VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Linfomi follicolari: varianti atipiche e meccanismi di sviluppo

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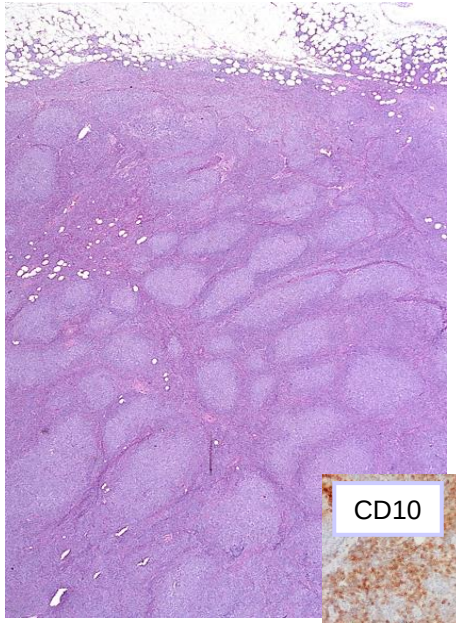
Bologna, Aula Prodi | 11-12 maggio 2026

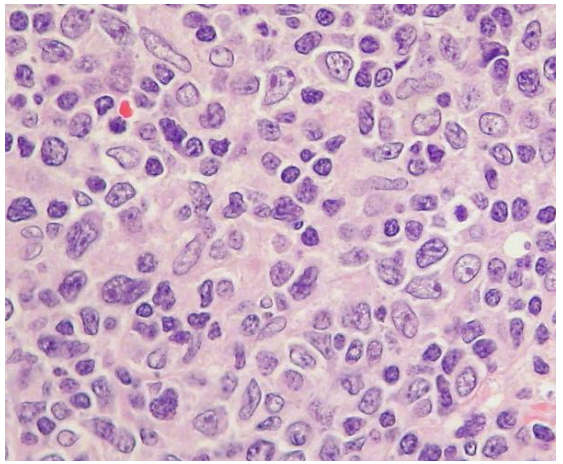
Disclosures of Marco Lucioni

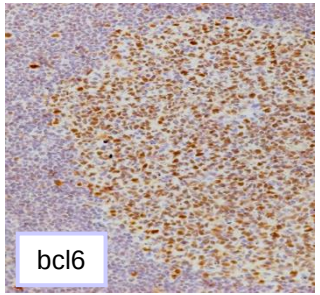
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

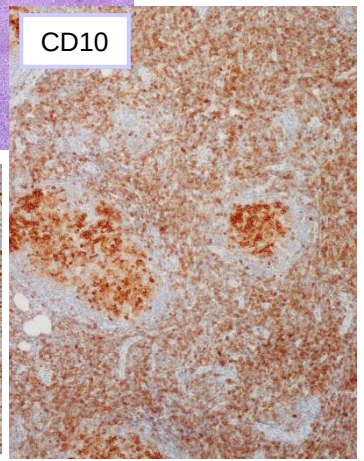
Conventional follicular lymphoma

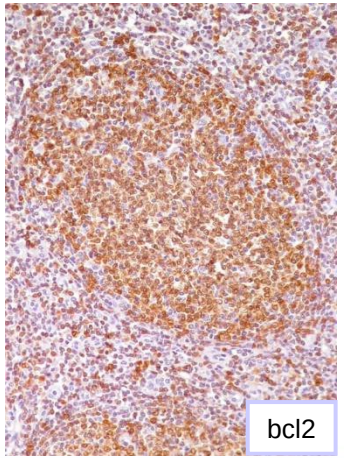
- Neoplasm deriving from GC B-cells, composed of centrocytes and centroblasts usually in follicular distribution
- GC-phenotype (CD10, BCL6, HGAL, LMO2)
- Abnormal expression of BCL2 due to t(14;18)(*IGH-BCL2*)
- Typical clinical presentation of predominantly nodal disease and a generally indolent clinical course



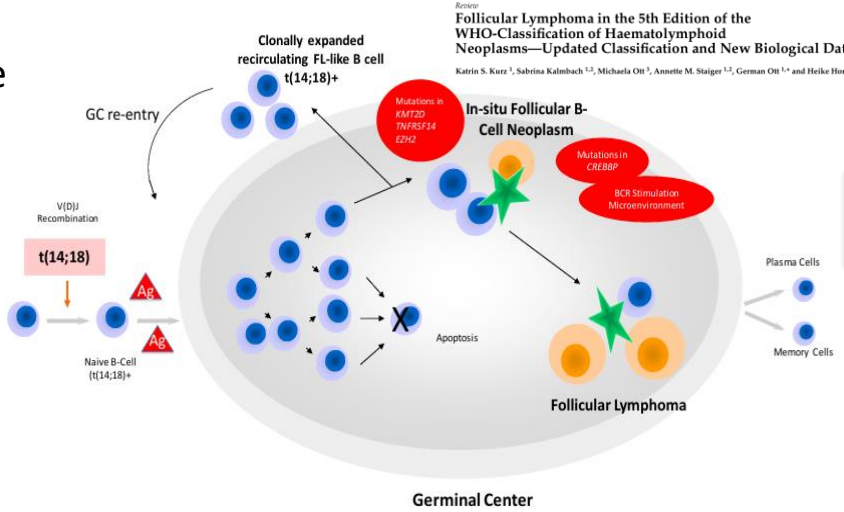








- t (14,18)(q32;q21) is the initiating event in 85-90% of cFL; V(D)J recombination error in a BM pre-B cell; rare t variants involve IGL instead of IGH; differentiated t(14;18)+ memory-like B-cells clones in >70% of healthy adults
- t(14;18)+ cells accumulate within nodal GCs as centrocytes
- Via several re-entries into GCs, t(14;18)+ B-cells acquire additional mutations enabling them to be founders of ISFN or manifest lymphoma
- Although linear clonal evolution has been reported, most FL follow a branching evolution.
- Multiple sub-clones can be identified in early disease phases, providing the substrate for progression/ transformation «via» a series of mutational events.



Review

Follicular Lymphoma in the 5th Edition of the WHO-Classification of Haematolymphoid Neoplasms—Updated Classification and New Biological Data

Katrin S. Kurz [1], Sabrina Kalmbach [1,2], Michaela Ott [3], Annette M. Staiger [1,2], German Ott [1,4] and Heike Horn [1,2]

Most frequent gene alterations in BCL2-rearranged FL at diagnosis

Gene	Frequency of alterations (%)[a]	Predominant type of alteration
KMT2D (MLL2)	50-70%	Mutations
CREBBP	50-70%	Mutations (~60%), deletions
EPHA7	70%	Deletion, methylation
TNFRSF14	45-65%	Deletions, mutations (~30%)
BCL2	~50%	Mutations
SESTRIN1	30-40%	Deletions
CDK4	~30%	Gains
EZH2	20-40%	Mutations (~20%), gains
HIST1H1B-E	15-30%	Mutations
CTSS	15-20%	Mutations (~5%), amplifications
BCL6	~15%	Translocation, mutation (~5%)
FOXO1	10-15%	Mutations
STAT6	10-15%	Mutations
ARID1A	10-15%	Mutations
EP300	10-15%	Mutations
CARD11	10-15%	Mutations
MEF2B	10-15%	Mutations
ATP6V1B2	~10%	Mutations
ATP6AP1	~10%	Mutations
GNA13	~10%	Mutations
RB1	~10%	Deletions, mutations (<5%)
SOCS1	~10%	Mutations
RRAGC	5-15%	Mutations
IRF8	5-15%	Mutations
POU2F2	5-10%	Mutations
SGK1	5-10%	Mutations
CDKN2A/B	5-10%	Deletion
TNFAIP3	5-10%	Deletion, mutation (<5%)
HVCN1	5-10%	Mutations
EBF1	5-10%	Mutations
TP53	~5%	Mutation, deletion
CD79B	~5%	Mutations
FAS	<5%	Mutations

Regular Article

LYMPHOID NEOPLASIA

Hierarchy in somatic mutations arising during genomic evolution and progression of follicular lymphoma

Michael R. Green,[1,2] Andrew J. Gentles,[2,3] Ramesh V. Nair,[2] Jonathan M. Irish,[1,4] Shingo Kihira,[1] Chih Long Liu,[1] Itai Kela,[1] Erik S. Hopmans,[5] June H. Myklebust,[1,6] Hanlee Ji,[1,5] Sylvia K. Plevritis,[2,3] Ronald Levy,[1,2] and Ash A. Alizadeh[1,2]

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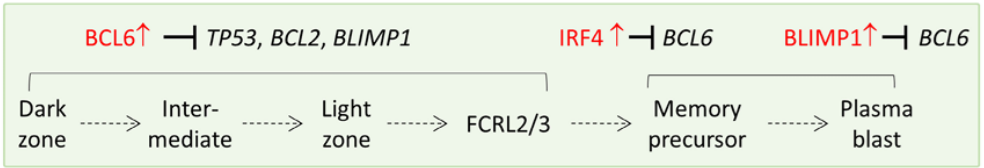
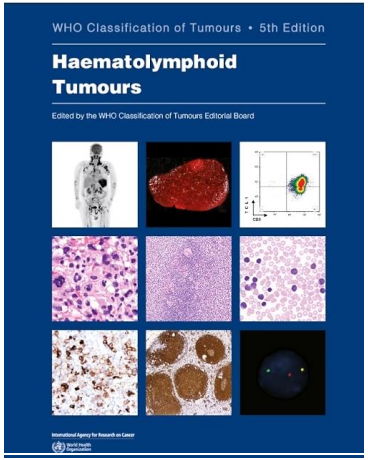
Major genetic changes in FL with and without BCL-2 rearrangement

