

Mediastinal B-cell Lymphomas

A Spectrum of Diseases

Wyndham H. Wilson, MD, PhD



Mediastinal B-cell Lymphomas

- Nodular sclerosis Hodgkin Lymphoma
- Mediastinal grey zone lymphoma
- Primary mediastinal B-cell lymphoma

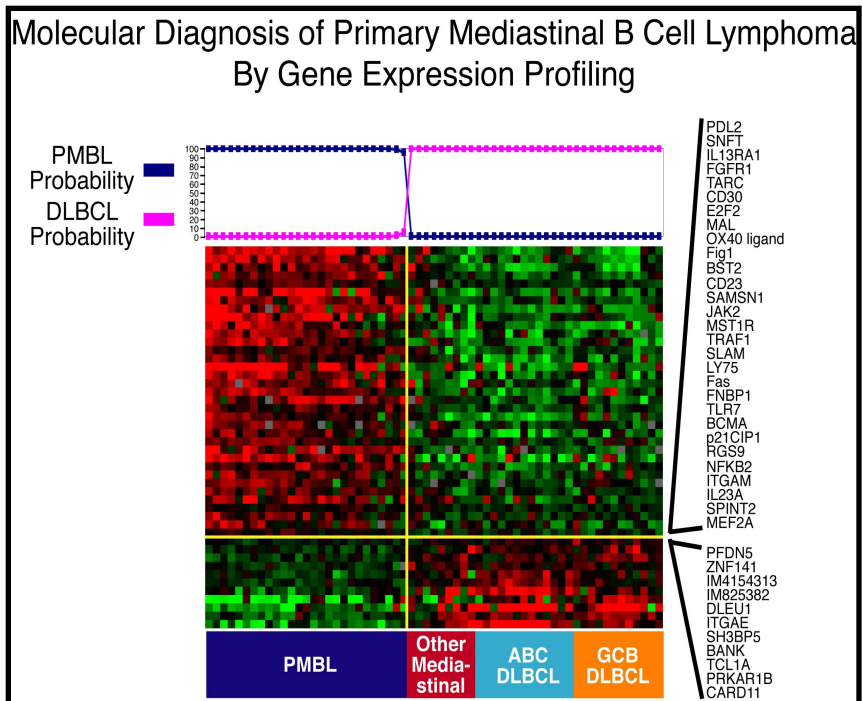
Shared clinical features

- Mediastinal presentation (typically localized)
- Young age at presentation (3rd-4th decade)
- Predominance in young women
- Favorable prognosis

Mediastinal Lymphomas

Molecular Overlap

PMBL and NS-Hodgkin Lymphoma

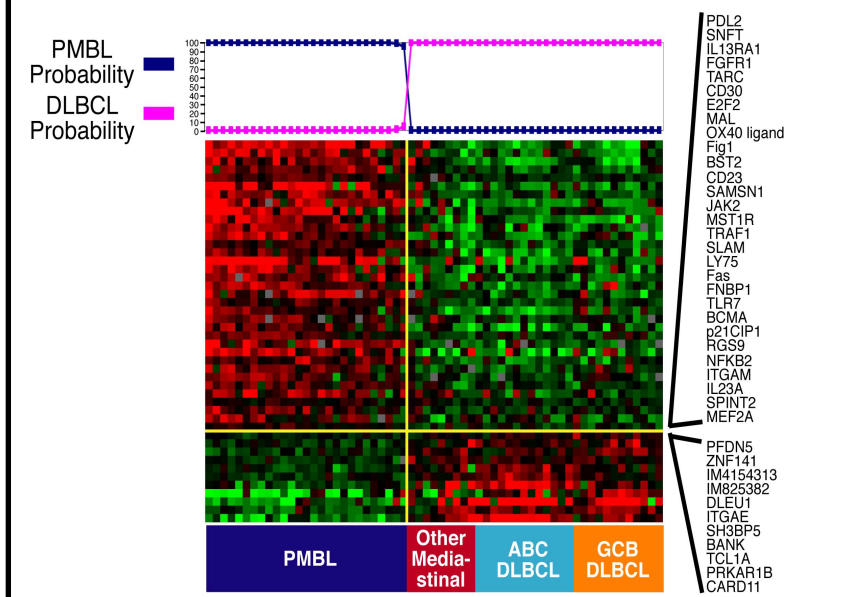


Mediastinal Lymphomas

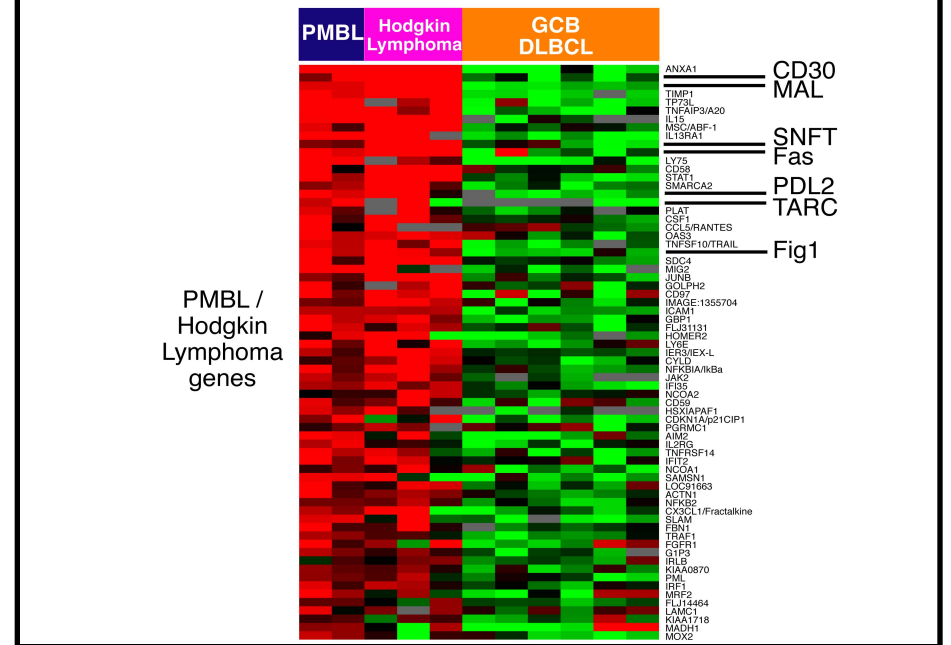
Molecular Overlap

PMBL and NS-Hodgkin Lymphoma

Molecular Diagnosis of Primary Mediastinal B Cell Lymphoma
By Gene Expression Profiling



Extensive Gene Expression Overlap Between Hodgkin Lymphoma and
Primary Mediastinal Large B Cell Lymphoma



IHC Phenotype of Thymic B-cell Lymphomas

Neg	CD20	↑
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↑	CD15	Neg
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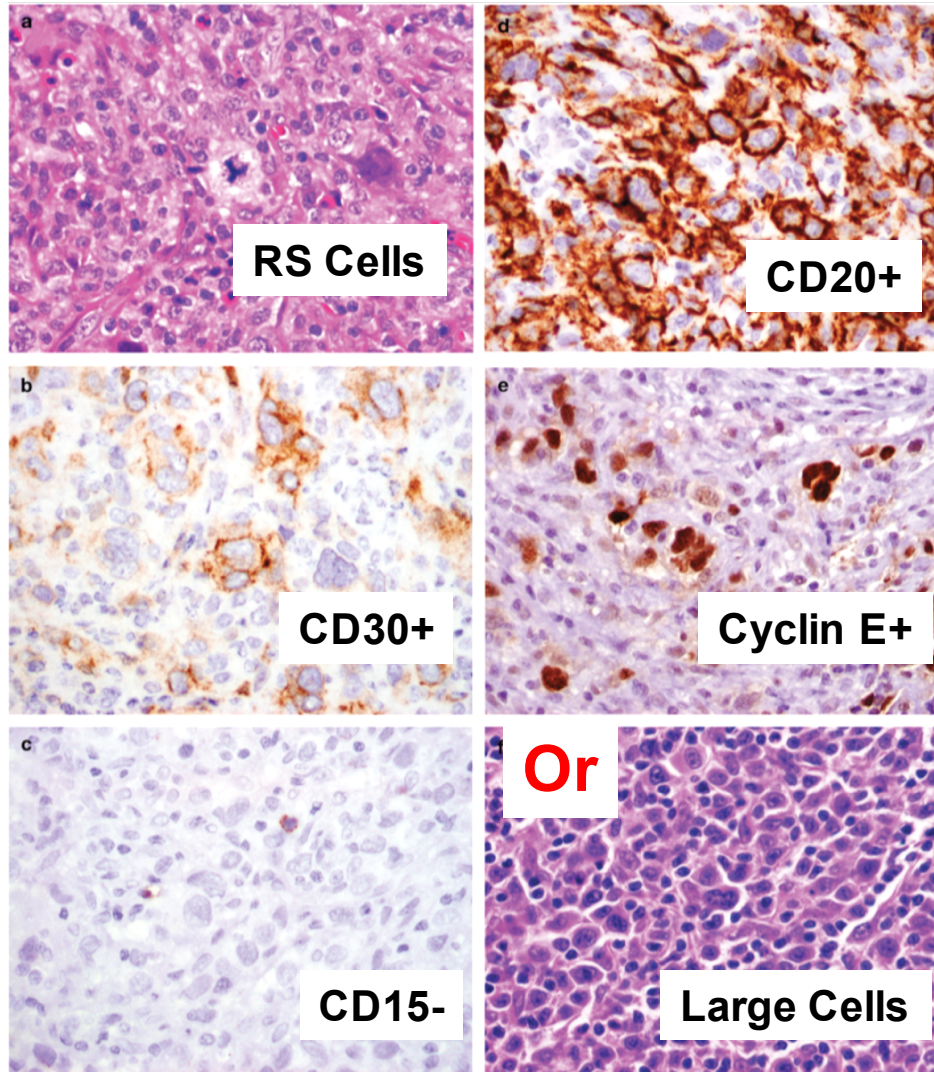
↑	CD30	↓
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↓	Tumor Density	↑
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Mediastinal Grey Zone Lymphoma

