

Follicular Lymphoma Cells Induce Changes in T-Cell Gene Expression and Function that Alter Prognosis and Risk of Transformation

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Methods

Ethical considerations and samples

Ethical approval for the study was obtained from the East London and The City HA Local Research Ethics Committee 3, REC reference number 05/Q0605/140 in compliance with the recently revised Helsinki protocol. The cryopreserved cell suspensions were obtained from a Tissue Bank (Human Tissue Act 2004 deemed license no. 12199), collected and maintained by the Centre of Haemato-Oncology of St Bartholomew's Hospital. All patients consented to storage of specimens for research purposes. Control PBMCs were obtained from healthy volunteers and buffy coats supplied by the National Blood Service. Mononuclear cells were obtained by Ficoll-Hypaque (Axis Shield) density gradient centrifugation.

Cryopreserved single cell suspensions of lymph node (LN) were obtained from previously untreated FL patients at diagnosis (12 for gene array and real-time, 4 for co-culture and 7 for motility assay), reactive tonsils (7 for gene array, 10 for real-time, 4 for co-culture and 4 for motility assay) and, PBMCs from 10 AML patient and fresh PBMCs from 10 age-matched healthy volunteers. After flow sorting, in three patient samples there were insufficient number of CD8 TILs for study.

Immunophenotyping and cell sorting

All antibodies were obtained from BD Biosciences. All cells were initially preincubated for 20 minutes with human anti-globulin (Sigma-Aldrich) to block Fc receptors. For gene array analysis highly purified TIL subsets were obtained by cell sorting on a BD Aria by excluding debris/nonviable cells and gating on CD19⁻CD4⁺ and CD19⁻CD8⁺ cells. Staining of these cells was performed with phycoerythrin (PE)-conjugated anti-CD4, fluorescein isothiocyanate (FITC)-conjugated anti-CD8, and Peridinin-Chlorophyll-Protein Complex (PerCP)-conjugated anti-CD19 Abs before resuspension in a 4,6 diamidino-2-phenylindole (DAPI) containing solution of 2% heat-inactivated fetal calf serum (FCS) with phosphate buffered solution (PBS). Subsequently a portion of cells were checked for purity using flow cytometry (FACS) on a BD LSR2 after adding allophycocyanin (APC)-conjugated anti-CD3 Ab and by gating on CD19⁻CD3⁺CD4⁺, CD19⁻CD3⁺CD8⁺ and, CD19⁺ which for all samples purity verified over 96% with < 2% B-cell contamination. FACS data analysis was performed using FlowJo (TreeStar Inc) software. For other purposes untouched T-cells were sorted using CD4 and CD8 T-Cell Isolation Kits II (Miltenyi Biotec) and purity checks were performed thereafter. B cells were positively separated using Miltenyi's CD19 magnetic microbead. Purity of the magnetically sorted cells was always >90%.

Gene expression profiling

The Affymetrix Expression GeneChip Protocol 1-cycle procedure was used to synthesize biotin-labelled cRNA which following fragmenting was used for hybridization onto Affymetrix Human Genome U133 plus 2.0 GeneChips. One µg total RNA was used as starting material. Following hybridization, quality-control data (noise signal, scale factor, background noise, present or absent probes and, 3'/5' signal ratio for housekeeping genes) were assessed before further analysis and they all passed the required criteria. GeneChip data analysed using Partek and R softwares by two independent experts who reached to 99% similarity in the extracted results. Pathway analysis was performed using Ingenuity software (Ingenuity Systems Inc). The gene profiling data discussed in this publication have been deposited in

National Centre for Biotechnology Information (NCBI)'s Gene Expression Omnibus (GEO) and are accessible through GEO Series accession number GSE27928.

RNA extraction and cDNA synthesis

RNAs were always extracted from cell fractions using the RNeasy Mini Kit (Qiagen) according to manufacturer's instruction. Quality and quantity of RNAs were checked using Agilent Bioanalyzer and NanoDrop Spectrophotometer (Thermo Scientific), respectively, before subsequent use. For QRT-PCR, cDNA was generated from 100 ng RNA using random hexamers and M-MLV RT(H-) (Promega) in a 25 μ L reaction according to manufacturer's instruction.

Quantitative Real Time-PCR (QRT-PCR)

Gene expression changes observed by microarray were validated by QRT-PCR. cDNA (0.5 μ L) was subsequently used in 20 μ L QRT-PCR reactions using Applied Biosystems Taqman Gene Expression Assays. 18S ribosomal RNA was used as endogenous control. Reactions were performed in triplicates on Applied Biosystems 7900HT Fast Real-Time PCR machine using the standard thermal cycler protocol. After preliminary validation the change in expression of each target gene was calculated relative to the endogenous control gene using the $2^{-\Delta\Delta CT}$ method as previously described¹. All the primer/probe sets (PMCH, ETV1, CAV1, CRTAM and, CXCL13) and reaction materials were purchased from Applied Biosystems.

The reason for choosing genes for further study

Five dysregulated genes were selected for further investigation, two of which (PMCH and ETV1) were up-regulated in common in both CD4 and CD8 cells, CAV1 and CXCL13 over-expressed on CD8 cells and CRTAM over-expressed on CD4 cells. These genes were selected since they have minimal expression in FL cells, tonsillar B cells, PB T cells of AML patients (another B-cell malignancy) and healthy donors and appear specific for TILs in FL patients, suggest their potential involvement in the pathophysiology of this disease. Importantly, we demonstrate that changes in these genes can be induced at the healthy T cells following short-term co-culture with direct or indirect contact with FL cells. Two Abs for CD137 (TNFRSF9) and two for ACTN1 were tested for TMA but did not provide reliable results.

Tissue Microarrays

The results of the gene expression profiling were also verified using Tissue Microarrays (TMAs) of 4 genes (PMCH, ETV1, NAMPT (Visfatin-1), and CD200) for which appropriate Abs for paraffin embedded sections were available (mouse anti-PMCH, Abnova; rabbit anti-ETV1, Abcam; rabbit anti-NAMPT, Sigma; rabbit anti-CD200, Sigma). The validation set TMAs was prepared as triplicates from 1-mm diameter cores selected from patients with FL (n= 172) at diagnosis at St Bartholomew's hospital in whom clinical outcome was available. Median age of the patients was 56yr (range 24-85) with 40% female and 41 patients had undergone subsequent histologic transformation confirmed by biopsy at the time of transformation. Reactive follicular hyperplasia lymph node samples (n=12) were arrayed as controls. TMAs construction, immunohistochemistry (IHC) staining and analysing was performed as previously described². Stained slides were evaluated for percentage of positive cells and expression (mean intensity) using computerized image analysis system (Ariol,

Applied Imaging™, Genetix) using pathologist-trained visual parameters including location relative to the neoplastic follicle: interfollicular, intrafollicular, and total core area (interfollicular-intrafollicular). Expert histopathologist analysis independently validated the IHC staining and automated analysis results. The double immunofluorescence labelling of paraffin embedded sections was performed as previously mentioned³ using antibodies anti-CD3 (Labvision, clone SP7), anti-PMCH (Abnova), anti-MCHR2 (Sigma SAB2900027) and anti-CD68 (DAKO clone KP1). All patients provided consent for excess biopsy tissue to be used for research purposes and ethical approval obtained (05/Q0605/140).

Co-culturing

To study the direct impact of FL cells on T-cells, pure healthy allogeneic PB T-cells (1×10^6 /mL) and FL cells or healthy allogeneic tonsillar B cells (1×10^6 /mL) were co-cultured together in full culture medium for 48 hr (6-well culture plate). To analyze the impact on T cells of soluble-derived tumor factors, healthy T cells (lower well; 1×10^6 /mL) were incubated with FL cells or healthy allogeneic B-cells (upper chamber; 1×10^6 /mL; 1:1 ratio) in 6-well transwell plates (0.4 μ m pore cell culture insert 353090, BD) for 48 hrs. After co-culture, cells were harvested and T cells isolated by MACS negative selection for subsequent flow cytometry purity analysis (>90%) and QRT-PCR.

Time-lapse imaging

Random movement of CD4 and CD8 TILs were assessed on Intercellular Adhesion Molecule (ICAM)-1 coated slides. Sorted CD4 and CD8 TILs were incubated for overnight in RPMI 1640 supplemented with 10% heat-inactivated FCS at 37°C and 5% CO₂ prior to the assay. We coated μ -Slides VI ibiTreat 80606 (ibidi GmbH, Germany) overnight at 4°C with 3 μ g/ml ICAM-1-Fc and then blocked them with 2% BSA in PBS at room temperature for 1hr as previously published⁴. The slide was then washed twice and 1×10^5 lymphocytes in 100 μ L of HBSS with 20 mM HEPES buffer and 1 μ g chemokine C-X-C motif ligand 12 (CXCL12(SDF1- α); R&D, Minneapolis, MN 55413, USA) were mixed and applied to the slide. Images were taken with a Nikon BioStation IM microscope (Nikon UK Limited, UK), using a 20 \times objective lens and the BioStation software (Nikon) at 20-sec intervals for 1hr. The cells were tracked and analysed with NIS-Element AR software (Nikon). Motility Index was calculated by the average frequency of motile cells from three microscopic fields of 20x objective lens multiplied by their average velocity (μ m/S).

Statistical analysis

The expression data was analysed within the R statistical environment⁵ using Bioconductor (<http://www.bioconductor.org>) packages. Stringent quality control criteria were applied to the data and no probes were found to be of low quality. To detect differentially expressed genes between healthy and FL samples for both CD4 and CD8 subtypes Limma⁶ was used to fit a linear model to normalise expression data for each probe. False Discovery Rates (FDRs) were estimated using the Benjamini-Hochberg method⁷. An FDR cut-off of 0.05 and a log₂ fold change cut-off of 1 was applied to filter the list of differentially expressed genes. For survival analysis Kaplan-Meier plot and the Gehan-Breslow-Wilcoxon method was used. For the multivariate analysis patients' gender, age, grade and, stage together with PMCH, ETV1 and NAMPT levels were used to fit a multivariate statistical model using the Cox Proportional Hazards regression model. Two models were created one using time to death/date of last

follow up as the end point and another using time to transformation/date of last follow up as the end point. The confidence interval for p-value significance was set to 0.95. Cases with missing data were excluded from analysis. Recursive partitioning was used to generate optimal cut-off values discriminating prognostic groups for the survival parameters and group comparisons performed by the chi-square test⁸. The accuracy of the applied cut-off levels was also independently checked by T-test which also revealed to be highly significant ($p < 0.0003$). Unpaired t-test was performed to determine whether the incidence of antigen expression was significantly different between samples from patients and controls and the significance level was set below 0.05. T-test was also applied to the Motility Index derived from time-lapse study. All statistical tests were two-sided.

