

Supplemental Information

A Novel Dominant-Negative CARD11 Variant Causes Atopy and Immunodeficiency Syndrome

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Patient descriptions

1.1 Clinical description of the index patient (II-2)

Currently 19-year-old female, who was born full-term to non-consanguineous Finnish family. Her growth was normal. At the age of one, she presented with severe atopic dermatitis which was treated with topical tacrolimus. She also showed elevated IgE levels towards egg white and peanut. Atopic dermatitis was resolved when she started school.

Starting around age 9, she started to have a bruising and nosebleed tendency, with underlying thrombocytopenia identified. Retrospectively, low platelet counts, and mild leukopenia had been noted as early as 2008 when she was 1 year old.

At the age of 9 she had chicken pox without complications. At age of 9, she suffered from *Streptococcus viridians* sepsis, which was treated with piperacillin-tazobactam, followed by oral amoxicillin. Simultaneously neutropenia (lowest value $0.11 \times 10^9/L$) and lymphopenia was noted. She recovered well from the sepsis. Additionally, she has had a few throat infections and upper respiratory tract infections requiring antibiotic treatment, but no other serious or opportunistic bacterial infections, Schwachman-Diamond-syndrome, and celiac disease were ruled out.

Bone marrow samples were investigated at the age of 9, 10, and 11. The finding was hypoplastic marrow for all the cell lineages, and no signs of malignancy. Bone marrow samples did not reveal any chromosomal or genetic alterations in the panel studies (myeloid malignancy mutation panel).

At the age of 13 high resolution chest CT showed normal bronchial structure. However, there was mild localized area of mild wall thickening and slight bronchial dilatation in the anterior segment of the right upper lobe.

Her pneumococcal antibody responses to both polysaccharide and conjugate vaccines were low, but immunoglobulin levels have remained within the normal range indicating specific antibody deficiency. Her neutrophil count has been fluctuating over time with occasional neutropenia episodes. Most recent neutrophil counts have been within normal range (Fig. S1). Her total lymphocyte counts have remained below the reference range and her lymphocyte responses to mitogens PHA, ConA lowered.

She has been on trimethoprim/sulfamethoxazole prophylaxis since the age of 10 and immunoglobulin replacement therapy since the age of 14. She is currently on Cutaquig 4950mg once per week (90 mg/kg/week).

1.2 Clinical description of the index's mother (I-2)

Currently 57-year-old female, non-smoker. She has received all the regular vaccines. At the age of 12 she suffered from thyroiditis and thyroxin substitution was initiated for 2 years. Thyroxin substitution was readministered when she was 20 years old.

She suffered from recurrent tonsillitis (approximately 2 antibiotic courses per year) as an adolescent, but besides that there was no infectious history. Tonsillectomy was performed when she was 35 and after that she was free from recurrent tonsillitis. She also has a history of atopy.

When she was 49, she was evaluated in an immunodeficiency outpatient clinic. Her basic blood differential, lymphocyte counts, as well as immunoglobulin levels were normal. However, her CD4⁺ T cell stimulation responses for ConA and PHA were slightly impaired, and her CD8⁺ T cells responded poorly to ConA. Her naïve CD4⁺ T cells and CD4⁺ RTEs were low. Because of very mild laboratory abnormalities and mild infectious history, follow-up in immunodeficiency clinic was not arranged.

She also suffers from hypercholesterolemia, hypertension, and intracranial hypertension. She was diagnosed with epilepsy at the age of 54. At the age of 57, she was diagnosed with ST-elevation myocardial infarction and underwent primary percutaneous coronary intervention.

Her current regular medication includes thyroxin 125 µg daily, acetazolamide 250mg twice per day, losartan 100mg daily, lamotrigine 100mg + 75mg daily, ticagrelor 90mg twice per day, bisoprolol 1.25mg twice per day, ezetimibe 10mg per day, acetylsalicylic acid 100mg per day, and atorvastatin 80mg per day.

1. Methods

2.1 Whole Exome Sequencing and Variant Calling

Whole exome sequencing was performed for our index for the first time at 12-years-old. Exome sequencing was performed with 101 bp read length on the HiSeq1500 sequencing platform (Illumina) after target enrichment performed with the SeqCap EZ MedExome target enrichment kit (Roche). Read mapping and variant calling were performed on genome version GRCh37 using an in-house pipeline and variant annotation was performed with ANNOVAR [10]. Trio-based exome variant filtering was performed. In the absence of candidate variants, the analysis was expanded to include rare (gnomAD [11], population frequency <0.01 for recessive and <0.001 for dominant) variants identified in the index patient within genes associated with inborn errors of immunity [12]. Variant impact was assessed using in silico pathogenicity prediction tools (SIFT [13], PolyPhen [14], CADD [15], REVEL [16]). The trio filtering scheme, IEI filtering scheme, and variant filtering outputs are shown in Supplementary Tables 9, 10 and 2, respectively. The trio WES analysis repeated to our index at the age of 17 with no new findings.

2.2 Sanger Sequencing

Genomic DNA was extracted from EDTA blood samples using the Puregene blood kit (Qiagen, #158023). PCR reactions were prepared using the DreamTaq Green PCR Master Mix, and amplicons cleaned for sequencing using the ExoSAP-IT™ PCR Product Cleanup reagent (ThermoFisher). Capillary sequencing was performed at the sequencing core facility of the Institute for Molecular Medicine Finland (FIMM).

The oligos used for Sanger sequencing were
CARD11_L22S_Fw: GAGTAGGTGATGGACTGCGG and
CARD11_L22S_Rv: GCTGTTCCAGTGAGACTGCT.

2.3 Allelic Imbalance Analysis with Digital Droplet PCR

Allelic imbalance was studied from CD4⁺ T cells enriched from frozen PBMCs with CD4⁺ T Cell Isolation Kit (Miltenyi, #130-096). RNA was isolated with NucleoSpin RNA (Macherey-

Nagel, #740955) and transcribed to cDNA with iScript Advanced cDNA synthesis kit for qPCR (Bio-Rad, #1725037).

Primers spanning 60bp around our variant and internal probes that differentiate between the reference (WT-HEX) and variant allele (L22S-FAM), were designed with primer3 and manufactured by Metabion. Oligos used were CARD11_ddPCR_Fwd: ACATGGAGACGCTGAAGGATG and CARD11_ddPCR_rev: TGCCGGTTACACTCCAC ATT. We used controls samples without RT transcriptase to identify possible environmental contaminations in the RNA samples when turning them into cDNA.

For positive control for the L22S variant, we used a PCR amplicon made from pUNO1-hCARD11-Leu22Ser-3xFLAG, and as a negative, WT control, an amplicon from pUNO1-hCARD11-V5. Control mixtures of WT/L22S amplicons of 0/100, 12.5/87.5, 25/75, 50/50, 75/25, 87.5/12.5, 100/0 and 0/0 were used to generate the standard curve.

ddPCR was performed with ddPCR Supermix for Probes (No dUTP) (Bio-Rad, #1863023 with the probes CARD11_WT: HEX-CTCCACAAAGGCGTCCTCTT-BHQ and CARD11_MUT: FAM-CTCCACGAGGCGTCCTCTT-BHQ. Droplets were generated with QX200 AutoDG ddPCR System (Bio-Rad), after PCR amplification was performed with C1000 Thermal Cycler. The droplets were detected with QX200 Droplet Reader (Bio-Rad) and analyzed with QuantaSoft v1.7.4.0917 (Bio-Rad).

2.4 Transcriptomic Analyses

Three million freshly isolated PBMCs were cultured with or without 20 ng/ml PMA stimulation (Sigma, #P1585) for 3 hours, after which the RNA was isolated with NucleoSpin RNA kit (Macherey-Nagel, 740955.250). Sample quality control with Agilent Tapestation, library preparation with NEBNext Ultra II Directional RNA Library Prep and sequencing with NovaSeq S4 was performed at the University of Helsinki Biomedicum Functional Genomics Unit (FuGens).

The quality of reads was assessed with fastqc (v0.12.1) and mapped to GRCh38.p13 with STAR (v2.7.10b)[10]. Transcript quantification was performed with featureCounts (v2.0.3). Gene symbols were assigned to the counts using org.Hs.eg.db (v3.17.0) and Ensembl BioMart [11] (v2.56.1) for maximum annotation coverage. Differential gene expression analysis and functional analyses were performed with R packages DESeq2 (v1.40.2)[12] and clusterProfiler (v4.8.3)[13] with R (v4.3.1).

Differential expression was assessed with full dataset interaction model testing condition-specific stimulation response (~ stimulation + condition + stimulation:condition). The main condition effect (condition_Patient_vs_Control) was tested to identify constitutive differences between patients and controls across stimulation conditions. Normalized counts were vst-transformed for visualization. Log2FoldChange was shrinked with apegglm. P-values were adjusted for multiple testing (FDR < 0.1). Gene set enrichment analysis (GSEA) was performed with clusterProfiler using Gene Ontology terms, KEGG pathways and Human Molecular Signatures Database Hallmarks gene sets.

2.5 Intracellular Cytokine Assay

The frozen PBMCs were thawed and let to rest O/N before starting the experiments. The cells were stimulated with Cell Activation Cocktail (BioLegend, 423304) that contains PMA,

ionomycin and Brefeldin A for 6 h 30min at 37°C with 5% CO₂. The cells were then fixed with Fixable Viability Dye eFluor™ 506 (Invitrogen) and cell surface markers. The cells were then fixed and permeabilized with BD Cytfix/Cytoperm kit according to the manufacturer's instructions. The cells were incubated in Fix/Perm buffer for 20 min at +4°C. The cells were stained for intracellular markers in Perm/Wash buffer for 30 min at +4°C.

2.6 Activation Marker Assay

The frozen PBMCs were thawed and rested O/N before starting the experiments. The cells were activated with platebound anti-CD3 (clone Hit3a, BioLegend, #300333), soluble 1µg/ml anti-CD28 (clone 28.2, BioLegend, #302943), and 10 U/ml IL-2 (R&D Systems, #202-IL) for 24 and 48 hours. After stimulation, the cells were stained with fixable Viability Dye eFluor 506 (Invitrogen) and then with antibodies for surface antigens for 30 min at +4°C in 0.4% BSA/PBS before flow cytometry.

2.7 Proliferation Assay

Proliferation was assessed from freshly isolated (I-4, II-2) or frozen (I-2) PBMCs with CellTrace™ CFSE Cell Proliferation Kit (Invitrogen, #C34554). The cells were rested O/N in cRPMI after isolation or thawing, before CFSE labeling with 1:2500 CFSE in PBS. The cells rested for four hours after CFSE labeling before stimulating with 1000 ng/ml anti-CD3 and 200ng/ml anti-CD28 for four days. The cells were then stained for surface markers as described in the immunophenotyping section for flow cytometry.

2.8 Protein Phosphorylation Assay

In the experiments with shorter stimuli, frozen PBMCs were thawed and starved O/N in RPMI with 1% FBS before starting the experiments. The PBMCs were then resuspended to complete media with surface marker antibodies and stimulated with 10ng/ml PMA (Sigma-Aldrich) for 20min at +37°C. The experiments with TCR-mediated stimuli were performed on T cell blasts. For blasting, T cells were stimulated with 1µg/ml anti-CD3 and 1µg/ml anti-CD28 for three days. After that the cells were cultured in cRPMI with 200 U/ml IL-2 for 10 days. T cell blasts were then starved O/N in RPMI with 1% FBS and then stimulated with plate-bound 1µg/ml anti-CD3, soluble 0.2µg/ml anti-CD28, and 10U/ml IL-2 for 24 h with or without 5mM glutamine at +37°C, 5% CO₂. The stimulation was ended with ice cold PBS to the cells after which the cells were fixed with BD Phosphoflow™ Lyse/Fix Buffer for 20 min at +37°C. The cells were then stained for surface markers for 30min @+37°C or 1 hour @RT and permeabilized with ice cold 90% methanol for 10 min at +4°C or O/N at -20°C before staining for intracellular makers in 0.4% BSA and 0.05% Triton-X-100 in PBS for 60 min at RT.

2.9 Statistical analysis

Flow cytometry data were analyzed with fixed effects for Group (Control vs Patient), Stimulation (Unstimulated vs Stimulated), and Glutamine (Absent vs Present), including all interactions when applicable. Biological replicates (Specimen) and independent experiment repeats (Batch) were used as random intercepts to account for inter-individual variation and batch effects, respectively. Model formulas varied by experimental design: two-group comparisons used 'Variable ~ Group + (1|Specimen) + (1|Batch)'; experiments with stimulation used 'Variable ~ Group * Stimulation + (1|Specimen) + (1|Batch)'; and experiments with stimulation and glutamine as a variable used 'Variable ~ Group * Stimulation * Glutamine

+ (1|Specimen) + (1|Batch)'. Statistical significance was assessed using Satterthwaite's approximation for degrees of freedom.

