Children's Hospital Boston
Department of Pathology

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NODAL T CELL LYMPHOMAS

TFH and ALCL lymphoma

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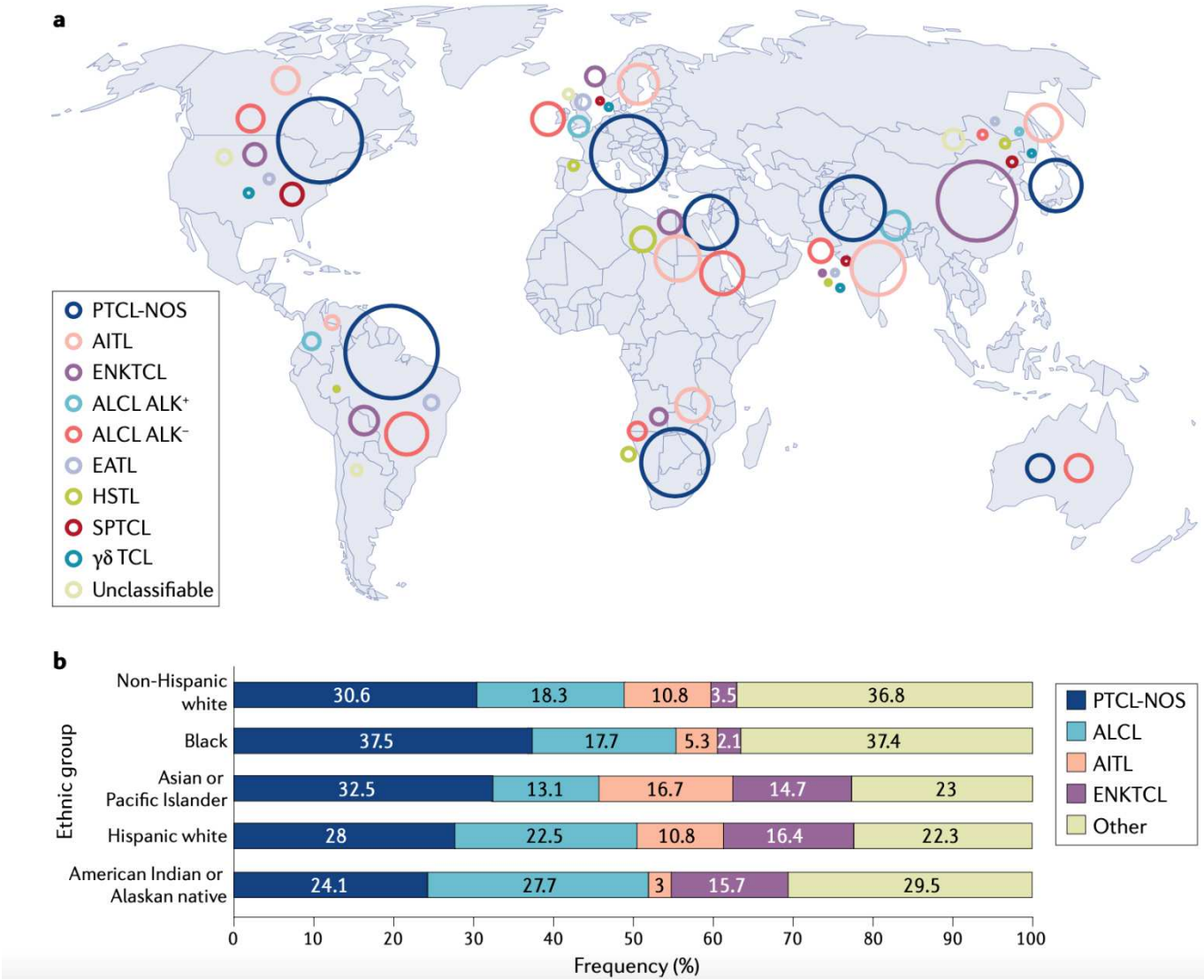
World Health Organization Classification for Neoplastic Disease of the Lymphoid Tissues

T-Cell Neoplasms

Precursor T-cell lymphoblastic leukemia/lymphoma
Mature T-cell and NK-cell neoplasms
- **T-cell prolymphocytic leukemia**
- **T-cell large granular lymphocytic leukemia**
- **NK-cell leukemia**
- **Extranodal NK/T-cell lymphoma, nasal-type (*angiocentric lymphoma*)**
- **Mycosis fungoides**
- **Sézary syndrome**
- **Angioimmunoblastic T-cell lymphoma**
- **Peripheral T-cell lymphoma (unspecified)**
- **Adult T-cell leukemia/lymphoma (HTLV1+)**
- **Systemic anaplastic large cell lymphoma (T- and null-cell types)**
- **Primary cutaneous anaplastic large cell pymphoma**
- **Subcutaneous panniculitis-like T-cell lymphoma**
- **Enteropathy-type intestinal T-cell lymphoma**
- **Hepatosplenic γ/δ T-cell lymphoma**

Classification and ethnic and geographic distribution of most recurrent T cell lymphoproliferative disorders



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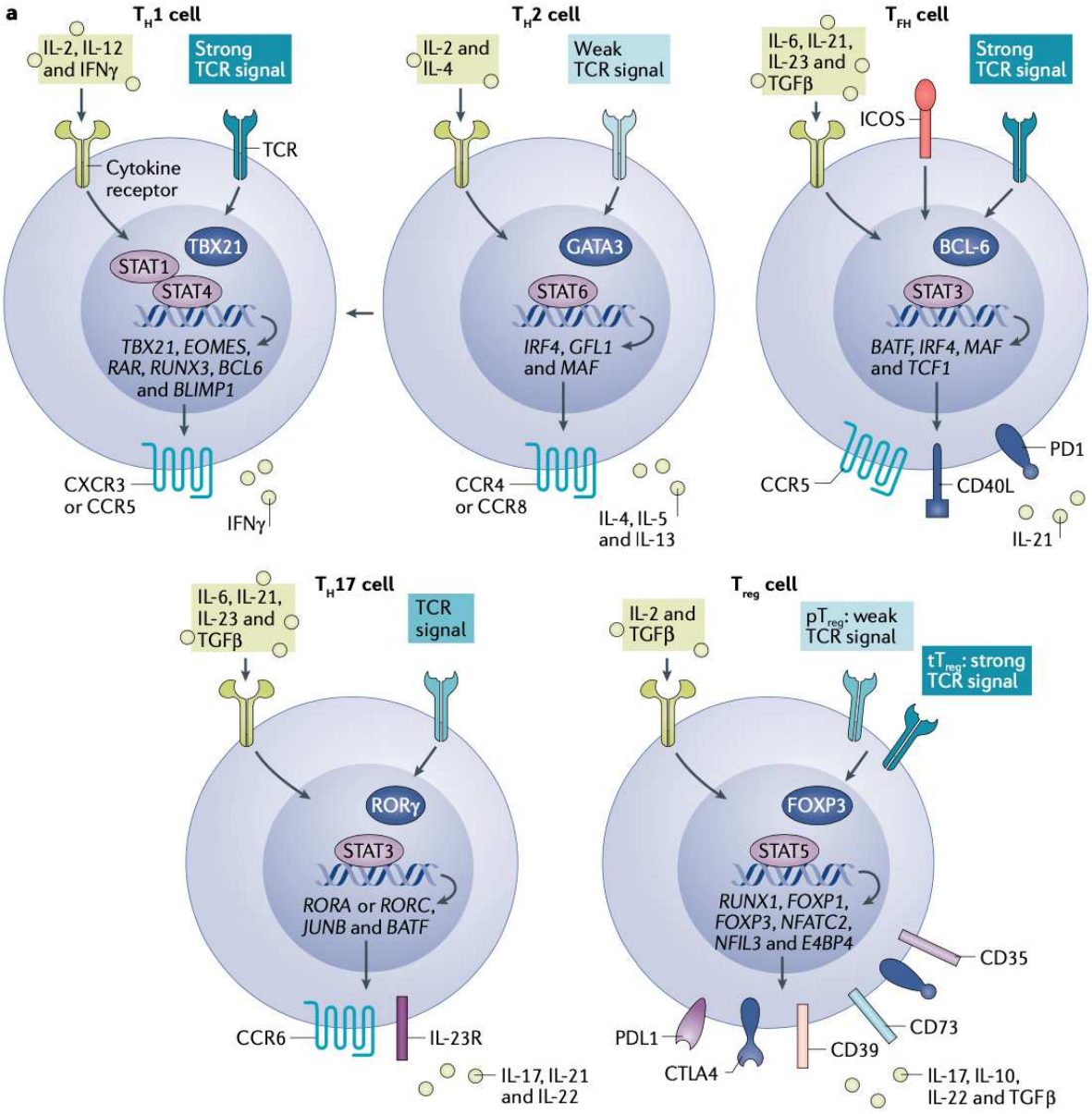
Transcription factors regulate the phenotype and function of T cells



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PTCL cell of origin

- PTCL-NOS includes a heterogeneous group of neoplasms derived from mature CD4+ or CD8+ αβ TCR T lymphocytes.
They can be stratified in at least two groups: GATA3 positive or TBX21 positive.

- Naive T cells homing to the germinal centre differentiate into T follicular helper cells (TFH cells) after a multistep differentiation process, driven by the interaction with dendritic cells (DCs), cytokines and B cells via a strong TCR signal. TFH cells are considered the normal counterpart of follicular T cell lymphoma, angioimmunoblastic T cell lymphoma and nodal PTCL with TFH cell phenotype

- Extranodal natural killer (NK) cell/T cell lymphomas derive from the transformation of NK cells or cytotoxic innate T cells. They are Epstein–Barr virus positive and have a distinct geographic distribution.

- Regulatory T cells (Treg cells) could be the precursors of adult T cell leukaemia/lymphoma and Sezary syndrome, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma and subcutaneous panniculitis-like T cell lymphoma.

PTCL cell of origin

- Anaplastic lymphoma kinase (ALK) fusion-positive (ALK+) anaplastic large cell lymphoma (ALCL) has been suggested to derive from thymocytes, whereas the origin of ALK– ALCL is still debated.

- Hepatosplenic T cell lymphoma, enteropathy-associated T cell lymphoma and monomorphic epitheliotropic intestinal T cell lymphoma may derive from either innate cells (NK-T cells, γδ TCR CD3+, and group 1, 2 and 3 innate lymphoid cells), adaptive cells (CD4+ and CD8+ αβ TCR) or CD3 γδ TCR intestinal intraepithelial lymphocytes.

- Enteropathy-associated T cell lymphomas are closely linked to coeliac disease.

- Cutaneous T cell lymphoma derives from CD4+ cells.

- Chronic antigen stimulation and ‘ad hoc’ lymphokine environments contribute to the pathogenesis of lymphomatoid papulosis, cutaneous anaplastic large cell lymphoma and breast implant-associated ALCL, likely derived from CD4+ cells.

