www.nature.com/modpathol

REVIEW ARTICLE

Genetic profiling and biomarkers in peripheral T-cell lymphomas: current role in the diagnostic work-up

Francisco Vega[1]✉, Catalina Amador[2], Amy Chadburn[3], Eric D. Hsi[4], Graham Slack[5], L. Jeffrey Medeiros[1] and Andrew L. Feldman[6]

Peripheral T-cell lymphomas are a heterogeneous, and usually aggressive, group of mature T-cell neoplasms with overlapping clinical, morphologic and immunologic features. A large subset of these neoplasms remains unclassifiable with current diagnostic methods ("not otherwise specified"). Genetic profiling and other molecular tools have emerged as widely applied and transformative technologies for discerning the biology of lymphomas and other hematopoietic neoplasms. Although the application of these technologies to peripheral T-cell lymphomas has lagged behind B-cell lymphomas and other cancers, molecular profiling has provided novel prognostic and diagnostic markers as well as an opportunity to understand the biologic mechanisms involved in the pathogenesis of these neoplasms. Some biomarkers are more prevalent in specific T-cell lymphoma subsets and are being used currently in the diagnosis and/or risk stratification of patients with peripheral T-cell lymphomas. Other biomarkers, while promising, need to be validated in larger clinical studies. In this review, we present a summary of our current understanding of the molecular profiles of the major types of peripheral T-cell lymphoma. We particularly focus on the use of biomarkers, including those that can be detected by conventional immunohistochemical studies and those that contribute to the diagnosis, classification, or risk stratification of these neoplasms.

Modern Pathology (2022) 35:306–318; https://doi.org/10.1038/s41379-021-00937-0

INTRODUCTION

Peripheral T cell lymphomas (PTCLs) represent lymphoid malignancies derived from mature (peripheral or post-thymic) T cells and constitute ~10–15% of all non-Hodgkin lymphomas in Western countries. PTCLs are rare, with an age-adjusted incidence of less than 1 per 100,000 and fewer than 4000 total cases diagnosed annually in the United States[1]. PTCLs are more common in Asian nations.

In the current World Health Organization (WHO) classification of lymphomas, more than 30 established and provisional neoplastic T-cell entities are recognized, subdivided into four major groups based on clinical presentation and disease site: nodal, extranodal, leukemic and cutaneous[2]. Nodal PTCLs account for over 50% of all mature T-cell neoplasms, and include PTCL, not otherwise specified (PTCL-NOS), systemic ALK-positive (ALK+) and ALK-negative (ALK-) anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL) and related lymphomas with a T follicular helper (TFH) cell phenotype. Extranodal and leukemic subtypes include hepatosplenic T-cell lymphoma, extranodal NK/T-cell lymphoma, aggressive and indolent intestinal lymphomas, adult T-cell leukemia-lymphoma and Sezary syndrome among others. Mycosis fungoides (MF) is the most common form of primary cutaneous T cell lymphoma. Leukemic T-cell lymphomas, MF and other primary cutaneous T cell lymphomas, except primary cutaneous ALCL, will not be discussed here.

In most academic institutions, the diagnostic approach for most mature T-cell neoplasms is based mostly on a combination of clinical, morphologic and immunophenotypic findings[3]. Genetic profiling is a routine component of the diagnostic workup for an increasing number of neoplasms, and is used to predict clinical outcomes and responses to targeted therapies, e.g., in acute leukemias and myelodysplastic syndromes. Although the mutational and genetic landscape of most PTCLs have not been fully characterized and genetic profiling of T-cell neoplasms is not part of the routine work up at most centers, a growing body of research data from molecular studies is helping to refine the current classification and support the incorporation of additional entities to the current schema. In addition, these genetic and molecular studies contribute to refining prognostic models and facilitating novel treatment opportunities in some PTCL patients[4].

In this paper, we summarize the current mutational and genetic landscape of PTCLs emphasizing biomarkers that have an established or potential role in the work-up of these neoplasms. A list of biomarkers with potential relevance in the work-up of mature T-cell lymphomas is listed in Table 1. Additional work is needed to confirm the utility of some of these biomarkers, to extend emerging biological findings to a biomarker-driven

[1]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [2]Department of Pathology and Microbiology, University of Nebraska, Omaha, NE, USA. [3]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY, USA. [4]Department of Laboratory Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA. [5]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada. [6]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. ✉email: fvega@mdanderson.org

Received: 6 August 2021 Revised: 15 September 2021 Accepted: 16 September 2021
Published online: 28 September 2021

Table 1. Genetic findings and biomarkers with potential relevance in the work-up of ALCL.

Biomarker	Test	Purpose	Disease	Comment
ALK expression	IHC	Diagnosis	ALCL, ALK+	Surrogate for *ALK* rearrangement
ALK rearrangements	FISH or NGS	Diagnosis	ALCL, ALK+	Useful when ALK IHC is non-contributory
ALK mutations	NGS	Predictor of response	ALCL, ALK+	Resistance to ALK inhibitors
NOTCH1 mutation[a,16]	NGS	Predictor of response	ALCL, AL +	Potential sensitivity to targeted therapy
DUSP22 rearrangement[19,20]	FISH	Prognosis and treatment	ALCL, ALK−	Favorable prognosis in systemic ALCL; consideration of modified treatment algorithm
TP63 rearrangement[24]	FISH	Prognosis	ALCL, ALK−	Aggressive behavior in systemic ALCL
JAK1 and *STAT3*[27]	NGS	Prognosis and treatment	ALCL, ALK−	Could help in the diagnosis of ALK-ALCL and potentially targetable
Loss chr 20[a,41]	FISH	Diagnosis	BIA-ALCL	Relatively specific

ALK anaplastic lymphoma kinase, *ALCL* anaplastic large cell lymphoma, *DUSP22* dual specificity phosphatase 22, *IHC* immunohistochemistry, *BIA-ALCL* breast implant-associated anaplastic large cell lymphoma.
[a]Based on limited data, pending validation.

classification, and to improve the risk stratification and treatment of patients with these neoplasms.

ANAPLASTIC LARGE CELL LYMPHOMAS (ALCL)

ALK-positive ALCL

ALK-positive ALCL is a systemic T-cell lymphoma defined by neoplastic cells with characteristic morphology (hallmark cells), uniform expression of CD30, and rearrangement of the *ALK* gene[5,6]. ALK-positive ALCL has a slight male predominance but, unlike most other T-cell neoplasms, has a peak incidence in the second decade of life. ALK-positive ALCL typically involves lymph nodes but involvement of extranodal sites, including skin, soft tissue, bones, lungs, and liver, is often seen. Several morphologic variants are recognized. Immunohistochemistry demonstrates the presence of CD30 and ALK. Aberrant loss of one or more T-cell markers is common. Most patients have a favorable prognosis. Treatment approaches include systemic combination chemotherapy, the CD30 antibody-drug conjugate brentuximab vedotin, and in some cases ALK small molecule inhibitors[7,8].

Genetics and molecular profiling

ALK-positive ALCLs carry rearrangements of *ALK* on chromosome 2p23. The most common partner gene is *NPM1* on chromosome 5q35.1, followed by *TPM3*, *ATIC*, and a variety of other rare partners[5]. The biological and clinical significance of the partner gene is unknown. *ALK* rearrangements result in gene fusions that encode ALK fusion proteins; these proteins homodimerize, leading to constitutive ALK activation and a wide array of oncogenic functions including JAK-STAT3 pathway activation[9]. Other chromosomal rearrangements have not been comprehensively studied, although concurrent *MYC* rearrangements may be associated with adverse outcomes. Recurrent chromosomal gains (e.g., 1q, 2, 7q, 8q, 11, 17q) and losses (e.g., 4, 6q, 13q, 17p) have been reported but are less common than in ALK-negative ALCL[5,10,11]. ALK-positive ALCL has a reproducible gene expression signature, in part attributable to JAK-STAT3 activation, expression of cytotoxic molecules, and Th17-like features[12–14]. The mutational landscape of ALK-positive ALCL has not been entirely characterized, but includes recurrent mutations of *TP53*, epigenetic modifying genes, and genes in the T-cell receptor and Notch signaling pathways[15,16]. Recurrent *NOTCH1* T349P and T311P mutations may confer sensitivity to targeted therapy[16].

ALK-negative ALCL

ALK-negative ALCL is a systemic T-cell lymphoma lacking *ALK* rearrangements but otherwise resembling ALK-positive ALCL, including the presence of hallmark cells and expression of CD30[6,17]. Like ALK-positive ALCL, ALK-negative ALCL has a slight male predominance, but this disease is relatively more common in older adults with a peak incidence in the 6th decade.

ALK-negative ALCL typically involves lymph nodes; extranodal involvement occurs but is less common than in ALK-positive ALCL. Morphologic variants are not recognized. Aberrant T-cell antigen loss is common. Patients generally have a poorer prognosis than patients with ALK-positive ALCL, but prognosis also varies by genetic subtype (see below)[18,19]. Front-line treatment approaches include combination chemotherapy and BV, with or without consolidative autologous stem-cell transplantation[7].

Genetics and molecular profiling

ALK-negative ALCLs, by definition, lack ALK rearrangements. Two recurrent chromosomal rearrangements with clinical significance have been identified. Rearrangements of *DUSP22* on chromosome 6p25.3 occur in about 30% of ALK-negative ALCLs and can be detected by fluorescence in situ hybridization (FISH)[19,20]. About half of these cases have a non-genic partner locus on 7q32.3, whereas the partners in other cases have not been characterized. ALK-negative ALCLs with *DUSP22* rearrangements have distinct features. Morphologically, these neoplasms are composed of a monotonous population of medium-sized cells, often with nuclear pseudoinclusions (doughnut cells)[21]. By immunohistochemistry, they generally express LEF1 and HLA-DR and lack expression of cytotoxic markers and phosphorylated STAT3[14,19]. These neoplasms have a unique gene expression signature characterized by cancer-testis antigen expression and show global DNA hypomethylation[14,22]. Clinically, patients have a favorable prognosis, like patients with ALK-positive ALCL, although high-risk cases with aggressive disease have been described[23].

A second group of ALK-negative ALCLs, about 8%, have rearrangements of *TP63* on chromosome 3q28, most frequently resulting from an inversion involving *TBLXR1* on 3q26.3[24]. The rearrangement encodes a fusion protein that lacks the transactivation domain of *TP63* analogous to oncogenic ΔNp63 isoforms. Patients with these neoplasms have extremely poor outcomes[19]. Occasional cases have co-existing *DUSP22* rearrangements[25]. Other fusions seen recurrently in ALK-negative ALCL involve the tyrosine kinase genes *TYK2* or *ROS1* and contribute to JAK-STAT3 activation analogous to the role of *ALK* fusions in ALK-positive ALCL[26,27].

Recurrent oncogenic truncation of *ERBB4* also has been described[28]. Losses involving *TP53* and/or *PRDM1* occur more frequently in ALK-negative ALCL than in ALK-positive ALCL and have adverse prognostic significance[11]. Genes recurrently mutated in ALK-negative ALCL include *TP53*, *JAK1*, *STAT3*, *PRDM1*, *KMT2D*, *KRAS*, *TET2*, and *NOTCH1*[27]. A single point mutation E116K

of the basic helix-loop-helix gene *MSC* is highly recurrent in ALK-negative ALCL with *DUSP22* rearrangements[29].