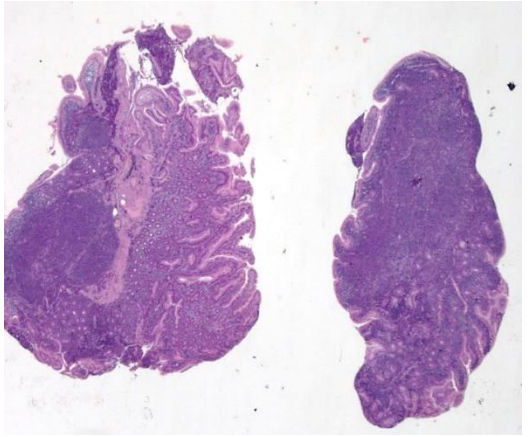
Genetic alteration	All FL	BCL2-R FL (85%)	BCL2-uR FL (15%)
BCL6 rearrangement	15-20%	15-20%	22-35%
Gene mutations (also subclonal)			
KMT2D	50-70%	46%	8-27%
CREBBP	50-70%	61%	38-70%
TNFRSF14	45-65%	18%	15-39%
BCL2	50%	50%	0%
EZH2	20%	14%	15-18%
STAT6	10-15%	14%	23-57%
EP300	10-15%	7%	7-15%
MEF2B	10-15%	9%	2%
IRF8	5-15%	4%	15%
TP53	5%	4%	8%



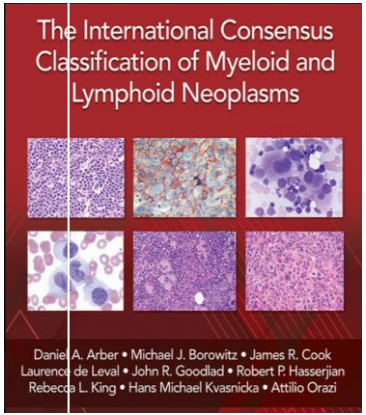
- FL develops from a stepwise acquisition of cooperating genetic events
- These genetic changes dysregulate the B-cell maturation/differentiation process in the GC and, consequently, 'imprint' their effects on the phenotype and biological properties of lymphoma cells, together with the microenvironmental milieu
- Insights into the genetic landscape of FL have also helped to define the current spectrum of distinct clinic-pathological variants

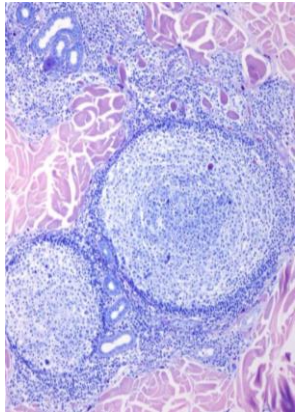


- In situ follicular B-cell neoplasm
- Follicular lymphoma
  - Classic follicular lymphoma
  - FL with unusual cytological features
  - FL with a predominantly diffuse growth pattern
  - Folllicular large B-cell lynphoma
- Pediatric-type follicular lymphoma
- Duodenal-type follicular lymphoma
- Primary cutaneous follicle centre lymphoma



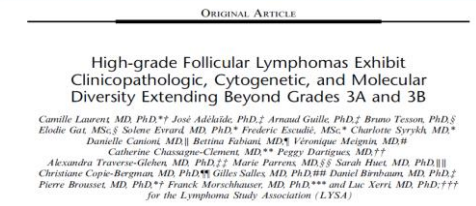
- Follicular lymphoma
- Early lesion of follicular lymphoma
  - In situ follicular lymphoma
  - Duodenal-type follicular lymphoma
- BCL2-rearangement negative, CD23-positive follicle center lymphoma
- Pediatric-type follicular lymphoma
- Testicular follicular lymphoma
- Primary cutaneous follicle centre lymphoma
- Large B-cell lymphoma with IRF4 rearrangement





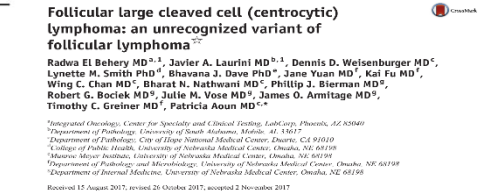
FL with unusual cytological features

- Nodular proliferation of small to medium-sized blasts or large cleaved cells (large centrocytes)
- Higher Ki-67 and IRF4/MUM-1 expression
- Lower frequency of *BCL-2* rearrangements and more *BCL-6* rearrangements
- Less frequent mutations in BCL2, KMT2D, KMT2B, MYC and CREBBP than FL3A.
- *IRF4*-FISH test required for diagnosis in cases strongly expressing IRF4 protein
- Clinical outcome may diverge from cFL but further studies requested to provide a better risk stratification


ORIGINAL ARTICLE

High-grade Follicular Lymphomas Exhibit Clinicopathologic, Cytogenetic, and Molecular Diversity Extending Beyond Grades 3A and 3B

Camille Laurent, MD, PhD,*† José Adélaïde, PhD,‡ Arnaud Guille, PhD,‡ Bruno Texson, PhD,§ Elodie Gat, MSc,§ Solene Evrard, MD, PhD,* Frederic Escudié, MSc,* Charlotte Syrykh, MD,* Danielle Canioni, MD,‖ Bettina Fabiani, MD,¶ Véronique Meignin, MD,# Catherine Chassagne-Clement, MD,** Peggy Dartigues, MD,†† Alexandra Traverse-Glehen, MD, PhD,‡‡ Marie Parrens, MD,§§ Sarah Huet, MD, PhD,‖‖ Christiane Copie-Bergman, MD, PhD,¶¶ Gilles Salles, MD, PhD,## Daniel Birnbaum, MD, PhD,‡ Pierre Brousset, MD, PhD,*† Franck Morschhauser, MD, PhD,*** and Luc Xerri, MD, PhD;††† for the Lymphoma Study Association (LYSA)


Follicular large cleaved cell (centrocytic) lymphoma: an unrecognized variant of follicular lymphoma☆☆

Radwa El Behery MD[a,1], Javier A. Laurini MD[b,1], Dennis D. Weisenburger MD[c], Lynette M. Smith PhD[d], Bhavana J. Dave PhD[e], Jane Yuan MD[f], Kai Fu MD[f], Wing C. Chan MD[c], Bharat N. Nathwani MD[c], Phillip J. Bierman MD[g], Robert G. Bociek MD[g], Julie M. Vose MD[g], James O. Armitage MD[g], Timothy C. Greiner MD[f], Patricia Aoun MD[c,*]

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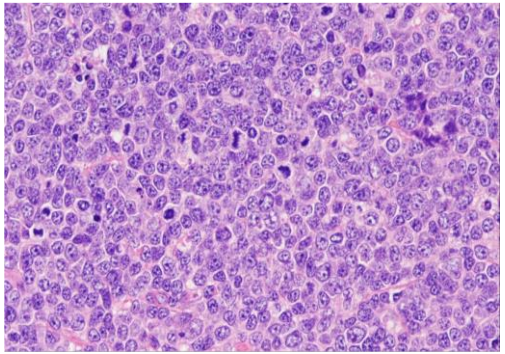
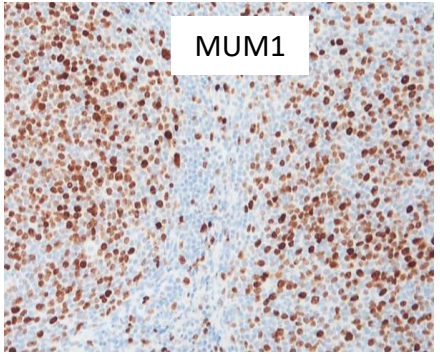
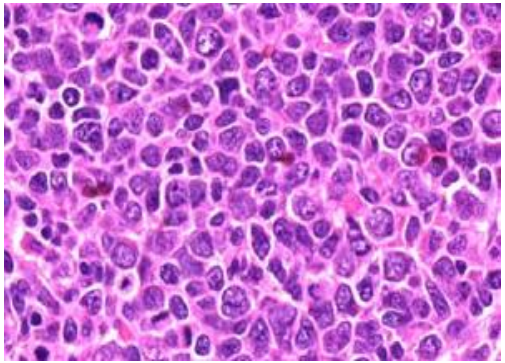
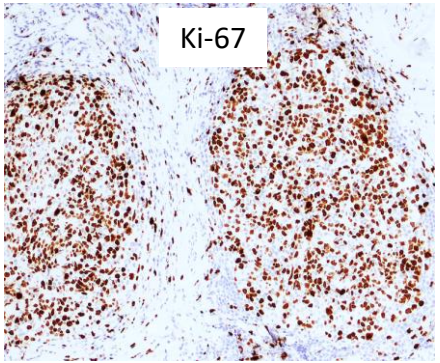