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Supplemental Table 1

Dysregulated genes in CD4 TILs			
AGI	Gene symbol	Gene Name	log2FC
NM_0012674	PMCH	pro-melanin-concentrating hormone	3.20357727
AI935096	NR4A2	nuclear receptor subfamily 4, group A, member 2	3.13820137
AA873350	NAMPT	nicotinamide phosphoribosyltransferase	2.58129289
BF339445	CHN1	chimerin (chimaerin) 1	2.336788
NM_001561	TNFRSF9	tumor necrosis factor receptor superfamily, member 9	2.26320435
NM_021963	NAP1L2	nucleosome assembly protein 1-like 2	2.25298879
AK026714	PELI1	pellino homolog 1 (Drosophila)	2.16680283
AV713062	MAP3K8	mitogen-activated protein kinase kinase kinase 8	2.16147163
AI857639	PMAIP1	phorbol-12-myristate-13-acetate-induced protein 1	2.12556752
NM_002104	GZMK	granzyme K (granzyme 3; tryptase II)	2.11447536
AA769986	NUPL1	nucleoporin like 1	2.11380035
AA828049	YME1L1	YME1-like 1 (S. cerevisiae)	2.01925314
NM_006732	FOSB	FBJ murine osteosarcoma viral oncogene homolog B	1.99063985
AA215701	SNORA28	small nucleolar RNA, H/ACA box 28	1.97345271
NM_019604	CRTAM	cytotoxic and regulatory T cell molecule	1.96843725
NM_005442	EOMES	eomesodermin homolog (Xenopus laevis)	1.93324808
AA580082	GSPT1	G1 to S phase transition 1	1.92210241
X99268	TWIST1	twist homolog 1 (Drosophila)	1.91073647
NM_001394	DUSP4	dual specificity phosphatase 4	1.88557152
AI819150	ASXL1	additional sex combs like 1 (Drosophila)	1.88160687
AI671885	SLC20A1	solute carrier family 20 (phosphate transporter), member	1.83856843
BC036731	ZBTB24	zinc finger and BTB domain containing 24	1.81621939
AA872471	SNRPA1	small nuclear ribonucleoprotein polypeptide A'	1.8150811
BE247450	CHD2	chromodomain helicase DNA binding protein 2	1.76502373
AI813331	DIAPH3	diaphanous homolog 3 (Drosophila)	1.75107636
AI760495	CYCS	cytochrome c, somatic	1.74010784
BF446578	RASGEF1A	RasGEF domain family, member 1A	1.68319254
NM_003151	STAT4	signal transducer and activator of transcription 4	1.67479941
AV726956	BEX5	brain expressed, X-linked 5	1.66606876
AV700298	CD44	CD44 molecule (Indian blood group)	1.65821769
AL519710	CADM1	cell adhesion molecule 1	1.64319157
AI094580	NME7	non-metastatic cells 7, protein expressed in (nucleoside-d	1.63315494
AF050145	IDS	iduronate 2-sulfatase	1.61948057
U39226	MYO7A	myosin VIIA	1.6140942
AI208342	DCAF8	DDB1 and CUL4 associated factor 8	1.60348695
AF130079	PRO2852	hypothetical protein PRO2852	1.60318971
BE549540	CYSLTR1	cysteinyl leukotriene receptor 1	1.5944598
NM_006159	NELL2	NEL-like 2 (chicken)	1.58296466
AV683684	RPS27	ribosomal protein S27	1.58121633
AL136944	SLC40A1	solute carrier family 40 (iron-regulated transporter), mem	1.57186124
AK096036	FLJ38717	FLJ38717 protein	1.57130165
AA828371	VPS13C	vacuolar protein sorting 13 homolog C (S. cerevisiae)	1.56680733
NM_005780	LHFP	lipoma HMGIC fusion partner	1.55421285
AF052094	EPAS1	endothelial PAS domain protein 1	1.53347743
AA974416	PPP2R2B	protein phosphatase 2 (formerly 2A), regulatory subunit E	1.52176519
AY034790	CCNL1	cyclin L1	1.51349776
AA741493	ZFAND6	zinc finger, AN1-type domain 6	1.50300985
BE646573	NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer ir	1.49839047
AI631159	SLC2A3	solute carrier family 2 (facilitated glucose transporter), m	1.49546306
BF514552	FCRL3	Fc receptor-like 3	1.48381018
AI795908	PHLDA1	pleckstrin homology-like domain, family A, member 1	1.47510751

AB023212	PCNX	pecanex homolog (Drosophila)	1.47149851
BF438386	RAB27B	RAB27B, member RAS oncogene family	1.46416438
AI700608	MORF4L2	mortality factor 4 like 2	1.46320402
BE675139	CREB3L2	cAMP responsive element binding protein 3-like 2	1.45930084
AI239832	UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, y	1.45218227
AL832250	SNRPN	small nuclear ribonucleoprotein polypeptide N	1.44999677
U23772	XCL1	chemokine (C motif) ligand 1	1.44725128
BF673779	TMEM155	transmembrane protein 155	1.43451077
AL562860	MBNL1	muscleblind-like (Drosophila)	1.43352182
NM_000956	PTGER2	prostaglandin E receptor 2 (subtype EP2), 53kDa	1.41554349
NM_005201	CCR8	chemokine (C-C motif) receptor 8	1.40939489
AI936531	SFRS18	splicing factor, arginine/serine-rich 18	1.40131482
NM_016533	NINJ2	ninjurin 2	1.39186734
BC042469	RP3-527F8.2	hypothetical protein LOC100128420	1.37926251
AI261467	IKZF4	IKAROS family zinc finger 4 (Eos)	1.37570982
AL834350	PPP2R5C	protein phosphatase 2, regulatory subunit B', gamma isof	1.37009731
NM_002371	MAL	mal, T-cell differentiation protein	1.35442785
NM_003243	TGFBR3	transforming growth factor, beta receptor III	1.35328027
BG542501	C13orf15	chromosome 13 open reading frame 15	1.35221815
NM_000919	PAM	peptidylglycine alpha-amidating monooxygenase	1.35137584
AW978896	TRA2A	transformer 2 alpha homolog (Drosophila)	1.34630959
NM_004289	NFE2L3	nuclear factor (erythroid-derived 2)-like 3	1.34586878
NM_000589	IL4	interleukin 4	1.34580258
AW084068	N4BP2L2	NEDD4 binding protein 2-like 2	1.34084107
AI300126	SCARNA17	small Cajal body-specific RNA 17	1.33764188
K03122	IL2RA	interleukin 2 receptor, alpha	1.33579122
NM_014380	NGFRAP1	nerve growth factor receptor (TNFRSF16) associated prot	1.33459371
NM_053055	THEM4	thioesterase superfamily member 4	1.33323944
NM_012317	LDOC1	leucine zipper, down-regulated in cancer 1	1.3270985
BE552334	EIF5	eukaryotic translation initiation factor 5	1.32134724
AB028966	TTC28	tetratricopeptide repeat domain 28	1.31973837
AW665138	RTKN2	rhotekin 2	1.31130531
AI590088	TEAD1	TEA domain family member 1 (SV40 transcriptional enhar	1.31059614
AA805939	REV3L	REV3-like, catalytic subunit of DNA polymerase zeta (yeas	1.3105575
AB014511	ATP9A	ATPase, class II, type 9A	1.30926791
BF446719	WIPF1	WAS/WASL interacting protein family, member 1	1.30456442
AI244908	SOCS3	suppressor of cytokine signaling 3	1.30243801
NM_001677	ATP1B1	ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	1.28608692
T97717	PSME4	proteasome (prosome, macropain) activator subunit 4	1.2835857
NM_004114	FGF13	fibroblast growth factor 13	1.27571163
W93523	EPC1	enhancer of polycomb homolog 1 (Drosophila)	1.27339811
BE675435	KLF6	Kruppel-like factor 6	1.26868716
BE046511	FNBP1	formin binding protein 1	1.26147582
AA250935	LPXN	leupaxin	1.25874507
BF002296	JMJD1C	jumonji domain containing 1C	1.24971477
BE881590	ETV1	ets variant 1	1.24719052
BC022477	RNF103	ring finger protein 103	1.24685367
AL047052	LOC100190986	hypothetical LOC100190986	1.24398447
U23850	ITPR1	inositol 1,4,5-triphosphate receptor, type 1	1.2373586
AA579047	PIK3C2A	phosphoinositide-3-kinase, class 2, alpha polypeptide	1.23699016
NM_152641	ARID2	AT rich interactive domain 2 (ARID, RFX-like)	1.23603435
NM_013416	NCF4	neutrophil cytosolic factor 4, 40kDa	1.2307508
NM_022162	NOD2	nucleotide-binding oligomerization domain containing 2	1.23052705

NM_000594	TNF	tumor necrosis factor (TNF superfamily, member 2)	1.22286131
AU150319	VAMP1	vesicle-associated membrane protein 1 (synaptobrevin 1)	1.2226736
NM_014241	PTPLA	protein tyrosine phosphatase-like (proline instead of catal	1.2122228
NM_052889	CARD16	caspase recruitment domain family, member 16	1.19733803
BE964043	SKP1	S-phase kinase-associated protein 1	1.19652667
NM_003877	SOCS2	suppressor of cytokine signaling 2	1.19069114
NM_001449	FHL1	four and a half LIM domains 1	1.18814037
AF188179	GNG8	guanine nucleotide binding protein (G protein), gamma 8	1.18730706
AW973232	NCRNA00182	non-protein coding RNA 182	1.18670863
M87507	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleuk	1.18060299
NM_018015	CXorf57	chromosome X open reading frame 57	1.17302261
BF593977	MED31	mediator complex subunit 31	1.16773356
AA935633	QKI	quaking homolog, KH domain RNA binding (mouse)	1.16413104
AI458439	IKZF2	IKAROS family zinc finger 2 (Helios)	1.16111037
AI972469	ZBTB11	zinc finger and BTB domain containing 11	1.15585841
AL574435	B4GALT1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, poly	1.15100969
AK027156	PCSK7	proprotein convertase subtilisin/kexin type 7	1.1501584
AW170571	CPNE2	copine II	1.14825046
NM_005466	MED6	mediator complex subunit 6	1.14809307
AF161419	ING3	inhibitor of growth family, member 3	1.14781254
BF345728	LOC147727	hypothetical LOC147727	1.13358853
NM_004538	NAP1L3	nucleosome assembly protein 1-like 3	1.1321794
AU147079	KRR1	KRR1, small subunit (SSU) processome component, homoc	1.13030028
BF672975	LPL	lipoprotein lipase	1.12718208
AI692879	DLG1	discs, large homolog 1 (Drosophila)	1.11956799
AV700621	TGFB1	transforming growth factor, beta receptor 1	1.1166463
AI475544	MALAT1	metastasis associated lung adenocarcinoma transcript 1 (i	1.1137717
BF063235	RLIM	ring finger protein, LIM domain interacting	1.10976026
NM_003855	IL18R1	interleukin 18 receptor 1	1.10962834
AL832081	ZNF131	zinc finger protein 131	1.10900954
AA994334	BCL10	B-cell CLL/lymphoma 10	1.10817552
NM_001616	ACVR2A	activin A receptor, type IIA	1.1064223
NM_004527	MEOX1	mesenchyme homeobox 1	1.10486457
AI949827	NFE2L3	nuclear factor (erythroid-derived 2)-like 3	1.10182886
AK091504	SFXN3	sideroflexin 3	1.10123168
AI435248	SFRS4	splicing factor, arginine/serine-rich 4	1.09788396
AU147899	B2M	beta-2-microglobulin	1.09571862
AA504356	PCBP2	poly(rC) binding protein 2	1.09206066
BE646398	MYO1G	myosin IG	1.09085471
NM_022083	FAM129A	family with sequence similarity 129, member A	1.08944272
AW361702	PSMD7	proteasome (prosome, macropain) 26S subunit, non-ATP-	1.08898631
BF725121	SKIL	SKI-like oncogene	1.08704229
BC010948	ATXN1	ataxin 1	1.08568744
BF973568	SELM	selenoprotein M	1.0847604
NM_016061	YPEL5	yippee-like 5 (Drosophila)	1.0831084
AA669336	COCH	coagulation factor C homolog, cochlin (Limulus polyphemus	1.08105049
AI916528	CYP4V2	cytochrome P450, family 4, subfamily V, polypeptide 2	1.07661865
NM_001558	IL10RA	interleukin 10 receptor, alpha	1.07201362
NM_006566	CD226	CD226 molecule	1.06845226
NM_025105	NGLY1	N-glycanase 1	1.06758597
AI041854	SFRS15	splicing factor, arginine/serine-rich 15	1.06564608
M23254	CAPN2	calpain 2, (m/II) large subunit	1.06055373
X16354	CEACAM1	carcinoembryonic antigen-related cell adhesion molecule	1.06023253

