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Supplemental Table S2. SCFCL and PCFCL (systemic) mutations found in COSMIC hotspots and functionally validated

COSMIC hotspot ≥ 20 mutations

Gene	Amino acid change	# Mutations in COSMIC in hotspot area (+/- 5 amino acids)	# Mutations in COSMIC at amino acid position	Functional validation	Target-able	# SCFCL samples with mutation	% SCFCL samples with mutation	# PCFCL (systemic) samples with mutation	% PCFCL (systemic) samples with mutation	# SCFCL and PCFCL (systemic) samples with mutation	% SCFCL and PCFCL (systemic) samples with mutation
KRAS	p.G13D	42944	6056	Y	Y	0	0%	1	50%	1	13%
EZH2	p.Y646S	405	392	Y	Y	1	17%	0	0%	1	13%
EZH2	p.Y646N	405	392	Y	Y	1	17%	0	0%	1	13%
CREBBP	p.R1446C	75	63	Y		1	17%	1	50%	2	25%
CREBBP	p.Y1482H	40	12	Y		1	17%	0	0%	1	13%
CREBBP	p.Y1503C	36	26	Y		1	17%	0	0%	1	13%
STAT6	p.D419N	33	23	Y	Y	1	17%	0	0%	1	13%
EZH2	p.D185H	28	23	Y†	Y	0	0%	1	50%	1	13%

COSMIC hotspot < 20 mutations

Gene	Amino acid change	# Mutations in COSMIC in hotspot area (+/- 5 amino acids)	# Mutations in COSMIC at amino acid position	Functional validation	Target-able	# SCFCL samples with mutation	% SCFCL samples with mutation	# PCFCL (systemic) samples with mutation	% PCFCL (systemic) samples with mutation	# SCFCL and PCFCL (systemic) samples with mutation	% SCFCL and PCFCL (systemic) samples with mutation
IL4R	p.I242N	11	6	Y	Y	1	17%	0	0%	1	13%
CREBBP	p.L1621P	13	1	Y†		1	17%	0	0%	1	13%

Mutations found in COSMIC hotspot reflects those in a COSMIC region within 5 amino acids of the original mutation position. Y= yes. † = Hotspot but not exact amino acid change has been previously functionally validated as tumorigenic.

Supplemental Table S3. PCFCL (skin restricted) mutations found in COSMIC hotspot

COSMIC hotspot > 20 mutations

Gene	Amino acid change	# Mutations in COSMIC in hotspot area (+/- 5 amino acids)	# Mutations in COSMIC at amino acid position	Functional validation	Targetable	# PCFCL (skin restricted) samples with mutation	% PCFCL (skin restricted) samples with mutation
EZH2	p.Y646F	405	392	Y	Y	1	6%
JAK3	p.V722I	42	31	Y	Y	1	6%
MYC	p.P60A	80	8	Y		1	6%
CARD11	p.G123D	40	4	Y	Y	1	6%
MYC	p.P63S	30	3	Y*		1	6%
FOXO1	p.T24A	29	4	Y		1	6%
MYC	p.N260L	20	2	Y		1	6%

COSMIC hotspot ≤ 20 mutations

Gene	Amino acid change	# Mutations in COSMIC in hotspot area (+/- 5 amino acids)	# Mutations in COSMIC at amino acid position	Functional validation	Targetable	# PCFCL (skin restricted) samples with mutation	% PCFCL (skin restricted) samples with mutation
RHOA	p.F39C	10	1	Y		1	6%

Mutations found in COSMIC hotspot reflects those in a COSMIC region within 5 amino acids of the original mutation position. Y= yes. * = Hotspot but not exact amino acid change has been previously functionally validated as tumorigenic.