2. Supplemental Tables

Supplemental Table 1. Flow cytometry antibodies

Antibody	Identifier	Manufacturer
eBioscience™ Fixable Viability Dye eFluor™ 506	65-0866-18	Invitrogen™
BD Pharmingen™ Alexa Fluor® 700 Mouse Anti-Human CD3	557943	BD Biosciences
Brilliant Violet 421™ anti-human CD4 Antibody	300532	BioLegend
APC/Cyanine7 anti-human CD8a Antibody	301016	BioLegend
PE-CF594 Mouse Anti-Human CD45RO	562299	BD Biosciences
Alexa Fluor® 488 Mouse anti-S6 (pS235/pS236)	560434	BD Biosciences
FITC anti-human CD69 Antibody	310904	BioLegend
PE anti-human CD25 Antibody	302606	BioLegend
PE/Cyanine7 anti-human CD194 (CCR4) Antibody	359409	BioLegend
BD Horizon™ BV605 Mouse Anti-Human CD196/CCR6	562724	BD Biosciences
FITC anti-human IL-2 Antibody	500304	BioLegend
BD Horizon™ BV711 Mouse Anti-Human IFN-γ	564039	BD Biosciences
APC/Cyanine7 anti-human CD183 (CXCR3) Antibody	353721	BioLegend
BD Pharmingen™ Alexa Fluor® 647 Rat Anti-Human CXCR5 (CD185)	558113	BD Biosciences
APC/Cyanine7 anti-human CD279 (PD-1) Antibody	329922	BioLegend
CellTrace™ CFSE Cell Proliferation Kit, for flow cytometry	C34554	Invitrogen™
BD Pharmingen™ Alexa Fluor®488 Mouse Anti-Human CD4	557695	BD Biosciences
BD Pharmingen™ PerCP-Cy™5.5 Mouse Anti-Human CCR10	564772	BD Pharmingen
CD127 Monoclonal Antibody (eBioRDR5), FITC, eBioscience™	11-1278-42	eBioscience
BD Horizon™ BV510 Mouse Anti-Human CD10	563032	BD Biosciences
BD Pharmingen™ PE Mouse Anti-Human CD19	555413	BD Pharmingen
PE/Dazzle™ 594 anti-human CD21 Antibody	354922	BioLegend
BD OptiBuild™ BV711 Mouse Anti-Human CD20	740644	BD Biosciences
CD27 Monoclonal Antibody (O323), PE-Cyanine7, eBioscience™	25-0279-42	eBioscience
IkappaB alpha (L35A5) Mouse Monoclonal Antibody (Amino-terminal Antigen) (Alexa Fluor® 488 Conjugate)	5743	Cell Signaling Technology
BD Phosflow™ PE Mouse anti-NF-κB p65 (pS529)	558423	BD Biosciences

Supplemental Table 2. WES filtering output

Table S1 Variant filtering output of WES analysis

Index patient's rare variants in IEI genes													gnomAD_exome genotype	gnomAD_exom e heterozygotes	gnomAD_exom e homozygotes	gnomAD_gnomAD genome_gnomAD e_FIN	GERP ++_R S	phyloP100 way_vert ebrate	REVE	CADD_phr ed	SIFT_sco re	SIFT_pre d	Polyphe n2_HDIV _score	Polyphe n2_HDI _V_pred																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
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_FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	ExAC_FI N	gnomAD_exome _ALL	gnomAD_exome _FIN	ExAC_ALL	Ex

Supplemental Table 3. DE genes

Table S2 Significantly differentially expressed genes across stimulation condition between CARD11-L22S patients and healthy controls.

Gene_ENSEMBL	baseMean	log2 FoldChange	lfcSE	pvalue	padj	Gene_symbol
ENSG00000006451	8356.076038	0.524071176	0.174297822	0.00014242	0.060425198	RALA
ENSG000000040531	1567.972706	0.515532828	0.143748198	1.72E-05	0.023466407	CTNS
ENSG000000049860	8969.860943	0.868649588	0.287187903	0.000145091	0.060425198	HEXB
ENSG000000054523	3240.936167	0.718614009	0.254748302	0.000255197	0.078270735	KIF1B
ENSG000000069956	11597.4208	0.505647866	0.179327452	0.000251585	0.078270735	MAPK6
ENSG000000071553	8060.299539	0.565415315	0.204367251	0.000291705	0.081161252	ATP6AP1
ENSG000000078596	7610.078343	-0.948638583	0.351876036	0.000129127	0.057253084	ITM2A
ENSG000000082014	570.1866873	1.122514251	0.310334862	2.04E-05	0.023466407	SMARCD3
ENSG000000083457	2915.603642	0.745158234	0.267869969	0.00028757	0.081161252	ITGAE
ENSG000000086015	1322.761742	0.648639296	0.237244553	0.000320118	0.085345887	MAST2
ENSG000000087245	368.8318066	1.880083433	0.630014764	0.000274416	0.079904121	MMP2
ENSG000000091073	1411.242421	0.472596649	0.103292843	3.11E-07	0.00121525	DTX2
ENSG00000100364	10872.24492	0.868771657	0.251864185	3.48E-05	0.030855499	KIAA0930
ENSG00000101255	2861.979026	-1.193466386	0.366136974	2.03E-05	0.023466407	TRIB3
ENSG00000101298	940.9954869	-1.355772395	0.285934525	4.48E-08	0.0002184	SNPH
ENSG00000102547	570.3212707	0.475150341	0.163387159	0.000194353	0.070215396	CAB39L
ENSG00000104205	1455.319883	0.624321419	0.198808073	9.05E-05	0.044144249	SGK3
ENSG00000105357	47.09191105	-0.004651876	0.073352181	0.000370968	0.091774465	MYH14
ENSG00000108828	3818.572072	1.089752794	0.37582825	0.000235827	0.076449428	VAT1
ENSG00000110651	12362.8438	0.649934729	0.166178494	6.82E-05	0.039609949	CD81
ENSG00000111802	6631.777268	0.608539391	0.145749242	1.75E-06	0.00426555	TDP2
ENSG00000113648	17498.4699	0.673709115	0.211583202	8.16E-05	0.044144249	MACROH2A1
ENSG00000114446	1738.541699	-0.513473088	0.175013682	0.000105817	0.048008888	IFT57
ENSG00000114450	2159.854677	0.796532835	0.25461435	0.000101353	0.048008888	GNB4
ENSG00000114999	3626.184503	0.481448213	0.145324883	5.53E-05	0.034788637	TTL
ENSG00000116016	2124.310893	1.207417364	0.431293288	0.000334891	0.085965668	EPAS1
ENSG00000118515	71810.3466	0.991812724	0.327076928	0.00014867	0.060425198	SGK1
ENSG00000119147	29.08854894	-1.544727805	0.543621771	6.90E-05	0.039609949	ECRG4
ENSG00000119899	2188.343739	0.658884955	0.225198591	0.000181288	0.06673114	SLC17A5
ENSG00000125675	14.00981453	-0.008243508	0.073817031	0.00017301	0.06490862	GRIA3

ENSG00000126467	40.05519467	-0.014668093	0.075295983	8.66E-05	0.044144249	TSKS
ENSG00000130203	1176.22562	3.104053751	0.732960836	1.14E-08	7.39E-05	APOE
ENSG00000130208	162.9311335	3.05621959	0.643595809	2.21E-09	2.16E-05	APOC1
ENSG00000134184	192.1895403	-0.002406165	0.073193858	2.48E-05	0.026911716	GSTM1
ENSG00000134369	697.7381929	1.145040812	0.331639729	4.07E-05	0.032572556	NAV1
ENSG00000135912	2183.838704	0.700582499	0.209218884	4.67E-05	0.032572556	TTLL4
ENSG00000136478	2127.524742	1.014136393	0.240019244	1.68E-06	0.00426555	TEX2
ENSG00000137504	14764.11999	-0.215883587	0.075399896	0.00028373	0.081161252	CREBZF
ENSG00000137824	2724.396217	0.369826234	0.13034311	0.000260782	0.078270735	RMDN3
ENSG00000142166	9953.956885	0.440863636	0.158978973	0.000295374	0.081161252	IFNAR1
ENSG00000143198	1564.277513	0.604697384	0.217242006	0.000273545	0.079904121	MGST3
ENSG00000147872	6664.450673	1.066755023	0.293048219	1.87E-05	0.023466407	PLIN2
ENSG00000151704	41.84006408	1.804039614	0.514198696	4.40E-05	0.032572556	KCNJ1
ENSG00000152270	16865.63783	-0.738494817	0.174590369	6.89E-07	0.002241322	PDE3B
ENSG00000152348	298.3960194	-0.796070417	0.275509399	8.63E-05	0.044144249	ATG10
ENSG00000154447	321.7829507	1.113277169	0.325400994	4.25E-05	0.032572556	SH3RF1
ENSG00000154639	39.5930317	-1.318010091	0.450668034	7.21E-05	0.04019721	CXADR
ENSG00000155252	5160.16768	0.665156004	0.198476901	4.61E-05	0.032572556	PI4K2A
ENSG00000157045	1177.973189	0.759351646	0.220482287	3.40E-05	0.030855499	NTAN1
ENSG00000159228	833.8520406	-0.748952713	0.293594739	0.000226503	0.076187037	CBR1
ENSG00000159720	9107.500739	0.628380195	0.160084929	5.27E-06	0.010273606	ATP6V0D1
ENSG00000162461	498.6461602	0.821640652	0.275862415	0.000162461	0.064012991	SLC25A34
ENSG00000165092	411.0076946	1.420069328	0.509545029	0.000388802	0.093643793	ALDH1A1
ENSG00000165886	473.9237375	0.729864108	0.220733623	5.36E-05	0.034788637	UBTD1
ENSG00000167601	490.8526701	1.535232583	0.517820978	0.000239039	0.076449428	AXL
ENSG00000171798	174.67652	-0.013347366	0.074925309	5.51E-05	0.034788637	KNDC1
ENSG00000173578	114.1056421	2.053365249	0.56440937	3.06E-05	0.029876823	XCR1
ENSG00000173890	1007.839674	-1.254277213	0.519665828	0.00020665	0.071991598	GPR160
ENSG00000174238	10366.15363	0.625794317	0.20176732	0.000105688	0.048008888	PITPNA
ENSG00000174891	1092.40209	0.284250235	0.088056604	8.95E-05	0.044144249	RSRC1
ENSG00000182871	3001.428473	-0.018664872	0.076657044	4.20E-05	0.032572556	COL18A1
ENSG00000184216	16886.99617	0.534785021	0.196385403	0.000330226	0.085898382	IRAK1
ENSG00000184986	194.9483661	-1.537695704	0.424780553	5.12E-06	0.010273606	TMEM121
ENSG00000187908	14.95987725	-0.008851611	0.07392143	0.000165667	0.064012991	DMBT1
ENSG00000198431	90644.40164	0.673765631	0.246438548	0.000323727	0.085345887	TXNRD1
ENSG00000204745	45.45564716	-0.88343755	0.380928354	0.000414035	0.097318137	LOC102724642
ENSG00000211667	34.55703016	-0.015216277	0.075447561	0.000200418	0.071090213	IGLV3-12

ENSG00000211895	15585.6874	-0.039780891	0.08972073	0.000405397	0.096449866	IGHA1
ENSG00000211950	70.72886954	-1.14748544	0.435070413	0.000146174	0.060425198	IGHV1-24
ENSG00000211967	102.3089447	-1.813904513	0.58692084	2.68E-05	0.027480947	IGHV3-53
ENSG00000213699	2356.139609	0.763553009	0.211551628	1.86E-05	0.023466407	SLC35F6
ENSG00000223609	17.85534328	1.488587845	1.131573707	0.000376337	0.091774465	HBD
ENSG00000224186	79.79636773	0.863386112	0.263124925	6.07E-05	0.037005302	PITX1-AS1
ENSG00000227500	2461.290799	0.495350749	0.167526532	0.000167341	0.064012991	SCAMP4
ENSG00000230387	8.547741944	0.010670548	0.074006677	6.59E-06	0.011682444	LOC100505664
ENSG00000236297	24.04001631	-0.879483951	0.368026205	0.000376049	0.091774465	EEF1A1P23
ENSG00000237973	3701.840381	3.45855066	0.583824569	7.64E-10	1.49E-05	MTCO1P12
ENSG00000255569	125.2551773	-0.02387224	0.078870787	0.000306532	0.083057407	TRAV1-1
ENSG00000255582	15.16386583	-0.011383152	0.074429783	0.000211367	0.072343248	OR10G2
ENSG00000265479	26.35066872	1.115261351	0.389027437	0.000236555	0.076449428	DTX2P1-UPK3BP1- PMS2P11
ENSG00000266412	22141.4226	0.397074401	0.145736838	0.000350979	0.088925438	NCOA4
ENSG00000276953	280.2962617	-0.901218327	0.36614622	0.00025808	0.078270735	TRBV12-4
ENSG00000290418	126.6630395	1.906339328	0.489281215	1.00E-05	0.016269314	TPTEP1

Supplemental Table 4. Enriched GO Biological Processes

Table S3 List of all significantly enriched GO biological processes with GSEA.

ID	Description	setSize	enrichment Score	NES	pvalue	p.adjust	qvalue	rank	leading_ edge
GO:0007059	chromosome segregation	432	-0.843561119	-1.934113703	2.06E-08	5.45E-06	3.97E-06	541	tags=11%, list=2%, signal=11%
GO:0000280	nuclear division	449	-0.836698192	-1.93049362	1.20E-08	5.45E-06	3.97E-06	539	tags=9%, list=2%, signal=9%
GO:0044772	mitotic cell cycle phase transition	453	-0.824793134	-1.903118363	1.76E-08	5.45E-06	3.97E-06	274	tags=8%, list=1%, signal=8%
GO:0000070	mitotic sister chromatid segregation	198	-0.91345041	-1.893735382	8.00E-09	5.45E-06	3.97E-06	87	tags=12%, list=0%, signal=12%
GO:0140014	mitotic nuclear division	285	-0.880418387	-1.892991875	1.43E-08	5.45E-06	3.97E-06	87	tags=11%, list=0%, signal=11%
GO:0098813	nuclear chromosome segregation	338	-0.864140288	-1.913868056	2.80E-08	6.18E-06	4.50E-06	541	tags=12%, list=2%, signal=12%
GO:0000819	sister chromatid segregation	249	-0.890253867	-1.877772741	4.92E-08	9.31E-06	6.78E-06	87	tags=14%, list=0%, signal=14%
GO:0007093	mitotic cell cycle checkpoint signaling	139	-0.928489162	-1.861510556	5.91E-08	9.79E-06	7.13E-06	274	tags=15%, list=1%, signal=15%
GO:0048285	organelle fission	495	-0.81136769	-1.915536782	9.30E-08	1.23E-05	8.97E-06	539	tags=8%, list=2%, signal=8%
GO:1901991	negative regulation of mitotic cell cycle phase transition	184	-0.908221157	-1.856863545	8.68E-08	1.23E-05	8.97E-06	274	tags=12%, list=1%, signal=12%

