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Genetics of Anaplastic Large Cell Lymphoma

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Abstract

Anaplastic large cell lymphoma (ALCL) comprises a group of T-cell non-Hodgkin lymphomas unified by common morphologic and immunophenotypic characteristics, but with a spectrum of clinical presentations and behaviors. Early identification of anaplastic lymphoma kinase (*ALK*) gene rearrangements in some ALCLs led to recognition of *ALK* as an important diagnostic and prognostic biomarker, and a key driver of ALCL pathobiology. Rearrangements and other genetic abnormalities of *ALK* subsequently were identified in diverse other human malignancies. Recent clinical, pathologic, and genetic data have begun to shed light on *ALK*-negative ALCLs, revealing significant heterogeneity within this more ill-defined entity.

Keywords

Anaplastic large cell lymphoma; genetics; T-cell non-Hodgkin lymphoma; *ALK*; *DUSP22*; p63

Introduction

Anaplastic large cell lymphoma (ALCL) refers to a group of CD30-positive T-cell non-Hodgkin lymphomas comprising 3 morphologically and immunophenotypically similar but clinically distinct entities: systemic *ALK*-positive ALCL, systemic *ALK*-negative ALCL, and primary cutaneous (pc) ALCL [1–3]. *ALK*-positive ALCL is characterized by recurrent chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene, which encode constitutively activated *ALK* fusion proteins that regulate several downstream pathways involved in cell survival, cell growth, and cell-cycle control [4]. While the diagnosis of *ALK*-positive ALCL is facilitated by *ALK* immunohistochemistry and sometimes genetic testing for *ALK* rearrangements, distinction of *ALK*-negative ALCL from CD30-positive peripheral T-cell lymphoma, not otherwise specified (PCTL, NOS); Hodgkin lymphoma; and other CD30-positive lymphomas is more challenging.

This review outlines current knowledge of the genetics of the various forms of ALCL, including the role of *ALK* and new genetic markers in *ALK*-negative ALCL and pcALCL. In addition to chromosomal rearrangements, other genetic abnormalities, gene expression

profiles, and microRNA profiles of these entities also are discussed, as is the biologic relevance of these findings.

ALK rearrangements

Recurrent chromosomal rearrangements are common pathogenic events in hematologic malignancies [5]. Among T-cell non-Hodgkin lymphomas, *ALK* rearrangements with *NPM1* and other partners are the most common and by far the best characterized rearrangements (Table 1). The majority of ALK-positive ALCLs have a t(2;5)(p23;q35) fusing the *ALK* gene to *NPM1*; variant translocations involving *ALK* and other partner genes on chromosomes 1,2, 3, 17, 19, 22 and X also occur. The partners of ALK include *TPM3*, *TPM4*, *TFG*, *ATIC*, *MYH9*, *CLTC*, *MSN*, and *ALO17* [6,7]. All these translocations result in expression of ALK fusion proteins. The ALK fusion partner determines the intracellular localization of the fusion protein. NPM-ALK fusion proteins are characterized by nuclear and cytoplasmic ALK staining whereas variant ALK fusion proteins are expressed exclusively in the cytoplasm (Figure 1). TPM3-ALK is the second most prevalent fusion gene, with both cytoplasmic ALK staining and membranous reinforcement [8]. Using deep RNA sequencing, our group recently identified a novel *TRAF1-ALK* fusion in an ALCL patient with cytoplasmic ALK immunoreactivity only [9]. Rearrangements of the *MYC* gene, frequently detected in high-grade B-cell lymphomas, have been reported in 3 cases of ALK-positive ALCL [10–12]. All 3 patients with dual *ALK* and *MYC* rearrangements demonstrated an aggressive clinical course, with systemic and extranodal presentation, early tumor relapse, and bone marrow involvement during the course of the disease.