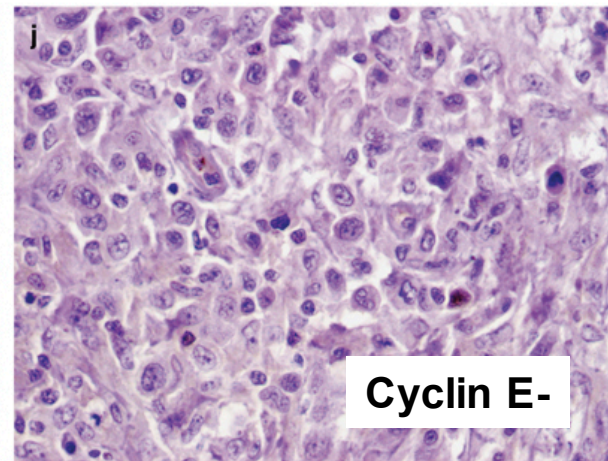
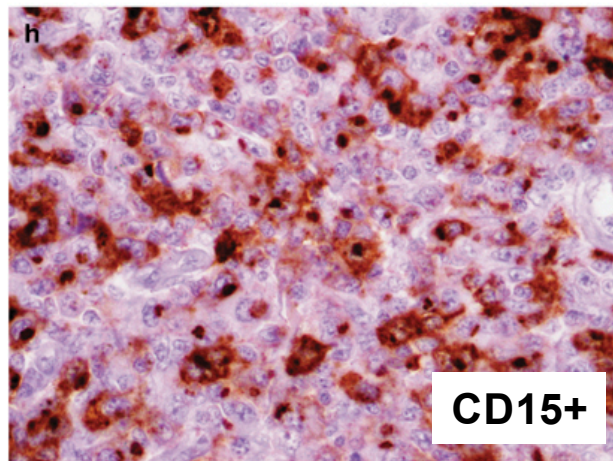
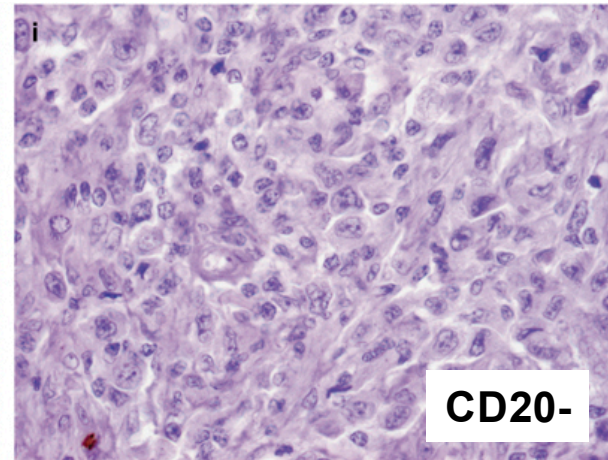
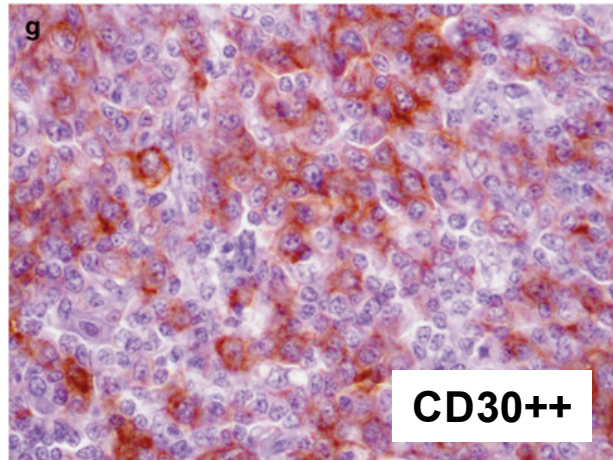
NsHL Morphology but PMBL IHC



