LETTER TO THE EDITOR

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

## Authors

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**Supplementary Table 1. Disease and Case Overview.**

| No. | Fusion(s) & Demographics at Dx. | Index Lesion Description[1] | Clinical Dx | Immunophenotype | Disease Course |
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| **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 |

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| 8 | ***CD69-MKL1***<br>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***<br>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***<br>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***<br>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***<br>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***<br>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***<br>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***<br>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 |

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| **Best Characterized as Primary Cutaneous Peripheral T-cell Lymphoma** | | | | | |
| 16 | ***SETD2-LMCD1***<br>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***<br>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. |

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| ***RUNX1-LOC105371750*** | *RUNX1* exon 2, NM_001754 | Kinase: No<br>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)<br>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<br>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<br>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<br>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<br>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. |

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| ***PML-FBXO25*** | in-frame; *PML* exon 2, NM_002675; *FBXO25* exon 2, NM_183421 | Kinase: No<br>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<br>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<br>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<br>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<br>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)<br>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. |

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| | | | | 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<br>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<br>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.** Mutational Profiles, Fusion Reads, Tumor Purity.