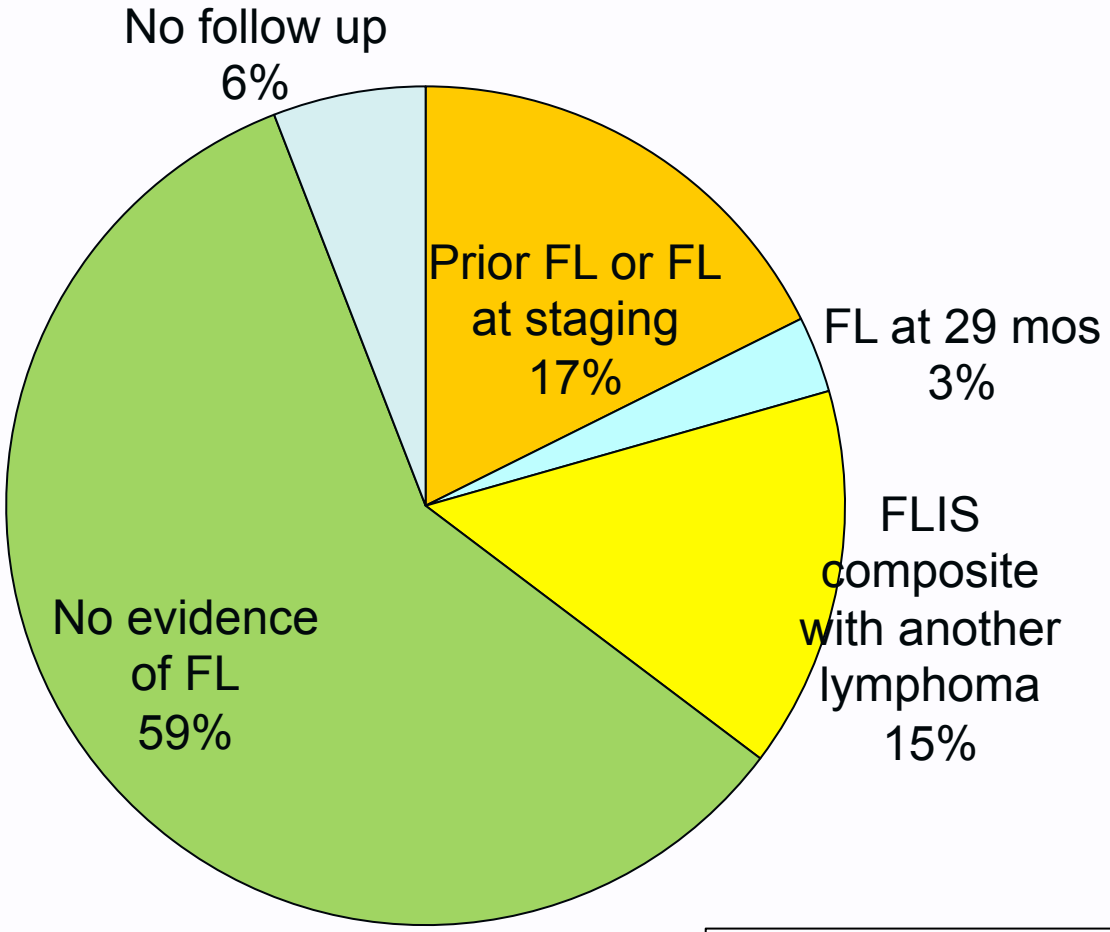
BCL2/IGH in Healthy Individuals

(Limpens et al. 1991; Roulland et al. 2006)

- *BCL2/IGH* is found in peripheral blood of up to 70% of normal adults over age 50
  - Numbers increase with age
  - Numbers increase with pesticide use in farmers
- *BCL2/IGH* + B-cells are *not* naïve B-cells
  - Memory B-cells, Class switched
  - Have encountered the germinal center reaction
  - Prone to intense trafficking among germinal centers
- Rare cases of FLIS & FL-like B-cells in same pt (Cheung et al. Leukemia 2009)

