Genetic Landscape and Classification of Peripheral T Cell Lymphomas

Rosalind F. Sandell[1], **Rebecca L. Boddicker**[1], and **Andrew L. Feldman**[1]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Abstract

Purpose of review—Peripheral T cell lymphomas (PTCLs) are markedly heterogeneous at the clinical, pathological, and molecular levels. This review will discuss genetic findings in PTCL with special emphasis on how they impact lymphoma classification.

Recent findings—Sequencing studies have identified recurrent genetic alterations in nearly every PTCL subtype. In anaplastic large cell lymphoma, these studies have revealed novel chromosomal rearrangements and mutations that have prognostic significance and may suggest new therapeutic approaches. Angioimmunoblastic T cell lymphoma has been found to have mutations overlapping some cases of PTCL, not otherwise specified with a T follicular helper cell phenotype. Across various subtypes, recurrent mutations and structural alterations affecting genes involved in epigenetic regulation, T cell receptor signaling, and immune response may represent targets for precision therapy approaches.

Summary—New genetic findings are refining the classification of PTCLs and are beginning to be used clinically for diagnosis, risk stratification, and individualized therapy.

Keywords

Peripheral Tcell lymphoma; Molecular genetics; Angioimmunoblastic Tcell lymphoma; Anaplastic large cell lymphoma; Extranodal NK/Tcell lymphoma

Introduction

Peripheral T cell lymphomas (PTCLs) are a group of rare lymphomas originating from mature (i.e., post-thymic or "peripheral") T lymphocytes and NK cells [1]. PTCLs comprise approximately 10–15% of all non-Hodgkin lymphomas and, with the exception of a few relatively indolent entities, generally are aggressive tumors which carry a poor prognosis [2, 3••]. PTCLs most commonly affect adults and the elderly, and overall are more common in Asia than in the West [4–6]. One likely contributor to this geographic variability is different

exposures to viral infectious agents that are associated with specific PTCL entities, including Epstein-Barr virus (EBV) and human T-lymphotropic virus 1 (HTLV-1) [7].

The 2008 World Health Organization (WHO) Classification scheme broadly grouped PTCLs into four categories based on the predominant clinical presentation: leukemic (disseminated), nodal, extranodal, and cutaneous (Table 1) [5]. It is recognized, however, that in practice PTCLs can be difficult to subclassify due to evolving diagnostic criteria, multiple subtypes, overall rarity, and the relative paucity of known, specific genetic abnormalities in comparison to B cell lymphomas. Even within established subtypes, PTCLs can exhibit pronounced clinical, histological, immunophenotypic, cytogenetic, and molecular heterogeneity. However, despite these challenges, significant molecular advances have increased understanding of PTCL pathobiology and impacted current classification. In the 2016 revision of the WHO classification of lymphoid neoplasms, mature T and NK cell lymphomas and lymphoproliferative disorders will encompass 27 distinct entities in addition to PTCL, not otherwise specified (NOS), comprising T cell lymphomas not meeting criteria for one of the more specific categories [3••]. The current review discusses the genetic findings and classification of some of the more common PTCLs.

Angioimmunoblastic T Cell Lymphoma

Angioimmunoblastic T cell lymphoma (AITL) is one of the most common PTCL subtypes, comprising between 22 and 34% of cases, depending on geographic region [12]. AITL most frequently affects middle-aged adults and the elderly, and is characterized by advanced stage disease, generalized lymphadenopathy, hepatosplenomegaly, skin rash, and polyclonal hypergammaglobulinemia. The clinical course generally is aggressive and often is complicated by infection due to disease-associated immunosuppression. AITL demonstrates a T follicular helper cell (T_{FH}) phenotype and typically is associated with B cells infected by EBV; the neoplastic T cells are EBV-negative. Some patients also develop diffuse large B cell lymphoma, which often is EBV-positive [13].

Recent genetic advances have revealed recurrent abnormalities, including both mutations and structural alterations, in a large proportion of AITLs (Table 2). Somatic mutations in *TET2*, *DNMT3A*, *RHOA*, *CD28*, and *IDH2* have been found in varying frequencies in AITL, offering clues into the pathogenesis of this PTCL subtype [14, 15, 16•, 17•, 18•, 19–21, 46]. $RHOA^{G17V}$ mutations have been identified in both AITL (50–71%) and PTCL, NOS (8–18%), and likely serve a dominant negative function, blocking RHOA GTPase activity [16•, 17•, 18•]. Recently, a novel activating variant, $RHOA^{K18N}$, has been described [22]. *IDH2* mutations are relatively specific for AITL, occurring in 20–45% of cases, and particularly involve $IDH2^{R172}$ [19, 21]. $IDH2^{R172}$ mutations lead to accumulation of the (R)-enantiomer of 2-hydroxyglutarate, which inhibits TET family and other enzymes and leads to alterations in DNA and histone methylation. In a study of 190 PTCLs, Lemonnier et al. found *TET2* mutations in AITL (47%) and PTCL, NOS (38%), but not in other PTCLs except for 2/10 enteropathy-associated T cell lymphomas. Cases of PTCL, NOS with *TET2* mutations were more likely to express T_{FH} markers and/or share common histologic features with AITL. *TET2* mutations in both AITL and PTCL, NOS were associated with advanced stage disease, thrombocytopenia, high International Prognostic Index scores, and shorter

progression-free survival times [46]. Of note, mutations involving *TET2*, *DNMT3A*, *RHOA*, and *IDH2* often co-occur in the same case, including PTCLs in which all four of these genes are mutated [16•, 17•, 18•, 22]. Data suggest that among these mutations, those involving *DNMT3A* may be particularly early events, and sometimes are present in cells of non-T cell lineage from the same patient [14]. Although the molecular pathogenesis of AITL and other T_{FH}-derived PTCLs remains incompletely understood, the relationship of the aforementioned genes to epigenetic regulation suggests that disruption of gene expression via epigenetic mechanisms may be involved in disease development and/or progression [3••, 19, 47], and might in part explain observed clinical responses of AITL to epigenetic modifying drugs such as histone deacetylase inhibitors [48].

