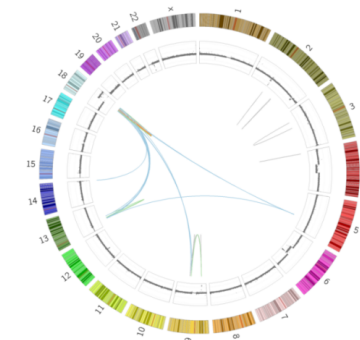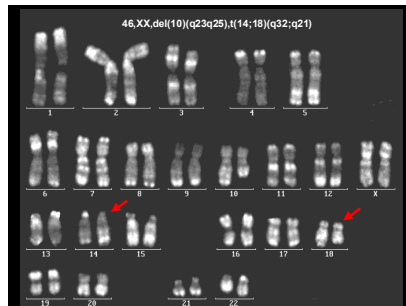# INDOLENT LYMPHOMA WORKSHOP

FOLLICULAR LYMPHOMA
Histopathology and Biology

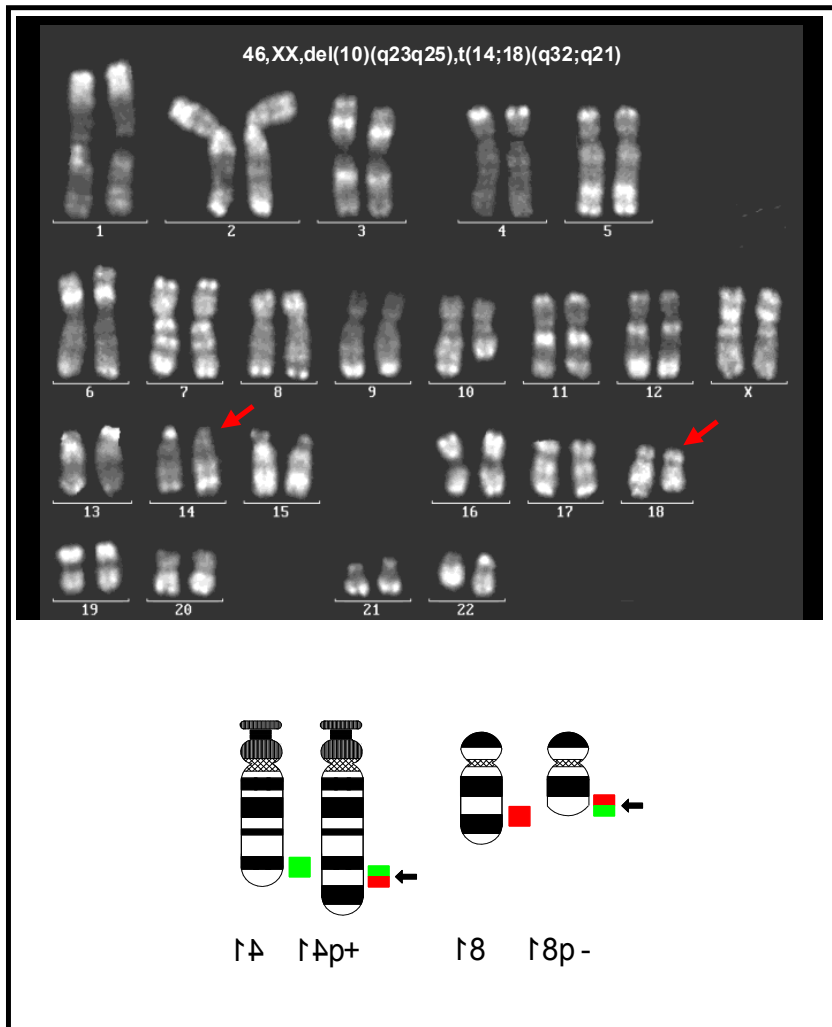# (CYTO)GENETICS

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The translocation t(14;18)(q32;q21)

46,XX,del(10)(q23q25),t(14;18)(q32;q21)

Juxtaposition of the

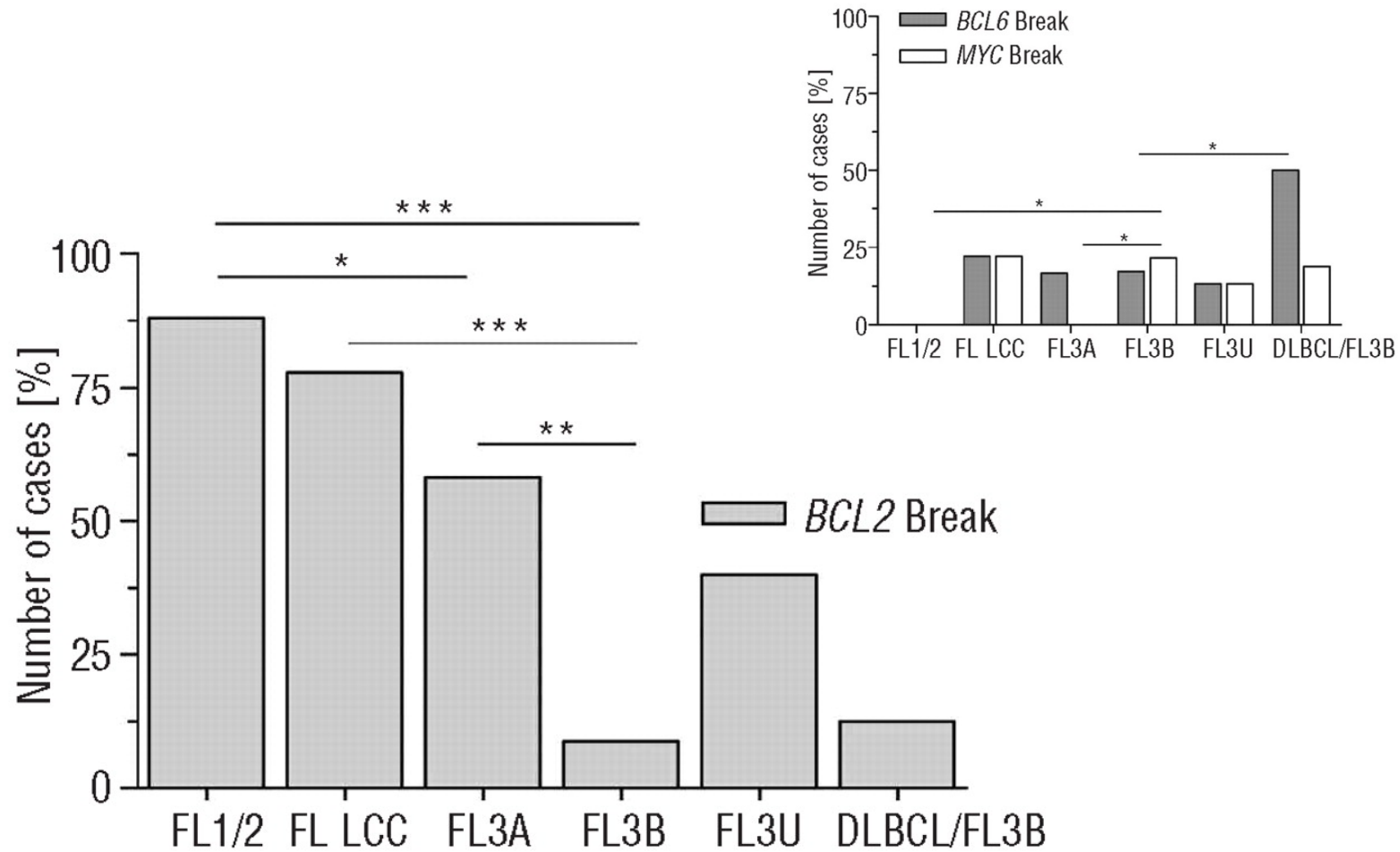***BCL2* oncogene (18q21)**

next to

Immunglobulin-Heavy-Chain (*IGH*)-

Locus (14q32)