GO:0030003	intracellular monoatomic cation homeostasis	500	0.810891086	1.740306051	1.24E-07	1.49E-05	1.09E-05	1283	tags=15%, list=4%, signal=15%
GO:0045786	negative regulation of cell cycle	390	-0.830472056	-1.901585179	3.23E-07	3.30E-05	2.40E-05	316	tags=7%, list=1%, signal=7%
GO:0000086	G2/M transition of mitotic cell cycle	134	-0.927864106	-1.854162295	3.06E-07	3.30E-05	2.40E-05	274	tags=14%, list=1%, signal=14%
GO:0000075	cell cycle checkpoint signaling	187	-0.906496307	-1.853016463	3.97E-07	3.61E-05	2.63E-05	309	tags=13%, list=1%, signal=13%
GO:0045930	negative regulation of mitotic cell cycle	231	-0.882698214	-1.84717806	4.08E-07	3.61E-05	2.63E-05	274	tags=10%, list=1%, signal=10%
GO:0010948	negative regulation of cell cycle process	306	-0.855158666	-1.860148584	5.56E-07	4.41E-05	3.22E-05	316	tags=9%, list=1%, signal=9%
GO:01901988	negative regulation of cell cycle phase transition	263	-0.86675419	-1.845450958	5.66E-07	4.41E-05	3.22E-05	309	tags=10%, list=1%, signal=10%
GO:01902850	microtubule cytoskeleton organization involved in mitosis	160	-0.904602255	-1.831066685	1.00E-06	7.40E-05	5.39E-05	87	tags=9%, list=0%, signal=9%
GO:01901987	regulation of cell cycle phase transition	442	-0.797902682	-1.839429572	1.35E-06	8.98E-05	6.54E-05	610	tags=10%, list=2%, signal=10%
GO:0010876	lipid localization	490	0.793461493	1.701826365	1.34E-06	8.98E-05	6.54E-05	1846	tags=15%, list=5%, signal=14%
GO:0007088	regulation of mitotic nuclear division	117	-0.916837436	-1.7977748	2.58E-06	0.000162515	0.000118393	87	tags=13%, list=0%, signal=13%
GO:0015711	organic anion transport	429	0.792824927	1.672917311	4.09E-06	0.000246559	0.000179619	2160	tags=16%, list=6%, signal=15%
GO:0007051	spindle organization	197	-0.879085289	-1.816150594	5.57E-06	0.000320931	0.000233798	316	tags=12%, list=1%, signal=12%
GO:0045132	meiotic chromosome segregation	109	-0.922318692	-1.823451179	6.81E-06	0.000368888	0.000268735	478	tags=13%, list=1%, signal=13%
GO:0006260	DNA replication	277	-0.839111189	-1.796255351	6.96E-06	0.000368888	0.000268735	1138	tags=16%, list=3%, signal=16%
GO:01901990	regulation of mitotic cell cycle phase transition	343	-0.811054278	-1.80159257	8.61E-06	0.000381463	0.000277896	610	tags=11%, list=2%, signal=11%
GO:0032886	regulation of microtubule-based process	251	-0.844670277	-1.786600511	8.10E-06	0.000381463	0.000277896	222	tags=7%, list=1%, signal=7%
GO:0050817	coagulation	227	0.843065147	1.679901908	8.50E-06	0.000381463	0.000277896	2102	tags=21%, list=6%, signal=20%
GO:0030100	regulation of endocytosis	212	0.852321361	1.675374394	8.61E-06	0.000381463	0.000277896	1734	tags=22%, list=5%, signal=21%
GO:0032102	negative regulation of response to external stimulus	430	0.793403363	1.675296066	8.64E-06	0.000381463	0.000277896	1397	tags=12%, list=4%, signal=11%
GO:0007052	mitotic spindle organization	129	-0.9078953	-1.812906333	1.02E-05	0.000412615	0.00030059	66	tags=10%, list=0%, signal=10%
GO:0051225	spindle assembly	130	-0.908070589	-1.808805535	1.03E-05	0.000412615	0.00030059	212	tags=13%, list=1%, signal=13%

GO:0015849	organic acid transport	351	0.809095008	1.67579129	9.82E-06	0.000412615	0.00030059	1402	tags=11%, list=4%, signal=10%
GO:0044839	cell cycle G2/M phase transition	149	-0.897976357	-1.815020727	1.16E-05	0.00044037	0.00032081	274	tags=13%, list=1%, signal=13%
GO:0006066	alcohol metabolic process	365	0.810926483	1.681801769	1.15E-05	0.00044037	0.00032081	1971	tags=16%, list=6%, signal=15%
GO:0006261	DNA-templated DNA replication	160	-0.885198921	-1.791791082	1.34E-05	0.000492344	0.000358673	1138	tags=19%, list=3%, signal=19%
GO:0046942	carboxylic acid transport	350	0.809257188	1.674202987	1.38E-05	0.000492745	0.000358965	1402	tags=11%, list=4%, signal=11%
GO:0006874	intracellular calcium ion homeostasis	301	0.817125663	1.662461292	1.41E-05	0.000492745	0.000358965	1283	tags=13%, list=4%, signal=13%
GO:0007596	blood coagulation	223	0.840616871	1.668337428	1.59E-05	0.000540315	0.000393619	2102	tags=21%, list=6%, signal=19%
GO:0006898	receptor-mediated endocytosis	254	0.830064025	1.6646181	1.67E-05	0.000552159	0.000402248	2027	tags=24%, list=6%, signal=23%
GO:0006869	lipid transport	441	0.785219419	1.663146185	1.98E-05	0.000640663	0.000466723	1846	tags=14%, list=5%, signal=13%
GO:0007599	hemostasis	229	0.839625638	1.670325095	2.04E-05	0.000643121	0.000468514	2102	tags=21%, list=6%, signal=19%
GO:0015718	monocarboxylic acid transport	177	0.851724859	1.658186809	3.01E-05	0.000927503	0.000675686	667	tags=7%, list=2%, signal=7%
GO:0055074	calcium ion homeostasis	325	0.80354442	1.643388506	3.26E-05	0.000982486	0.000715741	2313	tags=18%, list=7%, signal=17%
GO:0030168	platelet activation	132	0.866586946	1.670462745	3.81E-05	0.001122356	0.000817637	2102	tags=23%, list=6%, signal=22%
GO:0050866	negative regulation of cell activation	222	0.827592392	1.642514794	3.90E-05	0.00112363	0.000818565	1553	tags=15%, list=5%, signal=14%
GO:0048675	axon extension	119	0.883871629	1.678078643	4.06E-05	0.001143175	0.000832804	738	tags=11%, list=2%, signal=11%
GO:0061387	regulation of extent of cell growth	105	0.894968147	1.680498304	4.33E-05	0.001171209	0.000853226	738	tags=12%, list=2%, signal=12%
GO:0008361	regulation of cell size	178	0.850406994	1.659143507	4.26E-05	0.001171209	0.000853226	1359	tags=15%, list=4%, signal=14%
GO:0050878	regulation of body fluid levels	359	0.786133924	1.629329307	4.65E-05	0.001233291	0.000898453	2271	tags=17%, list=7%, signal=16%
GO:0050804	modulation of chemical synaptic transmission	475	0.763102507	1.633593778	5.82E-05	0.001512523	0.001101874	1905	tags=11%, list=6%, signal=11%
GO:0033044	regulation of chromosome organization	249	-0.840216898	-1.772231996	6.06E-05	0.001545071	0.001125585	542	tags=13%, list=2%, signal=13%
GO:0090066	regulation of anatomical structure size	488	0.755715594	1.620346737	7.05E-05	0.001763426	0.001284657	3122	tags=23%, list=9%, signal=21%

GO:0051983	regulation of chromosome segregation	129	- 0.887773736	-1.772727129	7.20E-05	0.001766359	0.001286794	87	tags=17%, list=0%, signal=17%
GO:0006639	acylglycerol metabolic process	126	0.880894603	1.681364355	7.98E-05	0.001923468	0.001401247	802	tags=13%, list=2%, signal=12%
GO:00070507	regulation of microtubule cytoskeleton organization	154	- 0.873755561	-1.76425732	9.80E-05	0.002317685	0.001688435	168	tags=7%, list=0%, signal=7%
GO:0006638	neutral lipid metabolic process	127	0.878659597	1.679681003	0.0001015	0.00235967	0.001719021	802	tags=13%, list=2%, signal=12%
GO:00061982	meiosis I cell cycle process	134	- 0.888195978	-1.774892986	0.0001044	0.00238471	0.001737262	494	tags=9%, list=1%, signal=9%
GO:00099177	regulation of trans-synaptic signaling	476	0.762019531	1.632821647	0.0001106	0.002484377	0.00180987	1905	tags=11%, list=6%, signal=11%
GO:00046486	glycerolipid metabolic process	382	0.768440736	1.60516712	0.0001215	0.002682324	0.001954074	1758	tags=16%, list=5%, signal=15%
GO:00048771	tissue remodeling	173	0.846103656	1.642929098	0.0001379	0.002957522	0.002154556	2155	tags=20%, list=6%, signal=19%
GO:00050727	regulation of inflammatory response	396	0.763320517	1.592074536	0.0001384	0.002957522	0.002154556	2094	tags=16%, list=6%, signal=15%
GO:00031570	DNA integrity checkpoint signaling	131	- 0.887168603	-1.774787292	0.0001544	0.00311115	0.002266474	398	tags=12%, list=1%, signal=12%
GO:00007040	lysosome organization	100	0.884008231	1.648537755	0.000155	0.00311115	0.002266474	1764	tags=43%, list=5%, signal=41%
GO:00080171	lytic vacuole organization	100	0.884008231	1.648537755	0.000155	0.00311115	0.002266474	1764	tags=43%, list=5%, signal=41%
GO:00051235	maintenance of location	339	0.786243183	1.618986011	0.0001496	0.00311115	0.002266474	2393	tags=20%, list=7%, signal=19%
GO:00000079	regulation of cyclin-dependent protein serine/threonine kinase activity	106	- 0.893963791	-1.76298645	0.0001601	0.003167051	0.002307198	52	tags=7%, list=0%, signal=7%
GO:00090068	positive regulation of cell cycle process	257	- 0.806017808	-1.718000059	0.0001689	0.003290993	0.00239749	610	tags=11%, list=2%, signal=11%
GO:00051051	negative regulation of transport	461	0.7487665	1.588873979	0.0001816	0.003487841	0.002540894	2303	tags=16%, list=7%, signal=15%
GO:00016042	lipid catabolic process	329	0.779630878	1.597045363	0.0001863	0.003526036	0.002568719	1090	tags=11%, list=3%, signal=10%
GO:00015748	organophosphate ester transport	148	0.845936866	1.63603865	0.0002027	0.003732411	0.002719063	2006	tags=22%, list=6%, signal=20%
GO:000191617	organic hydroxy compound biosynthetic process	241	0.816429313	1.631121338	0.0002028	0.003732411	0.002719063	1727	tags=16%, list=5%, signal=15%
GO:00007127	meiosis I	129	- 0.876309964	-1.749836003	0.0002058	0.003734911	0.002720885	494	tags=9%, list=1%, signal=8%
GO:00003018	vascular process in circulatory system	262	0.792038305	1.591785277	0.000215	0.00384889	0.002803918	822	tags=5%, list=2%, signal=5%
GO:000140694	non-membrane-bounded organelle assembly	389	- 0.750772098	-1.716050371	0.0002417	0.00405431	0.002953567	981	tags=12%, list=3%, signal=12%

GO:0015914	phospholipid transport	104	0.873416331	1.635370188	0.00024	0.00405431	0.002953567	1092	tags=16%, list=3%, signal=16%
GO:0097237	cellular response to toxic substance	120	0.857040923	1.62876445	0.0002323	0.00405431	0.002953567	760	tags=14%, list=2%, signal=14%
GO:1901214	regulation of neuron death	327	0.778779498	1.594821402	0.0002413	0.00405431	0.002953567	1763	tags=15%, list=5%, signal=14%
GO:0034329	cell junction assembly	439	0.748553501	1.584765431	0.0002326	0.00405431	0.002953567	2098	tags=13%, list=6%, signal=13%
GO:0045787	positive regulation of cell cycle	344	-0.766063134	-1.700418548	0.0002466	0.004084081	0.002975255	610	tags=8%, list=2%, signal=8%
GO:0031589	cell-substrate adhesion	355	0.770717585	1.597718481	0.000258	0.004220022	0.003074288	2204	tags=19%, list=7%, signal=18%
GO:0007033	vacuole organization	215	0.818772051	1.618119838	0.0003099	0.004990655	0.003635695	1764	tags=31%, list=5%, signal=29%
GO:0007626	locomotory behavior	201	0.817020142	1.603425725	0.0003126	0.004990655	0.003635695	1249	tags=11%, list=4%, signal=11%
GO:0035150	regulation of tube size	141	0.843014734	1.625391101	0.0003347	0.005278768	0.003845585	447	tags=4%, list=1%, signal=4%
GO:0001763	morphogenesis of a branching structure	203	0.818818946	1.606165569	0.0003461	0.005395277	0.003930462	1387	tags=10%, list=4%, signal=10%
GO:0050806	positive regulation of synaptic transmission	161	0.836518185	1.627922578	0.0003559	0.005483922	0.00399504	909	tags=7%, list=3%, signal=7%
GO:0070997	neuron death	372	0.765476331	1.594328366	0.0003651	0.005559757	0.004050286	2958	tags=23%, list=9%, signal=21%
GO:1904029	regulation of cyclin-dependent protein kinase activity	110	-0.891137177	-1.760991906	0.0003759	0.005660114	0.004123396	52	tags=6%, list=0%, signal=6%
GO:0051321	meiotic cell cycle	283	-0.790631943	-1.70252598	0.0003946	0.00587396	0.004279183	544	tags=8%, list=2%, signal=8%
GO:0050808	synapse organization	463	0.72823129	1.547392224	0.0004119	0.006064707	0.004418142	2958	tags=16%, list=9%, signal=15%
GO:0010975	regulation of neuron projection development	450	0.740615629	1.571631473	0.0004333	0.006309174	0.004596236	1487	tags=14%, list=4%, signal=13%
GO:0098754	detoxification	136	0.851017096	1.641333128	0.0004534	0.006530273	0.004757307	760	tags=13%, list=2%, signal=13%
GO:0001558	regulation of cell growth	417	0.73602562	1.555446578	0.000469	0.006681569	0.004867527	1570	tags=13%, list=5%, signal=13%
GO:0015908	fatty acid transport	116	0.86065314	1.636189957	0.0004887	0.006816517	0.004965836	667	tags=8%, list=2%, signal=8%
GO:0016125	sterol metabolic process	155	0.840780704	1.6290497	0.000484	0.006816517	0.004965836	963	tags=12%, list=3%, signal=11%
GO:0050728	negative regulation of inflammatory response	176	0.817817239	1.591233634	0.0004996	0.006894961	0.005022982	1458	tags=14%, list=4%, signal=13%
GO:190748	cellular detoxification	111	0.864971679	1.62544935	0.0005349	0.007306143	0.005322528	760	tags=15%, list=2%, signal=15%
GO:1902749	regulation of cell cycle G2/M phase transition	110	-0.88474434	-1.748358909	0.0005445	0.007362518	0.005363598	274	tags=14%, list=1%,