Among structural abnormalities, *CTLA4-CD28* fusion genes have been identified in AITL and several other PTCL subtypes, though analysis of different PTCL cohorts has uncovered variation in the frequency of this finding [23, 49, 50]. The resultant fusion protein is thought to transform inhibitory T cell signals into activating signals, and may represent a target for anti-CTLA4 immunotherapy [23]. Copy number alterations and loss of heterozygosity also have been demonstrated in AITL and PTCL, NOS; among genes within regions of frequent copy number gains, poor prognosis was associated with overexpression of *CARMA1* at 7p22 and *MYCBP2* at 13q22 [24].

As noted above, recurrent genetic alterations in AITL also have been found in cases of PTCL, NOS with a T_{FH} phenotype. While the 2008 WHO classification considered these cases within the spectrum of PTCL, NOS, the 2016 revision will introduce two provisional T_{FH}-related entities: follicular T cell lymphoma and nodal PTCL with T_{FH} phenotype [1, 3••, 46].

Anaplastic Large Cell Lymphoma, ALK-Positive

Anaplastic large cell lymphoma (ALCL) is another of the more common PTCL subtypes, accounting for ~12% of all cases [12]. ALCL is a general heading comprising several distinct WHO entities based on clinical presentation and presence or absence of *ALK* (anaplastic lymphoma kinase) gene rearrangements: ALK-positive ALCL, ALK-negative ALCL (upgraded from provisional to definite entity in 2016 revision), primary cutaneous ALCL, and breast implant-associated ALCL (new provisional entity in 2016 revision) [3••, 25, 51]. Systemic ALCL often presents with advanced stage disease, frequently including B-symptoms such as high fevers. All ALCL subtypes share common pathological features, including the presence of morphologically distinctive cells designated "hallmark" cells (Fig. 1a) and consistent expression of the lymphocyte activation marker, CD30.

ALK-positive ALCL affects a younger patient population than ALK-negative ALCL and other PTCLs, occurring most commonly during the first three decades of life [25]. ALK-positive ALCL was the first PTCL in which a recurrent genetic abnormality was recognized [52]. About half of ALCLs subsequently were found to have *ALK* rearrangements [25]. The *ALK* gene was characterized from a t(2;5)(p23;q35) translocation in ALCL, resulting in the fusion of nucleophosmin (*NPM1*) to *ALK* and encoding *NPM1/ALK* fusion transcripts [26]. The t(2;5) translocation is present in approximately 75–85% of ALK-positive ALCLs; more

than 20 other *ALK* partners have been found, accounting for the remaining ALK-positive ALCLs as well as now being recognized in other lymphomas and non-lymphoid cancers [25, 51]. The frequency of the t(2;5) compared to variant *ALK* rearrangements may be slightly higher in pediatric than in adult ALK-positive ALCLs [53], but identifying the *ALK* fusion partner is not considered necessary in routine clinical practice.

Both *NPM1/ALK* and variants lead to expression of ALK fusion proteins with constitutive ALK tyrosine kinase activity [25, 27, 54, 55]. Central to the function of ALK fusion proteins is activation of the downstream oncogenic transcription factor, STAT3 [28•]. ALK-induced STAT3 activation plays a variety of roles in cancer cells, including regulation of availability of hypoxia-inducible factors under hypoxic conditions [56]. ALK tyrosine kinase activity can be targeted by clinically available inhibitors, and pharmacologic ALK inhibition is effective in a variety of clinical scenarios, including relapsed/refractory ALK-positive ALCL [47, 57–59]. Even with conventional cytotoxic chemotherapy, ALK-positive ALCL has a more favorable prognosis than ALK-negative ALCL as a whole (see section below) and most other PTCL subtypes, with overall 5-year survival rates of 70 to 85% [29•, 60, 61]. The *ALK* partner gene (*NPM1* or variant) does not appear to be a significant prognostic factor [62].

Anaplastic Large Cell Lymphoma, ALK-Negative

Systemic PTCLs that are morphologically compatible with ALCL and express CD30, but lack *ALK* rearrangements, now are considered a separate subtype [3••, 63]. ALK-negative ALCL affects an older patient population than ALK-positive ALCL, and the molecular genetics remain incompletely understood [29•, 51, 63]. Although, as a whole, ALK-negative ALCL generally has been found to have a prognosis inferior to that of ALK-positive ALCL, some studies have found similar overall survival (OS) rates after adjusting for age [60, 64].

Distinguishing ALK-negative ALCL from CD30-positive PTCL, NOS is diagnostically challenging, but is of critical importance due to the potential prognostic and therapeutic implications. Gene expression profiling studies have shown not only that ALK-negative ALCL and ALK-positive ALCL share a common signature, but also that the signature of ALK-negative ALCL is distinct from that of PTCL, NOS [3••, 65•, 66, 67]. A three-gene model (*TNFRSF8*, *BATF3*, and *TMOD1*) has been proposed to help distinguish ALK-negative ALCL from PTCL, NOS in tissue samples, but is not in routine clinical use [68].

Recently, Crescenzo et al. reported that the JAK/STAT3 pathway was constitutively activated via multiple genomic mechanisms in ALK-negative ALCL [28•]. The *JAK1* and *STAT3* genes each were recurrently mutated in a subset of cases, but were not found in other PTCLs, including ALK-positive ALCL and PTCL, NOS (including 16 CD30-positive cases). In addition, RNA sequencing identified a small subset of ALK-negative ALCLs that lacked these mutations but harbored gene fusions involving non-*ALK* tyrosine kinase genes, including *ROS1* and *TYK2*, leading to constitutive activation of *STAT3*. Thus, STAT3 may drive oncogenesis in the majority ALCLs, independent of ALK status.

