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Non-JAK-family gene fusions in cutaneous T-cell lymphoma highlights genetic diversity and potential therapeutic targets

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TITLE: Non-JAK-family gene fusions in cutaneous T-cell lymphoma highlights genetic diversity and potential therapeutic targets

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To the Editor,

Chromosomal translocations resulting in gene fusions have important implications in human cancer, ranging from diagnostic input to treatment indications.[1] Several recurrent gene fusions are described in the mature T- and NK-cell neoplasms, which comprise a rare, heterogenous group of over 30 distinct clinicopathologic entities. The hallmark example is recurrent *ALK* translocations in anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (ALK+ ALCL), which genetically define the disease and offer therapeutic opportunity through the use of ALK tyrosine kinase inhibitors. Other examples include recurrent *IRF4*/*DUSP22* and *TP63* rearrangements in ALK-negative ALCL and recurrent *JAK2*-*STAT3* fusions in indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. In the cutaneous T-cell lymphomas (CTCL), gene fusions are less well-described. Notable exceptions include recurrent *JAK2* fusions in cytotoxic CTCL, in particular primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) and recurrent *TYK2* fusions in primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs). These events are well described, including a contemporaneous report from our center and a recent report of pediatric cases.[2,3] However, in other CTCLs, including mycosis fungoides (MF), the frequency, identity, and implications of non-*JAK*-family gene fusions are undefined. Recently, we identified a cohort of patients with CTCL harboring non-*JAK*-family fusions and herein describe their molecular features and clinical course.

Through a retrospective analysis of 113 specimens from 99 unique patients from our institutional CTCL clinic, we identified patients with CTCL harboring predicted productive non-*JAK*-family gene fusions. Fusions were detected through the RNA-based Archer FusionPlex™ Custom Heme Panel, which uses anchored multiplex PCR[4] to detect expressed fusion transcripts. This panel consists of 199 cancer-related genes known to be recurrently involved in chromosomal rearrangements in hematologic malignancies. When available, we also reviewed next-generation sequencing results from MSK-IMPACT Heme panel, a custom paired tumor and normal DNA hybridization capture-based next generation sequencing platform

(see reference for genes covered).[5] For diagnostic confirmation and characterization of cutaneous T-cell lymphoma, clinical and pathology records and images underwent re-review by a dermatopathologist, a dermatologist, and an oncologist with specific expertise in the field. All research was conducted under an IRB-approved retrospective research protocol.

In total, we identified 17 patients with 20 unique gene fusions (three patients had multiple fusions). An overview of these patients is shown in **Supplementary Table 1**. Fusions were seen across histologies. Six patients were best characterized as primary cutaneous CD30+ T-cell LPDs, including two with clinicopathologic presentations consistent with lymphomatoid papulosis (LYP) and one with primary cutaneous ALCL. Five patients were best characterized as MF with a typical CD4+ phenotype, whereas three were considered MF with an unusual phenotype, which included one 'double-positive' case (CD4+/CD8+), one 'double-negative' case with a gamma-delta phenotype, and one CD8+ MF with large cell transformation (LCT). Finally, two patients were best characterized as primary cutaneous peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and one as CD8+ AECTCL.

As for recurrent gene fusions, *TP63* fusions were detected in three patients with CD30+ T-cell LPDs (two cases with *TBL1XR1-TP63* and one with *FOXK2-TP63*, both of which have been previously reported[6,7]). *TBL1XR1*, which has broad biological function, was involved in a separate fusion involving *BCL6* in the patient with CD8+ MF with LCT, and *BCL6* was involved in separate fusion with *CXCL8* in a patient with LYP. Finally, two *ROS1* fusions were detected, one in a patient with LYP (*VIM1-ROS1*, novel) and one in the case of double-negative MF with a gamma-delta phenotype (*LMNA-ROS1*, previously reported[8]). All other cases were unique within this cohort.

The *TP63* fusions we identified have been previously shown to act as *bona fide* oncogenes.[6] The patients with these fusions (patients 1, 2, and 6) had generally aggressive clinical courses with multiply refractory disease requiring several sequential treatments, including two allogeneic hematopoietic stem cell

transplants (alloSCT) in patient 2. Together with prior literature,[6,7] these cases support that structural abnormalities in *TP63* or events that alter *TP63* function may correlate with aggressive clinical behavior and resistance to standard therapies. For the other unique non-*TP63* fusions, we did not detect any clear unifying features to categorize these events. **Supplementary Table 2** shows additional details of each fusion, including whether a kinase or transcription factor was involved, prior reports in the literature, and hypothesized function. Of the 20 total fusions in our cohort, 14 have not been reported to our knowledge, cross-referencing cases against the Mitelman Database of Gene Fusions in Cancer, a comprehensive online database of over 34,000 gene fusions previously reported in human cancers (https://mitelmandatabase.isb-cgc.org). Of the six previously reported fusions (*FOXK2-TP63*, *TBL1XR1-TP63*, *NEK6-PBLX1*, *IKZF2-ERBB4*, *FIP1L1-PDGFRA*, *LMNA-ROS1*), two had not been reported previously in T-cell lymphoma (*NEK6-PBX1* has been reported in one instance in mantle cell lymphoma[9] and *FIP1L1-PDGFRA* is a hallmark of various hypereosinophilic syndromes, though this patient had no peripheral eosinophilia nor evidence of organ system eosinophilia[10]). Six cases involved kinases (*NEK6, PDGFRA, GUCY2C, ERBB4, ROS1*) and 11 cases involved transcription factors (*FOXK2, TP63, NF-κB, BCL6, PBX1, ETV, RUNX1, ZFHX3, MKL1, IKZF2, RORA*). Aside from three patients with stage IA disease and one patient with stage IB disease responsive to phototherapy, all others had advanced disease (≥ stage IB) requiring multiple therapies, with three patients undergoing alloSCT and five patients dying of disease and/or infection.