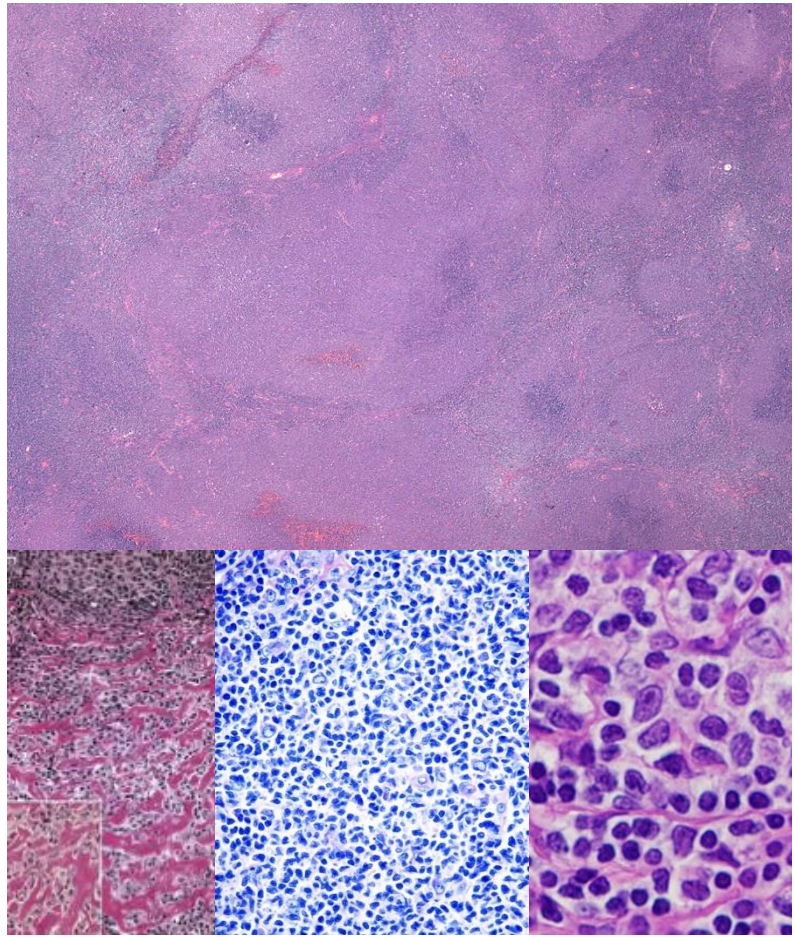




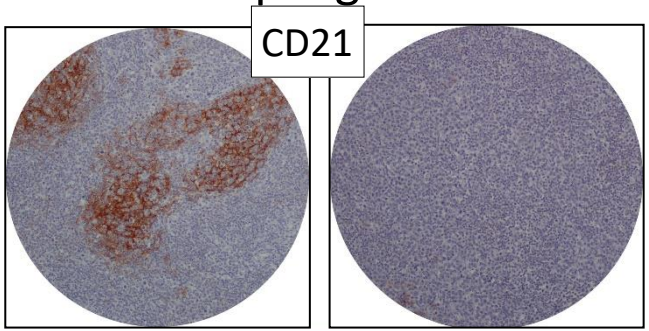


FL with predominantly diffuse growth pattern

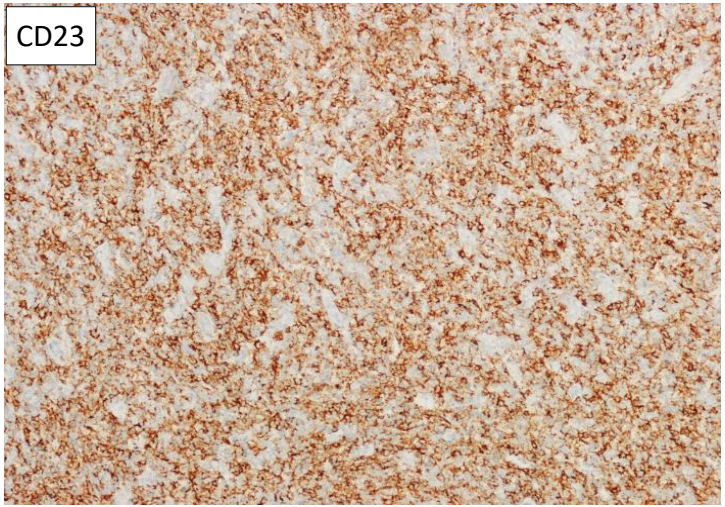
- Mainly inguinal regions, sometimes large tumour masses; often limited stage disease and favourable outcome
- Predominantly diffuse growth pattern; sclerosis and fibrosis may be observed
- Lymphoma cells mainly consist of centrocytes
- D.D. with cFL exhibiting a partially diffuse growth pattern; extensive sampling



- FDCs lacking other than residual microfollicles



- Lymphoma cells usually CD10+ and CD23+, but CD10 may be absent; bcl2 weak to absent
- Absence of *BCL2* and *BCL6* rearrangements
- CNLOH 1p36 (*TNFRSF14*)
- CNLOH 16p13 (*CREBBP, CIITA, SOCS1*)



Modern Pathology (2016) 29, 570–581

Characterization of a variant of t(14;18) negative nodal diffuse follicular lymphoma with CD23 expression, 1p36/*TNFRSF14* abnormalities, and *STAT6* mutations

Imran N Siddiqi[1], Julia Friedman[2], Keegan Q Barry-Holson[1], Charles Ma[2], Venkata Thodima[2], Irene Kang[3], Raghavendra Padmanabhan[2], Lizalynn M Dias[2], Kevin R Kelly[3], Russell K Brynes[1], Sitharthan Kamalakaran[2] and Jane Houldsworth[2]

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STAT6 mutations more frequent than in cFL

A distinctive subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma characterized by a predominantly diffuse growth pattern and deletions in the chromosomal region 1p36

Tiemo Katzenberger,[1] Jörg Kalla,[1] Ellen Leich,[1] Heike Stöcklein,[1,2] Elena Hartmann,[1] Sandra Barnickel,[1] Swen Wessendorf,[3] M. Michaela Ott,[4] Hans Konrad Müller-Hermelink,[1] *Andreas Rosenwald,[1] and *German Ott[1,2]

[1]Department of Pathology, University of Würzburg, Würzburg; [2]Department of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart; [3]Clinic for Internal Medicine III, University Hospital of Ulm, Ulm; and [4]Department of Pathology, Caritas-Krankenhaus, Bad Mergentheim, Germany

ARTICLE Open Access

CREBBP and *STAT6* co-mutation and 16p13 and 1p36 loss define the t(14;18)-negative diffuse variant of follicular lymphoma

Rena R. Xian[1,2,3], Yi Xie[4,5], Lisa M. Haley[1], Raluca Yonescu[1], Aparna Pallavajjala[1], Stefania Pittaluga[4], Elaine S. Jaffe[4], Amy S. Duffield[1,2], Chad M. McCall[1,6], Shereen M. F. Gheith[7] and Christopher D. Gocke[1,2]

STAT6 and lymphomagenesis

- STAT6 mutations are mostly gain-of-function
- Activation of IL-4/JAK/STAT signaling pathway
- IL4 producing TFH cells from the tumour microenvironment are known to sustain the growth of neoplastic B-cells
- The concurrent gain of function of STAT6 and loss of its negative regulator SOCS1 may drive high levels of anti-apoptotic BCL-xL as a surrogate for BCL2 excess
- Frequent CREBBP and CIITA co-deletion/mutation point to a putative immune evasion process

Check for updates

Regular Article

LYMPHOID NEOPLASIA

Activating STAT6 mutations in follicular lymphoma

Mehmet Yildiz,[1] Hongxiu Li,[1] Denzil Bernard,[1] Nisar A. Amin,[1] Peter Ouillette,[1] Siân Jones,[2] Kamlai Saiva-Cork,[1] Brian Parkin,[1] Kathryn Jacobi,[1] Kerby Shedden,[3] Shaomeng Wang,[1]

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Key Points

- FL-associated STAT6 mutations hyperactivate the IL-4/JAK/STAT6 axis.

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Interleukin-4-mediated Protection of Primary B Cells from Apoptosis through Stat6-dependent Up-regulation of Bcl-xL*

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Leukemia (2010) 24, 2080–2089

www.nature.com/leu

ORIGINAL ARTICLE

Follicular lymphoma cell niche: identification of a preeminent IL-4-dependent T_{FH}–B cell axis

C Pangault[1,2,10], P Amé-Thomas[1,2,10], P Ruminy[3], D Rossille[4], G Caron[1,2], M Baia[5,6], J De Vos[7], M Roussel[1], C Monvoisin[2], T Lamy[2,8], H Tilly[3,9], P Gaulard[5,6], K Tarte[1,2,11] and T Fest[1,2,11]

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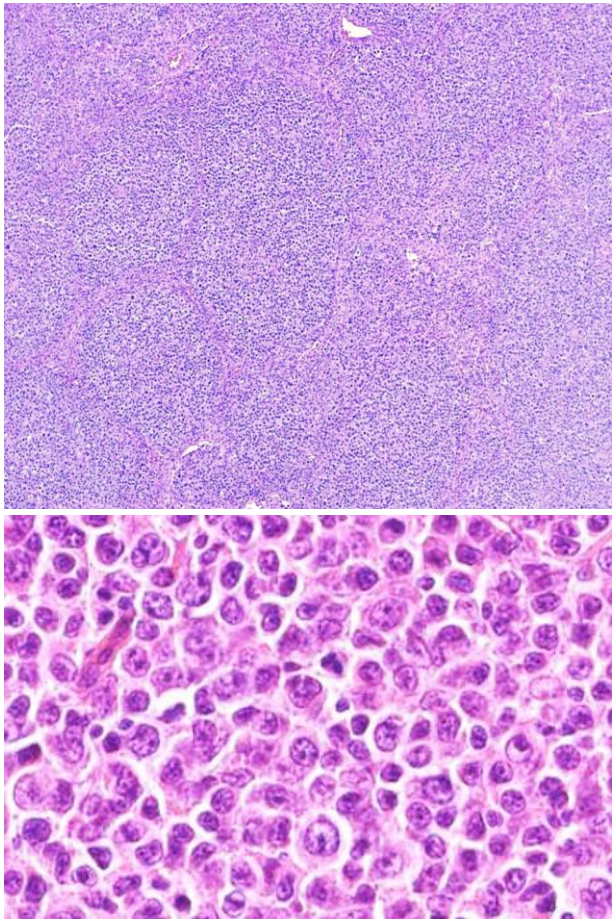
Follicular large B cell lymphoma

- New name of FL grade 3B; close relationship to DLBCL
- Follicles exclusively composed of sheets of centroblasts; no centrocytes
- «Pure» forms are very rare; FLBCL often coexists with DLBCL and rarely with cFL
- DLBCL must be excluded by careful sampling
- Variable positivity for CD10 (40%), BCL6 (50%), BCL-2 (50%) and MUM1 (42-100%)
- MUM1+ cases to be tested for *IRF4* rearrangement to exclude LBCL *IRF4*-R



- BCL2-R in <10% of cases
- BCL6-R (40%) and MYC-R (20%)

ARTICLE - Non-Hodgkin Lymphoma

Follicular lymphoma grade 3B and diffuse large B-cell lymphoma present a histopathological and molecular continuum lacking features of progression/ transformation

Karoline Koch,[1] Julia Richter,[1] Christoph Hänel,[1] Andreas Hüttmann,[2] Ulrich Dührsen[2] and Wolfram Klapper[1]

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ARTICLE
Non-Hodgkin Lymphoma