NM_005738	ARL4A	ADP-ribosylation factor-like 4A	1.05802608
NM_001924	GADD45A	growth arrest and DNA-damage-inducible, alpha	1.05583676
AI301948	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	1.05015722
NM_003473	STAM	signal transducing adaptor molecule (SH3 domain and ITA	1.04963627
AA903184	DDX50	DEAD (Asp-Glu-Ala-Asp) box polypeptide 50	1.04898691
AW438464	GOLGA4	golgin A4	1.04573533
BE220399	C19orf43	chromosome 19 open reading frame 43	1.04321216
AF147782	ETV7	ets variant 7	1.04074238
NM_004403	DFNA5	deafness, autosomal dominant 5	1.04036401
AA223204	LOC442113	similar to protein tyrosine phosphatase, non-receptor type	1.04001021
AW241752	SFRS11	splicing factor, arginine/serine-rich 11	1.0389254
AL136621	ZMYM2	zinc finger, MYM-type 2	1.03827635
NM_000880	IL7	interleukin 7	1.03804066
AA468591	CLK4	CDC-like kinase 4	1.02635143
BI868311	ARF1	ADP-ribosylation factor 1	1.02150658
W74622	SAMD4B	sterile alpha motif domain containing 4B	1.02040599
BC002646	JUN	jun oncogene	1.01443663
AW165960	PTP4A1	protein tyrosine phosphatase type IVA, member 1	1.0138522
BC039019	ST8SIA1	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase	1.01226112
AU122448	U2AF1	U2 small nuclear RNA auxiliary factor 1	1.00980915
NM_024770	METTL8	methyltransferase like 8	1.00916129
AA428240	RBMS3	RNA binding motif, single stranded interacting protein	1.00638132
AI880383	NKTR	natural killer-tumor recognition sequence	1.00500215
AW572402	RNF34	ring finger protein 34	1.00491187
NM_002502	NFKB2	nuclear factor of kappa light polypeptide gene enhancer in	1.00035606
NM_002569	FURIN	furin (paired basic amino acid cleaving enzyme)	-1.0040349
S67779	BCL6	B-cell CLL/lymphoma 6	-1.0094795
NM_023009	MARCKSL1	MARCKS-like 1	-1.0145132
NM_001877	CR2	complement component (3d/Epstein Barr virus) receptor :	-1.0240391
AF043294	BUB1	budding uninhibited by benzimidazoles 1 homolog (yeast)	-1.0432715
BG482805	IGKV4-1	immunoglobulin kappa variable 4-1	-1.0473336
AF069506	RASD1	RAS, dexamethasone-induced 1	-1.0503401
AF027205	SPINT2	serine peptidase inhibitor, Kunitz type, 2	-1.0551359
BG107456	SERTAD2	SERTA domain containing 2	-1.0685495
BE856336	FAM167A	family with sequence similarity 167, member A	-1.0818577
BG290193	ZNF703	zinc finger protein 703	-1.0850986
NM_021978	ST14	suppression of tumorigenicity 14 (colon carcinoma)	-1.0950844
X87344	HLA-DQB2	major histocompatibility complex, class II, DQ beta 2	-1.0951574
NM_006472	TXNIP	thioredoxin interacting protein	-1.0969601
AF349314	PNO1	partner of NOB1 homolog (S. cerevisiae)	-1.103313
K01144	CD74	CD74 molecule, major histocompatibility complex, class II	-1.1067794
AW193600	LOC439949	hypothetical protein LOC439949	-1.1465382
NM_021913	AXL	AXL receptor tyrosine kinase	-1.1796733
NM_006344	CLEC10A	C-type lectin domain family 10, member A	-1.2016088
U96394	IGLV1-44	immunoglobulin lambda variable 1-44	-1.2108348
AW474158	ZNF528	zinc finger protein 528	-1.2135818
NM_017412	FZD3	frizzled homolog 3 (Drosophila)	-1.2143797
NM_017911	FAM118A	family with sequence similarity 118, member A	-1.2355816
AL022324	IGLL3	immunoglobulin lambda-like polypeptide 3	-1.2392333
NM_006140	CSF2RA	colony stimulating factor 2 receptor, alpha, low-affinity (g	-1.242612
NM_005461	MAFB	v-maf musculoaponeurotic fibrosarcoma oncogene homolog	-1.2470962
U65590	IL1RN	interleukin 1 receptor antagonist	-1.2478804
AK001782	CXXC5	CXXC finger 5	-1.2525229

NM_005032	PLS3	plastin 3	-1.2608962
NM_014454	SESN1	sestrin 1	-1.2997153
NM_016184	CLEC4A	C-type lectin domain family 4, member A	-1.3114478
AV734646	FAM26F	family with sequence similarity 26, member F	-1.3136746
NM_006235	POU2AF1	POU class 2 associating factor 1	-1.3269469
AW264102	FAM43A	family with sequence similarity 43, member A	-1.3290174
AW299729	CDKL2	cyclin-dependent kinase-like 2 (CDC2-related kinase)	-1.3393427
BE139156	CASP2	caspase 2, apoptosis-related cysteine peptidase	-1.358683
NM_018384	GIMAP5	GTPase, IMAP family member 5	-1.3696036
NM_004817	TJP2	tight junction protein 2 (zona occludens 2)	-1.3739247
NM_019058	DDIT4	DNA-damage-inducible transcript 4	-1.3823462
U58515	CHI3L2	chitinase 3-like 2	-1.3906416
NM_021803	IL21	interleukin 21	-1.4107762
AI984221	COL5A3	collagen, type V, alpha 3	-1.4198621
BC003576	ACTN1	actinin, alpha 1	-1.4220032
AJ417079	RARA	retinoic acid receptor, alpha	-1.4241499
NM_004833	AIM2	absent in melanoma 2	-1.430941
NM_002356	MARCKS	myristoylated alanine-rich protein kinase C substrate	-1.4603311
NM_012072	CD93	CD93 molecule	-1.4628738
NM_002426	MMP12	matrix metalloproteinase 12 (macrophage elastase)	-1.4674305
NM_004369	COL6A3	collagen, type VI, alpha 3	-1.5021633
AL561834	TOP2A	topoisomerase (DNA) II alpha 170kDa	-1.5581727
NM_002029	FPR1	formyl peptide receptor 1	-1.5668204
NM_004390	CTSH	cathepsin H	-1.5888332
L35594	ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	-1.6218432
M60333	HLA-DRA	major histocompatibility complex, class II, DR alpha	-1.6409029
NM_012338	TSPAN12	tetraspanin 12	-1.6509415
NM_002110	HCK	hemopoietic cell kinase	-1.6590607
N66633	LHFPL2	lipoma HMGIC fusion partner-like 2	-1.7109757
NM_002583	PAWR	PRKC, apoptosis, WT1, regulator	-1.7260365
AA282495	C12orf32	chromosome 12 open reading frame 32	-1.7330491
NM_005195	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	-1.7546549
NM_000177	GSN	gelsolin (amyloidosis, Finnish type)	-1.7612447
AL040198	HEYL	hairy/enhancer-of-split related with YRPW motif-like	-1.8011696
NM_002432	MNDA	myeloid cell nuclear differentiation antigen	-1.8427189
M34455	IDO1	indoleamine 2,3-dioxygenase 1	-1.8464771
NM_018402	IL26	interleukin 26	-1.8939336
AK025298	AUTS2	autism susceptibility candidate 2	-1.8976307
NM_006498	LGALS2	lectin, galactoside-binding, soluble, 2	-1.9330548
BG485135	IGKC	immunoglobulin kappa constant	-1.9496626
NM_006332	IFI30	interferon, gamma-inducible protein 30	-1.9950294
NM_004591	CCL20	chemokine (C-C motif) ligand 20	-2.0027129
NM_031311	CPVL	carboxypeptidase, vitellogenic-like	-2.0138691
NM_001775	CD38	CD38 molecule	-2.0209288
AF228422	C15orf48	chromosome 15 open reading frame 48	-2.0396485
NM_005345	HSPA1A	heat shock 70kDa protein 1A	-2.0607916
NM_000690	ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	-2.0859511
NM_012258	HEY1	hairy/enhancer-of-split related with YRPW motif 1	-2.0924606
NM_014398	LAMP3	lysosomal-associated membrane protein 3	-2.0997785
NM_016081	PALLD	palladin, cytoskeletal associated protein	-2.1876794
AL567411	CDK5R1	cyclin-dependent kinase 5, regulatory subunit 1 (p35)	-2.4577767
M87790	IGL@	immunoglobulin lambda locus	-2.5257209
NM_001819	CHGB	chromogranin B (secretogranin 1)	-2.58262

NM_002286	LAG3	lymphocyte-activation gene 3	-2.6840389
NM_002155	HSPA6	heat shock 70kDa protein 6 (HSP70B')	-2.9177319
NM_003956	CH25H	cholesterol 25-hydroxylase	-3.0745672
Z58820	IL17A	interleukin 17A	-3.9434995

