T(14;18) translocation as a candidate marker of high-grade transformation in HCV-associated Malt lymphomas

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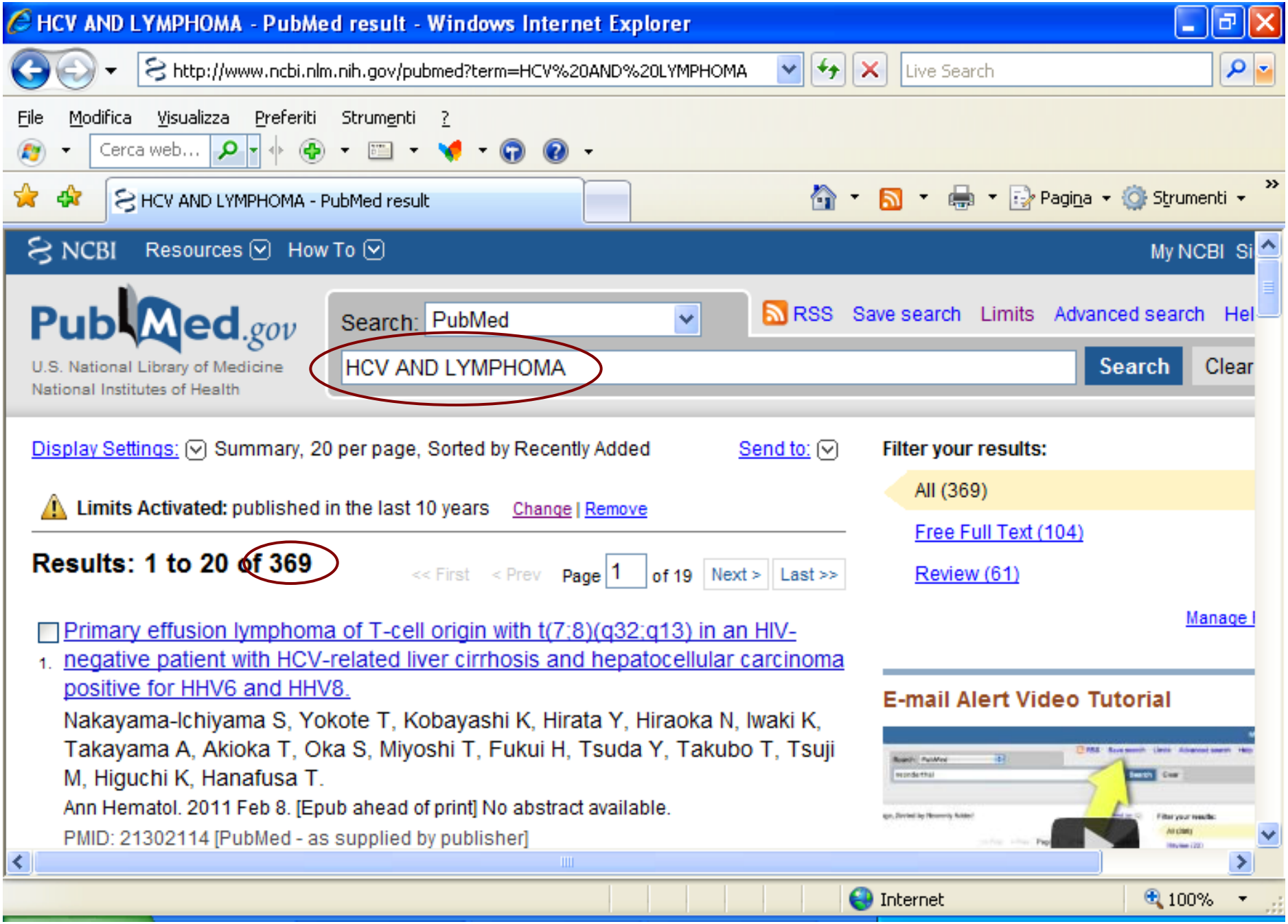
Table I. Prevalence of anti-HCV antibodies (Abs) and/or HCV-RNA among Italian case-control studies and case-series of non-Hodgkin's lymphoma patients.