PMBL Morphology but NsHL IHC

Mediastinal Gray Zone Lymphoma

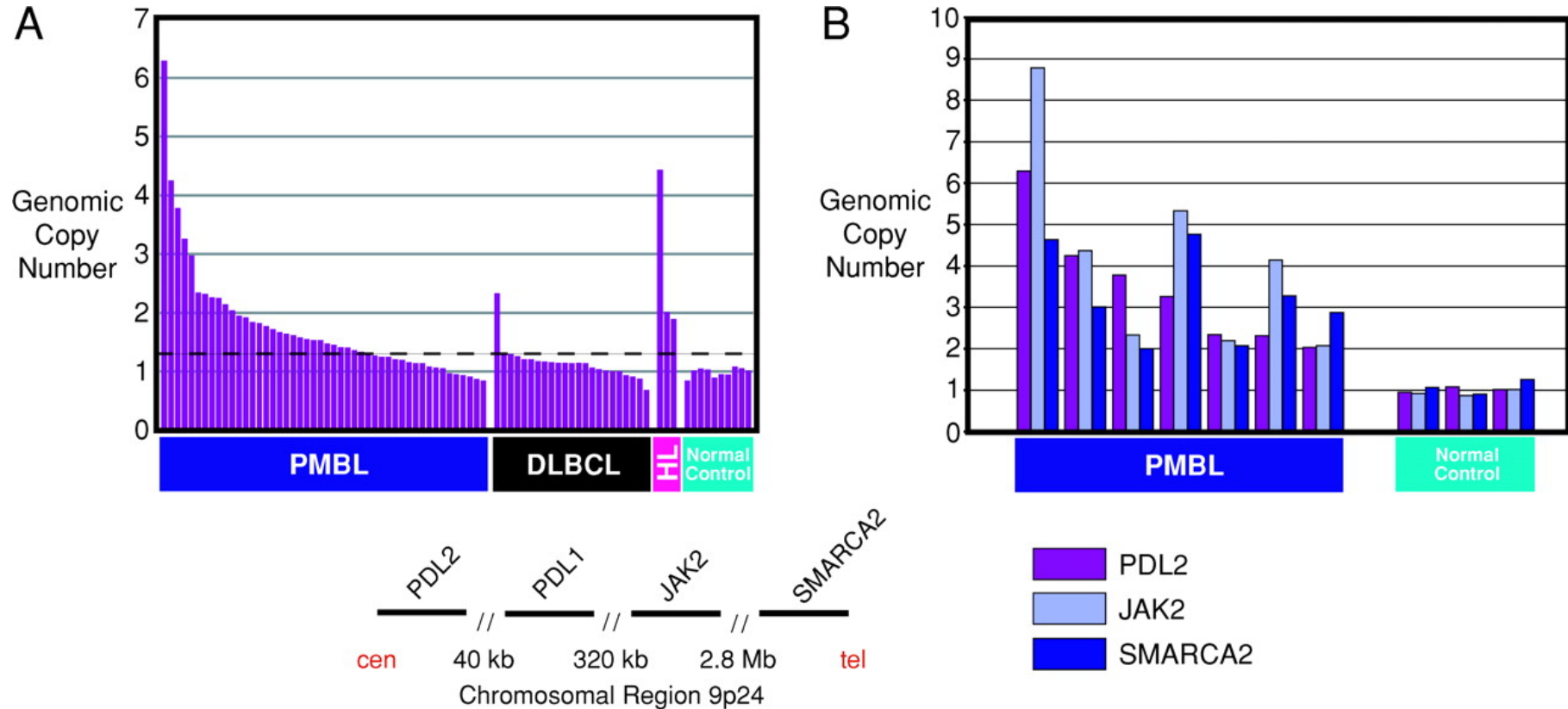
PMBL Morphology but NsHL IHC



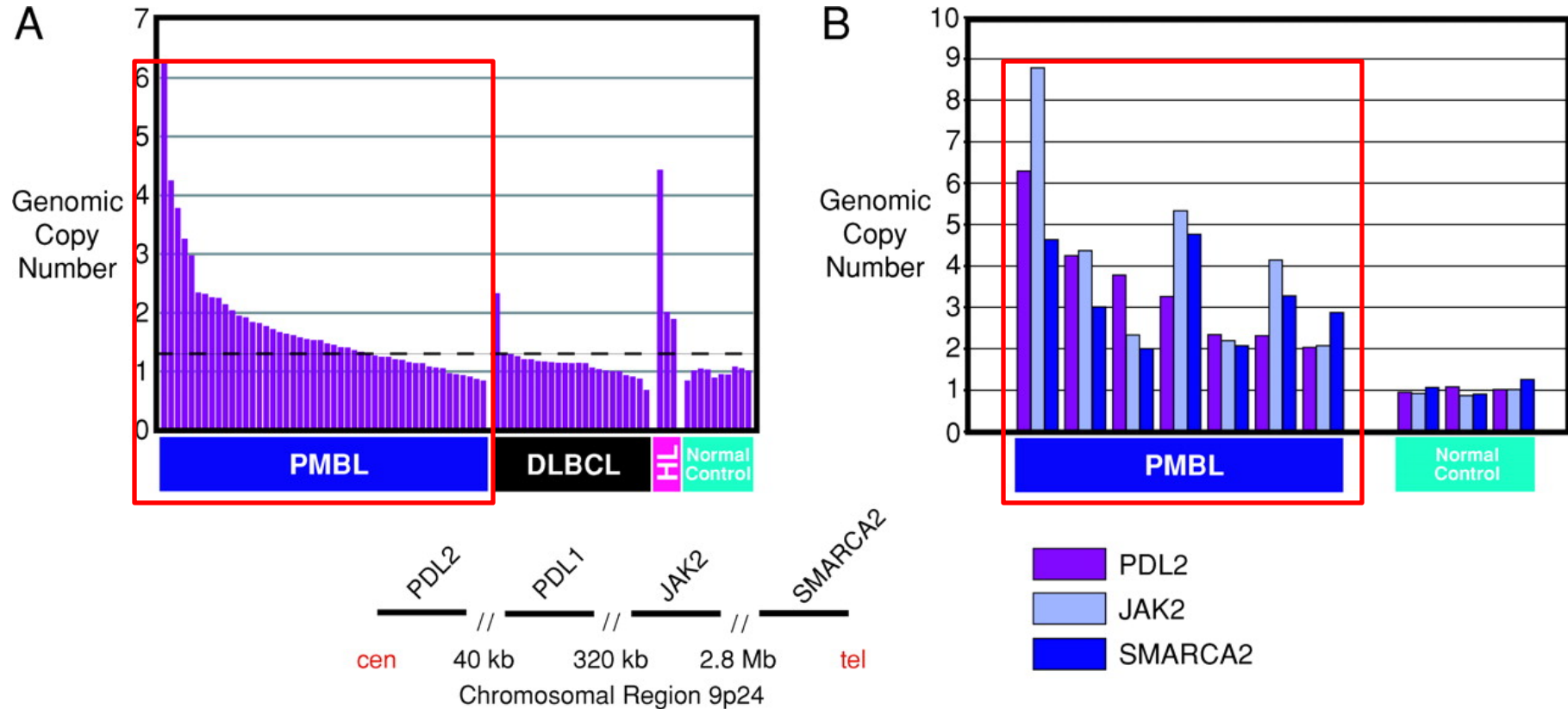
Mediastinal Gray Zone Lymphomas

- So: Is GZL biologically related to PMBL or NsHL or neither?
 - Tumor mutations

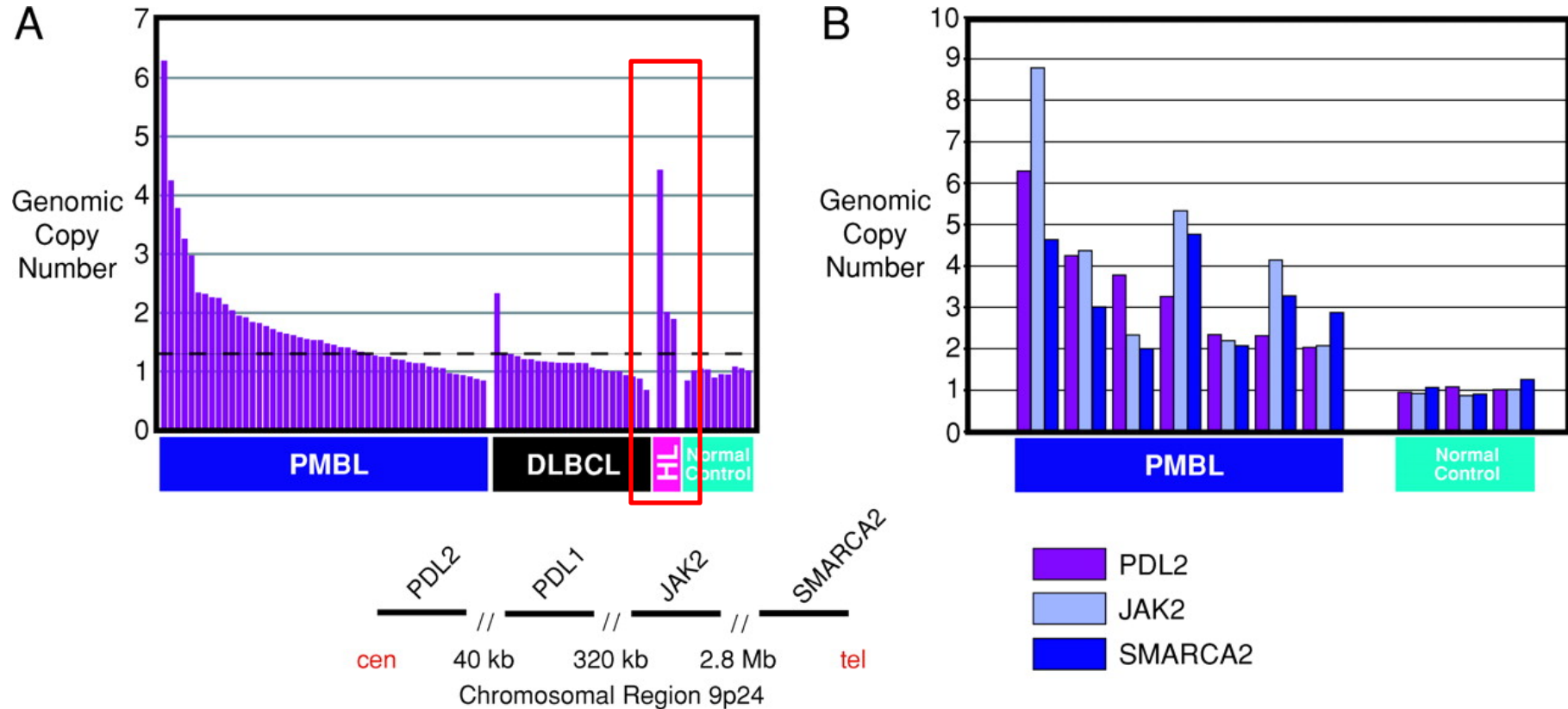
9-p24 amplification PMBL and nsHL



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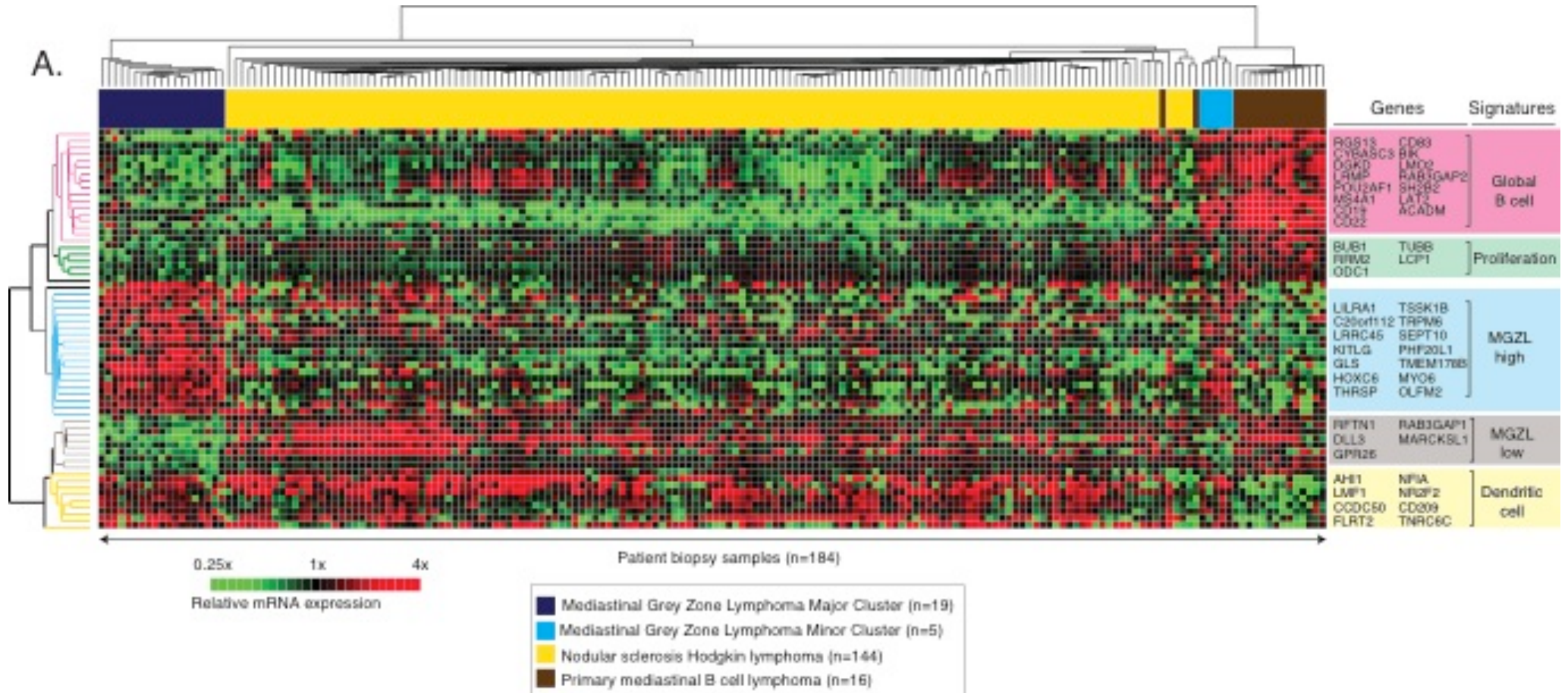
Mediastinal Grey Zone Lymphomas

