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

Chromosomal translocations resulting in gene fusions have important implications in human cancer, ranging from diagnostic input to treatment indications.[1] Several recurrent gene fusions have been described in mature T- and NK-cell neoplasms, which comprise a rare, heterogenous group of over 30 distinct clinicopathological entities. The hallmark example is recurrent *ALK* translocations in anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (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 (LPD). These events are well described, including a contemporaneous report from our center and a recent report of pediatric cases.[2,3] However, in other CTCL, 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 polymerase chain reaction[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 the 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 CTCL, 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 Institutional Review Board-approved retrospective research protocol.

In total, we identified 17 patients with 20 unique gene fusions (3 patients had multiple fusions). An overview of these patients is shown in *Online Supplementary Table S1*. Fusions were seen across histological types. Six patients were best characterized as having primary cutaneous CD30$^+$ T-cell LPD, including two with clinicopathological presentations consistent with lymphomatoid papulosis and one with primary cutaneous ALCL. Five patients were best characterized as having MF with a typical CD4$^+$ phenotype, whereas three were considered to have MF with an unusual phenotype, which included one 'double-positive' case (CD4$^+$/CD8$^+$), one 'double-negative' case with a γδ phenotype, and one CD8$^+$ MF with large cell transformation. Finally, two patients were best characterized as having primary cutaneous peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS) and one as having CD8$^+$ AECTCL. As for recurrent gene fusions, *TP63* fusions were detected in three patients with CD30$^+$ T-cell LPD (2 cases with *TBL1XR1-TP63* and 1 with *FOXK2-TP63*, both of which have been previously reported[6,7]). *TBL1XR1*, which has broad biological functions, was present in a separate fusion involving *BCL6* in the patient with CD8$^+$ MF with large cell transformation, and *BCL6* was involved in a separate fusion with *CXCL8* in a patient with lymphomatoid papulosis. Finally, two *ROS1* fusions were detected, one in a patient with lymphomatoid papulosis (*VIM1-ROS1*, novel) and one in the case of double-negative MF with a γδ 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 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. *Online Supplementary Table S2* 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