Authors/refs.	Location	All NHL cases	NHL cases[a]	Anti-HCV Abs positivity		HCV RNA positivity	
				NHL	% (95% CI)	NHL	% (95% CI)[b]
All studies		2810	2736	539	19.7 (18.2-21.2)	206	14.7 (12.8-16.6)
Case-control studies		1195	1168	272	23.3 (20.9-25.7)	124	21.6 (18.2-24.9)
Talamini *et al* (10)	Pordenone/Naples	225	202	40	19.8 (14.3-25.3)		
Mele *et al* (6)	9 Italian towns	400	400	70	17.5 (13.8-21.2)	60	15.0 (11.5-18.5)
Guida *et al* (86)	Bari	60	56	12	21.4 (10.7-32.2)		
Montella *et al* (87)	Naples	101	101	25	24.8 (16.3-33.2)		
Vallisa *et al* (88)	Piacenza	175	175	65	37.1 (30.0-44.3)	64	36.6 (29.4-43.7)
De Vita *et al* (89)	Aviano/Pordenone	84	84	20	23.8 (14.7-32.9)		
Musto *et al* (90)	Foggia	150	150	40	26.7 (19.6-33.7)		
Case series		1615	1568	267	17.0 (15.2-18.9)	82	9.9 (7.9-12.0)
De Renzo *et al* (91)	Naples	61	61	12	19.7 (9.7-29.6)		
Pioltelli *et al* (92)	Northern Italy	300	300	48	16.0 (11.9-20.1)	41	13.7 (9.8-17.6)
Luppi *et al* (93)	Modena	157	157	35	22.3 (15.8-28.8)		
Catassi *et al* (94)	8 Italian towns	143	104	15	14.4 (7.7-21.2)		
Silvestri *et al* (17)	Udine	470	470	42	8.9 (6.4-11.5)	31	6.6 (4.4-8.8)
Pivetti *et al* (95)	Turin	47	47	7	14.9 (4.7-25.1)		
Pioltelli *et al* (96)	Milan	126	126	26	20.6 (13.6-27.7)		
Musolino *et al* (97)	Messina	24	24	2	8.3 (0.0-19.4)	5	20.8 (4.6-37.1)
Mazzaro *et al* (5)	NorthEast Italy	199	197	55	27.9 (21.7-34.2)		
Andriani *et al* (98)	Rome	38	32	8	25.0 (10.0-40.0)	5	15.6 (3.0-28.2)
Ferri *et al* (99)	Pisa	50	50	17	34.0 (20.9-47.1)		


HCV AND LYMPHOMA - PubMed result - Windows Internet Explorer
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All (369)
Free Full Text (104)
Review (61)
Limits Activated: published in the last 10 years Change | Remove
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1. Primary effusion lymphoma of T-cell origin with t(7;8)(q32;q13) in an HIV-negative patient with HCV-related liver cirrhosis and hepatocellular carcinoma positive for HHV6 and HHV8.
Nakayama-Ichiyama S, Yokote T, Kobayashi K, Hirata Y, Hiraoka N, Iwaki K, Takayama A, Akioka T, Oka S, Miyoshi T, Fukui H, Tsuda Y, Takubo T, Tsuji M, Higuchi K, Hanafusa T.
Ann Hematol. 2011 Feb 8. [Epub ahead of print] No abstract available.
PMID: 21302114 [PubMed - as supplied by publisher]
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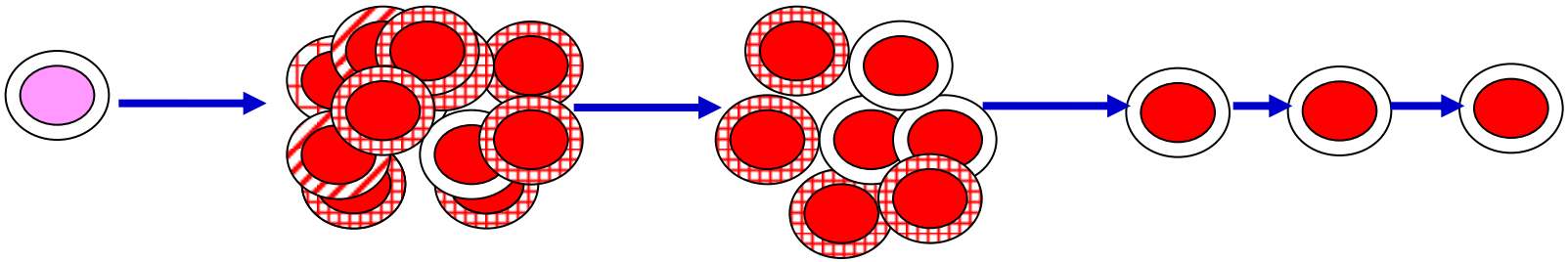
NATURAL HISTORY OF B-CELL LYMPHOMA