Gene expression profiling reveals a close relationship between follicular lymphoma grade 3A and 3B, but distinct profiles of follicular lymphoma grade 1 and 2

Heike Horn,[1] Christian Kohler,[2] Raphael Witzig,[3] Markus Kreuz,[4] Ellen Leich,[5] Wolfram Klapper,[6] Michael Hummel,[7] Markus Loeffler,[4] Lorenz Trümper,[8] Rainer Spang,[2] Andreas Rosenwald[9] and German Ott;[1] for the Molecular Mechanisms in Malignant Lymphomas (MMML) Network Project

[1]Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart and University of Tübingen; [2]Statistical Bioinformatics Department, Institute of Functional Genomics,

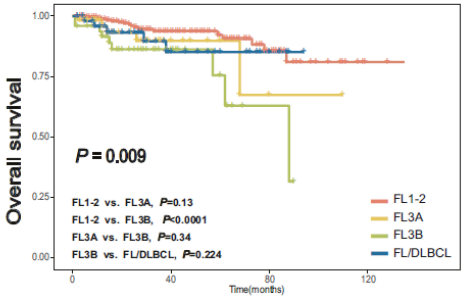
Haematologica 2018
Volume 103(7):1182-1190

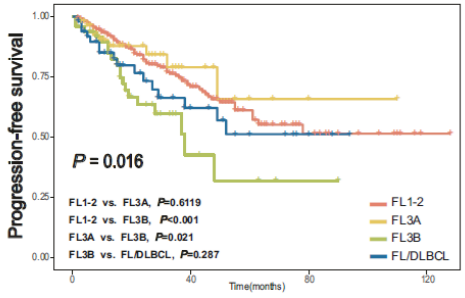
ARTICLE

LYMPHOMA

Molecular landscape of distinct follicular lymphoma histologic grades: insights from genomic and transcriptome analyses

Cong Sun[1,6], Wei Li[1,6], Jingwei Yu[1,6], Tingting Zhang[2,6], Wenchen Gong[3,6], Hengqi Liu[1,6], Fenghua Gao[1,4], Zheng Song[1], Lanfang Li[1], Lihua Qiu[1], Zhengzi Qian[1], Shiyong Zhou[1], Bin Meng[3], Yanan Gao[3], Junzhi Li[3], Xia Liu[1], Weicheng Ren[5] ✉, Qiang Pan-Hammarström[5] ✉, Xianhuo Wang[1] ✉ and Huilai Zhang[1] ✉





- FL1-2 and FL3A share a common genetic background
- FL3B and FL/DLBCL lack mutations in epigenetic regulators CREBBP and KMT2D but exhibit additional CNVs, such as 1p36.32 losses and 3p21.1 gains, which are linked to poor prognosis

- Upregulation of MYC, IRF4 and BATF expression associated with increase of the activity of metabolic and cell cycles pathways

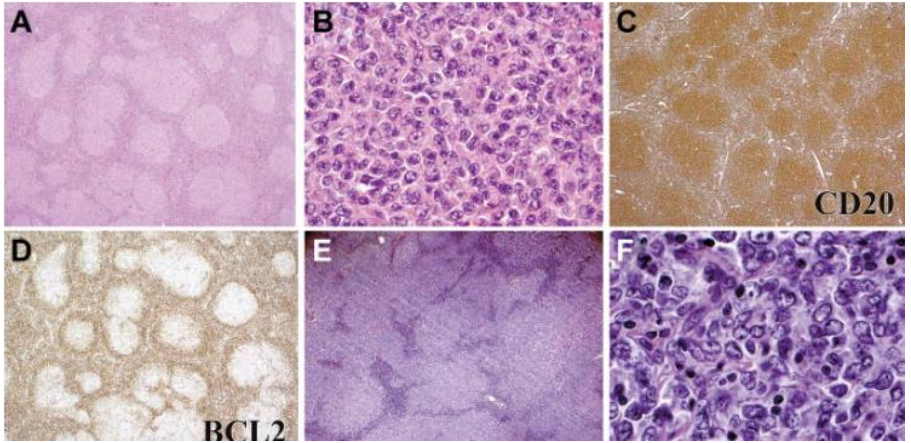
Paediatric type follicular lymphoma

- Localized, nodal B-cell lymphoma occurring primarily in pediatric, adolescent and young adult patients; 1-2% of all childhood NHL; M>F
- Single enlarged lymph node in head and neck region; Waldeyer ring
- Clonal proliferation of GC B-cells with a purely follicular growth pattern, a high proliferation index and absence of BCL2, BCL6 and IRF4 rearrangements
- Enlarged follicles (floral, serpiginous or confluent); mantle zone attenuated or absent; lack of zonation but tingible body macrophages; variable MZ differentiation
- Medium-sized to large blastoid cells
- CD10 and BCl6+, BCL2-, MUM1-, FOXP1+

CLINICAL TRIALS AND OBSERVATIONS

Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no *BCL2* rearrangement

Abner Louissaint Jr,[1] Adam M. Ackerman,[1] Dora Dias-Santagata,[1] Judith A. Ferry,[1] Ephraim P. Hochberg,[2] Mary S. Huang,[2] A. John Iafrate,[1] Daniel O. Lara,[1] Geraldine S. Pinkus,[3] Itziar Salaverria,[4] Zakir Siddiquee,[1] Reiner Siebert,[4] Howard J. Weinstein,[2] Lawrence R. Zukerberg,[1] Nancy Lee Harris,[1] and Robert P. Hasserjian[1]

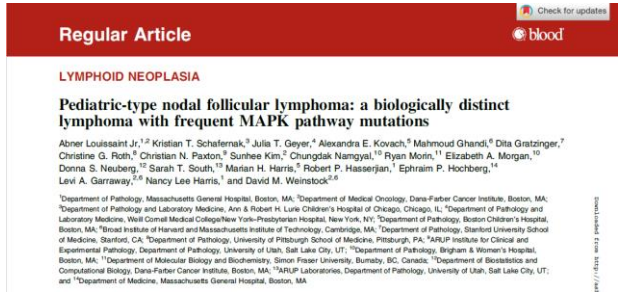


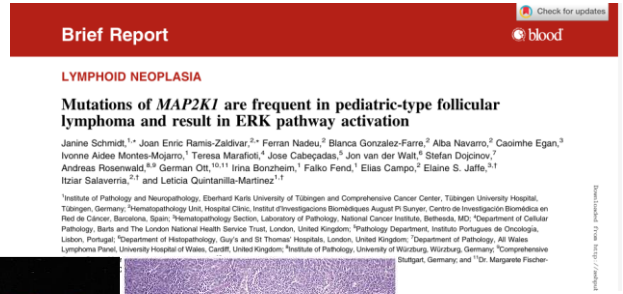
- Invariably excellent prognosis; watch and wait after complete excixson

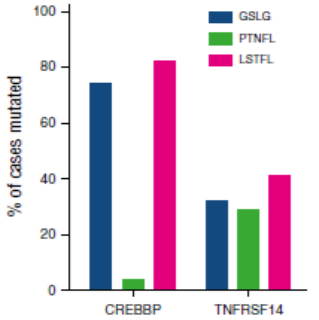
Novel markers in pediatric-type follicular lymphoma

Claudio Agostinelli[1] · Ayse U Akarca[2] · Alan Ramsay[3] · Hasan Rizvi[4] · Manuel Rodriguez-Justo[2,3] · Sabine Pomplun[3] · Ian Proctor[3] · Elena Sabattini[1] · David Linch[5] · Stephen Daw[6] · Stefania Pittaluga[7] · Stefano A Pileri[8] · Elaine S Jaffe[7] · Leticia Quintanilla-Martinez[9] · Teresa Marafioti[2,3]

- Clonal IG gene rearrangement
- BCL2, BCL6, IRF4 and MYC rearrangements absent by definitiom
- Epigenetic modifier genes (*EP300, CREBPP, EZH2, KMT2D, ARID1A*) rarely mutated
- Recurrent deletions and CNLOH at 1p36 (*TNFRSF14*; 25-40%)
- Mutations of *TNFRSF14* (44-54%) *MAP2K1* (43-49%) and *IRF8* (15%)


Regular Article
blood
LYMPHOID NEOPLASIA
Pediatric-type nodal follicular lymphoma: a biologically distinct lymphoma with frequent MAPK pathway mutations


Brief Report
blood
LYMPHOID NEOPLASIA
Mutations of *MAP2K1* are frequent in pediatric-type follicular lymphoma and result in ERK pathway activation



Key Points

- *TNFRSF14* and *MAP2K1* mutations are frequent in PTFL but do not occur together in the majority of cases.
- *MAP2K1* mutations lead to activation of the downstream target phosphorylated extracellular signal-regulated kinase.