Historically, *ALK* rearrangements have been absent in pcALCL. Recently, however, it has been increasingly recognized that a subset of pcALCLs are positive for ALK by immunohistochemistry and bear *ALK* gene rearrangements [13,14]. The frequency of ALK expression among pcALCLs is not known precisely but appears to be quite low, in marked contrast to the frequency of ALK expression among systemic ALCLs, in which 50–60% of cases are ALK-positive in most series. Though the precise classification of ALK-positive ALCLs presenting primarily in the skin has not been clarified by the WHO/EORTC, the existence of these cases is clinically important since it indicates that skin involvement by ALCL that is positive for ALK should not be automatically considered cutaneous involvement by systemic ALK-positive ALCL, which typically would require systemic chemotherapy. Rather, the few cases of true pcALCL that expressed ALK have behaved similarly to other pcALCL, i.e. with locoregional disease only and excellent outcomes. Thus, clinical staging of patients with ALCL involving the skin is important, regardless of ALK status. Interestingly, at least one ALK-positive pcALCL was reported to lack an *ALK* translocation, suggesting that alternative mechanisms for ALK overexpression exist [15].

Role of ALK in ALCL

The NPM-ALK fusion protein activates various signaling pathways in ALK-positive ALCL cells, including the JAK/STAT3, PI3K/AKT/mTOR, RAS/ERK, and PLC γ pathways [16–19]. A recent mass spectrometry-based phosphoproteomic screen has identified glycogen synthase kinase (GSK) 3 β as a novel mediator of NPM-ALK signaling [20]. NPM-ALK was

shown to phosphorylate S(9)-GSK3 β via the PI3K/AKT signaling pathway, resulting in inhibition of GSK3 β activity and accumulation of oncogenic CDC25A and MCL1. The transcription factor CCAAT enhancer binding protein (C/EBP β) also has been shown to play a crucial role in survival and growth of ALK-positive ALCL cells [21]. Target genes transcriptionally regulated by C/EBP β that may be responsible for these effects include *BCL2A1*, *G0S2*, and *DDX21* [22]. NPM-ALK also induces expression of ICOS (CD278), a member of the CD28 costimulatory receptor superfamily. NPM-ALK activates STAT3, which induces transcriptional activity of the *ICOS* promoter and also inhibits expression of the ICOS inhibitor, miR-219 [23].

Chromosomal Rearrangements in ALK-negative ALCL

Until recently, the genetics of ALK-negative ALCL has been unknown. Next generation sequencing of mate-pair DNA libraries has identified at least 2 recurrent chromosomal rearrangements in ALK-negative ALCL. The first involves the *DUSP22-IRF4* locus on 6p25.3 (referred to as *DUSP22* rearrangements), and is most commonly present as t(6;7)(p25.3;q32.3) [24]. Sanger sequencing showed breakpoints in intron 1 of *DUSP22* on 6p25.3 and immediately telomeric to the *FRA7H* fragile site on 7q32.3. The t(6;7)(p25.3;q32.3) was seen in both systemic and cutaneous ALK-negative ALCLs, and was associated with down-regulation of *DUSP22* gene expression and up-regulation of the miR-29 microRNA cluster. *DUSP22* is a dual-specificity phosphatase that inhibits T-cell receptor signaling in reactive T cells and Jurkat cells by inactivating the mitogen-activated protein kinase (MAPK), ERK2 [25]. Up-regulation of MIR29 micro-RNAs may have oncogenic function in ALCL with *DUSP22-FRA7H*, as has been proposed in acute myeloid leukemia and breast cancer [26,27].

An additional recurrent rearrangement involving the *TP63* gene was identified among a constellation of genetic abnormalities affecting p53-related genes in ALCLs and related T-cell lymphomas [28]. *TP63* rearrangements encoded fusion proteins homologous to Δ Np63, a dominant-negative p63 isoform with oncogenic properties in some models. The partner gene was most frequently *TBL1XR1*. *TP63* rearrangements were seen exclusively in ALK-negative ALCL, pcALCL, and in occasional CD30-positive PTCLs, NOS, and were associated with inferior overall survival. Interestingly, *TP63* rearrangements in pcALCL, which typically has an excellent prognosis, were associated with aggressive cutaneous disease refractory to multiple therapy regimens and early deaths.