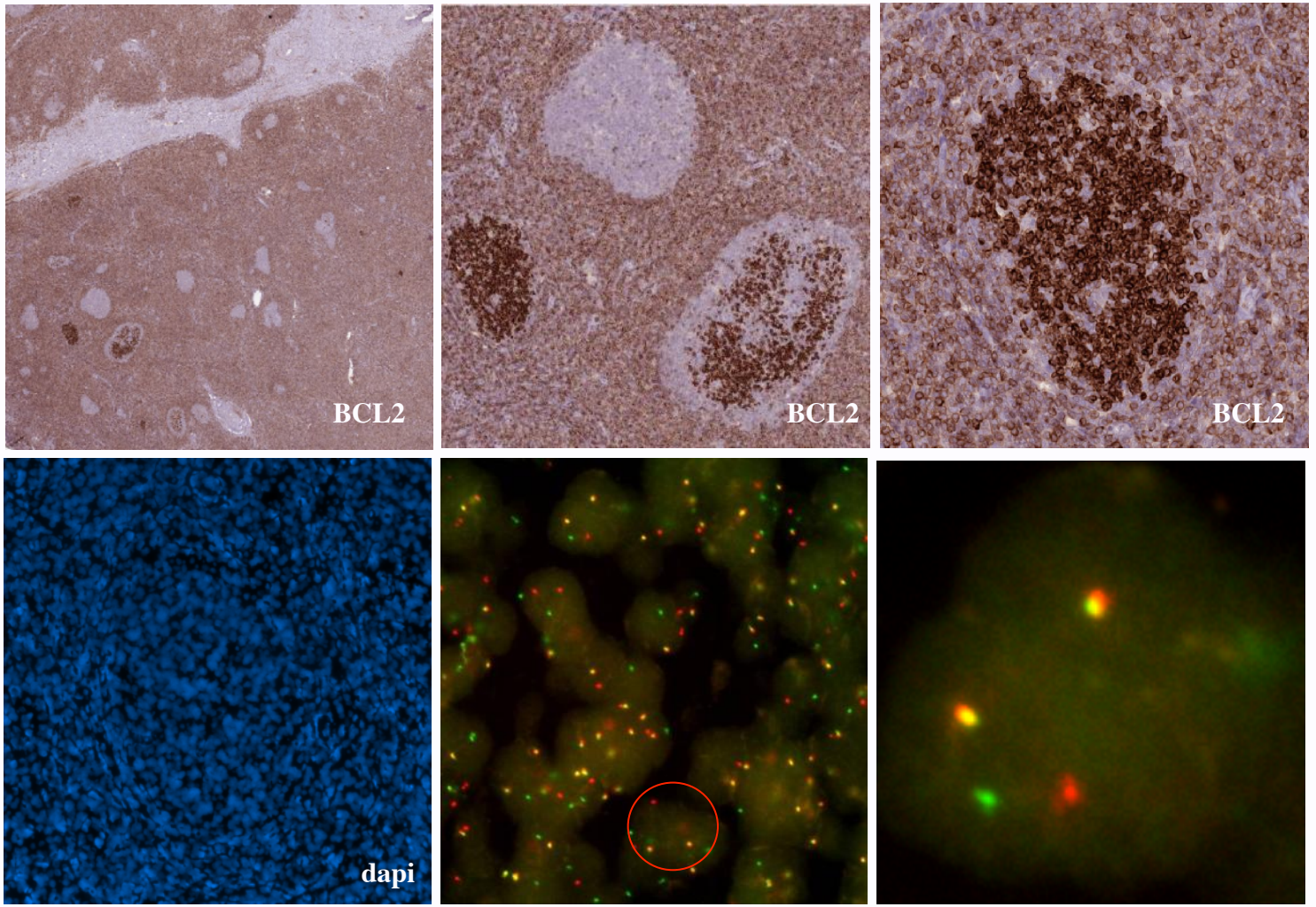
FLIS is most often an isolated event in a reactive LN
Very low risk of FL if not detected at initial staging (3%)
May be incidental finding with other B-cell lymphomas (15%)



Clinical Follow up (34 cases)
Median 41 mos. (10-118 mos.)

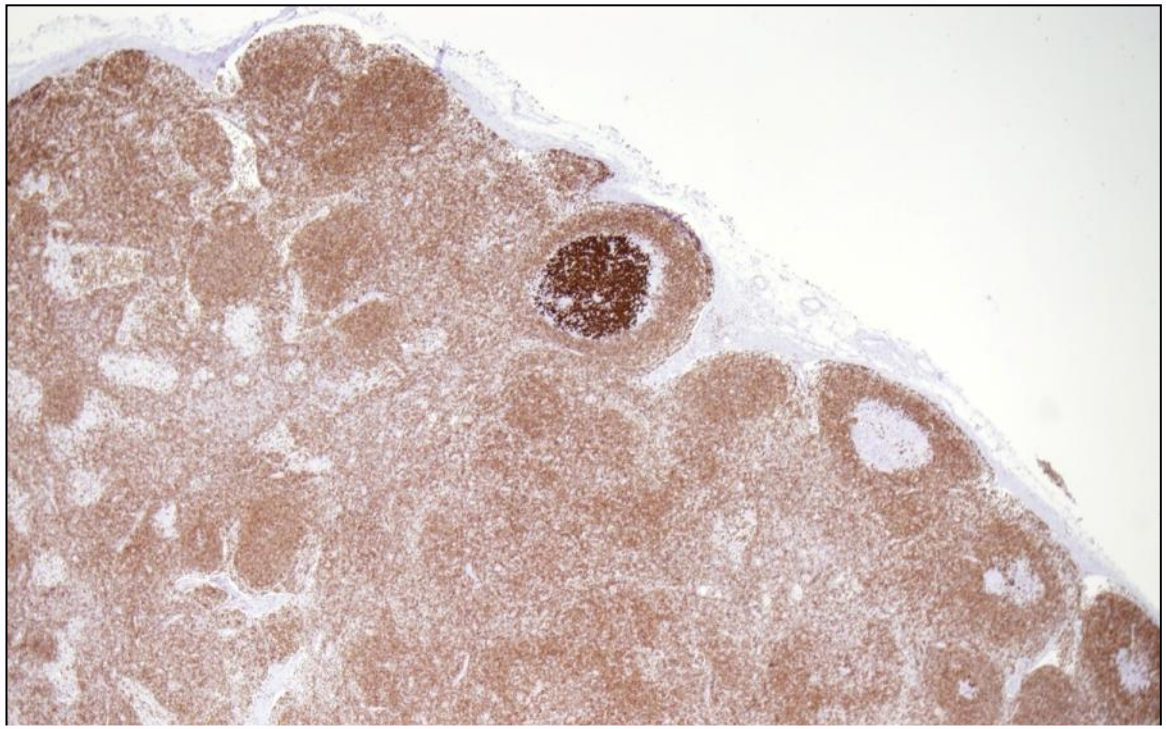
Jegalian et al Blood 2011

Composite FL in situ with Nodal MZL
(5 cases composite with another B-cell lymphoma)



FLIS in association with B-cell lymphomas

- A "FLIS-like" lesion can be detected in patients with known FL, either preceding diagnosis, at diagnosis, or at relapse
  - Should be considered a form of dissemination (17%; Jegalian et al)
- FLIS is often an incidental finding in patients with another B-cell lymphoma
  - 15-30 % Jegalian, Montes-Moreno, Pillai
  - CLL, CHL, SMZL, NMZL, LPL, DLBCL
- May suggest genomic instability, inc risk



