Molecular characterization of diffuse large B-cell lymphoma recurrences: clonal relationship and different modes of tumor evolution

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KEY POINTS

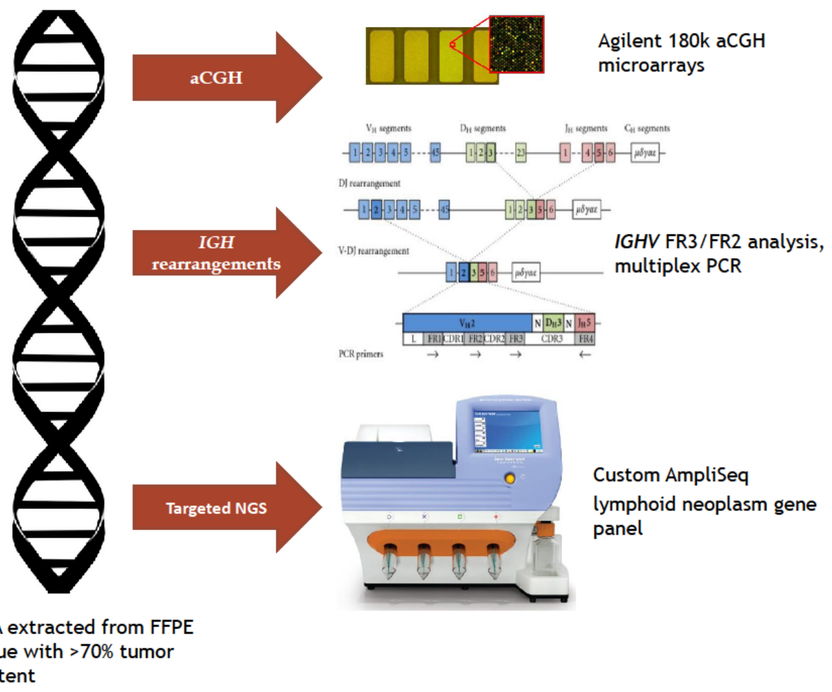
- Distinct genetic evolution patterns of diffuse large B-cell lymphoma relapse exist and include clonally unrelated *de novo* recurrences. These patterns can be reconstructed by interpreting DNA mutation and copy number aberration data.
- Genomes of relapsing and non-relapsing diffuse large B-cell lymphomas differ significantly in recurrent copy number aberrations.

INTRODUCTION

Recurrences of diffuse large B-cell lymphomas (DLBCL) represent a source of significant morbidity and mortality, but their underlying genetic and biological mechanisms remain to be elucidated. Although a few reports on clonally unrelated relapses have been published, second and subsequent presentations of DLBCL are generally regarded as direct outgrowths of the original neoplasm. We used immunoglobulin rearrangement analysis, copy number aberration profiling and next generation sequencing to investigate clonal relationship and genetic evolution in 20 matched primary-relapse DLBCL sample pairs. We compared this genomic data to the analogous data from 11 non-relapsing DLBCL cases attempting to identify relapse-specific genetic events.

MATERIALS AND METHODS

Group	Number of patients	Age median, y (range)	Time to relapse median, m (range)	Time without relapse median, y (range)
Relapsing DLBCL	20	66.5 (29-90)	22 (8-141)	n/a
Non-relapsing DLBCL	11	74 (36-84)	n/a	8 (6-12)



DNA extracted from FFPE tissue with >70% tumor content

CUSTOM LYMPHOID NEOPLASM TARGET ENRICHMENT PANEL

All exons		Hotspots				
TP53	GNA13	MYD88	KRAS	PIK3CA	STAT6	DNMT3A
CDKN2A	HIST1H1C	EZH2	CARD11	PIK3CD	PTPN11	CALR
IKZF1	MEF2B	NOTCH1	CREBBP	PIK3R1	IRF4	RHOA
KMT2D	PIM1	SF3B1	IDH2	MTOR	BCL10	SGK1
TNFAIP3	PAX5	CD79B	IDH1	EP300	IKZF3	KLHL6
ATM	PTPN1	BRAF	BCL6	MLL3	MCL1	XPO1
B2M	PTEN	JAK2	FBXW7	RELN	BCL2L11	CCND1
BCL2	EBF1	KIT	STAT3	TET2	MAP2K1	JAK3
PRDM1	MYC	NOTCH2	CD79A	TLN2	U2AF1	
BTG1	SOCS1	NRAS	CELSR2	FOXO1	FLT3	