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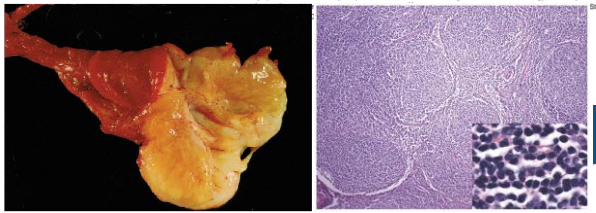
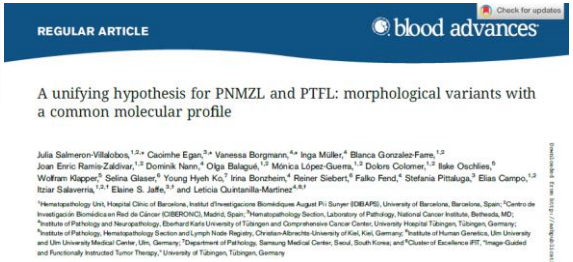
ORIGINAL ARTICLE

Primary follicular lymphoma of the testis in childhood: an entity with peculiar clinical and molecular characteristics

S A Pileri, E Sabattini, P Rosito, P L Zinzani, S Ascani, G Fraternali-Orcioni, B Gamberi, M Piccioli, D Vivenza, B Falini, G Gaidano

J Clin Pathol 2002;**55**:684–688

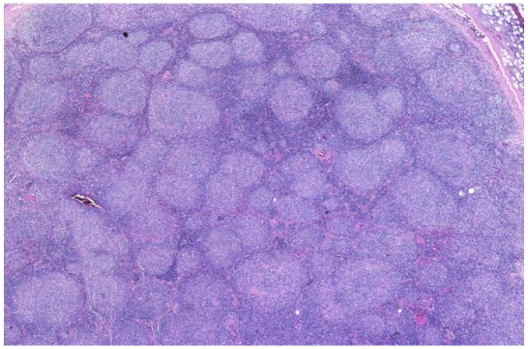


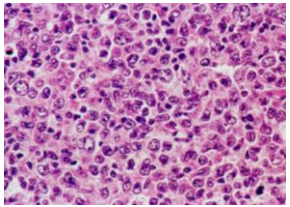

REGULAR ARTICLE
blood advances
A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile

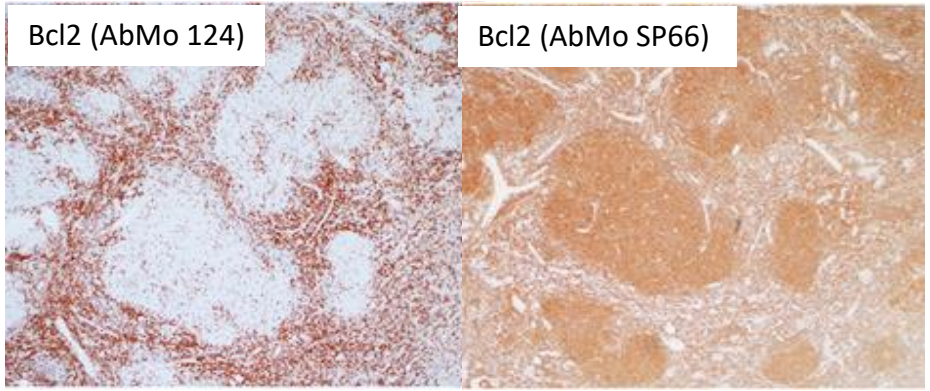
- Similarities with primary FL of the testis (children or adolescents, localized disease, intermediate to large cell cytology, immunophenotype, mutational landscape)

Conventional nodal FL without BCL2 rearrangement

- BCL2 IHC is not a perfect surrogate for t(14;18)
- BCL2 expressed in a subset of BCL2-uR FL
- Lack of BCL2 expression in some BCL2-R FL due to mutations altering antibody binding







REGULAR ARTICLE

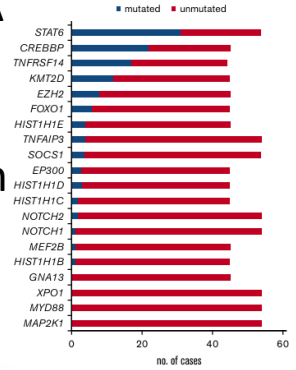
blood advances

Follicular lymphoma t(14;18)-negative is genetically a heterogeneous disease

Dominik Nann,[1,*] Joan Enric Ramis-Zaldivar,[2,3,*] Inga Müller,[1] Blanca Gonzalez-Farre,[2,3] Janine Schmidt,[1] Caoimhe Egan,[4] Julia Salmeron-Villalobos,[2,3] Guillem Clot,[2,3] Sven Mattern,[1] Franziska Otto,[1] Barbara Mankel,[1] Dolors Colomer,[2,3] Olga Balagué,[2,3] Vanessa Szablewski,[5] Carmen Lome-Maldonado,[6] Lorenzo Leoncini,[7] Stefan Dojcinov,[8] Andreas Chott,[9] Christiane Copie-Bergman,[10] Irina Bonzheim,[1] Falko Fend,[1] Elaine S. Jaffe,[4] Elias Campo,[2,3] Itziar Salaverria,[2,3,†] and Leticia Quintanilla-Martinez[1,†]

[1]Institute of Pathology and Neuropathology, Eberhard Karls University of Tübingen–Comprehensive Cancer Center, University Hospital Tübingen, Tübingen, Germany; [2]Hematopathology Unit, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain; [4]Hematopathology Section, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD; [5]Department of Pathology, Montpellier University Hospital, Montpellier, France; [6]Department of Pathology, Instituto Nacional de Cancerología, Mexico City, Mexico; [7]Section of Pathology, Department of Medical Biotechnology, University of Siena, Siena, Italy; [8]Department of Pathology, All Wales Lymphoma Panel, University Hospital of Wales, Cardiff, United Kingdom; [9]Institute of Pathology and Microbiology, Wilhelminenspital, Vienna, Austria; and [10]Department of Pathology, Henri Mondor Hospital, Assistance Publique–Hôpitaux de Paris, INSERM U955, Université Paris Est, Créteil, France

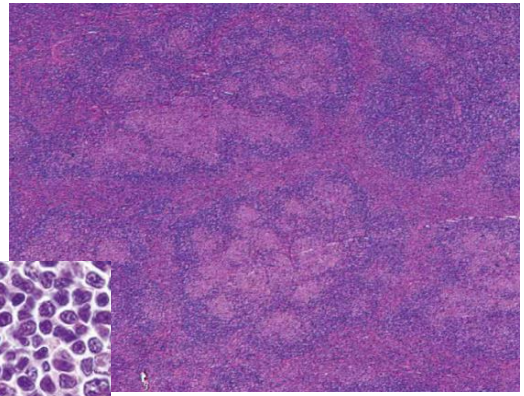
- Usually follicular growth pattern, grade 1-2 and 3A
- Nodal BCL2-R negative FL with BCL6-R (20%)
  - BCL6-R (3q27) with different partners; BCL6 upregulation, blocking terminal differentiation and promoting neoplastic transformation
- Nodal BCL2-R negative FL without BCL6-R
  - More advanced clinical stage; lack STAT mut

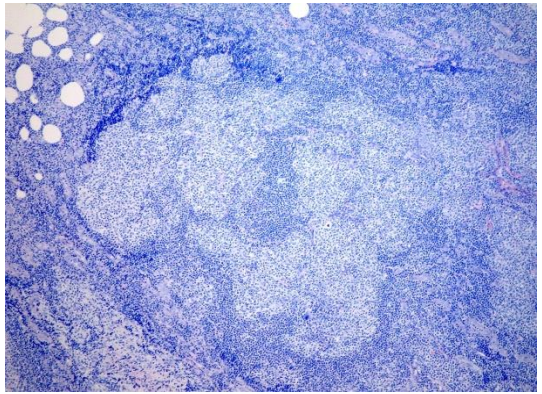


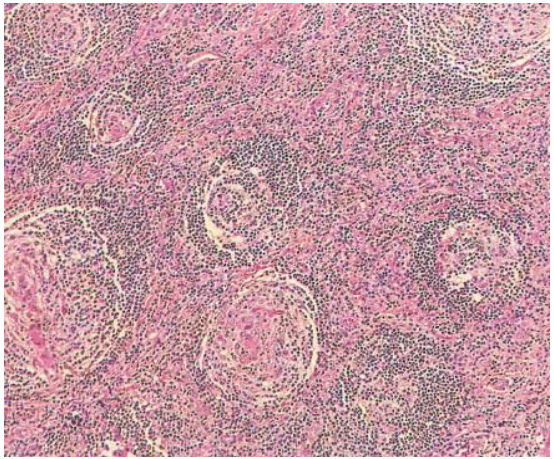
FL: other unusual features

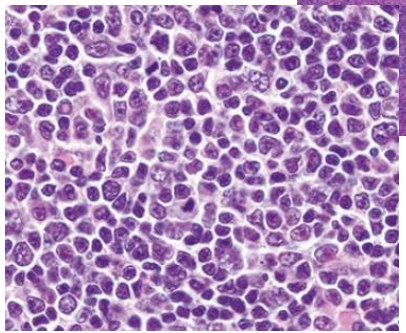
In addition to WHO established variants of FL, other unusual FLs may be encounterd in haematopahtology practice

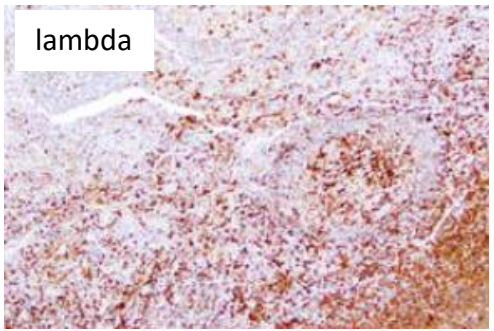
- FL with Castleman-like changes
- FL with Marginal zone differentiation
- FL with plasmacytic differentiation
  - Intrafollicular vs interfollicular PCD











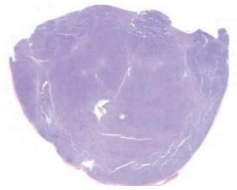
ARTICLE

Histopathologic, immunophenotypic, and mutational landscape of follicular lymphomas with plasmacytic differentiation

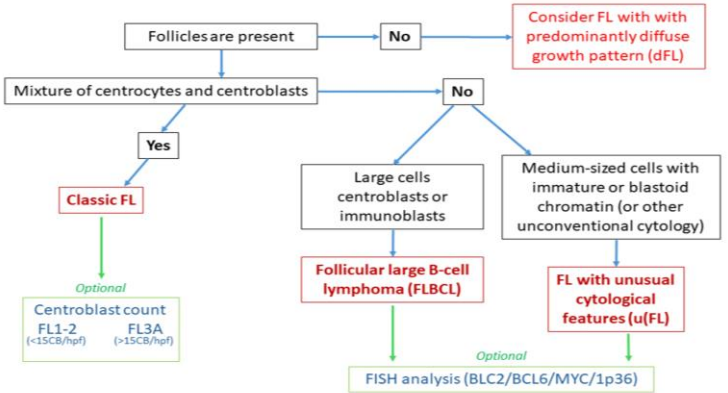
Sarah E. Gibson[1,2,3✉], Yen-Chun Liu[2,3,4], Svetlana A. Yatsenko[2,3], Nicholas J. Barasch[3,5] and Steven H. Swerdlow[2,3]