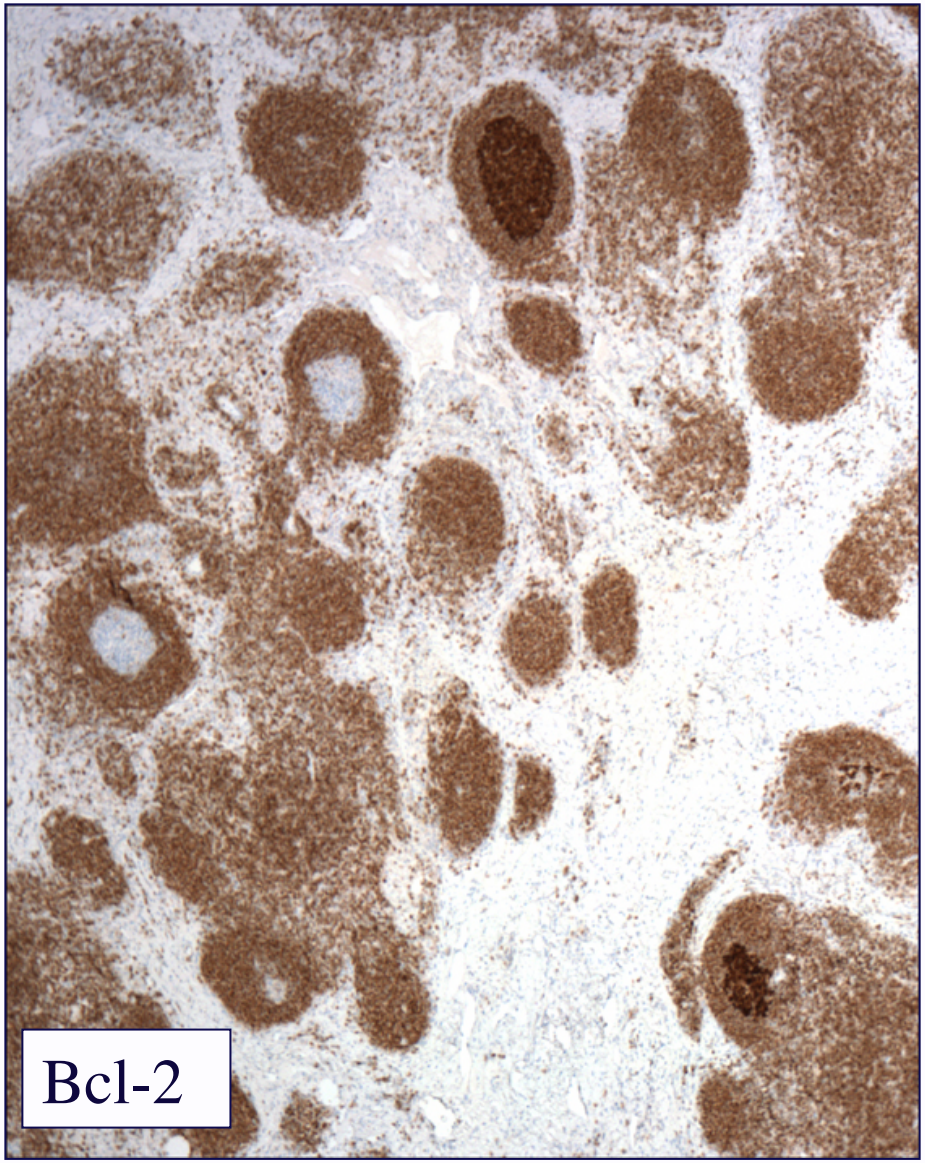
Why do FLIS lymph nodes get biopsied?

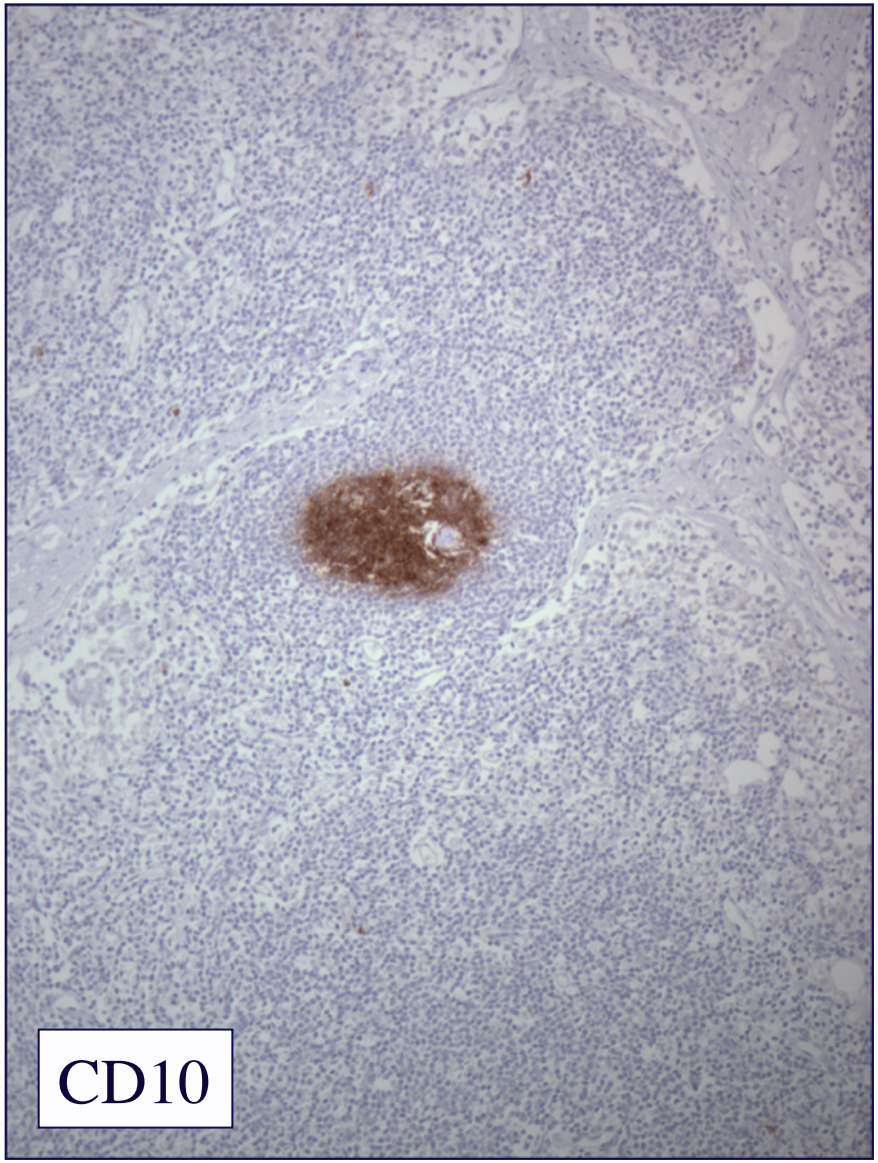
- Usually an incidental finding
  - 2.3% of unselected LN, Hennopp et al. 2011 (~1300 biopsies)
- Unrelated immune stimulus may lead to increased trafficking of FL-like B-cells to germinal centers
  - FLIS LN's usually show reactive hyperplasia
- HCV infection assoc with expansion of PB t(14;18) +
  - Numbers decrease with treatment of HCV