NORMAL B LYMPHOCYTE

POLICLONAL HYPERPLASIA

OLIGOCLONAL HYPERPLASIA

MONOCLONAL LYMPHOMA



ANTIGENIC STIMULATION

GENETIC ALTERATIONS

Chronic inflammation and antigenic stimulation may be caused by infection of:

- *Helicobacter pylori*
- *Chlamydia psittaci*
- *Epstein-Barr Virus*
- *Human Immunodeficiency Virus*
- ***Hepatitis C Virus***

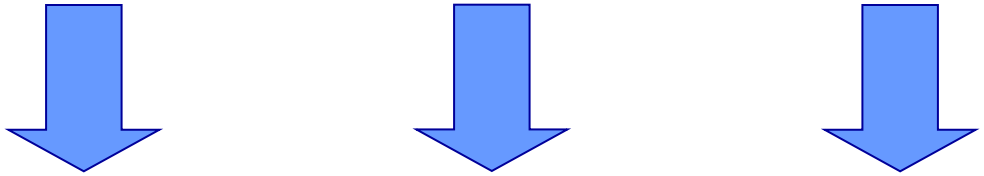
In the context of genetic alterations, previous studies have suggested a role for t(14;18) translocation in the development of lymphoproliferative disorders of HCV-infected individuals

Zignego *et al* Hepatology, 2000		**Zignego *et al*** Ann. Int. Med., 2002		**Libra *et al*** Leukemia, 2003	
Patient	**t(14;18)**	**Patient**	**t(14;18)**	**Patient**	**t(14;18)**
HCV + MC	5/7 (71%)	**HCV + MC**	28/37 (76%)	**HCV + NHL**	8/39 (20%)
HCV	13/50 (26%)	**HCV**	30/101 (38%)	**NHL/HCV-**	3/101 (3%)

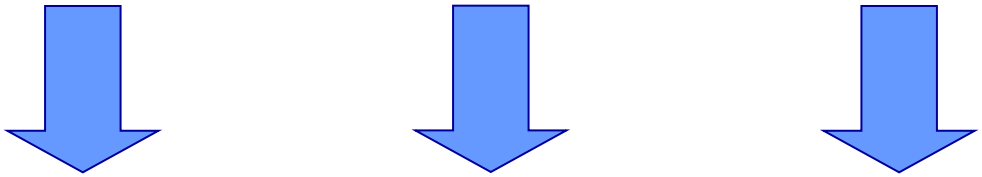
MALT Lymphoma

- MALT lymphomas are extra-nodal lymphomas and are typically indolent.
- The most common site of the disease is the stomach. Gastric MALT lymphoma is caused frequently by *Helicobacter pylori* infection.
- MALT lymphomas can be cured in many cases by antibiotics against *H. pylori.*
- However, approximately 15-20% of MALT lymphomas may develop into high-grade lymphomas.

We recently show for the first time that t(14;18) clusters in HCV-associated Malt lymphomas (Libra *et al*, J Hepatol. 2008)



It has been demonstrated that t(14;18) occurs in high-grade lymphomas derived from low-grade including Malt lymphomas (Capello *et al*, Blood 2000)



Therefore we hypothesized that t(14;18) may play a role in the high-grade transformation of Malt lymphomas, especially in those occurred among HCV+ patients

Cases

- 58 DLBCL samples derived from MALT lymphoma were included for the analysis
- A series of 124 *de novo* DLBCL were included as control group
- DLBLC samples derived from FL were excluded

Frequency of t(14;18) in 58 transformed DLBCL patients with and without HCV infection