									signal=14 %
GO:00 32535	regulation of cellular component size	352	0.75514427	1.566232439	0.0005904	0.0079022 02	0.0057567 58	1993	tags=17%, list=6%, signal=16 %
GO:00 31348	negative regulation of defense response	271	0.782751336	1.574836847	0.0006053	0.0080202 15	0.0058427 3	1458	tags=14%, list=4%, signal=13 %
GO:00 51783	regulation of nuclear division	145	- 0.855058643	-1.730710771	0.0006545	0.0085868 66	0.0062555 36	87	tags=10%, list=0%, signal=10 %
GO:00 08203	cholesterol metabolic process	140	0.848674924	1.637431287	0.0006784	0.0087273 25	0.0063578 61	963	tags=11%, list=3%, signal=11 %
GO:00 19221	cytokine-mediated signaling pathway	472	0.728670383	1.555134062	0.0006769	0.0087273 25	0.0063578 61	2833	tags=22%, list=8%, signal=20 %
GO:01 40013	meiotic nuclear division	196	- 0.817370554	-1.688615469	0.0007227	0.0092072 6	0.0067074 93	494	tags=10%, list=1%, signal=10 %
GO:00 06310	DNA recombination	324	- 0.760080826	-1.675115714	0.0007535	0.0095080 15	0.0069265 94	2165	tags=20%, list=6%, signal=19 %
GO:19 02652	secondary alcohol metabolic process	150	0.840369465	1.627115425	0.0007733	0.0096444 37	0.0070259 77	963	tags=11%, list=3%, signal=11 %
GO:00 31623	receptor internalization	125	0.849134414	1.619602959	0.0007934	0.0096444 37	0.0070259 77	1093	tags=20%, list=3%, signal=19 %
GO:00 22604	regulation of cell morphogenesis	243	0.789529873	1.574028059	0.0007821	0.0096444 37	0.0070259 77	2409	tags=25%, list=7%, signal=23 %
GO:00 09612	response to mechanical stimulus	214	0.791726994	1.560050693	0.0007927	0.0096444 37	0.0070259 77	2446	tags=17%, list=7%, signal=16 %
GO:00 06644	phospholipid metabolic process	372	0.751086811	1.564357982	0.0008683	0.0102949 2	0.0074998 54	2013	tags=19%, list=6%, signal=18 %
GO:00 51346	negative regulation of hydrolase activity	330	0.763971984	1.562666308	0.0008643	0.0102949 2	0.0074998 54	2790	tags=19%, list=8%, signal=18 %
GO:00 45229	external encapsulating structure organization	316	0.758477646	1.543147389	0.0008702	0.0102949 2	0.0074998 54	1417	tags=9%, list=4%, signal=8%
GO:00 33045	regulation of sister chromatid segregation	104	- 0.877258464	-1.741708558	0.0008885	0.0103554 67	0.0075439 63	87	tags=16%, list=0%, signal=16 %
GO:00 34446	substrate adhesion- dependent cell spreading	100	0.865708051	1.614410768	0.000891	0.0103554 67	0.0075439 63	2097	tags=29%, list=6%, signal=27 %
GO:19 01215	negative regulation of neuron death	219	0.797421483	1.578321768	0.0009086	0.0104687 37	0.0076264 8	1763	tags=16%, list=5%, signal=15 %
GO:19 05952	regulation of lipid localization	175	0.822031659	1.598525224	0.0009252	0.0105674 75	0.0076984 11	1894	tags=15%, list=6%, signal=15 %
GO:00 35296	regulation of tube diameter	140	0.843220453	1.626907446	0.0009661	0.0108485 96	0.0079032 08	447	tags=4%, list=1%, signal=4%
GO:00 97746	blood vessel diameter maintenance	140	0.843220453	1.626907446	0.0009661	0.0108485 96	0.0079032 08	447	tags=4%, list=1%, signal=4%
GO:00 30198	extracellular matrix organization	313	0.761561696	1.549329377	0.0010194	0.0113508 05	0.0082690 67	1417	tags=9%, list=4%, signal=8%
GO:19 03046	meiotic cell cycle process	215	- 0.809055211	-1.687976535	0.0010511	0.0116055 25	0.0084546 3	494	tags=10%, list=1%,

									signal=10%
GO:0010977	negative regulation of neuron projection development	142	0.820312111	1.582453193	0.0010758	0.011780128	0.008581829	1359	tags=13%, list=4%, signal=13%
GO:0061138	morphogenesis of a branching epithelium	188	0.812564575	1.588590563	0.0011949	0.012977583	0.009454176	1387	tags=10%, list=4%, signal=10%
GO:0043062	extracellular structure organization	314	0.760801541	1.547829643	0.0012265	0.013212438	0.009625268	1417	tags=9%, list=4%, signal=8%
GO:0031346	positive regulation of cell projection organization	351	0.750876626	1.555209831	0.0012737	0.013610242	0.009915068	1499	tags=15%, list=4%, signal=14%
GO:0044242	cellular lipid catabolic process	221	0.793758883	1.575425982	0.0012931	0.013706858	0.009985453	1873	tags=18%, list=6%, signal=17%
GO:0050770	regulation of axonogenesis	155	0.825281774	1.59901984	0.0013367	0.014056669	0.01024029	904	tags=10%, list=3%, signal=10%
GO:0055088	lipid homeostasis	167	0.804867788	1.56366472	0.001358	0.014167774	0.010321231	2227	tags=15%, list=7%, signal=14%
GO:0006885	regulation of pH	103	0.846962753	1.586060685	0.0013745	0.014228465	0.010365444	2153	tags=31%, list=6%, signal=29%
GO:0006665	sphingolipid metabolic process	160	0.819650419	1.592015624	0.0014142	0.014525835	0.010582078	1486	tags=22%, list=4%, signal=21%
GO:1901989	positive regulation of cell cycle phase transition	117	-0.851090566	-1.668855473	0.0014507	0.014786214	0.010771764	111	tags=10%, list=0%, signal=10%
GO:0001764	neuron migration	176	0.800076478	1.556715292	0.0014892	0.015062222	0.010972836	1526	tags=12%, list=5%, signal=11%
GO:0051302	regulation of cell division	186	-0.81033619	-1.659065448	0.0015192	0.015249613	0.01110935	752	tags=8%, list=2%, signal=8%
GO:0050807	regulation of synapse organization	232	0.780513171	1.556220959	0.001597	0.015909772	0.011590277	1506	tags=12%, list=4%, signal=11%
GO:0007229	integrin-mediated signaling pathway	111	0.846976024	1.591632029	0.0016714	0.016527366	0.012040194	2116	tags=23%, list=6%, signal=22%
GO:0051651	maintenance of location in cell	229	0.777598883	1.546931001	0.0017686	0.017231144	0.012552897	2294	tags=18%, list=7%, signal=17%
GO:0051402	neuron apoptotic process	258	0.766201094	1.539061988	0.0017671	0.017231144	0.012552897	2958	tags=22%, list=9%, signal=21%
GO:0046165	alcohol biosynthetic process	139	0.824830756	1.591382368	0.0018564	0.017824284	0.012984999	1727	tags=17%, list=5%, signal=16%
GO:0002237	response to molecule of bacterial origin	350	0.740367147	1.531682273	0.0018536	0.017824284	0.012984999	2833	tags=24%, list=8%, signal=22%
GO:0008360	regulation of cell shape	137	0.816630017	1.574312729	0.0019635	0.018716752	0.013635163	2409	tags=28%, list=7%, signal=27%
GO:0002831	regulation of response to biotic stimulus	453	0.708118307	1.502928825	0.0019859	0.018794748	0.013691983	2844	tags=23%, list=8%, signal=21%
GO:0031109	microtubule polymerization or depolymerization	127	-0.853077314	-1.701386293	0.0020482	0.019111525	0.013922756	212	tags=7%, list=1%, signal=7%

GO:0043524	negative regulation of neuron apoptotic process	155	0.816385967	1.581783821	0.0020396	0.019111525	0.013922756	1763	tags=13%, list=5%, signal=12%
GO:0043523	regulation of neuron apoptotic process	219	0.782763866	1.549310214	0.0021008	0.019465439	0.014180582	1906	tags=14%, list=6%, signal=13%
GO:0022612	gland morphogenesis	123	0.824609624	1.571155663	0.0021335	0.019630829	0.014301069	1458	tags=12%, list=4%, signal=12%
GO:0006275	regulation of DNA replication	136	-0.840561749	-1.686233434	0.0023264	0.021113054	0.01538087	1199	tags=18%, list=4%, signal=17%
GO:0042060	wound healing	433	0.711493765	1.503370063	0.0023237	0.021113054	0.01538087	2055	tags=18%, list=6%, signal=17%
GO:0018958	phenol-containing compound metabolic process	111	0.843188506	1.584514548	0.0023509	0.021178289	0.015428394	1727	tags=14%, list=5%, signal=13%
GO:0008202	steroid metabolic process	323	0.752774694	1.539079997	0.0023656	0.021178289	0.015428394	2298	tags=15%, list=7%, signal=14%
GO:0050767	regulation of neurogenesis	378	0.726124033	1.516245921	0.0024669	0.02193694	0.015981072	3101	tags=20%, list=9%, signal=18%
GO:0001704	formation of primary germ layer	127	0.835713977	1.597584429	0.00256	0.022463628	0.016364764	300	tags=6%, list=1%, signal=6%
GO:0044282	small molecule catabolic process	386	0.727612009	1.515664487	0.002544	0.022463628	0.016364764	2058	tags=16%, list=6%, signal=15%
GO:0032368	regulation of lipid transport	147	0.814530438	1.572276837	0.002582	0.022507368	0.016396629	1846	tags=14%, list=5%, signal=13%
GO:0048259	regulation of receptor-mediated endocytosis	113	0.850176192	1.603991219	0.002642	0.022786265	0.016599806	1016	tags=17%, list=3%, signal=16%
GO:0061564	axon development	477	0.709309722	1.520461532	0.0026572	0.022786265	0.016599806	909	tags=7%, list=3%, signal=7%
GO:0007178	transmembrane receptor protein serine/threonine kinase signaling pathway	382	0.724650691	1.513695731	0.0026656	0.022786265	0.016599806	2734	tags=16%, list=8%, signal=15%
GO:1905954	positive regulation of lipid localization	110	0.841297335	1.583840873	0.0027545	0.022810577	0.016617517	1894	tags=17%, list=6%, signal=16%
GO:0050803	regulation of synapse structure or activity	238	0.774507542	1.547363772	0.0027314	0.022810577	0.016617517	1506	tags=11%, list=4%, signal=11%
GO:0071559	response to transforming growth factor beta	271	0.759826068	1.528712931	0.0027424	0.022810577	0.016617517	2446	tags=18%, list=7%, signal=17%
GO:0070372	regulation of ERK1 and ERK2 cascade	306	0.74882322	1.521832272	0.0026929	0.022810577	0.016617517	2834	tags=19%, list=8%, signal=18%
GO:0051960	regulation of nervous system development	457	0.711683684	1.512002718	0.0027384	0.022810577	0.016617517	3336	tags=20%, list=10%, signal=18%
GO:0032496	response to lipopolysaccharide	332	0.741226733	1.519526083	0.0027998	0.023042187	0.016786244	2833	tags=23%, list=8%, signal=22%
GO:0048660	regulation of smooth muscle cell proliferation	162	0.806018953	1.570767505	0.002821	0.02307265	0.016808437	491	tags=5%, list=1%, signal=5%
GO:0002683	negative regulation of immune system process	471	0.703929458	1.501244658	0.0028468	0.023141159	0.016858346	3507	tags=24%, list=10%, signal=22%

GO:0031023	microtubule organizing center organization	152	- 0.828281839	-1.666040936	0.0030531	0.0246668 74	0.0179698 3	1126	tags=18%, list=3%, signal=17%
GO:0034502	protein localization to chromosome	115	- 0.851241541	-1.680339325	0.0030904	0.0248166 81	0.0180789 65	589	tags=13%, list=2%, signal=13%
GO:0099173	postsynapse organization	184	0.789509712	1.542460759	0.0031333	0.0250100 46	0.0182198 31	1284	tags=11%, list=4%, signal=11%
GO:0007613	memory	124	0.823933599	1.570750486	0.0032598	0.0258634 5	0.0188415 36	237	tags=4%, list=1%, signal=4%
GO:0062013	positive regulation of small molecule metabolic process	146	0.805754766	1.556397606	0.0033592	0.0263365 62	0.0191861 99	1460	tags=11%, list=4%, signal=11%
GO:0007611	learning or memory	275	0.742847299	1.49634296	0.0033545	0.0263365 62	0.0191861 99	1375	tags=9%, list=4%, signal=9%
GO:0007098	centrosome cycle	136	- 0.831941011	-1.66893955	0.0034031	0.0263692 5	0.0192100 12	1126	tags=18%, list=3%, signal=18%
GO:0002685	regulation of leukocyte migration	222	0.767012751	1.522282953	0.0033995	0.0263692 5	0.0192100 12	2867	tags=23%, list=8%, signal=22%
GO:0009308	amine metabolic process	115	0.826208721	1.566953098	0.0034975	0.0269427 84	0.0196278 31	1971	tags=20%, list=6%, signal=19%
GO:0007162	negative regulation of cell adhesion	301	0.743984403	1.513653685	0.0035465	0.0271625 7	0.0197879 46	2102	tags=16%, list=6%, signal=15%
GO:0045834	positive regulation of lipid metabolic process	149	0.804354025	1.554442282	0.0035959	0.0272263 84	0.0198344 34	1995	tags=15%, list=6%, signal=15%
GO:0045088	regulation of innate immune response	364	0.716523974	1.487266098	0.0035938	0.0272263 84	0.0198344 34	2844	tags=25%, list=8%, signal=23%
GO:0071219	cellular response to molecule of bacterial origin	222	0.764855413	1.518001305	0.0037864	0.0285058 84	0.0207665 51	3300	tags=30%, list=10%, signal=27%
GO:0071560	cellular response to transforming growth factor beta stimulus	265	0.752456048	1.512256701	0.003834	0.0287011 92	0.0209088 33	2446	tags=17%, list=7%, signal=16%
GO:0000077	DNA damage checkpoint signaling	122	- 0.841872558	-1.676508845	0.0039405	0.0291682 51	0.0212490 85	398	tags=9%, list=1%, signal=9%
GO:0048659	smooth muscle cell proliferation	166	0.804402252	1.562848625	0.0039322	0.0291682 51	0.0212490 85	491	tags=5%, list=1%, signal=5%
GO:0002697	regulation of immune effector process	377	0.723732073	1.510471441	0.0040208	0.0294776 58	0.0214744 88	3293	tags=24%, list=10%, signal=22%
GO:0001503	ossification	415	0.710840435	1.499741766	0.0040268	0.0294776 58	0.0214744 88	3017	tags=21%, list=9%, signal=19%
GO:0019751	polyol metabolic process	116	0.817811128	1.554742897	0.00413	0.0300674 49	0.0219041 51	1837	tags=21%, list=5%, signal=20%
GO:0030301	cholesterol transport	119	0.818542743	1.554048179	0.0044999	0.0325809 16	0.0237352 14	963	tags=10%, list=3%, signal=10%
GO:0072659	protein localization to plasma membrane	283	0.742104385	1.496519841	0.0047867	0.0344692 22	0.0251108 45	2388	tags=24%, list=7%, signal=22%
GO:0043534	blood vessel endothelial cell migration	156	0.78918887	1.532910421	0.0050298	0.0360243 13	0.0262437 3	2298	tags=12%, list=7%, signal=11%