A recent study by our group identified *DUSP22* and *TP63* rearrangements in 30% and 8% of systemic ALK-negative ALCLs, respectively [29]. These rearrangements were mutually exclusive of each other, and were uniformly absent in ALK-positive ALCLs. *DUSP22*-rearranged cases had favorable outcomes similar to ALK-positive ALCLs; conversely *TP63*-rearranged ALCLs had a poor prognosis. Five-year overall survival rates for *DUSP22*- and *TP63*-rearranged ALCL were 90% and 17%, respectively, compared to 85% for ALK-positive ALCLs and 42% for cases lacking all three genetic markers (*ALK*, *DUSP22*, and *TP63* rearrangements, or so-called “triple-negative” ALCLs).

Distinguishing pcALCL from secondary skin involvement by systemic ALK-negative ALCL, lymphomatoid papulosis (LyP) and transformed mycosis fungoides (t-MF) with CD30 expression is a challenging diagnostic problem [2,3,30]. The role of *DUSP22* and *TP63* rearrangements in this differential diagnosis is incompletely established. Multiple studies support the presence of *DUSP22* rearrangements in pcALCL, with an overall frequency of around 30% [31–34]. Our group also has reported *DUSP22* rearrangements in a subset of patients with LyP [35]. These cases had characteristic clinicopathologic features, including presentation as localized crops of papules in the elderly, large transformed cells in the dermis with smaller atypical cells infiltrating the epidermis in a pagetoid reticulosis-like fashion, and biphasic staining intensity for CD30 (weaker in the epidermal component). Pathologically, these cases may resemble t-MF, but the clinical presentation is distinct and the subsequent course is indolent. The distinction of pcALCL from t-MF is more controversial and clinically more important, since t-MF typically is aggressive. All but 2 reported cases of t-MF have been negative for *DUSP22* rearrangements [33]. Of these 2 cases, one subsequently was reported to have other molecular features and clinical behavior more similar to pcALCL [36]. Recently, a case of t-MF with a *TP63* rearrangement has been reported [37]. Though *TP63* rearrangements were rare in MF overall, this case was particularly interesting in that the rearrangement was present not only in the MF prior to transformation, but also in a subset of the patient's T cells prior to the development of cutaneous disease.

We and others have reported cases resembling ALK-negative ALCL in mucosal sites or the upper aerodigestive tract [38,39]. These cases have a spectrum of clinical presentations, including localized, primary mucosal cases; systemic cases secondarily involving mucosal surfaces; and cases occurring in patients with cutaneous T-cell lymphoproliferative disease/lymphoma. Some primary mucosal cases bear *DUSP22* rearrangements. Regardless of genetics, primary mucosal cases tend to remain localized to the primary site and to have favorable outcomes even in the absence of systemic chemotherapy, similar to pcALCL. Therefore, clinical correlation and staging data are important in evaluating these patients and choosing a management strategy. A related and emerging entity is breast implant-associated ALCL, which pathologically resembles ALK-negative ALCL but typically arises in the seroma cavity surrounding breast implants and is associated with an indolent clinical course in most patients [40,41]. *DUSP22* rearrangements have not been reported in these cases to date or observed in the experience of one of the authors (A.L.F., unpublished data).

In summary, chromosomal rearrangements are key events in ALCL. *ALK* rearrangement is a diagnostic criterion for ALK-positive ALCL, and generally can be assessed clinically by surrogate immunohistochemical staining for ALK. Rearrangements of *DUSP22* and *TP63* can be seen in ALK-negative ALCL, and are associated with favorable and unfavorable outcomes, respectively. This prognostic significance may be sufficient to warrant clinical assessment for these rearrangements, which can be performed by fluorescence *in situ* hybridization. The clinical relevance of chromosomal rearrangements in pcALCL is less clear, but routine staining for ALK is recommended.