Primary cutaneous ALCL

Primary cutaneous (pc) ALCL is a localized form of ALCL presenting in the skin and is part of a spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders that also includes lymphomatoid papulosis and borderline cases[6,30]. Patients with documented MF are excluded. The male:female ratio is 2-3:1 and the median age is 60 years. Morphologic and immunophenotypic features are similar to systemic ALCL, and hallmark cells are generally present. CD30 should be expressed in >75% of the lymphoma cells. Nearly all cases are ALK negative. Clinical staging is required to exclude cutaneous involvement by systemic ALCL. Although pcALCL may be locally destructive, the prognosis is generally favorable.[31] Frontline treatment generally consists of surgical excision and/or radiotherapy, with BV and/or chemotherapy in more advanced cases[32].

Genetics and molecular profiling

pcALCL lacks *ALK* rearrangements in most cases[30]. The classification of the few (~3%) cases with *ALK* rearrangements and expression of ALK remains unclear; at least some cases have a clinical course similar to that of typical pcALCL[33]. Other rearrangements seen in systemic ALK-negative ALCL are also seen in pcALCL, including those involving *DUSP22*, *TP63*, and *TYK2*[6,20,24,26]. pcALCL shows copy number abnormalities distinct from mycosis fungoides and other cutaneous T-cell lymphomas[34,35]; however, molecular features distinguishing pcALCL from systemic ALCLs remain unclear. In a gene expression profiling study combining pcALCLs and systemic ALCLs, cases preferentially clustered by genetic subtype rather than by anatomic site of presentation[14]. Similarly, while the mutational landscape of pcALCL has not been completely elucidated, mutations seen in systemic ALK-negative ALCL are observed, including those involving *JAK1* and *STAT3* as well as *MSC* E116K in cases with *DUSP22* rearrangements[6,27,29].

Breast implant-associated ALCL

Breast implant-associated (BIA) -ALCL is a rare form of ALCL presenting in association with prosthetic breast implants placed for either cosmetic or reconstructive purposes[6,17]. Virtually all patients are women. The mean age at presentation is 50 years and the median interval after implant placement is 11 years. Early diagnosis may be established in cytology preparations from peri-implant seroma fluid. Tissue diagnosis is generally made in capsulectomy specimens and occasionally in locoregional lymph nodes or distant sites. Morphologic and phenotypic features are similar to other ALCL types. The neoplastic cells uniformly express CD30, are ALK negative and often show aberrant T-cell antigen loss. A TNM staging system has been proposed and invasion, the presence of a mass, and lymph node involvement are adverse prognostic features[36–38]. Localized disease may be managed with implant removal and capsulectomy alone, but systemic chemotherapy is required for patients with advanced stage disease[39].

Genetics and molecular profiling

All cases studied to date have lacked rearrangements of *ALK*, *DUSP22*, and *TP63*[40]. Recurrent losses of chromosome 20 have been reported and are relatively specific for BIA-ALCL[41]. Recurrent gains of 9p24.1 associated with *CD274* (PD-L1) expression have been reported[42]. BIA-ALCL has a unique gene expression profile that distinguishes it from other ALCL types and other T-cell lymphomas, including up-regulation of cell motility genes such as the tyrosine kinase *MET* and hypoxia-associated genes such as carbonic anhydrase IX (*CA9*)[43,44]. The levels of several proteins are elevated in seroma fluid from BIA-ALCL patients, including CD30, CA9, and cytokines such as IL10 and IL13[44]. Like other ALK-negative ALCLs, recurrent mutations of *JAK1*, *JAK3*, and *STAT3* occur in BIA-ALCL[6,40,45,46]. The frequencies of mutations in epigenetic modifying genes, particularly *KMT2C*, *CREBBP*, and *CHD2*, appear higher than in other ALCL types[46]. Germline mutations of *TP53* (Li-Fraumeni syndrome) and an increased prevalence of *BRCA1* and *BRCA2* mutations have been reported in women with BIA-ALCL[47,48].

Current role of genetic testing in workup of ALCLs

Genetic findings and potential biomarkers in all types of ALCL are summarized in Table 1. Immunohistochemistry for ALK is necessary in the work-up of all cases; FISH or next-generation sequencing (NGS) studies to assess *ALK* rearrangements may be helpful in some cases. FISH for *DUSP22* rearrangement should be performed in ALK-negative cases because of the prognostic implications and these patients may be considered for clinical algorithms used for patients with ALK-positive ALCL[49]. We also recommend FISH for *TP63* rearrangement for prognostic purposes and to identify rare cases with co-existent *DUSP22* and *TP63* rearrangements. Currently, mutation testing of ALCL cases is not standard in routine clinical practice.

Peripheral T cell lymphoma, not otherwise specified

PTCL-NOS is one of the most common types of PTCL, accounting for 30–50% of all PTCL cases. By definition, PTCL-NOS does not represent a uniform entity but instead is a heterogeneous group of lymphomas that cannot be assigned to more specific PTCL entities. Therefore, the morphologic, immunophenotypic, cytogenetic, and molecular features of PTCL-NOS are variable.

Genetics and molecular profiling

Using gene expression profiling (GEP), two novel biological subgroups with different diagnostic signatures have been identified within the PTCL-NOS group[13]. One subgroup is characterized by high expression of GATA3 and its target genes (e.g., *CCR4, IL18RA, CXCR7)* and is associated with high *MYC* and proliferation signatures, lack of a prominent microenvironmental signature, and poor clinical outcome. The other subgroup is characterized by high expression of TBX21 and its target genes (e.g., *EOMES, CXCR3, IL2RB, CCL3, IFN*γ) and enrichment of the NF-kB pathway and is characterized by a more favorable outcome. In addition, these groups show differences in their copy number aberrations, with higher genomic complexity in the high GATA3 subgroup[50]. The different outcomes of these subgroups were subsequently observed in an independent study using immunohistochemistry to categorize both subgroups[51]. An immunohistochemistry algorithm has been proposed using four antibodies specific for GATA3, CCR4, TBX21, and CXCR3 to apply this classification to clinical practice[51]. Whereas the identification of the GATA3 and TBX21 groups currently has no impact on frontline treatment decisions, this classification may impact the clinical management of PTCL-NOS patients in the future, as these two subgroups may be amenable to different treatments.

Limited data are available regarding the mutational landscape of PTCL-NOS. In addition, it is difficult to appreciate the actual frequency of genomic abnormalities in PTCL-NOS, in part because the WHO classification in 2016 recognized nodal PTCL with TFH phenotype, and in older studies these neoplasms were included within the PTCL-NOS group. Only a few studies have evaluated the genomic landscape of PTCL-NOS using current WHO classification criteria[50,52–54].

As in other hematologic neoplasms, mutations/deletions in tumor suppressor genes are frequently described in PTCL-NOS and are usually associated with a poorer prognosis. Aberrations in *TP53* signaling (biallelic deletions/mutations) are primary seen in PTCL-GATA3 cases and are associated with deletions of *PTEN* and *CDKN2A*[50]. These aberrancies are relevant because are associated with a poorer prognosis. TP53 mutations occur in the DNA binding

Table 2. Genetic findings and biomarkers with potential relevance in the work-up of PTCL-NOS.

Biomarker	Test	Purpose	Disease	Comment
TBX21/CXCR3 expression[51]	IHC	Prognosis	PTCL-TBX21	Biological subgroup of PTCL-NOS
GATA3/CCR4 expression[51]	IHC	Prognosis	PTCL-GATA3	Biological subgroup of PTCL-NOS
CDKN2A deletion[50]	FISH	Prognosis	PTCL, NOS	Deletion of *CDKN2A* and *PTEN* highly specific for PTCL-NOS
PTEN deletion[55]	FISH	Prognosis	PTCL, NOS	Deletion of *CDKN2A* and *PTEN* highly specific for PTCL-NOS
PT53 deletions and mutations[50]	FISH and NGS	Prognosis	PTCL-NOS	Enriched in PTCL-GATA3 cases[a]. Adverse prognosis.
FAT1 mutations[a,53]	NGS	Prognosis	PTCL, NOS	Adverse prognosis
JAK2 rearrangement[60]	FISH	Diagnosis	PTCL, NOS	Features resembling CHL including expression of CD15

PTCL-NOS peripheral T cell lymphoma, not otherwise specified, *CHL* Classic Hodgkin lymphoma, *TBX21* T-box transcription factor 21, *GATA3* GATA binding protein 3.
[a]Based on limited data, pending validation.

and tetramerization domains, including the hotspot $TP53^{R175H}$[50]. Immunohistochemistry is useful in identifying mutations in TP53, and therefore has some clinical utility in the diagnostic setting. A subsequent study identified a distinct poor prognosis subgroup characterized by *TP53/CDKN2A* mutations and deletions, accompanied by chromosomal instability and mutations in *IKZF2* and genes associated with immune escape (such as *HLA-A* and *HLA-B, CIITA, CD274*, and *CD58*)[52]. A whole genome sequencing study with subsequent FISH analysis showed that *CDKN2A* and *PTEN* deletions are frequently encountered in PTCL-NOS, 46% and 26% of cases, respectively, and similarly associated with a poorer prognosis[55]. Furthermore, coexisting co-deletion of *CDKN2A* and *PTEN* was reported to be a highly specific finding for PTCL-NOS as compared with AITL and ALK-negative and ALK-positive ALCL[55].

Mutations in genes encoding DNA modifying enzymes such as *TET2* and *DNMT3A* have been described in PTCL-NOS[50,52,54,56,57]. However, after separation of cases of PTCL with TFH phenotype from the PTCL-NOS group, it has become apparent that genetic aberrations in epigenetic regulators are less frequent in PTCL-NOS. *DNMT3* mutations are rarely detected in PTCL-NOS without a TFH phenotype[52,57]. On the other hand, *TET2* mutations occur in ~20% of cases of PTCL-NOS[52,54,57]. In one of these studies, *TET2* mutations occurred predominantly in association with *TP53/CDKN2A* alterations[52]. Similar to other types of T-cell lymphoma, mutations in *PLCG1* (~25%), *CD28* (~20%), *and VAV1 (~5%)* are encountered in PTCL-NOS[52,58]. These mutations have been recently described in association with *TP53/CDKN2A* alterations, and rarely in PTCL-NOS without these abnormalities[52]. $IDH2^{R172}$ [57,59] *and* $RHOA^{G17V}$ [57] mutations are usually not detected in PTCL-NOS cases. A targeted sequencing study identified recurrent mutations of *FAT1* in a subset of PTCL-NOS cases[53]. *FAT1* is a tumor suppressor gene that encodes a protein that binds to β-catenin and inhibits nuclear localization, thus inhibiting cell growth. Recurrent mutations in *FAT1* were observed in 39% of cases of PTCL-NOS and were associated with inferior outcome.

A recent study has described *JAK2* rearrangements in a small subset of PTCL cases expressing CD30 that have Hodgkin-like morphologic features. Five different fusion partners were identified: poly(A) binding factor 3 (*ILF3*), pericentriolar material 1 (*PCM1*) and microtubule associated protein 7 (*MAP7*)[60]. Recurrent fusion transcripts have been identified in a subset of PTCL-NOS cases including *VAV1-MYOF*, *VAV1-THAP4*, *VAV1-S100A7*, *TBL1XR1-TP63*, *FYN-TRAF3IP2*, *KHDRBS1-LCK*.[24,61,62] *FYN-TRAF3IP2* was also detected in some cases of nodal PTCL with TFH phenotype[61].

Current role of genetic testing in workup of PTCL-NOS

Genetic findings and potential biomarkers in PTCL-NOS are summarized in Table 2. The immunohistochemical algorithm for PTCL-NOS is not required for diagnosis, but we suggest this algorithm be used based on its prognostic value and the possibility that it likely will become standard-of-care in the future. The role of gene mutations in PTCL-NOS is currently being defined. Data described above suggest that routine testing for *TP53, CDKN2A*, and *PTEN* in PTCL-NOS may be relevant for refining the prognosis of PTCL-NOS patients. However, larger studies are needed to propose testing of these genes in routine clinical practice. Gene mutation testing also can be helpful in excluding other categories of T-cell lymphoma, particularly nodal PTCL with a TFH phenotype.