Dysregulated genes in CD8 TILs

AGI	Gene symbol	Gene Name	log2 FC
NM_006419	CXCL13	chemokine (C-X-C motif) ligand 13	5.192
NM_002674	PMCH	pro-melanin-concentrating hormone	4.67374
AU147399	CAV1	caveolin 1, caveolae protein, 22kDa	4.6688
AL519710	CADM1	cell adhesion molecule 1	4.2355
BE881590	ETV1	ets variant 1	4.12124
BF673779	TMEM155	transmembrane protein 155	3.8895
NM_024508	ZBED2	zinc finger, BED-type containing 2	3.77262
NM_001561	TNFRSF9	tumor necrosis factor receptor superfamily, member 9	3.6985
NM_001078	VCAM1	vascular cell adhesion molecule 1	3.63308
NM_003633	ENC1	ectodermal-neural cortex (with BTB-like domain)	3.4234
AI800110	SGPP2	sphingosine-1-phosphate phosphatase 2	3.36127
NM_025195	TRIB1	tribbles homolog 1 (Drosophila)	3.34527
AB014511	ATP9A	ATPase, class II, type 9A	3.33856
AA211909	TOX2	TOX high mobility group box family member 2	3.23703
AV713062	MAP3K8	mitogen-activated protein kinase kinase 8	3.17996
BC001638	ASCL1	achaete-scute complex homolog 1 (Drosophila)	3.09609
AA873350	NAMPT	nicotinamide phosphoribosyltransferase	3.07749
L21181	ICA1	islet cell autoantigen 1, 69kDa	3.06955
AI857639	PCAI1P1	phorbol-12-myristate-13-acetate-induced protein 1	3.02013
AL514445	RGS4	regulator of G-protein signaling 4	3.00727
NM_001394	DUSP4	dual specificity phosphatase 4	2.98301
H99792	GNB4	guanine nucleotide binding protein (G protein), beta polypeptide 4	2.97665
AI935096	NR4A2	nuclear receptor subfamily 4, group A, member 2	2.96055
AW150720	RDH10	retinol dehydrogenase 10 (all-trans)	2.91471
NM_000305	PON2	paraoxonase 2	2.91456
AL046017	FAM46C	family with sequence similarity 46, member C	2.86917
AV683684	RPS27	ribosomal protein S27	2.80697
AF063591	CD200	CD200 molecule	2.75053
AK026714	PELL1	pellino homolog 1 (Drosophila)	2.71535
U90273	CTLA4	cytotoxic T-lymphocyte-associated protein 4	2.66468
NM_000170	GLDC	glycine dehydrogenase (decarboxylating)	2.64799
NM_022367	SEMA4A	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and shc	2.62715
NM_016533	NINJ2	ninjurin 2	2.57526
BE674528	MAF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	2.55646
BF339445	CHN1	chimerin (chimaerin) 1	2.5553
NM_003326	TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	2.53871
AA470369	C6orf105	chromosome 6 open reading frame 105	2.46545
NM_021963	NAP1L2	nucleosome assembly protein 1-like 2	2.42185
BC003143	DUSP6	dual specificity phosphatase 6	2.36173
M17565	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	2.35728
AK025615	BCAT1	branched chain aminotransferase 1, cytosolic	2.34017
NM_018988	GFOD1	glucose-fructose oxidoreductase domain containing 1	2.32779
BF701166	TRPS1	trichorhinophalangeal syndrome 1	2.30289
NM_022162	NO2D	nucleotide-binding oligomerization domain containing 2	2.30067
AA156721	ALCAM	activated leukocyte cell adhesion molecule	2.29275
N52572	LOC285812	hypothetical protein LOC285812	2.28217
U12767	NR4A3	nuclear receptor subfamily 4, group A, member 3	2.25821
NM_002664	PLEK	pleckstrin	2.23815
AK026181	PHLDA1	pleckstrin homology-like domain, family A, member 1	2.23258
BF446578	RASGEF1A	RasGEF domain family, member 1A	2.22719
AF045452	NAB1	NGFI-A binding protein 1 (EGR1 binding protein 1)	2.2204
AA873600	SMPDL3A	sphingomyelin phosphodiesterase, acid-like 3A	2.21534
AI022882	PAM	peptidylglycine alpha-amidating monooxygenase	2.19245
U84744	LYST	lysosomal trafficking regulator	2.17376
AI961231	TOX	thymocyte selection-associated high mobility group box	2.17002
NM_014914	AGAP1	ArfGAP with GTPase domain, ankyrin repeat and PH domain 1	2.16208
NM_003670	BHLHE40	basic helix-loop-helix family, member e40	2.15248
N47315	PACSIN1	protein kinase C and casein kinase substrate in neurons 1	2.14487
NM_002847	PTPRN2	protein tyrosine phosphatase, receptor type, N polypeptide 2	2.12151
AI916948	STX11	syntaxin 11	2.1203
BC039019	ST8SIA1	ST8 alpha-N-acetylneuraminide alpha-2,8-sialyltransferase 1	2.10855
AA806965	BTNL9	butyrophilin-like 9	2.10694
AA828049	YME1L1	YME1-like 1 (S. cerevisiae)	2.09272
BF340083	SLC1A4	solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	2.09183
AW243081	CRIM1	cysteine rich transmembrane BMP regulator 1 (chordin-like)	2.08278
AI565067	KIAA1324	KIAA1324	2.06017
AI681917	IRX3	iroquois homeobox 3	2.05937
M27487	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	2.0536
AU155361	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	2.04769
NM_002286	LAG3	lymphocyte-activation gene 3	2.04412
AI671885	SLC20A1	solute carrier family 20 (phosphate transporter), member 1	2.04364
AA551142	PHACTR2	phosphatase and actin regulator 2	2.04026
AL554008	GPR56	G protein-coupled receptor 56	2.0311
NM_000572	IL10	interleukin 10	2.02592

NM_014747	RIMS3	regulating synaptic membrane exocytosis 3	2.01224
AW264102	FAM43A	family with sequence similarity 43, member A	2.01075
U16996	DUSP5	dual specificity phosphatase 5	2.00561
NM_000043	FAS	Fas (TNF receptor superfamily, member 6)	2.00521
AL541655	TMEM49	transmembrane protein 49	1.99981
AK002064	SPATS2L	spermatogenesis associated, serine-rich 2-like	1.9956
AA580082	GSPT1	G1 to S phase transition 1	1.98713
AW512550	TIGIT	T cell immunoreceptor with Ig and ITIM domains	1.98634
NM_000399	EGR2	early growth response 2	1.9778
AI692659	PRDM1	PR domain containing 1, with ZNF domain	1.97392
AA769986	NUPL1	nucleoporin like 1	1.96565
N36770	DUSP10	dual specificity phosphatase 10	1.94867
BE247450	CHD2	chromodomain helicase DNA binding protein 2	1.94488
NM_005261	GEM	GTP binding protein overexpressed in skeletal muscle	1.93466
AW290956	NDFIP2	Nedd4 family interacting protein 2	1.92701
AI937080	C14orf145	chromosome 14 open reading frame 145	1.91431
NM_021077	NMB	neuromedin B	1.89455
AA741493	ZFAND6	zinc finger, AN1-type domain 6	1.89004
AB018009	SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	1.88925
AI559701	HNRPLL	heterogeneous nuclear ribonucleoprotein L-like	1.8889
AA019893	SNAP47	synaptosomal-associated protein, 47kDa	1.88535
AW235612	ATXN1	ataxin 1	1.87947
AL110164	LIMS1	LIM and senescent cell antigen-like domains 1	1.86377
AL109824	TP53INP2	tumor protein p53 inducible nuclear protein 2	1.86131
NM_001066	TNFRSF1B	tumor necrosis factor receptor superfamily, member 1B	1.85344
NM_004485	GNG4	guanine nucleotide binding protein (G protein), gamma 4	1.85096
NM_001444	FABP5	fatty acid binding protein 5 (psoriasis-associated)	1.84424
AK027071	TSC2D1	TSC22 domain family, member 1	1.83887
AA626780	SYT11	synaptotagmin XI	1.83591
AI208342	DCAF8	DDB1 and CUL4 associated factor 8	1.81815
NM_006235	POU2AF1	POU class 2 associating factor 1	1.80659
AI810244	RILPL2	Rab interacting lysosomal protein-like 2	1.79323
NM_004867	ITM2A	integral membrane protein 2A	1.79219
AU146891	SMAD1	SMAD family member 1	1.79085
BC025250	METTL8	methyltransferase like 8	1.79049
AF065389	TFSPAN5	tetraspanin 5	1.79007
AW085505	AFF3	AF4/FMR2 family, member 3	1.78983
NM_001154	ANXA5	annexin A5	1.78682
BE439987	GAS7	growth arrest-specific 7	1.7813
D38122	FASLG	Fas ligand (TNF superfamily, member 6)	1.75508
W96225	CD44	CD44 molecule (Indian blood group)	1.74848
NM_000712	BLVRA	biliverdin reductase A	1.74314
AF450243	HAVCR2	hepatitis A virus cellular receptor 2	1.74132
NM_000611	CD59	CD59 molecule, complement regulatory protein	1.72069
NM_000237	LPL	lipoprotein lipase	1.70641
AI872284	ASB2	ankyrin repeat and SOCS box-containing 2	1.7034
AK026900	PPP1R16B	protein phosphatase 1, regulatory (inhibitor) subunit 16B	1.67881
M60333	HLA-DRA	major histocompatibility complex, class II, DR alpha	1.66871
NM_152641	ARID2	AT rich interactive domain 2 (ARID, RFX-like)	1.66598
NM_002121	HLA-DPB1	major histocompatibility complex, class II, DP beta 1	1.65709
AJ271869	SLAMF7	SLAM family member 7	1.65497
NM_002475	MYL6B	myosin, light chain 6B, alkali, smooth muscle and non-muscle	1.64738
NM_016285	KLF12	Kruppel-like factor 12	1.64502
AK000168	CD24	CD24 molecule	1.64434
AI339710	FAM108C1	family with sequence similarity 108, member C1	1.639
AI420319	SERP2	stress-associated endoplasmic reticulum protein family member 2	1.63145
BC004371	APLP2	amyloid beta (A4) precursor-like protein 2	1.6296
AA215701	SNORA28	small nucleolar RNA, H/ACA box 28	1.62287
AK056852	LOC144571	hypothetical protein LOC144571	1.62089
BE675139	CREB3L2	cAMP responsive element binding protein 3-like 2	1.6173
AA250935	LPXN	leupaxin	1.61531
AB023135	ICOS	inducible T-cell co-stimulator	1.60998
AW157571	JAKMIP1	janus kinase and microtubule interacting protein 1	1.60753
AI091372	CSRNP1	cysteine-serine-rich nuclear protein 1	1.60698
BF739885	SETBP1	SET binding protein 1	1.60499
NM_021995	UTS2	urotensin 2	1.59971
BC009205	C6orf114	chromosome 6 open reading frame 114	1.59368
BC038440	GALNT1	UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 1	1.59159
AF125393	RAB27A	RAB27A, member RAS oncogene family	1.58257
AA813332	DFNB31	deafness, autosomal recessive 31	1.57924
AL833750	SYTL3	synaptotagmin-like 3	1.57757
NM_006399	BATF	basic leucine zipper transcription factor, ATF-like	1.57392
BF001714	CPT1A	carnitine palmitoyltransferase 1A (liver)	1.56721
AI809325	GTSF1L	gametocyte specific factor 1-like	1.56358
AW438464	GOLGA4	golgin A4	1.56244
NM_025151	RAB11FIP1	RAB11 family interacting protein 1 (class I)	1.55677