Copy Number Abnormalities in ALCL

Comparative genomic hybridization (CGH) studies also have contributed to the understanding of ALCL. Salaverria et al have identified chromosomal imbalances in 58% of ALK-positive and 65% of ALK-negative ALCLs [42]. Gains of 17p and 17q24-qter, and losses of 4q13-q21 and 11q14 were seen in ALK-positive cases, whereas gains of 1q and 6p21 were more frequently observed in ALK-negative ALCL. Gains of 7p and 6q and losses of 13q were seen in both ALK-positive and ALK-negative cases. Chromosomal imbalances observed in ALK-negative ALCL also differ from those identified in PTCL, NOS; for example, one study identified relatively common losses of 5q (26%) and 9p (31%) in PTCL, NOS but not in ALK-negative ALCL [43]. More recently, genome-wide DNA profiling using high-density, single nucleotide polymorphism arrays has been reported in a series of 64 ALCLs and 7 cell lines [44]. Losses at 17p13 and at 6q21, encompassing the *TP53* and *PRDM1* genes, respectively, were the most common lesions. These losses were observed in 42% and 35% of ALK-negative ALCLs, respectively. Inactivation of *PRDM1* was observed more frequently, but not exclusively, in ALK-negative ALCL; *PRDM1* may function as a tumor suppressor gene in ALCL. Less is known about copy number abnormalities in pcALCL. van Kester et al have reported gains on chromosome 7q and 17q, and losses on 6q and 13q by CGH analysis [45]. PTCL, NOS similarly showed gains on 7q and 17q, but was distinguished by gains on chromosome 8 and losses at 9p21.

Despite the increasing amount of data on copy number abnormalities in the various subtypes of ALCL, the direct clinical relevance of these findings remains unclear and copy number testing is not performed routinely.

Gene Expression Profiling of ALCL

Gene expression profiling (GEP) is a valuable tool to identify differentially regulated genes and signaling pathways, define genomic classifiers, and discover genes associated with prognosis. Thompson et al have used cDNA microarray analysis to study gene expression in ALCL tumor tissue and identified kinases (*LCK*, protein kinase C, *VAV2*, and *NKIAMRE*) and anti-apoptotic molecules that were highly expressed in both ALK-positive and ALK-negative ALCLs, suggesting possible common pathogenetic mechanisms [46]. ALK-positive tumors over-expressed signal transduction genes (*SYK*, *LYN*, *CDC37*) and under-expressed transcription factor genes (including *HOXC6* and *HOXA3*) compared with the ALK-negative group. Cyclin D3 was over-expressed in ALK-positive ALCL and the cell cycle inhibitor *p19INK4D* was decreased in ALK-negative ALCL, suggesting different mechanisms of promoting G1/S transition. A subsequent study of 25 ALK-positive ALCLs, 7 ALK-negative ALCLs, and 5 cell lines found *BCL6*, *PTPN12*, *CEBPB*, and *SERPINA1* to be overexpressed in ALK-positive ALCL, whereas genes representing cytokine–cytokine receptor interactions, including *CCR7*, *CNTFR*, *IL22*, and *IL21*, were overexpressed in ALK-negative ALCL [47].

Piva et al have reported global transcriptional analysis of 16 ALK-positive and 20 ALK-negative ALCLs with comparison to PTCL-NOS, angioimmunoblastic T-cell lymphoma (AITL) and normal T-cells [48]. *IL1RAP*, *GAS1*, *PRF1*, *TMEM158*, and *IL2RA* were highly