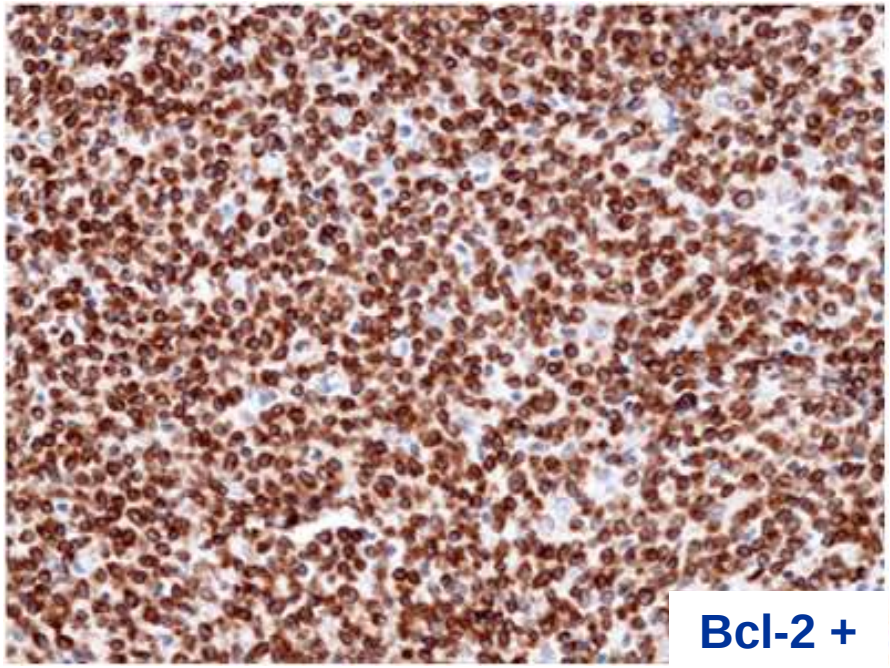
T(14;18)	HCV+	HCV-
+	4	2
-	9	43

P = 0.01; Fisher's Exact Test

Sequencing of the breakpoint in MALT and in the transformed DLBCL

	Bcl-2 3109	N region	J_H6 1483
MALT I diagnosis	tgcagtggtg	tttggttgcat	actactacta
Transformed DLBCL	tgcagtggtg	tttggttgcat	actactacta

Immunophenotyping



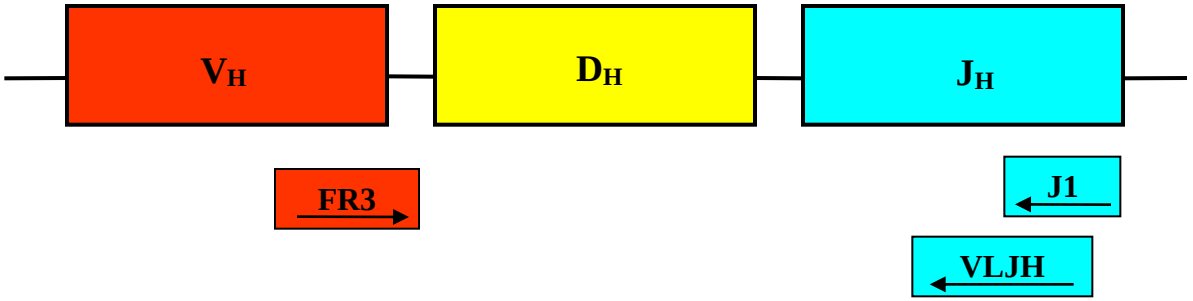
Bcl-2 +

The overexpression of Bcl-2 indicates that this genetic abnormality may sustain survival of B-cells preventing apoptosis

The null expression of CD10 and Bcl-6 excludes the follicular origin of the tumor samples harboring t(14;18) translocation

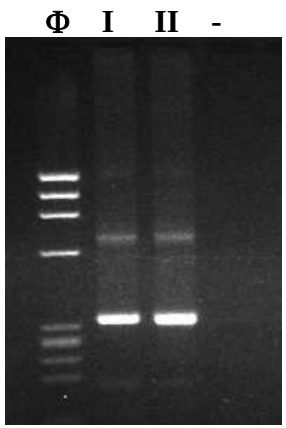
To further confirm that the transformed DLBCL originated from the metachronous MALT lymphoma, analysis of B-cell clonality was also performed by VDJ rearrangement