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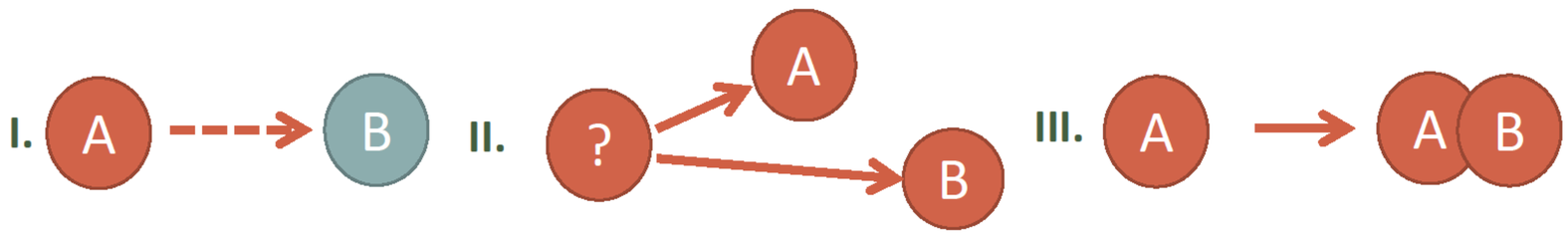
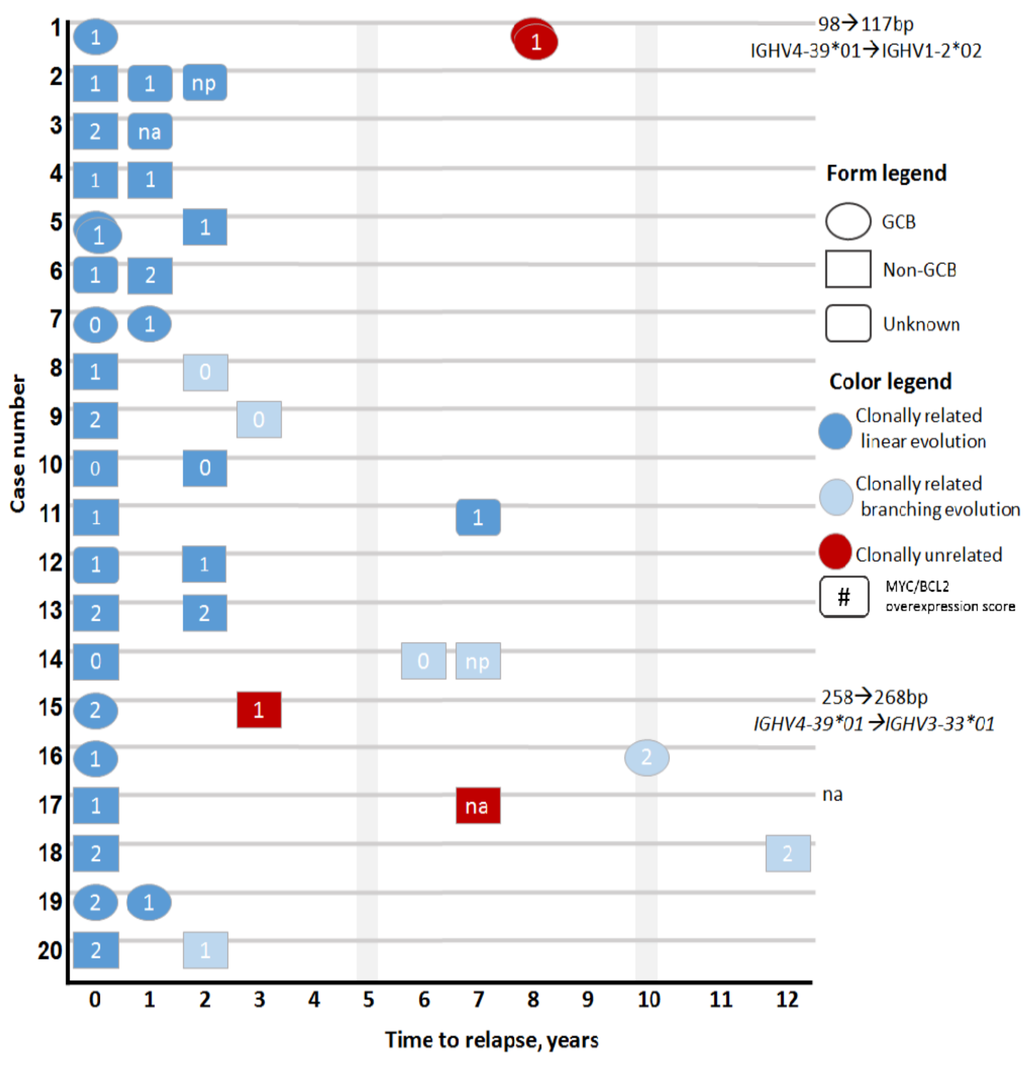
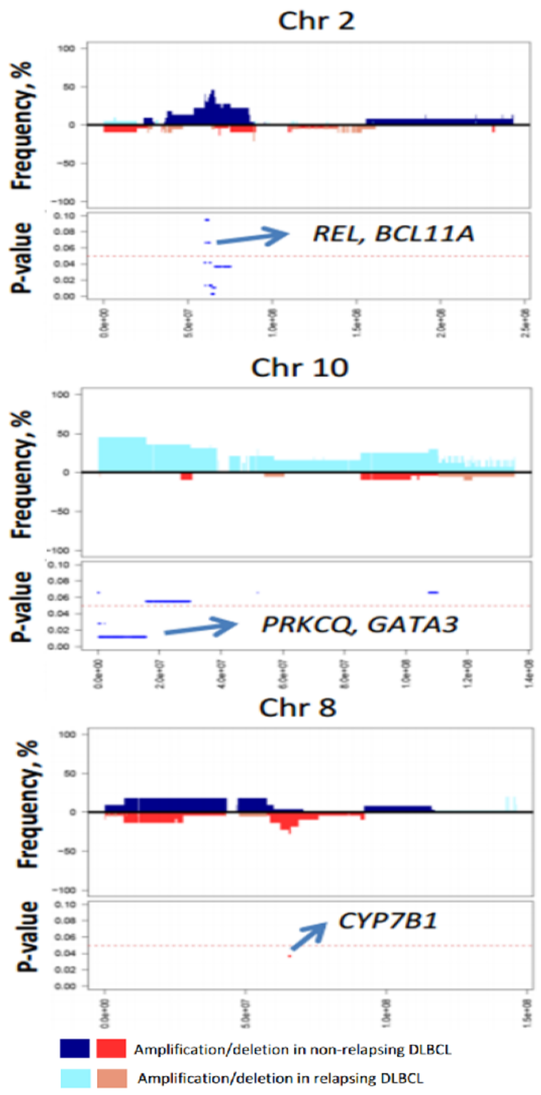
RESULTS Different patterns of DLBCL relapse