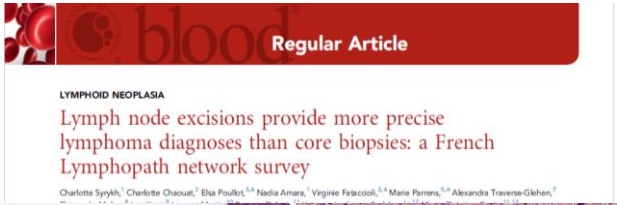
Nodal FL variants: diagnostic issues

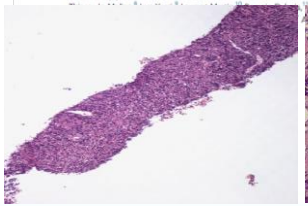
- Diagnosis of atypical variants of FL is challenging due to histopathologic overlap with reactive conditions and/or other B-cell NHL
- Definitive diagnosis of d-FL, LBCFL, PT-FL requires assessment of the whole lesional architecture
- MUM1+ (strong) cases with medium-sized to large cell cytology, GC phenotype and/or only partial nodular pattern require to exclude LBCL with IRF4-R
- Often a battery of additional FISH and NGS tests is needed
- Core biopsies usually not suitable for such diagnoses

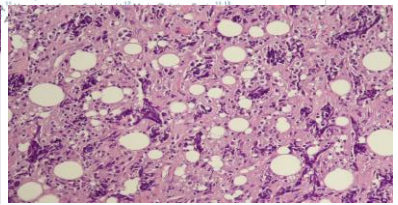


WHO 2024 FL alghorithm



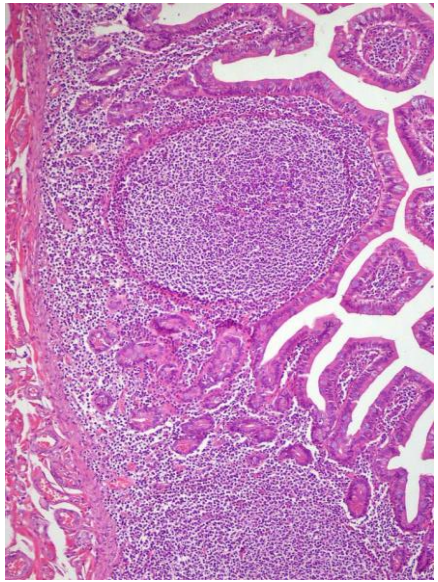
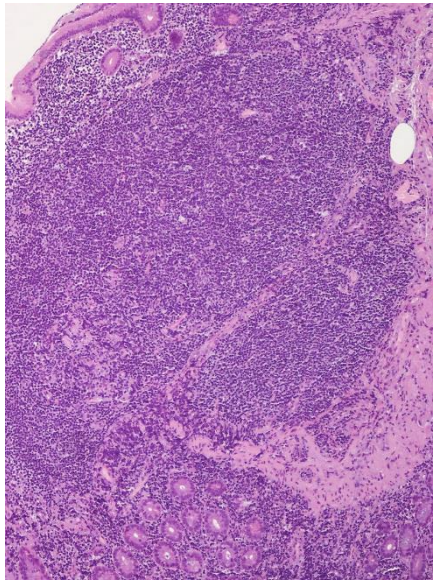
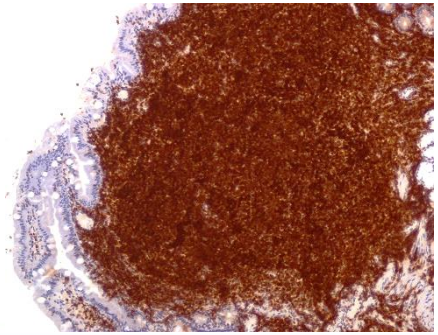
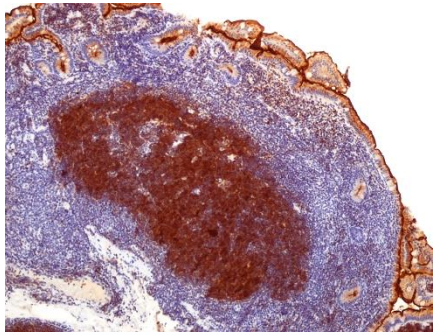






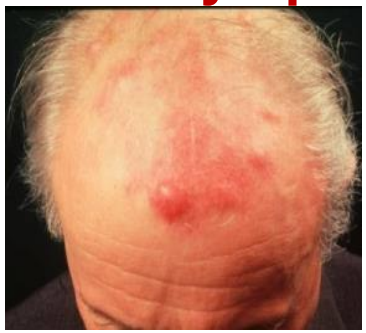
Duodenal-type FL

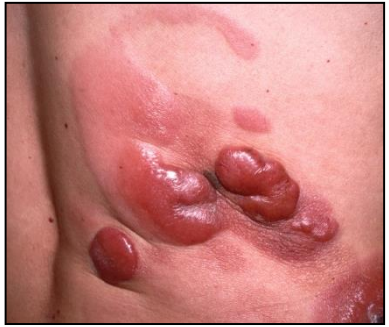
- Rare, 4% of all gastrointestinal lymphoma
- Small intestine, especially duodenum; rarely stomach, colon and rectum
- Neoplastic follicular proliferation in the mucosae/ submucosae of centrocyte-like cells harboring t(14;18)
- Usually an incidental finding; localized disease (stage IE or IIE) and a low risk of progression to systemic FL
- Mutational profile similar to cFL, with a lower genomic complexity, reminiscent of ISFN
- Decreased expression of AID; biased usage of IGVH4 and IGVH5, suggesting a role of antigen chronic stimulation
- GEP in DTFL has been found to be close to extranodal MZL of MALT

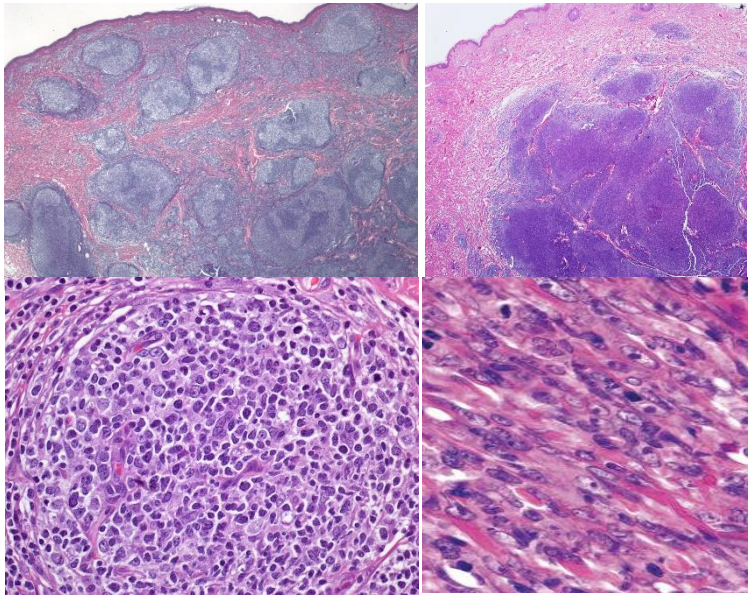





Primary cutaneous follicle center lymphoma

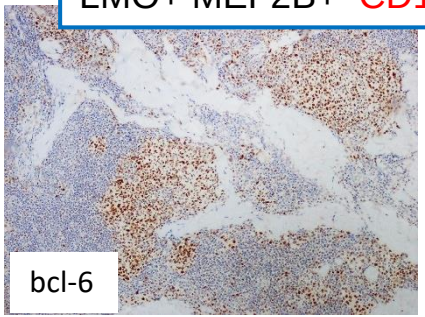
- Usually on the head and neck or trunk; erythematous to violaceous plaques, nodules or tumors
- Centrocytes and variable number of centroblasts; follicular, follicular and diffuse, or diffuse pattern

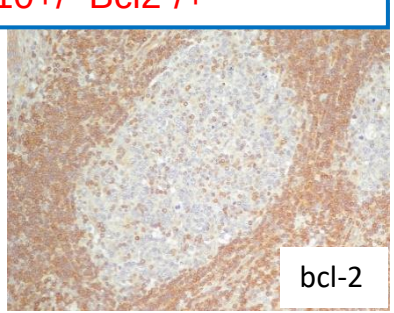






Immunophenotype: CD20+ CD79a+ Bcl6+ LMO+ MEF2B+ CD10+/- Bcl2-/+



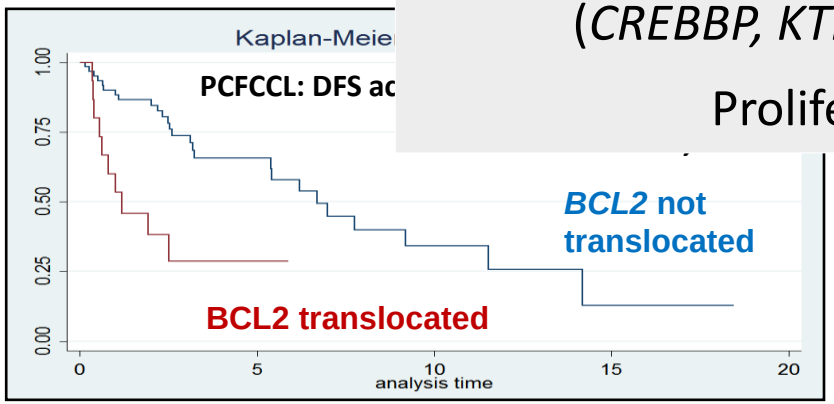


Excellent prognosis (>95% at 5 years), less favourable on the leg; relapses (30%), often close to the initial site

- Clonally rarranged, somaticaly hypermutated IGHV genes
- BCL2 rearrangement in a minority of cases; risk for possible subsequent systemic disease?