Supplemental Table S4. SCFCL and PCFCL (systemic) damaging mutations in BCL tumor suppressors

Gene	# SCFCL samples with damaging mutation	% SCFCL samples with damaging mutation	# PCFCL (systemic) samples with damaging mutation	% PCFCL (systemic) samples with damaging mutation	# SCFCL and PCFCL (systemic) samples with damaging mutation	% SCFCL and PCFCL (systemic) samples with damaging mutation
CREBBP	4	67%	1	50%	5	63%
KMT2D	3	50%	1	50%	4	50%
TNFRSF14	1	17%	1	50%	2	25%
FAS	0	0%	1	50%	1	13%
IKZF1	0	0%	1	50%	1	13%

SCFCL and PCFCL (systemic) tumor suppressors reflect putative driver genes wherein >20% of mutations from previous BCL studies are damaging.

Supplemental Table S5. PCFCL (skin restricted) damaging mutations in BCL tumor suppressors

Gene	# PCFCL (skin restricted) samples with damaging mutation	% PCFCL (skin restricted) samples with damaging mutation
TNFRSF14	4	25%
MSH2	2	13%
IRF8	1	6%
HIST1H1E	1	6%
EP300	1	6%
TET2	1	6%
KMT2C	1	6%
SETD2	1	6%
SOCS1	1	6%
B2M	1	6%
CD58	1	6%
FAS	1	6%
BTG1	1	6%
EBF1	1	6%
FBXO11	1	6%
GNA13	1	6%
MLH1	1	6%
PALB2	1	6%
RB1	1	6%

PCFCL (skin restricted) tumor suppressors reflect putative driver genes wherein >20% of mutations from previous BCL studies are damaging.

Supplemental Table S6. SCFCL and PCFCL (systemic) damaging mutations in canonical tumor suppressors

Gene	# SCFCL & PCFCL (systemic) samples with damaging mutation	% SCFCL & PCFCL (systemic) samples with damaging mutation
KMT2D	4	50%
TNFRSF14	2	25%
FAS	1	13%
IKZF1	1	13%

Canonical tumor suppressors reflect consensus cancer genes wherein >20% of mutations are damaging mutations in COSMIC.

Supplemental Table S7. PCFCL (skin restricted) damaging mutations in canonical tumor suppressors

Gene	# PCFCL (skin restricted) samples with damaging mutation	% PCFCL (skin restricted) samples with damaging mutation
TNFRSF14	4	25%
MSH2	2	13%
FAS	1	6%
IRF8	1	6%
KMT2C	1	6%
HIST1H1E	1	6%
TET2	1	6%
EP300	1	6%
SOCS1	1	6%
B2M	1	6%
CD58	1	6%
BTG1	1	6%
EBF1	1	6%
FBXO11	1	6%
GNA13	1	6%
MLH1	1	6%
PALB2	1	6%
PTCH1	1	6%
RB1	1	6%

Canonical tumor suppressors reflect consensus cancer genes wherein >20% of mutations are damaging mutations in COSMIC.

Supplemental Table S8. Frequencies of copy number alterations in 5 PCFCL cases

Region	Cytoband Location	Region Length (kb)	Event	Frequency (%)
chr1:143,862,902-146,627,564	q21.1	2764662	CN Gain	40
chr1:175,980,871-176,205,159	q25.1 - q25.2	224288	CN Gain	40
chr1:754,191-13,477,395	p36.33 - p36.21	12723204	CN Loss	60
chr2:60,722,241-62,448,399	p16.1 - p15	1726158	CN Gain	40
chr2:89,160,445-89,270,361	p11.2	109916	CN Loss	40
chr6:137,372,463-138,071,287	q23.3	698824	CN Loss	40
chr6:138,085,248-138,325,071	q23.3	239823	CN Loss	40
chr6:222,951-40,057,184	p25.3 - p21.2	39834233	LOH	80
chr7:41,421-159,118,443	p22.3 - q36.3	159077022	CN Gain	40
chr9:204,738-39,184,065	p24.3 - p13.1	38979327	LOH	60
chr9:21,795,661-22,019,732	p21.3	224071	CN Loss	40
chr10:63,025,417-67,436,888	q21.2 - q21.3	4411471	CN Loss	40
chr10:83,038,265-91,090,551	q23.1 - q23.31	8052286	CN Loss	40
chr14:106,157,764-106,353,338	q32.33	195574	CN Loss	60
chr18:18,554,307-60,785,638	q11.1 - q21.33	42231331	CN Gain	40