(mistaken VDJ-rearrangement)

rarely: variants: IGK (2p12), IGL (22q11)

-> activation of BCL2

(apoptosis inhibitor)

Chromosomal translocations and FL grading
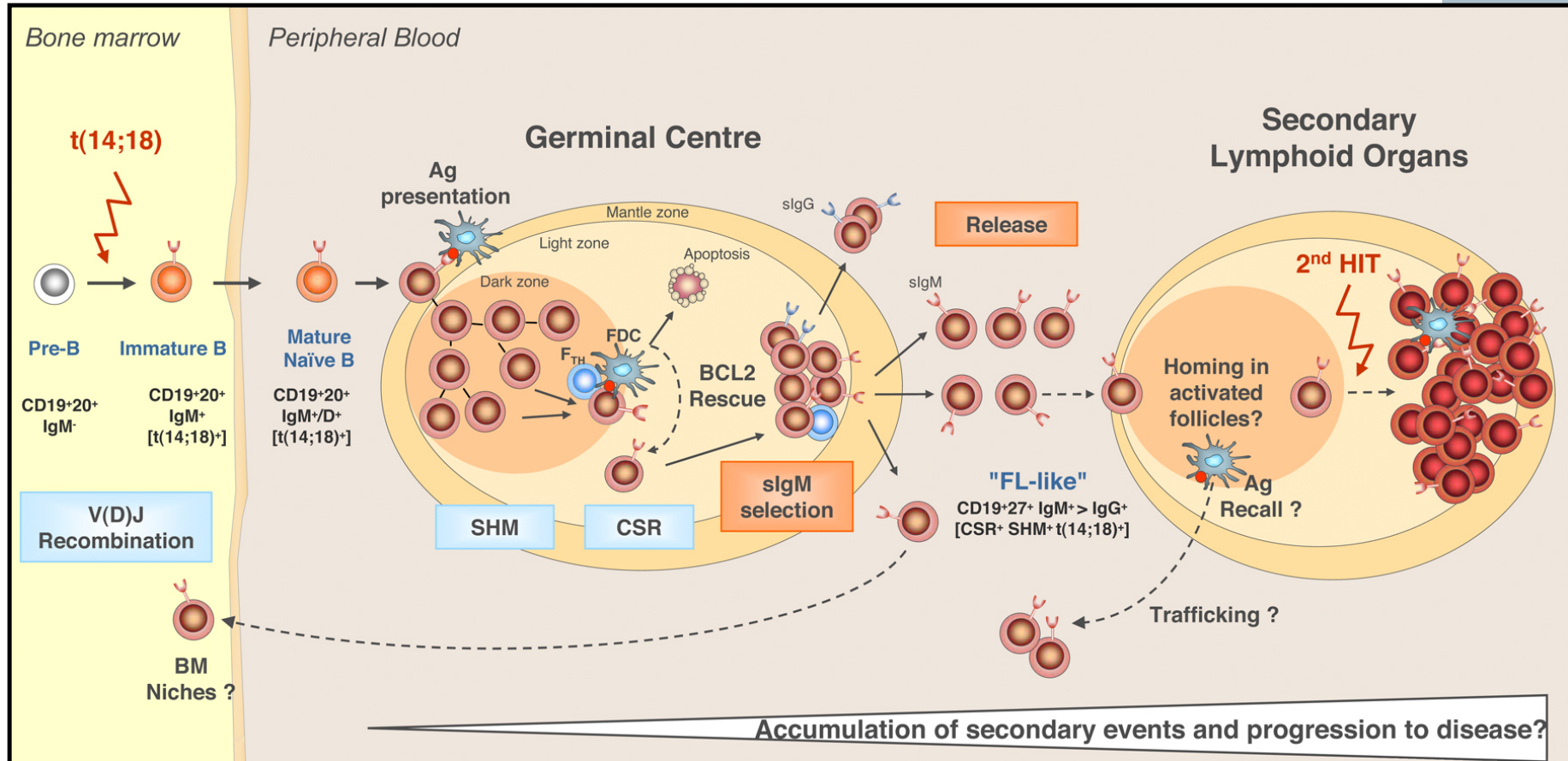
(CYTO)GENETICS OF FOLLICULAR LYMPHOMA

t(14;18)-positive Follicular Lymphoma
- pattern of genetic changes
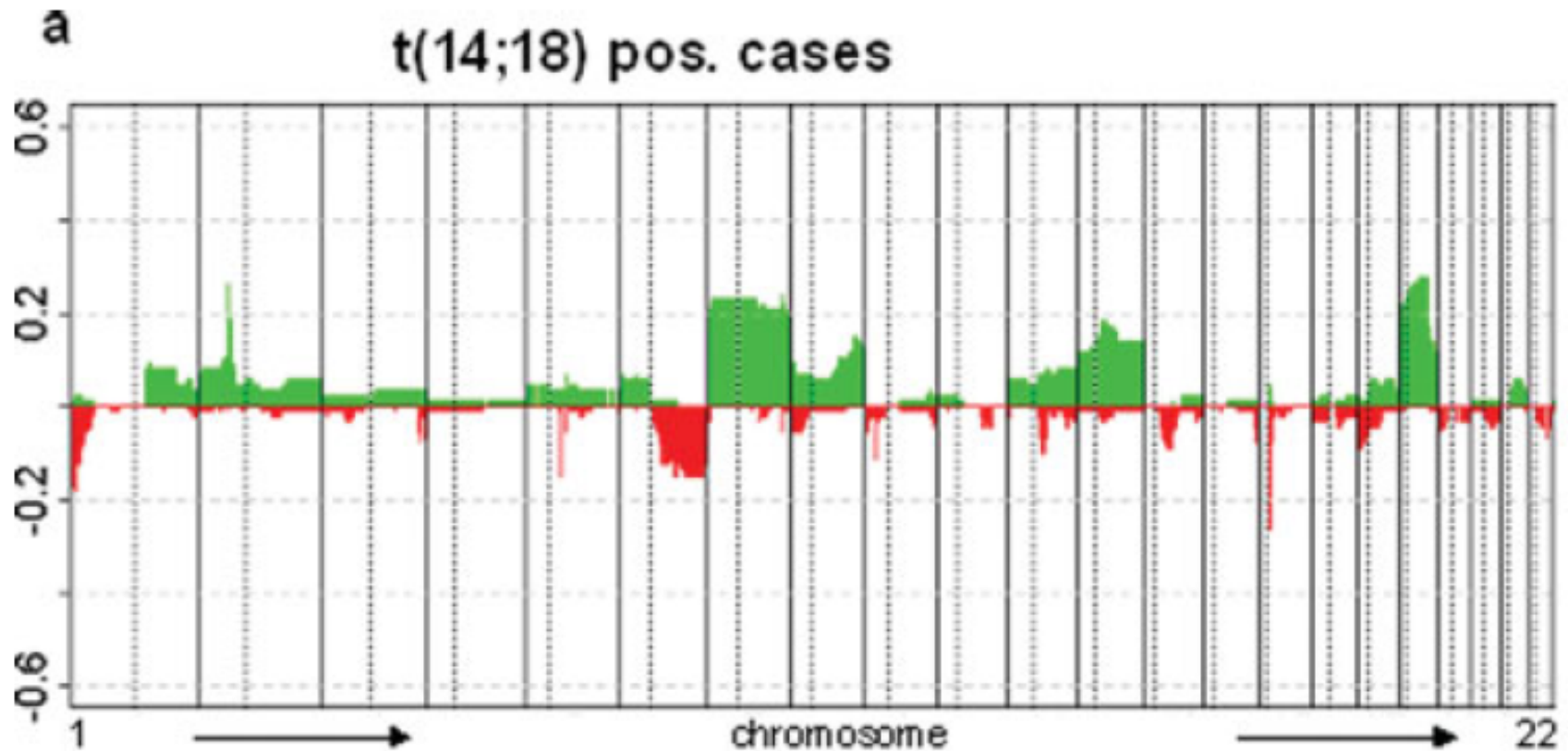- clonal evolution
- genetic aberrations and prognosis