Angioimmunoblastic T-cell lymphoma, nodal PTCL with a TFH phenotype and follicular T-cell lymphoma

Three nodal lymphomas express signatures typical for TFH cells: AITL and two related tumors, nodal PTCL with a TFH phenotype and follicular T-cell lymphoma (FTCL). The lymphoma cells have a TFH immunophenotype as shown by expression of TFH markers such as CD10, BCL-6, PD1/CD279, ICOS, and CXCL13.[2] The WHO classification recommends that at least, 2 but ideally 3 or more TFH markers be expressed to support TFH lineage.

Angioimmunoblastic T-cell lymphoma

AITL is the second most common type of PTCL in Northern Europe and in our own experience at our own institution, representing 15 to 20% of all cases[63]. AITL is most frequent in middle-aged and elderly patients. Patients usually present with generalized lymphadenopathy (typically less than 3 cm), hepatosplenomegaly, constitutional symptoms, and skin rash and usually have evidence of immune dysregulation (e.g., coombs-positive hemolytic anemia, cold agglutinins, polyclonal hypergammaglobulinemia)[64]. The diagnosis of AITL is based on a combination of clinical, histologic and immunophenotypic features. Distinctive histologic features include expansion of B-cells, proliferation of arborizing high endothelial venules (HEV) surrounded by expanded networks of follicular dendritic cells (FDCs), numerous plasma cells, and scattered EBV + activated B-cells (in ~80% of cases).

Genetics and molecular profiling

AITL shows lower genomic complexity than other PTCLs, with frequent co-occurring gains of chromosomes 5 and 21[50]. Other chromosomal gains (e.g., 7q, 11, 19 or 22q) occur in less than 10% of the cases.[57] AITL frequently has mutations in genes involved in epigenetic pathways such as *TET2* (40–80%), $IDH2^{R172}$ (20–45%) and *DNMT3A* (20–30%) as well as mutations in the small GTPase $RHOA^{G17V}$ (50–70%). Mutations in components of the T-cell receptor (TCR) signaling pathway such as *PLCG1*, *CD28*, *FYN*, and *VAV1* are also seen. Mutations in $RHOA^{G17V}$ and $IDH2^{R172}$ have been shown to correlate with some of the distinctive features of AITL. AITL with $RHOA^{G17V}$ mutations, in comparison with the *RHOA* wild-type cases, have higher blood vessel density, more FDC perivenular expansion and express a greater number of TFH markers[65,66]. AITL with $IDH2^{R172}$ mutations are characterized by medium-sized to large tumor cells, some with clear cytoplasm,

Table 3. Genetic findings and biomarkers with potential relevance in the work-up of AITL and other PTCL with a TFH phenotype.

Biomarker	Test	Purpose	Disease	Comment
RHOA^{G17V} *mutations*[51,71,73]	NGS	Diagnosis and treatment	TFH lymphomas	Predict response to HDACi
DNMT3A mutations[51,71,73]	NGS	Diagnosis and treatment	TFH lymphomas	Predict response to HDACi
IDH2^{R172} *mutations*[57,67]	NGS and IHC	Diagnosis and treatment	AILT	Specific for AILT. Predict response to HDACi
ITK-SYK[74]	FISH	Diagnosis and treatment	FTCL	Sensitivity to SYKi
FER and *FES* translocations[73]	FISH and sequencing	Diagnosis and treatment	FTCL	Potential use of FER and FESinh or STAT3i

IDH2 isocitrate dehydrogenase 2, *DNMT3A* DNA methyltransferase, *FTCL* follicular T-cell lymphoma, *TFH* T follicular helper, *AILT* angioimmunoblastic T cell lymphoma, *HDACi* histone deacetylase inhibitors, *SYK* spleen tyrosine kinase.

and strong CD10 and CXCL13 expression[67]. *IDH2*^{R172} mutated cases are also enriched for gains of chromosomes 5 and 21[50]. *TET2* and *DNMT3A* mutations are not specific to AITL; however, different from other neoplasms, these two mutations frequently co-occur in AITL. Interestingly, *TET2* and *DNMT3A* mutations are not restricted to T-cells, but also can be identified in the admixed B-cells and in hematopoietic stem cells of patients with AITL, whereas *RHOA*^{G17V} and *IDH2*^{R172} mutations appear confined to the neoplastic T-cells[68–70].

Nodal PTCL with a TFH phenotype

Some nodal CD4-positive TCLs that lack the diagnostic morphologic features of AITL nevertheless express several TFH markers and have a mutational and expression profiling similar to AITL, prompting the provisional category of nodal PTCL with a TFH immunophenotype in the WHO classification[2]. Nodal PTCL with a TFH immunophenotype is not a rare T-cell neoplasm, since ~40% of neoplasms once designated as PTCL-NOS express TFH markers.

Genetics and molecular profiling

The mutational profile of nodal PTCL with a TFH phenotype seems to be similar to AITL with mutations in *TET2, DNMT3A*, and *RHOA*^{G17V} [57,71]. However, *IDH2*^{R172} mutations seem to be restricted to AITL and *TET2* mutations seem to be slightly more frequent in nodal PTCL with a TFH phenotype[57]. Both neoplasms also share mutations in genes of the TCR signaling pathway, except *CD28* mutations that seem to be restricted to AITL[71]. The chromosomal copy number gains seen in AITL occur with similar frequencies in nodal PTCL with a TFH phenotype[57].

Follicular T-cell lymphoma

FTCL has a follicular growth pattern, mimicking follicular lymphoma, with follicles populated by aberrant T cells that express TFH markers[72]. In FTCL, Hodgkin and Reed-Sternberg (HRS)-like cells are frequently noted. These HRS-like cells are of B-cell lineage, positive for CD30 and, in a subset of cases, positive for CD15 and EBER raising concern for classic Hodgkin lymphoma. In contrast to AITL, FTCL lacks proliferation of HEVs and perivenular expansion of FDCs.

Genetics and molecular profiling

The mutational profile of FTCL seems to be similar to AITL and nodal PTCL with a TFH phenotype with mutations in *TET2, IDH2*^{R172}, *DNMT3A*, and *RHOA*^{G17V} [73]. *TET2* mutations seem to be more frequent in FTCL than in AITL and nodal PTCL with a TFH phenotype. FTCLs harbor a characteristic t(5;9)(q33;q22) resulting in an *ITK-SYK* fusion in ~40% of cases[74]. The ITK-SYK fusion acts as a constitutively active SYK tyrosine kinase and drives lymphomagenesis by triggering antigen-independent activation of TCR signaling. Translocations involving *FER* and *FES* have been recently described including *ITK-FER* and *RLTPR-FES* that result in activation of STAT3 signaling[73].

Current role of genetic testing in workup of T-cell lymphomas with TFH phenotype

Genetic findings and potential biomarkers in T-cell lymphomas with TFH phenotype are summarized in Table 3. Immunohistochemistry with an anti-IDH2^{R172K} antibody is highly sensitive for the detection of AITL with *IDH2*^{R172} mutations[75]. This test could be used as a first step for diagnosing AITL with *IDH2*^{R172} mutations. In addition to its diagnostic relevance, the identification of patients with mutated *IDH2* may be clinically relevant because specific IDH2 inhibitors are currently in clinical trials. Mutations in *DNMT3A, TET2, IDH2*^{R172}, and in *RHOA*^{G17V} are common in PTCLs with a TFH phenotype and are helpful in supporting the diagnosis. Early phase clinical trials with hypomethylating agents and histone deacetylase inhibitors show promise in T-cell lymphomas related to AITL, and there is interest in determining whether TFH-related lymphomas may preferentially respond to such agents[76].

The t(5;9)(q33;q22)/*ITK-SYK* appears to be specific for FTCL and is only rarely reported in AITL[77]. Targeted therapy with SYK inhibitors may be helpful in patients with these neoplasms[74,78]. *ITK-FER* and *RLTPR-FES* seem to be specific for FTCL and also represent potential targets for inhibition.

Extranodal NK/T cell lymphoma, nasal type

Extranodal NK/T cell lymphoma (ENKTL) is an EBV-associated neoplasm that is most common in Asia or Central/South America, but also occurs uncommonly in industrialized nations. About two-thirds of these lesions are thought to be of natural killer (NK) -cell origin, but one third are of T-cell lineage. The NK- and T-cell forms of ENKTL are morphologically and clinically very similar, but they differ with respect to immunophenotype and genotype. The NK-cell lesions express CD2, CD56, and cytoplasmic CD3 and lack evidence of T-cell clonality, whereas the T-cell lesions express surface CD3 and carry monoclonal T-cell receptor gene rearrangements. There are also two "anatomic variants" of ENKTL, nasal and extra-nasal, which are associated with different clinical findings and outcomes, with the extra-nasal form having a worse prognosis[3]. Morphologically, ENKTL with nasal or extra-nasal presentation is frequently characterized by vascular damage, tissue destruction and necrosis.

Genetics and molecular profiling

The genetic composition of ENKTL is complex and overlaid by EBV infection and the associated immune environment[79]. There are genetic differences based on geographic location implying differences in genetic predisposition[80]. Two major genome-wide association studies in Asian populations have been published with epidemiologic data suggesting that genetic or environmental factors predispose some individuals to ENKTL[81,82]. These studies identified single nucleotide polymorphisms (SNPs) in *IL118RAP* on chromosome 2q12.1, *HLA-DRB1* on chromosome 6p21.3, and *HLA-DPB1* on chromosome 6 as being associated with increased risk of ENKTL[81,82].

NK- and T-cell ENKTLs also show differences in genetic abnormalities[83]. It is important to clarify that primary EBV-positive nodal T-cell or NK-cell lymphomas are distinct and deserve to be classified separately from ENKTCL. Primary nodal cases are more common in elderly patients, lack nasal involvement, are of T-cell lineage and are currently referred to as EBV-positive nodal T-cell lymphoma or EBV-positive PTCL rather than ENKTL, although this entity may have been diagnosed as ENKTL in the past[83].

Alterations of the JAK-STAT pathway have been identified in up to 35% of ENKTL cases, particularly mutations of *JAK3, STAT3 and STAT5B*. Mutations of tumor suppressor genes are also relatively frequent, such as *BCOR* (up to 32%), *DDX3X* (up to 50%) and *TP53* (8–63%)[80,84–86]. There are some differences in the frequency of these mutations in ENKTLs based on geography; for example, *BCOR* and *DDX3X* mutations are more often seen in cases in Asia, whereas *STAT3* mutations are more common in cases in Latin America[80]. In addition, mutations in *STAT3, BCOR* and *DDX3X* are usually mutually exclusive, and *TP53* mutations only rarely overlap with *DDX3X* mutations[80,85]. The alterations in ENKTL cases can be grouped as those involving single genes (e.g., *survivin, AURKA, MYC, EZH2*, and *RUNX3*) and those involving signaling pathways (JAK-STAT, NF-kB, NOTCH1, and PDGFR). In general, ENKTL are characterized by activation of MYC and NF-kB and deregulation of P53[87]. Many copy number alterations have been shown in ENKTLs including loss of 1p36.11-p36.32, 6q21-q25, 6q26-q27, 7p15.3-p22.3, 9p21.3, 11q22.3-23.3 and gains in 1q22-q44, 2q22.2-q33.1, 6p21.3, 7q21.1-q36.3, 11q24.3, 13q14.2 and 17q21.2-q25.3[79,83,85,88,89]. Del(6)(q21;q25) is one of the more frequent abnormalities; this region encodes a variety of tumor suppressor genes, such as *PRDM1, FOXO3*, *AIM1*, and *ATG5*, as well as *PTPRK*, a gene known to encode for an enzyme that dephosphorylates phospho-STAT3 (pSTAT3)[79,85,88–90]. Loss of 14q11.2 (*TRA* locus) is more often seen in T-cell ENKTL[83].