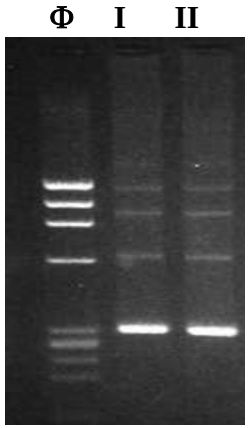
Immunoglobulin gene analysis



I FR3 - 5' gcg agg gac cga ttt tgt agt ggt gga gct cgc ttc gac tgg tac ttc gat ct 3'- VLJH

II FR3 - 5' gcg agg gac cga ttt tgt agt ggt gga gct cgc ttc gac tgg tac ttc gat ct 3'- VLJH





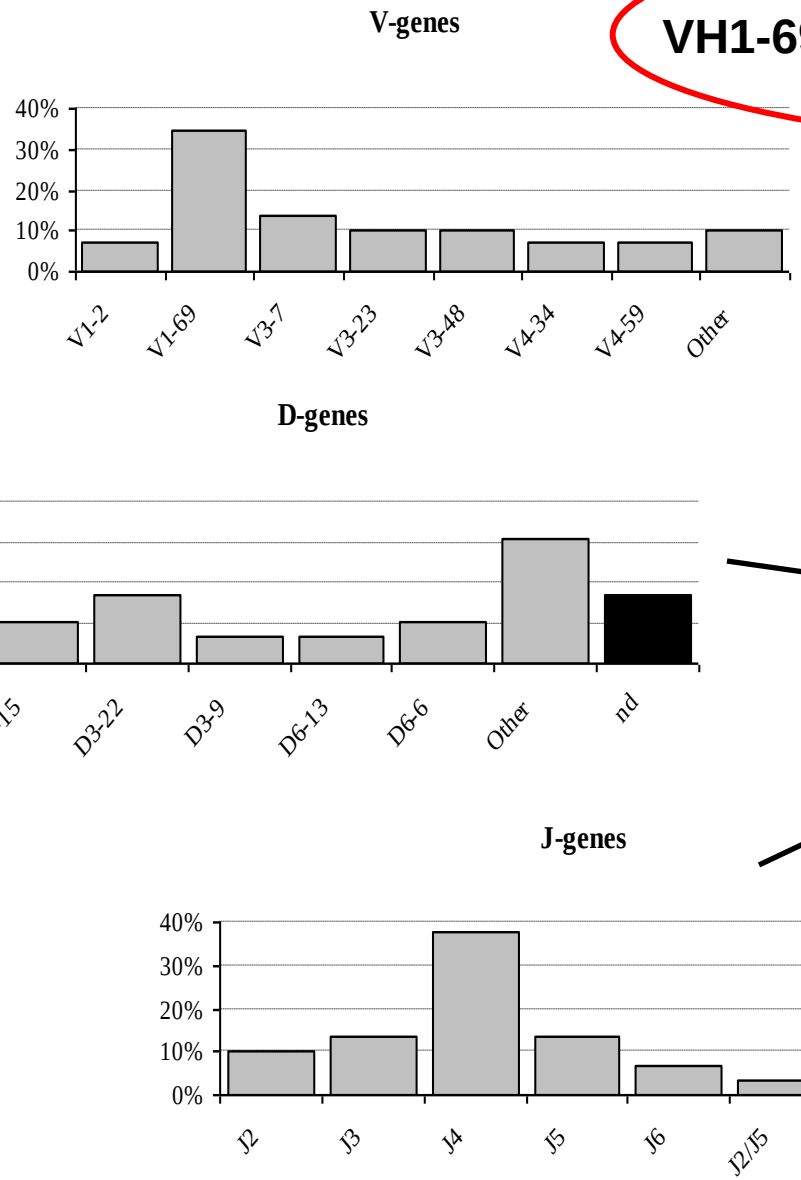
VH1-69 DH3-22 JH4 VK3-20 JK2

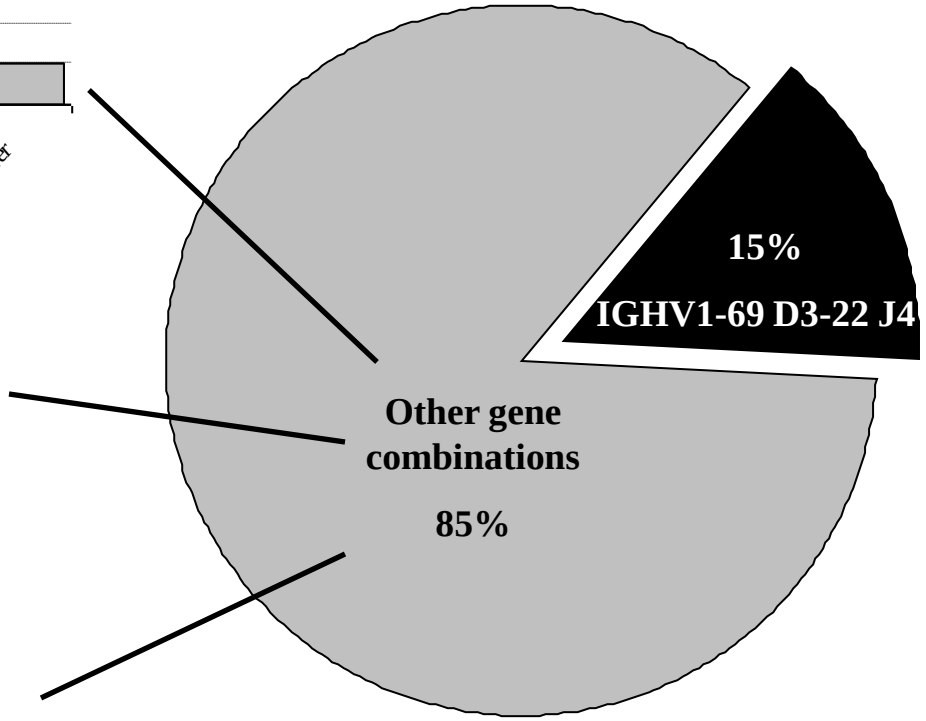
The results show that these tumors were clonally identical

The combination of genes in the heavy and light chains was the most common used among HCV-associated lymphomas previously reported

Distribution of VH, DH, and JH genes rearranged in B-cell NHL tissue from HCV-positive patients

VH1-69 DH3-22 JH4 **VK3-20 JK2**





Libra et al, FBS; 2005

Further molecular characterization of t(14;18) cases

It has been shown that SHM process of multiple oncogens occurs in B-NHL clustering within RGWY motifs (Pasqualucci L, Nature 2001)

Our previous studies show that this phenomenon was not observed in HCV-associated NHL (Libra M, J Pathol 2005)