<i>FISH analysis</i>	Extra-Mediastinal	Mediastinal	
2p16.1 (<i>BCL11, REL</i>) gain/amplification	25% (2/8)	36% (8/22)	0.68 _b
8q24 (<i>MYC</i>) gain	17% (1/6)	30% (6/20)	1.0 _b
9p24.1 (<i>JAK2, PDL2</i>) gain/amplification	38% (3/8)	61% (14/23)	0.41 _b
16p13.13 (<i>CIITA</i>) gain/amplification/break	44% (4/9)	33% (7/21)	0.69 _b

Mediastinal Gray Zone Lymphomas

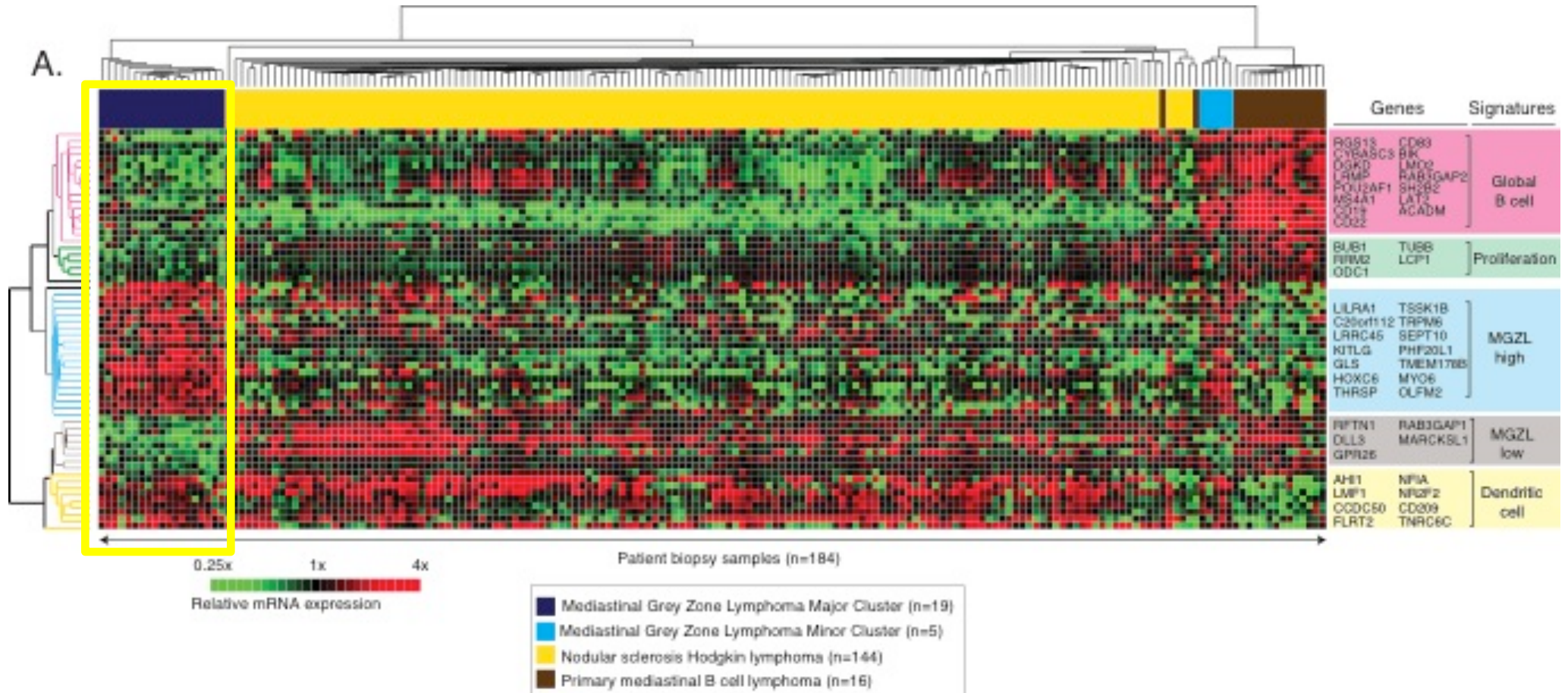
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 - Tumor mutations
 - **Gene expression**