informative in identifying ALK-positive ALCL. There was a trend toward overexpression of *CD86* and *ZNF267* in ALK-negative ALCL. The authors also proposed a set of 14 genes to distinguish ALK-negative ALCL from PTCL-NOS. A set of 30 genes differentially expressed in both ALK-positive and ALK-negative ALCLs suggested the existence of a common ALCL signature. Gene expression profiling performed after silencing the expression of ALK or STAT3 in ALK-positive ALCL cell lines suggested that two-thirds of ALK-regulated genes were dependent on STAT3. Agnelli and colleagues have reported a transcriptional profiling meta-analysis of 309 PTCLs, including 54 ALCLs [49]. The top up-regulated genes in ALK-positive ALCL were *PRF1*, *IL1RAP*, *CCND3*, *BCL3*, and *GAS1*; conversely, *CD80*, *CD86*, *CCND2* and *MIR155HG* were among the most significantly over-expressed genes in ALK-negative ALCL. The authors also reported a 6-gene classifier (*TNFRSF8*, *BATF3*, *TMOD1*, *TMEM158*, *MSC*, and *POPDC3*) informative in identifying ALK-negative ALCL. A 3-gene model (*TNFRSF8*, *BATF3*, and *TMOD1*) assessed by quantitative RT-PCR could separate ALK-negative ALCL from PTCL, NOS with 97% accuracy. Interestingly, Eckerle et al have reported that only few genes were differentially expressed between systemic ALCL and pcALCL despite their different clinical behaviors, and between ALK-negative ALCL and classical Hodgkin lymphoma, despite their different cellular origins [50]. van Kester et al have reported higher expression of the skin-homing chemokine receptor genes *CCR10* and *CCR8* in pcALCL, which might explain the lower tendency to disseminate to extracutaneous sites [45]. Interestingly, our group recently has reported that increased *CCR8* expression was more closely associated with the presence of *DUSP22* rearrangements than with the degree of systemic spread [51].

Although gene expression profiling has not yet found routine clinical use for ALCL, it has had a clear impact on elucidating ALCL biology. A signature comprising a limited number of genes that could distinguish ALK-negative ALCL from PTCL, NOS shows promise for clinical utility, either as a focused gene expression panel or possibly a panel of immunohistochemical markers.

MicroRNA Expression Profiling of ALCL

MicroRNAs (miRNAs) make up a class of small, noncoding RNA molecules of 20–22 nucleotides that play a crucial role in regulating gene expression by binding within the 3'-UTR regions of target messenger RNAs and inducing mRNA degradation or inhibiting translation [52,53]. Deregulated miRNAs have been observed in many cancers, playing a role in either oncogenic (miR-21, miR-17-92 cluster, miR-155) or tumor suppressor (miR-26a, miR-34a) functions [54]. Merkel et al have reported that 5 members of the miR-17–92 cluster (miR-17, miR-20a, miR-20b, miR-93, and miR-106a), as well as miR-886-3p, were expressed more highly in ALK-positive ALCL, whereas miR-155 was expressed more than 10-fold higher in ALK-negative ALCL [55]. Down-regulation of miR-101, miR-29c, and miR-26a was identified in ALCL cell lines and tumor tissue, and restoration of miR-101 attenuated cell proliferation in ALK-positive ALCL cell lines. A STAT3 binding site has been identified in the promoter region of the miR-17–92 cluster [56]. Using inducible knockdown approaches in ALK-positive ALCL cell lines, Spaccarotella and colleagues have identified 48 miRNAs concordantly modulated following ALK and STAT3 knockdown [57]. The miR-17-92 cluster was down-regulated by STAT3

knockdown and by a STAT3 inhibitor, while forced expression of the miR-17-92 cluster sustained proliferation and significantly protected STAT3-depleted ALCL cells from apoptosis. miR-17-92 has been associated with inhibition of apoptosis, promotion of proliferation, and induction of tumor angiogenesis through repression of its targets, including E2F1 and the tumor suppressors PTEN and p21 [58,59]. These studies suggest that inhibiting the miR-17-92 cluster may represent an alternative avenue to interfere with ALK signaling in ALCLs.