t(14;18)-negative Follicular Lymphoma
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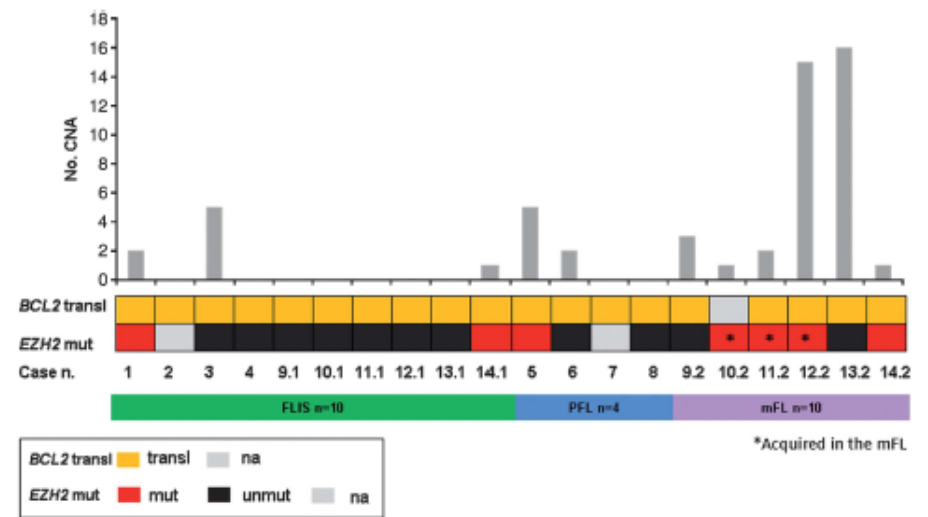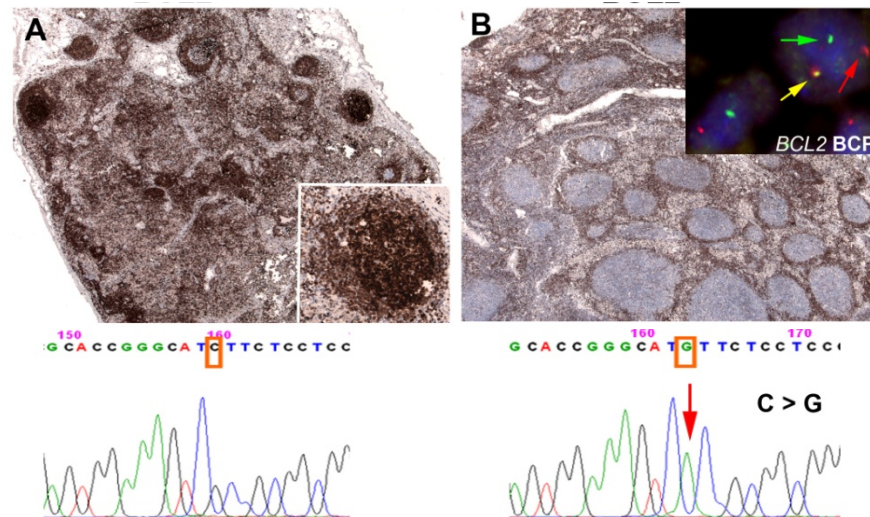- Primary cutaneous follicular lymphoma
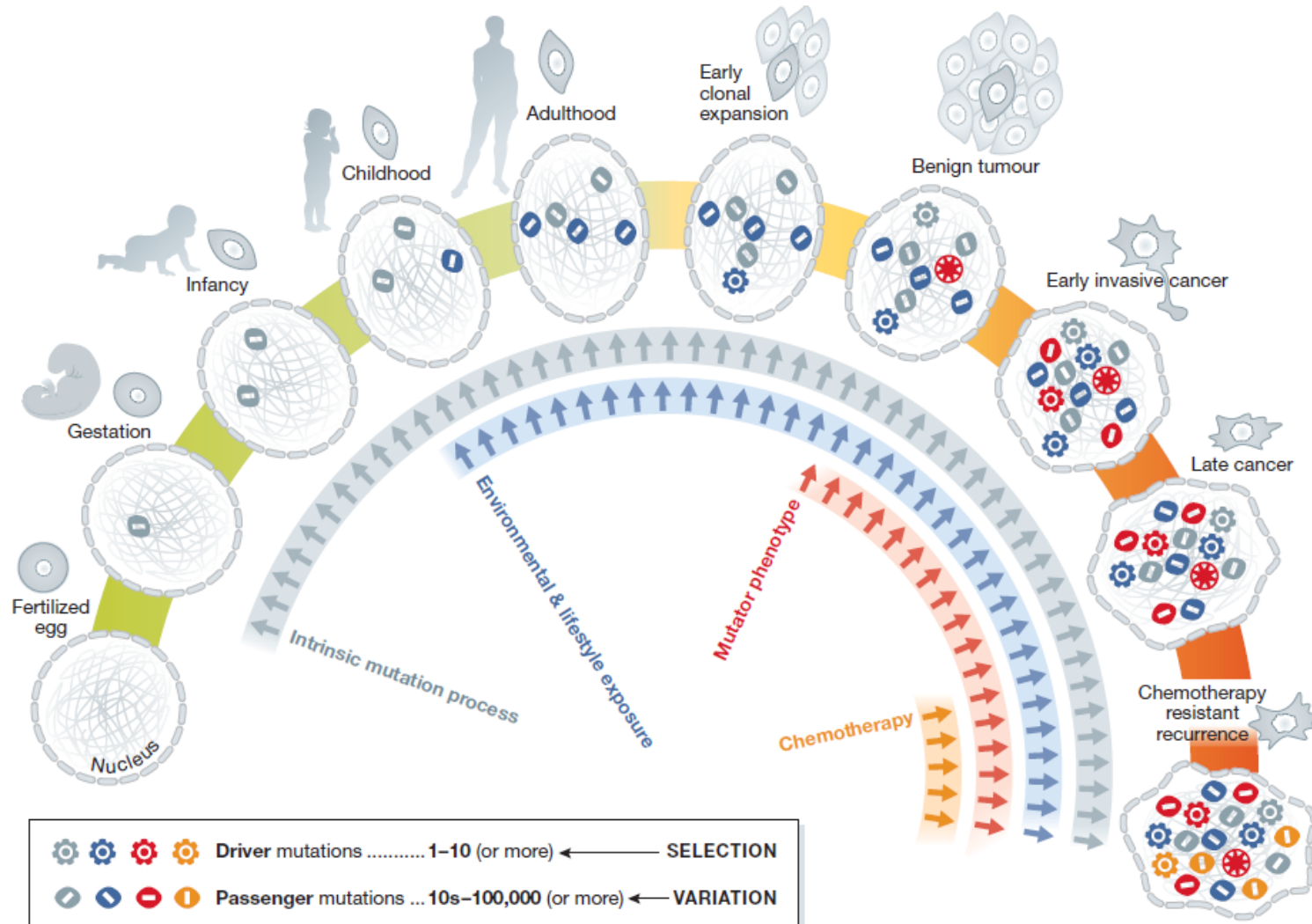
t(14;18)(q32;q21)