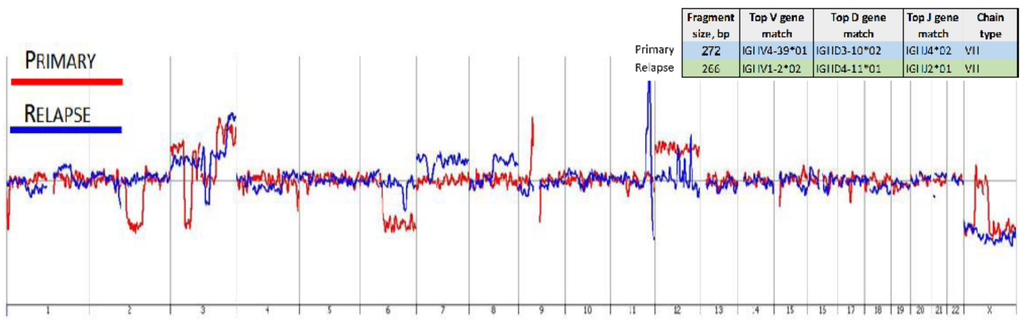
RESULTS OVERVIEW IN THE STUDY COHORT



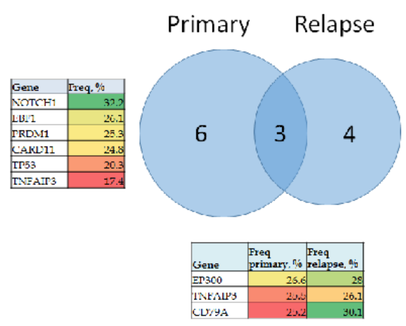
RECURRENT COPY NUMBER ABERRATIONS



I. CLONALLY-UNRELATED RELAPSES. NO ABERRATIONS WITH COMMON BREAKPOINTS ARE SHARED BETWEEN PRIMARY AND RELAPSE



	Fragment size, bp	Top V gene match	Top D gene match	Top J gene match	Chain type
Primary	272	IGHV4-39*01	IGHD3-10*02	IGHJ4*02	VII
Relapse	266	IGHV1-2*02	IGHD4-11*01	IGHJ2*01	VII