Liu et al have reported 5 up-regulated miRNAs (miR-512-3p, miR-886-5p, miR-886-3p, miR-708, and miR-135b) and 2 down-regulated miRNAs (miR-146a and miR-155) significantly associated with ALK-positive ALCL [60]. Seven other miRNAs (miR-7b, miR-7d, miR-155, miR-126, miR-145, miR-34a, and miR-886-5p) were shared by both ALK-positive and ALK-negative ALCLs. A subset of miRNAs (miR-517c, miR-517a, miR-512-3p, miR-135b, miR-135a, miR-708, miR-886-5p, and miR-886-3p) was expressed more highly in ALCL than in other PTCLs. Finally, an 11-miRNA signature (4 up-regulated: miR-210, miR-197, miR-191, and miR-512-3p; 7 down-regulated: miR-451, miR-146a, miR-22, miR-455-3p, miR-455-5p, miR-143, and miR-494) differentiated ALK-negative ALCL from other PTCLs. Mehrotra et al have reported that miR-486-5p, miR-500-3p, and miR-629 were expressed at higher levels in ALK-positive ALCL, while miR-155, miR-29a, miR-29b-1-5p, and miR-720 were higher in ALK-negative ALCL [61]. *ZNF652*, *BACH1*, *RBAK*, *BACH1*, *E2F2*, and *TP53INP1*, which are directly or indirectly involved in regulation of the PI3K/AKT pathway, JAK-STAT signaling, and DNA mismatch repair, were predicted to be potential targets of miR-155. Matsuyama et al have reported that NPM-ALK strongly promoted the expression of miR-135b and the *LEMD1* gene via STAT3 activation [62]. Up-regulated miR-135b targeted *FOXO1* in ALCL cells and suppressed the Th2 master regulators STAT6 and GATA3, while blockade of miR-135b attenuated IL-17 production and paracrine inflammatory response by ALCL cells. These findings suggested that miR-135b-mediated Th2 suppression might promote a Th17-like immunophenotype in ALCL cells. Benner et al have reported differences in miRNA expression between pcALCL and benign inflammatory dermatoses, including up-regulation of miR-155, miR-27b, miR-30c, and miR-29b [63]. Differential expression of miR-155, miR-27b, miR-93, miR-29b, and miR-92a between tumor-stage MF and pcALCL also were identified.

While miRNA data continues to be biologically informative and an important area of further study, it remains unclear the setting in which these markers might find clinical utility. The ability to integrate miRNA biomarkers into other gene expression panels, as discussed above, may represent one means of clinical translation.

Summary

ALCL is not a single disease but a group of clinicopathologic entities whose definitions and borderlands are still being defined. At the morphologic, immunophenotypic, and gene expression levels, all ALCLs share some common features. The most genetically uniform subgroup is ALK-positive ALCL, defined in part by consistent rearrangements of *ALK*. ALK-negative ALCLs are genetically and biologically heterogeneous, and fluorescence *in*

situ hybridization tests can identify chromosomal rearrangements that distinguish among prognostically disparate subgroups. The impact of other genetic changes, including mutations and copy number abnormalities, is an area of continued and intense study, as is the clinical translation of reported findings in gene and miRNA expression that could facilitate accurate diagnosis and further molecular stratification.

The clinical utility of the new genetic findings in ALCL, aside from the well-studied *ALK* rearrangements, remains the most important issue for further study in this field. The biologic implications of the recently documented genetic heterogeneity within systemic ALK-negative ALCL, particularly regarding *DUSP22* and *TP63* rearrangements, require elucidation. The role of these rearrangements, especially *DUSP22*, in the evolving diagnostic criteria of ALK-negative ALCL will need to be addressed. It is likely that additional findings arising from recent gene expression studies also will contribute to formulating more precise criteria that distinguish this entity from PTCL, NOS. Finally, determining the role of genetics in the diagnosis and classification of localized ALCLs will be critical. The findings that not all pcALCLs are ALK-negative and that localized ALCLs occur in non-cutaneous sites, including mucosal surfaces and the breast, need to be reflected in newer classification updates to avoid possible overtreatment.