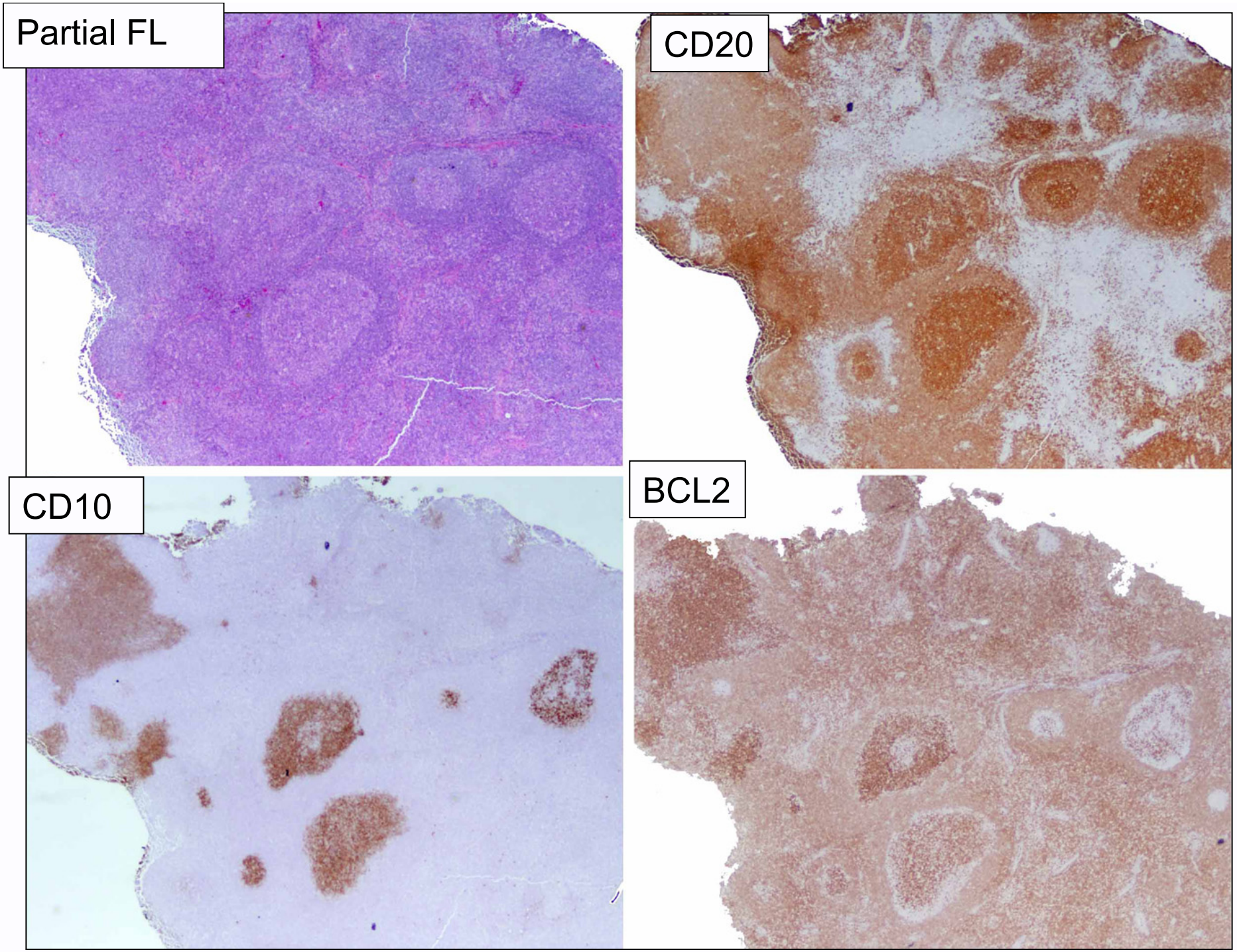
In Situ FL vs. Partial Involvement

In situ FL	Partial FL
• Architecture intact	• Altered architecture
• Follicle size normal	• Follicle size often expanded
• Involved follicles widely scattered	• Involved follicles close together, adjacent
• Intact mantle cuff with sharp edge to GC	• Blurred edge to GC – attenuated mantle cuff
• Very strong BCL2 and CD10 expression	• BCL2 and CD10 not as strong and more variable
• Almost pure centrocytes	• Cytology more varied, CB/CC