Chromosomal imbalances

Schwänen et al., Genes Chrom Cancer, 2009

t(14;18)(q32;q21)-positive FL in situ

Bonzheim et al., Blood, 2011, Schmidt et al., Leukemia. 2014

Mutational Signatures in FL

Cytogenetic evolution in t(14;18)+ FL

Berglund et al., Mod Path, 2007
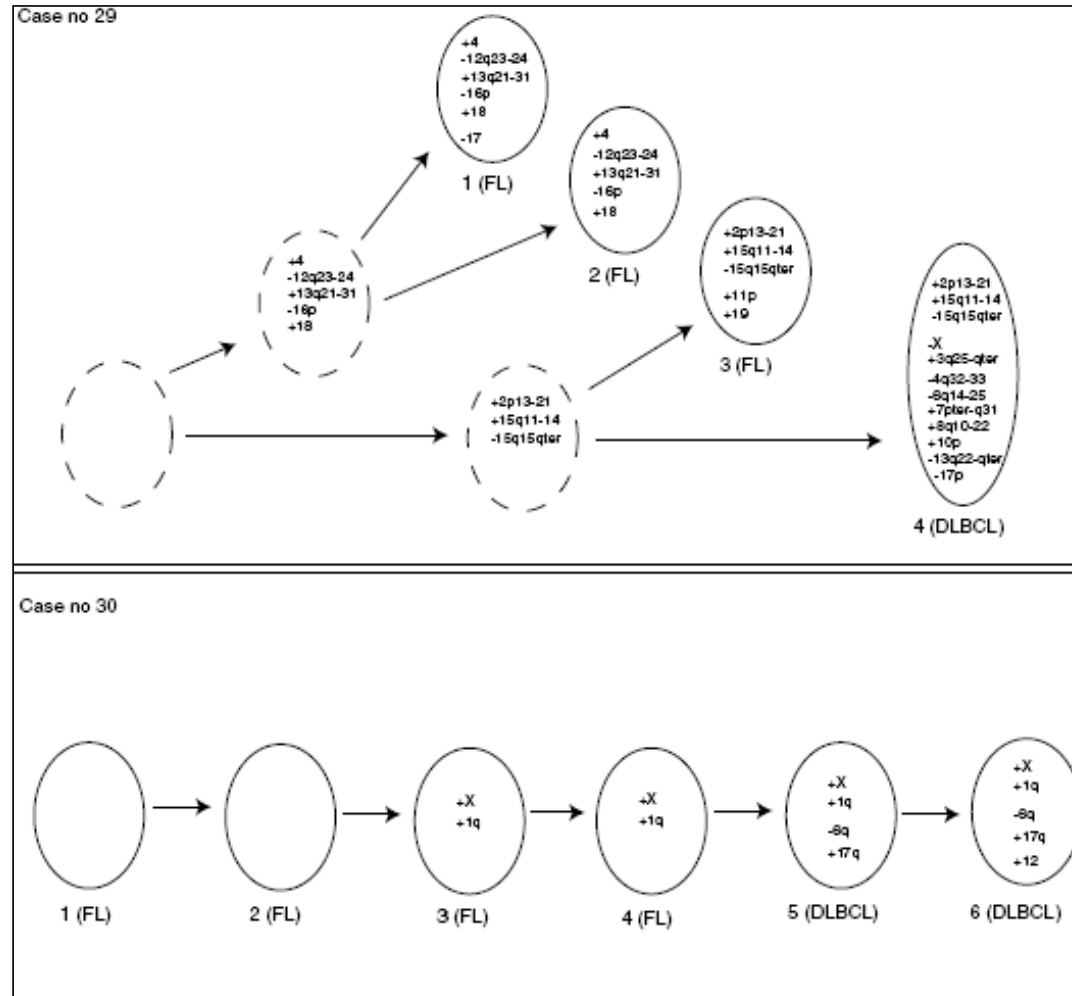
Genetic evolution in t(14;18)+ FL
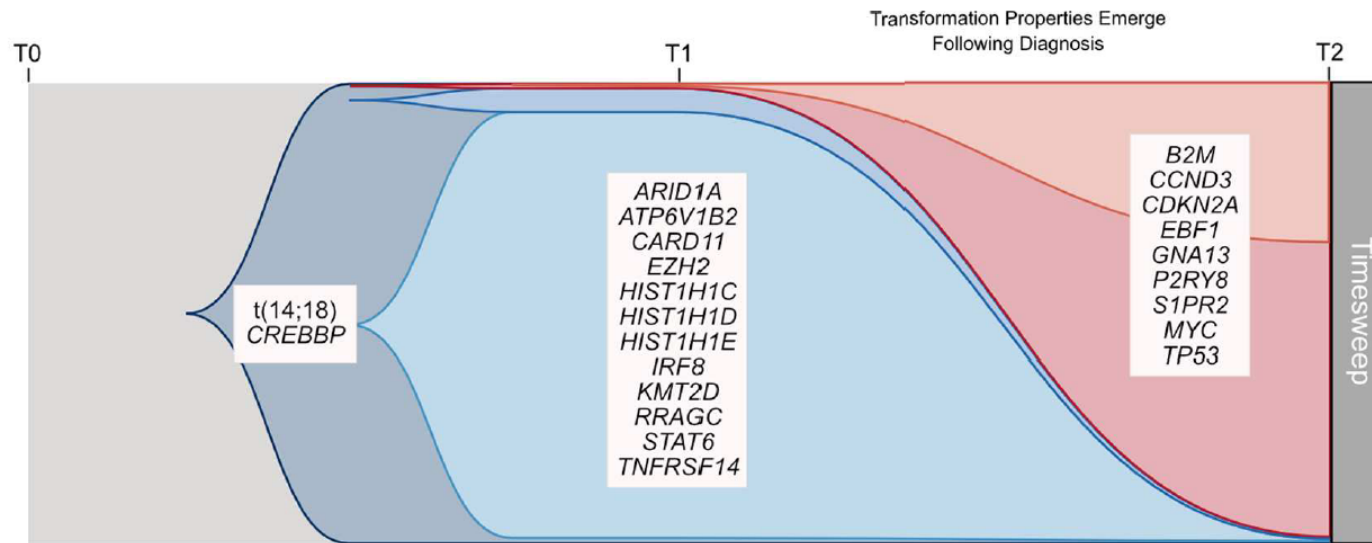
Transformation
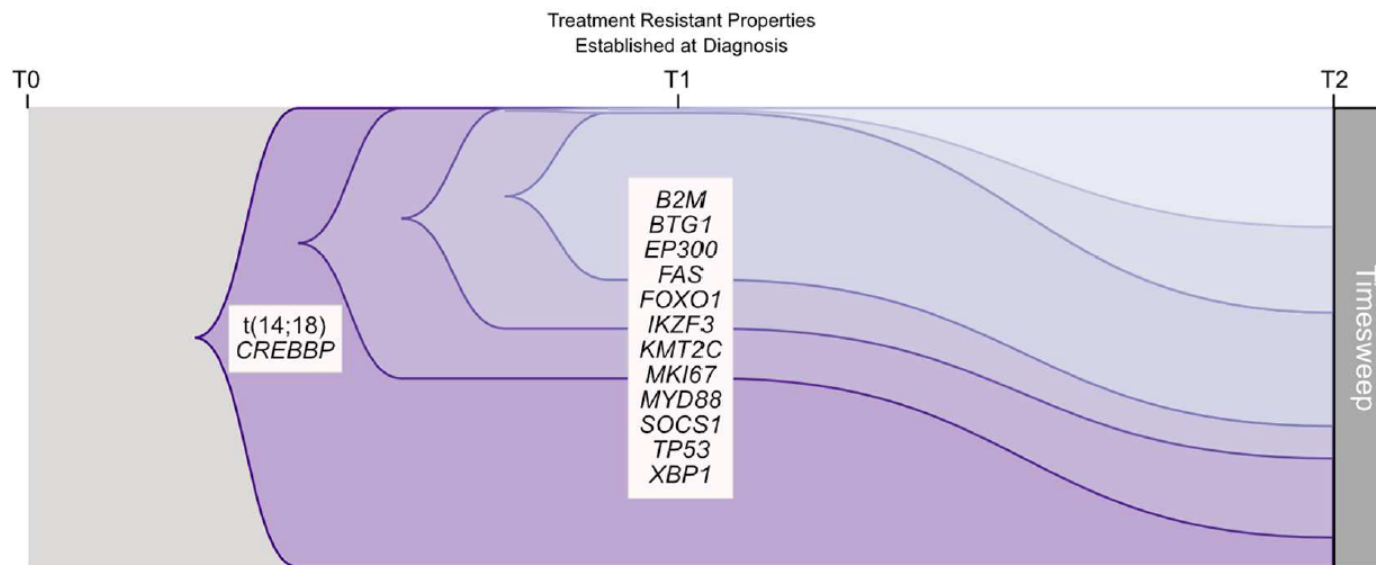
Progression under treatment