Visual representation in Figure S2

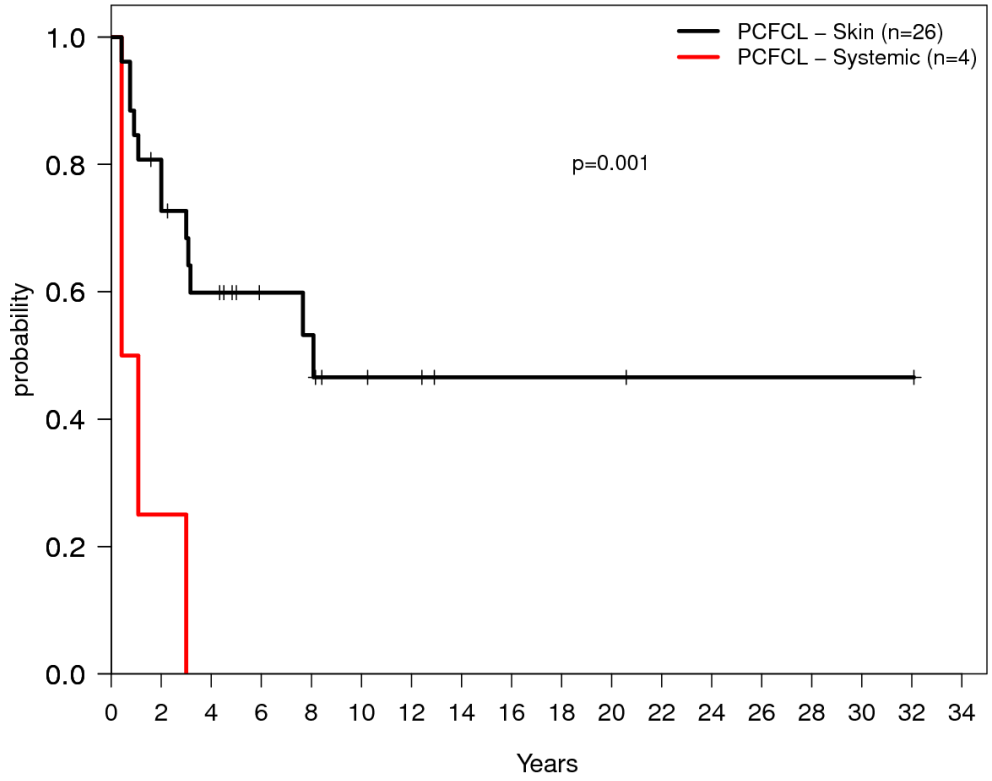
Supplemental Table S9. Recurrently mutated genes in PCFCL and SCFL occurring in 3 or more cases