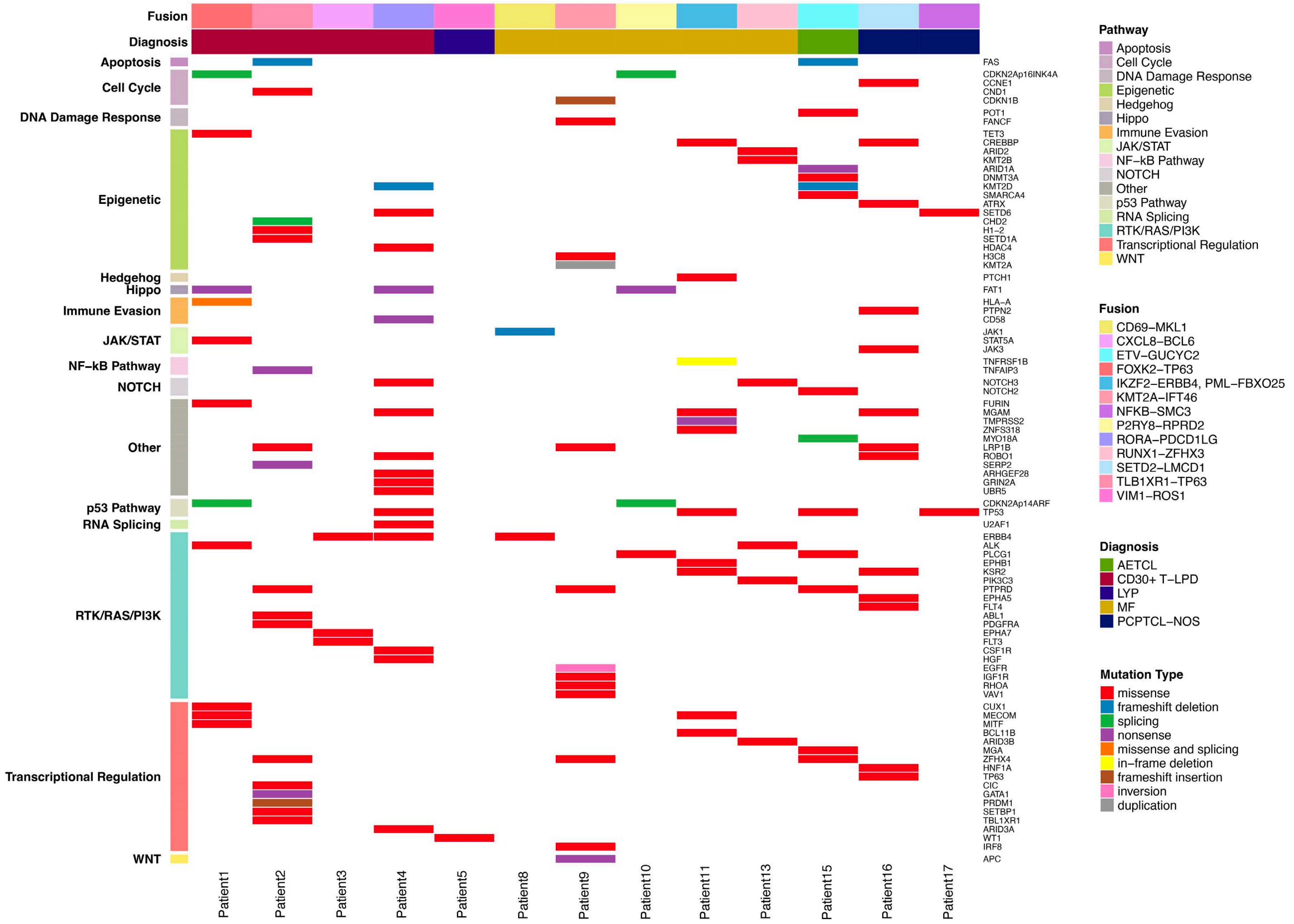


Figure 1. Integrated OncoPrint of genomic alterations. The OncoPrint summarizes alterations across patients. Each column represents an individual patient and each row corresponds to a particular gene. Genes are grouped by biological pathways (left sidebar). Colored bars within the matrix indicate specific mutation types. The top annotation bar shows the detected gene fusion, and the bar immediately below denotes the diagnosis. AETCL: aggressive epidermotropic cytotoxic T-cell lymphoma; CD30⁺ T-LPD: CD30⁺ T-cell lymphoproliferative disorder; LYP: lymphomatoid papulosis; MF: mycosis fungoides; PCPTCL-NOS: primary cutaneous peripheral T-cell lymphoma not otherwise specified.

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 previously reported 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 allogeneic hematopoietic stem cell transplantation and five patients dying of disease and/or infection. The tumor mutational burden varied across cases (Figure 1, *Online Supplementary Table S3*). Some patients had a generally high burden, including patients 1 and 2, each with CD30$^+$ T-cell LPD, *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 a generally low burden, including the two patients with disease behavior most consistent with lymphomatoid papulosis (patients 3 and 5) and the one patient with limited-stage CD4$^+$ MF responsive to topical steroids (patient 7), each having fewer than three mutations (patient 3 with lymphomatoid papulosis had a *WT1* mutation, patient 5 with lymphomatoid papulosis had *FLT3, EPHA7, ERBB4* mutations, and patient 7 with CD4$^+$ MF had no detected mutations). Finally, across histological types, seven patients had *TP53* and/or *CDKN2A* mutations (patients 1, 2, 4, 10, 11, 15, 17), generally uncommon events in CTCL although 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 *Online Supplementary Table S3* as %Reads). Doing so revealed 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. CTCL 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 CTCL, even within the same patient. Gene fusions have been described in PTCL, but their contribution to the pathogenesis and behavior of CTCL 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 did indeed involve either kinases or transcription factors, although despite our attempt to hypothesize function, the true consequences of most of these events and their contribution to pathogenesis are unclear and would require functional studies. The noteworthy exceptions 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 the development of aggressive B- and T-cell lymphomas.[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, although 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, the interpretation of these metrics requires 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 subclonal 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 hematoxylin & eosin 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 subclonality 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 popula-