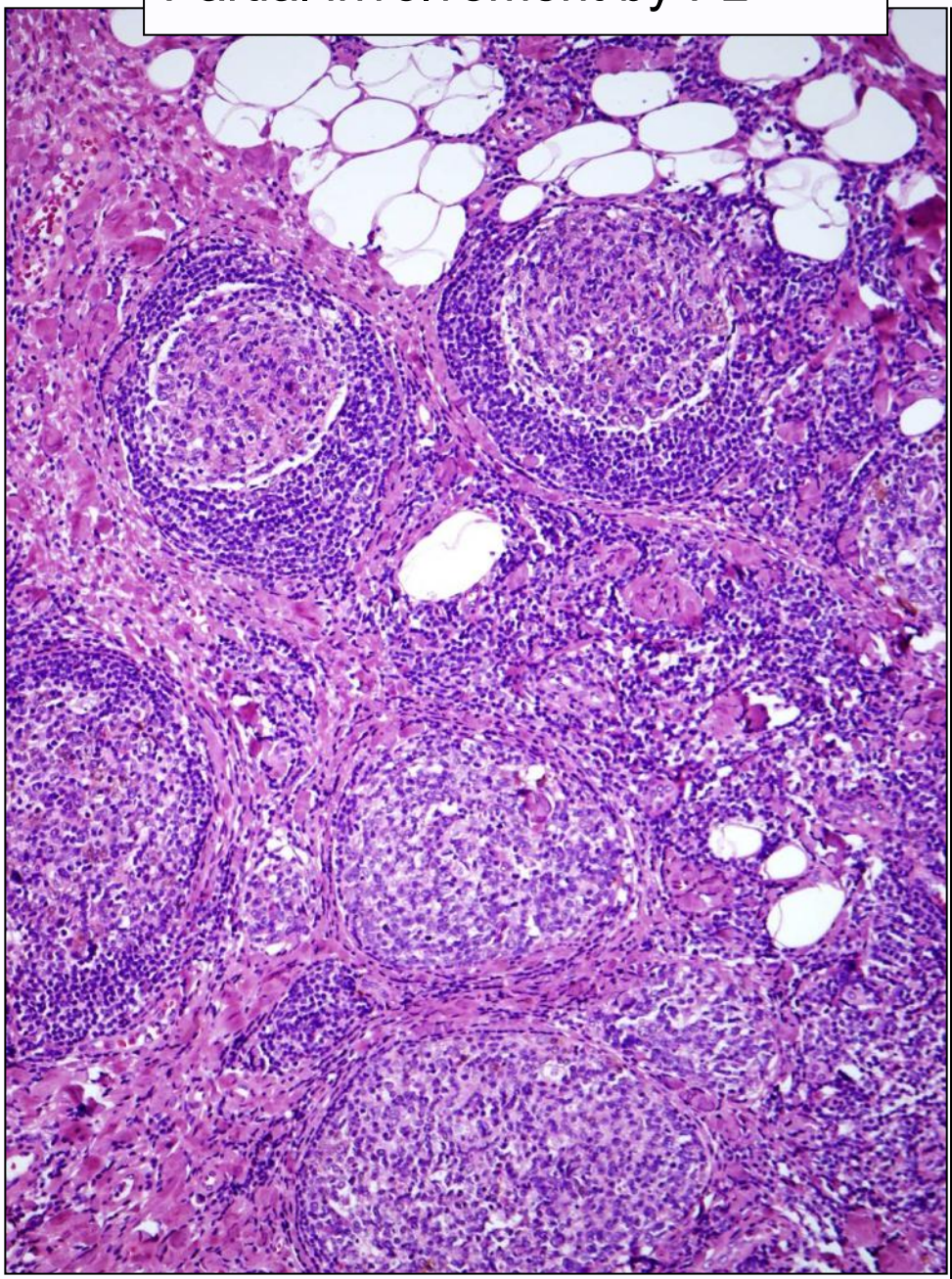
FLIS

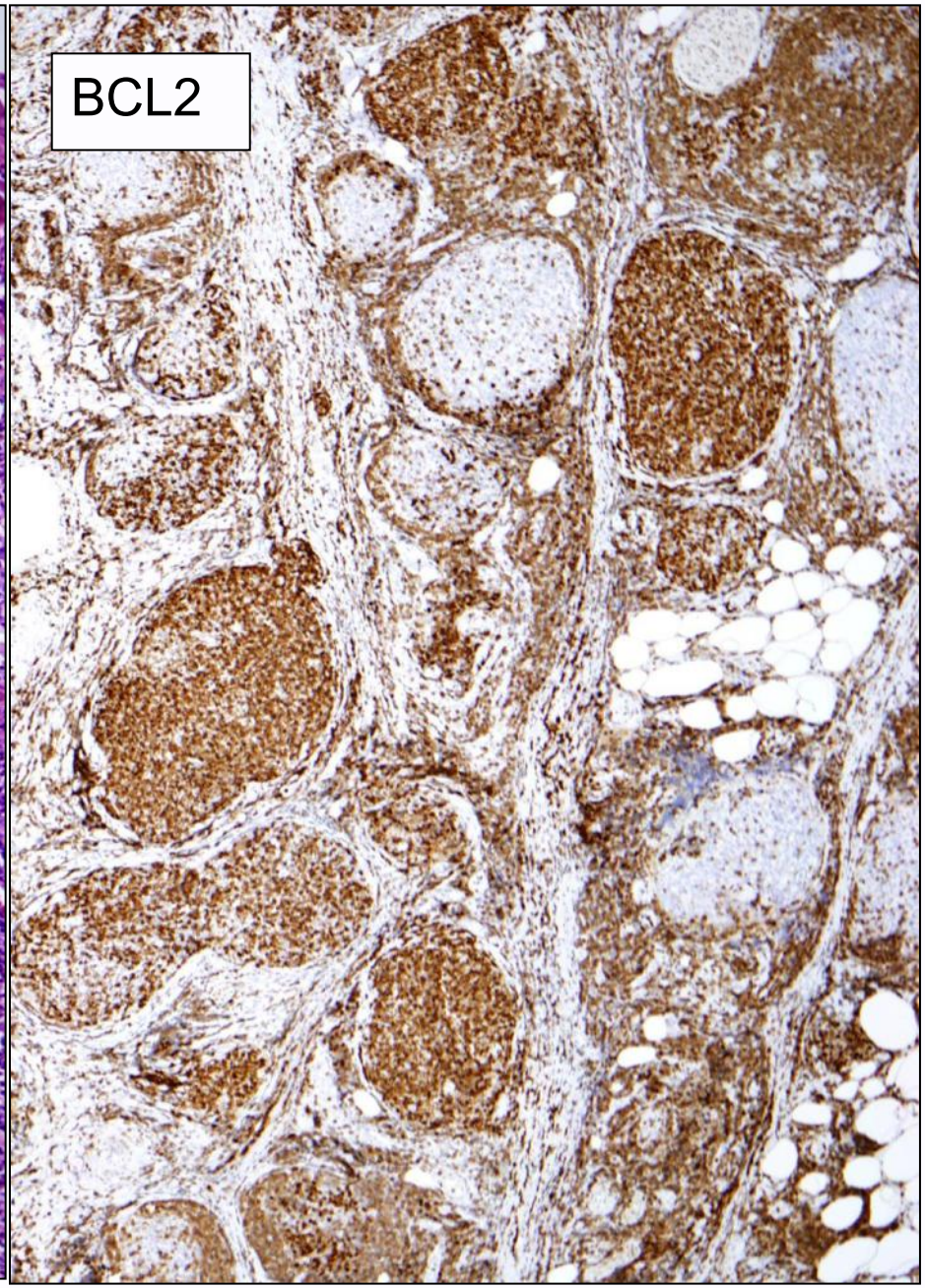





Partial FL
CD20
CD10
BCL2

Partial involvement by FL





What are the genetic differences between FLIS and Follicular Lymphoma

Bonzheim et al. Blood 2011