Similarly, it was observed in t(14;18) cases analyzed in the present study

Further molecular characterization of t(14;18) cases

Table 3. Features of *PIM-1*, *PAX-5*, *RhoH/TTF*, *c-MYC*, and *BCL-6* mutations in HCV-associated NHL

Locus	Mutations/ 100 bp	Deletions or insertions	Single bp substitutions	Transitions/ transversions	G + C	A + T	G + C mutations/ 100 bp†	A + T Mutations/ 100 bp*	RGYW†
PIM-1	0.19 (0.05–0.28)	1	13	9/4 (2.25)	11	2	0.20	0.079	4 ($p = 0.88$)
PAX-5	0.17 (0.06–0.58)	0	15	11/4 (2.75)	15	0	0.26	0	6 ($p = 0.36$)
RhoH/TTF	0.22 (0.06–0.89)	1	19	11/8 (1.37)	9	10	0.18	0.26	8 ($p = 0.18$)
c-*MYC* exon 1	0.038	0	4	4/0	4	0	0.067	0	2 ($p = 0.52$)
c-*MYC* exon 2	0	0	0	0/0	0	0	0	0	0
Total	NA	2	51	35/16 (2.18)	39	12	0.19	0.084	20 ($p = 0.08$)
BCL-6	0.16 (0.07–0.27)	0	34	19/15 (1.26)	19	15	0.18	0.15	12 ($p = 0.01$)

* Calculated from the number of G + C and A + T nucleotides in the wild-type gene sequences.
† The frequency of mutations within RGYW motifs was compared with the frequency of mutations outside RGYW motifs by the χ^2 test.