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Figure 1.

Typical findings in anaplastic large cell lymphoma (ALCL). A–C. ALK-positive ALCL. A high-power photomicrograph of a hematoxylin-and-eosin stained tissue section shows sheets of large atypical lymphocytes (A) that are positive by immunohistochemistry for CD30 (B). Immunohistochemistry also shows positivity for ALK, a surrogate for the presence of an *ALK* rearrangement (C). The nuclear and cytoplasmic localization of the ALK staining indicates the *ALK* fusion partner most likely is *NPM1*. D–F. ALK-negative ALCL. The histological findings are similar to ALK-positive ALCL (D). Immunohistochemistry for CD30 is positive (E), but ALK is negative (E, inset). This case showed rearrangement of the *DUSP22* locus, a finding seen in ~30% of ALK-negative ALCLs (F). Fluorescence *in situ* hybridization using a breakapart probe for this locus demonstrates a cell with only one normal, intact red-green fusion signal (*f*); the green and red signals for the other allele are separated (arrows), indicating a rearrangement. The blue color in the background represents the nuclear counterstain. G–I. Primary cutaneous ALCL. At high power, the histological findings are similar to other ALCLs (G). The tumor cells are positive for CD30 (H) and negative for ALK (H, inset). A low-power photomicrograph shows the relationship to the skin, with intact epidermis (*e*) overlying extensive involvement of the dermis (*d*) by sheets of tumor cells.

Table 1

Summary of the main genetic findings in anaplastic large cell lymphoma (ALCL).

Disease		
	ALK-positive ALCL	ALK-negative ALCL
Chromosomal rearrangements		
ALK	Rearranged in all cases; variable partners (<i>NPM1</i> most common)	Absent by definition
DUSP22	No rearrangements reported	Rearranged in ~30% of cases; variable partners (<i>FRA7H</i> most common); associated with favorable prognosis
TP63	No rearrangements reported	Rearranged in ~8% of cases; variable partners (<i>TBL1XR1</i> most common); associated with poor prognosis
Primary cutaneous ALCL		
Rare cases with rearrangements and primary cutaneous presentation reported		
Rearranged in ~28% of cases; clinical significance unknown		
Rare cases with rearrangements and aggressive clinical behavior reported		
Copy number abnormalities		
Gains	6q, 7p, 17p, 17q24-qter	1q, 6p21, 7p
Losses	4q13-q21, 11q14, 13q	6q21, 13q, 17p13
Gene expression		
Up	<i>BCL3</i> , <i>BCL6</i> , <i>CCND3</i> , <i>CDC37</i> , <i>CEBPB</i> , <i>GAS1</i> , <i>IL1RAP</i> , <i>IL2RA</i> , <i>LYN</i> , <i>PRF1</i> , <i>PTPN12</i> , <i>SERPINA1</i> , <i>SYK</i>	<i>BATF3</i> , <i>CCND2</i> , <i>CCR7</i> , <i>CD80</i> , <i>CD86</i> , <i>CNTFR</i> , <i>IL21</i> , <i>IL22</i> , <i>MSC</i> , <i>POPD3</i> , <i>TMEM158</i> , <i>TMOD1</i> , <i>TNFRSF8</i> , <i>ZNF267</i>
Down	<i>HOXA3</i> , <i>HOXC6</i>	<i>CDKN2D</i>
MicroRNA expression		
Up	miR-17, miR-20a, miR-20b, miR-93, miR-106a, miR-135b, miR-486-5p, miR-500-3p, miR-512-3p, miR-629, miR-708, miR-886-3p, miR-886-5p	miR-29a, miR-29b-1-5p, miR-155, miR-191, miR-197, miR-210, miR-512-3p, miR-720
Down	miR-146a, miR-155	miR-27b, miR-29b, miR-30c, miR-155

See text for references.