AA504356	PCBP2	poly(rC) binding protein 2	1.55536
AW242297	MAP7	microtubule-associated protein 7	1.54566
AA935633	QKI	quaking homolog, KH domain RNA binding (mouse)	1.54515
AU147899	B2M	beta-2-microglobulin	1.543
AA262583	LRRFIP1	leucine rich repeat (in FLII) interacting protein 1	1.53836
NM_021983	HLA-DRB4	major histocompatibility complex, class II, DR beta 4	1.53828
NM_002984	CCL4	chemokine (C-C motif) ligand 4	1.53367
NM_003234	TFRC	transferrin receptor (p90, CD71)	1.52032
NM_001613	ACTA2	actin, alpha 2, smooth muscle, aorta	1.51754
BE046511	FNBP1	formin binding protein 1	1.51752
AI760495	CYCS	cytochrome c, somatic	1.51663
AF070569	C17orf91	chromosome 17 open reading frame 91	1.51549
BF514079	KLF4	Kruppel-like factor 4 (gut)	1.51481
AI826881	CTNNA1	catenin (cadherin-associated protein), alpha 1, 102kDa	1.51221
AL037917	MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	1.50791
R43202	AKAP5	A kinase (PRKA) anchor protein 5	1.49997
AL047052	LOC100190986	hypothetical LOC100190986	1.4999
BF244402	FBXO32	F-box protein 32	1.49841
NM_000647	CCR2	chemokine (C-C motif) receptor 2	1.49261
AW973232	NCRNA00182	non-protein coding RNA 182	1.49132
AI830331	KDM6B	lysine (K)-specific demethylase 6B	1.4877
NM_002133	HMOX1	heme oxygenase (decycling) 1	1.48767
BF111651	PPAPDC1B	phosphatidic acid phosphatase type 2 domain containing 1B	1.4866
M29383	IFNG	interferon, gamma	1.48199
BE299456	C16orf45	chromosome 16 open reading frame 45	1.47793
AI819150	ASXL1	additional sex combs like 1 (Drosophila)	1.47121
D14826	CREM	cAMP responsive element modulator	1.47079
NM_004360	CDH1	cadherin 1, type 1, E-cadherin (epithelial)	1.46955
NM_018413	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	1.46912
BC042665	CD80	CD80 molecule	1.46883
NM_002923	RGS2	regulator of G-protein signaling 2, 24kDa	1.4634
NM_003811	TNFSF9	tumor necrosis factor (ligand) superfamily, member 9	1.46236
AA828371	VPS13C	vacuolar protein sorting 13 homolog C (S. cerevisiae)	1.45718
AV726956	BEX5	brain expressed, X-linked 5	1.45523
BG231494	METRNL	meteorin, glial cell differentiation regulator-like	1.45093
AW293441	SQSTM1	sequestosome 1	1.44079
AW237307	CLECL1	C-type lectin-like 1	1.43894
AI263909	RHOB	ras homolog gene family, member B	1.43544
AF050145	IDS	iduronate 2-sulfatase	1.43294
AA007424	LOC6444656	hypothetical protein LOC6444656	1.43107
NM_021603	FXYD2	FXYD domain containing ion transport regulator 2	1.42949
AI768512	WNK1	WNK lysine deficient protein kinase 1	1.42943
U58515	CHI3L2	chitinase 3-like 2	1.42683
AI263819	SRGAP2	SLIT-ROBO Rho GTPase activating protein 2	1.42413
NM_000575	IL1A	interleukin 1, alpha	1.42031
AA872471	SNRPA1	small nuclear ribonucleoprotein polypeptide A'	1.41388
AA805939	REV3L	REV3-like, catalytic subunit of DNA polymerase zeta (yeast)	1.41285
BF446719	WIPF1	WAS/WASL interacting protein family, member 1	1.39244
NM_020179	C11orf75	chromosome 11 open reading frame 75	1.39108
AV713773	MCOLN2	mucolipin 2	1.38471
BC005022	SNX9	sorting nexin 9	1.38373
NM_002922	RGS1	regulator of G-protein signaling 1	1.3835
AF130079	PRO2852	hypothetical protein PRO2852	1.38342
NM_005780	LHFP	lipoma HMGIC fusion partner	1.38288
AL834350	PPP2R5C	protein phosphatase 2, regulatory subunit B', gamma isoform	1.38129
NM_001779	CD58	CD58 molecule	1.38075
AI936531	SFRS18	splicing factor, arginine/serine-rich 18	1.37935
AA742596	RBM6	RNA binding motif protein 6	1.37755
NM_003272	GPR137B	G protein-coupled receptor 137B	1.37694
NM_173648	CDCDC141	coiled-coil domain containing 141	1.37504
NM_004219	PTTG1	pituitary tumor-transforming 1	1.3719
D64109	TOB2	transducer of ERBB2, 2	1.36698
NM_014800	ELMO1	engulfment and cell motility 1	1.3663
AA468591	CLK4	CDC-like kinase 4	1.36121
AA807529	MCM5	minichromosome maintenance complex component 5	1.3602
BE646414	GGA2	golgi-associated, gamma adaptin ear containing, ARF binding protein 2	1.35834
AI692879	DLG1	discs, large homolog 1 (Drosophila)	1.35731
AL574435	B4GALT1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	1.35184
NM_002460	IRF4	interferon regulatory factor 4	1.35146
NM_025105	NGLY1	N-glycanase 1	1.34825
BF576458	NCOA1	nuclear receptor coactivator 1	1.34751
BE464843	SR140	U2-associated SR140 protein	1.34522
NM_015895	GMNN	geminin, DNA replication inhibitor	1.34442
NM_001716	CXCR5	chemokine (C-X-C motif) receptor 5	1.3375
AF031824	CST7	cystatin F (leukocystatin)	1.3363
AW276078	LOC387763	hypothetical protein LOC387763	1.33619

BG231961	MIR155HG	MIR155 host gene (non-protein coding)	1.33305
NM_000594	TNF	tumor necrosis factor (TNF superfamily, member 2)	1.32983
AB029316	RNF19A	ring finger protein 19A	1.3292
AL050378	DKFZP586I1420	hypothetical protein DKFZp586I1420	1.32834
NM_001908	CTSB	cathepsin B	1.32677
NM_018639	WSB2	WD repeat and SOCS box-containing 2	1.32586
NM_003740	KCNK5	potassium channel, subfamily K, member 5	1.32022
AA994334	BCL10	B-cell CLL/lymphoma 10	1.31663
AA715041	MLL	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila)	1.31459
NM_014298	QPRT	quinolinate phosphoribosyltransferase	1.31401
NM_002104	GZMK	granzyme K (granzyme 3; tryptase II)	1.31343
AA223204	LOC442113	similar to protein tyrosine phosphatase, non-receptor type 11	1.31233
NM_000130	F5	coagulation factor V (proaccelerin, labile factor)	1.311
AK096036	FLJ38717	FLJ38717 protein	1.30615
AA448956	CAMK2D	calcium/calmodulin-dependent protein kinase II delta	1.30449
AL562860	MBNL1	muscleblind-like (Drosophila)	1.30324
BC000006	ATP1B1	ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	1.29939
AA584310	CTHRC1	collagen triple helix repeat containing 1	1.29792
NM_005410	SEPP1	selenoprotein P, plasma, 1	1.29773
NM_004999	MYO6	myosin VI	1.29728
AI765445	BTG3	BTG family, member 3	1.295
BC046241	TRAPPC10	trafficking protein particle complex 10	1.29445
AI659561	LRBA	LPS-responsive vesicle trafficking, beach and anchor containing	1.29381
U84246	NEU1	sialidase 1 (lysosomal sialidase)	1.29353
BE676543	ZCCHC2	zinc finger, CCHC domain containing 2	1.28986
AL136621	ZMYM2	zinc finger, MYM-type 2	1.28782
AW367507	RAB18	RAB18, member RAS oncogene family	1.28764
BE544837	PHF19	PHD finger protein 19	1.28757
AK025272	TAGAP	T-cell activation RhoGTPase activating protein	1.28569
AI986192	SERPINB9	serpin peptidase inhibitor, clade B (ovalbumin), member 9	1.28547
NM_002245	KCNK1	potassium channel, subfamily K, member 1	1.28492
AL831839	DENND1B	DENN/MADD domain containing 1B	1.282
AV724325	SAMD12	sterile alpha motif domain containing 12	1.27285
M28590	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	1.27007
AI689935	HBP1	HMG-box transcription factor 1	1.26746
AU120130	LOC728153	similar to FAM133B protein	1.26727
AI914323	MIAT	myocardial infarction associated transcript (non-protein coding)	1.26163
NM_017522	LRP8	low density lipoprotein receptor-related protein 8, apolipoprotein e receptor	1.26055
AI239832	UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)	1.25986
NM_005384	FIL3	nuclear factor, interleukin 3 regulated	1.25344
NM_014661	FAMS5B	family with sequence similarity 53, member B	1.25257
AK023140	C3orf64	chromosome 3 open reading frame 64	1.24708
NM_022365	DNAJC1	DnaJ (Hsp40) homolog, subfamily C, member 1	1.24584
NM_000540	RYR1	ryanodine receptor 1 (skeletal)	1.24581
BF126155	S100A10	S100 calcium binding protein A10	1.24551
NM_019886	CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	1.24449
NM_005231	CTTN	cortactin	1.24206
BF981280	MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	1.24093
AF100540	SH2D1A	SH2 domain protein 1A	1.2396
D13889	ID1	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	1.2394
NM_022337	RAB38	RAB38, member RAS oncogene family	1.23893
R15072	SLC16A14	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	1.23711
AW978896	TRA2A	transformer 2 alpha homolog (Drosophila)	1.23685
AA603041	LOC150381	hypothetical LOC150381	1.23389
AW275658	HECTD1	HECT domain containing 1	1.23335
NM_004311	ARL3	ADP-ribosylation factor-like 3	1.23246
BF439282	RAPGEF2	Rap guanine nucleotide exchange factor (GEF) 2	1.2322
AF345567	GPR174	G protein-coupled receptor 174	1.22723
BC028028	STXBP3	syntaxin binding protein 3	1.22406
L35594	ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	1.22176
NM_016448	DTL	denticleless homolog (Drosophila)	1.22006
AK024341	USP34	ubiquitin specific peptidase 34	1.21936
BF971873	TMEM107	transmembrane protein 107	1.21803
L48516	PON3	paraoxonase 3	1.21792
BE964043	SKP1	S-phase kinase-associated protein 1	1.21769
AA279462	PRKRA	protein kinase, interferon-inducible double stranded RNA dependent activator	1.21547
BC000091	ATG7	ATG7 autophagy related 7 homolog (<i>S. cerevisiae</i>)	1.21477
AA209239	ABHD6	abhydrolase domain containing 6	1.21373
AK091504	SFXN3	sideroflexin 3	1.21346
AA748418	MCTP2	multiple C2 domains, transmembrane 2	1.21271
AA657818	TOX4	TOX high mobility group box family member 4	1.21206
NM_006599	NFAT5	nuclear factor of activated T-cells 5, tonicity-responsive	1.21162
N49935	RASSF4	Ras association (RalGDS/AF-6) domain family member 4	1.20899
AW361702	PSMD7	proteasome (prosome, macropain) 26S subunit, non-ATPase, 7	1.20527
M38083	NAGA	N-acetylgalactosaminidase, alpha-	1.20398
BE676408	HECA	headcase homolog (Drosophila)	1.2032