Xiong et al.[90] recently defined three ENKTL molecular subtypes: TSIM, MB and HEA. The TSIM-subtype is associated with JAK/STAT activation, NK-origin and PD-L1 overexpression. The MB-subtype shows MYC overexpression and poor outcome, and the HEA-subtype is characterized by epigenetic changes, NF-kB activation, and T-cell origin. These molecular subtypes differ significantly in progression-free survival (PFS) and overall survival (OS) and are sensitive to different targeted therapeutic strategies. The predicted 3-year OS rates for the TSIM, MB and HEA subtypes were 79.1%, 38,5%, and 91.7%, respectively.

EBV in ENKTL expresses LMP1 (latency II pattern), which functions as a CD40 ligand, thereby activating the NF-kB pathway[91]. Most cases of ENKTL in Asia (>90%) harbor EBV with a 30 bp deletion in LMP1, which is associated with more aggressive behavior. However, EBV with the del-LMP1 form is less frequent in Central and South America, ranging from 0% in Peru to 42% in Argentina[80,92,93]. EBV is hypothesized, through epigenetic mechanisms, to be involved in tumor pathogenesis[94]. Furthermore, in ENKTL EBV frequently shows alterations in latent (EBNAs, LMP1 and LMP2) and lytic (*BBLF2/3*, *BPLF1*, and *BALF3*) genes. *BALF3* is thought to contribute to ENKTL pathogenesis by causing DNA damage leading to genomic instability. However, in comparison with EBV-associated nasopharyngeal and gastric carcinoma, ENKTLs exhibit lower transcription of EBV-associated genes and have more T-cell epitope alterations, suggesting that immune evasion plays a role in pathogenesis[90,95]. Recent evaluation of the ENKTL immune microenvironment by gene expression profiling and immunohistochemistry shows three different immune microenvironments termed immune tolerance, immune evasion and immune silenced that are associated with different expression levels of PD-L1 and response to PD-L1 inhibitors and outcome. These features highlight the interplay of EBV, the microenvironment, tumor pathogenesis and clinical behavior[96].

Current role of genetic testing in workup of extranodal NK/T-cell lymphomas

Some of the genetic findings in ENKTLs are shown in Table 4. Currently, genetic testing is not required for the workup of ENKTLs, with the exception of T-cell receptor gene rearrangement studies to distinguish NK- from T-cell neoplasms. We believe that this situation is likely to change because many genetic alterations in ENKTL represent potential therapeutic targets. The activity associated with pSTAT3 may be abrogated by increasing the expression of *PTPRK* employing demethylating agents such as 5-azacytidine to demethylate its promoter. Other therapeutic agents such as the JAK inhibitors, ruxolitinib and tofacitinib, or a STAT3 inhibitor may be helpful. Other therapeutic agents under consideration to treat ENKTL patients include daratumumab (anti-CD38), brentuximab vedotin, bortezomib, EZH2 inhibitors and the PD1 inhibitor pembrolizumab.

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is an aggressive T-cell neoplasm that tends to occur in young men and can arise in the setting of chronic immunosuppression. Patients present with hepatosplenomegaly, bone marrow involvement and cytopenias without lymphadenopathy. Although this neoplasm was initially thought to be derived from cells that express TCRγ/δ, a subset of HSTCL cases express TCRα/β[97–100]. Lesions that express TCRα/β occur more often in women and in older individuals[99]. Morphologically, the neoplastic cells are usually of intermediate-size; however, there is variability in the cytologic appearance, ranging from cells that have condensed chromatin and inconspicuous nucleoli to those that have finely dispersed chromatin and prominent nucleoli, reminiscent of blasts[97,101].

Table 4. Genetic findings and biomarkers with potential relevance in the work-up of ENKTL.

Biomarker	Test	Purpose	Disease	Comment
TCR gene rearrangements	PCR	Diagnosis	ENKTL	NK versus T-cell origin
EBER	ISH	Diagnosis	ENKTL	Important for diagnosis
Del14q11.2[83]	FISH	Diagnosis	ENKTL	Potential indicator of T-cell origin
JAK3 mutations[a,80,84–86]	NGS	Therapy?	ENKTL	Potentially targetable
STAT3 mutations[a,80,84–86]	NGS	Therapy?	ENKTL	Potentially targetable
TP53 mutations[a,80]	NGS	Prognosis	ENKTL	Associated with extranasal or lymph node involvement
BCOR[b] mutations[80,84–86]	NGS	Therapy?	ENKTL	Potential role of NOTCH inhibitors
DDX3X mutations[86]	NGS	Prognosis	ENKTL	Poor prognosis

JAK3 janus kinase 3, *STAT3* signal transducer and activator of transcription 3, *BCOR* BCL6 co-repressor, *DDX3X* EAD-Box Helicase 3 X-Linked.
[a]Non-specific for diagnosis; they are seen in other T-cell lymphomas.
[b]Based on limited data, pending validation. BCOR mutations are rare in lymphomas; reported also in splenic diffuse red pulp small B-cell lymphoma.

Table 5. Genetic findings and biomarkers with potential relevance in the work-up of HSTCL.

Biomarker	Test	Purpose	Disease	Comment
i(7q)	FISH	Diagnosis	HSTCL	FISH is more sensitive than karyotyping
SETD2 mutations[a,100]	NGS	Diagnosis	HSTCL	Could help in the diagnosis
STAT5B mutations[a,100,106]	NGS	Diagnosis	HSTCL	Potentially targetable
STAT3 mutations[a,100,106]	NGS	Diagnosis	HSTCL	Potentially targetable

SETD2 SET domain containing 2, histone lysine methyltransferase, *STAT3* signal transducer and activator of transcription 3.
[a]Non-specific; they are seen in other T-cell lymphomas but in the right clinical setting could support the diagnosis of HSTCL.

Genetics and molecular profiling

The most consistent genetic finding in HSTCL is isochromosome 7q [i(7q)], which is present in 25–70% of cases using either conventional cytogenetics or FISH. Although i(7q) can be seen in other diseases, this abnormality is thought to be a primary lesion in HSTCL. Trisomy 8 is another frequent cytogenetic finding, usually seen in association with i(7q). Additional cytogenetic abnormalities often occur with disease progression[97,98,100,102,103].

HSTCL is a monoclonal T cell neoplasm[98,99,103–105]. In most cases, the T-cells express TCR γ/δ[97,100,103,104] and usually exhibit Vδ1 usage at both the DNA and protein level. Furthermore, this Vδ1 usage parallels that of normal TCRγ/δ cells in the spleen and correlates with CD56 expression by the neoplastic cells[102,104].

GEP shows a clear separation of HSTCL cases from other T-cell lymphomas, including PTCL-NOS, AITL and ENKTL. The profile appears to be more similar to ENKTL than other PTCL types[103]. Upregulated genes include *S1PR5*, which is involved in NK-cell homing to the spleen, and *ABCB1*, which encodes p-glycoprotein multidrug transported (MDR1). Other overexpressed genes (in comparison with PTCL-NOS) include *KIRS, NCAM1*, and *CD244*[103]. Genes underexpressed in HSTCL compared with PTCL-NOS, include those encoding for TFH-associated proteins such as *CXCL13* and *ICOS*, and genes encoding immune modulating proteins such as *IL411*, *CD5* and the tumor suppressor gene *AIM1*. Genes associated with cytotoxic molecules, such as *Granzyme B* and *Granzyme H* are also underexpressed (consistent with lack of expression of these markers as assessed by immunohistochemistry). In comparison to normal TCRγ/δ cells, the neoplastic cells in HSTCL overexpress *S1PR5* and the oncogenes *FOS* and *VAV3*[103]. Furthermore, many of the underexpressed- and overexpressed genes are involved in a variety of pathways, including the AP1 and WNT pathways, and thus are likely important in the pathogenesis of this disease.

Whole exome sequencing has identified a variety of recurrent mutations that can be grouped into three categories. Chromatin modifying genes, such as *SETD2*, *ARID1B*, *INO80*, *TET3,* and *SMARCA2*, are mutated in >60% of cases and constitute the largest category of genes mutated. *SETD2*, a tumor suppressor gene, is the most frequent mutated gene (~70%) in this category. A second group have frequently mutations, usually missense mutations, occurring in signaling pathway genes, most commonly in *STAT5B (31%), STAT3* and *PIK3CD*[100,106]. *STAT5B* and *STAT3* mutations are activating mutations which are usually mutually exclusive in HSTCL cases.[100] The last group of mutations consists of mutations in other genes such as *TP53, UBR5*, and *IDH2* (5–10% of cases)[100,106,107].

A variety of epigenetic changes occur in HSTCL, including hypermethylation of *AIM1, BCL11B, LTA, GIMAP7, SEPT9, CD5*, and *CXCR6*, all of which have relevance in the pathogenesis of T-cell lymphomas. Furthermore, hypermethylation in HSTCL has been associated with lack of protein expression, suggesting a mechanism for the frequent lack of expression of many markers in this disease, such as CD5. In addition, hypomethylation in *ADARB1, NFIC, NR1H2*, and *ST3GAL3* has been described. Overall, the methylation changes are seen preferentially in regulatory elements, such as enhancers[103,105].

Current role of genetic testing in workup of HSTCL

Genetic findings and potential biomarkers in HSTCL are summarized in Table 5. As i(7q) is seen in many cases of HSTCL, conventional cytogenetic analysis is helpful for establishing the diagnosis. This cytogenetic abnormality can be seen by karyotyping; however, FISH is often more sensitive. Trisomy 8 is seen in many additional cases. TCR gene rearrangement analysis is helpful in proving the presence of a monoclonal T-cell population. Additional genetic studies including single gene mutation analysis, whole exome sequencing and epigenetic studies are not required for diagnosis or the planning of therapy at this time point, but mutations in *STAT* genes are potentially targetable.

Primary intestinal T-cell lymphomas

Enteropathy-associated T-cell lymphoma (EATL). Enteropathy-associated T-cell lymphoma (EATL) is an aggressive neoplasm of intestinal intraepithelial T-lymphocytes that arises in patients with celiac disease or gluten sensitivity. Although rare, EATL is the most common intestinal T-cell lymphoma in the Western world, seen with greater frequency in regions with a higher prevalence of celiac disease. EATL is more common in men, typically presents in patients 50–60 years of age, and is associated with the presence of HLA-DQ2 and HLA-DQ8 alleles. The small intestine is the most commonly affected site, but other gastrointestinal (GI) tract sites can be involved as well as extraintestinal sites.

EATL is characterized by a proliferation of pleomorphic, variably sized atypical lymphocytes, sometimes with large cell or anaplastic morphology, in a background rich in histiocytes and eosinophils. Adjacent uninvolved small intestine typically shows features of celiac disease. The malignant lymphocytes are CD3+, CD103+ T-cells that express cytotoxic proteins, are negative for CD56, and usually lack expression of CD4 and CD8. The lymphoma cells show variable expression of CD30 and express TCRα/β more often than TCRγ/δ.