The tumor mutational burden varied across cases (**Figure 1, Supplemental Table 3**). Some patients had generally high burden, including patients 1 and 2, each with CD30+ T-cell LPDs, TP63 fusions, and > 10 mutations. Other patients with comparably high burden among the cohort included patient 4 (CD30+ T-cell LPD, *RORA-PDCD1LG2*, 18 mutations, multiply relapsed), patient 9 (MF, *KMT2A-IFT46*, 11 mutations, died of disease), patient 11 (MF, *IKZF2-ERBB4* and *PML-FBXO25*, 11 mutations, died of disease), patient 15 (CD8+ AECTCL, *ETV-GUCY2C*, 15 mutations, multiply relapsed), and patient 16 (primary cutaneous PTCL-NOS, *SETD2-LMCD1*, 15 mutations, died of disease). In contrast, other patients had generally low burden, including the two patients with disease behavior most consistent with LYP

(patients 3 and 5) and the one patient with limited-stage CD4+ MF responsive to topical steroids (patient 7), each having less than three mutations (patient 3 with LYP had a *WT1* mutation, patient 5 with LYP had *FLT3*, *EPHA7*, *ERBB4* mutations, and patient 7 with CD4+ MF had no detected mutations). Finally, across histologies, seven patients had *TP53* and/or *CDKN2A* mutations (patients 1, 2, 4, 10, 11, 15, 17), generally uncommon events in CTCL though previously shown to associate with increased tumor burden and poor prognosis.[11] All of these patients had multiply relapsed courses and two died of disease.

To gain insight into the potential clonality of the identified fusions (which could provide insight on driver function), we integrated the quantitative read support for each fusion (expressed as the percentage of unique breakpoint-spanning reads) with the estimated tumor purity of the sequenced sample (shown in **Supplementarty Table 3** as %Reads). Doing so reveals a spectrum of findings. In several cases, high fusion %Reads were observed in samples with substantial tumor purity, suggesting a clonal, potentially driver event. For instance, in patient 2 (*TBL1XR1-TP63*, 80% tumor purity), the fusion was supported by over 50% of reads. Conversely, other fusions were detected at lower %Reads even in samples with moderate tumor purity. For example, the *FIP1L1-PDGFRA* fusion in patient 12 (30% tumor purity) was supported by only 3.55% of reads.

Herein we describe 20 gene fusions across CTCL, 14 of which are previously unreported. CTCLs have complex mutational landscapes, with few recurrent mutations and a high proportion of somatic copy number variants comprising driver mutations.[11] Our study contributes to this complexity, showing that multiple gene fusions are detectable in CTCLs, even within the same patient. Gene fusions have been described in PTCL, but their contribution to the pathogenesis and behavior of CTCLs remains poorly characterized. Many gene fusions create constitutively active kinase or transcription factor fusion proteins,[1] hence our attempt to categorize events based on the suspected fusion product. Most of the cases here indeed involved either kinases or transcription factors, though despite our attempt to hypothesize function, the true consequences of most of these events and contribution to pathogenesis is unclear and would require

functional studies. The noteworthy exception are the three *TP63* fusions, which have been shown through intricate pre-clinical experiments to coordinate the recruitment of epigenetic modifying complexes and drive upregulation of *MYC* and *EZH2*, thereby contributing to aggressive B- and T-cell lymphoma development.[6] The patients with these fusions in our cohort had aggressive, multiply refractory disease. Knowing that *TP63* rearrangements are associated with inferior survival in PTCL and have been previously demonstrated in aggressive cases of MF,[12] these findings support the notion that *TP63* rearrangements correlate with aggressive disease biology. As for the other events, with the exception of the *NEK6-PBX1* fusion, all are in-frame, which at least suggests that these fusions could produce functional proteins, though the oncogenic activity and contribution to disease of these proteins would require further study. While we attempted to gain insight into such through integration of read support and tumor purity, these metrics require caution due to technical and biological factors. First, the %Reads metric is derived from RNA sequencing, thereby reflecting transcript abundance, not direct DNA allele frequency. As such, a low %Reads could indicate multiple scenarios, including a genetically sub-clonal event present in only a fraction of tumor cells, low expression of the fusion transcript relative to wild-type alleles, or contribution from non-tumor cells not fully accounted for in the H&E tumor purity estimate. For example, low read support for the *KMT2A-IFT46* fusion in patient 9 (2.36 %Reads, <5% tumor purity) highlights a case in which low tumor content and potential sub-clonality complicate interpretation, whereas high support for the *VIM1-ROS1* fusion in patient 5 (66.78 %Reads) despite a modest tumor purity (15%) seems to suggest high expression and clonal representation within the predominant tumor cell population. Therefore, while a high fusion fraction in a high-purity sample strongly supports a truncal driver role, a low fraction cannot be dismissed as non-pathogenic, as it could be a sub-clonal driver, an event with low transcriptional output, or an artifact of sampling heterogeneity. This quantitative framework highlights the candidate fusions for which orthogonal DNA-level validation or single-cell analysis would be most informative.