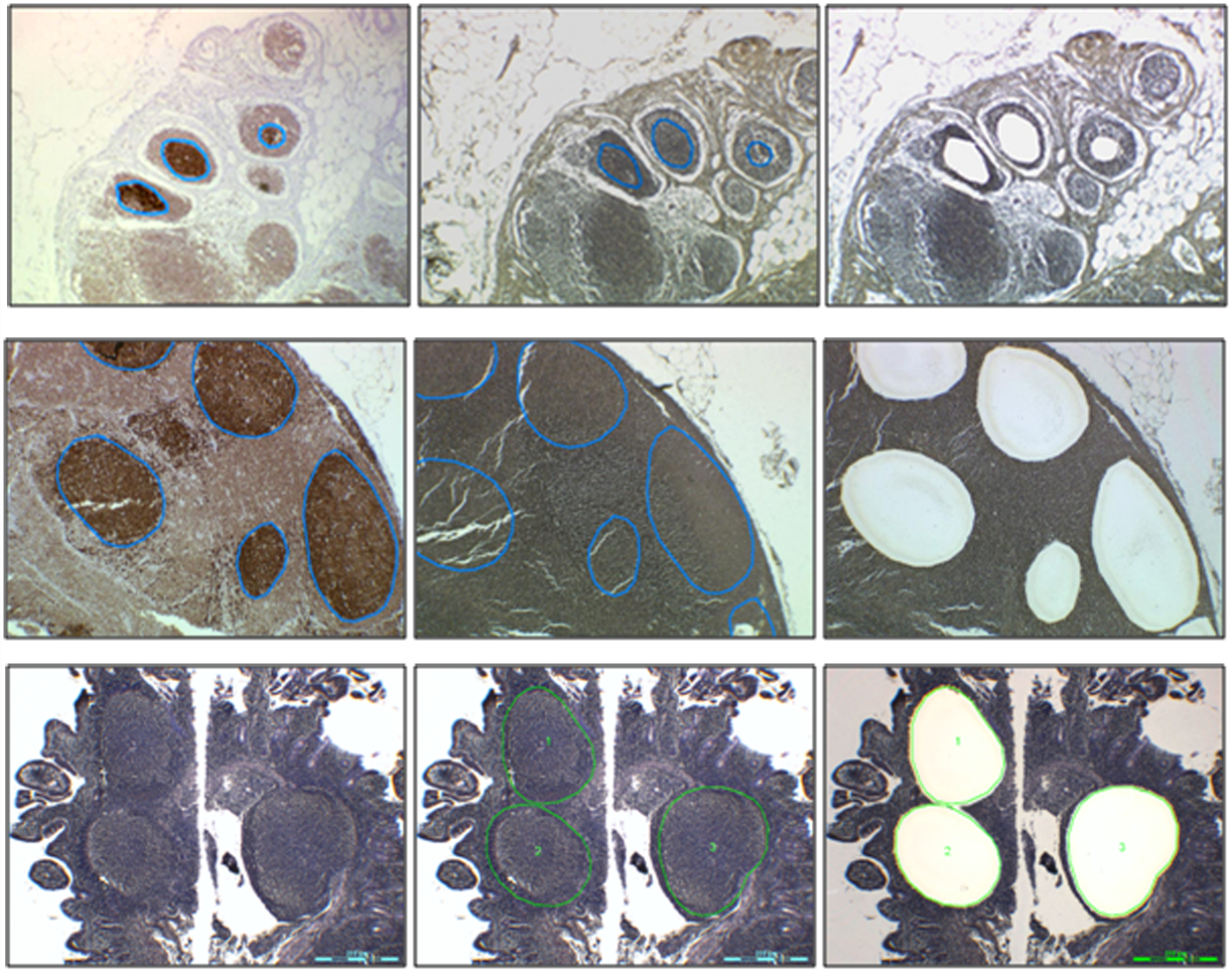
- Array CGH to compare FLIS with FL
  - Synchronous FL was negative for BCL2 protein
  - Point mutation found in BCL2 gene
- Other genetic changes acquired in FL
  - Gains n 6p22.2
  - Losses in 6q14.1
  - FISH confirmed 6q loss in FL