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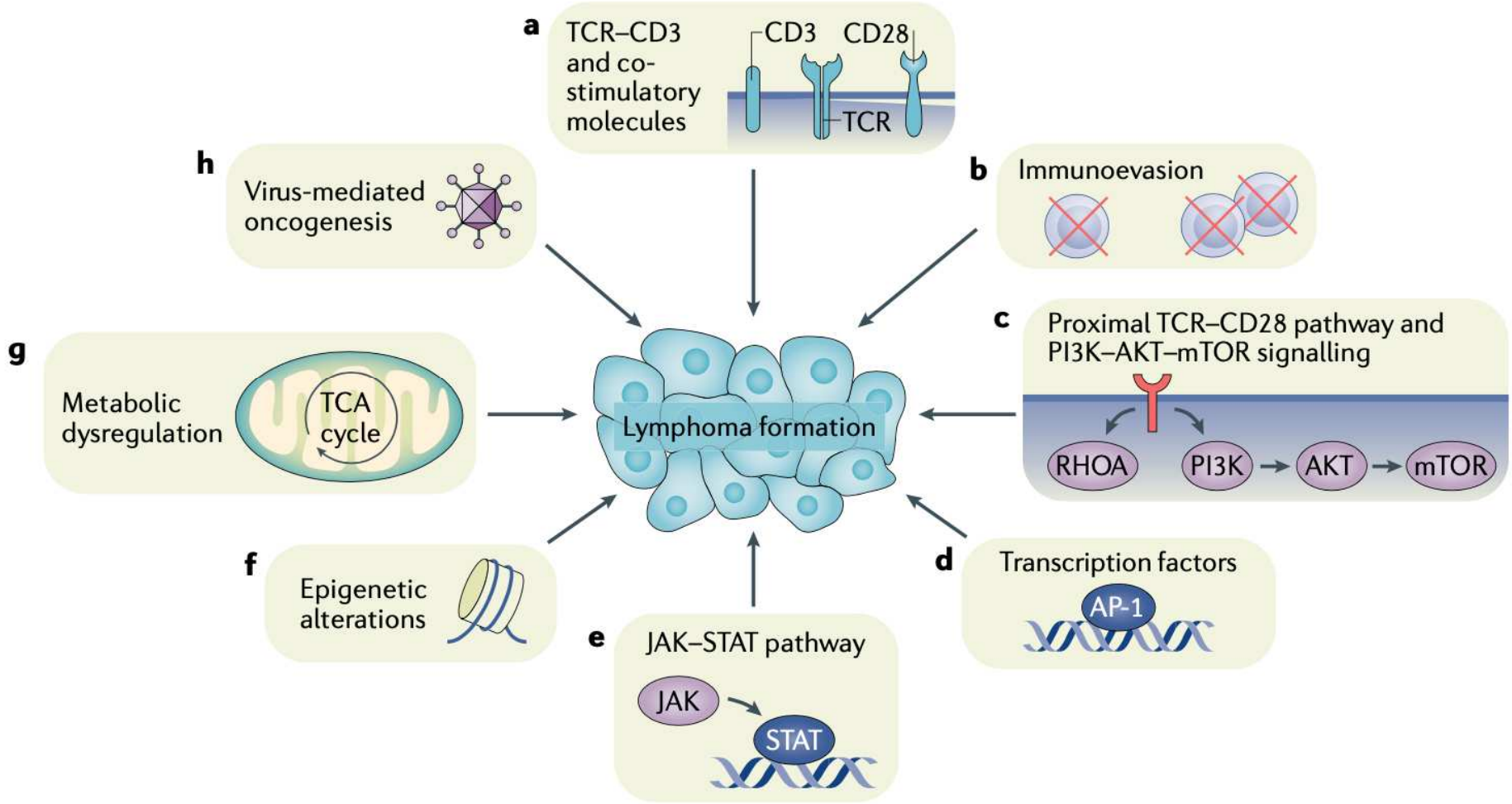
The mechanisms of PTCL transformation



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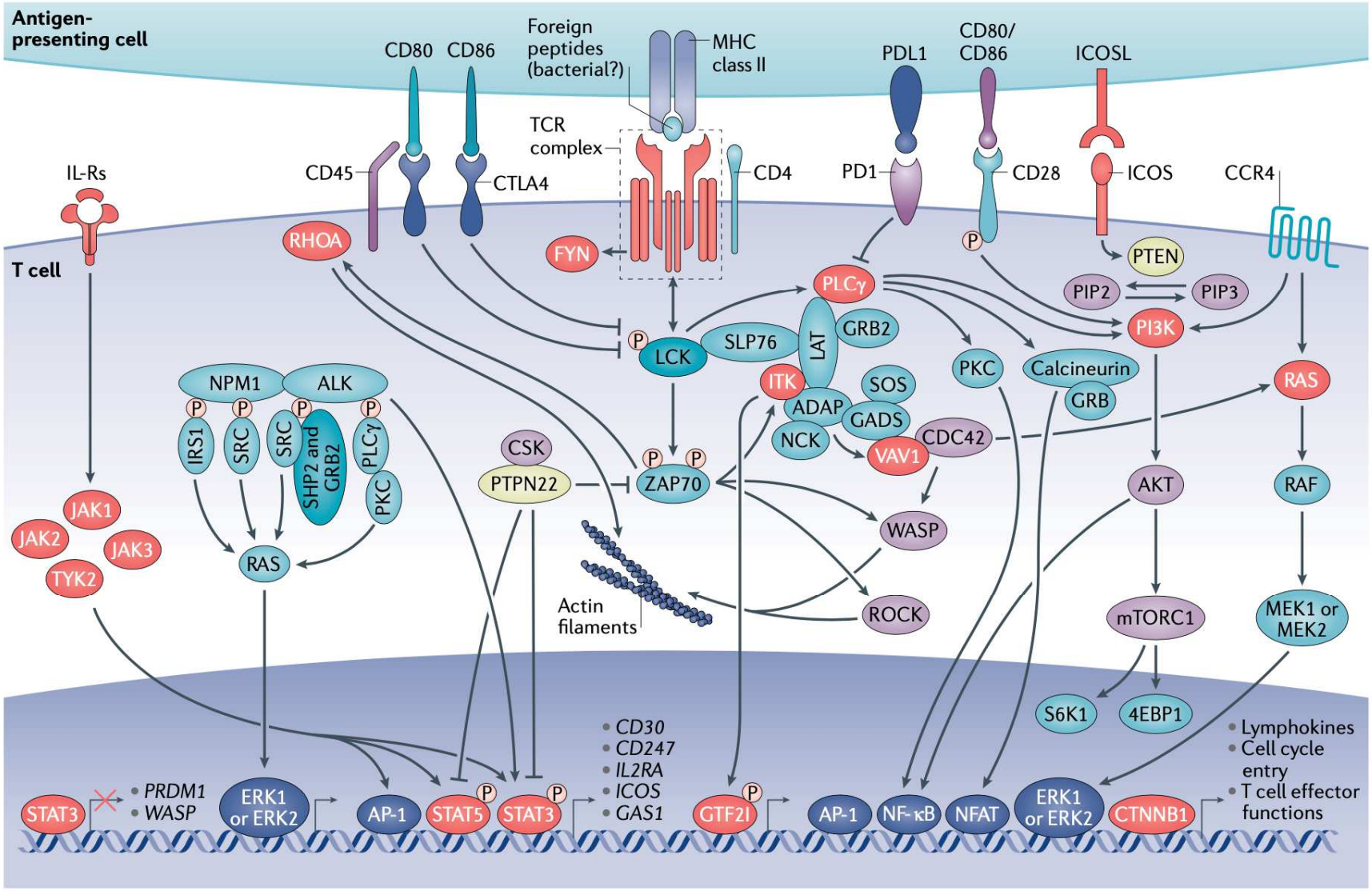
Dysregulated signalling pathways in PTCL



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Pathogenic mechanisms relevant to the most frequent PTCL entities

Lymphoma type	Dysregulated pathways	Associated molecular events	Microenvironmental modulation	Virus-mediated oncogenesis
AITL and T_{FH} PTCL	TCR	Mutations: *CD28*, *VAV1*, *PLCG1*, *CTNNB1*, *GTF2I*, PI3K pathway components	Reduced immunogenicity (*B2M* mutations); increased response to co-stimulatory signals (*CD28* mutation); altered response to proapoptotic signals; cytokine, T_{reg} cell-mediated and endothelial cell-mediated immunomodulation; immune checkpoint regulation	EBV^+ B cells, the pathogenetic role of which remains unclear (lymphokine mediated signals, antigen-driven stimulation?)
	RHOA	Mutations: *RHOA*; fusion protein: VAV1–STAP2		
	Epigenetic modifiers	Mutations: *TET2*, *IDH2*, *DNMT3A*		
PTCL-NOS	TCR and NF-κB	Mutations and/or CNVs: *CD28*, *PLCG1*, *CARD11*, *FYN*, *VAV1*, *TNFAIP3*, *PTPRC*; fusion protein: ITK–SYK	Reduced immunogenicity; altered cell–cell interactions (*CD58* and *LFA1* mutations); altered response to proapoptotic signals and immunoregulation; cytokine-mediated, T_{reg} cell-mediated and TAM-mediated immunomodulation; immune checkpoint regulation	Putative pathogenic role for EBV in a minority of cases
	T cell trafficking	Mutations: *CCR4*, *CCR7*		
	JAK–STAT	Pathway mutations and/or CNVs; fusion protein: PCM1–JAK2		
	Notch	Mutations and/or CNVs: *NOTCH1*; gene loss: *LEF1*, *TCF1*		
	RHOA	Mutations: *RHOA*; fusion proteins: VAV1–THAP4, VAV1–MYO, VAV1–S100A7		
	PI3K–AKT	Pathway mutations and/or CNVs; hyperactivation (GEP signatures)		
	Transcriptional regulation	Mutations and/or CNVs: *IKZF2*, *PRDM1*, *ETV6*, *FOXP1*, *TBL1XR1*, *IRF2BP2*, *YTHDF2*, *DDX3X*		
	Epigenetic modifiers	Mutations and/or CNVs: *TET2*, *DNMT3A*, *KMT2C*, *KMT2D*, *SETD1B*, *SETD2*, *CREBBP*, *EP300*, *ARID1A*, *KDM6A*		
	Tumour suppressors	Mutations and/or CNVs: *TP53*, *CDKN2A* (non-T_{FH} cell PTCL-NOS), *ATM*		
ALK^+ ALCL	TCR and CD30	Activation by ALK fusion proteins	Altered response to proapoptotic signals; T_{reg} cell-mediated and TAM-mediated immunoregulation; immune checkpoint regulation	No pathogenic role
	JAK–STAT	Gene loss: phosphatases		
	Notch	Activation by ALK fusion proteins		
	PI3K–AKT	Activation by ALK fusion proteins		
	AP-1	Hyperactivation		
ALK^- ALCL	TCR and CD30	Fusion proteins: DUSP22–FRA7H, TP63–TBL1XR1	Altered response to proapoptotic signals; T_{reg} cell-mediated and TAM-mediated immunoregulation; immune checkpoint regulation	No pathogenic role
	JAK–STAT	Mutations: *JAK1*, *STAT3*; fusion proteins: NCOR2–ROS1, NFKB2–ROS1, PABCA2–TYK2, NFKB2–TYK2; gene losses: phosphatases		
	Notch	Constitutive activation		
	Epigenetic modifiers	Mutations: *TET2*		
	Tumour suppressors	Mutation/deletion: *TP53*, *PRDM1*		

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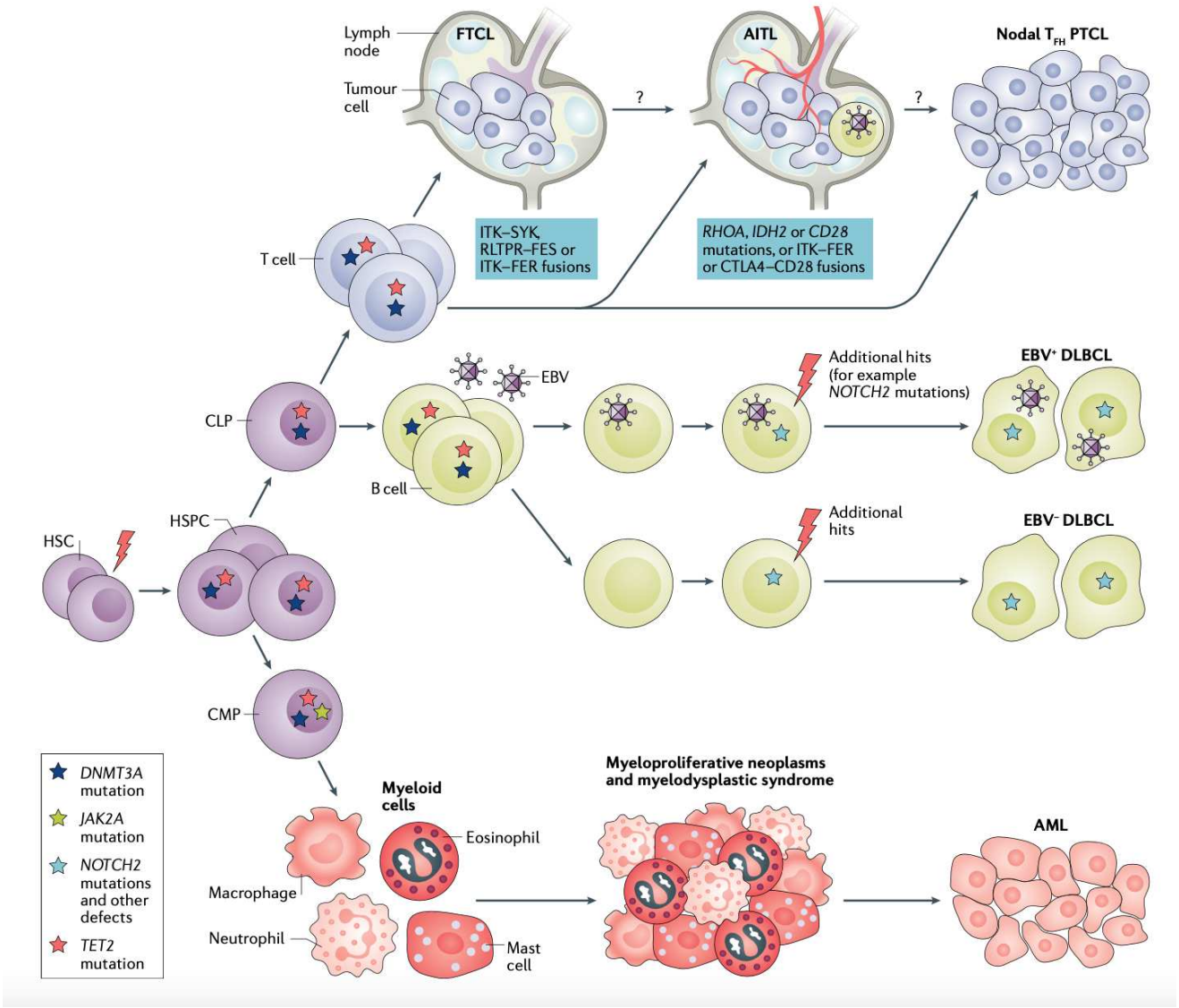
Clonal haematopoiesis and T cell lymphoma of follicular helper cell origin