AW276914	MBNL2	muscleblind-like 2 (Drosophila)	1.20261
NM_000376	VDR	vitamin D (1,25- dihydroxyvitamin D3) receptor	1.19939
NM_006763	BTG2	BTG family, member 2	1.19526
AI085338	CASZ1	castor zinc finger 1	1.19448
AW235671	THAP2	THAP domain containing, apoptosis associated protein 2	1.19313
BG231932	TPP1	tripeptidyl peptidase I	1.19254
AL544094	TMX4	thioredoxin-related transmembrane protein 4	1.19086
NM_004900	APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	1.19035
H15278	TULP4	tubby like protein 4	1.18888
NM_004327	BCR	breakpoint cluster region	1.18774
H43976	MORF4L2	mortality factor 4 like 2	1.18765
AW292752	OFD1	oral-facial-digital syndrome 1	1.18612
AF131780	TXNDC11	thioredoxin domain containing 11	1.18487
BF002296	JMJD1C	jumonji domain containing 1C	1.18482
NM_018986	SH3TC1	SH3 domain and tetratricopeptide repeats 1	1.18396
BC036731	ZBTB24	zinc finger and BTB domain containing 24	1.18298
AL832081	ZNF131	zinc finger protein 131	1.18258
H48516	DLEU2	deleted in lymphocytic leukemia 2 (non-protein coding)	1.18123
NM_003645	SLC27A2	solute carrier family 27 (fatty acid transporter), member 2	1.1812
AI919493	RRN3P2	RNA polymerase I transcription factor homolog (S. cerevisiae) pseudogene 2	1.18002
AF237813	ABAT	4-aminobutyrate aminotransferase	1.17737
NM_003319	TTN	titin	1.17736
BC031525	PTPRC	protein tyrosine phosphatase, receptor type, C	1.17619
NM_001995	ACSL1	acyl-CoA synthetase long-chain family member 1	1.17446
AF251061	NCALD	neurocalcin delta	1.17101
NM_000389	CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	1.16986
BC013132	GDAP2	ganglioside induced differentiation associated protein 2	1.16972
CA391618	GPBP1L1	GC-rich promoter binding protein 1-like 1	1.16945
NM_018638	ETNK1	ethanolamine kinase 1	1.16872
AW157311	C16orf87	chromosome 16 open reading frame 87	1.16702
AI202969	OSBPL3	oxysterol binding protein-like 3	1.16653
U08015	NFATC1	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1	1.16552
NM_004384	CSNK1G3	casein kinase 1, gamma 3	1.16484
NM_018454	NUSAP1	nucleolar and spindle associated protein 1	1.16479
AA504595	DCP2	DCP2 decapping enzyme homolog (S. cerevisiae)	1.16105
NM_004523	KIF11	kinesin family member 11	1.15815
NM_003243	TGFB3	transforming growth factor, beta receptor III	1.15802
AK001782	CXXC5	CXXC finger 5	1.15781
U20350	CX3CR1	chemokine (C-X3-C motif) receptor 1	1.15749
NM_022349	MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	1.15526
BF732480	TMEM64	transmembrane protein 64	1.15309
BF514975	UFM1	ubiquitin-fold modifier 1	1.15044
AK090692	FYN	FYN oncogene related to SRC, FGR, YES	1.14906
NM_014380	NGFRAP1	nerve growth factor receptor (TNFRSF16) associated protein 1	1.14906
NM_025079	ZC3H12A	zinc finger CCCH-type containing 12A	1.14607
AF054818	CD84	CD84 molecule	1.14566
AB051513	ZC3H12C	zinc finger CCCH-type containing 12C	1.14441
NM_004356	CD81	CD81 molecule	1.14267
AI949827	NFE2L3	nuclear factor (erythroid-derived 2)-like 3	1.14198
AI880383	NKTR	natural killer-tumor recognition sequence	1.13965
AB017493	KLF6	Kruppel-like factor 6	1.13652
AI093579	ITGAV	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	1.13438
AI825832	CDHR1	cadherin-related family member 1	1.13248
NM_016061	YPEL5	yippee-like 5 (Drosophila)	1.12967
BC030578	EIF4G3	eukaryotic translation initiation factor 4 gamma, 3	1.12843
J03223	SRGN	serglycin	1.12832
BU950380	ZBTB1	zinc finger and BTB domain containing 1	1.12676
AB023212	PCNX	pecanex homolog (Drosophila)	1.12448
AB077208	TYMS	thymidylate synthetase	1.11932
NM_003405	YWHAH	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta	1.11676
NM_004184	WARS	tryptophanyl-tRNA synthetase	1.11521
BC008300	PCNXL2	pecanex-like 2 (Drosophila)	1.11288
BC015430	SELI	selenoprotein I	1.11119
BG913589	DNAJC3	DnaJ (Hsp40) homolog, subfamily C, member 3	1.11169
AK027074	ZNF451	zinc finger protein 451	1.11054
NM_022065	THADA	thyroid adenoma associated	1.1098
W79537	CELF2	CUGBP, Elav-like family member 2	1.10942
BC001465	HBS1L	HBS1-like (S. cerevisiae)	1.10801
NM_002436	MPP1	membrane protein, palmitoylated 1, 55kDa	1.1076
BQ944989	STRAP	serine/threonine kinase receptor associated protein	1.10709
NM_001992	F2R	coagulation factor II (thrombin) receptor	1.10679
NM_003358	UGCG	UDP-glucose ceramide glucosyltransferase	1.10648
AB032261	SCD	stearoyl-CoA desaturase (delta-9-desaturase)	1.1059
BG031974	IGF2R	insulin-like growth factor 2 receptor	1.10545
BF593977	MED31	mediator complex subunit 31	1.10531
AA903184	DDX50	DEAD (Asp-Glu-Ala-Asp) box polypeptide 50	1.10438

AF220023	TRIM4	tripartite motif-containing 4	-1.7122
NM_005010	NRCAM	neuronal cell adhesion molecule	-1.7688
NM_006417	IFI44	interferon-induced protein 44	-1.7792
AF349314	PNO1	partner of NOB1 homolog (S. cerevisiae)	-1.7843
NM_002526	NT5E	5'-nucleotidase, ecto (CD73)	-1.7892
NM_005232	EPHA1	EPH receptor A1	-1.8223
NM_002547	OPHN1	oligophrenin 1	-1.8232
AA005361	C2orf89	chromosome 2 open reading frame 89	-1.8705
NM_006472	TXNIP	thioredoxin interacting protein	-1.8708
AL136179	SOX4	SRY (sex determining region Y)-box 4	-1.8742
AI244661	MPP7	membrane protein, palmitoylated 7 (MAGUK p55 subfamily member 7)	-1.906
BE139156	CASP2	caspase 2, apoptosis-related cysteine peptidase	-1.9088
AW474158	ZNF528	zinc finger protein 528	-1.9122
AF288571	LEF1	lymphoid enhancer-binding factor 1	-1.9223
NM_024906	SCD5	stearoyl-CoA desaturase 5	-1.9368
NM_003328	TXK	TXK tyrosine kinase	-1.9895
AK025298	AUTS2	autism susceptibility candidate 2	-2.0109
NM_005825	RASGRP2	RAS guanyl releasing protein 2 (calcium and DAG-regulated)	-2.0246
NM_000574	CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	-2.0424
NM_007334	KLRD1	killer cell lectin-like receptor subfamily D, member 1	-2.0424
AJ417079	RARA	retinoic acid receptor, alpha	-2.1008
NM_001838	CCR7	chemokine (C-C motif) receptor 7	-2.1201
NM_001877	CR2	complement component (3d/Epstein Barr virus) receptor 2	-2.1209
AB007892	CDC5L	CDC5 cell division cycle 5-like (S. pombe)	-2.126
NM_020404	CD248	CD248 molecule, endosialin	-2.231
NM_002467	MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	-2.2583
NM_020405	PLXDC1	plexin domain containing 1	-2.2832
NM_003956	CH25H	cholesterol 25-hydroxylase	-2.2836
AB014719	APBA2	amyloid beta (A4) precursor protein-binding, family A, member 2	-2.3187
AI082078	ACTN1	actinin, alpha 1	-2.4699
NM_021813	BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	-2.4836
NM_006433	GNLY	granulysin	-2.7134
AA156873	PELO	pelota homolog (Drosophila)	-2.7464
NM_002261	KLRC3	killer cell lectin-like receptor subfamily C, member 3	-2.7661
NM_002155	HSPA6	heat shock 70kDa protein 6 (HSP70B')	-2.8485
AL442092	LRRN3	leucine rich repeat neuronal 3	-2.9263
NM_006746	SCML1	sex comb on midleg-like 1 (Drosophila)	-2.9851
NM_005345	HSPA1A	heat shock 70kDa protein 1A	-2.9989

Supplemental Table 2. Disrupted pathways in TILs of patients with FL.

Disrupted pathways in CD4 TILs	No. of Genes	Gene symbol
Nicotinate and Nicotinamide Metabolism	7	NEK2, PRKCQ, CD38, NAMPT, PLK1, MAP3K8, ACVR2A
Role of Cytokines in Communication	5	IL26, IL1RN, IL22, IL17F, IL17A
T Helper Cell Differentiation	5	STAT4, IL10RA, FOXP3, IL17F, IL17A
Primary Immunodeficiency Signaling	4	IGKC, IGL@, IGHM, IGHD
Huntington's Disease Signaling	8	PRKCQ, HSPA1L, HSPA1A, HSPA6, CASP1, CYCS, ITPR1, CDK5R1
Leukocyte Extravasation Signaling	7	WIPF1, PRKCQ, NCF4, MAP3K4, MMP12, ACTN1, CTNND1
Altered T Cell and B Cell Signaling	4	IL1RN, LTA, IL22, IL17A
CD27 Signaling in Lymphocytes	3	CYCS, MAP3K8, MAP3K4
Inositol Phosphate Metabolism	5	NEK2, PRKCQ, PLK1, MAP3K8, ACVR2A
Mitotic Roles of Polo-Like Kinase	3	PPP2R5C, PPP2R2B, PLK1
mTOR Signaling	5	PRKCQ, DDIT4, PPP2R5C, RHOC, PPP2R2B
NF-κB Signaling	5	PRKCQ, BMPR1A, IL1RN, LTA, MAP3K8
Cholecystokinin/Gastrin-mediated Signaling	4	PRKCQ, IL1RN, RHOC, ITPR1
IL-22 Signaling	2	IL22RA2, IL22
Breast Cancer Regulation by Stathmin1	6	ARHGEF12, PRKCQ, TUBA1A, PPP2R5C, PPP2R2B, ITPR1
PI3K/AKT Signaling	4	PPP2R5C, PPP2R2B, MAP3K8, THEM4
Cell Cycle Regulation by BTG Family Proteins	2	PPP2R5C, PPP2R2B
Reelin Signaling in Neurons	3	ARHGEF12, LRP8, CDK5R1
TGF-β Signaling	3	BMPR1A, ACVR1, ACVR2A
Systemic Lupus Erythematosus Signaling	4	IL1RN, IGKC, IGL@, IGHM
Cell Cycle: G2/M DNA Damage Checkpoint	2	PLK1, SKP1
Ceramide Signaling	3	PPP2R5C, PPP2R2B, CYCS
GNRH Signaling	4	PRKCQ, MAP3K8, ITPR1, MAP3K4
Regulation of Actin-based Motility by Rho	3	WIPF1, RHOC, GSN
Hepatic Cholestasis	4	PRKCQ, SREBF1, IL1RN, MAP3K4
Synaptic Long Term Depression	4	PRKCQ, PPP2R5C, PPP2R2B, ITPR1
CDK5 Signaling	3	PPP2R5C, PPP2R2B, CDK5R1
RANK Signaling in Osteoclasts	3	MAP3K8, MAP3K4, GSN
Dendritic Cell Maturation	4	STAT4, COL5A3, IL1RN, LTA
Calcium-induced T Lymphocyte Apoptosis	2	PRKCQ, ITPR1
Lysine Degradation	4	FURIN, PPP2R5C, CASP1, YME1L1
HGF Signaling	3	PRKCQ, MAP3K8, MAP3K4
Semaphorin Signaling in Neurons	2	ARHGEF12, RHOC
TREM1 Signaling	2	NOD2, CASP1
Lymphotoxin β Receptor Signaling	2	LTA, CYCS
Parkinson's Signaling	1	CYCS
Renin-Angiotensin Signaling	3	PRKCQ, PTGER2, ITPR1
RhoA Signaling	3	SEPT8, ARHGEF12, SEPT2
Actin Cytoskeleton Signaling	4	ARHGEF12, SSH2, GSN, ACTN1
Regulation of eIF4 and p70S6K Signaling	3	PPP2R5C, PPP2R2B, EIF1
Granzyme B Signaling	1	CYCS
Phenylalanine, Tyrosine and Tryptophan Biosynthesis	1	ENO2
IL-12 Signaling and Production in Macrophages	3	STAT4, PRKCQ, MAP3K8
Glyoxylate and Dicarboxylate Metabolism	1	HYI
Wnt/β-catenin Signaling	4	PPP2R5C, PPP2R2B, ACVR1, ACVR2A
IL-10 Signaling	2	IL1RN, IL10RA
IL-15 Signaling	2	AXL, IL17A
Endothelin-1 Signaling	4	PRKCQ, CASP1, PTGER2, ITPR1
ILK Signaling	4	PPP2R5C, RHOC, PPP2R2B, ACTN1
p70S6K Signaling	3	PRKCQ, PPP2R5C, PPP2R2B