Finally, we note that when MSK-IMPACT Heme was performed, many cases demonstrated multiple additional mutations and copy number variants, some of which are considered to be oncogenic according

to OncoKB,[13] the precision-oncology knowledge base developed and maintained at our institution (highlighted in Supplemental Table 3). While the presence of these other oncogenic events could suggest that the fusions are passengers and more indicative of broad genomic instability, without functional characterization it is not possible to know for sure.

Whether any of the detected fusions represent therapeutic vulnerabilities is intriguing. EZH inhibition in *TP63*-rearranged cell lines and transgenic mice impairs tumor growth, and at least one patient with *TP63*-rearranged PTCL treated with the EZH inhibitor valemetostat in a phase I/II trial (NCT04703192) showed an initial disease response in the peripheral blood (though subsequently experienced cytomegalovirus reactivation and was removed from study).[6] EZH inhibition is being investigated in CTCL (NCT06733441, NCT05944562) and could represent a therapeutic option for these aggressive cases. Other potential targetable fusions in our series include imatinib against *FIP1L1-PDGFRA*,[10] pan-HER inhibitors, such as lapatinib, against *ERBB4* fusions,[14] tyrosine kinase inhibitors against *ROS1* fusions,[15] and checkpoint blockade, such as pembrolizumab, against *PDCD1LG2* fusions, which could amplify PD-L2 and promote immune evasion. Acknowledging the uncertain contribution of these fusions to disease progression and the anecdotal nature of these "n of 1" cases, we see promise in the identification of a potential vulnerability in many of these otherwise refractory cases through fusion detection.

In summary, we identified several novel gene fusions across various CTCLs, highlighting the genomic complexity in these heterogenous diseases. While not routine, evaluation for fusions in multiply relapsed disease may lend insight to disease biology and uncover unrealized potential therapeutic options.

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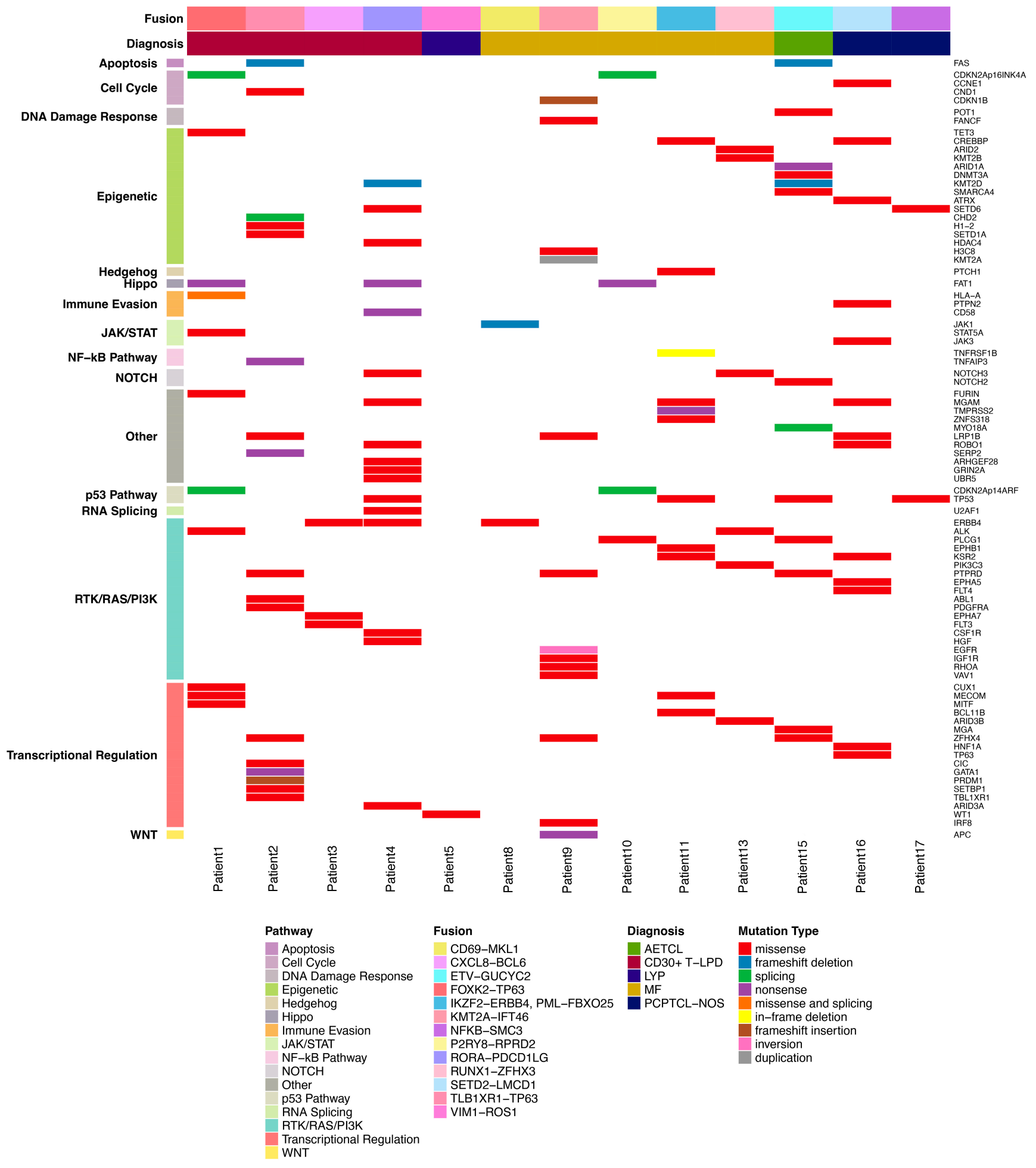
Figure 1. Integrated OncoPrint of Genomic Alterations. The OncoPrint summarizes alterations across patients. Each column represents an individual patient and each row corresponds to a particular gene. Genes are grouped by biological pathways (left sidebar). Colored bars within the matrix indicate specific mutations types. The top annotation bar shows the detected gene fusion, and the bar immediately below denotes the diagnosis.