Kridel et al., PlosMed, 2016

Genetic evolution in t(14;18)+ FL
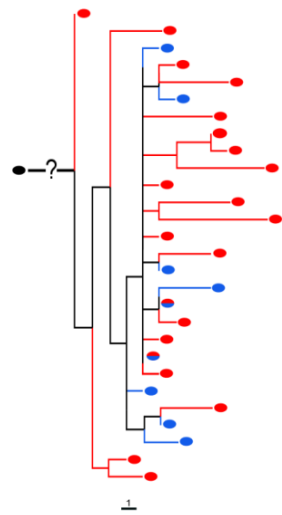
no evolution (8 pairs)
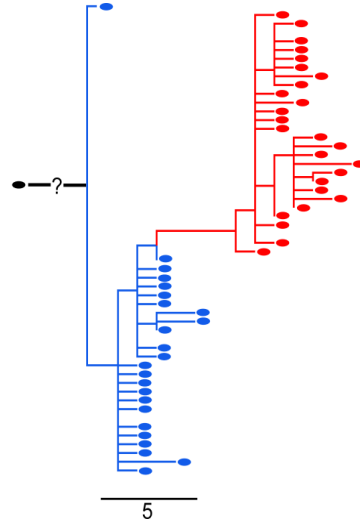
sequential evolution (5 pairs)
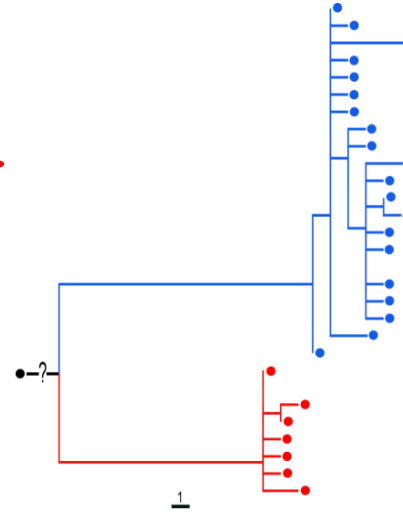
divergent evolution (6 pairs)
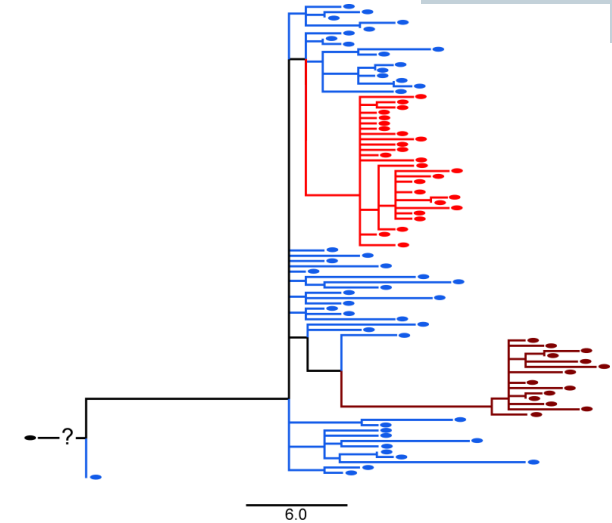
complex evolution (4 pairs)