GO:0043473	pigmentation	112	0.825227545	1.550667506	0.005162	0.036575485	0.026645259	1443	tags=18%, list=4%, signal=17%
GO:0016052	carbohydrate catabolic process	160	0.792812587	1.539888221	0.00515	0.036575485	0.026645259	1365	tags=18%, list=4%, signal=17%
GO:0090288	negative regulation of cellular response to growth factor stimulus	119	0.816065126	1.549344287	0.0052089	0.036711767	0.02674454	1790	tags=11%, list=5%, signal=10%
GO:0006694	steroid biosynthetic process	175	0.787269284	1.530926205	0.0052546	0.036837828	0.026836376	1458	tags=10%, list=4%, signal=10%
GO:0071222	cellular response to lipopolysaccharide	212	0.765732744	1.505170573	0.0054463	0.037981048	0.027669212	3300	tags=29%, list=10%, signal=27%
GO:0046434	organophosphate catabolic process	160	0.791441285	1.537224726	0.0056003	0.038850195	0.028302386	1077	tags=11%, list=3%, signal=10%
GO:0032200	telomere organization	184	0.759970645	-1.553764494	0.0058336	0.040258058	0.029328015	2218	tags=23%, list=7%, signal=21%
GO:0002367	cytokine production involved in immune response	121	0.796378355	1.513502061	0.0061023	0.0418938	0.030519654	1460	tags=17%, list=4%, signal=17%
GO:0090101	negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	156	0.784550004	1.523899947	0.006156	0.042044804	0.03062966	1524	tags=10%, list=5%, signal=9%
GO:1903531	negative regulation of secretion by cell	148	0.787210007	1.522461131	0.0061936	0.042084635	0.030658677	1340	tags=14%, list=4%, signal=13%
GO:0072006	nephron development	151	0.788684451	1.530151469	0.0063819	0.043142917	0.031429637	587	tags=6%, list=2%, signal=6%
GO:0006643	membrane lipid metabolic process	207	0.771923764	1.520508474	0.0064362	0.043289476	0.031536404	1486	tags=20%, list=4%, signal=19%
GO:0006650	glycerophospholipid metabolic process	295	0.736407022	1.489451182	0.0065036	0.04352178	0.031705639	2013	tags=19%, list=6%, signal=18%
GO:0006672	ceramide metabolic process	105	0.824440833	1.548067856	0.0066129	0.043925074	0.031999438	1629	tags=27%, list=5%, signal=25%
GO:0001818	negative regulation of cytokine production	332	0.72276952	1.481688515	0.0066302	0.043925074	0.031999438	3173	tags=20%, list=9%, signal=18%
GO:0010810	regulation of cell-substrate adhesion	218	0.755932818	1.494805974	0.0070653	0.046575006	0.033929915	2082	tags=20%, list=6%, signal=19%
GO:0015918	sterol transport	133	0.811763151	1.567477665	0.0072661	0.047661588	0.03472149	1720	tags=16%, list=5%, signal=15%
GO:0042445	hormone metabolic process	240	0.737036078	1.47588357	0.0075094	0.048846274	0.035584535	2743	tags=14%, list=8%, signal=13%
GO:0010721	negative regulation of cell development	281	0.72751851	1.467250273	0.0075205	0.048846274	0.035584535	3072	tags=20%, list=9%, signal=19%
GO:0150115	cell-substrate junction organization	103	0.814091326	1.524504168	0.0076415	0.049150681	0.035806296	1479	tags=19%, list=4%, signal=19%
GO:0002695	negative regulation of leukocyte activation	199	0.771258297	1.513306006	0.0076359	0.049150681	0.035806296	1553	tags=14%, list=5%, signal=14%

GO:0042770	signal transduction in response to DNA damage	183	-0.779006003	-1.583348626	0.0077427	0.049322797	0.035931682	398	tags=7%, list=1%, signal=7%
GO:0050890	cognition	316	0.715741067	1.456198431	0.0077329	0.049322797	0.035931682	2779	tags=15%, list=8%, signal=14%
GO:0022407	regulation of cell-cell adhesion	481	0.666742581	1.429036933	0.0078554	0.049800684	0.036279823	2041	tags=15%, list=6%, signal=14%

Supplemental Table 5. Enriched GO Molecular Functions

Table S4 List of all significantly enriched GO molecular functions with GSEA.

ID	Description	setSize	enrichmentScore	NES	pvalue	p.adjust	qvalue	rank	leading_edge
GO:0005543	phospholipid binding	472	0.820983458	1.74950194	1.40049E-08	2.64693E-06	1.82801E-06	1758	tags=19%, list=5%, signal=18%
GO:1903231	mRNA base-pairing translational repressor activity	167	-0.90807144	-1.829587747	9.62914E-08	9.09954E-06	6.28428E-06	17	tags=1%, list=0%, signal=1%
GO:0016298	lipase activity	125	0.851325795	1.624786591	0.000215245	0.012705263	0.008774451	232	tags=8%, list=1%, signal=8%
GO:0035091	phosphatidylinositol binding	274	0.788281024	1.594903495	0.000268894	0.012705263	0.008774451	1985	tags=25%, list=6%, signal=24%
GO:0030371	translation repressor activity	195	-0.819813986	-1.684627622	0.000386234	0.014599642	0.010082738	462	tags=2%, list=1%, signal=2%
GO:0004222	metalloendopeptidase activity	121	0.842100736	1.603898048	0.000930592	0.025125973	0.017352385	952	tags=8%, list=3%, signal=8%
GO:0005319	lipid transporter activity	169	0.821470572	1.593271894	0.000905743	0.025125973	0.017352385	1032	tags=11%, list=3%, signal=10%
GO:0052689	carboxylic ester hydrolase activity	132	0.823279312	1.572345859	0.001362064	0.029299145	0.020234441	232	tags=7%, list=1%, signal=7%
GO:0015293	symporter activity	144	0.811601428	1.558596531	0.001446046	0.029299145	0.020234441	1267	tags=11%, list=4%, signal=11%
GO:0015294	solute:monoatomic cation symporter activity	112	0.825425475	1.554174596	0.002033569	0.029299145	0.020234441	1221	tags=12%, list=4%, signal=11%
GO:0043177	organic acid binding	211	0.786157912	1.547524802	0.002170307	0.029299145	0.020234441	351	tags=6%, list=1%, signal=6%
GO:1901681	sulfur compound binding	266	0.761967654	1.539930889	0.002147969	0.029299145	0.020234441	3124	tags=18%, list=9%, signal=17%
GO:0061134	peptidase regulator activity	226	0.775518768	1.538857874	0.001954754	0.029299145	0.020234441	2500	tags=18%, list=7%, signal=17%
GO:0022804	active transmembrane transporter activity	424	0.71846792	1.515214057	0.001707643	0.029299145	0.020234441	2328	tags=20%, list=7%, signal=18%
GO:1902936	phosphatidylinositol bisphosphate binding	106	0.834015497	1.575009661	0.002855284	0.035976574	0.024845977	1465	tags=15%, list=4%, signal=14%
GO:0008094	ATP-dependent activity, acting on DNA	121	-0.822207352	-1.592394785	0.006319098	0.041325142	0.02853978	2049	tags=28%, list=6%, signal=26%
GO:0003735	structural constituent of ribosome	165	-0.782144698	-1.569951226	0.005057738	0.041325142	0.02853978	2652	tags=50%, list=8%, signal=47%
GO:0002020	protease binding	136	0.801284181	1.542015814	0.006193755	0.041325142	0.02853978	2812	tags=27%, list=8%, signal=25%
GO:0008237	metallopeptidase activity	196	0.773505538	1.527086732	0.006175239	0.041325142	0.02853978	1011	tags=7%, list=3%, signal=7%
GO:0004866	endopeptidase inhibitor activity	169	0.785267435	1.523054601	0.005278761	0.041325142	0.02853978	2471	tags=15%, list=7%, signal=14%

GO:001717	serine hydrolase activity	190	0.776548505	1.522422381	0.006033887	0.041325142	0.02853978	2185	tags=11%, list=6%, signal=10%
GO:1901981	phosphatidylinositol phosphate binding	178	0.780506185	1.516512345	0.005704191	0.041325142	0.02853978	1963	tags=20%, list=6%, signal=19%
GO:0008201	heparin binding	166	0.77866078	1.514449547	0.005885438	0.041325142	0.02853978	1895	tags=7%, list=6%, signal=7%
GO:0061135	endopeptidase regulator activity	183	0.775573766	1.511625445	0.00401824	0.041325142	0.02853978	2471	tags=17%, list=7%, signal=16%
GO:0031406	carboxylic acid binding	199	0.766727468	1.510702242	0.004087221	0.041325142	0.02853978	1384	tags=10%, list=4%, signal=10%
GO:0022853	active monoatomic ion transmembrane transporter activity	232	0.761022488	1.506939248	0.006340895	0.041325142	0.02853978	2160	tags=19%, list=6%, signal=18%
GO:0030414	peptidase inhibitor activity	176	0.776033193	1.504965248	0.005686932	0.041325142	0.02853978	2471	tags=15%, list=7%, signal=14%
GO:0048018	receptor ligand activity	481	0.684864201	1.457913742	0.005149694	0.041325142	0.02853978	362	tags=2%, list=1%, signal=2%
GO:0030546	signaling receptor activator activity	489	0.680320579	1.44758924	0.005172052	0.041325142	0.02853978	362	tags=2%, list=1%, signal=2%
GO:0046943	carboxylic acid transmembrane transporter activity	162	0.776870482	1.507846491	0.006792471	0.042792567	0.029553207	1751	tags=16%, list=5%, signal=15%
GO:0106310	protein serine kinase activity	362	-0.670595218	-1.522416295	0.007441675	0.04468146	0.030857706	833	tags=8%, list=2%, signal=8%
GO:0015291	secondary active transmembrane transporter activity	252	0.728265529	1.454771036	0.007565115	0.04468146	0.030857706	2160	tags=15%, list=6%, signal=15%
GO:0004620	phospholipase activity	103	0.812299293	1.526850313	0.00831409	0.046216557	0.031917867	1191	tags=11%, list=4%, signal=10%
GO:0005539	glycosaminoglycan binding	229	0.74672608	1.481028871	0.008105278	0.046216557	0.031917867	3191	tags=14%, list=9%, signal=13%
GO:0008514	organic anion transmembrane transporter activity	228	0.756911941	1.502233174	0.008656649	0.046745906	0.032283444	2160	tags=20%, list=6%, signal=19%
GO:0005342	organic acid transmembrane transporter activity	163	0.776511278	1.507261123	0.009108925	0.047821854	0.03302651	1751	tags=16%, list=5%, signal=15%

Supplemental Table 6. Enriched GO Cellular Components

Table S5 List of all significantly enriched GO cellular components with GSEA.

ID	Description	setSize	enrichmentScore	NES	pvalue	p.adjust	qvalue	rank	leading_gene
GO:0098687	chromosomal region	387	-0.853277333	-1.90216313	1.5494E-08	1.4177E-06	9.215E-07	601	tags=12%, list=2%, signal=12%
GO:0062023	collagen-containing extracellular matrix	412	0.833635791	1.72294479	1.1079E-08	1.4177E-06	9.215E-07	513	tags=5%, list=2%, signal=5%
GO:0005765	lysosomal membrane	409	0.823081574	1.70108005	1.0022E-07	4.5851E-06	2.9803E-06	2379	tags=39%, list=7%, signal=36%
GO:0098852	lytic vacuole membrane	409	0.823081574	\$	1.0022E-07	4.5851E-06	2.9803E-06	2379	tags=39%, list=7%, signal=36%
GO:0000793	condensed chromosome	269	-0.87159791	-1.85257411	1.447E-07	5.2959E-06	3.4423E-06	544	tags=13%, list=2%, signal=13%
GO:0000775	chromosome, centromeric region	247	-0.877025848	-1.85437953	1.8455E-07	5.6288E-06	3.6586E-06	201	tags=12%, list=1%,