Disrupted pathways in CD8 TILs	No. of Genes	Gene symbol
Antigen Presentation Pathway	10	B2M,IFNG, HLA-DMA,HLA-DRB4,HLA-DRA,HLA-DQA1, HLA-DRB1, CD74, HLA-DPB1, HLA-DPA1
Crosstalk between Dendritic Cells and NK Cells	16	IFNG,KIR3DL1,KIR2DL3, KLRD1,ACTA2,HLA-DRB1, FAS, CAMK2D, HLA-DRB4,KIR2DL5A
Allograft Rejection Signaling	15	B2M,HLA-DMA,IFNG,IL10,HLA-DQA1,HLA-DRB1,HLA-DQB1, HLA-DPA1, FAS, HLA-DRB4
T Helper Cell Differentiation	14	HLA-DMA,IFNG, IL10,IL21R,HLA-DQA1,HLA-DRB1,HLA-DQB1, IL17A,ICOS,CD8
Altered T Cell and B Cell Signaling	15	HLA-DMA,IFNG, IL1A,IL10,HLA-DQA1,HLA-DRB1,HLA-DQB1, FAS,IL17A,CD80
IL-4 Signaling	10	PIK3R3,HLA-DMA,NFAT5,IRF4,PIK3C2A,HLA-DRA,HLA-DQA1, HLA-DRB1, NFATC1,HLA-DQB1
Communication between Immune Cells	12	B2M,IFNG, IL1A,CCL4,HLA-DRB4,CD80, IL10,HLA-DRA, HLA-DRB1, CCL3
Graft-versus-Host Disease Signaling	12	KIR2DL3, IFNG, HLA-DMA,IL1A,CD80,HLA-DRA,HLA-DQA1, HLA-DRB1, HLA-DQB1, TNF
iCOS-iCOSL Signaling	16	HLA-DMA, CAMK4, PIK3C2A, HLA-DQA1, TRAT1, HLA-DRB1,NFATC1,HLA-DQB1, PTPRC, PIK3R3
Dendritic Cell Maturation	16	B2M,HLA-DMA,IL1A,PIK3C2A,IL10,HLA-DQA1,HLA-DRB1, CD58, HLA-DQB1,PIK3R3
Systemic Lupus Erythematosus Signaling	14	IL1A,CAMK4,PIK3C2A,IL10,IGKC,NFATC1,PTPRC,PIK3R3,NFAT5,CD80
Death Receptor Signaling	9	CASP2, TNFRSF25,CYCS,CFLAR, TNFRSF1B,TNF,FAS,FASLG, CASP10
Virus Entry via Endocytic Pathways	12	B2M,PIK3R3,FYN,CD55,PIK3C2A,ACTA2,CAV1,ITGA6,ITGA5,TFRC
Hepatic Fibrosis / Hepatic Stellate Cell Activation	15	IFNG, IL18RAP, IL1A, VCAM1, IL10, ACTA2, MYL6B, FAS, LY96, CSF1
Primary Immunodeficiency Signaling	6	IL7R,PTPRC,ICOS,IGKC,IGHM,IGHD
CD28 Signaling	10	HLA-DMA,FYN,CAMK4,PIK3C2A,HLA-DQA1,HLA-DRB1, NFATC1, HLA-DQB1, CTLA4, PTPRC
Autoimmune Thyroid Disease Signaling	9	HLA-DMA,CD80, IL10,HLA-DRA,HLA-DQA1,HLA-DRB1, HLA-DQB1, FAS,FASLG
Integrin Signaling	19	FYN,TSPAN5,PIK3C2A,ACTA2,LIMS1,ITGA6,ITGA5,ITGB8,BRAF, ACTN1
PI3K/AKT Signaling	10	CD81,PTPRC,FYN,NFAT5,CAMK4,CAMK2D,BCL10,NFATC1, PLEKHA2,CR2
Caveolar-mediated Endocytosis Signaling	10	B2M,FYN,CD55,ACTA2,ITGAV,CAV1,ITGA6,ITGA5,ITGA1,ITGB8
Myc Mediated Apoptosis Signaling	8	PIK3R3,MYC, YWHAH,PIK3C2A,IGF1R,CYCS,FAS,FASLG
T Cell Receptor Signaling	10	PTPRC,PIK3R3,FYN,TKK,NFAT5,CAMK4,PIK3C2A,BCL10,NFATC1,CTLA4
CTLA4 Signaling in Cytotoxic T Lymphocytes	12	PIK3R3,FYN,HLA-DMA,CD80, PPP2R5C, PIK3C2A, HLA-DRA, HLA-DQA1, TRAT1, HLA-DRB1
Glioma Invasiveness Signaling	7	PIK3R3,F2R,PIK3C2A,RHOB,ITGAV,CD44,FNBP1
IL-9 Signaling	5	PIK3R3,SOCS3,PIK3C2A,CISH,TNF
HMGB1 Signaling	9	PIK3R3,IFNG, IL1A, VCAM1, PIK3C2A, RHOB, TNFRSF1B, TNF,FNBP1
Role of NFAT in Regulation of the Immune Response	16	HLA-DMA, AKAP5, FYN, CAMK4, PIK3C2A, CSNK1G3, GNA12, HLA-DQA1, HLA-DRB1, NFATC1
mTOR Signaling	10	PIK3R3,HMOX1,RPS27,PPP2R5C,PIK3C2A,RHOB,EIF4G3,RPS27L,FNBP1,EIF4E
Clathrin-mediated Endocytosis Signaling	12	MYO6,PIK3R3,SNX9,F2R,PIK3C2A,SH3GL3,ACTA2,ITGA5,TFRC,LDLRAP1
NF-κB Activation by Viruses	10	PIK3R3,IL1A,PIK3C2A,BCL10,TGFBR3,IGF1R,MAP3K8, TNFRSF1B,IGF2R,TNF
Acute Myeloid Leukemia Signaling	7	PIK3R3,BRAF,MYC,PIK3C2A,RARA,LEF1,FLT3LG
IL-10 Signaling	7	HMOX1,IL18RAP,SOCS3,IL1A,BLVRA,IL10,TNF
IL-8 Signaling	13	VCAM1,PIK3C2A,GNA12,PIK3R3,BRAF,HMOX1,GNB4,CDH1, CCND2, RHOB
Ceramide Signaling	7	PIK3R3,PPP2R5C,PIK3C2A,CYCS,TNFRSF1B,TNF,KSR1
Actin Cytoskeleton Signaling	14	TIAM1,F2R,PIK3C2A,ACTN1, GNA12, ACTA2, ITGA5, PIP5K1B, MYL6B, PIK3R3
Pathogenesis of Multiple Sclerosis	2	CCL4, CCL3

CCR5 Signaling	6	GNB4, CAMK4, CCL4, CCL3, FAS, FASLG
Thyroid Cancer Signaling	4	BRAF, MYC, CDH1, LEF1
ILK Signaling	13	PPP2R5C, PIK3C2A, ACTA2, LIMS1, ITGB8, MYL6B, PIK3R3, MYC, RHOB, ACTN1
Inositol Phosphate Metabolism	9	PIK3R3, BRAF, INPP4B, INPP1, INPP5F, PIK3C2A, TRAT1, MAP3K8, PIP5K1B
RhoA Signaling	8	RAPGEF2, GNA12, EPHA1, ACTA2, IGF1R, PIP5K1B, MYL6B, SEPT2
cAMP-mediated Signaling	12	BRAF, AKAP5, RGS2, AKAP2/PALM2-AKAP2, CAMK4, CAMK2D, PDE3B, PDE9A, DUSP6, CREM
Apoptosis Signaling	8	CASP2, CYCS, TNFRSF1B, TNF, FAS, FASLG, MCL1, CASP10
ERK/MAPK Signaling	13	FYN, PPP2R5C, YWHAH, PIK3C2A, DUSP6, ITGA5, NFATC1, EIF4E, KSR1, PIK3R3
Role of Cytokines in Communication	5	IFNG, IL1A, IL10, TNF, IL17A
LXR/RXR Activation	8	IL18RAP, SCD, LY96, IL1A, LPL, TNFRSF1B, TNF, PON3
Rac Signaling	8	PIK3R3, TIAM1, PIK3C2A, CYFIP1, CD44, ITGA5, PIP5K1B, NCKAP1
Cytotoxic T Lymphocyte-mediated Apoptosis	12	B2M, HLA-DMA, HLA-DRB4, HLA-DRA, HLA-DQA1, HLA-DRB1, CYCS, HLA-DQB1, HLA-DPB1, HLA-DPA1
SAPK/JNK Signaling	7	PIK3R3, GADD45A, PIK3C2A, DUSP10, GNA12, NFATC1, DUSP4
Wnt/ β -catenin Signaling	11	SOX4, MYC, CDH1, SOX6, PPP2R5C, WNT10A, CSNK1G3, TGFB3, RARA, CD44

Supplemental Table 3

symbol	NAME	fold change in CD4	fold change in CD8
PMCH	pro-melanin-concentrating hormone	3.20	4.67
NR4A2	nuclear receptor subfamily 4, group A, member 2	3.14	2.96
NAMPT	nicotinamide phosphoribosyltransferase	2.58	3.08
CHN1	chimerin (chimaerin) 1	2.34	2.56
TNFRSF9	tumor necrosis factor receptor superfamily, member 9	2.26	3.70
NAP1L2	nucleosome assembly protein 1-like 2	2.25	2.42
PELI1	pellino homolog 1 (Drosophila)	2.17	2.72
MAP3K8	mitogen-activated protein kinase kinase kinase 8	2.16	3.18
PMAIP1	phorbol-12-myristate-13-acetate-induced protein 1	2.13	3.02
GZMK	granzyme K (granzyme 3; tryptase II)	2.11	1.31
NUPL1	nucleoporin like 1	2.11	1.97
YME1L1	YME1-like 1 (S. cerevisiae)	2.02	2.09
SNORA28	small nucleolar RNA, H/ACA box 28	1.97	1.62
GSPT1	G1 to S phase transition 1	1.92	1.99
DUSP4	dual specificity phosphatase 4	1.89	2.98
ASXL1	additional sex combs like 1 (Drosophila)	1.88	1.47
ATP1B1	ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	1.87	1.30
SLC20A1	solute carrier family 20, member 1	1.84	2.04
ZBTB24	zinc finger and BTB domain containing 24	1.82	1.18
SNRPA1	small nuclear ribonucleoprotein polypeptide A'	1.82	1.41
CHD2	chromodomain helicase DNA binding protein 2	1.77	1.94
CYCS	cytochrome c, somatic	1.74	1.52
RASGEF1A	RasGEF domain family, member 1A	1.68	2.23
BEX5	brain expressed, X-linked 5	1.67	1.46
CD44	CD44 molecule (Indian blood group)	1.66	1.53
MORF4L2	mortality factor 4 like 2	1.65	1.19
CADM1	cell adhesion molecule 1	1.64	4.24
IDS	iduronate 2-sulfatase	1.62	1.43
DCAF8	DDB1 and CUL4 associated factor 8	1.60	1.82
PRO2852	hypothetical protein PRO2852	1.60	1.38
RPS27	ribosomal protein S27	1.58	2.81
FLJ38717	FLJ38717 protein	1.57	1.31
VPS13C	vacuolar protein sorting 13 homolog C (S. cerevisiae)	1.57	1.46
LHFP	lipoma HMGIC fusion partner	1.55	1.38
ZFAND6	zinc finger, AN1-type domain 6	1.50	1.89
PCNX	pecanex homolog (Drosophila)	1.47	1.12
CREB3L2	cAMP responsive element binding protein 3-like 2	1.46	1.62
UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog)	1.45	1.26
TMEM155	transmembrane protein 155	1.43	3.89
MBNL1	muscleblind-like (Drosophila)	1.43	1.30
PHLDA1	pleckstrin homology-like domain, family A, member 1	1.41	2.23
SFRS18	splicing factor, arginine/serine-rich 18	1.40	1.38
NINJ2	ninjurin 2	1.39	2.58
PPP2R5C	protein phosphatase 2, regulatory subunit B', gamma 5	1.37	1.38
TGFBR3	transforming growth factor, beta receptor III	1.35	1.16
PAM	peptidylglycine alpha-amidating monooxygenase	1.35	2.47
TRA2A	transformer 2 alpha homolog (Drosophila)	1.35	1.26
NFE2L3	nuclear factor (erythroid-derived 2)-like 3	1.35	1.04
NGFRAP1	nerve growth factor receptor (TNFRSF16) associated protein 1	1.33	1.15
REV3L	REV3-like, catalytic subunit of DNA polymerase zeta (yeast)	1.31	1.41
ATP9A	ATPase, class II, type 9A	1.31	3.34
WIPF1	WAS/WASL interacting protein family, member 1	1.30	1.39