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Clinical studies on new agents in patients with peripheral T cell lymphoma

Targets	Treatments	Phase	Dosing	Patients[a]	ORR (%)	CRR (%)	Survival
DNA methylation	Azacitidine	NA (retrospective review)	75 mg m^{-2} (subcutaneously), days 1–7 every 28 days	12 (AITL)	75	50	mPFS: 15 months; mOS: 21 months
JAK1 and JAK2	Ruxolitinib	II	20 mg (orally) twice daily	33	21–40[b]	3	NR
SYK, JAK1 and JAK3	Cerdulatinib	IIa	30 mg (orally) twice daily	41 (PTCL)	34	27	NR
				27 (CTCL)	26	7	NR
PI3Kδ and PI3Kγ	Duvelisib	I	25–100 mg (dose-finding trial) (orally) twice daily	16 (PTCL)	50	19	mPFS: 8.3 months; mOS: 8.4 months
			MTD (75 mg) (orally) twice daily	19 (CTCL)	32	0	PFS (1 year): 26.5%; OS (1 year): 78.9%
PI3Kδ, PI3Kγ and histone deacetylases	Duvelisib + romidepsin	I	Duvelisib: 75 mg twice daily (expansion cohort); romidepsin: 10 mg m^{-2}, days 1, 8 and 15 every 28 days	38	55	24[c]	NR
PI3Kδ, PI3Kγ and proteasome	Duvelisib + bortezomib	I	Duvelisib: 25 mg twice daily; bortezomib: 1 mg m^{-2}, days 1, 4, 8 and 11 every 28 days	31	35	13[c]	NR
Cereblon	Lenalidomide	II	Lenalidomide (25 mg per day for 14 days every 21 days) + CHOP (standard, every 21 days)	80 (treatment-naive patients with AITL)	47	44	PFS (2 years): 42%; OS (2 years) 60%
CD30	Brentuximab vedotin	III[d]	Brentuximab vedotin: 1.8 mg kg^{-1} every 21 days	64 (MF)	56 (REF.[14])	NR	mPFS: 16.7 months
			Standard: methotrexate or bexarotene	64 (MF)	13[e]	NR	mPFS: 3.5 months
CD30	Brentuximab vedotin	III[d]	Brentuximab vedotin (1.8 mg kg^{-1} every 21 days) + CHP	226 (treatment-naive patients with PTCL)	83	68	PFS (3 years): 57%
			Standard: CHOP	226 (treatment-naive patients with PTCL)	72	56	PFS (3 years): 44%
CCR4	Mogamulizumab	II	1.0 mg kg^{-1} once weekly for 8 weeks	37	35	14	mPFS: 3.0 months
				35 (PTCL)	11	3	mPFS: 2.1 months
CD25/IL-2Rα	Camidanlumab tesirine	I	3–150 μg kg^{-1} every 21 days; most responses at 60–80 μg kg^{-1}	22	42	5	NR

Angioimmunoblastic T-cell lymphoma

AITL

Angioimmunoblastic T-cell lymphoma

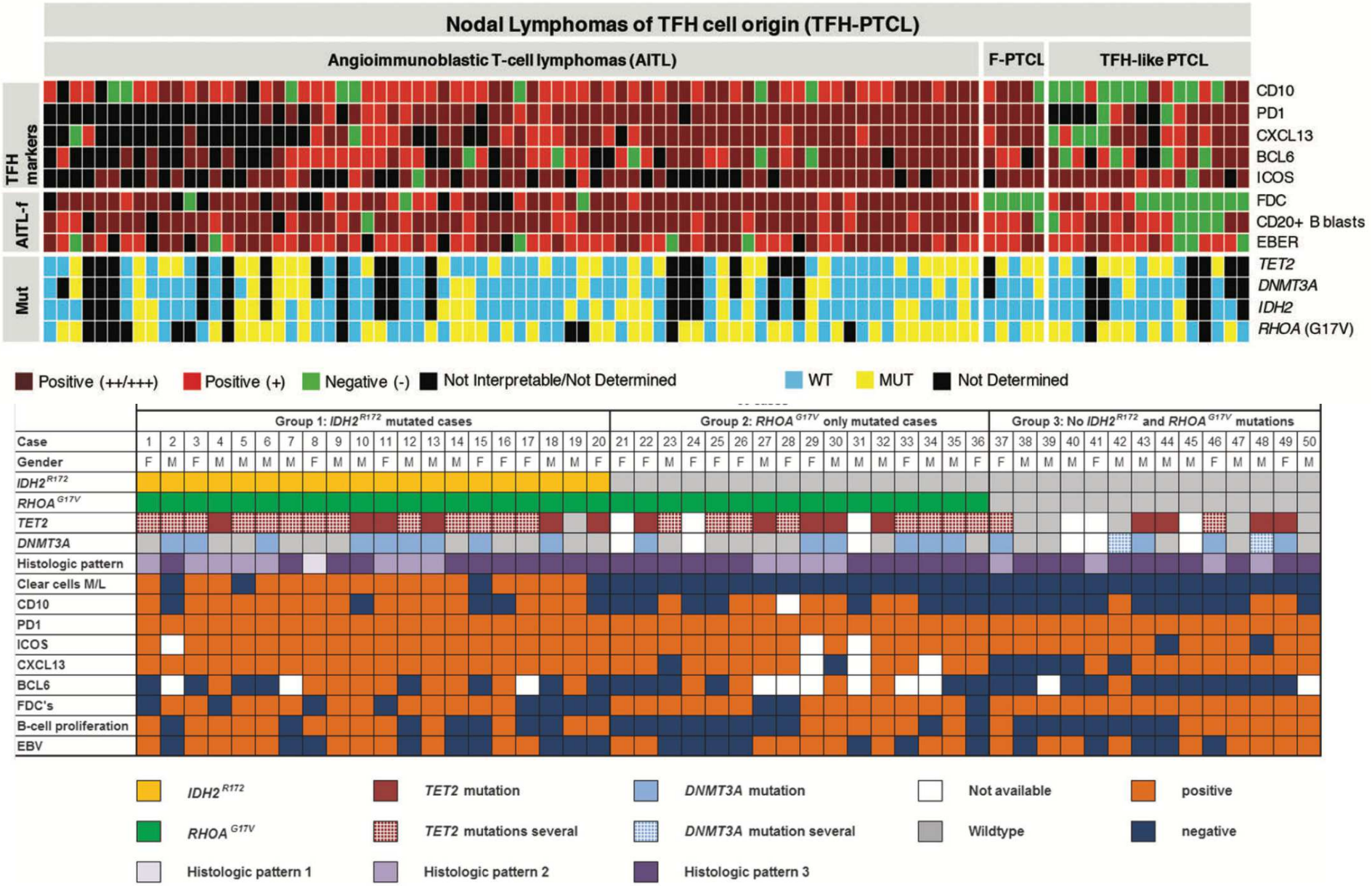
Follicular T-cell lymphoma (more often presents with localized disease, with fewer systemic symptoms)

Nodal peripheral T-cell lymphoma with TFH phenotype

- The neoplastic cells should express at least 2 or 3 TFH-related antigens, including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5

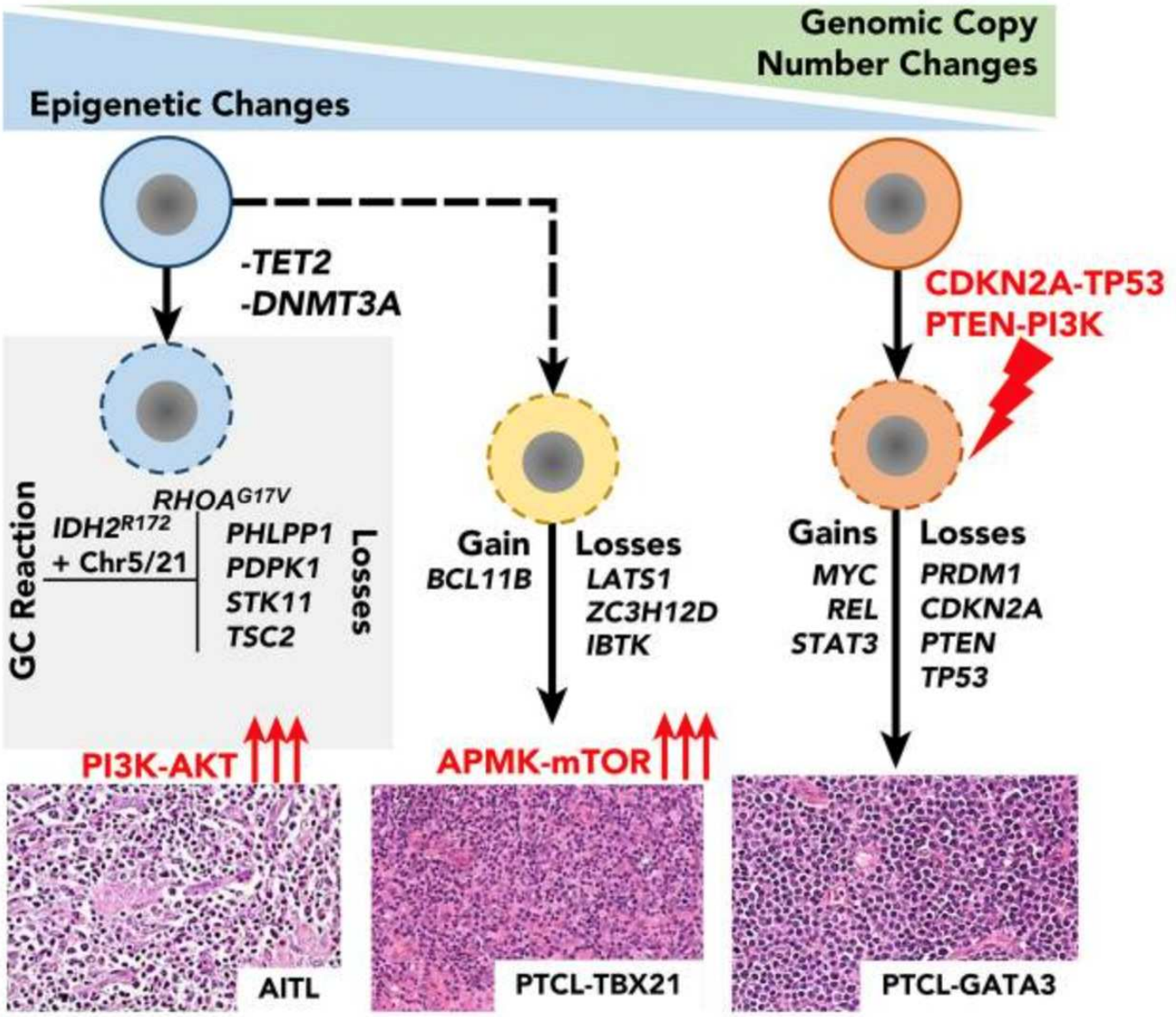
- Recurrent genetic abnormalities include TET2, IDH2, DNMT3A, RHOA, and CD28 mutations, as well as gene fusions such as ITK-SYK or CTLA4-CD28