Fusion
Diagnosis
Apoptosis
Cell Cycle
DNA Damage Response
Epigenetic
Hedgehog
Hippo
Immune Evasion
JAK/STAT
NF−kB Pathway
NOTCH
Other
p53 Pathway
RNA Splicing
RTK/RAS/PI3K
Transcriptional Regulation
WNT
FAS
CDKN2Ap16INK4A
CCNE1
CND1
CDKN1B
POT1
FANCF
TET3
CREBBP
ARID2
KMT2B
ARID1A
DNMT3A
KMT2D
SMARCA4
ATRX
SETD6
CHD2
H1−2
SETD1A
HDAC4
H3C8
KMT2A
PTCH1
FAT1
HLA−A
PTPN2
CD58
JAK1
STAT5A
JAK3
TNFRSF1B
TNFAIP3
NOTCH3
NOTCH2
FURIN
MGAM
TMPRSS2
ZNFS318
MYO18A
LRP1B
ROBO1
SERP2
ARHGEF28
GRIN2A
UBR5
CDKN2Ap14ARF
TP53
U2AF1
ERBB4
ALK
PLCG1
EPHB1
KSR2
PIK3C3
PTPRD
EPHA5
FLT4
ABL1
PDGFRA
EPHA7
FLT3
CSF1R
HGF
EGFR
IGF1R
RHOA
VAV1
CUX1
MECOM
MITF
BCL11B
ARID3B
MGA
ZFHX4
HNF1A
TP63
CIC
GATA1
PRDM1
SETBP1
TBL1XR1
ARID3A
WT1
IRF8
APC
Patient1
Patient2
Patient3
Patient4
Patient5
Patient8
Patient9
Patient10
Patient11
Patient13
Patient15
Patient16
Patient17
Pathway
Apoptosis
Cell Cycle
DNA Damage Response
Epigenetic
Hedgehog
Hippo
Immune Evasion
JAK/STAT
NF−kB Pathway
NOTCH
Other
p53 Pathway
RNA Splicing
RTK/RAS/PI3K
Transcriptional Regulation
WNT
Fusion
CD69−MKL1
CXCL8−BCL6
ETV−GUCYC2
FOXK2−TP63
IKZF2−ERBB4, PML−FBXO25
KMT2A−IFT46
NFKB−SMC3
P2RY8−RPRD2
RORA−PDCD1LG
RUNX1−ZFHX3
SETD2−LMCD1
TLB1XR1−TP63
VIM1−ROS1
Diagnosis
AETCL
CD30+ T−LPD
LYP
MF
PCPTCL−NOS
Mutation Type
missense
frameshift deletion
splicing
nonsense
missense and splicing
in−frame deletion
frameshift insertion
inversion
duplication

Supplementary Table 1. Disease and Case Overview.