tion. 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 subclonal 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 the MSK-IMPACT Heme Panel was used, 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 *Online Supplementary Table S3*). 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 CTCL, highlighting the genomic complexity in these heterogeneous diseases. While not routine, evaluation for fusions in multiply relapsed disease may lend insight into disease biology and uncover unrealized potential therapeutic options.

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Contributions

RS, HT, SG and MP identified and annotated the patients, analyzed the data, and drafted the manuscript. RS, HT and MP conceived and designed the study, drafted and revised the manuscript, and approved the final version. All authors contributed to the patients’ care, reviewed the final manuscript, and approved its submission.

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Data-sharing statement

The data used for this study are not publicly available in order to protect patients’ confidentiality. Reasonable requests for deidentified data should be directed to the corresponding author.

References

1. Mertens F, Johansson B, Fioretos T, Mitelman F. The emerging complexity of gene fusions in cancer. Nat Rev Cancer. 2015;15(6):371-381.
2. Geller S, Liao V, Lavin L, et al. JAK2 fusions in adult patients with mycosis fungoides and CD30 lymphoproliferative disorders. JAMA Dermatol. 2026;162(1):41-46.
3. Fischer GM, Tsai HK, Huang J, et al. Genomic profiling of pediatric mycosis fungoides, lymphomatoid papulosis, and

primary cutaneous anaplastic large cell lymphoma identifies recurrent tyrosine kinase gene fusions. Mod Pathol. 2025;38(12):100908.
4. Zheng Z, Liebers M, Zhelyazkova B, et al. Anchored multiplex PCR for targeted next-generation sequencing. Nat Med. 2014;20(12):1479-1484.
5. Ptashkin RN, Ewalt MD, Jayakumaran G, et al. Enhanced clinical assessment of hematologic malignancies through routine paired tumor and normal sequencing. Nat Commun. 2023;14(1):6895.
6. Wu G, Yoshida N, Liu J, et al. TP63 fusions drive multicomplex enhancer rewiring, lymphomagenesis, and EZH2 dependence. Sci Transl Med. 2023;15(714):eadi7244.
7. Chavan RN, Bridges AG, Knudson RA, et al. Somatic rearrangement of the TP63 gene preceding development of mycosis fungoides with aggressive clinical course. Blood Cancer J. 2014;4(10):e253.
8. DeRosa PA, Alqutub S, Papastavros V, Lichy JH, Maiberger M, Nava VE. Refractory periungual stage II mycosis fungoides with novel LMNA-ROS1 fusion. JAAD Case Rep. 2020;6(9):942.
9. Chen X, Wang W, Yeh J, et al. Clinical validation of FusionPlex RNA sequencing and its utility in the diagnosis and classification of hematologic neoplasms. J Mol Diagn. 2023;25(12):932-944.
10. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med. 2003;348(13):1201-1214.
11. Argyropoulos KV, Pulitzer M, Maura F, et al. Targeted genomic analysis of cutaneous T cell lymphomas identifies a subset with aggressive clinicopathological features. Blood Cancer J. 2020;10(11):1-5.
12. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. Blood. 2012;120(11):2280-2289.
13. Suehnholz SP, Nissan MH, Zhang H, et al. Quantifying the expanding landscape of clinical actionability for patients with cancer. Cancer Discov. 2024;14(1):49-65.
14. Scarfò I, Pellegrino E, Mereu E, et al. Identification of a new subclass of ALK-negative ALCL expressing aberrant levels of ERBB4 transcripts. Blood. 2016;127(2):221-232.
15. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21(2):261-270.