Recurrent rearrangements of non-tyrosine kinase genes also have been identified in ALK-negative ALCL, notably including rearrangements of the *DUSP22-IRF4* locus on 6p25.3 (*DUSP22* rearrangements, Fig. 1b) or of *TP63* on 3q28 [30, 31]. Parrilla Castellar et al. have shown that these rearrangements have prognostic significance in ALK-negative ALCL [29•]. *DUSP22* rearrangements were seen in 30% of ALK-negative ALCLs and were associated with a favorable prognosis (90% 5-year OS), similar to that observed in ALK-positive ALCL (85%). *TP63* rearrangements were seen in 8% of ALK-negative ALCLs and were associated with a 5-year OS rate of only 17%; ALCLs lacking rearrangements of *ALK*, *DUSP22*, and *TP63* (so-called triple-negative cases) had an intermediate 5-year OS rate of 42%. For comparison, PTCL, NOS has been found to have a 5-year OS rate of 32% (and only 19% for cases with CD30 expression in 80% of cells) [12].

Scarfo et al. recently identified *ERBB4* and *COL29A1* as gene expression outliers in 24% of ALK-negative ALCLs [32]. They found that ERBB4 deregulation resulted from expression of two truncated transcripts with intronic transcriptional start sites. Truncated ERBB4 showed in vitro and in vivo oncogenic potential, and an ERBB4-positive patient-derived xenograft model showed sensitivity to pharmacologic ERBB4 inhibition. A genome-wide copy-number study using single nucleotide polymorphism arrays recently reported frequent losses at 6p21 and 17p13, corresponding to the *PRDM1* (encoding the tumor suppressor, BLIMP1) and *TP53* genes, respectively [33]. *PRDM1* was found to be inactivated via multiple mechanisms in 56% of ALK-negative ALCLs and only 6% of ALK-positive ALCLs. Additionally, losses in 6q21 and/or 17p were associated with inferior OS among ALK-negative ALCLs.

It should be noted that systemic ALCL needs to be distinguished from primary cutaneous ALCL (pcALCL), which is an indolent entity with excellent disease-specific survival rates; pcALCL presents in the skin, and although it occasionally involves regional lymph nodes, it rarely disseminates [51, 69, 70]. The reasons that pcALCL is more indolent than systemic ALCL are incompletely understood, but may relate to specific profiles of cytokines and chemokine receptors, partly shared with breast implant-associated ALCLs, that could limit dissemination and suggest distinct initiating events related to chronic antigenic stimulation [71, 72]. Because systemic ALCL can involve the skin secondarily, patients with skin biopsies showing ALCL should undergo staging procedures. Though pcALCL is not specifically covered in this review, it should be noted that it shares some genetic features with systemic ALK-negative ALCL, including *DUSP22* rearrangements in 28% [73], *TYK2* rearrangements in 13% [74], *STAT3* mutations in 5% [28•], and occasional *TP63* rearrangements [31]. pcALCL generally is considered an ALK-negative entity, but rare, otherwise similar cases with *ALK* rearrangements have been reported [75].

Extranodal NK/T Cell Lymphoma, Nasal Type

Extranodal NK/T cell lymphoma, nasal type (NKTCL) is an aggressive lymphoma that most often originates from natural killer (NK) cells, but in some cases is derived from cytotoxic T cells [76, 77]. NKTCL primarily affects adults within Asian and Central and South American populations. The nasal cavity and adjacent structures are the most common sites of presentation, but other extranodal locations may be involved. Patients often present with

symptoms of nasal obstruction, epistaxis, or with midfacial destructive lesions ("lethal midline granuloma"). Histologically, NKTCL features an angiocentric and angiodestructive growth pattern. The neoplastic cells are associated with EBV in virtually all cases, suggesting a likely pathogenic role of the virus. The prognosis of NKTCL is generally unfavorable but can vary. Tumors occurring outside the nasal cavity have been found to be highly aggressive and generally do not respond well to chemotherapy. Of note, chemoresistance of NKTCLs is partly attributable to expression of P-glycoprotein, encoded by the multidrug resistance gene, *MDR1*; drug combinations not affected by P-glycoprotein, particularly L-asparaginase-based regimens, have been associated with improved outcomes [78].

A variety of somatic mutations has been identified in NKTCL, most commonly involving the RNA helicase gene *DDX3X* (20% of cases) and *JAK3* (35% of cases) [36, 37]. Mutations of *STAT5B* and *STAT3* also have been identified in NKTCL and PTCLs derived from $\gamma\delta$-T cells, further emphasizing the role of JAK/STAT signaling in this and related diseases [38]. As discussed above, *CTLA4-CD28* fusions may be identified in NKTCLs [23]. Other structural abnormalities include copy number losses at 6q21, including the *PRDM1* gene [40].

Peripheral T Cell Lymphoma, Not Otherwise Specified

PTCL, NOS is an intentionally heterogeneous entity, sometimes referred to as a "wastebasket" category, comprising nodal and extranodal PTCLs that do not fulfill criteria for any of the more specific PTCL subtypes [79]. The fact that PTCL, NOS accounts for approximately ~30% of all PTCLs, making it the most common entity, attests to the need for new molecular and other data to increase understanding of these cases. PTCL, NOS most often presents in the lymph nodes; however, any site can be involved. The most frequent extranodal sites of involvement are the gastrointestinal tract and the skin [79]. As noted above, PTCL, NOS has a generally poor prognosis (5-year OS rate, 32%) [12].

The genetic findings in PTCL, NOS are heterogeneous and demonstrate significant overlap with other PTCL subtypes. As discussed above, this overlap may guide development of criteria to place cases in a more specific entity, such as the new provisional categories for non-angioimmunoblastic T_{FH}-derived PTCLs [3••]. Recent gene expression profiling studies have identified at least two major subgroups of PTCL, NOS that are characterized by high expression of either *GATA3* or *TBX21*, with the former associated with inferior prognosis [3••, 65•, 80]. Poor clinical outcomes also were observed when TBX21-associated cases expressed a cytotoxic gene signature.