The spectrum and genetics of nodal TFH lymphoma



Dobay et al. Hematologica 2017 *Steinhilber et al. Modern Pathology 2019*

Molecular distinction between AITL and PTCL-NOS



Heavican et al. Blood 2019

Angioimmunoblastic T-cell lymphoma

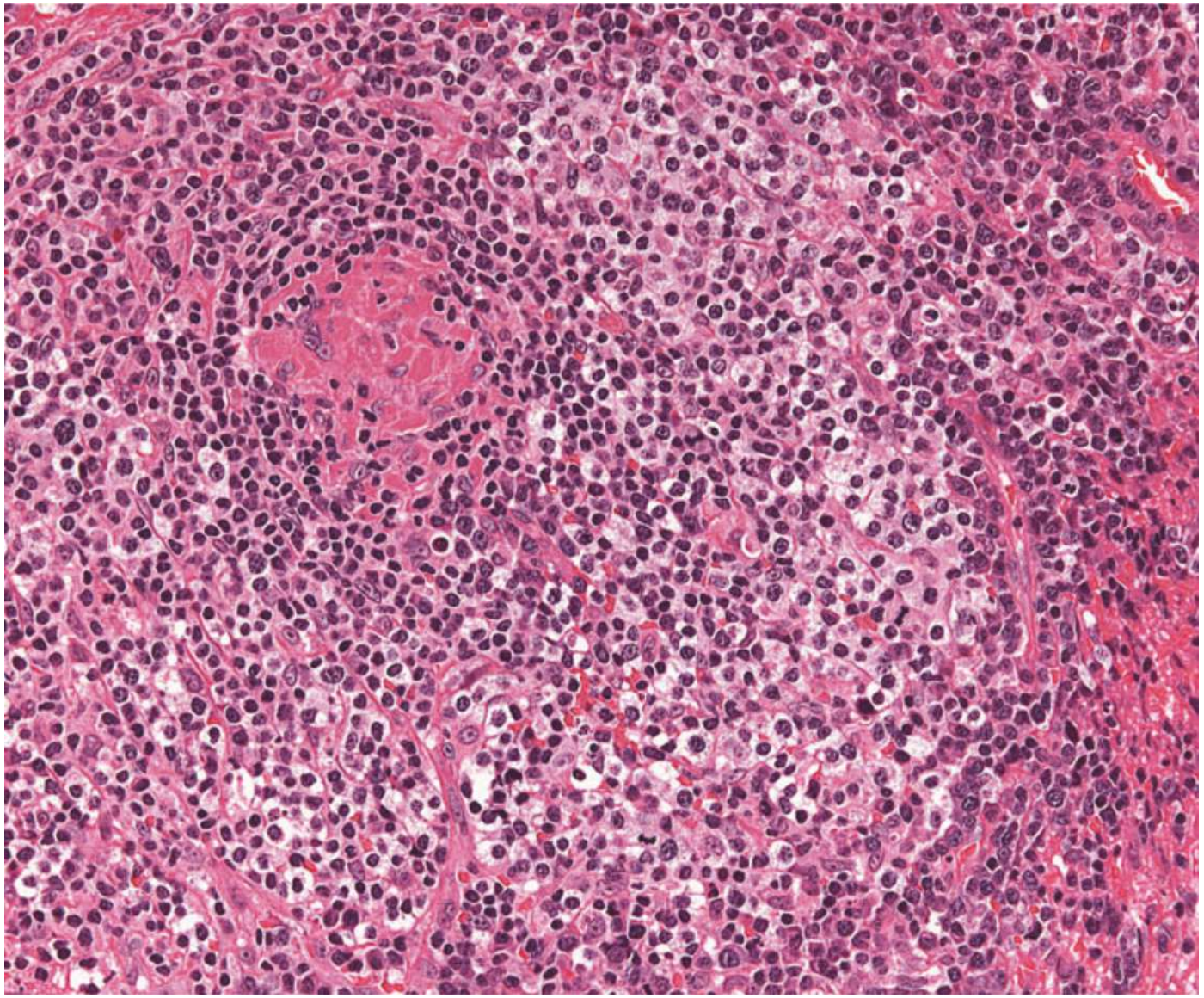
AITL

Both AITL and FTCL may contain B-cell blasts, often EBV+, in addition to the neoplastic TFH cells.

In some cases, the atypical B-cell blasts simulate Hodgkin–Reed-Sternberg cells, leading to a mistaken diagnosis of classical Hodgkin lymphoma (CHL).

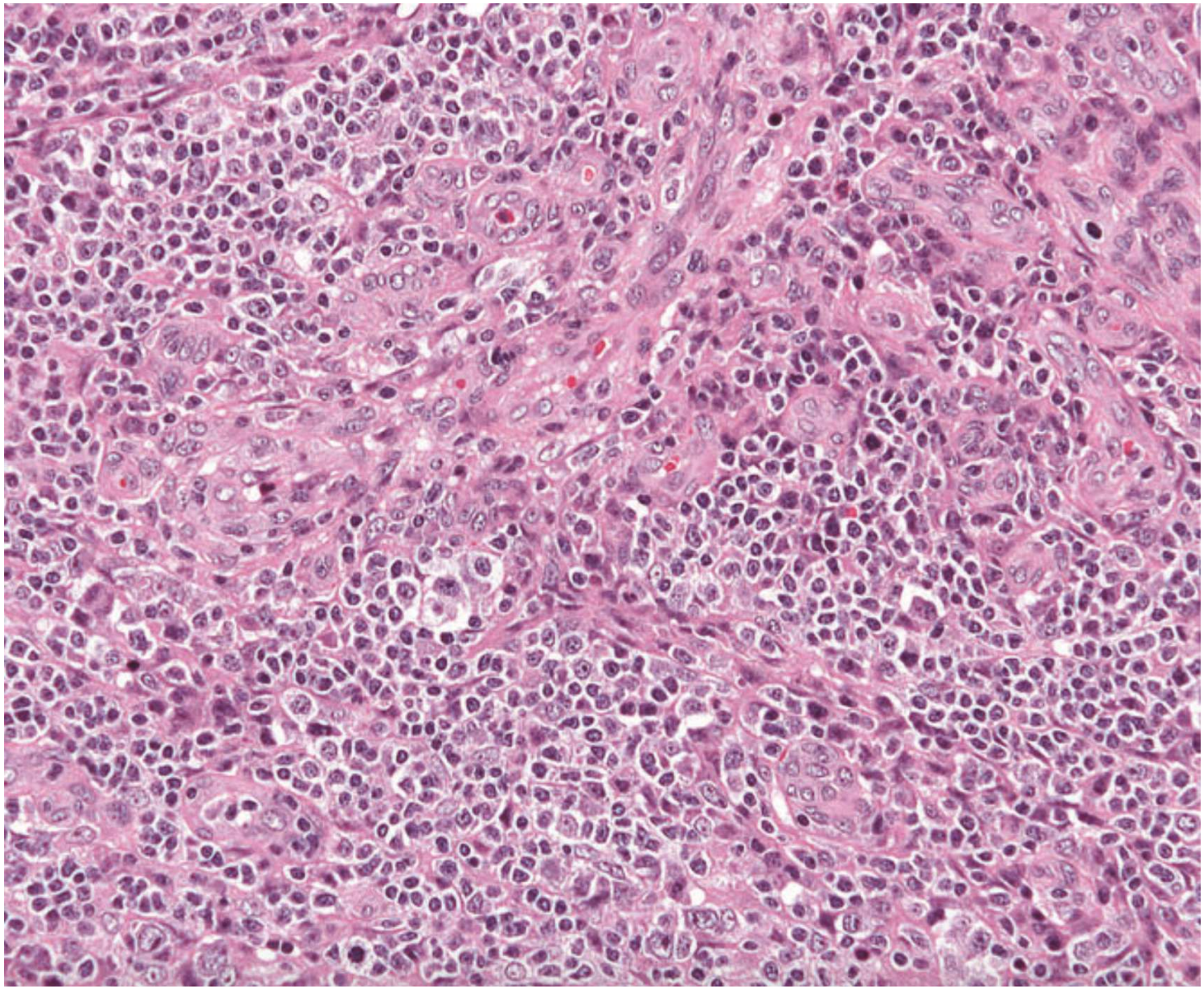
Progression to EBV+, and more rarely EBV-, B-cell neoplasms may occur in a subset of cases.

AITL



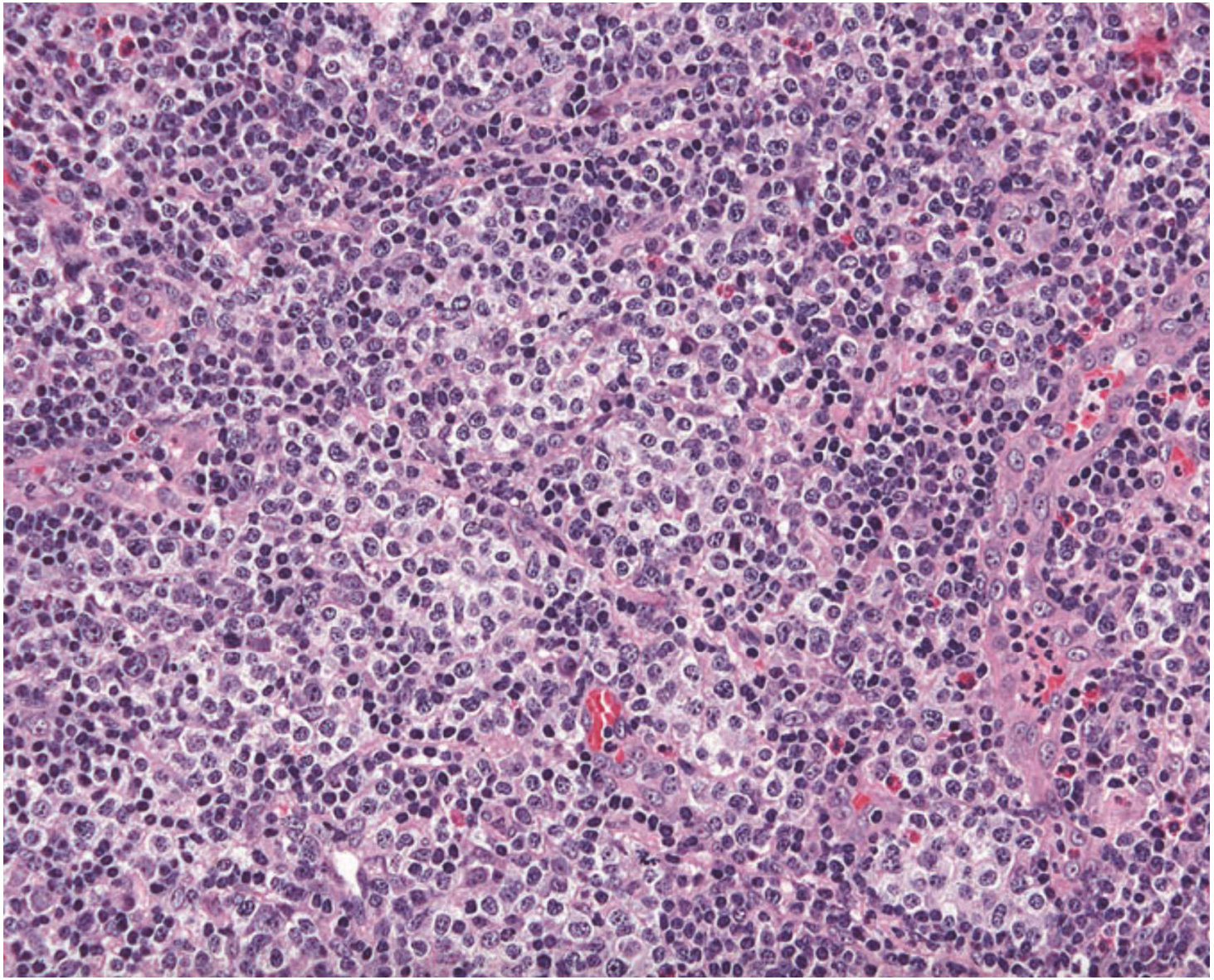
Steinhilber et al. Modern Pathology 2019

AITL



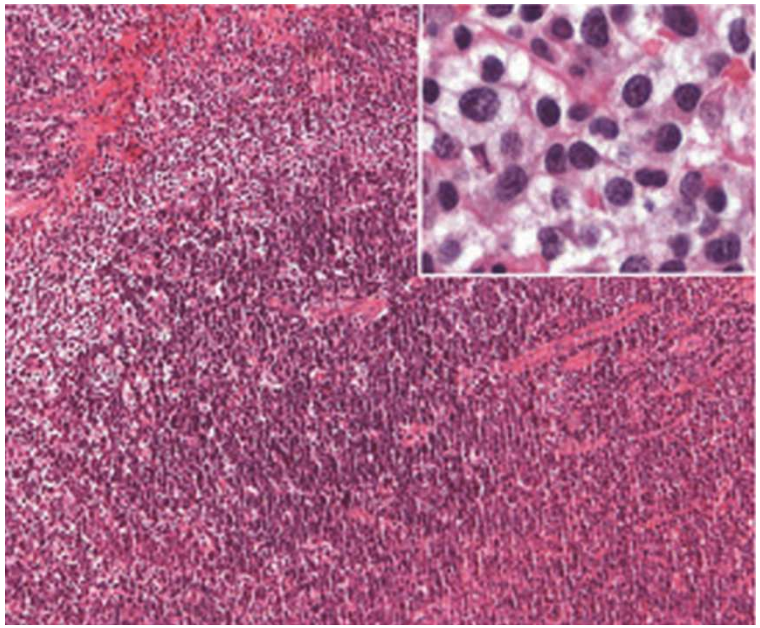
Steinhilber et al. Modern Pathology 2019