SOCS3	suppressor of cytokine signaling 3	1.30	1.02
KLF6	Kruppel-like factor 6	1.27	1.16
FNBP1	formin binding protein 1	1.26	1.52
LPXN	leupaxin	1.26	1.62
JMJD1C	jumonji domain containing 1C	1.25	1.18
ETV1	ets variant 1	1.25	4.12
LOC100190986	hypothetical LOC100190986	1.24	1.50
PIK3C2A	phosphoinositide-3-kinase, class 2, alpha polypeptide	1.24	1.08
ARID2	AT rich interactive domain 2 (ARID, RFX-like)	1.24	1.67
NOD2	nucleotide-binding oligomerization domain containing 2	1.23	2.30
TNF	tumor necrosis factor (TNF superfamily, member 2)	1.22	1.33
SKP1	S-phase kinase-associated protein 1	1.20	1.22
NCRNA00182	non-protein coding RNA 182	1.19	1.49
MED31	mediator complex subunit 31	1.17	1.11
QKI	quaking homolog, KH domain RNA binding (mouse)	1.16	1.55
B4GALT1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, p	1.15	1.35
MED6	mediator complex subunit 6	1.15	1.02
LPL	lipoprotein lipase	1.13	1.69
DLG1	discs, large homolog 1 (Drosophila)	1.12	1.36
MALAT1	metastasis associated lung adenocarcinoma transcript 1	1.11	1.34
ZNF131	zinc finger protein 131	1.11	1.18
BCL10	B-cell CLL/lymphoma 10	1.11	1.32
SFXN3	sideroflexin 3	1.10	1.21
SFRS4	splicing factor, arginine/serine-rich 4	1.10	1.01
B2M	beta-2-microglobulin	1.10	1.54
PCBP2	poly(rC) binding protein 2	1.09	1.56
PSMD7	proteasome (prosome, macropain) 26S subunit, non-A'	1.09	1.21
SKIL	SKI-like oncogene	1.09	1.08
ATXN1	ataxin 1	1.09	1.91
YPEL5	yippee-like 5 (Drosophila)	1.08	1.13
IL10RA	interleukin 10 receptor, alpha	1.07	1.03
NGLY1	N-glycanase 1	1.07	1.35
SFRS15	splicing factor, arginine/serine-rich 15	1.07	1.09
GADD45A	growth arrest and DNA-damage-inducible, alpha	1.06	1.05
DDX50	DEAD (Asp-Glu-Ala-Asp) box polypeptide 50	1.05	1.10
GOLGA4	golgin A4	1.05	1.56
LOC442113	similar to protein tyrosine phosphatase, non-receptor tyrosine	1.04	1.31
ZMYM2	zinc finger, MYM-type 2	1.04	1.29
CLK4	CDC-like kinase 4	1.03	1.36
ST8SIA1	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase	1.01	2.11
METTL8	methyltransferase like 8	1.01	1.30
NKTR	natural killer-tumor recognition sequence	1.01	1.14
RNF34	ring finger protein 34	1.00	1.08
CR2	complement component (3d/Epstein Barr virus) receptor 2	-1.02	-2.12
TXNIP	thioredoxin interacting protein	-1.10	-1.87
PN01	partner of NOB1 homolog (S. cerevisiae)	-1.10	-1.78
ZNF528	zinc finger protein 528	-1.21	-1.91
SESN1	sestrin 1	-1.30	-1.49
CASP2	caspase 2, apoptosis-related cysteine peptidase	-1.36	-1.91
DDIT4	DNA-damage-inducible transcript 4	-1.38	-1.24
ACTN1	actinin, alpha 1	-1.42	-1.95
RARA	retinoic acid receptor, alpha	-1.42	-2.10
AUTS2	autism susceptibility candidate 2	-1.90	-2.01

HSPA1A	heat shock 70kDa protein 1A	-2.06	-3.00
HSPA6	heat shock 70kDa protein 6 (HSP70B')	-2.92	-2.85
CH25H	cholesterol 25-hydroxylase	-3.07	-2.28
IL17A	interleukin 17A	-3.94	-1.21

Supplemental Table 4. Summary of clinical characteristics of patients' samples used in the TMA.

	No. of patients	Percentage
Total No. of patients	172	100
Median age at diagnosis, yr (range)		55 (24-85)
Gender		
Male	100	58.14
Female	72	41.86
Specimen type		
FFPE	172	100
Therapy regimen		
RITUXIMAB	33	19.18
Non-RITUXIMAB	139	80.82
Bone Marrow Involvement	81	47.09
Stage at diagnosis		
I	25	14.53
II	21	12.21
III	28	16.28
IV	98	56.98
FLIPI score		
Low [1]	42	24.42
Intermediate [2]	37	21.50
High [3]	47	27.33
Not assessable [4]	35	20.35
Not known	11	6.40
Grade at diagnosis		
1	87	50.59
2	58	33.72
3A	9	5.23
3B	3	1.74
unknown	15	8.72
Histological pattern		
Follicular	170	98.84
Follicular and diffuse	2	1.16
Proceeded to Transformation	41	23.84
Time to Transformation, yr		
0-5	25	60.98*
6-10	9	21.95*
>11	7	17.07*
Cause of death		
Alive	51	29.65
Disease	75	43.61
Unrelated	37	21.51
unknown	9	5.23

(FFPE) Formalin-fixed paraffin-embedded, (TT) Time to Transformation, * Of transformed

Supplemental Table 5 Representative genes with altered expression in both CD4 and CD8 TILs in FL compared to tonsil. Gene products highlighted in yellow were studied using MAbs in TMA. For those proteins highlighted in green no MAbs tested worked reliably in paraffin embedded tissue and for those highlighted in blue, no MAbs could be found.

Gene Title	Gene Symbol	Fold change in CD4	Fold change in CD8
pro-melanin-concentrating hormone	PMCH	3.20	4.67
nuclear receptor subfamily 4, group A, member 2	NR4A2	3.14	2.96
Nicotinamide phosphoribosyltransferase	NAMPT(Visfatin-1)	2.58	3.08
chimerin (chimaerin) 1	CHN1	2.34	2.55
CD200	CD200	-	2.75
tumor necrosis factor receptor superfamily, member 9	TNFRSF9	2.26	3.70
nucleosome assembly protein 1-like 2	NAP1L2	2.25	2.42
Pellino homolog 1 (Drosophila)	PEL1	2.17	2.72
Mitogen-activated protein kinase kinase kinase 8	MAP3K8	2.16	3.18
phorbol-12-myristate-13-acetate-induced protein 1	PMAIP1	2.13	3.02
Nucleoporin like 1	NUPL1	2.11	1.97
granzyme K (granzyme 3; tryptase II)	GZMK	2.11	1.31
YME1-like 1 (S. cerevisiae)	YME1L1	2.02	2.09
small nucleolar RNA, H/ACA box 28	SNORA28	1.97	1.02
G1 to S phase transition 1	GSPT1	1.92	1.99
Solute carrier family 20, member 1	SLC20A1	1.84	2.04
Small nuclear ribonucleoprotein polypeptide A'	SNRPA1	1.82	1.41
Chromodomain helicase DNA binding protein 2	CHD2	1.77	1.95
cytochrome c, somatic	CYCS	1.74	1.52
FLJ38717 protein	FLJ38717	1.57	1.31
Zinc finger, AN1-type domain 6	ZFAND6	1.50	1.89
pleckstrin homology-like domain, family A, member 1	PHLDA1	1.48	2.23
peptidylglycine alpha-amidating monooxygenase	PAM	1.35	2.19
ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	ATP1B1	1.29	1.30
ets variant 1	ETV1 (ER81)	1.25	4.12
nucleotide-binding oligomerization domain containing 2	NOD2	1.23	2.30
complement component receptor 2	CR2	-1.02	-2.12
sestrin 1	SESN1	-1.30	-1.49
actinin, alpha 1	ACTN1	-1.42	-2.47
autism susceptibility candidate 2	AUTS2	-1.90	-2.01
heat shock 70kDa protein 1A	HSPA1A	-2.06	-3.00
heat shock 70kDa protein 6 (HSP70B')	HSPA6	-2.92	-2.85
cholesterol 25-hydroxylase	CH25H	-3.07	-2.85
interleukin 17A	IL17A	-3.94	-1.21

Supplemental Table 6- Univariate, multivariate and cut-off points used for OS, DSS and TT.

End point	Model variables	Cut-off	Univariate analysis			Multivariate analysis		
			HR	95% CI	p	HR	95% CI	p
OS	No of PMCH positive cells in intrafollicular area: high vs low	24.27	3.29	1.11-4.11	0.034	0.96	0.46-1.98	0.91
	No of PMCH positive cells in interfollicular area: high vs low	1148.98	0.68	0.02-1.29	0.0002	0.92	0.5-1.8	0.82
	No of ETV1 positive cells in intrafollicular area: high vs low	209.12	1.60	0.67-2.06	0.045	1.8	0.86-4.65	0.15
	No of ETV1 positive cells in interfollicular area: high vs low	197.66	1.53	-0.025-1.32	0.03	0.9	0.41-1.89	0.75
	No of NAMPT positive cells in intrafollicular area: high vs low	75.9	2.32	-0.060-1.31	0.02	0.8	0.37-1.55	0.55
	No of NAMPT positive cells in interfollicular area: high vs low	70.29		-0.041-1.18	0.008	0.9	0.45-1.7	0.75
	Combined model of PMCH, NAMPT and ratio of ETV1					0.32	0.1-0.61	0.007
	Age: above vs below median					1.1	1.06-1.1	0.009
	Gender					0.75	0.45-1.28	0.3
	Grade: 1-3					0.98	0.85-1.25	0.95
	Stage: 1-4					1.25	1.03-1.6	0.04
TT	No of PMCH positive cells in intrafollicular area: high vs low	344.67	0.22	0.07-0.69	0.029	1.55	0.46-5.22	0.48
	MI of PMCH expression in intrafollicular area: high vs low	65.58	2.06	1.03-5.15	0.040	3.07	0.97-9.63	0.049
	No of PMCH positive cells in interfollicular area: high vs low	1171.3	4.88	1.75-13.63	0.033	0.27	0.10-0.71	0.008
	MI of PMCH expression in total area: high vs low	16.85	0.39	0.18-0.84	0.015	4.73	0.88-25.25	0.07
	No of ETV1 positive cells in intrafollicular area: high vs low	12	0.35	0.15-0.78	0.022	3.21	0.4-25.31	0.27
	MI of ETV1 expression in interfollicular area: high vs low	46.17	4.60	1.75-12.14	0.005	1.75	0.68-4.46	0.23
	MI of NAMPT expression in intrafollicular area: high vs low	75.14	0.40	0.19-0.82	0.003	0.36	0.15-0.86	0.02
	MI of NAMPT expression in total area: high vs low	68.15	3.47	1.11-10.79	0.043	0.79	0.65-1.43	0.32
	percentage of NAMPT positive cells in total area: high vs low	2.03	6.54	1.83-23.36	0.025	0.39	0.11-1.32	0.13
	Combined model of ratio of PMCH, and level of NAMPT and ETV1 expression					0.19	0.09-0.47	0.003
	Age: above vs below median					1.04	1.00-1.09	0.04
	Gender:					3.7	1.52-9.31	0.004
	Grade: 1-3					0.80	0.59-1.09	0.16

Note: Hazard ratios (HRs) >1 or <1 indicate an increased or decreased risk, respectively, of an event for the 1st category listed.
Abbreviations: DSS, disease specific survivals; TT, time to transformation; MI, mean intensity.