									signal=12%
GO:0005774	vacuolar membrane	454	0.809695525	1.68788266	2.4743E-07	6.4685E-06	4.2044E-06	2379	tags=37%, list=7%, signal=34%
GO:0005769	early endosome	419	0.807677882	1.66850799	5.4958E-07	1.2572E-05	8.1714E-06	2828	tags=36%, list=8%, signal=33%
GO:0000779	condensed chromosome, centromeric region	169	-0.895233013	-1.8273801	2.2936E-06	4.6636E-05	3.0312E-05	541	tags=15%, list=2%, signal=15%
GO:0005819	spindle	420	-0.786730317	-1.7843889	5.1275E-06	9.3833E-05	6.099E-05	1218	tags=16%, list=4%, signal=15%
GO:0034774	secretory granule lumen	320	0.816694214	1.65897694	5.9552E-06	9.9072E-05	6.4395E-05	1932	tags=23%, list=6%, signal=22%
GO:0005775	vacuolar lumen	174	0.872348871	1.65539594	6.8999E-06	0.00010522	6.8394E-05	1784	tags=28%, list=5%, signal=27%
GO:0031983	vesicle lumen	325	0.814925931	1.65701463	8.3801E-06	0.00010869	7.0648E-05	1932	tags=23%, list=6%, signal=22%
GO:0060205	cytoplasmic vesicle lumen	323	0.815378964	1.65612914	7.9994E-06	0.00010869	7.0648E-05	1932	tags=23%, list=6%, signal=22%
GO:0005770	late endosome	291	0.82535833	1.65184212	1.0584E-05	0.00010869	7.0648E-05	1827	tags=28%, list=5%, signal=27%
GO:0030136	clathrin-coated vesicle	210	0.846193875	1.64909266	1.0476E-05	0.00010869	7.0648E-05	1984	tags=28%, list=6%, signal=26%
GO:0005766	primary lysosome	151	0.877374029	1.64456809	1.1285E-05	0.00010869	7.0648E-05	2194	tags=40%, list=6%, signal=38%
GO:0042582	azurophil granule	151	0.877374029	1.64456809	1.1285E-05	0.00010869	7.0648E-05	2194	tags=40%, list=6%, signal=38%
GO:0005788	endoplasmic reticulum lumen	311	0.813591363	1.64347764	9.5834E-06	0.00010869	7.0648E-05	1558	tags=14%, list=5%, signal=13%
GO:0030135	coated vesicle	305	0.811658093	1.63473556	1.7286E-05	0.00015817	0.00010281	2273	tags=30%, list=7%, signal=28%
GO:0000776	kinetochore	158	-0.883855898	-1.76860398	2.0959E-05	0.00018264	0.00011871	541	tags=14%, list=2%, signal=14%
GO:0042470	melanosome	111	0.890401619	1.62474561	2.9066E-05	0.00023127	0.00015032	1719	tags=41%, list=5%, signal=39%
GO:0048770	pigment granule	111	0.890401619	1.62474561	2.9066E-05	0.00023127	0.00015032	1719	tags=41%, list=5%, signal=39%
GO:0000228	nuclear chromosome	221	-0.842316972	-1.74866717	6.8032E-05	0.00051874	0.00033717	645	tags=12%, list=2%, signal=12%
GO:0030139	endocytic vesicle	341	0.793090277	1.62321555	7.1612E-05	0.0005242	0.00034072	2444	tags=26%, list=7%, signal=24%
GO:0030662	coated vesicle membrane	196	0.828822126	1.59668889	0.00012627	0.00088875	0.00057767	1719	tags=27%, list=5%, signal=25%
GO:0030665	clathrin-coated vesicle membrane	132	0.862067581	1.60610368	0.00013482	0.00091376	0.00059393	1719	tags=25%, list=5%, signal=25%

									signal=24%
GO:0030666	endocytic vesicle membrane	191	0.826382623	1.58820372	0.00016373	0.00107011	0.00069556	1747	tags=23%, list=5%, signal=21%
GO:0030667	secretory granule membrane	316	0.764403331	1.54883781	0.00036765	0.00232003	0.00150798	2194	tags=27%, list=6%, signal=25%
GO:0072562	blood microparticle	141	0.846141688	1.57916031	0.00047223	0.00288057	0.00187233	1070	tags=7%, list=3%, signal=7%
GO:0005811	lipid droplet	103	0.865076491	1.57567491	0.00056095	0.00320792	0.0020851	1918	tags=24%, list=6%, signal=23%
GO:0030027	lamellipodium	200	0.808412652	1.56390376	0.00055142	0.00320792	0.0020851	2778	tags=36%, list=8%, signal=33%
GO:0000922	spindle pole	171	-0.837056032	-1.70861946	0.00058557	0.00324725	0.00211067	610	tags=11%, list=2%, signal=10%
GO:0016442	RISC complex	245	-0.784897809	-1.66041765	0.00069916	0.00365562	0.0023761	17	tags=1%, list=0%, signal=1%
GO:0031332	RNAi effector complex	245	-0.784897809	-1.66041765	0.00069916	0.00365562	0.0023761	17	tags=1%, list=0%, signal=1%
GO:0101002	ficolin-1-rich granule	184	0.798468329	1.53178639	0.00138004	0.00701518	0.00455977	2317	tags=32%, list=7%, signal=30%
GO:0005875	microtubule associated complex	155	-0.821697986	-1.66201152	0.00176646	0.00873681	0.0056788	522	tags=9%, list=2%, signal=9%
GO:0031902	late endosome membrane	151	0.819458878	1.53601073	0.0018723	0.00901659	0.00586065	2014	tags=32%, list=6%, signal=30%
GO:0031901	early endosome membrane	184	0.787769043	1.51126081	0.00219489	0.01029911	0.00669428	2407	tags=33%, list=7%, signal=31%
GO:0070820	tertiary granule	163	0.799754836	1.49999954	0.00229661	0.01050698	0.00682939	2152	tags=28%, list=6%, signal=26%
GO:0072686	mitotic spindle	180	-0.799169937	-1.62776773	0.00312164	0.01393317	0.00905636	615	tags=11%, list=2%, signal=11%
GO:0005874	microtubule	458	-0.664052313	-1.52584347	0.00394407	0.01718486	0.01116991	600	tags=7%, list=2%, signal=7%
GO:0019867	outer membrane	237	0.753947692	1.4792141	0.00406484	0.0172992	0.01124423	2938	tags=29%, list=9%, signal=26%
GO:0031968	organelle outer membrane	235	0.753620582	1.47746903	0.00420614	0.01749371	0.01137066	2938	tags=29%, list=9%, signal=26%
GO:0098791	Golgi apparatus subcompartment	373	0.715021116	1.47785383	0.00552748	0.02247843	0.01461066	3105	tags=32%, list=9%, signal=30%
GO:0005796	Golgi lumen	101	0.816173697	1.48618448	0.00661293	0.02630798	0.01709981	3099	tags=19%, list=9%, signal=17%
GO:0005793	endoplasmic reticulum-Golgi intermediate compartment	132	0.793402582	1.47817507	0.00694812	0.0270533	0.01758426	2206	tags=30%, list=7%, signal=28%
GO:0045177	apical part of cell	445	0.687055662	1.42947337	0.00826483	0.03139304	0.02040502	1388	tags=10%, list=4%,

									signal=10%
GO:0097060	synaptic membrane	389	0.689186334	1.42394267	0.00840579	0.03139304	0.02040502	1947	tags=10%, list=6%, signal=10%
GO:0044391	ribosomal subunit	183	-0.768784032	-1.56775938	0.0100278	0.03598209	0.02338784	2693	tags=49%, list=8%, signal=46%
GO:0030133	transport vesicle	417	0.689765706	1.42623344	0.00994937	0.03598209	0.02338784	2823	tags=26%, list=8%, signal=24%
GO:0055037	recycling endosome	197	0.733228075	1.41436497	0.01250298	0.04400086	0.02859993	2347	tags=30%, list=7%, signal=28%
GO:0045335	phagocytic vesicle	139	0.771844885	1.44558298	0.01311782	0.04529359	0.02944018	3533	tags=42%, list=10%, signal=38%
GO:0030016	myofibril	232	0.725276084	1.42228799	0.01376564	0.04665022	0.03032197	3032	tags=19%, list=9%, signal=17%
GO:0005840	ribosome	216	-0.732194016	-1.51678694	0.01549742	0.04975487	0.03233995	2693	tags=45%, list=8%, signal=42%
GO:0005741	mitochondrial outer membrane	207	0.748440449	1.45744192	0.01528136	0.04975487	0.03233995	3046	tags=29%, list=9%, signal=27%
GO:0005802	trans-Golgi network	251	0.708586692	1.39680226	0.0151979	0.04975487	0.03233995	3190	tags=35%, list=9%, signal=32%

Supplemental Table 7. Enriched MSigDB Hallmarks

Table S6 List of all significantly enriched MSigDB hallmarks with GSEA

Description	setSize	enrichmentScore	NES	pvalue	p.adjust	qvalue	rank	leading edge
HALLMARK_G2M_CHECKPOINT	200	-0.943197455	-1.91775	1.00E-10	2.50E-09	1.63E-09	87	tags=14%, list=0%, signal=14%
HALLMARK_E2F_TARGETS	200	-0.928604008	-1.88807	1.00E-10	2.50E-09	1.63E-09	296	tags=13%, list=1%, signal=13%
HALLMARK_COAGULATION	138	0.903172766	1.723271	1.30E-06	2.16E-05	1.41E-05	239	tags=9%, list=1%, signal=9%
HALLMARK_ADIPOGENESIS	200	0.838089151	1.648394	4.50E-05	0.000562	0.000367	1866	tags=26%, list=6%, signal=25%
HALLMARK_COMPLEMENT	200	0.833015799	1.638416	7.14E-05	0.0006634	0.000433	1757	tags=18%, list=5%, signal=17%
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	200	0.831463777	1.635363	7.96E-05	0.0006634	0.000433	1492	tags=12%, list=4%, signal=11%
HALLMARK_TNFA_SIGNALING_VIA_NFKB	200	0.774281604	1.522894	0.002746	0.0196171	0.012803	4037	tags=48%, list=12%, signal=42%
HALLMARK_INFLAMMATORY_RESPONSE	199	0.775499866	1.523224	0.00467	0.0291898	0.01905	2827	tags=31%, list=8%, signal=29%
HALLMARK_SPERMATOGENESIS	134	-0.815630568	-1.6506	0.005958	0.0297894	0.019441	66	tags=4%, list=0%, signal=4%
HALLMARK_PROTEIN_SECRETION	95	0.834857894	1.557257	0.005773	0.0297894	0.019441	2336	tags=46%, list=7%, signal=43%
HALLMARK_MITOTIC_SPINDLE	199	-0.781071104	-1.58903	0.007144	0.0324735	0.021193	265	tags=10%, list=1%, signal=10%

HALLMARK_HEME_METABOLISM	198	0.75342517	1.477605	0.008277	0.0344866	0.022507	942	tags=14%, list=3%, signal=13%
HALLMARK_NOTCH_SIGNALING	32	0.892464349	1.563861	0.012832	0.0458271	0.029908	1690	tags=31%, list=5%, signal=30%
HALLMARK_XENOBIOTIC_METABOLISM	200	0.74196972	1.459342	0.012632	0.0458271	0.029908	2154	tags=20%, list=6%, signal=19%
HALLMARK_ANDROGEN_RESPONSE	100	0.799706157	1.481925	0.015371	0.0512356	0.033438	2422	tags=29%, list=7%, signal=27%
HALLMARK_OXIDATIVE_PHOSPHORYLATION	199	0.729146616	1.432177	0.026832	0.0838495	0.054723	2759	tags=34%, list=8%, signal=31%

Supplemental Table 8. Enriched KEGG Pathways

Table S7 List of all significantly enriched KEGG pathways with GSEA.

ID	Description	set Size	enrichment Score	NES	pvalue	p.adjust	qvalue	rank	leading_edge
hsa04110	Cell cycle	158	-0.91403845	1.813604486	2.55E-07	8.94E-05	7.43E-05	129	tags=12%, list=0%, signal=12%
hsa04142	Lysosome	247	0.867018379	1.710741757	7.41E-07	0.000130115	0.000108088	1799	tags=45%, list=5%, signal=42%
hsa04914	Progesterone-mediated oocyte maturation	103	0.903074728	-1.75616626	9.62E-05	0.011260743	0.009354403	87	tags=9%, list=0%, signal=9%
hsa04979	Cholesterol metabolism	51	0.922517314	1.681841611	0.000412992	0.036240085	0.030104974	686	tags=16%, list=2%, signal=15%
hsa04145	Phagosome	150	0.834721728	1.601877143	0.000564129	0.039601873	0.032897642	2014	tags=32%, list=6%, signal=30%

Supplemental Table 9. Trio WES Filtering Scheme

Table S8 Trio filtering strategy for WES

Rare (<0.01 freq) exonic/splice variants in index patient (research WES)	259		
Inheritance mode	De novo	Homozygous	Comp het
Number of variants (after removal of artefacts and commonly variable regions)	1 (CFAP46)	1 (KIR3DL2)	1 (SHISA2)
Variants in genes associated with disease	0		

Supplemental Table 10. IEI Variant Filtering Scheme

Table S9 IEI variant filtering strategy for index patient

Variants			Variants	
All variants (WES)	174534			
Variants in IEI genes (IUIS update 2024; contains also UTR, intronic, and intergenic variants)	3828			
Rare (<0.01 in gnomAD) variants	217			
Exonic and splice (+/- 2 bp from exon ends) variants	15	→	Homozygous variants	0
			Genes with compound heterozygous variants	0
		↓		
Dominant filtering limit freq<0.001 (gnomAD)	5*	→	De novo	0
Conserved amino acid or nucleotide (GERP++, PhyloP>0)	3			
Predicted damaging by at least one prediction tool (REVEL, CADD, SIFT, PolyPhen)	2			
Predicted damaging by multiple tools (REVEL, CADD, SIFT, PolyPhen)	1			

* variants shown in table "Index patient rare variants in IEI genes"

(CARD11 p.Leu22Ser)

3. Supplemental Figures

Supplemental Figure 1. Complete blood count

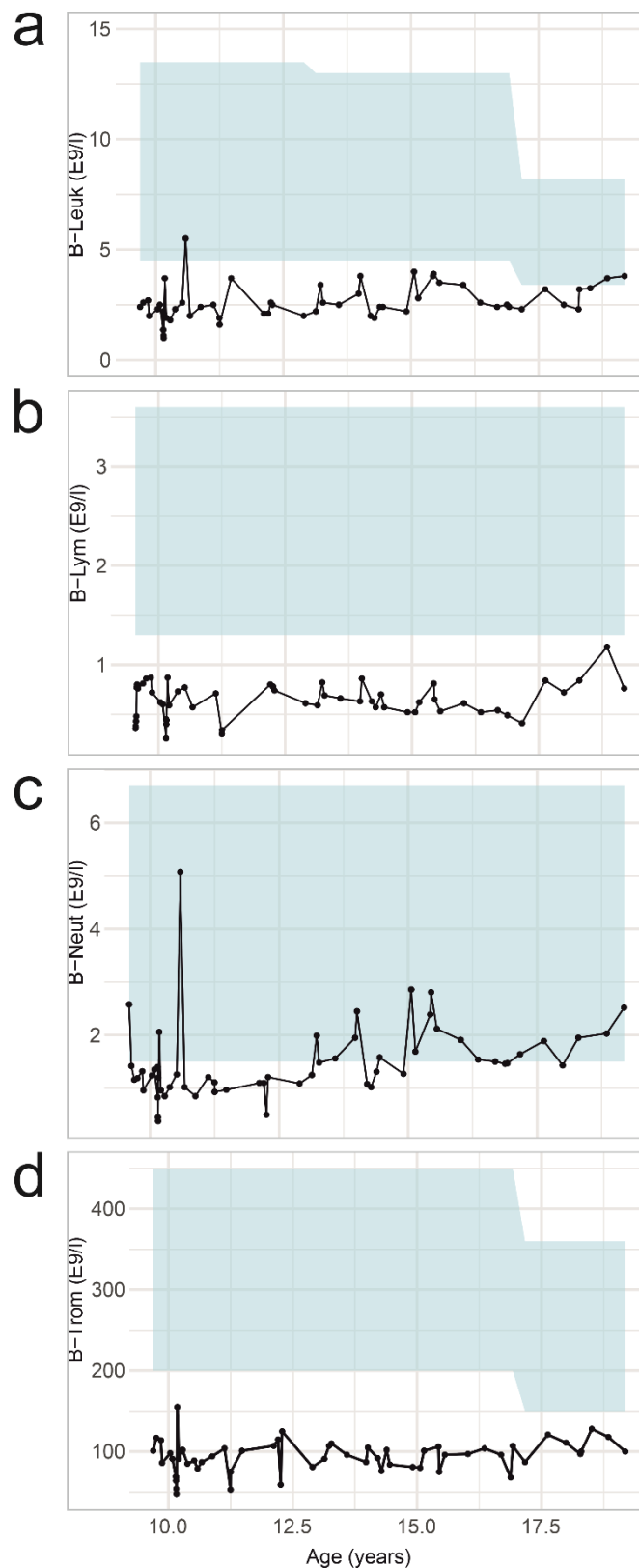


Figure S1 Longitudinal complete blood count of index patient, II-2, for the duration of 10 years. (a) leukocytes (b) lymphocyte fraction (c) neutrophils (d) platelets. The blue area indicates age-dependent reference range.