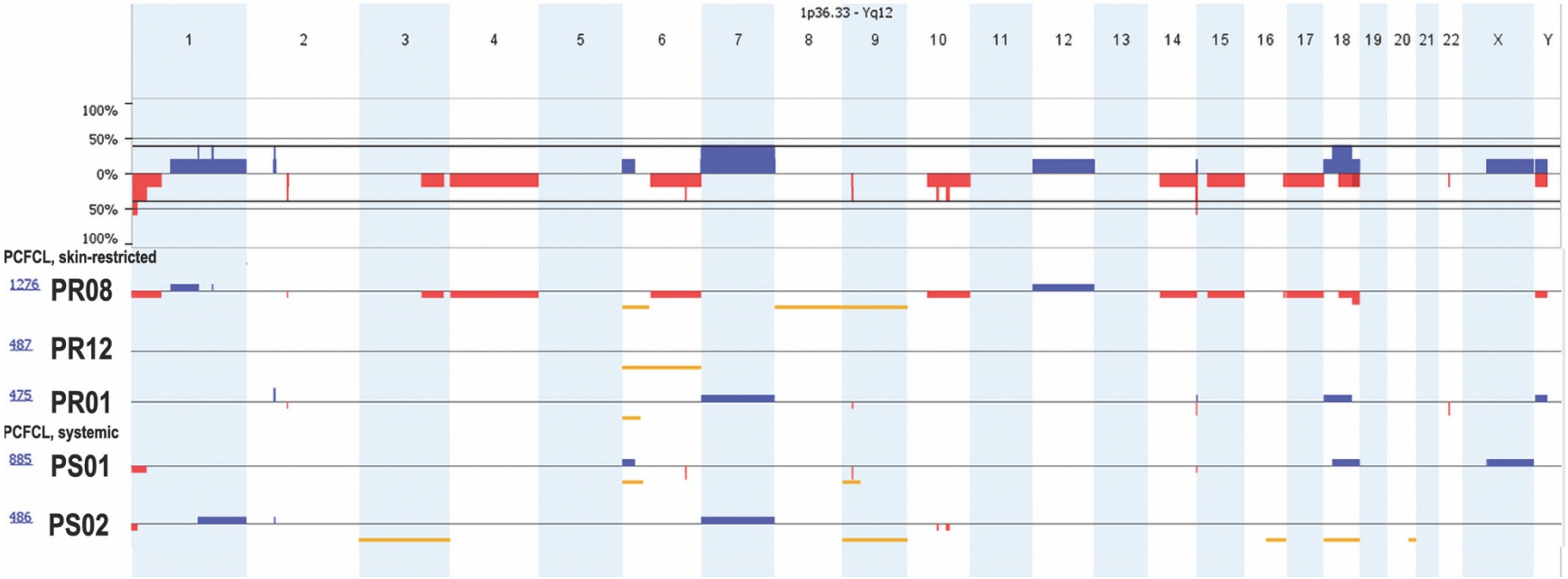
Includes non-functionally validated mutations

	PCFCL Cases	SCFL Cases	Gene Function
CREBBP	3/18	5/6	Lysine acetyltransferase that acetylates histones H3L18Ac and H3K27Ac. Functions as transcriptional coactivator by acetyating histones at regulary histones. Mutated in ~65% of usual systemic FLs.
KMT2D	4/18	3/6	Lysine methyltransferase responsible for the majority of H3K4 monomethylation at enhancer elements that leads to recruitment of other co-activators. Mutated in ~72% of usual systemic FLs.
HIST1H1E	4/18	0/6	Linker histone that binds DNA at entry and exit sites of nucleosome and are requred for stability of the higher-order chromatin structure. HISTH1E can be methylated at lysine 226 by EZH2 to create a docking site for HP1 and facilitate heterochromatin formation. Mutated in ~14% of usual systemic FLs.
MYC	3/18	0/6	Transcription factor that promotes transition from G0/G1 phase to S phase and drives cell proliferation and growth.
TNFRSF14	6/18	2/6	Encodes the herpes virus entry mediator (HVEM), which acts as a molecular switch through interactions with BTLA, LIGHT, CD160, lymphotoxin A and glycoprotein D. HVEM deficiency induces a tumor-supportive microenvironment by disupting inhibitor cell-cell interactions between HVEM and BTLA. Mutated in 18-46% of usual systemic FL patients
IRF8	3/18	1/6	Transcription factor with critical role in controlling early stage B cell development including follicular B cells and positively regulates BCL6. Mutated in 6% of usual systemic FL patients

Green MR. Chromatin modifying gene mutations in follicular lymphoma. Blood. 2018;131(6):595-604.
Li H, Kaminski MS, Li Y, et al. Mutations in linker histone genes HIST1H1 B, C, D, and E; OCT2 (POU2F2); IRF8; and ARID1A underlying the pathogenesis of follicular lymphoma. Blood. 2014;123(10):1487-1498.
Boice M, Salloum D, Mourcin F, et al. Loss of the HVEM Tumor Suppressor in Lymphoma and Restoration by Modified CAR-T Cells. Cell. 2016;167(2):405-418.e13.
Aukema SM, van Pel R, Nagel I, et al. MYC expression and translocation analyses in low-grade and transformed follicular lymphoma. Histopathology. 2017;71(6):960-971.