Various recurrent mutations have been identified in subsets of PTCL, NOS. Palomero et al. have identified novel mutations in the *FYN* gene, which encodes a tyrosine kinase that plays an important role in T cell activation [16•]. FYN kinase activity was successfully targeted by a multikinase inhibitor in vitro, thereby displaying promise for a therapeutic approach in the small subset of PTCL patients with these mutations. Several additional recurrent genetic mutations in PTCL, NOS were mentioned in the section on AITL, including the epigenetic modulator genes, *TET2*, *DNMT3A*, and *RHOA* [14, 16•, 1717•, 19]. Similarities between

AITL and other T$_{FH}$-derived PTCLs have been noted at the gene expression profiling level as well, though differences also exist [81, 82]. Interestingly, a recurrent t(5;9)(q33;q22) translocation leading to *ITK/SYK* fusion and overexpression and activation of spleen tyrosine kinase (SYK) has been identified in a subset of PTCLs with a follicular growth pattern and a T$_{FH}$ phenotype, and rarely in AITL [8, 44, 45, 83]. This fusion appears targetable with SYK inhibitors. Overall, these molecular similarities and differences have contributed to the introduction of the aforementioned provisional T$_{FH}$-derived PTCL categories, which separate these entities from the broader category of PTCL, NOS but also keep them distinct from AITL [3••].

As discussed above, *CTLA4-CD28* fusions occur in a subset of cases of PTCL, NOS [23]. Boddicker et al. recently discovered additional gene fusions in PTCL, NOS by integrating mate-pair DNA sequencing and RNA sequencing [34]. Of particular interest were recurrent *VAV1* fusions with varying partners, which were found not only in PTCL, NOS (11%) but also in ALK-negative ALCL (16%) and a single case of ALK-positive ALCL. Cells overexpressing a VAV1-GSS fusion protein showed increased growth and were sensitive to azathioprine, an inhibitor of RAC1 activity. Of note, mutations of *VAV1* also have been reported recently in various PTCL subtypes [22, 84].

As mentioned above, Fujiwara et al. have identified various loci with copy number alterations in PTCL, NOS and AITL, some of which were found to have prognostic implications [24]. Similar to AITL, overexpression of *CARMA1* was associated with poor prognosis in PTCL, NOS. Additionally, a recurrent loss at 9p21 was associated with reduced expression of *CDKN2A*, *CDKN2B*, and *MTAP*. Reduced levels of *CDKN2A* were found in 9% of PTCL, NOS samples and were associated with inferior outcomes.

Future Directions and Perspectives

The most recent update to the WHO classification highlights several emergent themes with regard to genetics and high-throughput molecular profiling. First, these approaches, particularly analysis of mutational landscapes and gene expression profiling, have identified areas of commonality between subsets of PTCL, NOS and other PTCL subtypes, as in the case of T$_{FH}$-derived PTCLs and AITL [3••]. As molecular understanding of PTCLs deepens, this trend is likely to continue, hopefully leading to a decrease in the number of patients given the "wastebasket" diagnosis of PTCL, NOS, albeit likely at the price of an increasing number of overall categories. Second, we are likely to deepen our understanding of the molecular heterogeneity within established entities (e.g., ALK-negative ALCL [29•]), giving rise to new prognostic biomarkers and/or tools for risk-stratifying patients for clinical research studies. Third, we are likely to see the introduction of new molecular tools that help refine the borderlands between related entities and aid clinical diagnosis [65•, 68]; digital gene expression analysis [85] is one technology that may find application here. New "omics" methodologies also may impact classification as they are applied more comprehensively, including epigenomics, proteomics, and metabolomics. Finally, increasing understanding of the scope and targetability of genetic alterations will help determine the role of individualized medicine approaches in clinical practice [86]. These approaches may be particularly applicable to complement the evolving molecular classification of PTCLs

(compared to B cell lymphomas, for example), given the overall rarity and molecular heterogeneity of this constellation of disorders.

Conclusions

The recent advances described above have provided insight into the genetic heterogeneity of PTCLs. These discoveries have shed light on the classification, prognosis, and potential targeted therapy of several of the more common PTCL subtypes, but there is still much progress to be made. Treatment outcomes for PTCLs have not yet shown significant improvement despite increased molecular understanding, partly due to a relative paucity of candidate therapeutic targets. As knowledge of the genetic drivers of PTCL increases, cooperative group studies, innovative clinical trial design, and biomarker investigations to guide therapy will be critical to make a tangible impact on patient outcomes.

Acknowledgments

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Attygalle AD, Cabecadas J, Gaulard P, et al. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward—report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology. Histopathology. 2014; 64(2):171–99. [PubMed: 24128129]

2. Armitage JO. The aggressive peripheral T-cell lymphomas: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012; 87(5):511–9. [PubMed: 22508369]

3••. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127(20):2375–90. Recently published summary of the 2016 revision of the WHO classification, including new provisional entities and incorporating genetic data not available when the 2008 WHO classification was published. [PubMed: 26980727]

4. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. Blood. 2011; 117(25):6756–67. [PubMed: 21493798]

5. Jaffe, ES., Harris, L., Stein, H., Campo, E., Pileri, SA., Swerdlow, SH. Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow, SH.Campo, E.Harris, L.Jaffe, ES.Pileri, S.Stein, H.Thiele, J., Vardiman, JW., editors. WHO classification of tumors of hematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer; 2008. p. 158-66.

6. Perry AM, Diebold J, Nathwani BN, et al. Non-Hodgkin lymphoma in the Far East: review of 730 cases from the international non-Hodgkin lymphoma classification project. Ann Hematol. 2016; 95(2):245–51. [PubMed: 26537613]

7. William BM, Armitage JO. International analysis of the frequency and outcomes of NK/T-cell lymphomas. Best Pract Res Clin Haematol. 2013; 26(1):23–32. [PubMed: 23768638]

8. Huang Y, Moreau A, Dupuis J, 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. 2009; 33(5):682–90. [PubMed: 19295409]

9. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol. 2014; 32(2):114–20. [PubMed: 24323027]

10. Roden AC, Macon WR, Keeney GL, Myers JL, Feldman AL, Dogan A. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. Mod Pathol. 2008; 21(4):455–63. [PubMed: 18223553]

11••. Swerdlow, S.Campo, E.Harris, N.Jaffe, E.Pileri, S.Stein, H.Thiele, J., Vardiman, J., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4. Lyon: International Agency for Research on Cancer; 2008. Most recent published edition of the WHO classification of lymphoid neoplasms at the time of this writing.

12. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008; 26(25):4124–30. [PubMed: 18626005]

13. Hoffmann JC, Chisholm KM, Cherry A, et al. An analysis of MYC and EBV in diffuse large B-cell lymphomas associated with angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma not otherwise specified. Hum Pathol. 2016; 48:9–17. [PubMed: 26772393]

14. Couronne L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. N Engl J Med. 2012; 366(1):95–6. [PubMed: 22216861]

15. Odejide O, Weigert O, Lane AA, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood. 2014; 123(9):1293–6. [PubMed: 24345752]

16•. Palomero T, Couronne L, Khiabanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral Tcell lymphomas. Nat Genet. 2014; 46(2):166–70. Identification of recurrent RHOA mutations in peripheral T-cell lymphomas. [PubMed: 24413734]

17•. Sakata-Yanagimoto M, Enami T, Yoshida K, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet. 2014; 46(2):171–5. Identification of recurrent RHOA mutations in peripheral T-cell lymphomas. [PubMed: 24413737]

18•. Yoo HY, Sung MK, Lee SH, et al. A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nat Genet. 2014; 46(4):371–5. Identification of recurrent RHOA mutations in peripheral T-cell lymphomas. [PubMed: 24584070]

19. Wang C, McKeithan TW, Gong Q, et al. IDH2R172 mutations define a unique subgroup of patients with angioimmunoblastic T-cell lymphoma. Blood. 2015; 126(15):1741–52. [PubMed: 26268241]

20. Rohr J, Guo S, Huo J, Bouska A, Lachel C, Li Y, Simone PD, Zhang W, Gong Q, Wang C, et al. Recurrent activating mutations of CD28 in peripheral T-cell lymphomas. Leukemia. 2015

21. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood. 2012; 119(8):1901–3. [PubMed: 22215888]

22. Vallois D, Dobay MP, Morin RD, et al. Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. Blood. 2016; 128(11): 1490–502. [PubMed: 27369867]

23. Yoo HY, Kim P, Kim WS, et al. Frequent CTLA4-CD28 gene fusion in diverse types of T-cell lymphoma. Haematologica. 2016; 101(6):757–63. [PubMed: 26819049]

24. Fujiwara SI, Yamashita Y, Nakamura N, et al. High-resolution analysis of chromosome copy number alterations in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified, with single nucleotide polymorphism-typing microarrays. Leukemia. 2008; 22(10): 1891–8. [PubMed: 18633432]

25. Delsol, G., Falini, B., Muller-Hermelink, HK., et al. Anaplastic large cell lymphoma, ALK-positive. In: Swerdlow, S.Campo, E.Harris, N.Jaffe, E.Pileri, S.Stein, H.Thiele, J., Vardiman, J., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th. Lyon: International Agency for Research on Cancer; 2008. p. 312-6.

26. Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1994; 263(5151):1281–4. [PubMed: 8122112]

27. Feldman AL, Vasmatzis G, Asmann YW, et al. Novel TRAF1-ALK fusion identified by deep RNA sequencing of anaplastic large cell lymphoma. Genes Chromosomes Cancer. 2013; 52(11):1097–102. [PubMed: 23999969]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

28•. Crescenzo R, Abate F, Lasorsa E, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell. 2015; 27(4):516–32. Discovery of varied genetic alterations driving JAK/STAT3 activation in anaplastic large cell lymphomas. [PubMed: 25873174]

29•. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood. 2014; 124(9): 1473–80. Report on the prognostic significance of DUSP22 and TP63 rearrangements in ALK-negative an-aplastic large cell lymphoma. [PubMed: 24894770]

30. Feldman AL, Dogan A, Smith DI, 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. 2011; 117(3):915–9. [PubMed: 21030553]

31. 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; 120:2280–9. [PubMed: 22855598]

32. Scarfo 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):221–32. [PubMed: 26463425]

33. Boi M, Rinaldi A, Kwee I, et al. PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma. Blood. 2013; 122(15):2683–93. [PubMed: 24004669]

34. Boddicker RL, Razidlo GL, Dasari S, et al. Integrated mate-pair and RNA sequencing identifies novel, targetable gene fusions in peripheral T-cell lymphoma. Blood. 2016; 128(9):1234–45. [PubMed: 27297792]

35. Melard P, Idrissi Y, Andrique L, Poglio S, Prochazkova-Carlotti M, Berhouet S, Boucher C, Laharanne E, Chevret E, Pham-Ledard A, et al. Molecular alterations and tumor suppressive function of the DUSP22 (Dual Specificity Phosphatase 22) gene in peripheral T-cell lymphoma subtypes. Oncotarget. 2016

36. Jiang L, Gu ZH, Yan ZX, et al. Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. Nat Genet. 2015; 47(9):1061–6. [PubMed: 26192917]

37. Koo GC, Tan SY, Tang T, et al. Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov. 2012; 2(7):591–7. [PubMed: 22705984]

38. Kucuk C, Jiang B, Hu X, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-Tor NK cells. Nat Commun. 2015; 6:6025. [PubMed: 25586472]

39. Quintanilla-Martinez L, Kremer M, Keller G, et al. p53 Mutations in nasal natural killer/T-cell lymphoma from Mexico: association with large cell morphology and advanced disease. Am J Pathol. 2001; 159(6):2095–105. [PubMed: 11733360]

40. Kucuk C, Iqbal J, Hu X, et al. PRDM1 is a tumor suppressor gene in natural killer cell malignancies. Proc Natl Acad Sci U S A. 2011; 108(50):20119–24. [PubMed: 22143801]

41. Iqbal J, Kucuk C, Deleeuw RJ, et al. Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. Leukemia. 2009; 23(6):1139–51. [PubMed: 19194464]

