Supplemental Figure 14



IL1RL1 **variants A433T and Q501R interact with the PI3K-p85 subunit, Mal, and MYD88.** Cell lysates from HEK293 cells co-expressing the ST2L variants, PI3K-p85-FLAG, Mal-c-myc, and MYD88-HA were immunoprecipitated by using anti-ST2L mAb, then immunoblotted by anti-FLAG for PI3K-p85 subunit, anti-c-myc for Mal, anti-HA for MYD88, or anti-His for ST2L variant protein. Precipitates and whole cell lysates were analyzed by immunoblot.

Supplemental Figure 15



Mal and MYD88 are required for the upregulation of sST2 levels by intracellular *IL1RL1* variants. KU812 cells expressing *IL1RL1* variants were treated with PBS, IL-33, IL-33 plus Mal-siRNA, or IL-33 plus PI3K-p85-siRNA. Culture media were collected after 72 hr treatment. Levels of sST2 were analyzed by ELISA. Three stable cell lines were analyzed in each group. Error bars represent mean ± s.e. from two independent experiments. *p<0.05 compared to PBS treated group, #p<0.05 compared to IL-33 treated group. &p<0.05 compared to IL-33 treated group.

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