Mediastinal Grey Zone GEP

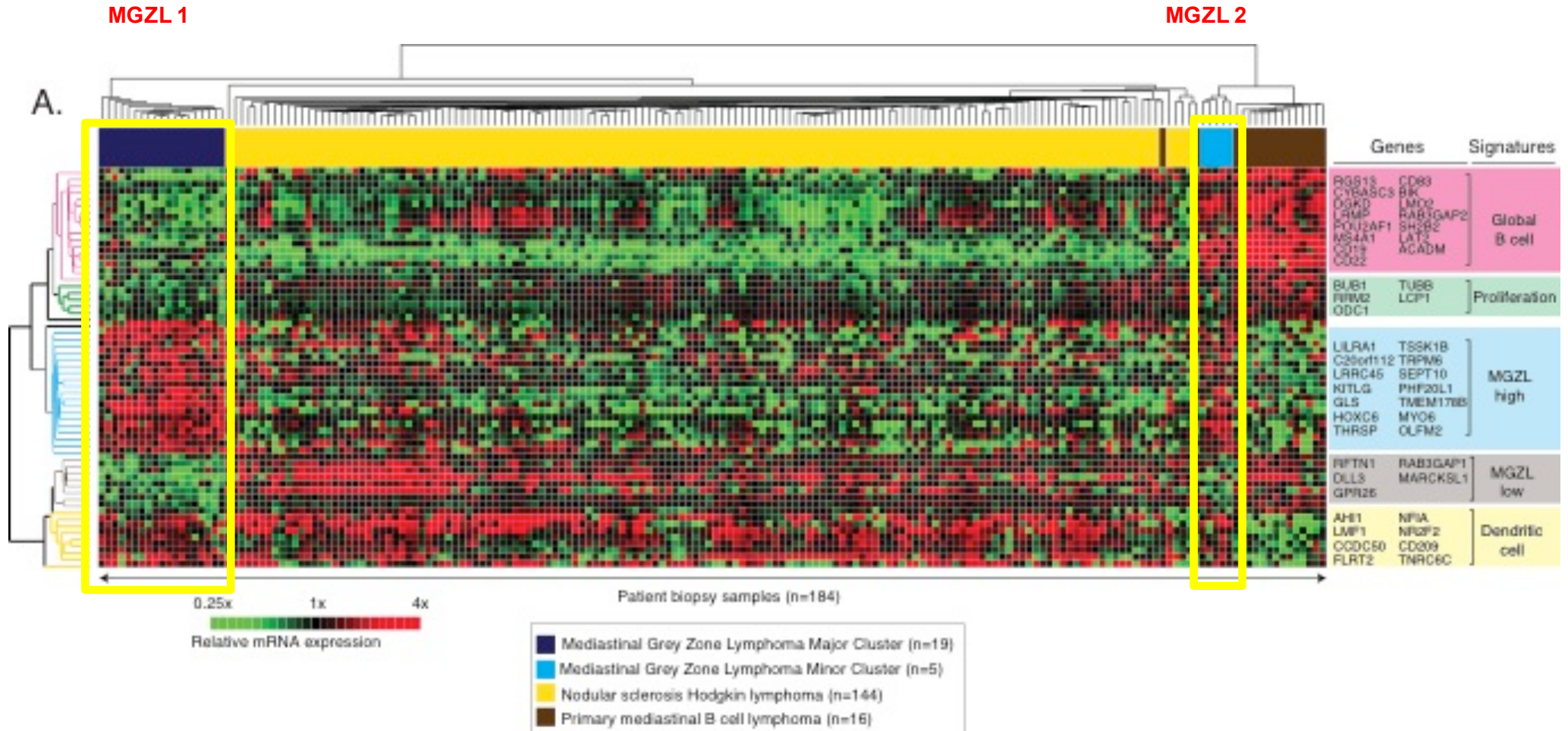


Mediastinal Grey Zone GEP

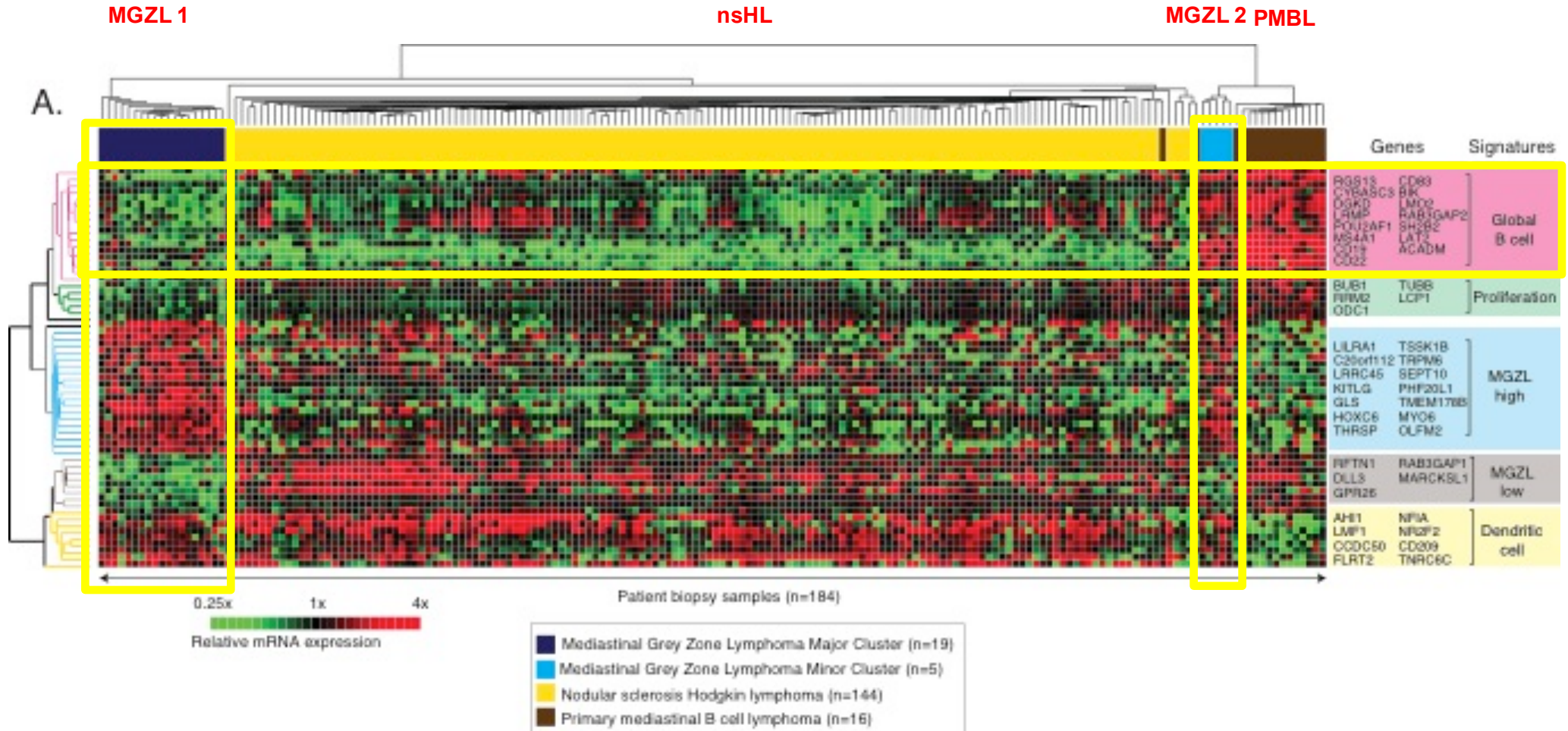
MGZL 1



Mediastinal Grey Zone GEP

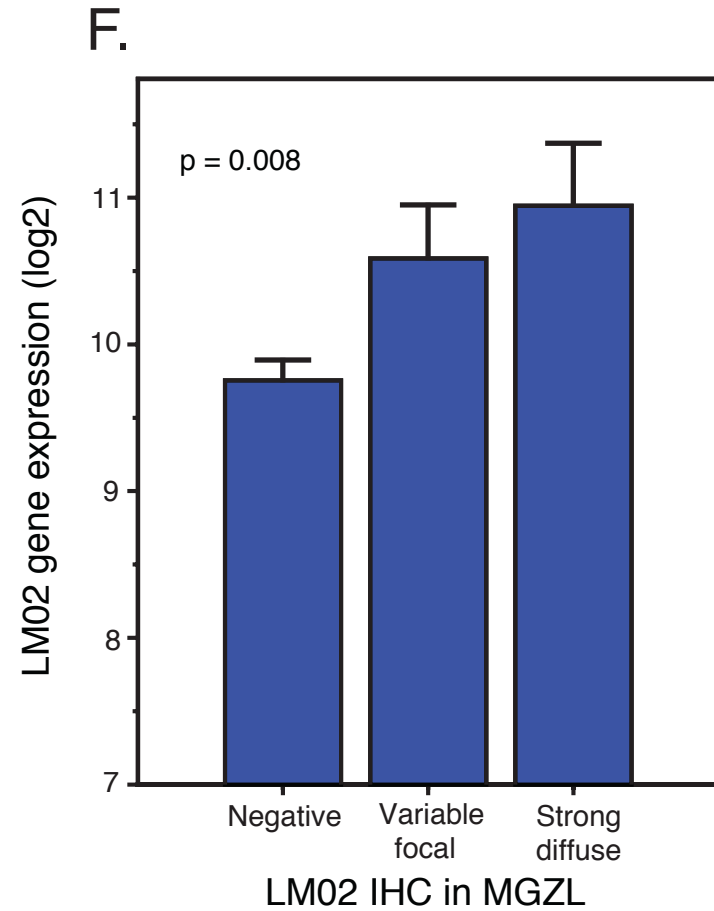
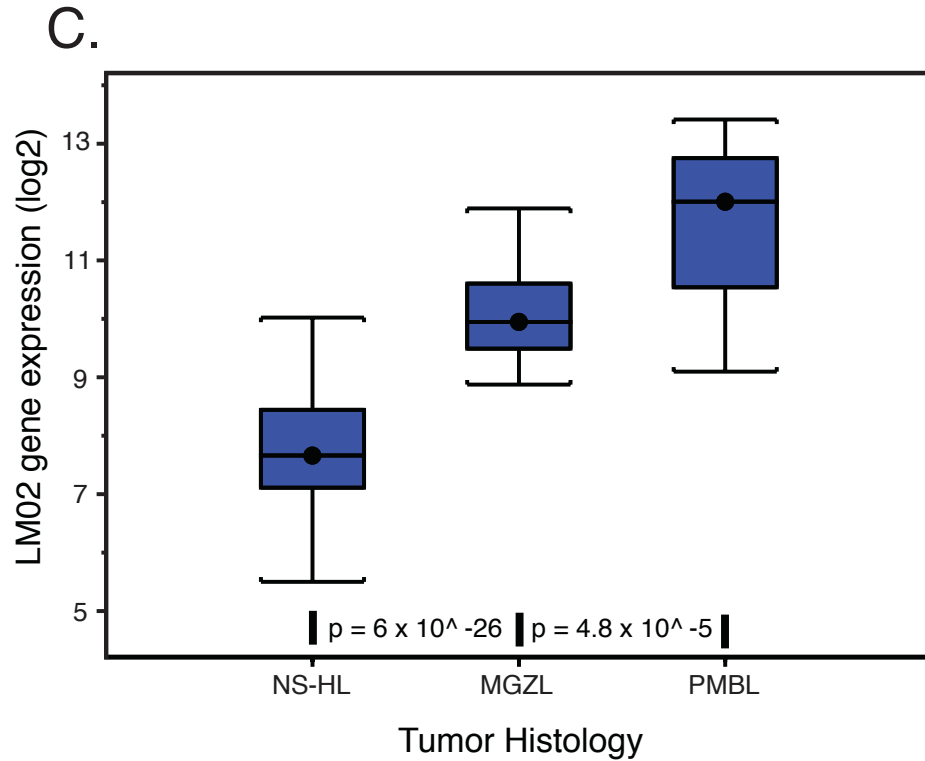


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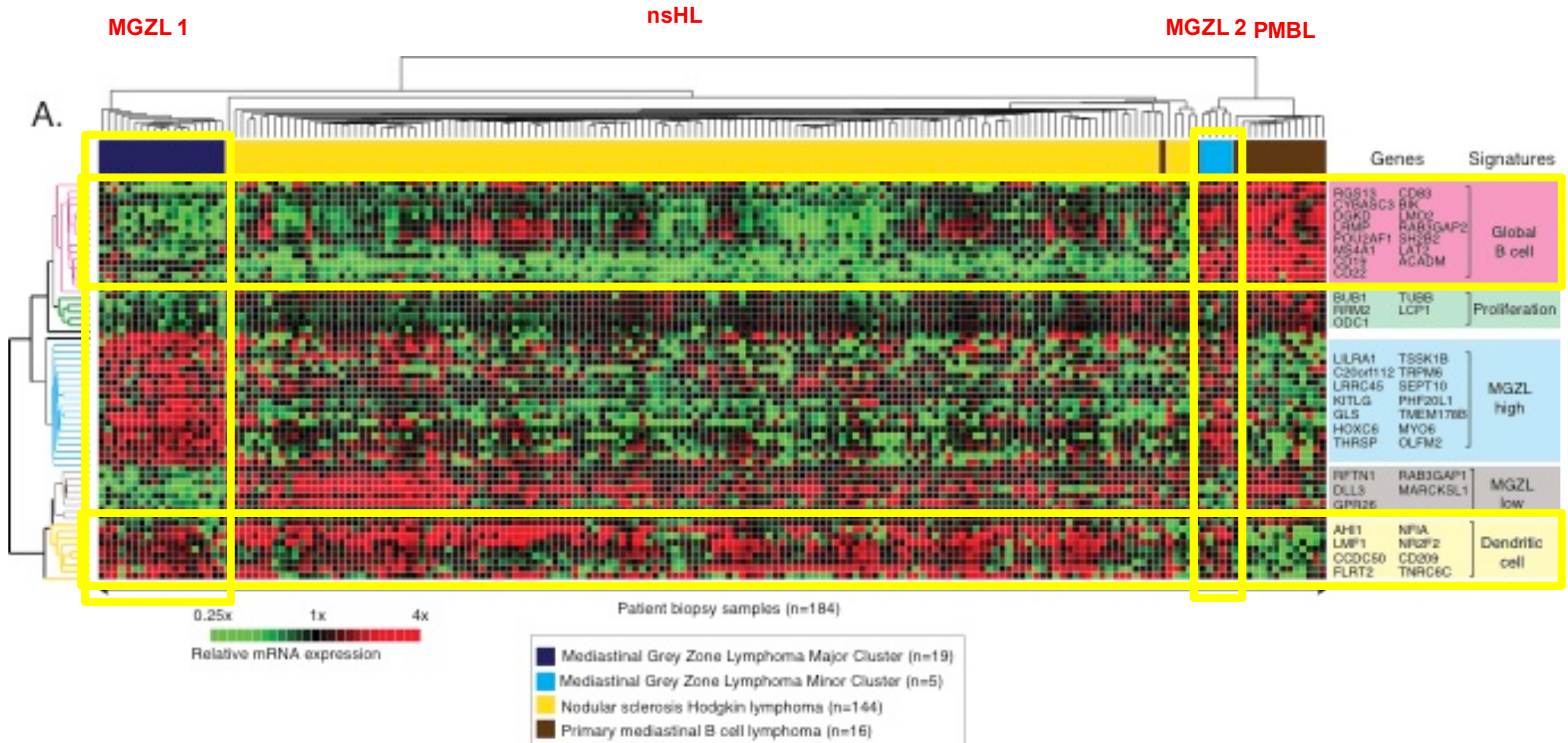