Supplemental Figure S1. Progression-free survival for PCFCL, systemic spread (n=26) vs. PCFCL, skin restricted cases (n=4)



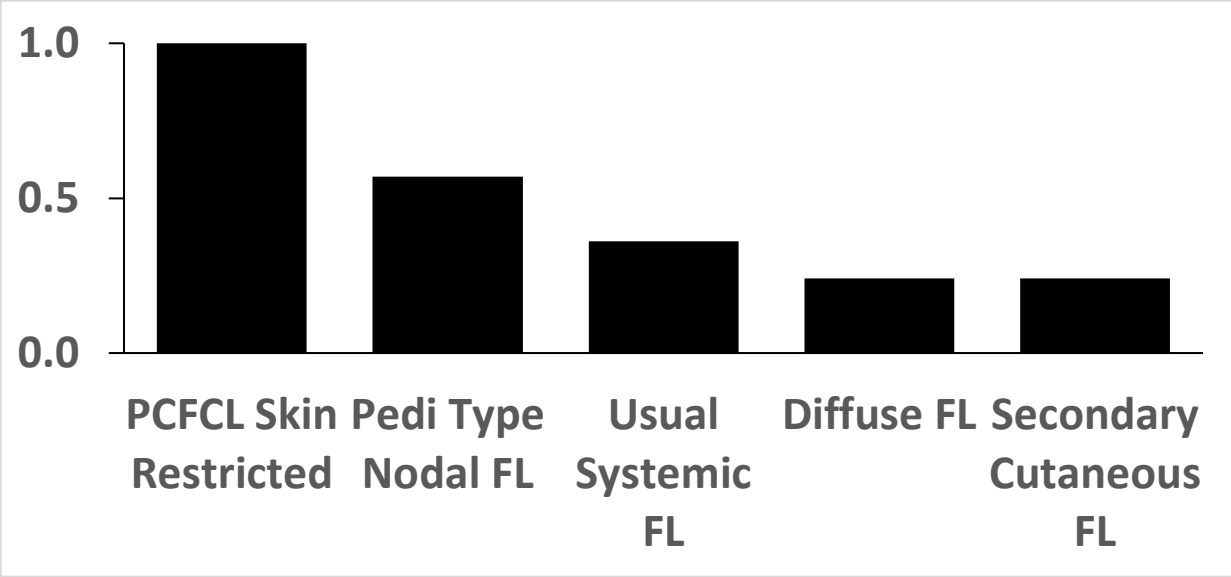


Supplemental Figure S2. Copy number analysis of 5 PCFCL samples using the OncoScan assay (3 PCFCL (skin restricted) and 2 PCFCL (systemic)). (a) Copy number variation (CNV) (red = loss, blue = gain) and (b) loss of heterozygosity (LOH) (yellow/orange) events are presented as colored bands sorted by chromosome for each sample (n=5).

	PCFCL (skin restricted)	SCFL*	PTFL	Usual Systemic FL	Diffuse FL
PCFCL (skin restricted)	1.00	0.24	0.57	0.36	0.24
SCFL*	0.33	1.00	0.40	0.91	0.69

*SCFL and PCFCL (systemic) are combined here given few PCFCL (systemic) samples and close similarity between SCFL and PCFCL (systemic)

Supplemental Figure S3. Correlation matrix of similarity comparing PCFCL (skin restricted) and SCFL with other FL subtypes. Similarity index is based on relative mutation prevalence in PCFCL (skin restricted) or SCFL of the most commonly mutated genes in each FL subtype and uses a scale from 0 to 1 where 1 = exact correlation and 0 = no correlation.



Supplemental Figure S4. Similarity index comparing PCFCL (skin restricted) with other FL subtypes. Similarity index is based on relative mutation prevalence in PCFCL (skin restricted) of the most commonly mutated genes in each FL subtype and uses a scale from 0 to 1 where 1 = exact correlation and 0 = no correlation.