Genetics and molecular profiling

EATL exhibits monoclonal rearrangements of *TRB* and *TRG* genes[108]. Several recurrent genetic changes have been described in EATL, many of which are shared with monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (see below). Using array comparative genomic hybridization (CGH), FISH, microsatellite markers, and qPCR, the most commonly identified abnormality is segmental amplification of 9q31.3-qter, encompassing *NOTCH1* and *ABCL1* and present in 70–80% of cases[109–111]. In addition, gains of 1q32-41, 5q, 6p21, 7q, 8q24, and 19q; and losses of 3p12, 3q26, 4q, 6p24, 7p21, 8p, 10p12-13, 11q14;-q23 13q22, 16q12, 17q23-25, 17p13.1, 18q22, and Xq have been reported. 9p31.3-qter gains and 16q12 losses occur in a seemingly mutually exclusive pattern[112]. Losses of 1q32-41 and 5q35 are reported more frequently in EATL (compared to MEITL) and gains of 8q24 are rare (unlike MEITL). 9p21 (*CDKN2A/2B*) loss is seen in ~55% of cases with concomitant loss of p16 protein expression by immunohistochemistry. Loss of 17p13 and/or *TP53* mutation is rare in EATL, but p53 protein overexpression by immunohistochemistry is seen in virtually all cases[113].

Targeted next-generation sequencing and whole exome sequencing have shown that the JAK/STAT pathway is most

frequently altered with gene mutations identified in 68% of cases, including *STAT5B*, *JAK3*, *JAK1*, *STAT3*, *SOCS3*, *SOCS1*, and *TYK2*[114]. *STAT5B* and *STAT3* mutations occur in a seemingly mutually exclusive pattern. MAP kinase pathway alterations are seen in about one quarter of EATL cases with mutations in *KRAS*, *NRAS*, and *BRAF* identified. Recurrent mutations of the tumor suppressor gene *SETD2* occur in ~30% of cases. Recurrent mutations are also seen in *TP53*, *TET2*, *TERT*, *EZH2*, *FYN*, *NOTCH1*, and *CD247*. Mutations known to occur in other T-cell lymphomas, including *IDH2*, *DNMT3A*, *RHOA*, *GNB1*, *PLCG1*, *CCR4*, *JAK2*, *IL7R*, and *CD130* have not been consistently observed. Gene expression profiling has also shown that EATL shows increased expression of *STAT3*, *STAT5A*, *IRF1*, *IRF4*, *TGM2*, and genes in the IFNγ pathway compared to MEITL[115].

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)

MEITL, formerly known as type II EATL, is another aggressive neoplasm derived from intestinal intraepithelial T-lymphocytes. In contrast to EATL, MEITL is not associated with celiac disease and occurs worldwide with a predilection for patients of Asian, Hispanic, and indigenous origin[112]. It is the most common intestinal T-cell lymphoma in Asia. MEITL is more common in men and is a disease of adults with a median age of 59 years (range, 23–89 years). The small intestine is the most frequently involved site, with the jejunum showing the highest rate of involvement. Mesenteric lymph node involvement is also common, but involvement of other gastrointestinal sites, such as stomach and colon is infrequent. Dissemination to other extra-intestinal sites including liver, lungs, bone marrow, central nervous system, and peripheral lymph nodes can occur[116].

MEITL is characterized by a proliferation of monomorphic medium-sized lymphocytes. An inflammatory background is absent, and necrosis is uncommon, but granulomas may be seen. There is prominent epitheliotropism, but adjacent uninvolved small intestine does not show features of celiac disease. The neoplastic T cells are CD3+, CD8+, and CD56+, express cytotoxic proteins, are negative for CD4 and CD30; and show variable expression of CD103. The neoplastic cells express TCRγ/δ more often than TCR α/β. Most cases also show expression of megakaryocyte-associated tyrosine kinase (MATK), which distinguishes MEITL from EATL if expressed in >80% of cells[117]. Aberrant CD20 expression has been seen in about 25% of cases[116].

Genetics and molecular profiling

MEITL exhibits monoclonal rearrangement of the T-cell receptor genes[108]. MEITL shows strong overlap and shares numerous genetic changes with EATL, albeit at different frequencies (see above). As in EATL, the most commonly encountered abnormalities in MEITL are gains of 9q31.3-qter and mutually exclusive losses of 16q12[109,110]. Gains in 8q24 (25–73%) are more common in MEITL, whereas losses of 1q32-41 and 5q35 are rare.

Targeted next-generation sequencing and whole exome sequencing studies[115] have shown that the JAK/STAT pathway is frequently altered in MEITL (80%) with *STAT5B* and *JAK3* mutations occurring more frequently than in EATL[114]. MAP kinase pathway alterations are also frequently identified in MEITL (32%). Alterations in the G-protein coupled receptor signaling pathways have been described with recurrent mutations of *GNAI2* reported in 24% of cases in one series[118]. The tumor suppressor gene *SETD2* which encoded a non-redundant H3K36-specific trimethyltransferase is altered in over 90% of western European cases, mainly by loss-of-function mutations and/or loss of the corresponding locus (3p21.31)[119]. *SETD2* alterations are also reported in about 70% of cases in North America and also are highly prevalent in Japanese patients. SETD2 inactivation consistently correlates with defective H3K36 trimethylation and seems to be a critical event in facilitating both neoplastic initiation and progression through decreasing H3K36me3[120]. *CREBBP* mutations are also described, occurring in 30% of cases, however they always occur in association with *STAT5B* and/or *JAK3* mutations, suggesting *CREBBP* mutations may not be initiating events[118]. Gene expression profiling[115] has shown that MEITL shows increased expression of *FASLG*, *SYK*, *TGBR1*, and *NCAM1* (encodes CD56), as well as the NK-like cytotoxicity pathway as compared with EATL. Despite the increased frequency of 8q24 gains, *MYC* expression is not increased in MEITL.

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (ITLPD)

ITLPD is a monoclonal T-cell lymphoproliferative disorder involving any part of the GI tract mucosa, most frequently the small intestine and colon. This neoplasm usually occurs in adults and affects men more often than women in a chronic relapsing pattern. Rarely, extra-intestinal sites including peripheral blood, bone marrow, and liver can be involved.

ITLPD is characterized by a non-destructive expansion of the lamina propria by a dense proliferation of monotonous small mature appearing lymphocytes without significant epitheliotropism. There is no significant inflammation or necrosis. The infiltrate is composed of CD3+ T-cells that express TCRα/β. The cells show variable expression of CD4 and CD8, with CD4+/CD8−, CD4−/CD8+ and CD4−/CD8− cases. CD8+ cases are usually positive for TIA1 and negative for granzyme B. All cases are negative for CD56 and CD30.

Genetics and molecular profiling

ITLPD exhibits monoclonal rearrangement of the TCR genes. Recurrent alterations involving the JAK/STAT pathway and epigenetic modifiers have been reported, including mutations of *STAT3*, *TET2*, *DNMT3A*, and *KMT2D*, as well as *SOCS1* deletion and *STAT3-JAK2* fusions[121,122]. CD4 + ITLPD are associated with *STAT3-JAK2* fusions[121]. CD8+ ITLPD cases can show structural alterations involving the untranslated region of *IL2*[122]. Other copy number changes have been described using SNP array analysis[123].

Current role of genetic testing in workup of intestinal lymphomas including ITLPD

There are no known genetic changes specific for EATL with wide overlap seen in the genetic landscape of EATL and MEITL (Table 6). The most common abnormality, 9q31.3-qter gain, is not associated with nodal T-cell lymphomas and may help distinguish primary intestinal lymphoma from intestinal involvement by nodal T-cell lymphoma. In addition, several recurrent genetic abnormalities identified in other T-cell lymphomas, including *IDH2*, *DNMT3A*, *RHOA*, *GNB1*, *PLCG1*, *CCR4*, *JAK2*, *IL7R*, and *CD130* have not been identified in EATL and may aid in distinguishing primary intestinal lymphoma from extraintestinal disease. Distinguishing EATL from MEITL currently depends clinical, morphologic, and immunophenotypic findings. Currently, genetic testing is of limited utility in establishing the diagnosis or guiding therapy.

There is a currently limited role for genetic testing in the workup of MEITL cases. There are no known genetic changes specific for MEITL and the genetic workup is similar to that of EATL. No biomarkers are available for cases of aggressive intestinal lymphomas classified as intestinal T-cell lymphoma, NOS.

JAK2 rearrangements present in ITLPD are not present in reactive infiltrates and have not been described in other intestinal TCLs, and therefore may serve as a useful marker to establish the diagnosis of ITLPD. In addition, a *STAT3-JAK2* fusion was identified in one of two patients with ITLPD that progressed to more aggressive lymphoma and could possibly serve as a poor prognostic marker[121]. This finding needs to be validated in larger series.

Table 6. Genetic findings and biomarkers with potential relevance in the work-up of Intestinal TCLs.

Biomarker	Test	Purpose	Disease	Comment
Gains of 9q31.3-qter[109–111]	FISH	Diagnosis	EATL	Occurs also in MEITL
Deletions of 16q12[112]	FISH	Diagnosis	EATL	Occurs also in MEITL
SETD2 mutations[a,119]	NGS	Diagnosis	EATL and MEITL	EATL (30%); MEITL (90%)
STAT5B mutations[114]	NGS	Diagnosis	MEITL	60% of cases (γ/δ phenotype)
Gains of 8q24 (MYC)	FISH	Diagnosis	EATL and MEITL	EATCL (20%); MEITL (73%)
MATK expression[117]	IHC	Diagnosis	MEITL	Can help in the differential diagnosis with EATCL
STAT3-JAK2[b,121]	FISH	Diagnosis and prognosis	ITLPD	Seen in CD4+ cases. Possible risk of progression
IL2 rearrangements[122]	FISH	Diagnosis	ITLPD	Seen in CD8+ cases (*IL2-RHOH* and *IL2-TNIP3*)

EATL enteropathy-associated T cell lymphoma, *MEITL* monomorphic epitheliotropic intestinal T-cell lymphoma, *MATK* megakaryocyte-associated tyrosine kinase, *ITLPD* Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract.
[a]Most frequently seen in MEITL than EATCL but too much overlap to be a reliable diagnostic biomarker of MEITL. However, in the right clinical context could be useful to support intestinal origin for a T-cell lymphoma involving lymph nodes or extraintestinal sites.
[b]Based on limited data, pending validation.

Adult T cell leukemia-lymphoma (ATLL)

ATLL is an aggressive T-cell neoplasm arising from post-thymic regulatory T cells and, caused by infection by the RNA retrovirus human T-cell leukemia virus 1 (HTLV-1). ATLL is the most frequent type of T-cell lymphoma/leukemia in Asia (25% of all T-cell cases) and is rare in North America (2%) and Europe (1%), where it affects primarily immigrants from endemic countries. ATLL is associated with four clinical subtypes (Shimoyama classification): two indolent (smoldering and chronic) and two aggressive (acute and lymphomatous)[124].

HTLV-1 is transmitted primarily by breastfeeding and infects CD4+ mature T-cells and immature thymocytes in early infancy. The virus is oncogenic by its expression of two genes, *TAX* and *HBZ*. It seems that *HBZ* is important for tumor maintenance and *TAX* is essential for early proliferation and initiation of the neoplasm[125]. However, the long latency interval from infection to tumor onset clearly points to additional genetic and/or epigenetic events involved in pathogenesis.

Genetics and molecular profiling

Genomic alterations are detected in most patients and are clustered in five main signaling pathways.[126,127] These pathways include TCR/NF-KB (~75%), *CD28*, *PLCG1*, *PRKCB*, *CARD11*, *CBLB*, *IRF4*, *CSNK1A1*, *FYN*, *RHOA,* and *VAV1*; T cell trafficking (~45%), *CCR4*, *CCR7*, and *GP183*; immune escape (~30%), *FAS*, *HLA-B*, *B2M*, and *CD58*; cell cycle regulation (~25%), *TP53*, *POT1*, and *RB1*; and JAK/STAT3, *JAK3*, *STAT3*, and *PTPN1*[126,127].