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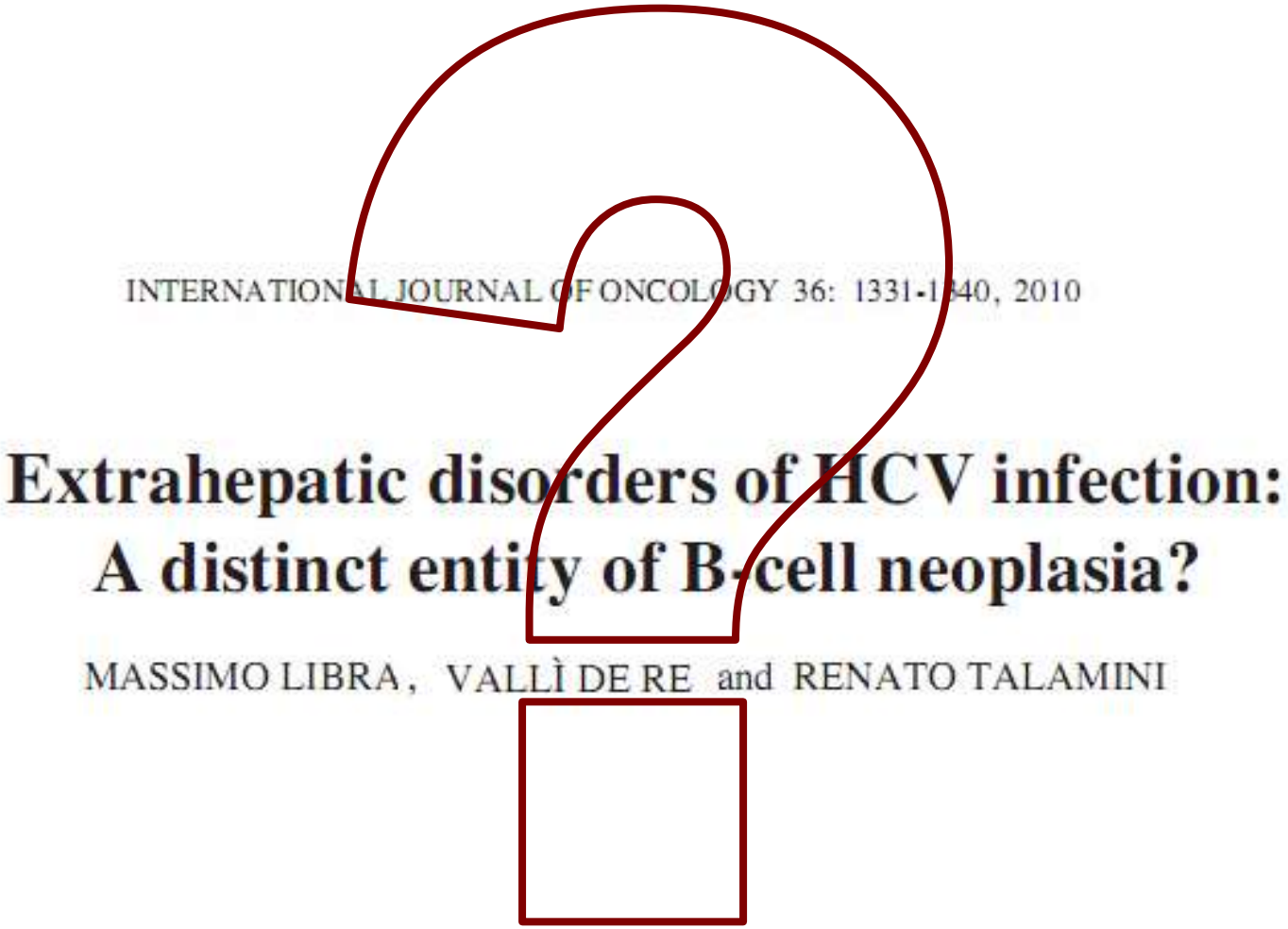
Taken together these data indicate that t(14;18) may be considered a marker of high-grade transformation in HCV-associated Malt lymphomas

FUTURE DIRECTIONS

- ✓FISH analysis in t(14;18) DLBCL cases
- ✓Microarray analysis of this subset of NHL
- ✓Gene set enrichment analysis (GSEA)



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Extrahepatic disorders of HCV infection: A distinct entity of B-cell neoplasia?

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