Mediastinal Grey Zone GEP

Germinal Center B-cell Expression

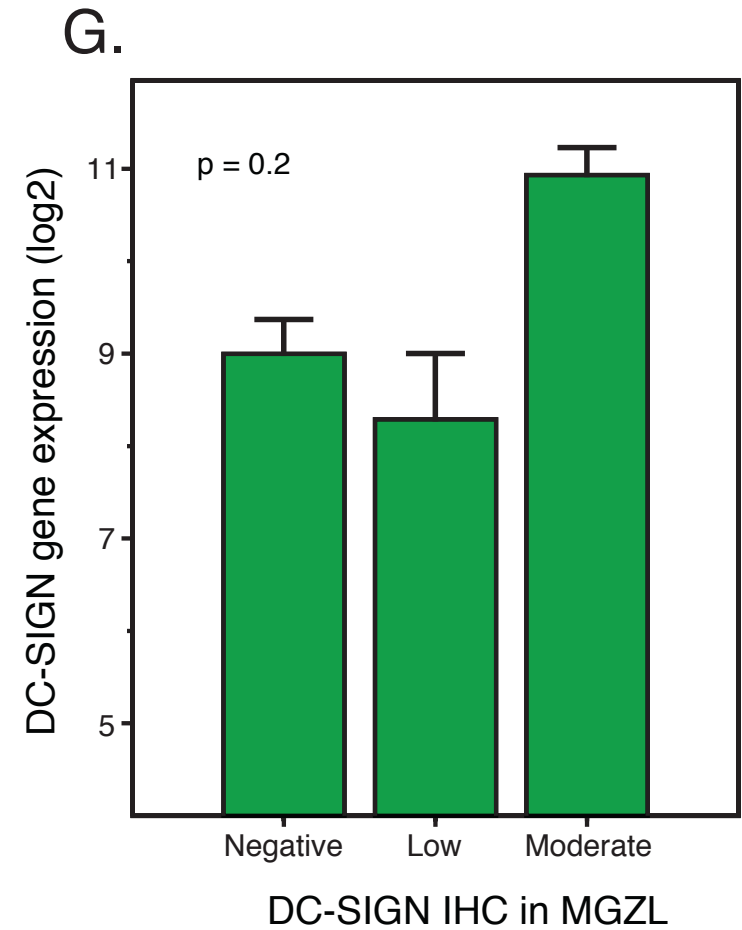
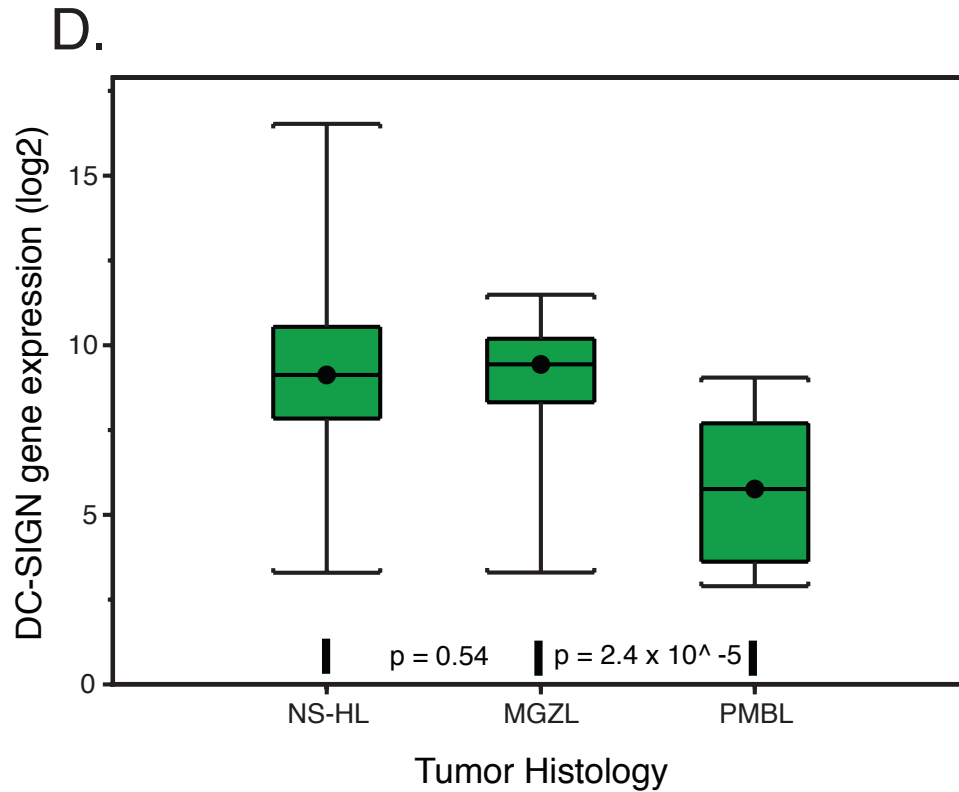


Mediastinal Grey Zone GEP



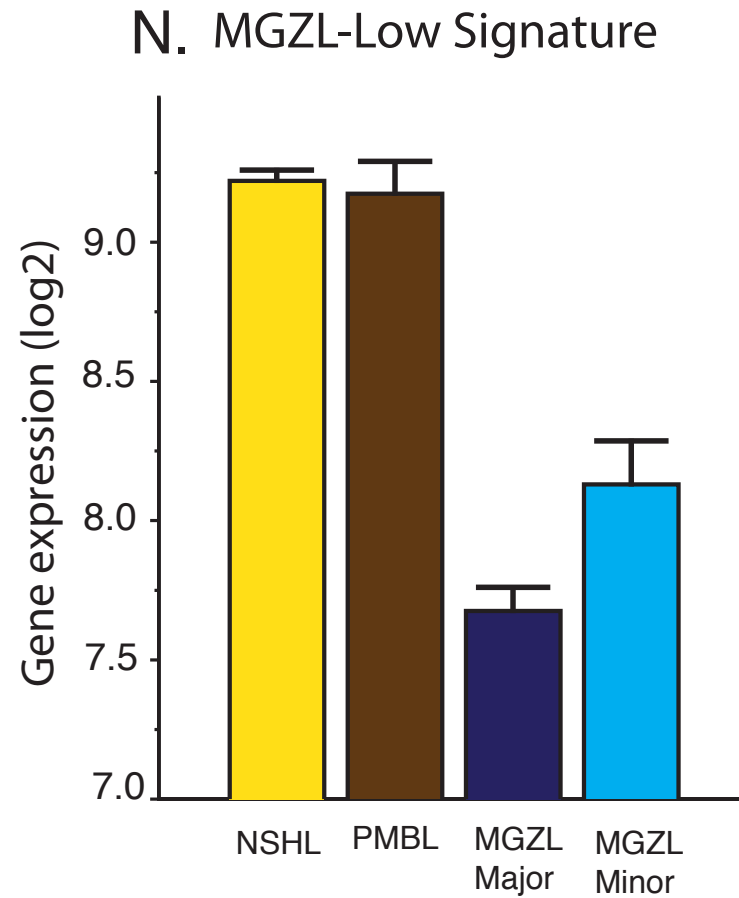
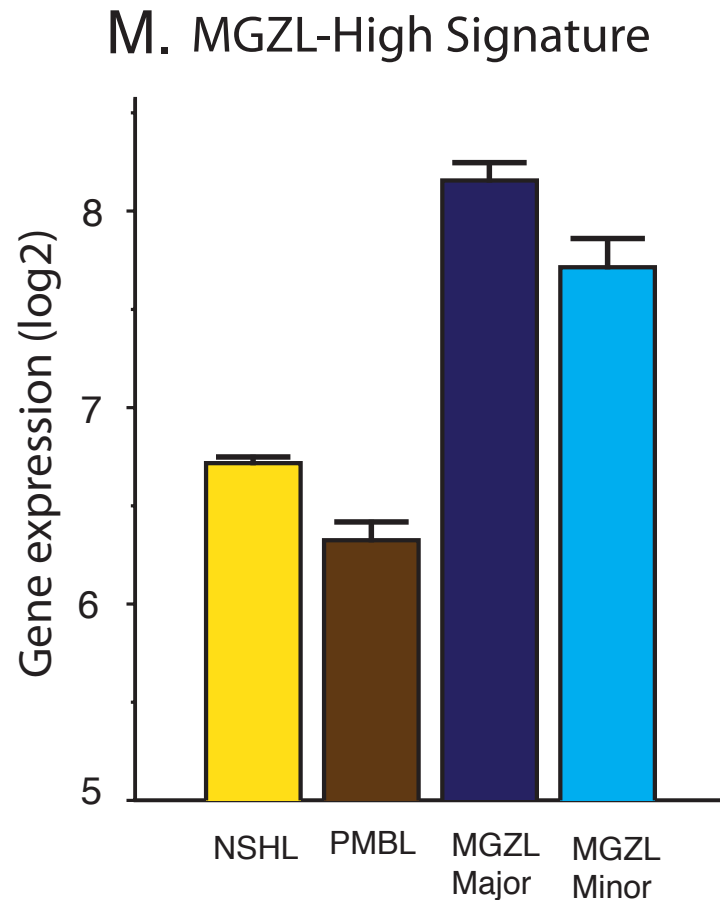
Mediastinal Grey Zone GEP

DC-SIGN (Dendritic cell) Gene Expression



Mediastinal Grey Zone GEP

Unique GZL Signatures



Mediastinal Grey Zone Lymphomas

Is GZL biologically related to PMBL or NsHL?