Alterations in TCR/NF-KB signaling, or associated pathways, is a hallmark feature detected in most patients with ATLL resulting in enhanced activation of TCR/NF-KB signaling[126]. One of the most frequently mutated genes is *PLCG1* (~33%), which encodes the phospholipase Cγ1, a key regulator of proximal TCR signaling[126]. This activating mutation enhances PLCγ1 activity. The second most frequently mutated gene is *PRKCB*, encoding a signaling molecule downstream of PLCγ1. *CARD11* is another frequently mutated gene. CARD11 is a cytoplasmic scaffolding protein required for NF-KB activation induced by antigen receptor activation. In ATLL, mutations and deletions in *CARD11* are clustered within its PKC-responsive inhibitory domain, which is implicated in the autoinhibition of CARD11[128]. Negative regulators of TCR/NF-KB signaling are also affected by frequent loss-of function mutations and deletions, including *CBLB*, *TRAF3*, *TNFAIP3*, *NFKB1A,* and *PTPRC* among others.

Approximately 10% of cases have in-frame fusions involving *CTLA4-CD28* and *ICOS-CD28*. The expected consequence of these fusions is prolonged and continuous CD28 costimulatory signaling contributing to NF-KB activation[126]. Other mechanisms resulting in NF-KB activation include transcriptional repression of negative regulators of TCR signaling, e.g., loss of PTPN6 (SHP1) expression, which is mediated by the oncoprotein TAX *via* a transcriptional mechanism[129].

C-C chemokine receptor 4 (CCR4) is highly expressed in ~90% of ATLL patients. Patients with CCR4-positive ATLL are more likely to experience skin infiltration and worse outcomes than patients with CCR4-negative ATLL. *CCR4* is also a frequent mutation in ATLL (up to 38% in some series)[126,127,130]. In most cases, the mutation results in truncation of the C-terminal cytoplasmic domain, preventing the internalization of receptor upon ligand stimulation and resulting in increased surface CCR4 expression, enhanced ligand-induced chemotaxis and activation of PI3K/AKT pathway[130,131]. The humanized monoclonal antibody against CCR4 mogamulizumab has shown some effects in ATLL (in both relapsed/aggressive ATLL and in front-line settings)[132].

IRF4 amplifications (25%) and *CDKN2A* deletions are characteristic copy number abnormalities in ATLL[126]. Highly expressed in ATLL, IRF4 drives cell proliferation and is associated with a poor prognosis and therapeutic resistance[133,134].

Epigenetic alterations in ATLL are also key to understand the pathogenesis of the disease. More than a third of cases of ATLL show widespread hypermethylation of CpG islands which is associated with transcriptional silencing[126].

Current role of genetic testing in the workup of ATLL

Genetic findings and potential biomarkers in ATLL are summarized in Table 7. Aside from identification of integrated HTLV-1 in isolated lymphoma cells or anti-HTLV1/2 antibodies in serum as an imperfect surrogate, there are no specific clinical, morphologic, immunophenotypic or molecular genetic features that are diagnostic of ATLL. In fact, without knowledge of viral infection, ATLL can be difficult to distinguish from other more common T-cell lymphomas[135].

Targeted molecular assessment can be useful to identify two molecular ATLL subgroups with clinical relevance. Group 1 is enriched for alterations affecting distal components of TCR/NF-KB signaling pathway (such as *CARD11*, *PRKCB*, and *IRF4*) and immune-related molecules (*HLA-A*, *HLA-B*, and *CD58*), whereas group 2 is enriched for alterations in proximal regulators of TCR/NF-KB signaling (*PLCG1*, *VAV1*, and *CD28*) and a JAK/STAT signaling molecule (*STAT3*). Group 1 cases have a larger number of mutations and CNAs than cases in group 2. Clinically, most cases of the lymphomatous subtype were classified as group 1, whereas group 2 mainly consisted of leukemic cases. Moreover, patients in group 1 showed poorer overall survival than patients in group 2, independent of clinical subtype. Fig. 1.

Patients with *CCR4* mutations have better responses to mogamulizumab[136]. Decreased expression of CCR4 using an

Table 7. Genetic findings and biomarkers with potential relevance in the work-up of ATLL.

Biomarker	Test	Purpose	Disease	Comment
PLCG1 mutations[126]	NGS	Treatment	ATLL	Clinical interest in developing PLCγ1i
CCR4 mutations[136]	NGS	Prognosis	ATLL	Associated with skin involvement and adverse prognosis
CCR4 expression[136,137]	IHC	Treatment	ATLL	Predicts better responses to mogamulizumab
IRF4 expression[126,133,134]	IHC	Prognosis	ATLL	Adverse prognosis and poor responses to therapy
TP53 mutations	NGS	Prognosis	ATLL	Adverse prognosis

ATLL adult T cell leukemia/lymphoma, *PLCG1* phospholipase C gamma 1, *CCR4* C-C Motif Chemokine Receptor 4, *IRF4* interferon regulatory factor 4.

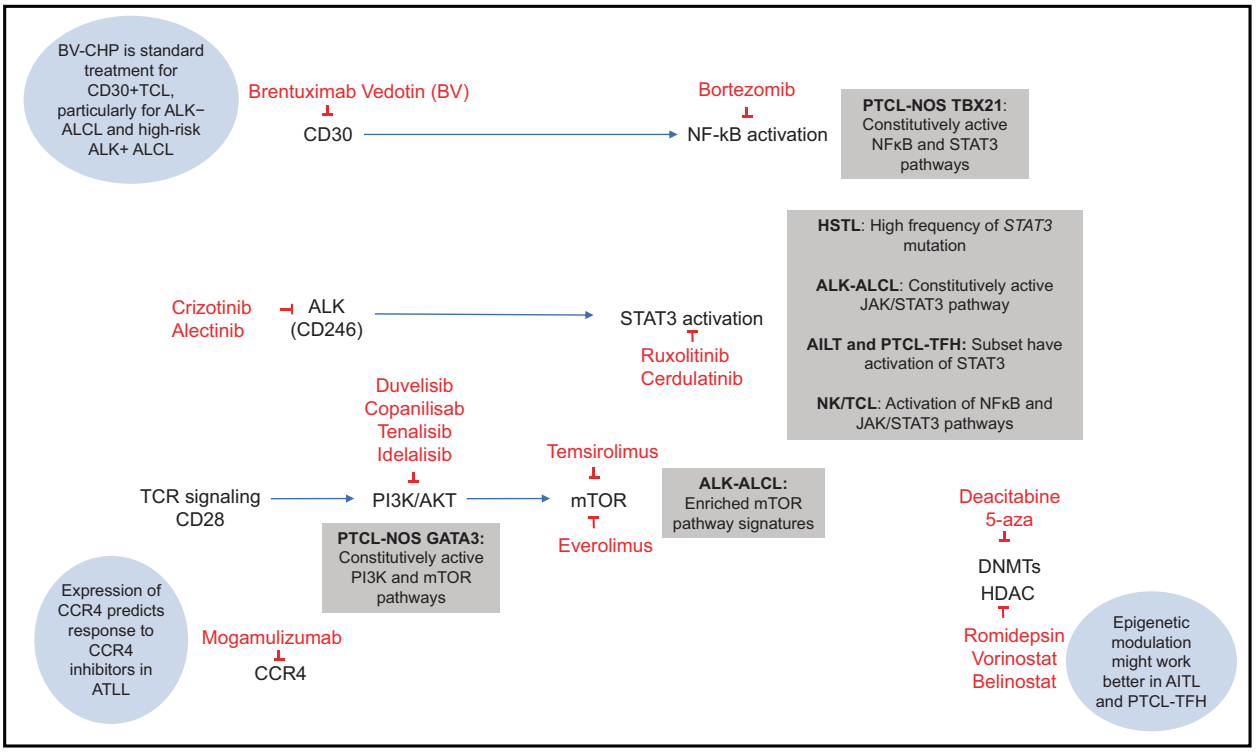

Fig. 1 Molecular pathways amenable to therapeutic intervention in PTCL. Some of the available inhibitors are listed in red. Note that cerdulatinib is a dual SYK/JAK inhibitor. The gray boxes indicate specific vulnerabilities in distinct PTCL subtypes, and the oval circles contain some treatment related comments. ALK anaplastic lymphoma kinase, ALCL anaplastic large cell lymphoma, HSTL hepatosplenic T cell lymphoma, AILT angioimmunoblastic T cell lymphoma, DNMT DNA methyltransferase, HDAC histone deacetylase, ATLL adult T cell leukemia/lymphoma.

antibody against the C-terminal domain of CCR4 is associated with the presence of *CCR4* mutations and predicts response to mogamulizumab[137]. This decrease in the expression signal is probably due to protein truncation generated by the mutation.

Molecular biomarkers reported to be associated with a poorer prognosis in ATLL patients include *TP53* mutation and *CDKN2A* deletion. There is clinical interest in developing and testing PLCγ1 inhibitors for patients with ATLL. Therefore, determination of PLCγ1 activation could be clinically relevant.

In summary, we have briefly summarized the genetic landscape of PTCLs emphasizing some biomarkers that have an established or a potential role in the work-up of patients with T-cell lymphomas. Although we have achieved significant progress, additional work is needed to extend emerging biological findings and to develop a biomarker-driven classification of this group of neoplasms. Development of biomarkers also will provide additional prognostic and predictive therapeutic biomarkers that can be exploited for more effective therapies. Biomarkers and molecular pathways amenable to therapeutic intervention in PTCL are illustrated in the figure.

REFERENCES

1. Chihara, D. et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. *Br. J. Haematol* **164**, 536–545 (2014).
2. Swerdlow, S. H. et al. *WHO classification of Tuours of Haematopoietic and Lymphoid Tissues (Revised 4th edition)*. (IARC: Lyon 2017, 2017).
3. Vega, F. et al. American Registry of Pathology Expert Opinions: Recommendations for the diagnostic workup of mature T cell neoplasms. *Ann. Diagn. Pathol.* **49**, 151623 (2020).
4. Chihara, D., Miljkovic, M., Iyer, S. P. & Vega, F. Targeted based therapy in nodal T-cell lymphomas. *Leukemia* **35**, 956–967 (2021).
5. Falini, B. et al. Anaplastic large cell lymphoma, ALK-positive. In: S. H. Swerdlow et al. (eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues World Health Organization Classification of Tumours* 413–418 (International Agency for Research on Cancer: Lyon, 2017).