Microdissection of RH, FLIS, PFL, iFL & FL

FLIS

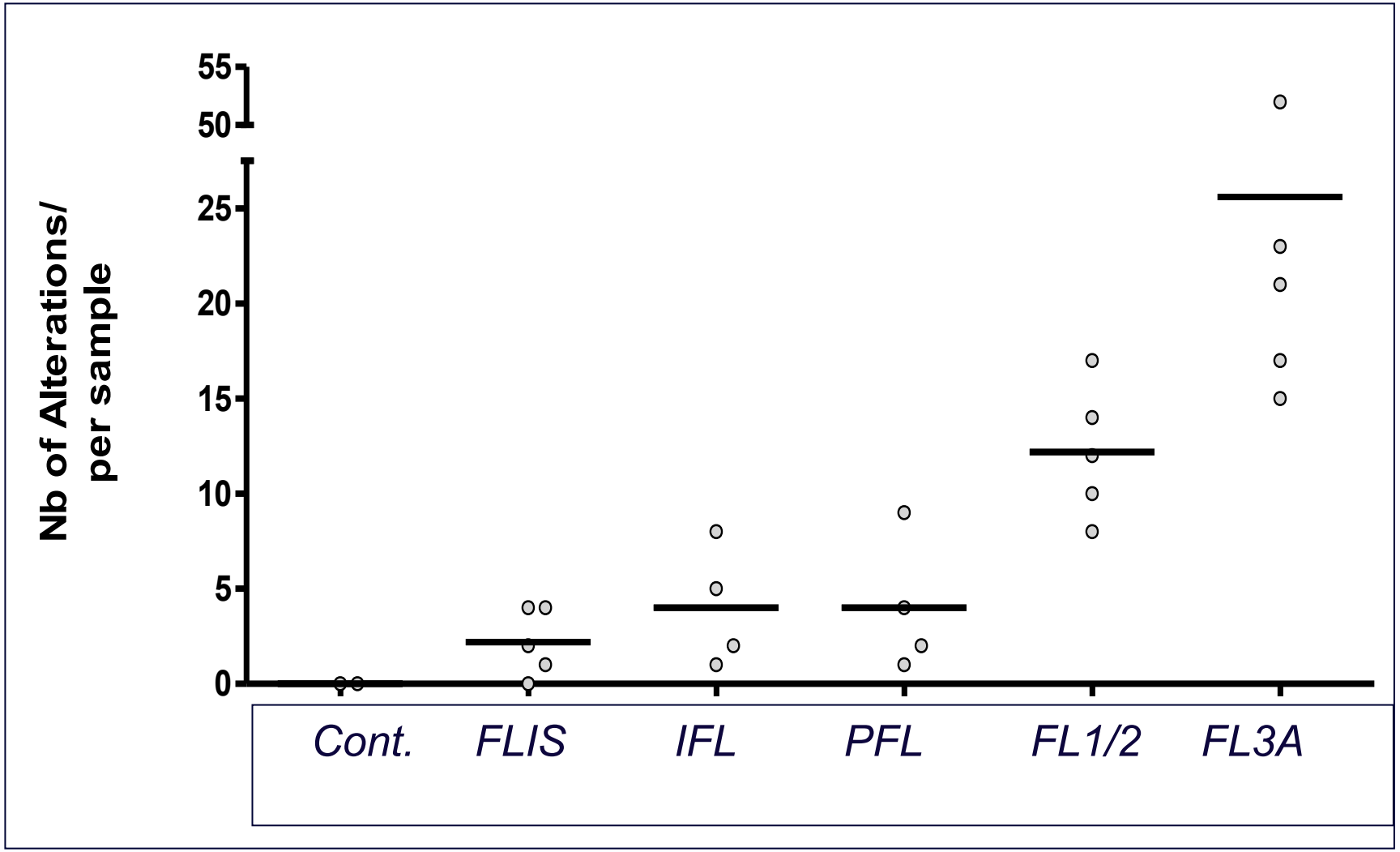
PFL

iFL

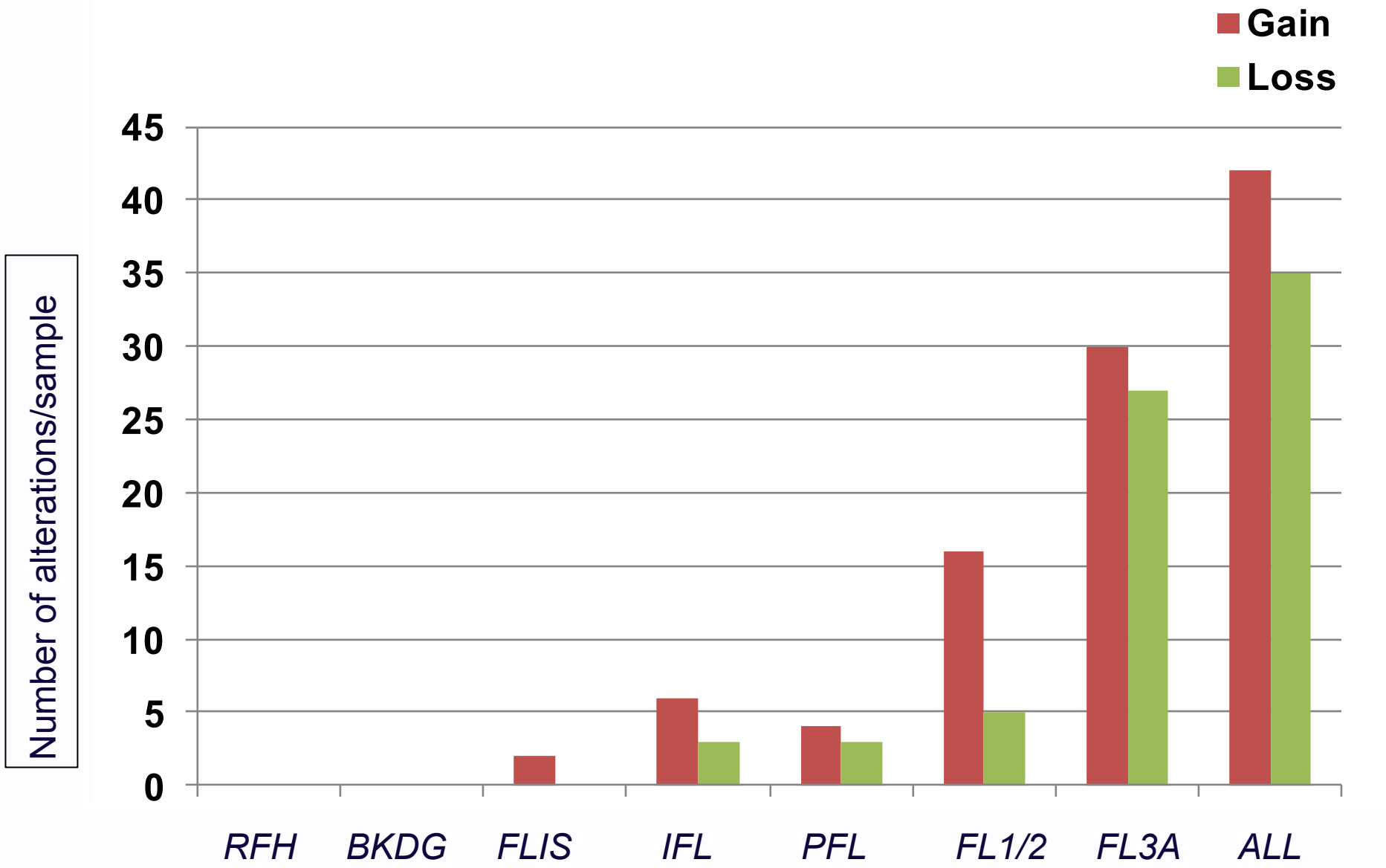


Array CGH: Number of major alterations per sample

Mamessier E et al.



Number of gains and losses in early-FL and FL samples (>700kb)



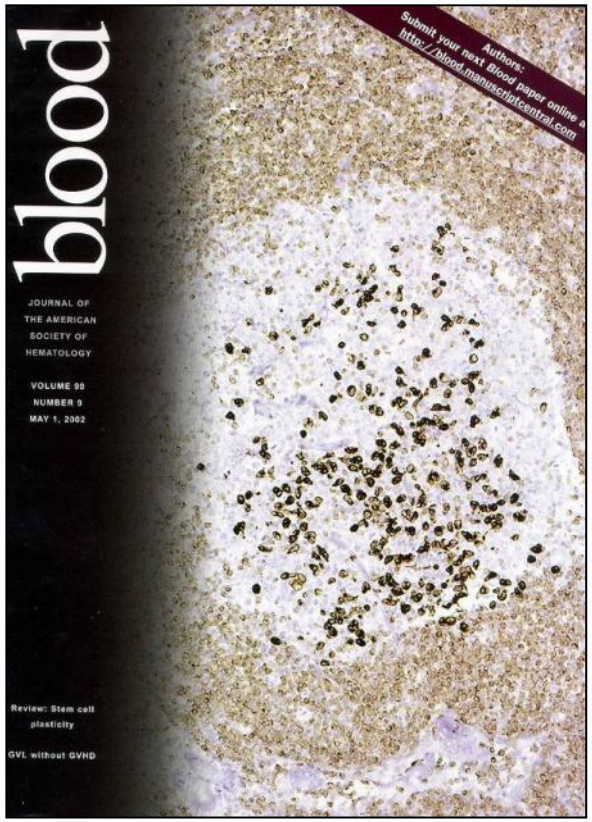
Conclusions

E. Mamessier, J. Song, S. Roulland, A. Chott, E. Jaffe, B. Nadel

- Array CGH data show a stepwise increase in chromosomal aberrations in FLIS, FL with partial involvement, duodenal FL, FL Grade 1-2, and FL Grade 3A
- Most of the affected regions in FLIS are the same as those altered in usual FL
- The specific genetic alterations that lead to progression are yet to be elucidated

What is the obligation of the pathologist to detect this and other in situ lesions?

- At present, no treatment is recommended for FLIS or other in situ lesions
- BCL2 and CyclinD1 immunohistochemistry need not be done on every reactive lymph node biopsy
- One can anticipate finding these in situ lesions in reactive lymph nodes without atypical features



- FL-like B-cells home to the germinal center environment
- Lack of progression in most patients suggests *BCL2/IGH* is necessary but not sufficient for neoplastic transformation
  - *Second hit is required*
- FL-like PB B-cells & FL in situ are different phases of the same incipient neoplasia

Terminology: Follicular lymphoma in situ (FLIS)
FL-like B-cells of Uncertain Significance (FLBUS)