No.	Fusion(s) & Demographics at Dx.	Index Lesion Description[1]	Clinical Dx	Immunophenotype	Disease Course
Best Characterized as Primary Cutaneous CD30+ T-cell Lymphoproliferative Disorder					
1	***FOXK2-TP63*** 56M, T2N0M0B0, IB	pink alopecic plaques w/ superficial erosion; jawline	CD30+ TLPD, w/ large cells	CD3+ CD4+ CD7- CD8- CD30+	**aggressive**, multiply relapsed, s/p nitrogen mustard, NBUVB, bexarotene, TSEBT, MTX, BV, mogamulizumab, investigational CAR T-cell therapy, other agents
2	***TBL1XR1-TP63*** 55M, T3N0M0B0, IIB	scaly erythematous nodular plaques; leg	CD30+ TLPD vs. CD4+ MF, w/ large cells	CD3+ CD4+ CD7- CD8- CD30+	**aggressive**, multiply relapsed, s/p two allogeneic hematopoietic stem cell transplants and other therapies, incl. TSEBT, bexarotene, BV, pralatrexate, romidepsin, duvelisib, investigational CAR T-cell therapy, other agents
3	***CXCL8-BCL6*** 43F, T1N0M0B0, IA	purple macules; forearm	CD30+ TLPD, most c/w LYP	CD3+ CD4+ CD7- CD8- CD30+	indolent, grouped lesions on the arms and trunk with spontaneous regression, consistent with LYP
4	***RORA-PDCD1LG2*** 48M, T2N0M0B0, IB	erythematous patches and plaques, eroded tumors; chest	CD30+ TLPD vs. CD4-/CD8- MF	CD3+ CD4- CD7- CD8- CD30+	multiply relapsed cutaneous disease, s/p NBUVB, topical therapies, bexarotene, BV, mogamulizumab, interferon, MTX, TSEBT
5	***VIM1-ROS1*** 54F, T1N0M0B0, IA	red papule and hyperpigmented plaque; axilla	CD30+ TLPD, most c/w LYP	CD3+ CD4+ CD7- CD8- CD30+	indolent, grouped lesions on the arms with spontaneous regression, consistent with LYP
6	***DENND1-PBX1, RUNX1-LOC105371750*** & ***TBL1XR1-TP63*** 58M, T3NXM0B0	cutaneous and subcutaneous nodules and tumors; cheek	CD30+ TLPD, most c/w pcALCL	CD3- CD4+ CD5- CD7- CD8- CD30+	originally thought to be Hodgkin lymphoma, treated with ICE (prior anthracycline), BV-nivolumab + autoSCT for refractory disease, BV for relapsed skin lesions
Best Characterized as Mycosis Fungoides					
7	***NEK6-PBX1*** 51M, T1N0M0B0, IA	erythematous patches; flank	CD4+ MF	CD3+ CD4+ CD7- (subset+) CD8-	indolent, limited-stage MF, treated with topical steroids

8	***CD69-MKL1*** 57M, T3N3M0B2, IVA2	xerotic patches; thigh	CD4+ MF/SS	CD3+ CD4+ CD5+ CD7dim (subset loss) CD8- CD30+ subset 50-60%	ongoing response to mogamulizumab, s/p NBUVB, methotrexate, BV, TSEBT
9	***KMT2A-IFT46*** 55F, T2N0M0B0, IB	erythematous papules, patches, plaques; chest	CD4+ MF	CD3+ CD4+ CD5- CD7- CD8- CD30-	**aggressive**, multiply relapsed, s/p alloSCT and other therapies, including bexarotene, romidepsin, BV, gemcitabine, liposomal doxorubicin, duvelisib, died of infection and disease
10	***P2RY8-RPRD2*** 55M, T3N0M0B0, IIB	ulcerated nodules and scaly macerated plaques; arm	CD4+ MF w/ LCT	CD2+ CD3+ CD4+ CD5+ CD7- CD8-,	**aggressive**, multiply relapsed, s/p TSEBT, bexarotene, romidepsin, died of infection, disease, medical complications
11	***IKZF2-ERBB4*** & ***PML-FBXO25*** 56F, T2NXM0B2, IVA1	erythematous plaques and tumors; leg	CD4+ MF/SS w/ LCT	CD2+ CD3+ CD4+ CD5+ CD7- CD8- CD30+ partial	**aggressive**, multiply relapsed, s/p allogeneic hematopoietic bone marrow transplant and other therapies, including BV, romidepsin, pembrolizumab, mogamulizumab, investigational CAR T-cell therapy, died of disease
Best Characterized as Mycosis Fungoides with an Unusual Phenotype					
12	***FIP1L1-PDGFRA*** & ***TBL1XR1-BCL6*** 55M, T2N0M0B0, IB	erythematous, hyperpigmented nodular plaques; foot	CD8+ MF w/ LCT	CD2+ CD3+ CD4- CD5+ CD7+ CD8+ PD-1+ CD30+ 10% TCR-alpha+	multiply relapsed cutaneous disease, s/p NBUVB, acitretin, MTX, BV, mogamulizumab
13	***RUNX1-ZFHX3*** 66M, T4N0M0B0, IIIA	scaly erythroderma; forearm	CD4+CD8+ MF	CD2- CD3- CD4/CD8 (double +) CD5+ CD7+ CD30 few	**aggressive**, multiply relapsed, s/p bexarotene, MTX, TSEBT, BV, romidepsin, mogamulizumab, CEP, died of infection, disease, complications of therapy
14	***LMNA-ROS1*** 34F, T2N0M0B0, IB	scaly hyper-pigmented annular plaque, buttock	CD4-/CD8- MF with γ/δ phenotype	CD3+ CD4- CD7- CD8- CD30 <5% TCR-delta+	ongoing NBUVB, has not required systemic therapy
Best Characterized as Aggressive Epidermotropic Cytotoxic T-cell Lymphoma					
15	***ETV-GUCY2C*** 60F, T2NXM0B0, IIA	ulcerated plaques; thigh	CD8+ cytotoxic T-cell lymphoma, most c/w CD8+ AETCL vs. pcPTCL-NOS	CD3+ CD4- CD7partial CD8+, Ki67 95%	**aggressive**, multiply relapsed, s/p pralatrexate, ICE, romidepsin, duvelisib, GemOx, ruxolitinib, BV, lacutamab, pembrolizumab