PCFCL and F

	BCL2 Expression
PCFCCL	43/107 (40%



Putative markers for higher risk of spread ?

Bcl2 rearrangement

Chromatin-modifying gene mutations

(*CREBBP, KTM2D, EZH2, EP300*)

Proliferation index

REGULAR ARTICLE

blood advances

Genomic landscape of cutaneous follicular lymphomas reveals 2 subgroups with clinically predictive molecular features

Xiaolong Alan Zhou, Jingyi Yang, Kimberly G. Ringbloom, Maria Estela Martinez-Escala, Kristen E. Stevenson, Alexander T. Wenzel, Damiano Fantini, Haley K. Martin, Andrea P. Moy, Elizabeth A. Morgan, Shannon Harkins, Christian N. Paxton, Bo Hong, Erica F. Andersen, Joan Guitart, David M. Weinstock, Lorenzo Cerroni, Jaehyuk Choi, and Abner Louissaint Jr.

Human PATHOLOGY

Original contribution

The molecular landscape and other distinctive features of primary cutaneous follicle center lymphoma

Nicholas J.K. Barasch MD, Yen-Chun Liu MD, PhD, Jonhan Ho MD, Nathanael Bailey MD, Nidhi Aggarwal MD, James R. Cook MD, PhD, Steven H. Swerdlow MD

%), *KTM2D* (21%),
than in classic FL
s in *TNFAIP3*
nd *TNFRSF14*
vel expression of

Concomitant 1p36 deletion and *TNFRSF14* mutations in primary cutaneous follicle center lymphoma frequently expressing high levels of EZH2 protein

Ambrus Gángó · Bence Bátai · Martin Varga · Dóra Kapczár · Gergő Papp · Márta Marschalkó · Enikő Kuroli · Tamás Schneider · Judit Csomor · András Matolcsy · Csaba Bödör · Ágota Szepesi

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Other extranodal FL presenting with localized disease

FL of the lower female genital tract (uterine cervix and vagina)

- Low stage disease without systemic involvement and excellent prognosis
- Lacking of *BCL2*-R, frequent *TNFRSF14* mutations; no chromatin-modifying genes mutations

ORIGINAL ARTICLE

Follicle Center Lymphoma (FCL) of the Lower Female Genital Tract (LFGT)

A Novel Variant of Primary Cutaneous Follicle Center Lymphoma (PCFCL)

Annapurna Saksena, MD, Ashish Jain, PhD,†‡ Svetlana D. Pack, PhD,* Jung Kim, PhD,* Ina Lee, MD, PhD,* Manoj Tyagi, PhD,* Liqiang Xi, MD,* Stefania Pittaluga, MD, PhD,* Mark Raffeld, MD,* and Elaine S. Jaffe, MD**

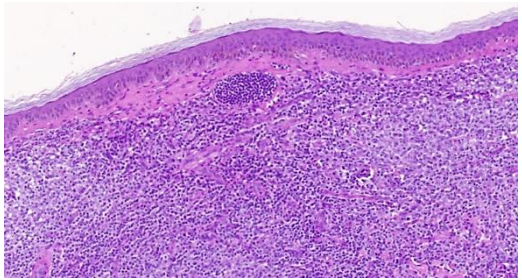
LEUKEMIA & LYMPHOMA
2024, VOL. 65, NO. 12, 1909–1912
https://doi.org/10.1080/10428194.2024.2381014
Taylor & Francis

LETTER TO THE EDITOR

Follicular lymphoma of the lower female genital tract: an indolent and localized extranodal follicular lymphoma with mutation of *TNFRSF14*

Luana Santos Louro[a], Yiannis Dimopoulos[a], Vasiliki Leventaki and Francisco Vega

Department of Hematopathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA



Primary thyroid FL

Primary splenic FL

- Less likely to have the classic IGH-BCL2 fusion and the associated chromosomal 14;18 translocation
- Higher proliferation index and histologic grade

ORIGINAL ARTICLE

Splenic Follicular Lymphoma

Clinicopathologic Characteristics of a Series of 32 Cases

Manuela Mollejo, MD, María S. Rodríguez-Pinilla, MD,† Santiago Montes-Moreno, MD,† Patrocinio Algara, PhD,§ Ahmet Dogan, MD,‡ Juan C. Cigudosa, MD,‖ Rocío Juarez, MD,* Teresa Flores, MD,¶ Jerónimo Forteza, MD,# Alberto Arribas, PhD,** and Miguel A. Piris, MD†*

IGH/BCL2 Status Better Predicts Clinico-Pathological Behavior in Primary Splenic Follicular Lymphoma than Histological Grade and Other Molecular Markers

Cherian Verghese[1], Weihong Li[2], Nanuli Gvazava[3], Emmanouil Alimpertis[4], Navkirat Kahlon[5], Hongliu Sun[6] and Robert Booth[7]

Clinical Pathology
Volume 15: 1–5
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DOI: 10.1177/2632010X22112924
SAGE

Absence of epigenetic modifier alterations in the *BCL2*-uR variant compared with cFL

Histopathology

Histopathology 2021, 79, 521–532. DOI: 10.1111/his.14378

Bcl-2-negative *IGH-BCL2* translocation-negative follicular lymphoma of the thyroid differs genetically and epigenetically from Bcl-2-positive *IGH-BCL2* translocation-positive follicular lymphoma

Yuichiro Hamamoto,[1,2] Yoji Kukita,[3] Masanori Kitamura,[1] Masako Kurashige,[2] Hiroaki Masaie,[4] Shigeo Fuji,[4] Jun Ishikawa,[4] Keiichiro Honma,[1] Tomoko Wakasa,[5] Hitoshi Hanamoto,[6] Mitsuyoshi Hirokawa,[7] Ayana Suzuki,[7] Eiichi Morii[2] & Shin-ichi Nakatsuka[8]

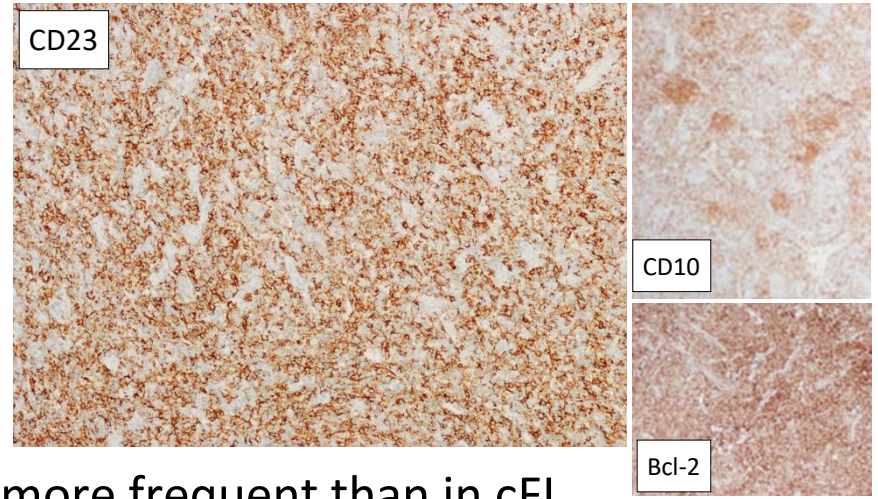
To take home messages

- The vast increase in genetic and molecular data FL within the last decade contributed to our ability of relating distinctive histomorphologic features with the underlying biology of FL.
- In contrast to cFL with *BCL2*-R, cases lacking *BCL2*-R are very heterogenous, including multiple distinct subtypes, whose identification is crucial due to their distinct treatment approach and prognosis
- The diagnostic criteria of these alternative forms of FL are based on specific anatomical sites of involvement, peculiar cytologic or morphologic features including growth pattern, the absence of t(14;18) with weak or negative expression of BCL2 staining, and a different frequency of genetic alterations compared with conventional FL
- While most cases of cFL are readily diagnosed with routine morphology and an appropriate panel of IHC stains, the diagnosis of FL variants may be challenging and require excisional biopsy and molecular studies, including FISH for *BCL2*-R and/or NGS.

Acknowledgments

» Dott.sa Erica Travaglino - Dott.sa Francesca Antoci - Dott Giuseppe Neri - Dott. Edoardo D'Este- Dott.sa Giuseppina Ferrario - Dott.sa Roberta Riboni - Dott.sa Emanuela Boveri Anatomic Pathology
» Dott.sa Roberta Sciarra - Prof. Luca Arcaini Hematology
» Dott.sa Valeria Brazzelli - Dermatology
» Prof. Marco Paulli – Director of Anatomic Pathology

- Lymphoma cells usually CD10+ and CD23+, but CD10 may be absent; bcl2 weak/absent
- Absence of *BCL2* and *BCL6* rearrangements
- CNLOH 1p36 (*TNFRSF14*)
- CNLOH 16p13 (*CREBBP, CIITA, SOCS1*)



Modern Pathology (2016) 29, 578–581

Characterization of a variant of t(14;18) negative nodal diffuse follicular lymphoma with CD23 expression, 1p36/*TNFRSF14* abnormalities, and *STAT6* mutations

Imran N Siddiqi[1], Julia Friedman[2], Keegan Q Barry-Holson[1], Charles Ma[2], Venkata Thodima[2], Irene Kang[3], Raghavendra Padmanabhan[2], Lizalynn M Dias[2], Kevin R Kelly[3], Russell K Brynes[1], Sitharthan Kamalakaran[2] and Jane Houldsworth[2]

[1]*Department of Pathology, Hematopathology Section, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA;* [2]*Cancer Genetics, Inc., Rutherford, NJ, USA and* [3]*Department of Medicine, Division of Hematology, University of Southern California, Los Angeles, CA. USA*

- STAT 6 mutations more frequent than in cFL
- Activation of JAK/STAT signaling pathway
- Upregulation of anti-apoptotic BCL-xL (surrogate for BCL2)

A distinctive subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma characterized by a predominantly diffuse growth pattern and deletions in the chromosomal region 1p36