42. Karube K, Nakagawa M, Tsuzuki S, et al. Identification of FOXO3 and PRDM1 as tumor-suppressor gene candidates in NK-cell neoplasms by genomic and functional analyses. Blood. 2011; 118(12):3195–204. [PubMed: 21690554]

43. Huang Y, de Reynies A, de Leval L, et al. Gene expression profiling identifies emerging oncogenic pathways operating in extranodal NK/T-cell lymphoma, nasal type. Blood. 2010; 115(6):1226–37. [PubMed: 19965620]

44. 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. 2006; 20(2):313–8. [PubMed: 16341044]

45. Dierks C, Adrian F, Fisch P, et al. The ITK-SYK fusion oncogene induces a T-cell lymphoproliferative disease in mice mimicking human disease. Cancer Res. 2010; 70(15):6193–204. [PubMed: 20670954]

46. Lemonnier F, Couronne L, Parrens M, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with T_{FH}-like features and adverse clinical parameters. Blood. 2012; 120(7): 1466–9. [PubMed: 22760778]

47. Piccaluga PP, Tabanelli V, Pileri SA. Molecular genetics of peripheral T-cell lymphomas. Int J Hematol. 2014; 99(3):219–26. [PubMed: 24481943]

48. Pro B, Horwitz SM, Prince HM, Foss FM, Sokol L, Greenwood M, Caballero D, Morschhauser F, Wilhelm M, Iyer SP, et al. Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. Hematol Oncol. 2016

49. Yoo HY, Kim P, Kim WS, et al. Author reply to Comment on: Frequent CTLA4-CD28 gene fusion in diverse types of T-cell lymphoma, by Yoo et al. Haematologica. 2016; 101(6):e271. [PubMed: 27252517]

50. Gong Q, Wang C, Rohr J, Feldman AL, Chan WC, McKeithan T. Comment on: Frequent CTLA4-CD28 gene fusion in diverse types of T-cell lymphoma, by Yoo et al. Haematologica. 2016; 101(6):e269–70. [PubMed: 27252516]

51. Xing X, Feldman AL. Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. Adv Anat Pathol. 2015; 22(1):29–49. [PubMed: 25461779]

52. Rimokh R, Magaud JP, Berger F, et al. A translocation involving a specific breakpoint (q35) on chromosome 5 is characteristic of an-aplastic large cell lymphoma ('Ki-1 lymphoma'). Br J Haematol. 1989; 71(1):31–6. [PubMed: 2917127]

53. Damm-Welk C, Klapper W, Oschlies I, et al. Distribution of NPM1-ALK and X-ALK fusion transcripts in paediatric anaplastic large cell lymphoma: a molecular-histological correlation. Br J Haematol. 2009; 146(3):306–9. [PubMed: 19545284]

54. Hapgood G, Savage KJ. The biology and management of systemic anaplastic large cell lymphoma. Blood. 2015; 126(1):17–25. [PubMed: 25869285]

55. Inghirami G, Pileri SA, European TCLSG. Anaplastic large-cell lymphoma. Semin Diagn Pathol. 2011; 28(3):190–201. [PubMed: 21850985]

56. Martinengo C, Poggio T, Menotti M, et al. ALK-dependent control of hypoxia-inducible factors mediates tumor growth and metastasis. Cancer Res. 2014; 74(21):6094–106. [PubMed: 25193384]

57. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med. 2011; 364(8):775–6. [PubMed: 21345110]

58. Mosse YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol. 2013; 14(6):472–80. [PubMed: 23598171]

59. Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst. 2014; 106(2):djt378. [PubMed: 24491302]

60. Savage KJ, Harris NL, Vose JM, 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. 2008; 111(12):5496–504. [PubMed: 18385450]

61. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood. 1999; 93(11):3913–21. [PubMed: 10339500]

62. Delsol, G., Falini, B., Muller-Hermelink, HK., et al. Anaplastic large cell lymphoma (ALCL), ALK-positive. In: Swerdlow, SH.Campo, E.Harris, L.Jaffe, ES.Pileri, S.Stein, H.Thiele, J., Vardiman, JW., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th. Lyon: International Agency for Research on Cancer; 2008. p. 312-6.

63. Mason, DY., Harris, L., Delsol, G., et al. Anaplastic large cell lymphoma, ALK-negative. In: Swerdlow, S.Campo, E.Harris, N.Jaffe, E.Pileri, S.Stein, H.Thiele, J., Vardiman, J., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th. Lyon: International Agency for Research on Cancer; 2008. p. 317-9.

64. Sibon D, Fournier M, Briere J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. J Clin Oncol. 2012; 30(32):3939–46. [PubMed: 23045585]

65•. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood. 2014; 123(19):2915–23. Major paper on the

role of gene expression profiling in segregating known entities and subgroups within peripheral T-cell lymphomas, not otherwise specified. [PubMed: 24632715]

66. Piva R, Agnelli L, Pellegrino E, et al. Gene expression profiling uncovers molecular classifiers for the recognition of anaplastic large-cell lymphoma within peripheral T-cell neoplasms. J Clin Oncol. 2010; 28(9):1583–90. [PubMed: 20159827]

67. Piccaluga PP, Fuligni F, De Leo A, et al. Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. J Clin Oncol. 2013; 31(24):3019–25. [PubMed: 23857971]

68. Agnelli L, Mereu E, Pellegrino E, et al. Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma. Blood. 2012; 120(6): 1274–81. [PubMed: 22740451]

69. Ralfkiaer, E., Willemze, R., Paulli, M., Kadin, ME. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders. In: Swerdlow, SH.Campo, E.Harris, L.Jaffe, ES.Pileri, S.Stein, H.Thiele, J., Vardiman, JW., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th. Lyon: International Agency for Research on Cancer; 2008. p. 300-1.