Visual Classification of IGHV-Sequence Trees

Epigenetic evolution in t(14;18)+ FL
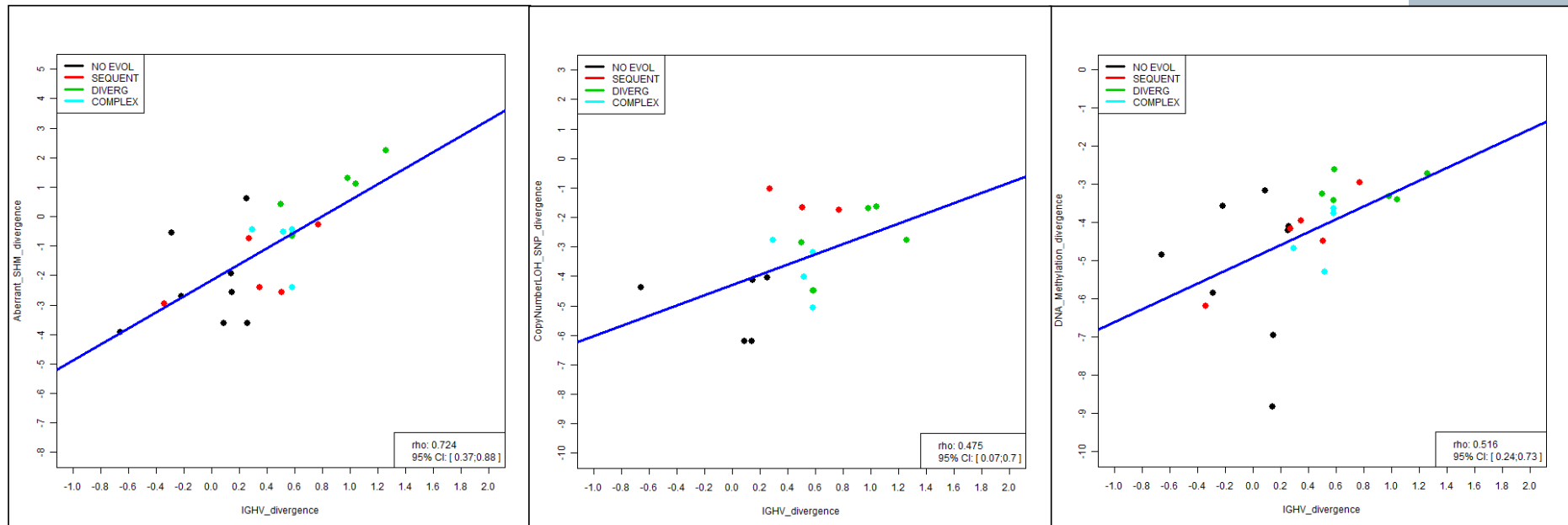
aSHM – divergence

Copy Number/LOH – divergence

DNA methylation - divergence

… but NOT with time between sampling

CREBBP mutation correlates significantly with DNA-methylation divergence

Löffler et al., Leukemia, 2014

Prognostic Importance of Genomic Aberrations

TABLE 4. Clinical Parameters and Genomic Aberrations Significantly Associated with Overall Survival ($n = 73$)

Clinical Parameters According to the FLIPI (Univariate) and IPI (Multivariate)

	n	P (Univariate)	P (Multivariate)	Hazard ratio (95%-Confidence Interval)
Parameter				
Age over 60 years	18	0.0239	0.012	3.7 (1.5–8.9)
Xnodal	7	**0.0007**	**0.007**	6.5 (2.2–19.4)
ECOG	10	0.0396	–	–
LDH	13	0.113	0.012	3.2 (1.2–8.5)
Stage > II	56	0.153	–	–

Genomic Aberrations (Multivariate Analysis Including IPI-Factors)

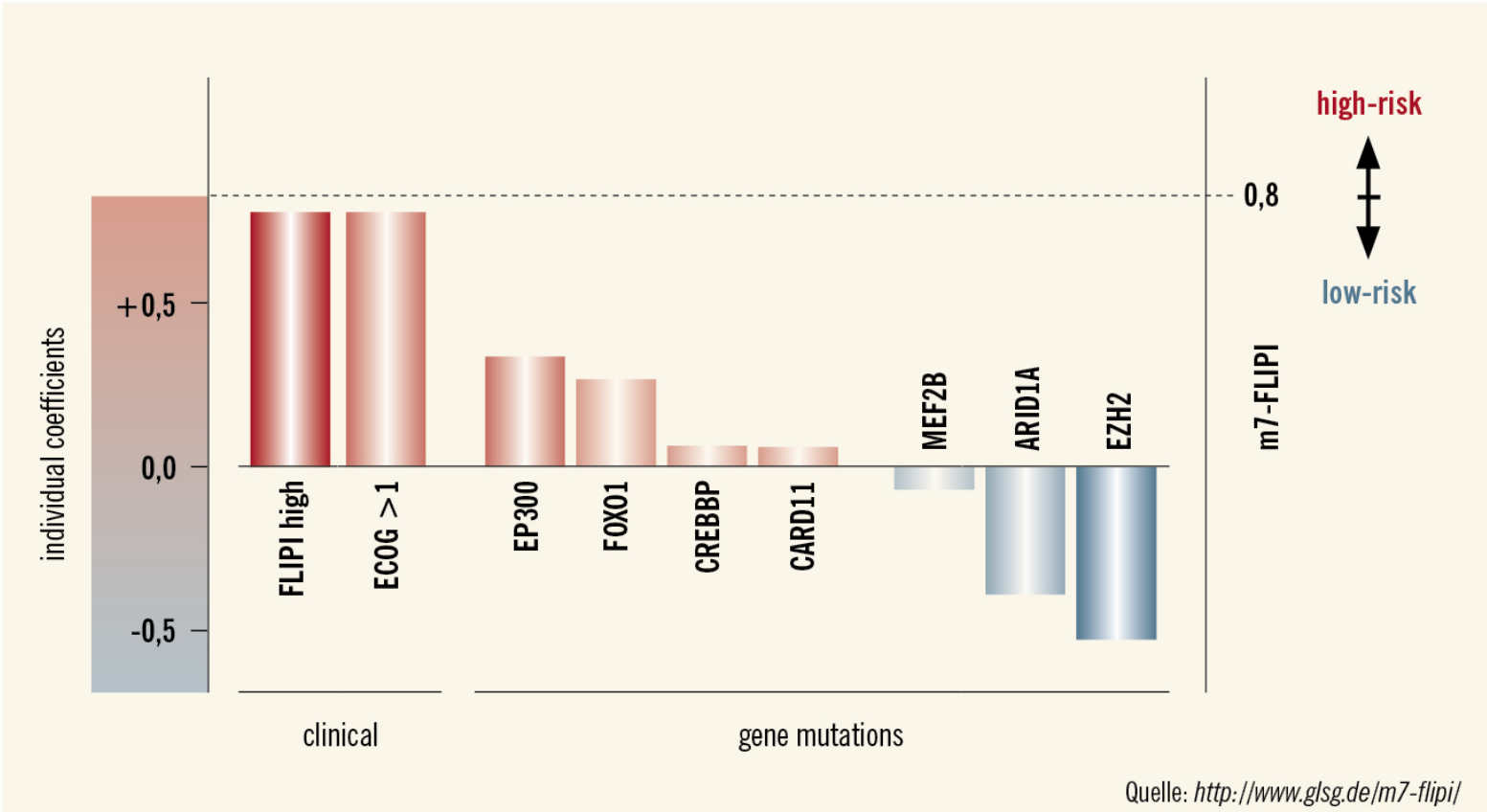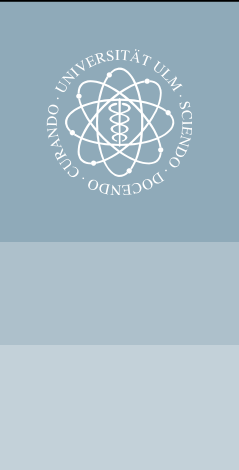|	n	P (Univariate)	P (Multivariate)	Hazard ratio (95%-Confidence Interval)
Aberration				
Gain 5p	4	**0.0163**	–	–
Del 6q25.1	9	0.0043	0.0037	4.9 (1.8–13.2)
Del 6q26	8	**<0.0001**	<0.0001	9.4 (3.2–27.7)
Del 9p21	7	**0.0163**	**0.004**	3.6 (1.4–9.4)
Gain 11q22	5	0.0035	–	–