Best Characterized as Primary Cutaneous Peripheral T-cell Lymphoma					
16	***SETD2-LMCD1*** 84F, T3N0M0B0, IIB	eroded and ulcerated tumors; buttock	pcPTCL-NOS vs. CD4-/CD8- MF	CD2- CD3+ CD4/CD8 (double -) CD7- CD30- CCR4+ TIA1+ granzyme B- CD94- TCR gamma/delta -	**aggressive**, multiply relapsed, s/ TSEBT, MTX, ruxolitinib, duvelisib, alemtuzumab, died of disease
17	***NFKB-SMC3*** 51F, T2N2M0B1, IIA	exophytic, hyperpigmented nodule with visible vessels; neck	CD8+ TLPD with admixed FL	CD3+ CD4- CD7- CD8+ CD30-partial TIA1+ Granzyme B+ Ki67 95%	**aggressive**, relapsed disease, initially presented w/ CD8+ T-cell LPD, s/p MTX, developed coexistent FL and DLBCL, treated with R-EPOCH and autoSCT, relapsed T-cell LPD and FL, ongoing treatment with rituximab-lenalidomide

1. This column lists the clinical appearance at the times of fusion detection, followed by the anatomical site of disease from which the fusion was detected.
alloSCT, allogeneic hematopoietic stem cell transplant; amp, amplification; autoSCT, autologous hematopoietic stem cell transplant; BV, brentuximab vedotin; CAR, chimeric antigen receptor; CEP, cyclophosphamide, etoposide, prednisone; CN, copy number; del, deletion; c/w, consistent with; DLBCL, diffuse large B-cell lymphoma; dupl, duplication; Dx., diagnosis; FL, follicular lymphoma; fs, frame shift; GemOx, gemcitabine, oxaliplatin; ICE, ifosfamide, carboplatin, etoposide; incl., including; inv, inversion; LCT, large cell transformation; LPD, lymphoproliferative disorder; MF, mycosis fungoides; MTX, methotrexate; NBUVB, narrow band ultraviolet B light; No., patient number; pcALCL, primary cutaneous anaplastic large cell lymphoma; pc-PTCL-NOS, primary cutaneous peripheral T-cell lymphoma, not otherwise specified; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; s/p, status-post; TSEBT, total skin electron beam therapy.

Supplementary Table 2. Fusion Details and Hypothesized Functions.

Fusion	Fusion Details	Kinase or Trans. Factor	Mutations/CNAs[1]	Prior Reports and Hypothesized Function
Best Characterized as Primary Cutaneous CD30+ T-cell Lymphoproliferative Disorder				
FOXK2-TP63	in-frame; *FOXK2* exon 3 NM_004514; *TP63* exon 4 NM_003722	Kinase: No TF: Both	13 mutations (incl. *CDKN2Ap16INK4*, *CDKN2Ap14ARF*, *FAT1*, *HLA-A*), 1 CN variant (13q loss)	Reported.[7,8] *TP63* fusions coordinate recruitment of epigenetic modifying complexes, including NCoR-HDAC3 and KMT2D. This fusion is predicted to produce a chimeric transcript that dysregulates TP63 expression and/or function, thereby promoting cell survival and proliferation.
TBL1XR1-TP63	in-frame; *TBL1XR1* exon 7, NM_024665; *TP63* exon, NM_003722	Kinase: No TF: TP63	18 mutations (incl. *PRDM1*, *LRP1B*, *TNFAIP3*, *FAS*), 7 CN variants (incl. *CDKN2A* whole gene del)	See above.
CXCL8-BCL6	in-frame; *CXCL8* exon 1, NM_000584; BCL6 exon 2, NM_001706	Kinase: No TF: BCL6	3 mutations (*FLT3*, *EPHA7*, *ERBB4*)	Novel. *CXCL8* encodes IL-8, a pro-inflammatory cytokine, and BCL6 is a transcriptional repressor and a known oncogene in B-cell lymphomas, in particular DLBCL. *BCL6* rearrangements in B-cell lymphoma result in constitutive BCL6 activity.
RORA-PDCD1LG2	in-frame; *RORA* intron 1, NM_134260; *PDCD1LG2* exon 1, NM_025239	Kinase: No TF: RORA	18 mutations (incl. two *TP53* mutations, *U2AF1*, *CD58*)	Novel. *PDCD1LG2* encodes PD-L2, which is involved in recurrent fusions in PMBL, contributing to immune evasion and showing sensitivity to immune-checkpoint blockade. Constitutive or ectopic expression of PD-L2 could allow immune evasion, and could also disrupt RORA-mediated tumor suppressor activity.
VIM1-ROS1	in-frame; *VIM* exon 2, NM_003380; *ROS1* exon 36, NM_002944	Kinase: ROS1 TF: No	1 mutation (*WT1*)	Novel. See above.
DENND1-PBX1	in-frame; *DENND1B* exon 2, NM_001195215; *PBX1* exon 3, NM_002585	Kinase: No TF: PBX1	not tested; concomitant *TBL1XR1-TP63* and *RUNX1-LOC105371750* fusions	Novel. *PBX1* is a TF and known fusion partner in pre-B-cell ALL, whereas DENND1 is a GEF involved in trafficking. This fusion retains PBX1 transcription factor activity and could result in constitutive PBX1 activity under the control of DENND1 promotor activity, resulting in disruption of PBX1 gene regulatory pathways.