70. Bekkenk MW, Geelen FA, van Voorst Vader PC, 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. 2000; 95(12):3653–61. [PubMed: 10845893]

71. van Kester MS, Tensen CP, Vermeer MH, et al. Cutaneous anaplas-tic large cell lymphoma and peripheral T-cell lymphoma NOS show distinct chromosomal alterations and differential expression of che-mokine receptors and apoptosis regulators. J Invest Dermatol. 2010; 130(2): 563–75. [PubMed: 19710685]

72. Kadin ME, Deva A, Xu H, Morgan J, Khare P, MacLeod RA, Van Natta BW, Adams WP Jr, Brody GS, Epstein AL. Biomarkers provide clues to early events in the pathogenesis of breast implant-associated anaplastic large cell lymphoma. Aesthet Surg J. 2016

73. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translo-cations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. Mod Pathol. 2011; 24(4): 596–605. [PubMed: 21169992]

74. Velusamy T, Kiel MJ, Sahasrabuddhe AA, et al. A novel recurrent NPM1-TYK2 gene fusion in cutaneous CD30-positive lymphoproliferative disorders. Blood. 2014; 124(25):3768–71. [PubMed: 25349176]

75. Oschlies I, Lisfeld J, Lamant L, et al. ALK-positive anaplastic large cell lymphoma limited to the skin: clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. Haematologica. 2013; 98(1):50–6. [PubMed: 22773605]

76. Chan, JC., Quintanilla-Martinez, L., Ferry, JA., Peh, SC. Extranodal NK/T-cell lymphoma, nasal type. In: Swerdlow, SH.Campo, E.Harris, L.Jaffe, ES.Pileri, S.Stein, H.Thiele, J., Vardiman, JW., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th. Lyon: International Agency for Research on Cancer; 2008. p. 285-8.

77. Pongpruttipan T, Sukpanichnant S, Assanasen T, et al. Extranodal NK/T-cell lymphoma, nasal type, includes cases of natural killer cell and alphabeta, gammadelta, and alphabeta/gammadelta T-cell origin: a comprehensive clinicopathologic and phenotypic study. Am J Surg Pathol. 2012; 36(4):481–99. [PubMed: 22314189]

78. Chaudhary RK, Bhatt VR, Vose JM. Management of extranodal natural killer/t-cell lymphoma, nasal type. Clin Lymphoma Myeloma Leuk. 2015; 15(5):245–52. [PubMed: 25659751]

79. Pileri, S., Ralfkiaer, E., Weisenburger, D., et al. Peripheral T-cell lymphoma, not otherwise specified. In: Swerdlow, SH.Campo, E.Harris, L.Jaffe, ES.Pileri, S.Stein, H.Thiele, J., Vardiman, JW., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th. Lyon: International Agency for Research on Cancer; 2008. p. 306-8.

80. Wang T, Feldman AL, Wada DA, et al. GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. Blood. 2014; 123(19):3007–15. [PubMed: 24497534]

81. de Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood. 2007; 109(11):4952–63. [PubMed: 17284527]

82. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. Cancer Res. 2007; 67(22):10703–10. [PubMed: 18006812]

83. Attygalle AD, Feldman AL, Dogan A. ITK/SYK translocation in angioimmunoblastic T-cell lymphoma. Am J Surg Pathol. 2013; 37(9):1456–7. [PubMed: 24076779]

84. Kataoka K, Nagata Y, Kitanaka A, et al. Integrated molecular analysis of adult T cell leukemia/ lymphoma. Nat Genet. 2015; 47(11):1304–15. [PubMed: 26437031]

85. Scott DW, Mottok A, Ennishi D, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. J Clin Oncol. 2015; 33(26):2848–56. [PubMed: 26240231]

86. Lazaridis KN, McAllister TM, Babovic-Vuksanovic D, et al. Implementing individualized medicine into the medical practice. Am J Med Genet C Semin Med Genet. 2014; 166C(1):15–23. [PubMed: 24616301]
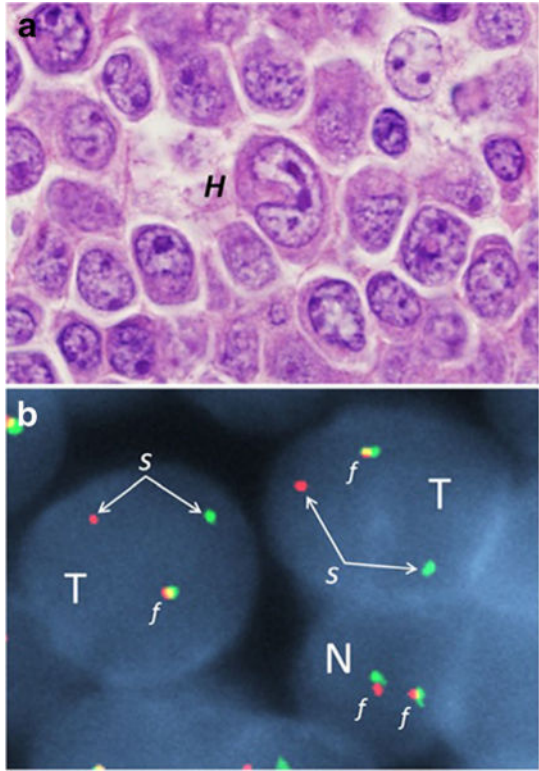
Fig. 1.
Anaplastic large cell lymphoma, ALK-negative, with *DUSP22* rearrangement. **a**
Photomicrograph demonstrating large, pleomorphic tumor cells, including a characteristic
"hallmark" cell (*H*) with a horseshoe-shaped nucleus in the center of the image. **b**
Fluorescence in situ hybridization image of two tumor cells (*T*) and one smaller, normal cell
(*N*) using a break-apart probe to the *DUSP22* gene region. The normal cell has two red-
green fusion signals (*f*), representing two intact alleles. The tumor cells each have one fusion
signal and one separated red-green signal (*s*), indicating a rearrangement of the *DUSP22*
gene region. This rearrangement has been associated with a favorable prognosis [29•]

Table 1

Classification of mature T and NK cell neoplasms[*]