AITL

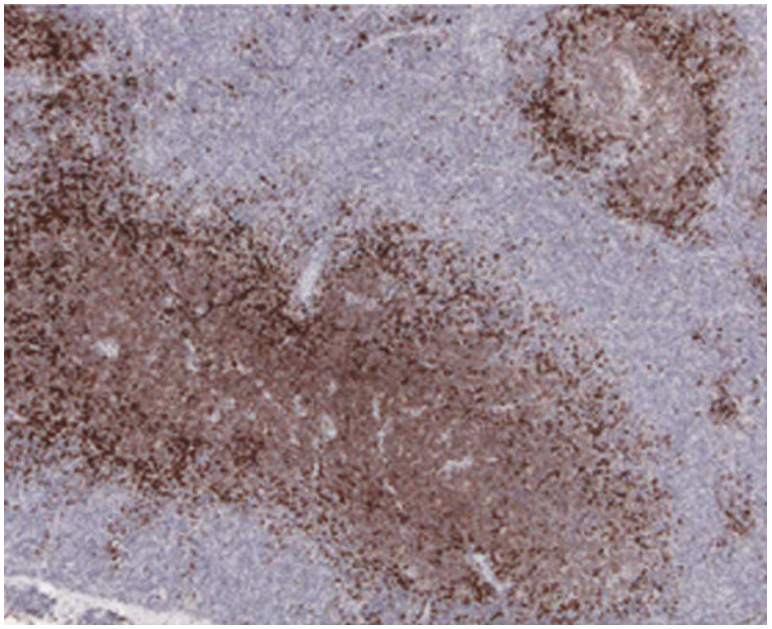


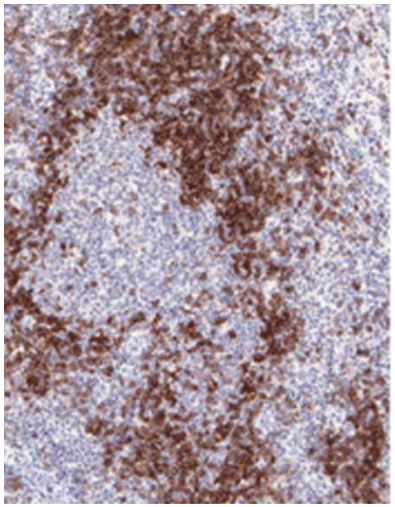
Steinhilber et al. Modern Pathology 2019

AITL

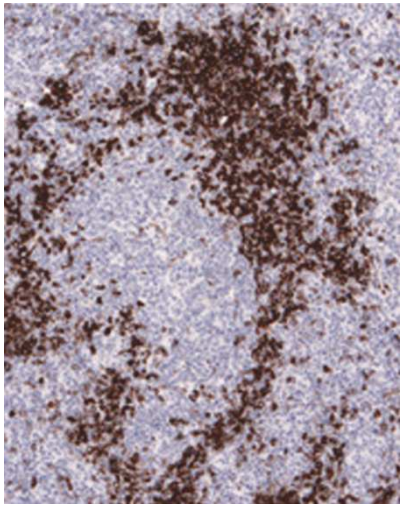


CD10

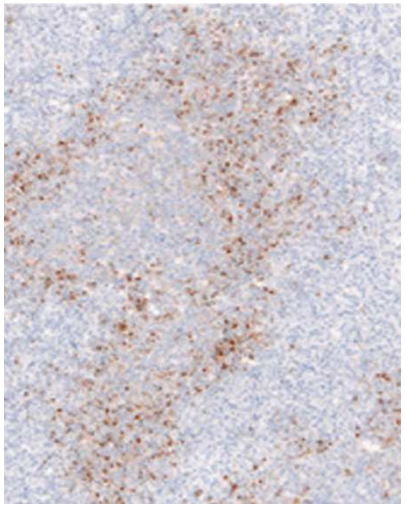




PD-1



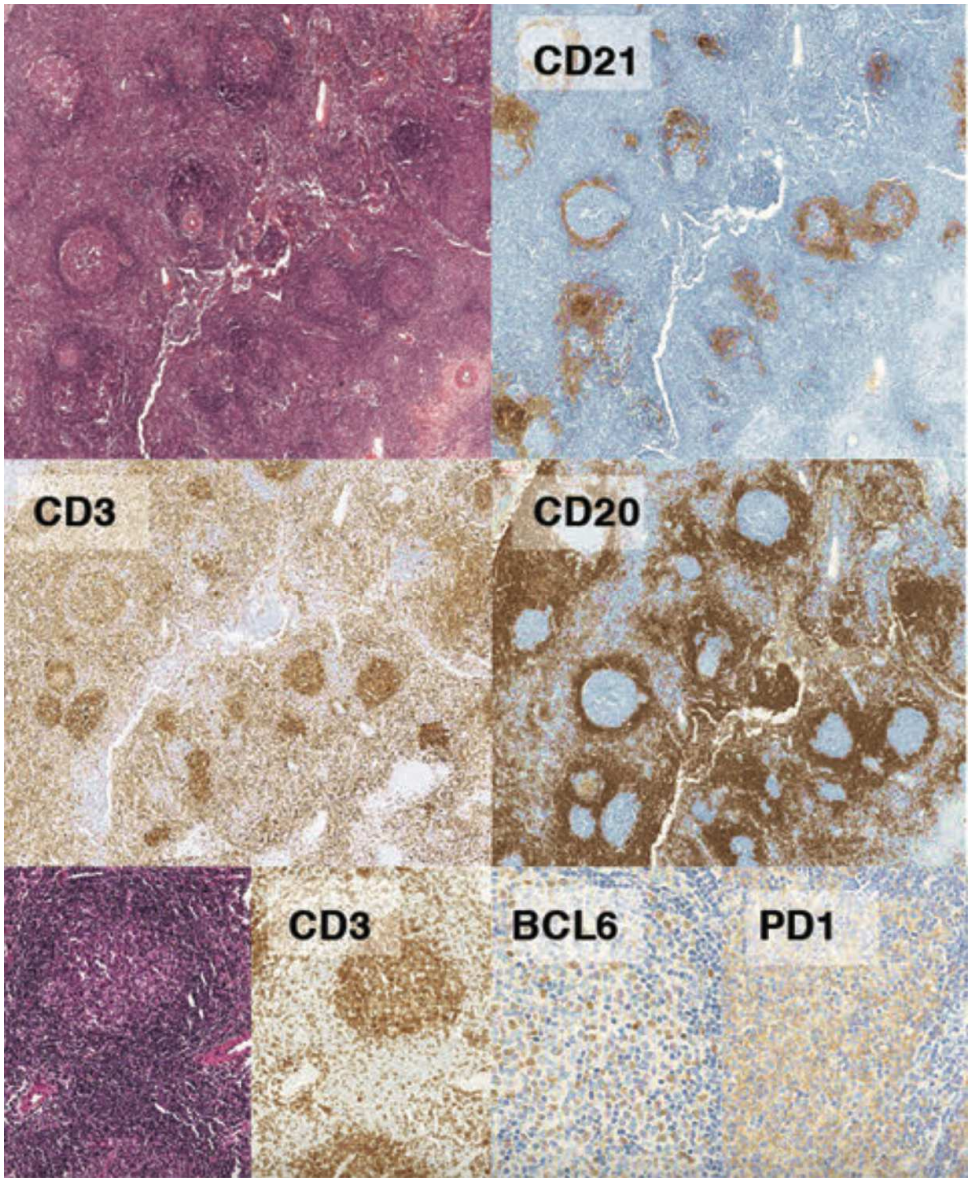
ICOS



CXCL13

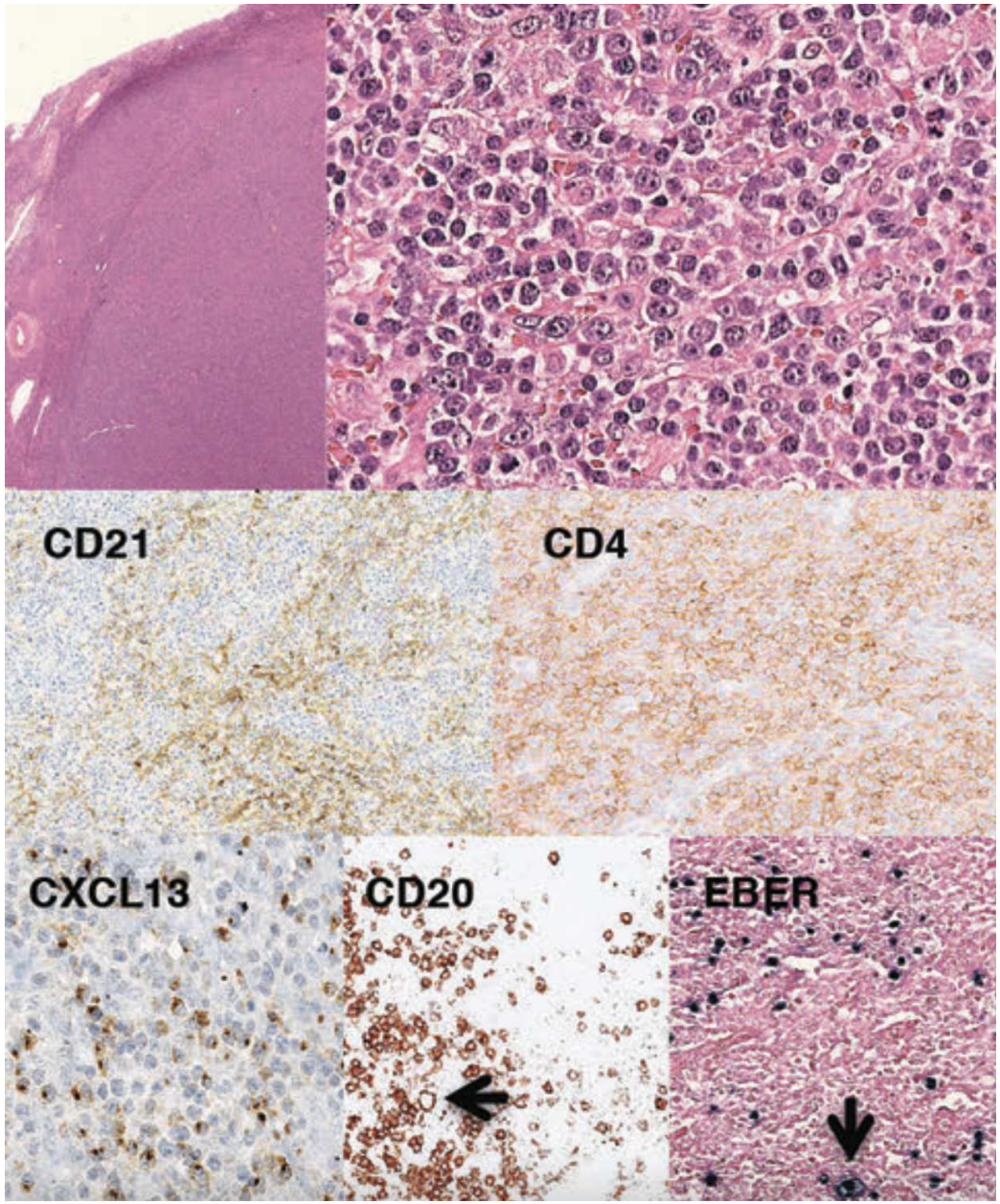
Steinhilber et al. Modern Pathology 2019