RUNX1-LOC105371750	*RUNX1* exon 2, NM_001754	Kinase: No TF: RUNX1	see above (not tested; concomitant *TBL1XR1-TP63* and *RUNX1-LOC105371750* fusions)	Novel. *RUNX1* fusions are common in myeloid leukemias and contribute to leukemogenesis through dominant-negative disruption of RUNX1, as the fusion protein outcompetes wild-type RUNX1 for DNA binding at target genes, frequently blocking differentiation.
Best Characterized as Mycosis Fungoides				
NEK6-PBX1	out-of-frame; *NEK6* exon 7, NM_014397; *PBX1* exon 4, NM_002585	Kinase: NEK6 (possible) TF: PBX1	none detected	Yes (in MCL).[11] *PBX1* is a TF and known fusion partner in pre-B-cell ALL, whereas NEK6 is a serine/threonine kinase that plays critical roles in mitotic progression and spindle formation. Unphysiological activation and truncation of *PBX1* could lead to trans-activation of several genes, promoting cell survival and proliferation.
CD69-MKL1	in-frame; *CD69* exon 1, NM_001781; *MKL1* exon, NM_020831	Kinase: No TF: MKL1	2 mutations (*JAK1*, *ERBB4*)	Novel. *MKL1:RBM15* fusions are associated with acute megakaryoblastic leukemia, and other *MKL1* fusions are observed in other myeloid and lymphoid leukemias. MKL1 is a coactivator of SRF, which has central roles in hematopoietic cell growth and differentiation. This fusion likely leads to constitutive SRF activation.
KMT2A-IFT46	in-frame; *KMT2A* exon 10, NM_005933; *IFT46* exon 9, NM_020153	Kinase: No TF: No (KMT2A is trans. regulator)	11 mutations (incl. *RHOA*, *CKDN1B*, *APC*), 2 structural variants (incl. *KMT2A* dupl. and *EGFR* inv)	Novel. *KMT2A* fusions are common in acute leukemias, though two *KMT2A* fusions have been reported in MF.[14] Most produce an in-frame oncoprotein leading to a gene expression profile normally seen in stem cells, although IFT46 would be a non-canonical partner and may lack coactivator motifs, resulting in a non-functional fusion or loss of *KMT2A* function.
P2RY8-RPRD2	in-frame; *P2RY8* exon 1, NM_178129; *RPRD2* exon2, NM_015203	Kinase: No TF: No	4 mutations (incl. *CDKN2Ap16INK4A*, *CDKN2Ap14ARF*), 3 CN alterations	Novel. P2RY8 is a GPCR frequently rearranged in B-ALL, often with *CRLF2*, resulting in JAK/STAT activation. RPRD2 is a nuclear protein involved DNA damage response, interacting with p53. This fusion is predicted to result in constitutive dimerization and activation via *P2RY8* exon 1 and aberrant nuclear signaling via *RPRD2*'s nuclear localization sequence.
IKZF2-ERBB4	in-frame; *IKZF2* exon 3, NM_016260; *ERBB4* exon2, NM_005235	Kinase: ERBB4 TF: IKZF2	11 mutations (incl. *TP53*, *CREBBP*), 13 CN alterations (incl. *CARD11* amp, *MYC* amp, *CDKN2A* whole gene del, *TP53* whole gene loss)	Reported.[2] This fusion is predicted to co-opt the *IKZF2* promoter for expression and result in overexpression of the ERBB4 kinase.