Subtype	Notes[a]	References
Predominantly leukemic diseases		
T cell prolymphocytic leukemia		
T cell large granular lymphocytic leukemia	Chronic lymphoproliferative disorder of NK cells remains a distinct, provisional entity	[3••]
Aggressive NK cell leukemia		
Adult T cell leukemia/lymphoma		
Predominantly nodal diseases		
Angioimmunoblastic T cell lymphoma[b]	Follicular T cell lymphoma and nodal peripheral T cell lymphoma with T follicular helper cell phenotype included as new provisional entities	[1, 3••, 8]
Anaplastic large cell lymphoma, ALK-positive[b]		
Anaplastic large cell lymphoma, ALK-negative[b]	Cases associated with breast implants represent new provisional entity	[3••, 9, 10]
Peripheral T cell lymphoma, not otherwise specified[b]		
Predominantly extranodal diseases		
Extranodal NK/T cell lymphoma, nasal type[b]		
Enteropathy-associated T cell lymphoma	Cases previously called "type II," not associated with celiac disease, now are designated monomorphic epitheliotropic intestinal T cell lymphoma	[3••]
Hepatosplenic T cell lymphoma		
Subcutaneous panniculitis-like T cell lymphoma		
Predominantly cutaneous diseases		
Mycosis fungoides/Sézary syndrome	Considered two distinct entities	
Primary cutaneous CD30-positive T cell lymphoproliferative disorders	Includes lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma	

[a]Based on major entities in the 2008 WHO classification [11••], with notes on anticipated updates in the 2016 revision [3••]

[b]Entities covered in the present review

Table 2

Recurrent genetic alterations in major subtypes of peripheral T cell lymphoma

Subtype	Genes involved	Notes		References
Angioimmunoblastic T cell lymphoma				
Mutations	*TET2, DNMT3A, RHOA, IDH2, CD28*	•	*TET2*: loss of function mutations in 76–83%	[14, 15, 16•, 17•, 18•, 19–22]
		•	*DNMT3A*: loss of function mutations in 26–38%	
		•	*RHOA*: G17V mutations in 50-71%; leads to loss of RHOA GTPase activity; rare K18N activating variant	
		•	*CD28*: activating mutations (D124, T195) in 11%; NFκB activation	
		•	*IDH2*: R172 mutations in 20–45%; accumulation of (R)-2-hydroxyglutarate (TET inhibitor); increased H3K27me3, DNA methylation	
Structural alterations	*CTLA4-CD28, CARMA1, MYCBP2*	•	*CTLA4-CD28*: gene fusions in a subset; promote T cell activation; potential target for anti-CTLA4 immunotherapy	[23, 24]
		•	*CARMA1, MYCBP2*: copy-number gains; poor prognosis	
Anaplastic large cell lymphoma, ALK-positive				
Structural alteration	*ALK*	•	*ALK:* gene fusions in 100% (by definition); multiple partners (*NPM1, TPM3* most common); sensitive to ALK inhibitors	[25–27]
Anaplastic large cell lymphoma, ALK-negative				
Mutations	*JAK1, STAT3, TET2, DNMT3A*	•	*JAK1*: mutations in 15%; JAK/STAT3 activation; sensitive to JAK/STAT inhibitors	[19, 28•]
		•	*STAT3*: mutations in ~10%; JAK/STAT3 activation, sensitive to JAK/STAT inhibitors	
		•	*TET2*: loss of function mutations in 33%	
		•	*DNMT3A*: loss of function mutations in ~16%	
Structural alterations	*DUSP22, TP63, ROS1, TYK2, VAV1, ERBB4, TP53, PRDM1*	•	*DUSP22*: rearrangements in 30%; most common partner at 7q32.3; decreased *DUSP22* expression (tumor suppressor); favorable prognosis	[28•, 29•, 30–35]
		•	*ROS1, TYK2*: fusions in 22%; JAK/STAT3 activation	
		•	*TP63*: fusions in 8%; *TBL1XR1* most common partner; poor prognosis	
		•	*VAV1*: fusions in 16%; VAV1 activation; sensitive to RAC1 inhibitors	

Subtype	Genes involved	Notes	References
		• *PRDM1*: deletions (6q21) in 56%; tumor suppressor; increased *MIR155HG* and *IRF4* expression	
		• *TP53*: deletions (17p13.3-p12) in 42%	
		• *ERBB4*: aberrant truncated transcripts in 24%; oncogenic function; sensitive to ERBB inhibitor	
Extranodal NK/T cell lymphoma, nasal type			
Mutations	*TP53, JAK3, DDX3X, STAT3, STAT5B*	• *TP53*: missense mutations in 18–24%	[18•, 36–39]
		• *JAK3*: mutations in 35%; JAK/STAT activation; sensitivity to JAK inhibitor	
		• *DDX3X*: mutations in 20%; activation of NFκB, MAPK pathways; poor prognosis	
		• *STAT3, STAT5B*: mutations seen in this entity and γδ T cell lymphomas	
Structural alterations	*CTLA4-CD28, PRDM1*	• *CTLA4-CD28*: gene fusions in a subset	[23, 40–43]
		• *PRDM1*: deletions in 20–44% (6q21); also *ATG5, AIM1, HACE1, FOXO3*	
Peripheral T cell lymphoma, not otherwise specified			
Mutations	*TET2, DNMT3A, RHOA, FYN*	• *TET2*: mutations in 46–49%	[14, 16•, 17•, 19]
		• *DNMT3A*: mutations in 27–36%	
		• *RHOA*: mutations in 8–18%	
		• *FYN*: mutations in 3%; activating; sensitive to kinase inhibitors	
Structural alterations	*ITK-SYK, CTLA4-CD28, VAV1, CDKN2A/B*	• *VAV1*: fusions in 11%	[23, 24, 34, 44, 45]
		• *CTLA4-CD28*: gene fusions in a subset	
		• *ITK-SYK*: gene fusions in 17%; sensitivity to SYK inhibitors	
		• *CDKN2A/B*: deletions at 9p21.3; reduced *CDKN2A* expression in 9%, associated with inferior outcomes; deleted region also includes *MTAP1*	

Includes entities covered in this review. See also Table 1