- Microenvironment overlap with NsHL
 - Dendritic cell signature
- Expression of B-cell program overlap with PMBL
 - GC B-cell genes
 - Pan-B cell genes (variable)
- Two unique signatures

Eligibility

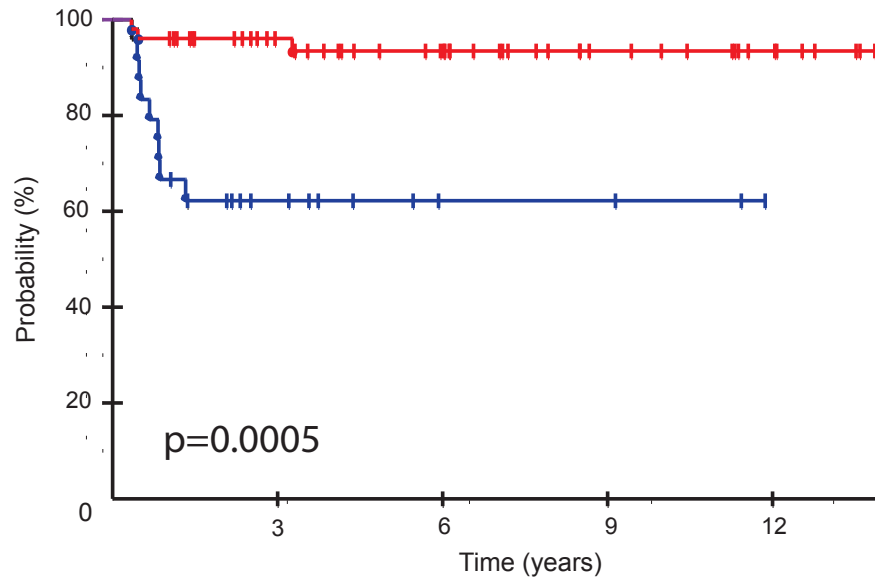
- Untreated PMBL and MGZL
- Age \geq 12 years
- Stage I if $>$ 5 cm and all stage II-IV
- Adequate organ function unless disease related
- HIV negative

Patient Characteristics

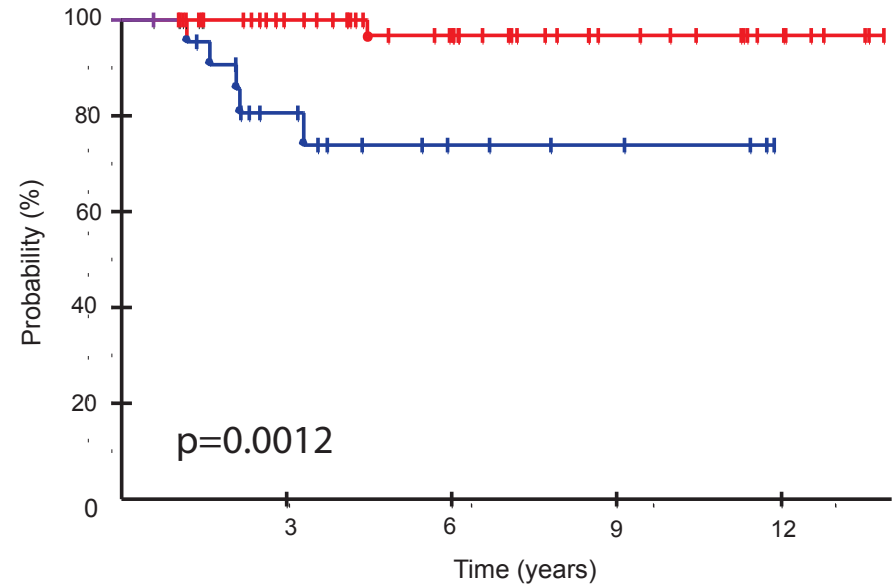
Characteristics	MGZL	PMBL	p2
Total Patients	24	51	
Male Gender	15 (63%)	21 (41%)	0.14
Age years median (range)	33 (14-59)	30 (19-52)	0.61
Bulky Tumor ≥ 10 cm [range]	11 (46%) [1.3-20]	33 (65%) [5-18]	0.14
Stage IV disease	3 (13%)	15 (29%)	0.15
LDH > Normal	12 (50%)	40 (78%)	0.017
Extranodal site	6 (25%)	27 (53%)	0.027
Pleural or pericardial effusion	5 (21%)	28 (55%)	0.006
ALC cells/mm³ median (range)	0.88 (0.3-2.88)	1.01 (0.24-2.15)	0.78
Predominant Tumor Morphology			
PMBL-Like	8 (33%)	NA	
NSHL-Like	15 (63%)	NA	
Composite (PMBL and NSHL)	1 (4%)	NA	
Immunohistochemistry*			
CD20+ (malignant cells)			
Any staining	24/24 (100%)	51/51 (100%)	1.0
Strong-diffuse staining	17/24 (71%)	51/51 (100%)	< 0.0001
CD30+ (malignant cells)	24/24(100%)	30/44 (68%)	0.001
CD15+ (malignant cells)	13/24 (54%)	2/34 (6%)	< 0.0001
BCL-6+ (malignant cells)	13/15 (86%)	33/37 (89%)	1.0
DC-SIGN+ (infiltrating cells)	10/19 (53%)	12/35 (34%)	0.25
CD68+ (infiltrating cells)	16/16 (100%)	26/28 (93%)	1.0

Mediastinal Gray Zone Lymphomas DA-EPOCH-R

A. Event-Free Survival (MGZL and PMBL)



B. Overall Survival (MGZL and PMBL)

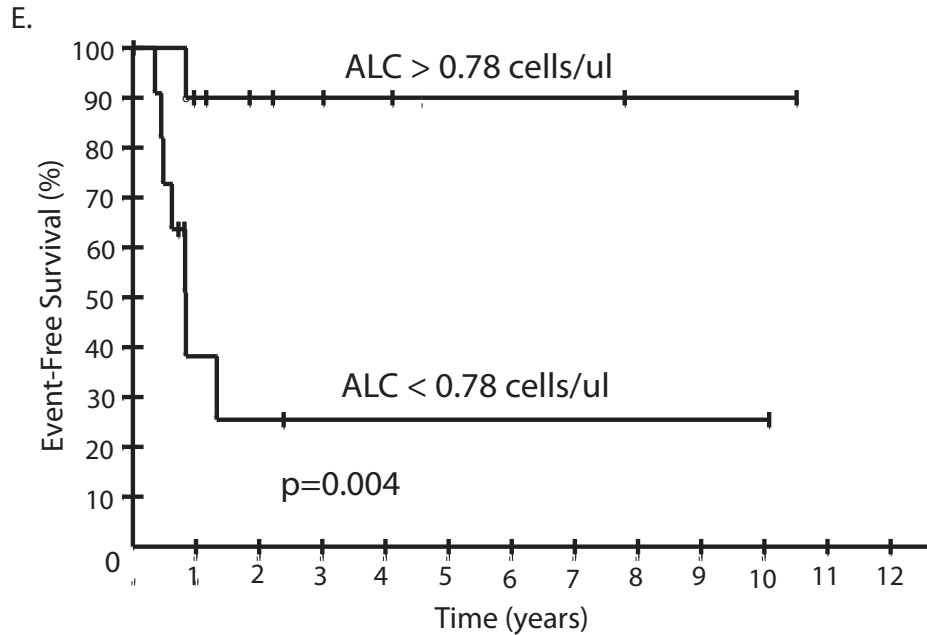


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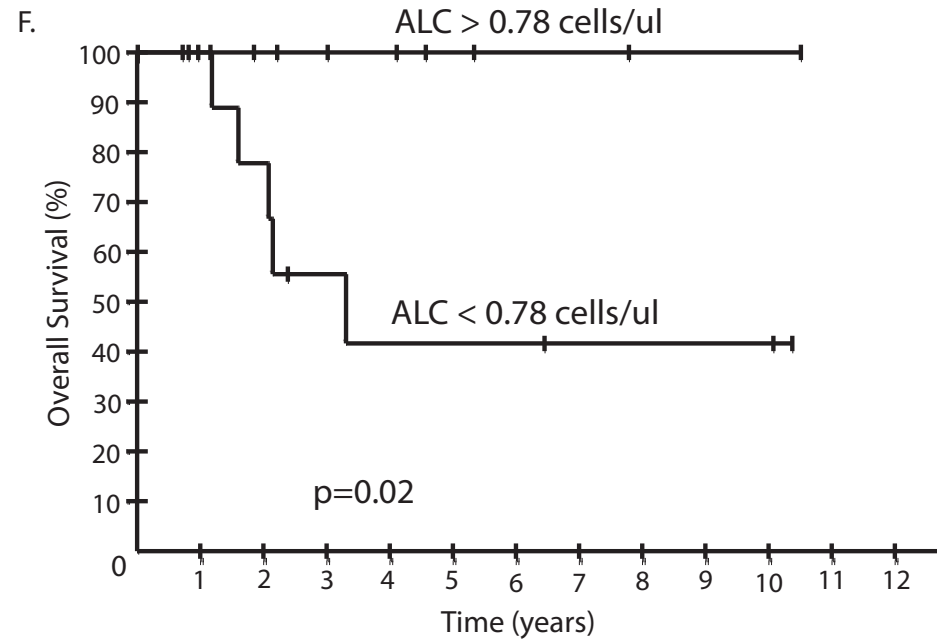
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Prognostic Factors in MGZL