Supplemental Figure 2. Sanger chromatogram of asymptomatic I-1

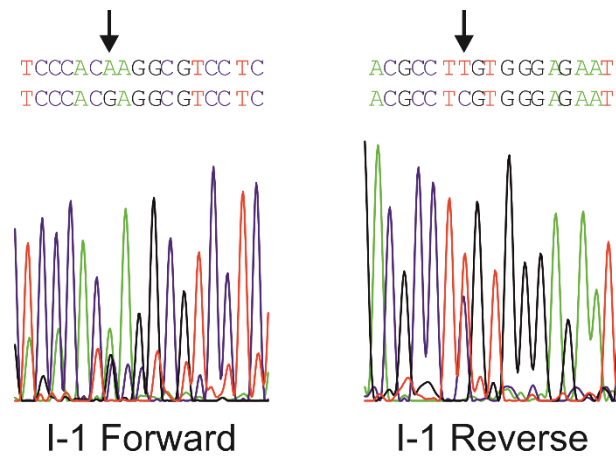


Figure S2 Sanger chromatogram for asymptomatic individual, I-1. DNA isolated from whole blood. Arrow indicates mutation site.

Supplemental Figure 3. Whole membrane blots of CARD11

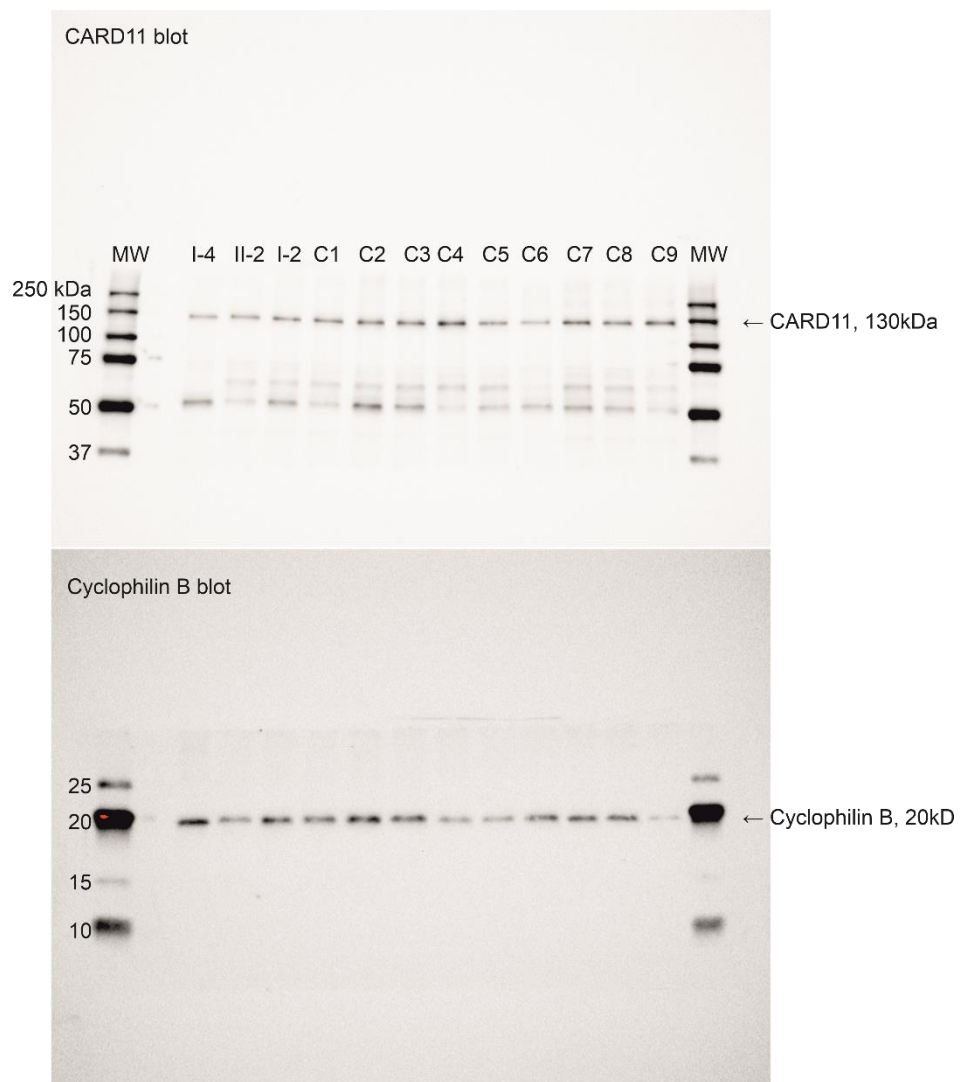


Figure S3 Whole membrane blots of CARD11 protein expression and housekeeping cyclophilin B

Supplemental Figure 4. PD-1 MFI

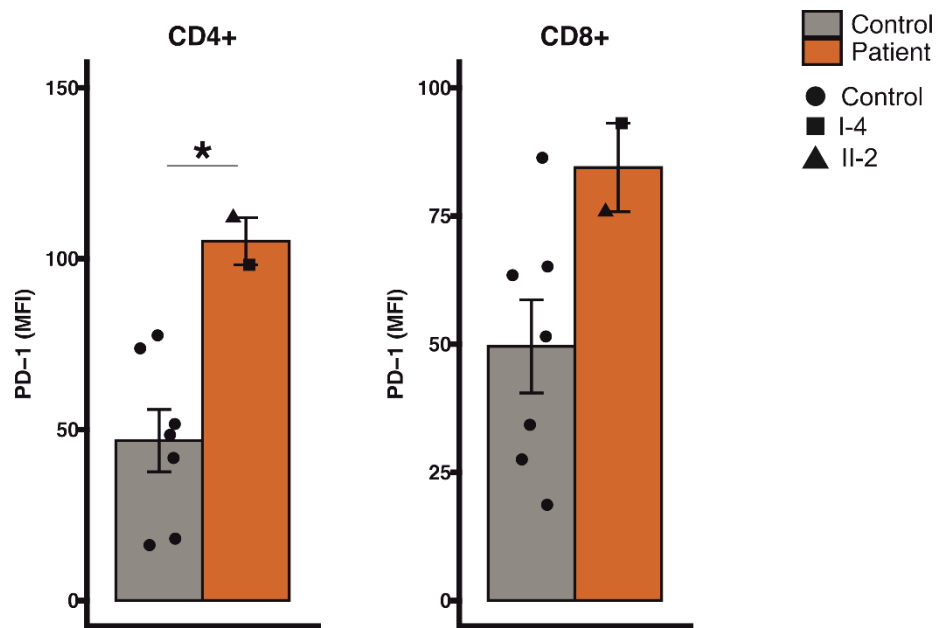


Figure S4 PD-1 expression (MFI) in CD4+ and CD8+ T cells (Pt, n=2; Ctrl, n=7) from two independent experiments.

Supplemental Figure 5. I-2's proliferation

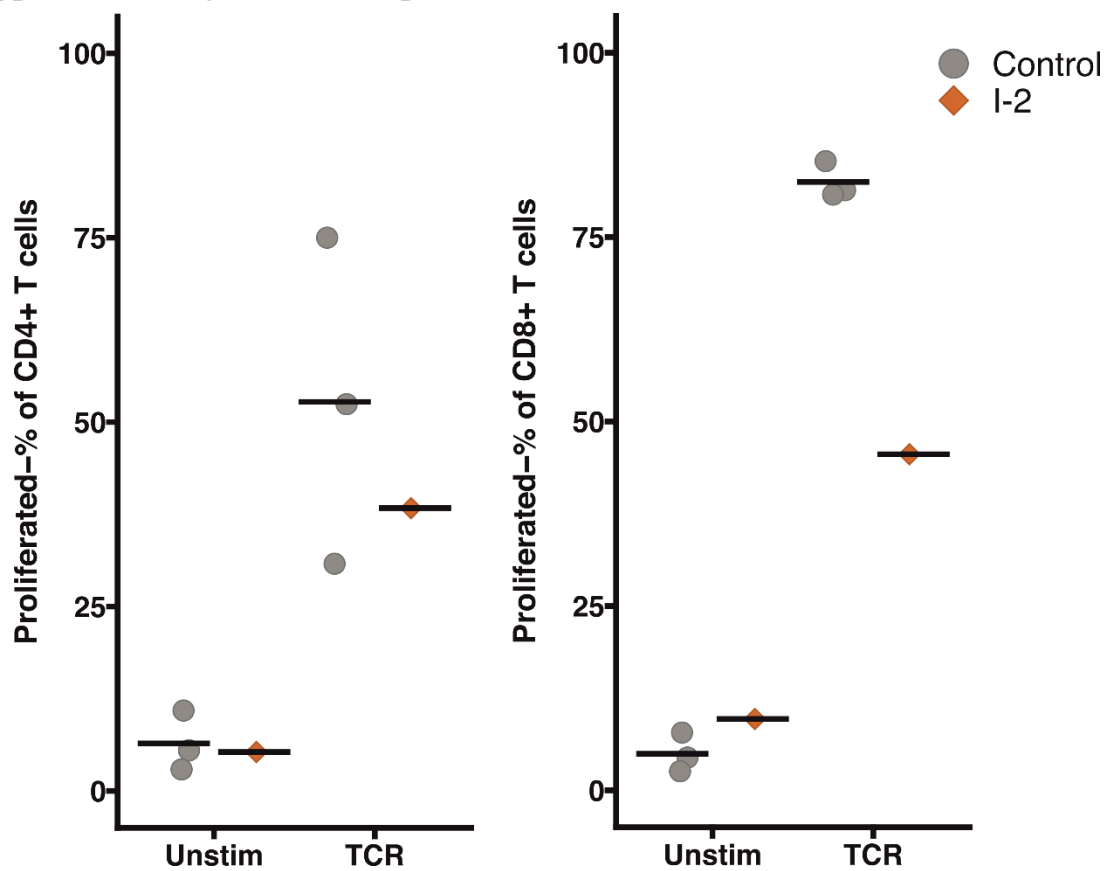


Figure S5 Percentage of proliferated cells from CFSE proliferation assay performed on frozen PBMCs (Pt; n=1, Ctrl, n= 3).

Supplemental Figure 6. Immunophenotype at the time of bulk RNAseq

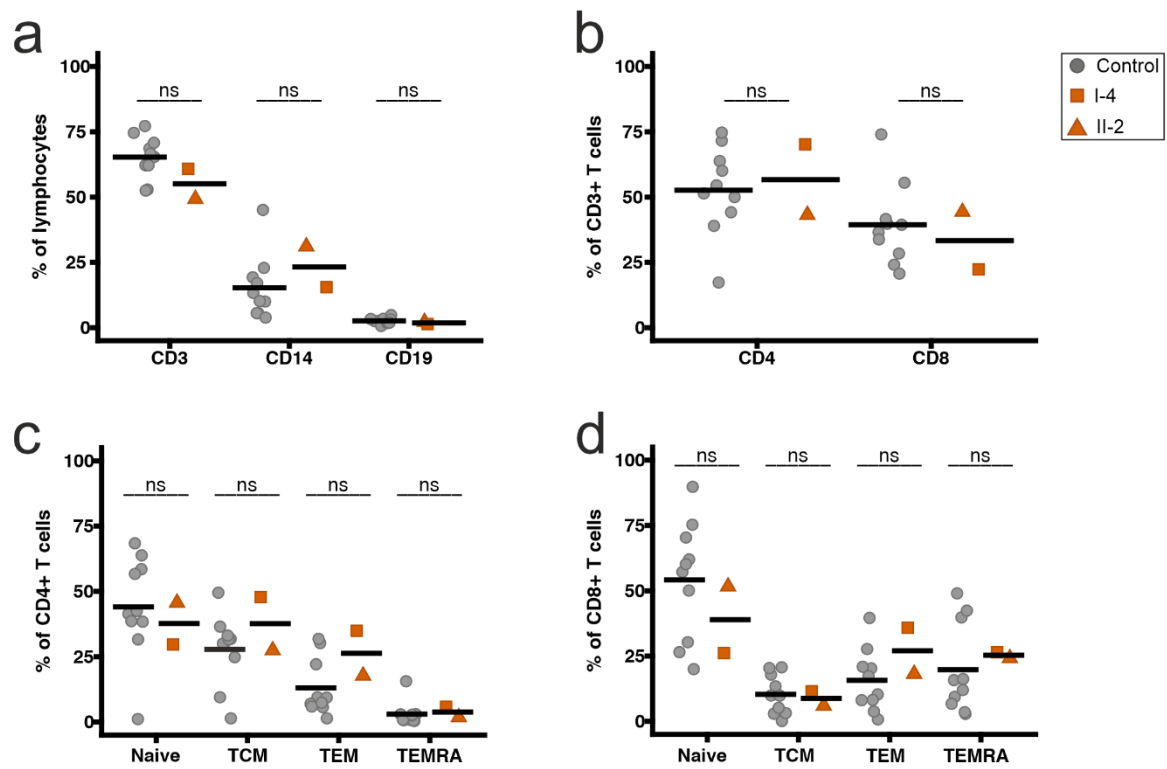
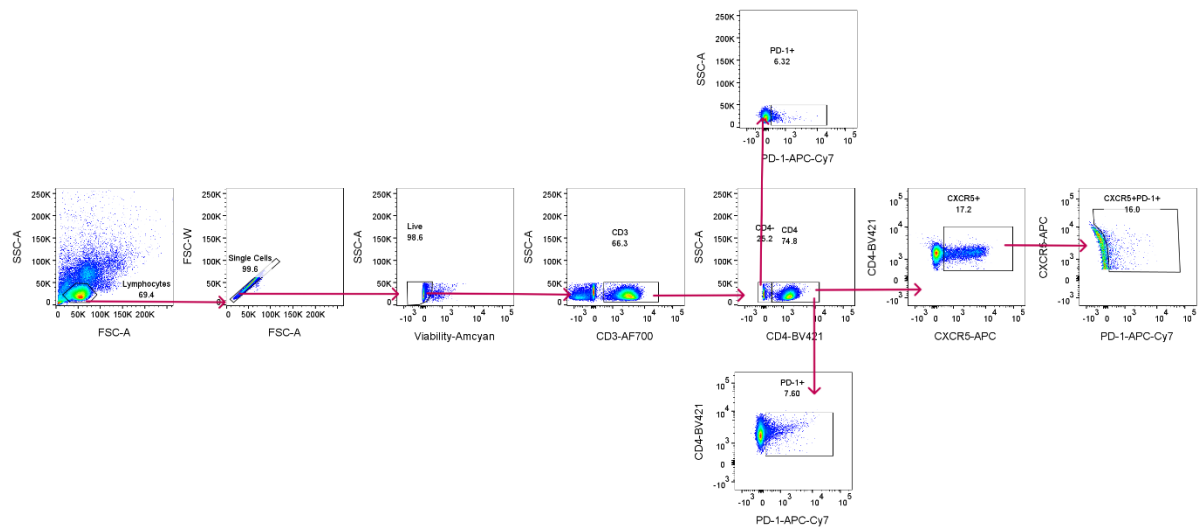


Figure S6 Characteristics of the PBMCs in bulk RNAseq experiment. a) Lymphocyte populations b) Ratio of CD4- and CD8- positive T cells, and naive/memory cell populations of c) CD4+ T and d) CD8+ T cells.