The spectrum of nodal TFH lymphoma



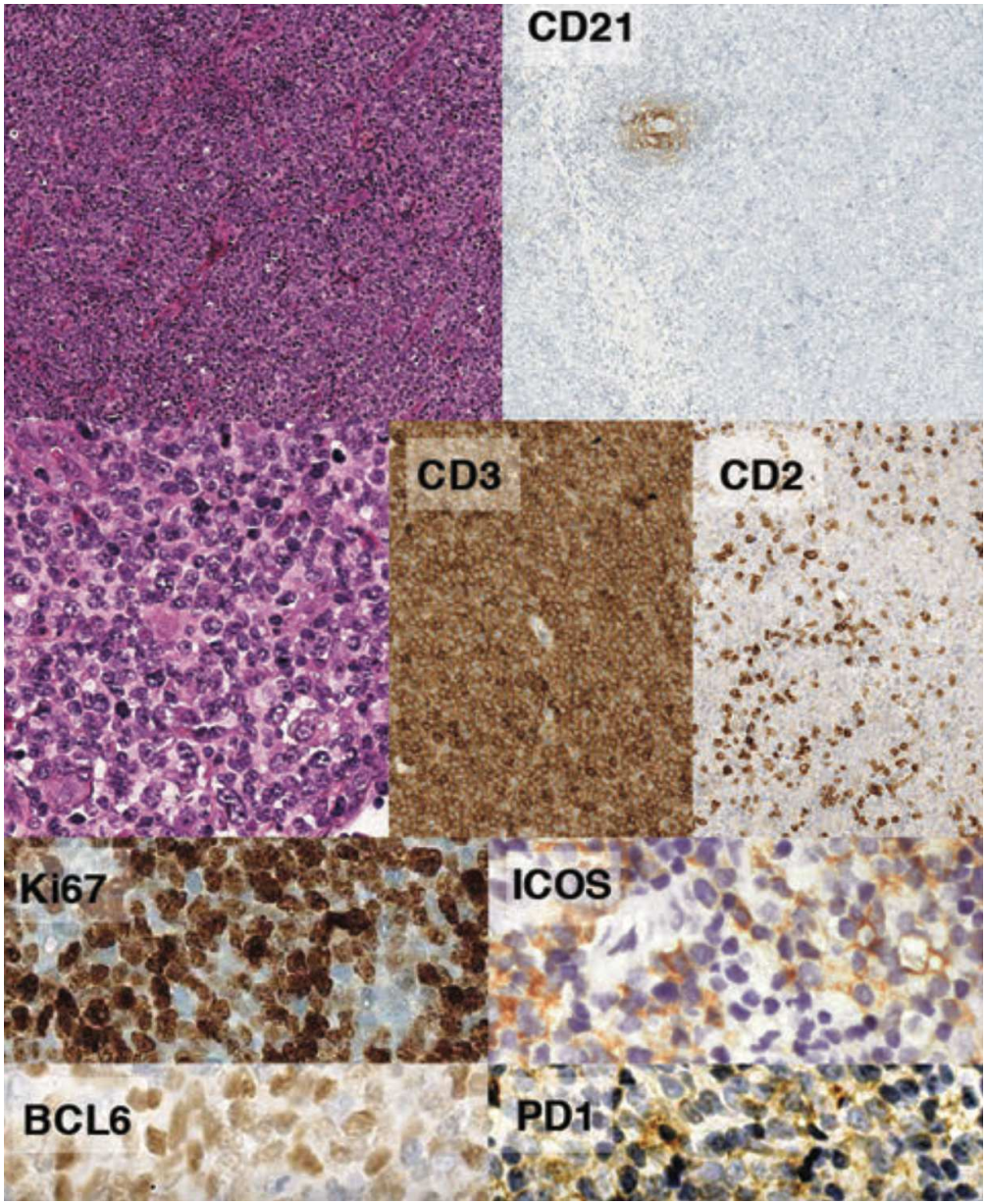
Dobay et al. Hematologica 2017

The spectrum of nodal TFH lymphoma



Dobay et al. Hematologica 2017

The spectrum of nodal TFH lymphoma



Dobay et al. Hematologica 2017

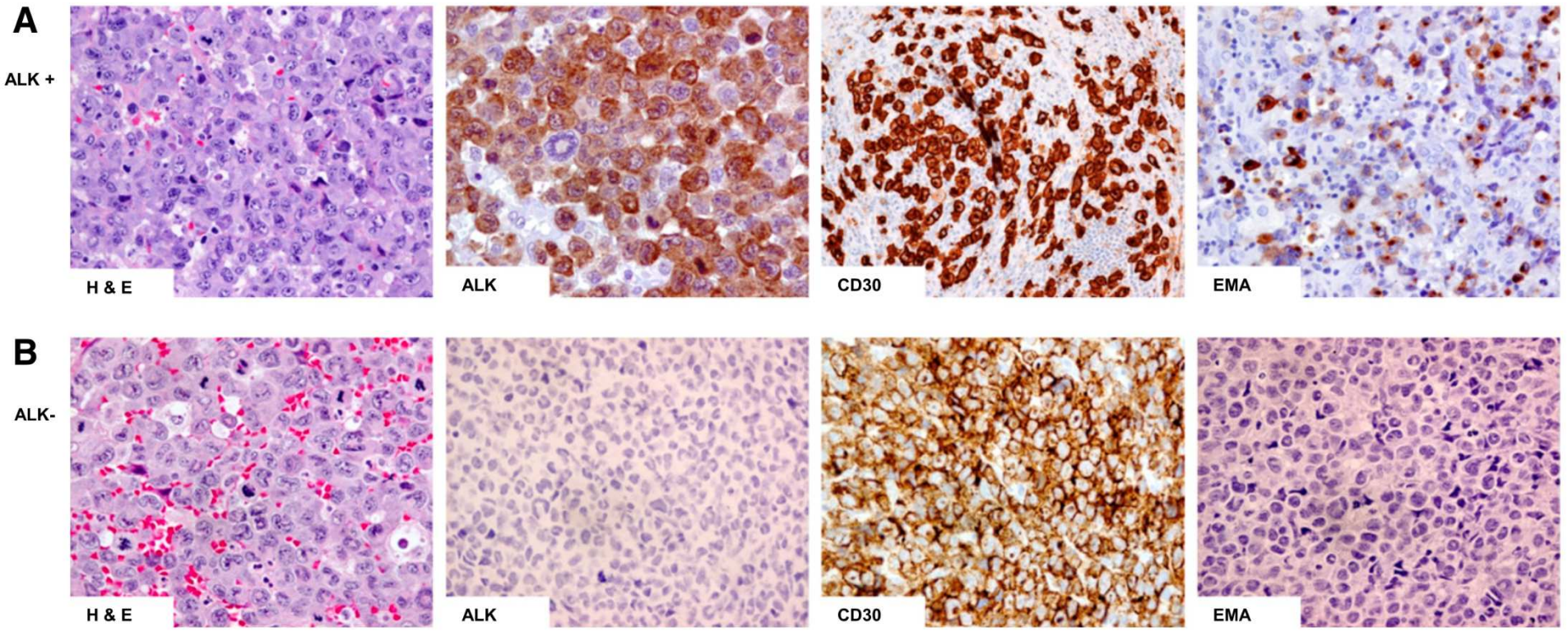
Anaplastic Large Cell Lymphoma - ALCL

Systemic ALCL, ALK+

Systemic ALCL, ALK-

Breast-implant associated (BIA)-ALCL

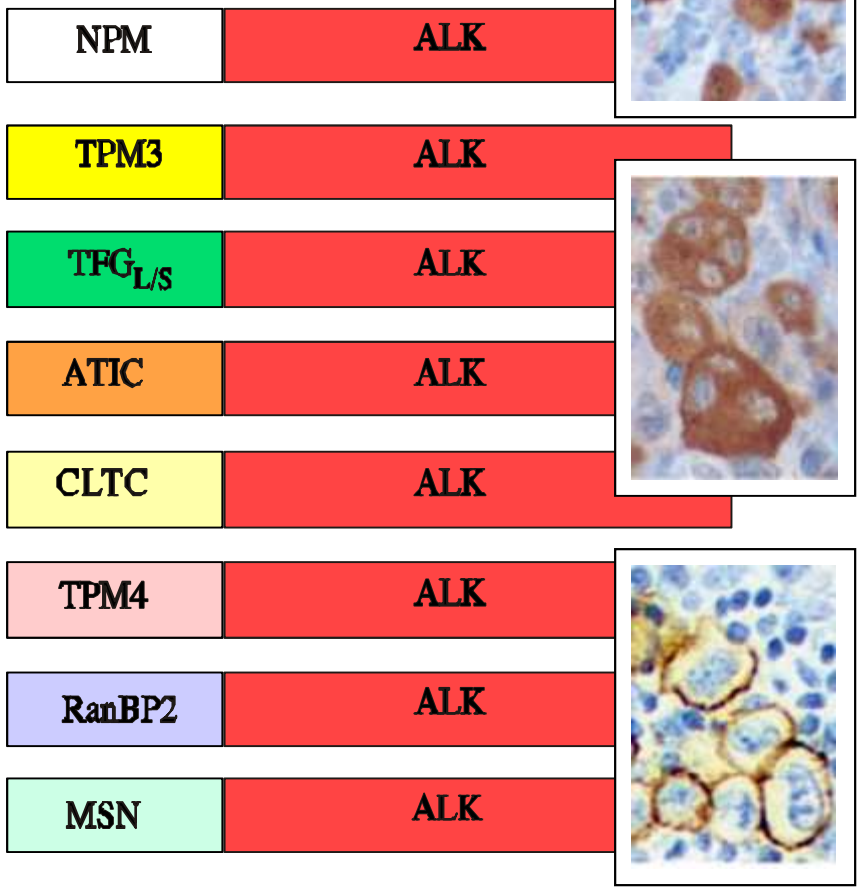
Anaplastic Large Cell Lymphoma - ALCL



Hapgood and Savage. Blood 2015

Translocations and fusion proteins involving the ALK gene in ALCL

Translocation	Frequency	Localization
t(2;5)(p23 ;q35)	70-80%	Cytoplasmic/Nuclear nucleolar
t(1;2)(q25 ;p23)	10-20%	Cytoplasmic
t(2;3)(p23 ;q21)	2-5%	Cytoplasmic
inv(2)(p23 ;q35)	2-5%	Cytoplasmic
t(2;17)(p23 ;q23)	2-5%	Cytoplasmic
t(2;19)(p23 ;q13,1)	-	Cytoplasmic
t(2;2)(p23 ;q11-13)?	-	Nuclear membrane
or inv(2)(p23 ;q11-13)?	-	
t(X;2)(q11-12 ;p23)	-	Membranous



Anaplastic Large Cell Lymphoma - ALCL

		ALCL		
Immunophenotype	**Cutoff (%)**	**ALK + (%)**	**ALK– (%)**	**PTCL-NOS (%)**
CD30	>20	100	100	23
ALK	Any	100	0	0
CD3	>20	11.5	45	95
CD4	>20	46	68	57
CD8	>20	8	16	19
CD2	>20	22	58	92
CD5	>20	36	19	67
TIA1	>20	54	27	42
CD45		48	59	79

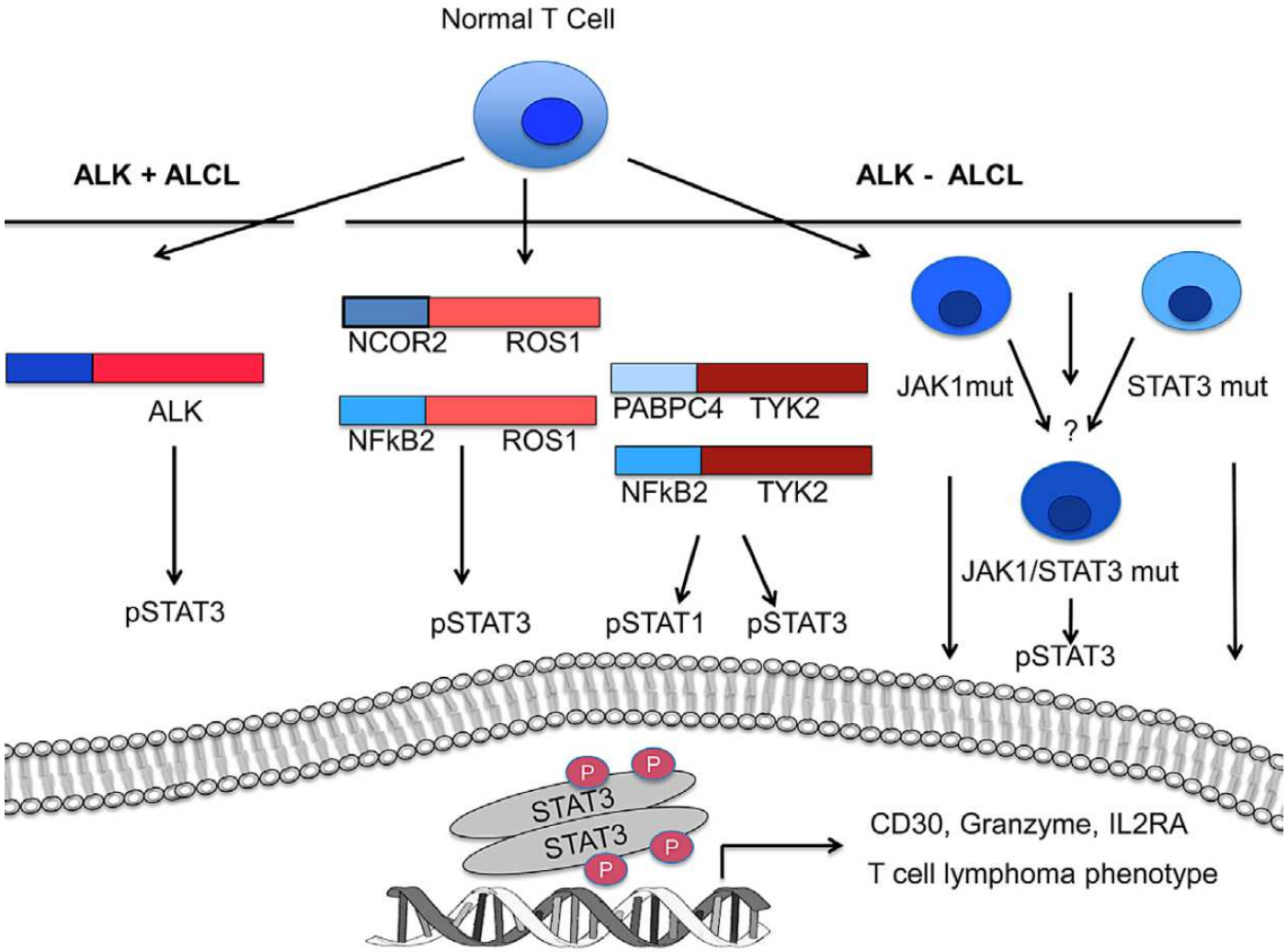
Hapgood and Savage. Blood 2015

Anaplastic Large Cell Lymphoma - ALCL

ALK+ ALCL	ALK- ALCL
Recurrent translocations involving ALK	Recurrent translocations involving *DUSP22:IRF4*
t(2;5)(p23;25) *ALK:NPM1* (85%)	(6p25.3) (30%)
t(2;v) (15%)	Recurrent translocations involving *TP63* (3q28) 8%
Gains: 7, 17p, 17q	Gains: 1q, 6p, 8q, 12q
Deletions: 4, 11q, 13q	Deletions: 6q, 4q, 13q