The aberrations and clinical characteristics marked in **boldface** included only cases at primary diagnosis ($n = 57$). Here, a significantly inferior overall survival was shown for: gain 5p, $P = 0.0037$; del6q26, $P = 0.0026$; del9p21, $P = 0.0352$ and extranodal involvement, $P < 0.0001$ in univariate and del9p21, $P = 0.0071$, HR = 4.06 and extranodal involvement, $P < 0.001$, HR = 29.97 in multivariate analysis.

Schwänen et al., Genes Chrom Cancer, 2009

Mutations and m7-FLIPI

Quelle: *http://www.glsg.de/m7-flipi/*
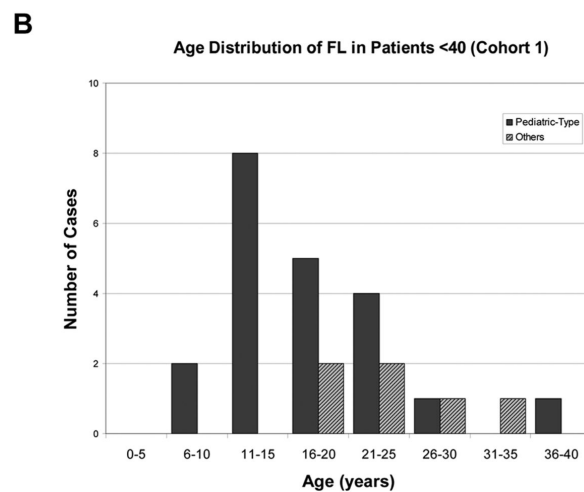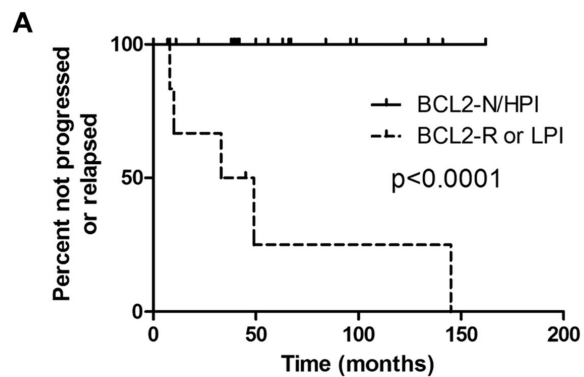
(CYTO)GENETICS OF FOLLICULAR LYMPHOMA

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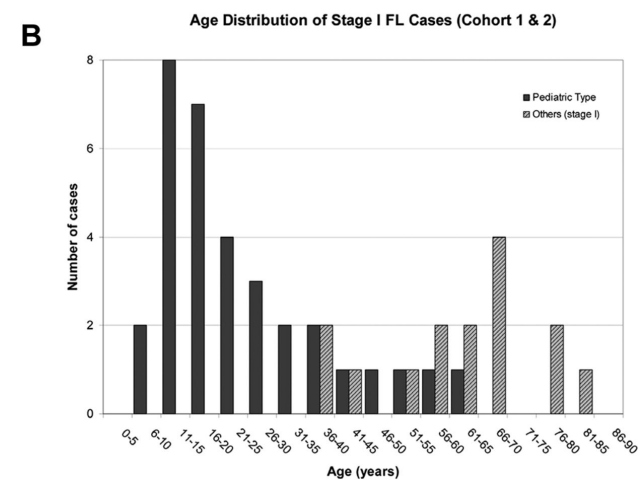- clonal evolution
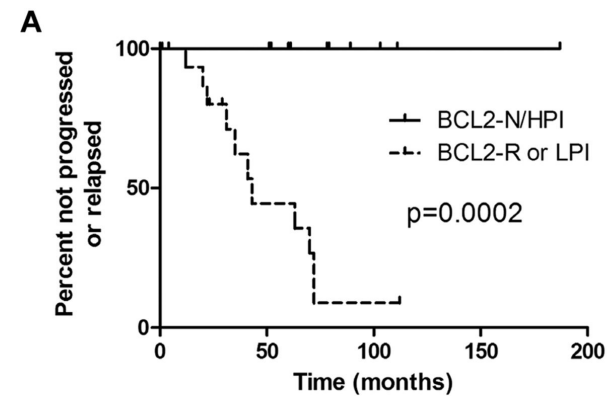- genetic aberrations and prognosis