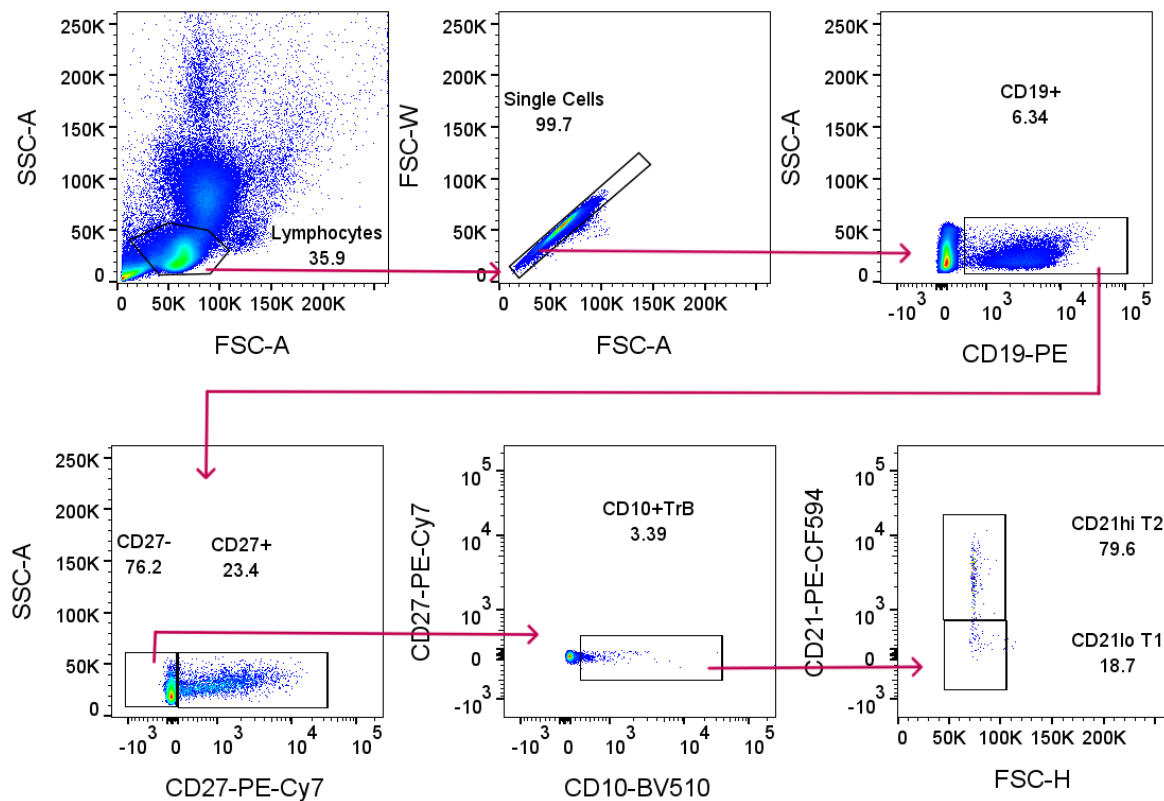
Gating Strategies

Gating of follicular T helper cells



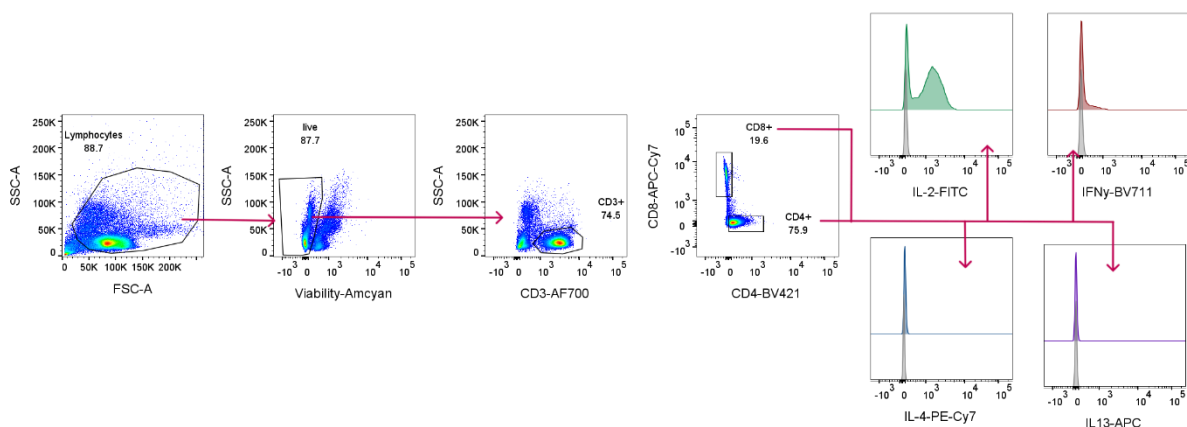
Gating Strategy 1 Gating of follicular T helper cells and cells expressing PD-1. Freshly isolated PBMCs were gated for lymphocytes on granularity and size with FSC-A vs SSC-A plot. The lymphocytes were then gated for single and viable cells. T cells were selected based on CD3 expression and further gated for CD4+ T cells. CXCR5-positive T_Hs were selected based on FMO sample. Both CD4+ and CD4- T cells and CD4+CXCR5+ T_Hs were gated for PD-1 expression with an FMO sample.

Gating of transitional B cells



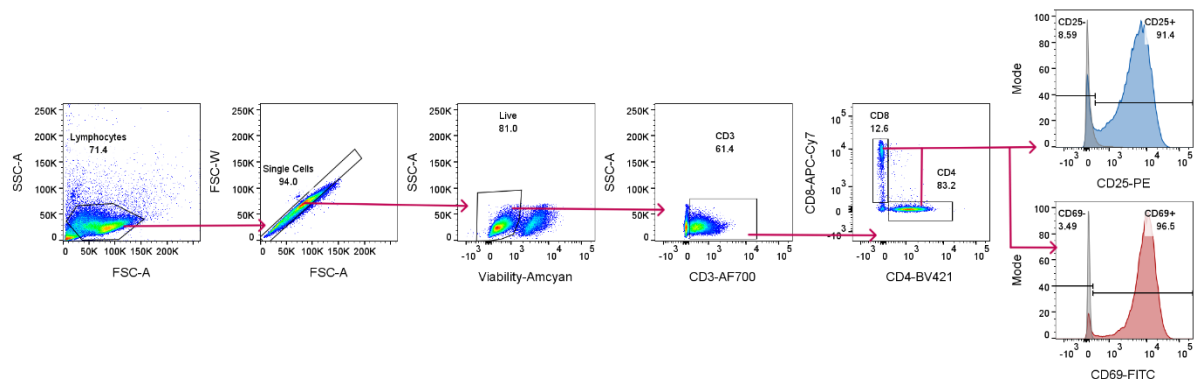
Gating Strategy 2 Gating of transitional B cells. Singlet, viable lymphocytes were selected from the freshly isolated PBMCs. B cells were identified with CD19. CD27-negative cells were selected for non-memory cells and CD10 was used to identify transitional B cells (TrB). TrBs were divided to T1 and T2 based on their CD21 expression. Selection of CD10, CD21, and CD27 positive cells were made with FMO samples.

Gating of intracellular cytokines



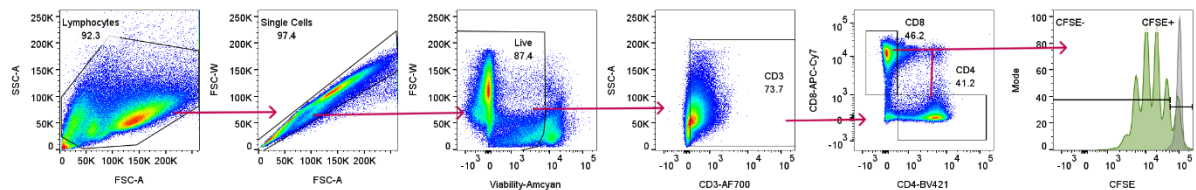
Gating Strategy 3 Gating of intracellular cytokines. Lymphocytes were gated from FSC-Avs SSC-A plot. Singlets and live cells based on the lack of Amcyan viability dye were selected. The cells were then gated for CD3-positive T cells and then divided into CD4+ and CD8+ T cells. The percentage of cells containing IL-2 (green), IFN γ (red), IL-4 (blue), and IL-13 (purple) was then assessed from the stimulated samples with the help of unstimulated samples (grey).

Gating of activation markers



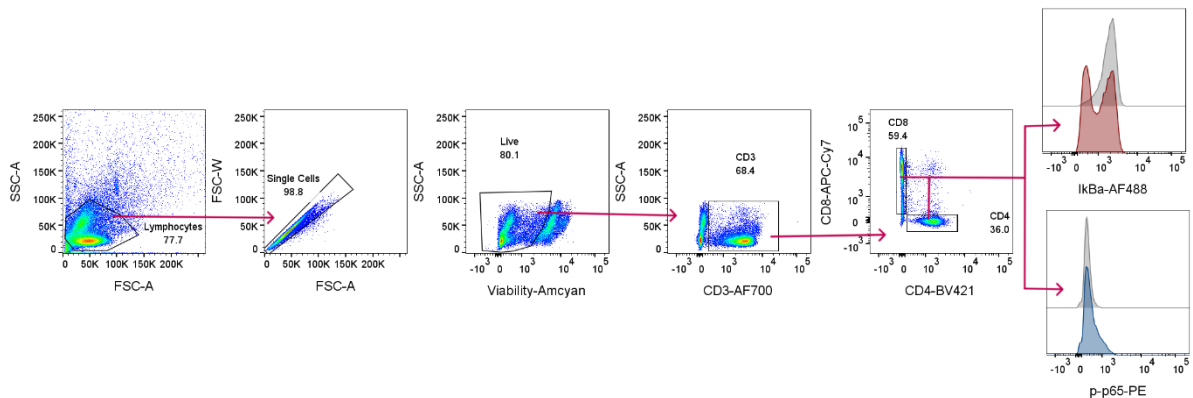
Gating Strategy 4 Gating of activation markers. Lymphocytes were selected from the FSC-Avs SSC-A plot, after which doublets (FSC-Avs FSC-W) and dead cells (Viability vs SSC-A) were excluded with eFluor506. T cells were gated with CD3 expression and divided into CD4+ and CD8+ T cells. CD25- (blue) and CD69-positive (red) cells from the stimulated samples were determined with the unstimulated (grey) samples.

Gating of proliferation assay



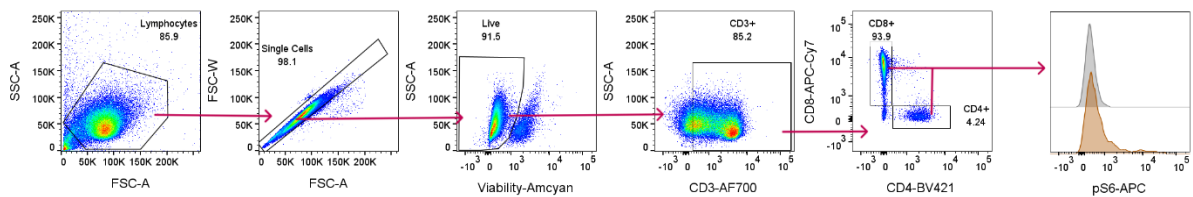
Gating Strategy 5 Gating for CFSE proliferation assay. Lymphocytes were gated from FSC-A vs SSC-A plot. The singlets were selected from FSC-A vs FSC-W plot and further gated for viability with eFluor506 viability dye (Viability vs SSC-A). T cells were selected based on CD3 expression and then further divided into CD4+ and CD8+ T cells from which the proliferation was determined. The peak of non-proliferated cells was determined with unstimulated samples (grey).

Gating of NF-kB pathway activity



Gating Strategy 6 Gating for IκBα degradation and p65 phosphorylation. First, live, single lymphocytes were selected from the PBMCs. Then, CD3+ T cells were selected and divided into CD4+ and CD8+ populations. The degradation of IκBα (red) and phosphorylation of p65 (blue) in stimulated samples were compared to unstimulated (grey) samples.

Gating of S6 phosphorylation



Gating Strategy 7 Gating for S6 phosphorylation assessment. T cell blasts were gated for singlets and viable cells. CD3+ T cells were divided into CD4+ and CD8+ populations out of which the S6 phosphorylation of stimulated cells (orange) was compared to the unstimulated (grey) samples.