Tiemo Katzenberger,[1] Jörg Kalla,[1] Ellen Leich,[1] Heike Stöcklein,[1,2] Elena Hartmann,[1] Sandra Barnickel,[1] Swen Wessendorf,[3] M. Michaela Ott,[4] Hans Konrad Müller-Hermelink,[1] *Andreas Rosenwald,[1] and *German Ott[1,2]

[1]Department of Pathology, University of Würzburg, Würzburg; [2]Department of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart; [3]Clinic for Internal Medicine III, University Hospital of Ulm, Ulm; and [4]Department of Pathology, Caritas-Krankenhaus, Bad Mergentheim, Germany

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CREBBP and *STAT6* co-mutation and 16p13 and 1p36 loss define the t(14;18)-negative diffuse variant of follicular lymphoma

Rena R. Xian[1,2,3], Yi Xie[4,5], Lisa M. Haley[1], Raluca Yonescu[1], Aparna Pallavajjala[1], Stefania Pittaluga[4], Elaine S. Jaffe[4], Amy S. Duffield[1,2], Chad M. McCall[1,6], Shereen M. F. Gheith[7] and Christopher D. Gocke[1,2]

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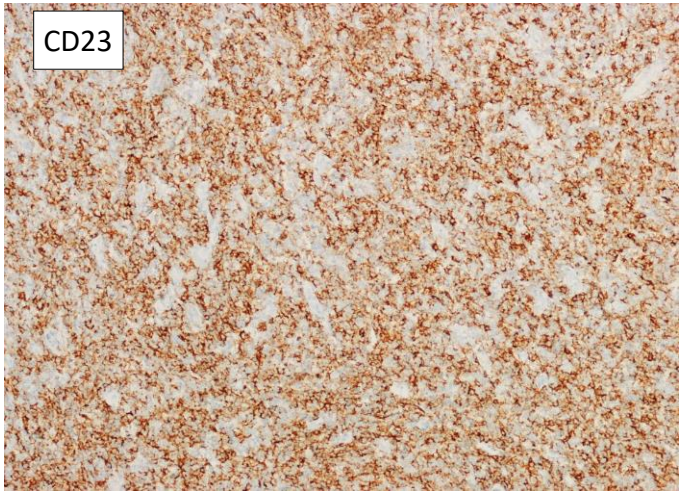

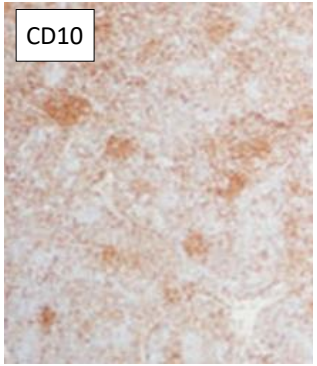

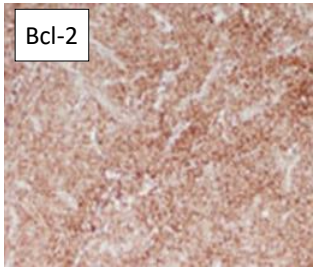

STAT 6 mutations more frequent than in cFL

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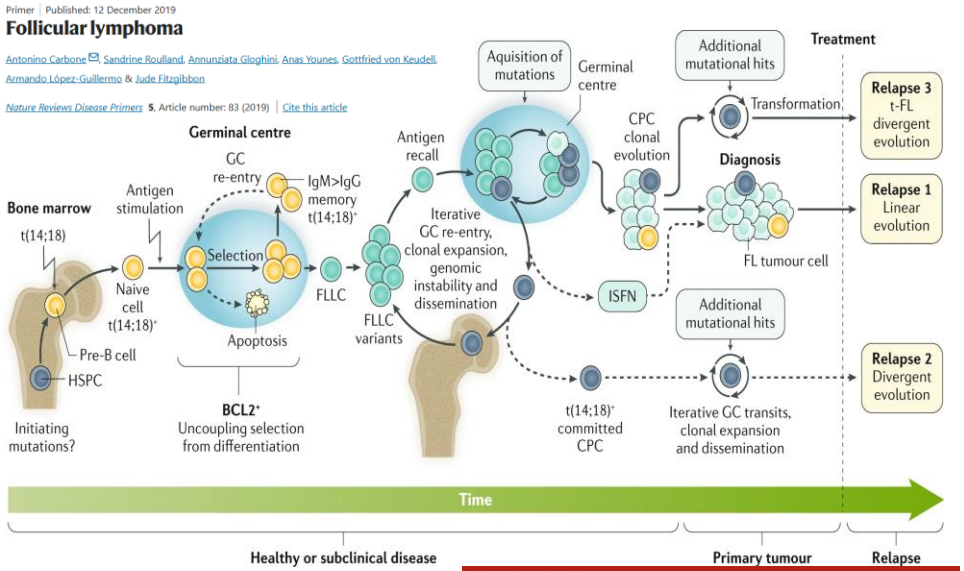
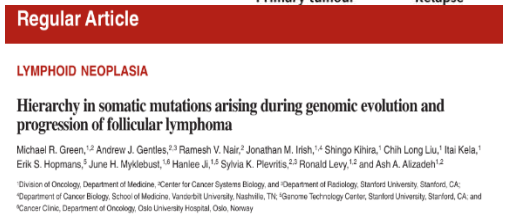
- t (14,18)(q32;q21) is the initiating event in 85-90% of cFL. It arises from a V(D)J recombination error in a BM pre-B cell; rare t variants involve IGL instead of IGH

- Differentiated t(14;18) + memory-like B-cell clones can be found in PB at very low levels in > 70% of healthy adults most of whom, however, never develop FL
- Although linear clonal evolution has been reported, most FL follow a branching evolution.
- Multiple sub-clones can be identified in early disease phases, providing the substrate for progression/transformation «via» a series of mutational events.




Regular Article

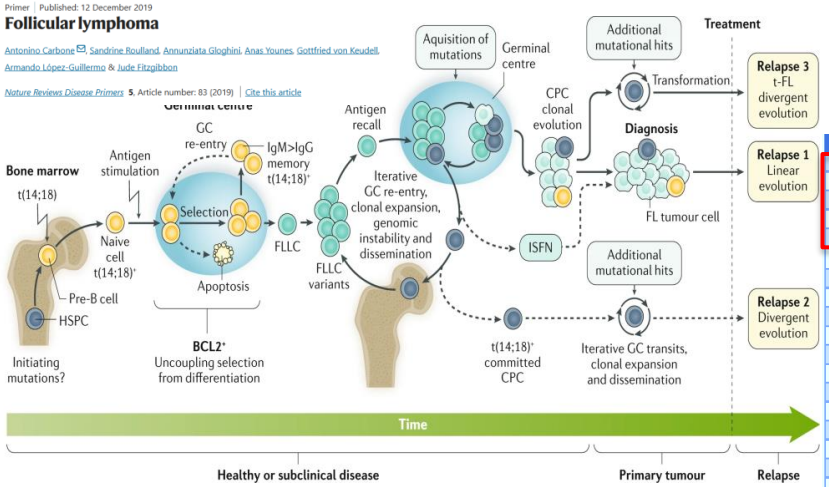
LYMPHOID NEOPLASIA

Hierarchy in somatic mutations arising during genomic evolution and progression of follicular lymphoma

Michael R. Green,[1,2] Andrew J. Gentles,[2,3] Ramesh V. Nair,[2] Jonathan M. Irish,[1,4] Shingo Kihira,[1] Chih Long Liu,[1] Itai Kela,[1] Erik S. Hopmans,[5] June H. Myklebust,[1,6] Hanlee Ji,[1,5] Sylvia K. Plevritis,[2,3] Ronald Levy,[1,2] and Ash A. Alizadeh[1,2]

[1]Division of Oncology, Department of Medicine, [2]Center for Cancer Systems Biology, and [3]Department of Radiology, Stanford University, Stanford, CA; [4]Department of Cancer Biology, School of Medicine, Vanderbilt University, Nashville, TN; [5]Genome Technology Center, Stanford University, Stanford, CA; and [6]Cancer Clinic, Department of Oncology, Oslo University Hospital, Oslo, Norway

- t (14,18)(q32;q21) is the initiating event in 85-90% of cFL; V(D)J recombination error in a BM pre-B cell; rare t variants involve IGL instead of IGH; differentiated t(14;18)+ memory-like B-cells clones in >70% of healthy adults
- t(14;18)+ cells accumulate within nodal GCs as centrocytes with a low proliferation rate and propensity to re-enter the GC with iterative cycles of GC reaction, increasing the risk of accumulation of genomic alterations



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Most frequent gene alterations in BCL2-rearranged FL at diagnosis

Gene	Frequency of alterations (%)[a]	Predominant type of alteration
KMT2D (MLL2)	50-70%	Mutations
CREBBP	50-70%	Mutations (~60%), deletions
EPHA7	70%	Deletion, methylation
TNFRSF14	45-65%	Deletions, mutations (~30%)
BCL2	~50%	Mutations
SESTRIN1	30-40%	Deletions
CDK4	~30%	Gains
EZH2	20-40%	Mutations (~20%), gains
HIST1H1B-E	15-30%	Mutations
CTSS	15-20%	Mutations (~5%), amplifications
BCL6	~15%	Translocation, mutation (~5%)
FOXO1	10-15%	Mutations
STAT6	10-15%	Mutations
ARID1A	10-15%	Mutations
EP300	10-15%	Mutations
CARD11	10-15%	Mutations
MEF2B	10-15%	Mutations
ATP6V1B2	~10%	Mutations
ATP6AP1	~10%	Mutations
GNA13	~10%	Mutations
RB1	~10%	Deletions, mutations (<5%)
SOCS1	~10%	Mutations
RRAGC	5-15%	Mutations
IRF8	5-15%	Mutations
POU2F2	5-10%	Mutations
SGK1	5-10%	Mutations
CDKN2A/B	5-10%	Deletion
TNFAIP3	5-10%	Deletion, mutation (<5%)
HVCN1	5-10%	Mutations
EBF1	5-10%	Mutations
TP53	~5%	Mutation, deletion
CD79B	~5%	Mutations
FAS	<5%	Mutations