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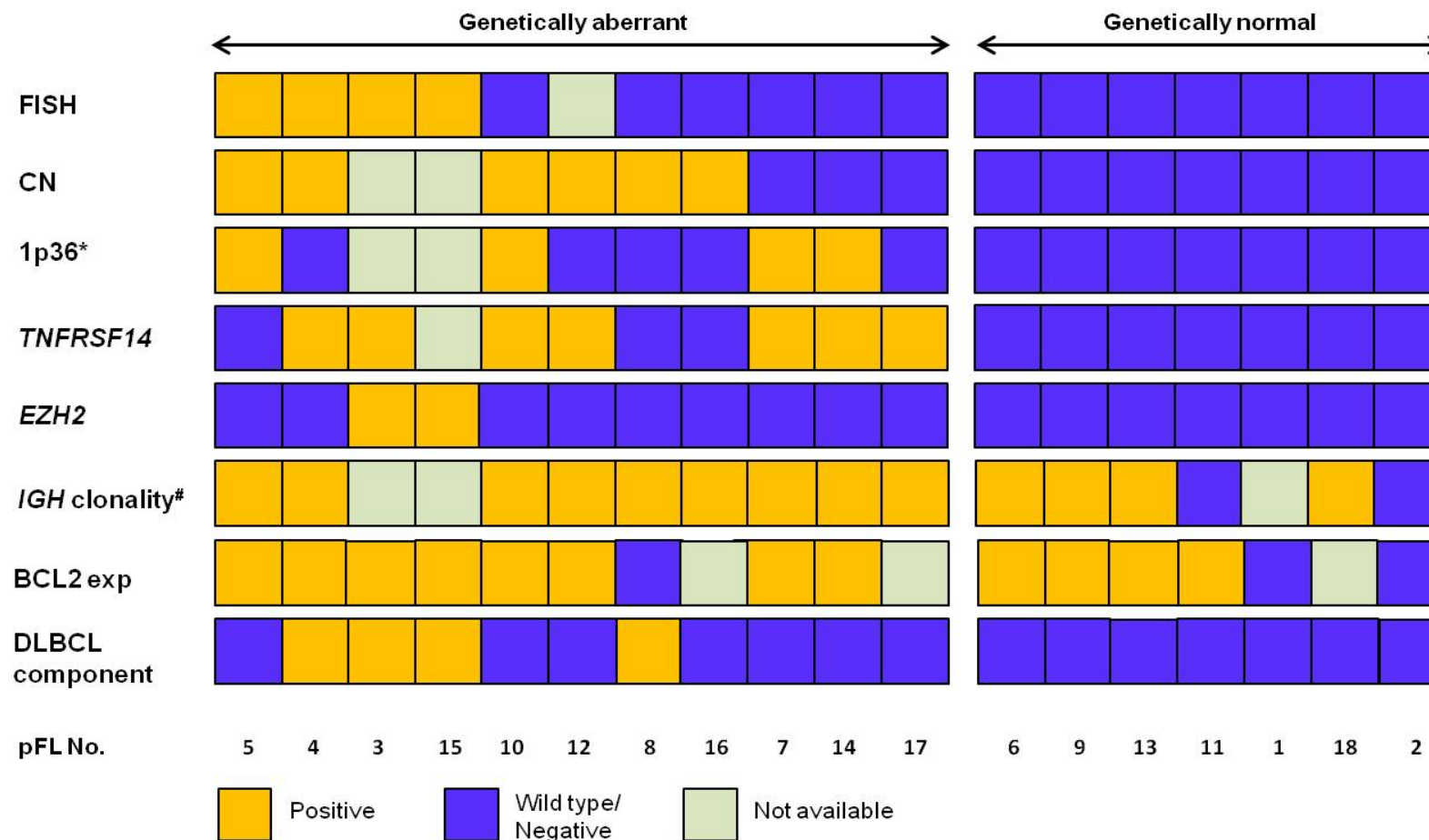# Follicular lymphoma, pediatric type

Outcome and age distribution of cohort 1 FL patients (< 40 years of age).

Outcome and age distribution of Stage I FL cases.

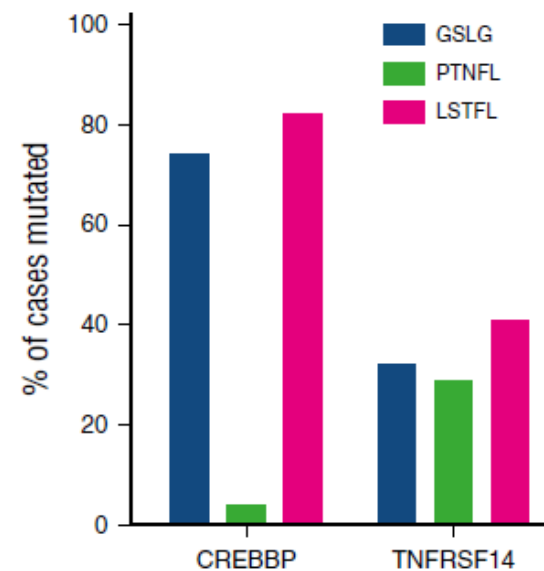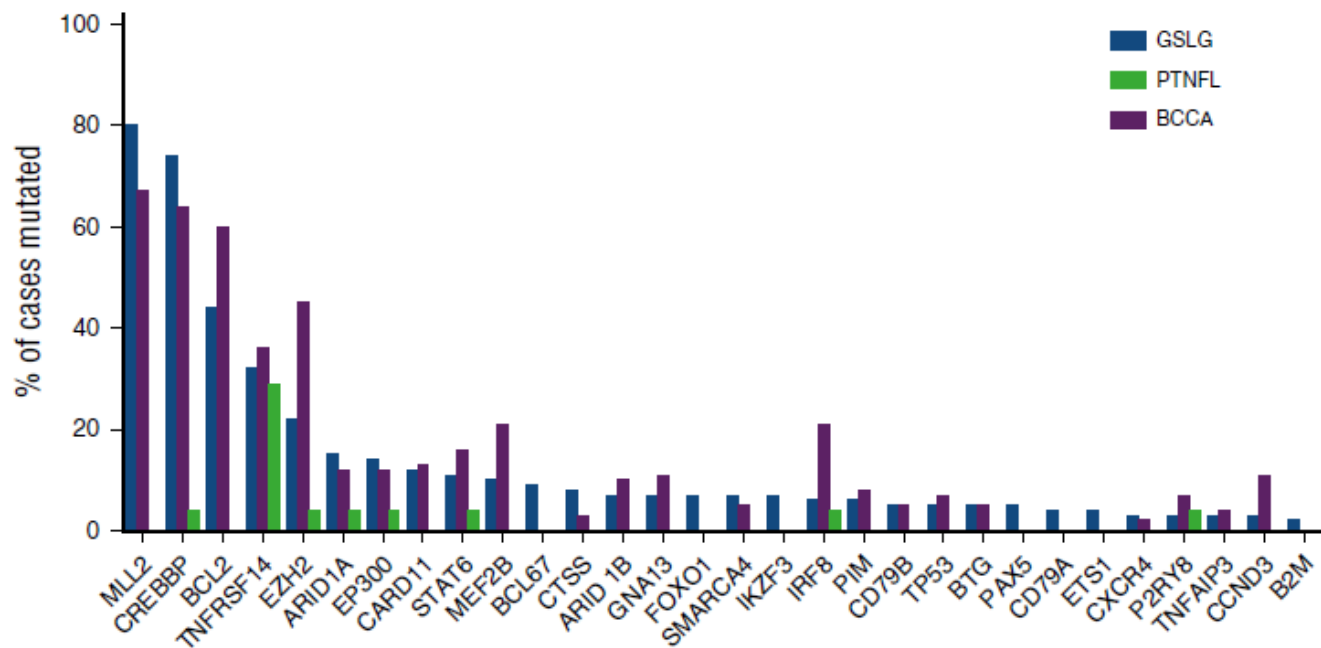# Follicular lymphoma, pediatric type

Martin-Guerrero et al., Haemtologica, 2013

Follicular lymphoma, pediatric type

TNFRSF14, MAP2K1, IRF8, …

Loussaint et al., Blood, , 2016

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