6. Amador, C. & Feldman, A. L. How i diagnose anaplastic large cell lymphoma. *Am. J. Clin. Pathol.* **155**, 479–497 (2021).
7. Horwitz, S. et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* **393**, 229–240 (2019).
8. Prokoph, N., Larose, H., Lim, M. S., Burke, G. A. A. & Turner, S. D. Treatment options for paediatric anaplastic large cell lymphoma (ALCL): current Standard and beyond. Cancers **10**, 99 (2018).
9. Werner, M. T., Zhao, C., Zhang, Q. & Wasik, M. A. Nucleophosmin-anaplastic lymphoma kinase: the ultimate oncogene and therapeutic target. *Blood* **129**, 823–831 (2017).
10. Youssif, C. et al. Genomic profiling of pediatric ALK-positive anaplastic large cell lymphoma: a Children's Cancer and Leukaemia Group Study. *Genes Chromosomes Cancer* **48**, 1018–1026 (2009).
11. Boi, M. et al. PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma. *Blood* **122**, 2683–2693 (2013).
12. Piva, R. et al. Gene expression profiling uncovers molecular classifiers for the recognition of anaplastic large-cell lymphoma within peripheral T-cell neoplasms. *J. Clin. Oncol.* **28**, 1583–1590 (2010).
13. Iqbal, J. et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood* **123**, 2915–2923 (2014).
14. Luchtel, R. A. et al. Molecular profiling reveals immunogenic cues in anaplastic large cell lymphomas with DUSP22 rearrangements. *Blood* **132**, 1386–1398 (2018).
15. Lobello, C. et al. STAT3 and TP53 mutations associate with poor prognosis in anaplastic large cell lymphoma. *Leukemia* https://doi.org/10.1038/s41375-020-01093-1 (2020).
16. Larose, H. et al. Whole Exome Sequencing reveals NOTCH1 mutations in anaplastic large cell lymphoma and points to Notch both as a key pathway and a potential therapeutic target. *Haematologica* https://doi.org/10.3324/haematol.2019.238766 (2020).
17. Feldman, A. L. et al. Anaplastic large cell lymphoma, ALK-negative. In: S. H. Swerdlow et al. (eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues World Health Organization Classification of Tumours* 418-421 (International Agency for Research on Cancer: Lyon, 2017).
18. Savage, K. J. et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood* **111**, 5496–5504 (2008).
19. Parrilla Castellar, E. R. et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood* **124**, 1473–1480 (2014).
20. Feldman, A. L. et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively-parallel genomic sequencing. *Blood* **117**, 915–919 (2011).
21. King, R. L. et al. Morphologic features of ALK-negative anaplastic large cell lymphomas with DUSP22 rearrangements. *Am. J. Surg. Pathol.* **40**, 36–43 (2016).
22. Hapgood, G. et al. Identification of high-risk DUSP22-rearranged ALK-negative anaplastic large cell lymphoma. *Br. J. Haematol.* **186**, e28–e31 (2019).
23. Parrilla Castellar, E. et al. Rearrangements at the 6p25.3 locus identify a subset of systemic ALK-negative anaplastic large cell lymphomas with favorable prognosis. *Lab. Invest.* **92**, 359A (2012). (abstract).
24. Vasmatzis, G. et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. *Blood* **120**, 2280–2289 (2012).
25. Karube, K. & Feldman, A. L. "Double-hit" of DUSP22 and TP63 rearrangements in anaplastic large cell lymphoma, ALK-negative. *Blood* **135**, 700 (2020).
26. Velusamy, T. et al. A novel recurrent NPM1-TYK2 gene fusion in cutaneous CD30-positive lymphoproliferative disorders. *Blood* **124**, 3768–3771 (2014).
27. Crescenzo, R. et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. *Cancer Cell* **27**, 516–532 (2015).
28. Scarfo, I. et al. Identification of a new subclass of ALK-negative ALCL expressing aberrant levels of ERBB4 transcripts. *Blood* **127**, 221–232 (2016).
29. Luchtel, R. A. et al. Recurrent MSC (E116K) mutations in ALK-negative anaplastic large cell lymphoma. *Blood* **133**, 2776–2789 (2019).
30. Willemze, R. et al. (eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues World Health Organization Classification of Tumours* 392–396 (International Agency for Research on Cancer: Lyon, 2017).
31. Bekkenk, M. W. et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood* **95**, 3653–3661 (2000).
32. Shinohara, M. M. & Shustov, A. How I treat primary cutaneous CD30(+) lymphoproliferative disorders. *Blood* **134**, 515–524 (2019).
33. Melchers, R. C. et al. Clinical, histologic, and molecular characteristics of anaplastic lymphoma kinase-positive primary cutaneous anaplastic large cell lymphoma. *Am. J. Surg. Pathol.* **44**, 776–781 (2020).
34. van Kester, M. S. et al. Cutaneous anaplastic large cell lymphoma and peripheral T-cell lymphoma NOS show distinct chromosomal alterations and differential expression of chemokine receptors and apoptosis regulators. *J. Invest. Dermatol.* **130**, 563–575 (2010).
35. Laharanne, E. et al. Genome-wide analysis of cutaneous T-cell lymphomas identifies three clinically relevant classes. *J. Invest. Dermatol.* **130**, 1707–1718 (2010).
36. Clemens, M. W. et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. *J. Clin. Oncol.* **34**, 160–168 (2016).
37. Ferrufino-Schmidt, M. C. et al. Clinicopathologic features and prognostic impact of lymph node involvement in patients with breast implant-associated anaplastic large cell lymphoma. *Am. J. Surg. Pathol.* **42**, 293–305 (2018).
38. Laurent, C. et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. *Ann. Oncol.* **27**, 306–314 (2016).
39. Clemens, M. W. & Horwitz, S. M. NCCN consensus guidelines for the diagnosis and management of breast implant-associated anaplastic large cell lymphoma. *Aesthet. Surg. J.* **37**, 285–289 (2017).
40. Oishi, N. et al. Genetic subtyping of breast implant-associated anaplastic large cell lymphoma. *Blood* **132**, 544–547 (2018).
41. Los-de Vries, G. T. et al. Chromosome 20 loss is characteristic of breast implant-associated anaplastic large cell lymphoma. *Blood* **136**, 2927–2932 (2020).
42. Tabanelli, V. et al. Recurrent PDL1 expression and PDL1 (CD274) copy number alterations in breast implant-associated anaplastic large cell lymphomas. *Hum Pathol* **90**, 60–69 (2019).
43. Di Napoli, A. et al. Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. *Mod Pathol* **32**, 216–230 (2019).
44. Oishi, N. et al. Molecular profiling reveals a hypoxia signature in breast implant-associated anaplastic large cell lymphoma. *Haematologica* https://doi.org/10.3324/haematol.2019.245860 (2020).
45. Blombery, P. et al. Frequent activating STAT3 mutations and novel recurrent genomic abnormalities detected in breast implant-associated anaplastic large cell lymphoma. *Oncotarget* **9**, 36126–36136 (2018).
46. Laurent, C. et al. Gene alterations in epigenetic modifiers and JAK-STAT signaling are frequent in breast implant-associated ALCL. *Blood* **135**, 360–370 (2020).
47. Adlard, J., Burton, C. & Turton, P. Increasing evidence for the association of breast implant-associated anaplastic large cell lymphoma and Li Fraumeni syndrome. *Case Rep. Genet*. **2019**, 5647940 (2019).
48. de Boer, M. et al. Increased prevalence of BRCA1/2 mutations in women with macrotextured breast implants and anaplastic large cell lymphoma of the breast. *Blood* **136**, 1368–1372 (2020).
49. Horwitz, S. M. et al. NCCN guidelines insights: T-cell lymphomas, Version 1.2021. *J. Natl. Compr. Canc. Netw.* **18**, 1460–1467 (2020).
50. Heavican, T. B. et al. Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma. *Blood* **133**, 1664–1676 (2019).
51. Amador, C. et al. Reproducing the molecular subclassification of peripheral T-cell lymphoma-NOS by immunohistochemistry. *Blood* **134**, 2159–2170 (2019).
52. Watatani, Y. et al. Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. *Leukemia* **33**, 2867–2883 (2019).
53. Laginestra, M. A. et al. Whole exome sequencing reveals mutations in FAT1 tumor suppressor gene clinically impacting on peripheral T-cell lymphoma not otherwise specified. *Mod. Pathol.* **33**, 179–187 (2020).
54. Lemonnier, F. et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. *Blood* **120**, 1466–1469 (2012).
55. Maura, F. et al. CDKN2A deletion is a frequent event associated with poor outcome in patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). *Haematologica* Online ahead of print (2020).
56. Schatz, J. H. et al. Targeted mutational profiling of peripheral T-cell lymphoma not otherwise specified highlights new mechanisms in a heterogeneous pathogenesis. *Leukemia* **29**, 237–241 (2015).
57. Dobay, M. P. et al. Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. *Haematologica* **102**, e148–e151 (2017).
58. Rohr, J. et al. Recurrent activating mutations of CD28 in peripheral T-cell lymphomas. *Leukemia* **30**, 1062–1070 (2016).
59. Cairns, R. A. et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. *Blood* **119**, 1901–1903 (2012).