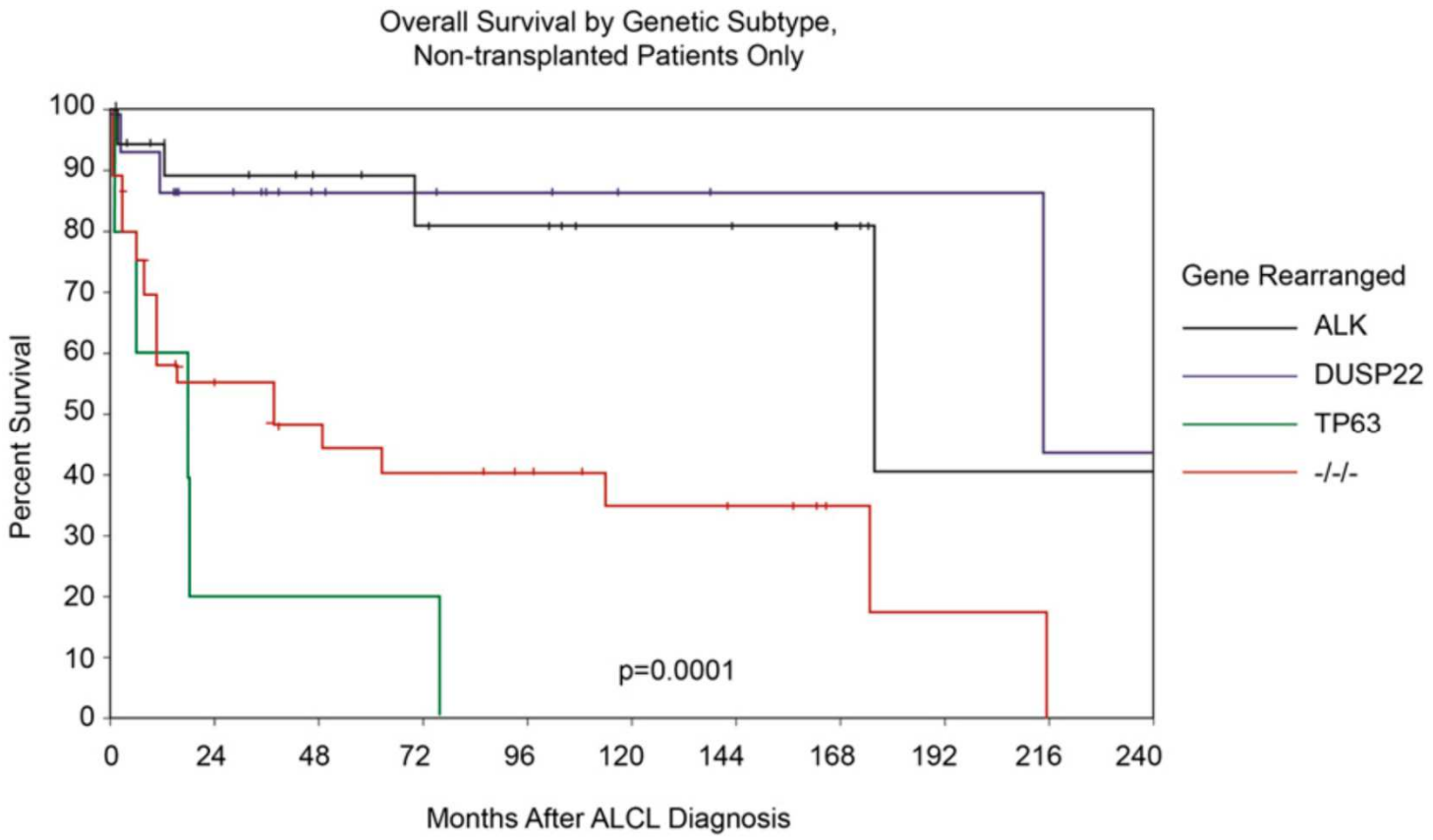
Hapgood and Savage. Blood 2015

Anaplastic Large Cell Lymphoma - ALCL



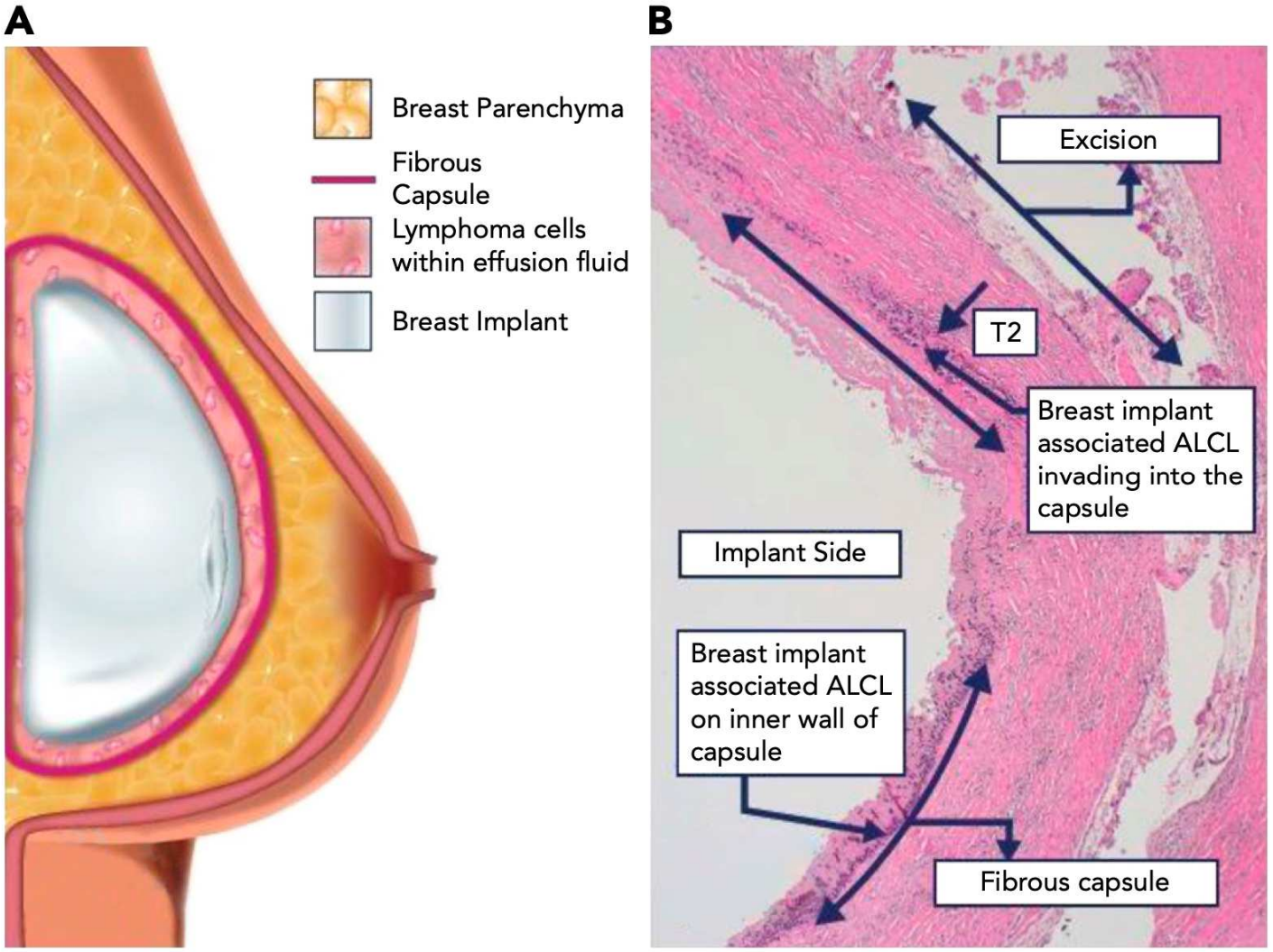
Crescenzo et al. Cancer Cell 2015

Anaplastic Large Cell Lymphoma - ALCL



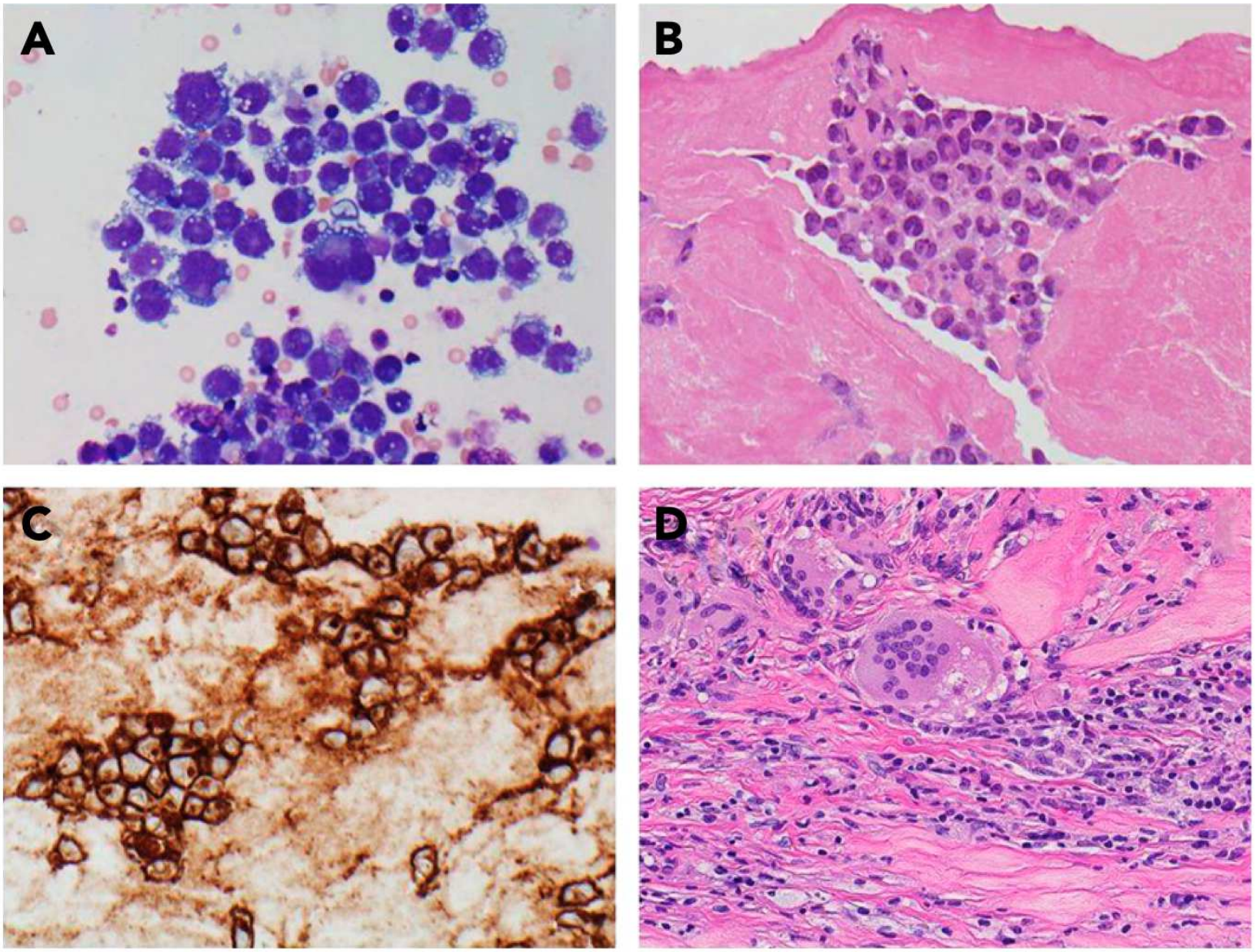
Parilla Castellar et al. Blood. 2014

BIA- ALCL



Mehta-Shah et al. Blood. 2018

BIA- ALCL

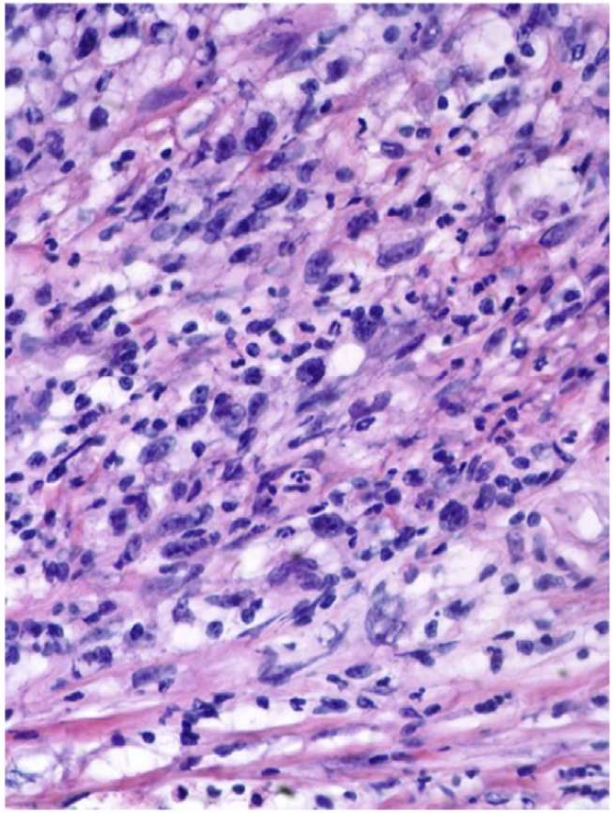


CD30

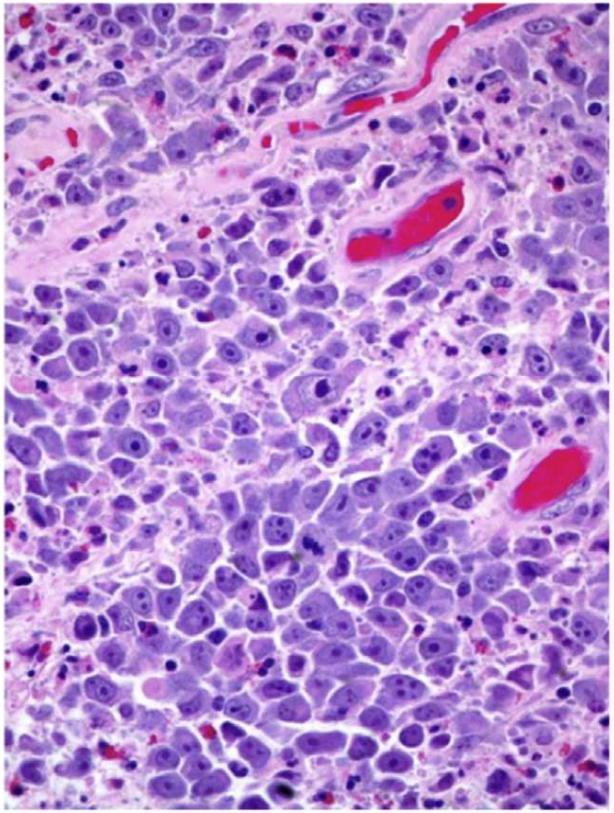
Mehta-Shah et al. Blood. 2018

BIA- ALCL

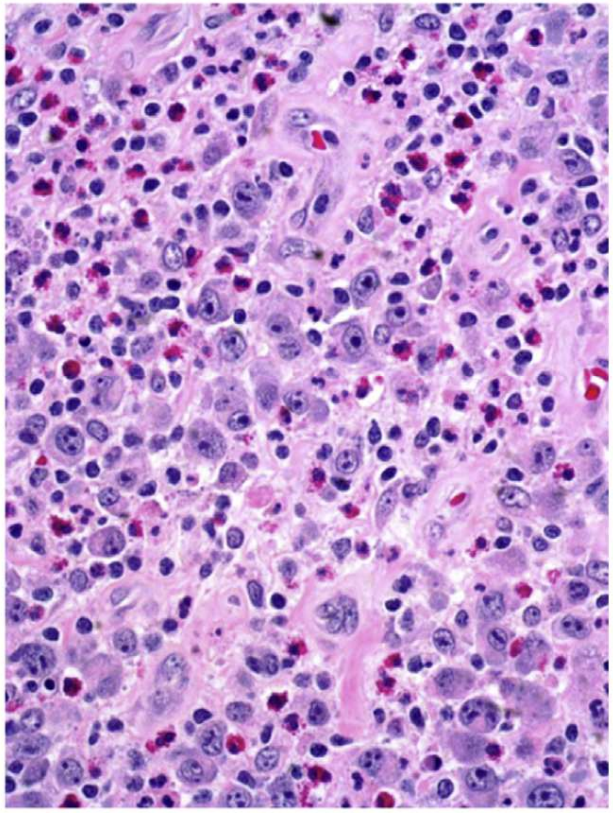
Seroma cell block