Event-Free Survival



Overall Survival

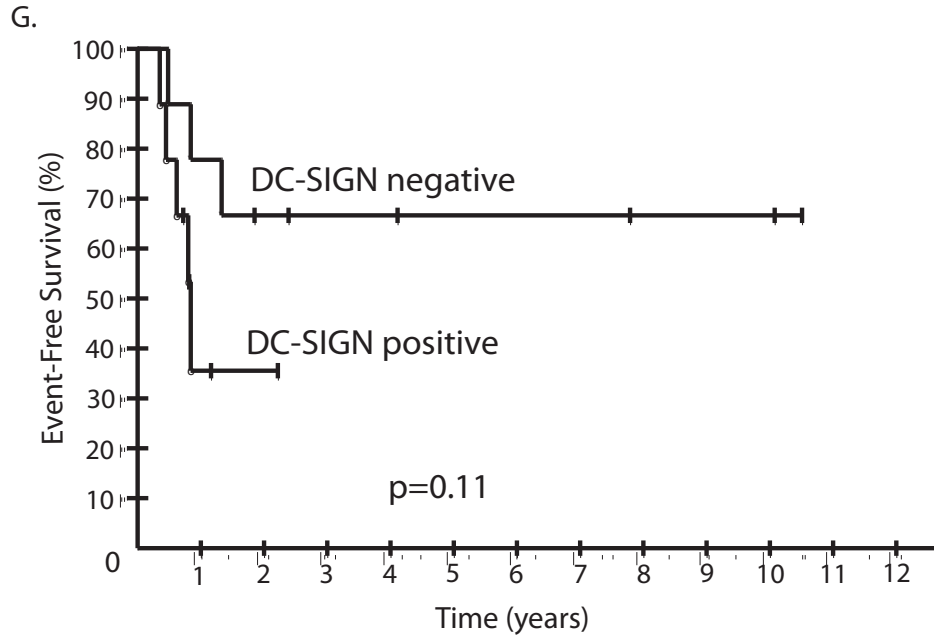


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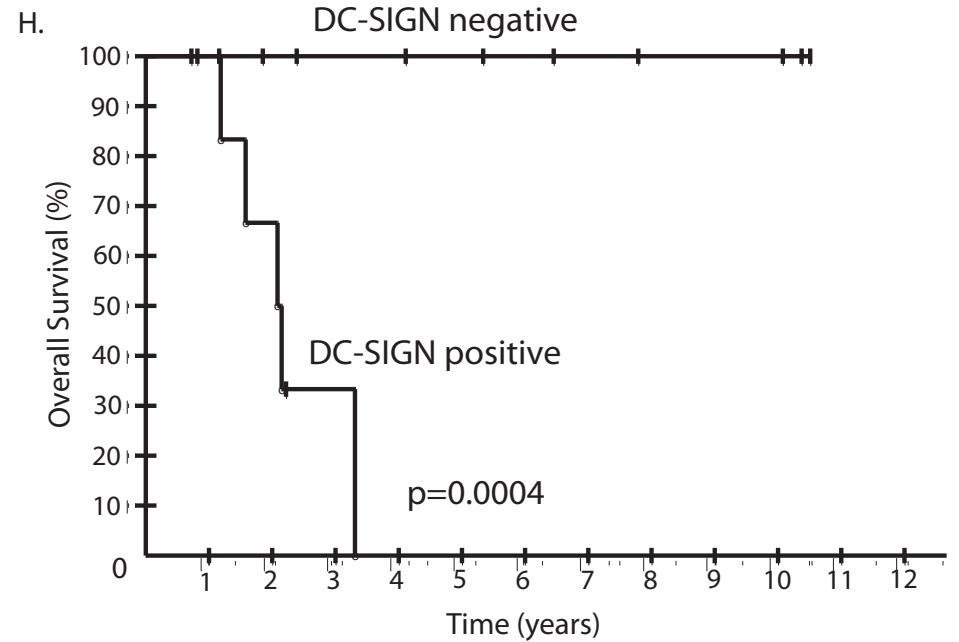
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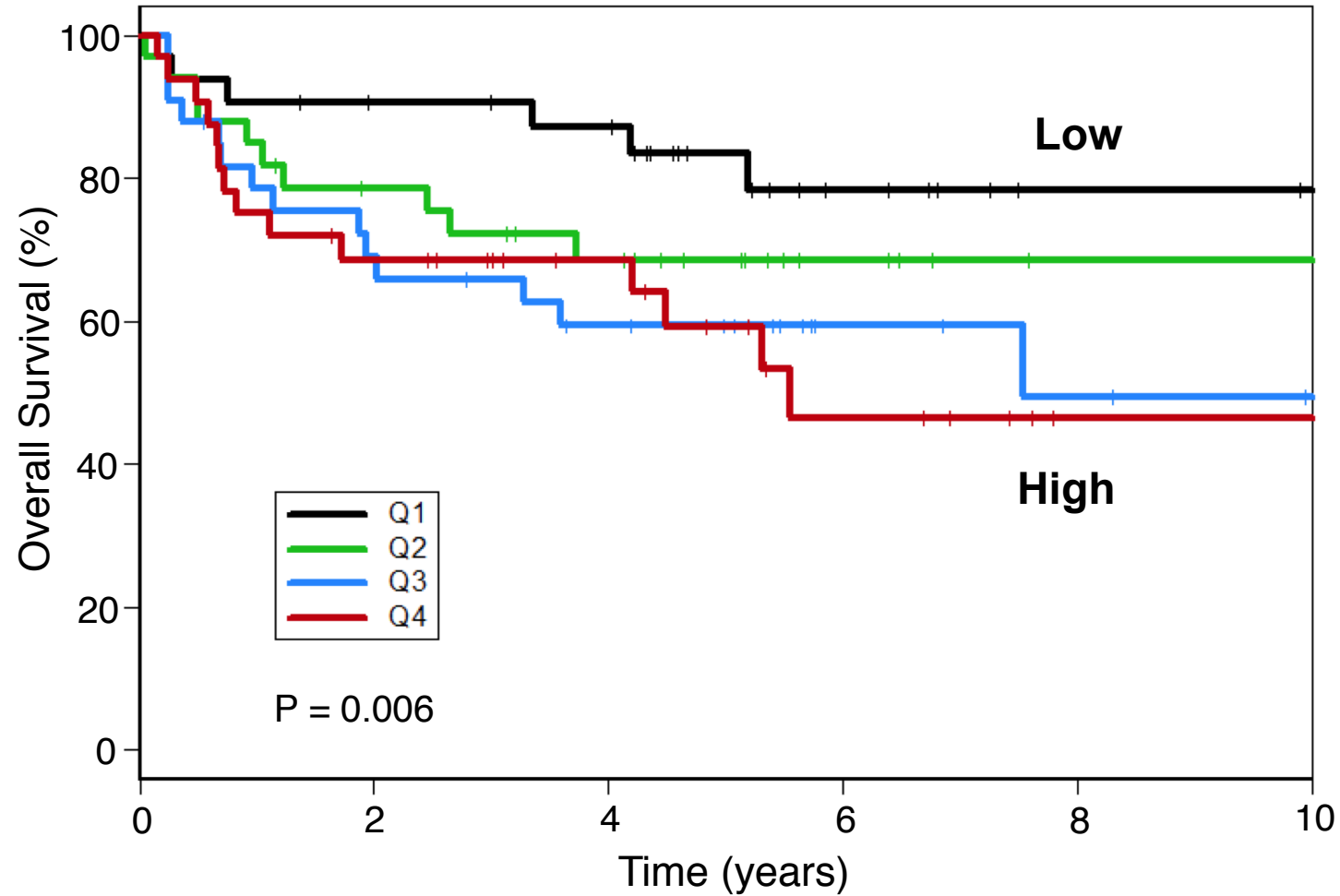
Event-Free Survival



Overall Survival



Prognostic Effect of DC-SIGN Gene Expression in NS-HL



End of Treatment FDG-PET

Variables	SUV _{max} ≤ Mediastinal Blood Pool (N=11)		SUV _{max} > Mediastinal Blood Pool (N=10)	
	No Uptake	SUV _{max} ≤ Mediastinal Blood Pool	SUV _{max} < Liver	SUV _{max} ≥ Liver
Deauville Score	1	2	3	4-5
Disease absent	7	2	4	0
Disease documented	1	1	1	5
Outcome Measures				
Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	
63%	100%	100%	81%	

Abbreviations: SUV_{max}-maximal standard uptake value. Deauville score 1-3 and 4-5 interpreted as negative and positive, respectively.

Conclusions

MGZL

- Patients with MGZL lymphoma have a significantly worse outcome compared to PMBL
- Post-therapy FDG-PET has a good negative predictive value for relapse
- MGZL presents with two types
 - One histologically like nsHL but B-cell program
 - One histologically like PMBL but nsHL microenvironment

Acknowledgments

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Jason Lih

Randy Gascoyne