60. Fitzpatrick, M. J. et al. JAK2 rearrangements are a recurrent alteration in CD30+ systemic T-cell lymphomas with anaplastic morphology. *Am. J. Surg. Pathol.* **45**, 895–904 (2021).
61. Debackere, K. et al. Fusion transcripts FYN-TRAF3IP2 and KHDRBS1-LCK hijack T cell receptor signaling in peripheral T-cell lymphoma, not otherwise specified. *Nat Commun* **12**, 3705 (2021).
62. Abate, F. et al. Activating mutations and translocations in the guanine exchange factor VAV1 in peripheral T-cell lymphomas. *Proc. Natl. Acad. Sci. USA* **114**, 764–769 (2017).
63. de Leval, L. et al. Angioimmunoblastic T-cell lymphoma is the most common T-cell lymphoma in two distinct French information data sets. *Haematologica* **100**, e361–e364 (2015).
64. Lachenal, F. et al. Angioimmunoblastic T-cell lymphoma: clinical and laboratory features at diagnosis in 77 patients. *Med (Baltim)* **86**, 282–292 (2007).
65. Ondrejka, S. L. et al. Angioimmunoblastic T-cell lymphomas with the RHOA p. Gly17Val mutation have classic clinical and pathologic features. *Am. J. Surg. Pathol.* **40**, 335–341 (2016).
66. Nagao, R. et al. Clinicopathologic Analysis of Angioimmunoblastic T-cell Lymphoma With or Without RHOA G17V Mutation Using Formalin-fixed Paraffin-embedded Sections. *Am. J. Surg. Pathol.* **40**, 1041–1050 (2016).
67. Steinhilber, J. et al. The pathological features of angioimmunoblastic T-cell lymphomas with IDH2(R172) mutations. *Mod. Pathol.* **32**, 1123–1134 (2019).
68. Quivoron, C. et al. TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. *Cancer Cell* **20**, 25–38 (2011).
69. Nguyen, T. B. et al. Identification of cell-type-specific mutations in nodal T-cell lymphomas. *Blood Cancer J* **7**, e516 (2017).
70. Lewis, N. E. et al. Clonal hematopoiesis in angioimmunoblastic T-cell lymphoma with divergent evolution to myeloid neoplasms. *Blood Adv.* **4**, 2261–2271 (2020).
71. Vallois, D. et al. Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. *Blood* **128**, 1490–1502 (2016).
72. Huang, Y. et al. Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. *Am. J. Surg. Pathol.* **33**, 682–690 (2009).
73. Debackere, K., van der Krogt, J. A., Tousseyn, T. & Ferreiro, J. A. F. Van Roosbroeck, K., Marcelis, L. *et al*. FER and FES tyrosine kinase fusions in follicular T-cell lymphoma. *Blood* **135**, 584–588 (2020).
74. Streubel, B., Vinatzer, U., Willheim, M., Raderer, M. & Chott, A. Novel t(5;9)(q33; q22) fuses ITK to SYK in unspecified peripheral T-cell lymphoma. *Leukemia* **20**, 313–318 (2006).
75. Dupuy, A. et al. Multiple ways to detect IDH2 mutations in angioimmunoblastic T-cell lymphoma from immunohistochemistry to next-generation sequencing. *J. Mol. Diagn.* **20**, 677–685 (2018).
76. Ghione, P. et al. T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma. *Blood Adv.* **4**, 4640–4647 (2020).
77. Attygalle, A. D., Feldman, A. L. & Dogan, A. ITK/SYK translocation in angioimmunoblastic T-cell lymphoma. *Am. J. Surg. Pathol.* **37**, 1456–1457 (2013).
78. Feldman, A. L. et al. Overexpression of Syk tyrosine kinase in peripheral T-cell lymphomas. *Leukemia* **22**, 1139–1143 (2008).
79. Huang, Y. et al. Gene expression profiling identifies emerging oncogenic pathways operating in extranodal NK/T-cell lymphoma, nasal type. *Blood* **115**, 1226–1237 (2010).
80. Montes-Mojarro, I. A. et al. Mutational profile and EBV strains of extranodal NK/T-cell lymphoma, nasal type in Latin America. *Mod. Pathol.* **33**, 781–791 (2020).
81. Lin, G. W. et al. Genetic risk of extranodal natural killer T-cell lymphoma: a genome-wide association study in multiple populations. *Lancet Oncol.* **21**, 306–316 (2020).
82. Li, Z. et al. Genetic risk of extranodal natural killer T-cell lymphoma: a genome-wide association study. *Lancet Oncol*. **17**, 1240–1247 (2016).
83. Ng, S. B. et al. Epstein-Barr virus-associated primary nodal T/NK-cell lymphoma shows a distinct molecular signature and copy number changes. *Haematologica* **103**, 278–287 (2018).
84. Zhang, Y., Li, C., Xue, W., Zhang, M. & Li, Z. Frequent mutations in natural Killer/T cell lymphoma. *Cell Physiol. Biochem* **49**, 1–16 (2018).
85. de Mel, S. et al. The genomics and molecular biology of natural killer/T-cell lymphoma: opportunities for translation. *Int. J. Mol. Sci.* **19** (2018).
86. Jiang, L. et al. Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. *Nat. Genet.* **47**, 1061–1066 (2015).
87. Ng, S. B. et al. Activated oncogenic pathways and therapeutic targets in extranodal nasal-type NK/T cell lymphoma revealed by gene expression profiling. *J. Pathol.* **223**, 496–510 (2011).
88. Nakashima, Y. et al. Genome-wide array-based comparative genomic hybridization of natural killer cell lymphoma/leukemia: different genomic alteration patterns of aggressive NK-cell leukemia and extranodal Nk/T-cell lymphoma, nasal type. *Genes Chromosomes Cancer* **44**, 247–255 (2005).
89. Iqbal, J. et al. Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. *Leukemia* **23**, 1139–1151 (2009).
90. Xiong, J. et al. Genomic and transcriptomic characterization of natural killer T cell lymphoma. *Cancer Cell* **37**, 403–419 e406 (2020).
91. Liebowitz, D. Epstein-Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. *N. Engl. J. Med.* **338**, 1413–1421 (1998).
92. Suzumiya, J. et al. Nasal lymphomas in Japan: a high prevalence of Epstein-Barr virus type A and deletion within the latent membrane protein gene. *Leuk. Lymphoma* **35**, 567–578 (1999).
93. Hu, L. F. et al. Clonability and tumorigenicity of human epithelial cells expressing the EBV encoded membrane protein LMP1. *Oncogene* **8**, 1575–1583 (1993).
94. Tempera, I. & Lieberman, P. M. Epigenetic regulation of EBV persistence and oncogenesis. *Semin Cancer Biol.* **26**, 22–29 (2014).
95. Peng, R. J. et al. Genomic and transcriptomic landscapes of Epstein-Barr virus in extranodal natural killer T-cell lymphoma. *Leukemia* **33**, 1451–1462 (2019).
96. Cho, J. et al. Immune subtyping of extranodal NK/T-cell lymphoma: a new biomarker and an immune shift during disease progression. *Mod. Pathol.* **33**, 603–615 (2020).
97. Yabe, M., Miranda, R. N. & Medeiros, L. J. Hepatosplenic T-cell Lymphoma: a review of clinicopathologic features, pathogenesis, and prognostic factors. *Hum. Pathol.* **74**, 5–16 (2018).
98. Yabe, M. et al. Prognostic factors of hepatosplenic T-cell lymphoma: clinicopathologic study of 28 cases. *Am. J. Surg. Pathol.* **40**, 676–688 (2016).
99. Macon, W. R. et al. Hepatosplenic alphabeta T-cell lymphomas: a report of 14 cases and comparison with hepatosplenic gammadelta T-cell lymphomas. *Am. J. Surg. Pathol*. **25**, 285–296 (2001).
100. McKinney, M. et al. The genetic basis of hepatosplenic T-cell lymphoma. *Cancer Disco*. **7**, 369–379 (2017).
101. Vega, F. et al. Hepatosplenic gamma/delta T-cell lymphoma in bone marrow. A sinusoidal neoplasm with blastic cytologic features. *Am. J. Clin. Pathol.* **116**, 410–419 (2001).
102. Belhadj, K. et al. Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood* **102**, 4261–4269 (2003).
103. Travert, M. et al. Molecular features of hepatosplenic T-cell lymphoma unravels potential novel therapeutic targets. *Blood* **119**, 5795–5806 (2012).
104. Przybylski, G. K. et al. Hepatosplenic and subcutaneous panniculitis-like gamma/delta T cell lymphomas are derived from different Vdelta subsets of gamma/delta T lymphocytes. *J. Mol. Diagn.* **2**, 11–19 (2000).
105. Bergmann, A. K. et al. DNA methylation profiling of hepatosplenic T-cell lymphoma. *Haematologica* **104**, e104–e107 (2019).
106. Kucuk, C. et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. *Nat. Commun* **6**, 6025 (2015).
107. Van Arnam, J. S., Lim, M. S. & Elenitoba-Johnson, K. S. J. Novel insights into the pathogenesis of T-cell lymphomas. *Blood* **131**, 2320–2330 (2018).
108. Ashton-Key, M., Diss, T. C., Pan, L., Du, M. Q. & Isaacson, P. G. Molecular analysis of T-cell clonality in ulcerative jejunitis and enteropathy-associated T-cell lymphoma. *Am. J. Pathol.* **151**, 493–498 (1997).
109. Zettl, A. et al. Chromosomal gains at 9q characterize enteropathy-type T-cell lymphoma. *Am. J. Pathol.* **161**, 1635–1645 (2002).
110. Cejkova, P. et al. Amplification of NOTCH1 and ABL1 gene loci is a frequent aberration in enteropathy-type T-cell lymphoma. *Virchows Arch.* **446**, 416–420 (2005).
111. Ko, Y. H. et al. Enteropathy-associated T-cell lymphoma-a clinicopathologic and array comparative genomic hybridization study. *Hum. Pathol.* **41**, 1231–1237 (2010).
112. Deleeuw, R. J. et al. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. *Gastroenterology* **132**, 1902–1911 (2007).
113. Obermann, E. C. et al. Loss of heterozygosity at chromosome 9p21 is a frequent finding in enteropathy-type T-cell lymphoma. *J. Pathol.* **202**, 252–262 (2004).
114. Nicolae, A. et al. Mutations in the JAK/STAT and RAS signaling pathways are common in intestinal T-cell lymphomas. *Leukemia* **30**, 2245–2247 (2016).
115. Moffitt, A. B. et al. Enteropathy-associated T cell lymphoma subtypes are characterized by loss of function of SETD2. *J. Exp. Med.* **214**, 1371–1386 (2017).
116. Tan, S. Y. et al. Type II EATL (epitheliotropic intestinal T-cell lymphoma): a neoplasm of intra-epithelial T-cells with predominant CD8alphaalpha phenotype. *Leukemia* **27**, 1688–1696 (2013).
117. Tan, S. Y. et al. Nuclear expression of MATK is a novel marker of type II enteropathy-associated T-cell lymphoma. *Leukemia* **25**, 555–557 (2011).
118. Nairismagi, M. L. et al. JAK-STAT and G-protein-coupled receptor signaling pathways are frequently altered in epitheliotropic intestinal T-cell lymphoma. *Leukemia* **30**, 1311–1319 (2016).

119. Roberti, A. et al. Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. *Nat. Commun* **7**, 12602 (2016).
120. Zhu, X. et al. Identification of functional cooperative mutations of SETD2 in human acute leukemia. *Nat Genet* **46**, 287–293 (2014).
121. Sharma, A. et al. Recurrent STAT3-JAK2 fusions in indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. *Blood* **131**, 2262–2266 (2018).
122. Soderquist, C. R. et al. Genetic and phenotypic characterization of indolent T-cell lymphoproliferative disorders of the gastrointestinal tract. *Haematologica* **105**, 1895–1906 (2020).
123. Margolskee, E. et al. Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. *PLoS One* **8**, e68343 (2013).
124. Shimoyama, M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). *Br. J. Haematol.* **79**, 428–437 (1991).
125. Matsuoka, M. & Jeang, K. T. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat. Rev. Cancer* **7**, 270–280 (2007).
126. Kataoka, K. et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat. Genet*. **47**, 1304–1315 (2015).
127. Marcais, A. et al. Targeted deep sequencing reveals clonal and subclonal mutational signatures in Adult T-cell leukemia/lymphoma and defines an unfavorable indolent subtype. *Leukemia* https://doi.org/10.1038/s41375-020-0900-3 (2020).
128. Sommer, K. et al. Phosphorylation of the CARMA1 linker controls NF-kappaB activation. *Immunity* **23**, 561–574 (2005).
129. Cheng, J. et al. Negative regulation of the SH2-homology containing protein-tyrosine phosphatase-1 (SHP-1) P2 promoter by the HTLV-1 Tax oncoprotein. *Blood* **110**, 2110–2120 (2007).
130. Nakagawa, M. et al. Gain-of-function CCR4 mutations in adult T cell *Leuk/lymphoma*. *J. Exp. Med.* **211**, 2497–2505 (2014).
131. Yamagishi, M. & Watanabe, T. Molecular hallmarks of adult T cell leukemia. *Front Microbiol*. **3**, 334 (2012).
132. Ishida, T. et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J. Clin. Oncol.* **30**, 837–842 (2012).
133. Imaizumi, Y. et al. Possible involvement of interferon regulatory factor 4 (IRF4) in a clinical subtype of adult T-cell leukemia. *Jpn. J. Cancer Res.* **92**, 1284–1292 (2001).
134. Ramos, J. C. et al. IRF-4 and c-Rel expression in antiviral-resistant adult T-cell leukemia/lymphoma. *Blood* **109**, 3060–3068 (2007).
135. Khanlari, M. et al. Adult T-cell leukemia/lymphoma can be indistinguishable from other more common T-cell lymphomas. The University of Miami experience with a large cohort of cases. *Mod. Pathol.* **31**, 1046–1063 (2018).
136. Sakamoto, Y. et al. CCR4 mutations associated with superior outcome of adult T-cell leukemia/lymphoma under mogamulizumab treatment. *Blood* **132**, 758–761 (2018).
137. Fujii, K. et al. Immunohistochemistry for CCR4 C-terminus predicts CCR4 mutations and mogamulizumab efficacy in adult T-cell leukemia/lymphoma. *J. Pathol. Clin. Res.* **7**, 52–60 (2021).

AUTHOR CONTRIBUTIONS

All the authors performed writing, reviewing, and revisions of the manuscript.

COMPETING INTERESTS

A.L.F. receives research funding from Seattle Genetics, is an inventor of technology related to T-cell lymphoma for which Mayo Clinic holds unlicensed patents, and has intellectual property licensed to Zeno Pharmaceuticals. F.V. receives research funding from NCI, CRISP Therapeutics, Geron corporation and received in the last 3 years honoraria from i3Health, Elsevier, America Registry of Pathology, Congressionally Directed Medical Research Program, Society of Hematology Oncology. There are no other competing financial interests to declare.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Francisco Vega.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.