Capsule-monomorphic pattern



Hodgkin-like pattern

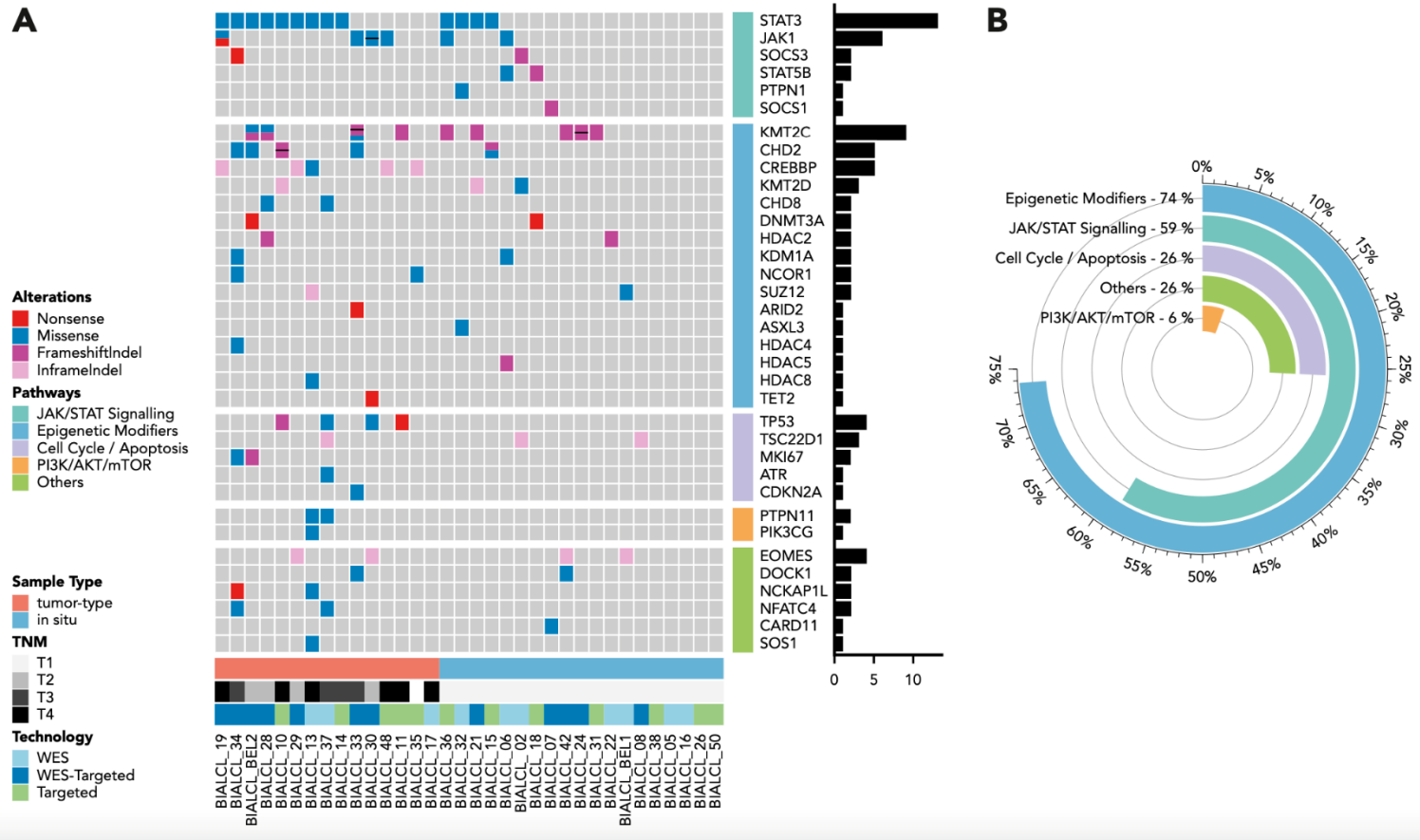


Turner et al. AJP. 2020

BIA- ALCL

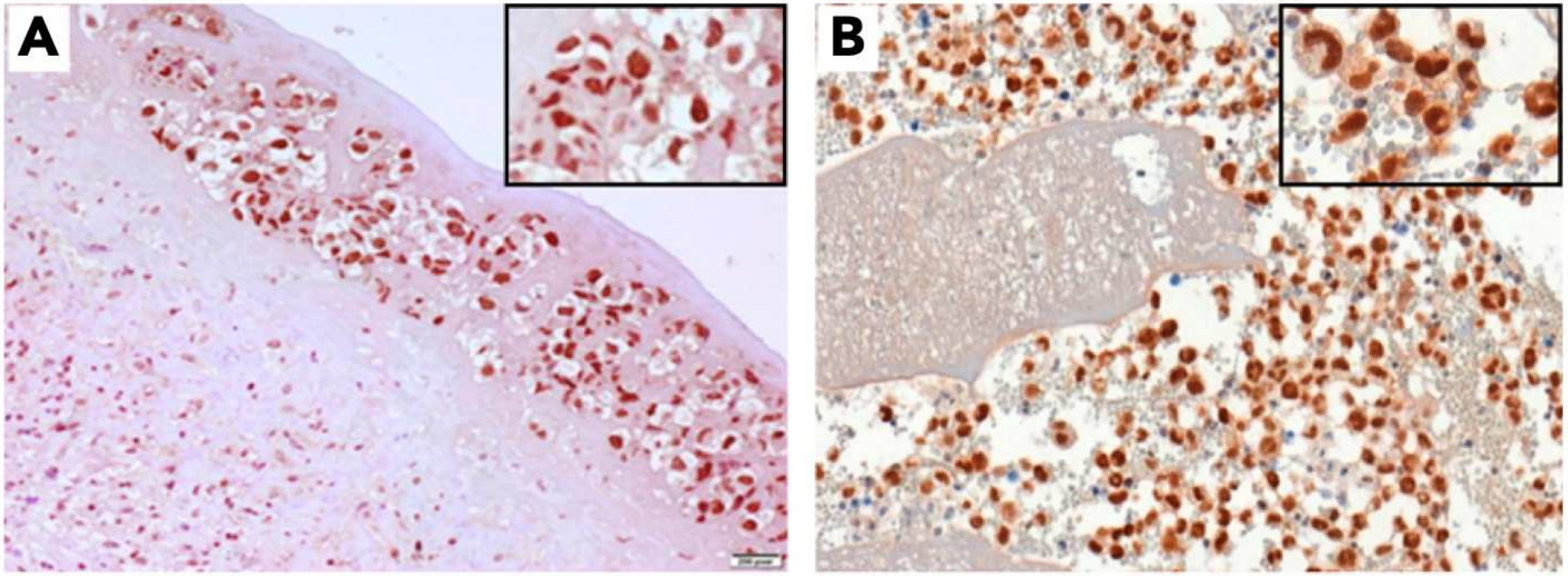
An accumulation of alterations in epigenetic modifiers and genes in the JAK/ STAT pathway likely drives BI-ALCL oncogenesis.

Frequent losses at chromosome 20q13.13 provide genetic justification to recognize BIA-ALCL as a separate disease entity



Los-de Vries et al. Blood. 2020 *Laurent et al. Blood. 2020*

BIA- ALCL



Activated Nuclear STAT3

Laurent et al. Blood. 2020

THANK YOU FOR YOUR ATTENTION!