PML-FBXO25	in-frame; *PML* exon 2, NM_002675; *FBXO25* exon 2, NM_183421	Kinase: No TF: No (PML is trans. regulator)	11 mutations (see above)	Novel. PML fusions are classically observed in APL. The hallmark *PML:RARA* fusion not only transcriptionally represses genes critical in myeloid differentiation but also activations proliferative and self-renewing functions. How this fusion would function in T-cell lineage neoplasms is uncertain.
Best Characterized as Mycosis Fungoides with an Unusual Phenotype				
FIP1L1-PDGFRA	in-frame; *FIP1L1* intron 14, NM_00113493; *PDGFRA* exon 12, NM_006206	Kinase: PDGFRA TF: No	no mutations, 4 CN variants (incl, *FGFR* and *NPM1* whole gene del)	*FIP1L1-PDGFRA* are characteristic of myeloid/lymphoid neoplasms with eosinophilia, most commonly chronic eosinophilic leukemia and hypereosinophilic syndromes. The FIP1L1 portion disrupts autoinhibitory domains of PDGFRA, causing dimerization-independent constitutive activation, sustaining survival pathways.
TBL1XR1-BCL6	in-frame; *TBL1XR1* exon 1, NM_024665; *BCL6* exon 2, NM_001706	Kinase: No TF: BCL6	no mutations (see above)	Novel. *TBL1XR1* has broad biological activity, and BCL6 is a transcriptional repressor and a known oncogene in B-cell lymphomas. See Patient 4.
RUNX1-ZFHX3	in-frame; *RUNX1* exon 2, NM_001754; *ZFHX3* exon 5, NM_006885	Kinase: No TF: Both	6 mutations (*ALK*, *ARID2*, *ARID3B*, *KMT2B*, *NOTCH3*, *PIK3C*)	Novel. *RUNX1* fusions are common in myeloid leukemias and contribute to leukemogenesis through dominant-negative disruption of RUNX1, as the fusion protein outcompetes wild-type RUNX1 for DNA binding at target genes, frequently blocking differentiation.
LMNA-ROS1	in-frame; *LMNA* exon 1, NM_170707; *ROS1* exon 36, NM_002944	Kinase: ROS1 TF: No	not tested	Yes.[6] This fusion likely results in constitutively active ROS1 kinase activity due to retention of the intact C-terminal kinase domain. The extracellular and transmembrane domains of ROS1 are here replaced with LMNA exon 1, which contains a dimerization motif, potentially forcing into a ligand-independent, hyperactive state, therapy sustaining pro-survival signaling (PI3K/AKT, MAPK, STAT3).
Best Characterized as Aggressive Epidermotropic Cytotoxic T-cell Lymphoma				
ETV-GUCY2C	in-frame; *ETV6* exon 1, NM_001987; *GUCY2C* exon 27, NM_004963	Kinase: GUCY2C (possible) TF: ETV	15 mutations (incl. *TP53* fs and *TP53* in-frame del., *FAS*, *KMT2D*, *PLCG1*, *ARID1A*), 12 CN variants (incl. *RAF1* whole gene amp)	Novel. *ETV6* is a common fusion partner in myeloid neoplasms. *ETV6* usually fuses with kinases and results in constitutive activity, though this exact fusion would not retain the pointed domain usually involved in dimerization.

				The kinase-like domain of GUCY2C is retained and could have active phosphorylation function.
Best Characterized as Primary Cutaneous Peripheral T-cell Lymphoma				
SETD2-LMCD1	in-frame; *SETD2* exon 5, NM_014159; *LMCD1* exon 4, NM_033378	Kinase: No TF: No (SETD2 is trans. regulator)	14 mutations (incl. *CREBBP*, *JAK3*, *PTPN2, TP63*), 4 CN alterations (incl. *CDKN1B* whole gene del)	Novel. *SETD2* aberrations are hallmark events in HSTL and MEITL, and fusions are observed in acute leukemias. This fusion likely results in premature truncation of SETD2 and loss of H3K36me3 activity, leading to epigenetic silencing, splicing dysregulation, and genomic instability.
NFKB-SMC3	in-frame; *NFKB* exon 17 NM_002502; SMC3 exon 2, NM_005445	Kinase: No TF: NFKB	2 mutations (*TP53*, *SETD6*), 5 CN variants (incl. *PTEN* and *FAS* whole gene del), also detected *ARHGAP44-TP53* inversion	Novel. *NFKB* coordinates multiple physiologic immune responses and has known dysregulated activity in multiple lymphomas, and *SMC3* is a part of the cohesin complex, which has key roles in chromosome integrity.

1. Listed mutations are considered likely oncogenic as referenced in the OncoKB knowledge base (oncokb.org).

ALL, acute lymphoblastic leukemia; APL, acute promyelocytic leukemia; DLBCL, diffuse large B-cell lymphoma; GEF, guanine nucleotide exchange factor; HSTL, hepatosplenic T-cell lymphoma; MCL, mantle cell lymphoma; MEITL, monomorphic epitheliotropic T-cell lymphoma; trans., transcription; TF, transcription factor.

Supplementary Table 3 provided as Excel file only. Mutational Profiles, Fusion Reads, Tumor Purity.