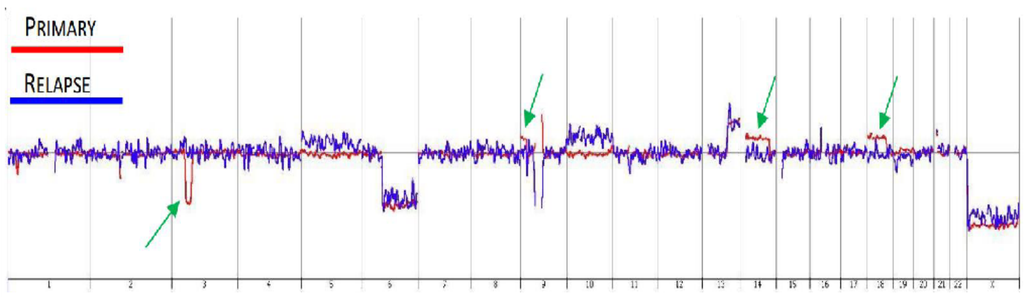


Gene	Freq, %
NOTCH1	32.0
LRP1	26.1
PRDM1	25.3
CARD11	24.8
TP53	20.3
TNFAIP3	17.4

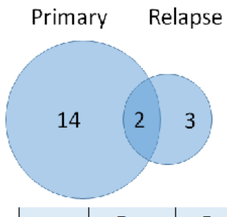
Gene	Freq, %
KMT2D	30.8
CARD11	28.8
KMT2D	26.6
KMT2D	7.2

Gene	Freq primary, %	Freq relapse, %
EP300	25.6	29
TNFAIP3	2.6	26.1
CD79A	2.6	30.1

II. CLONALLY-RELATED WITH COMMON PROGENITOR. PART OF THE COPY NUMBER ABERRATIONS PRESENT IN PRIMARY TUMOR BUT NOT PRESENT IN RECURRENCE.



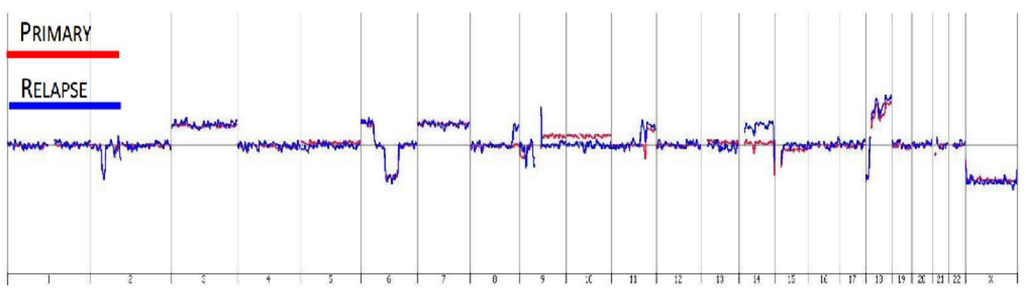
Gene	Freq, %
TET2	91.6
KMT2D	79.6
JAK2	30.5
PRDM1	23.5
TET2	23.3
KMT2D	20.4
KLHL6	18.7
BTG1	18.7
BCL6	17.8
RELN	16.4
EBF1	16.1
PTEN	6.8
KMT2D	5
TET2	4.3



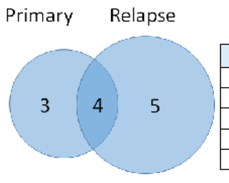
Gene	Freq primary, %	Freq relapse, %
CD79B	34	41.3
CD79B	33.7	41.3

Gene	Freq, %
MEF2B	77.9
TNFAIP3	41.4
KMT2D	40

III. CLONALLY-RELATED WITH OR WITHOUT LINEAR PROGRESSION. SAME COPY NUMBER ABERRATIONS OR/AND GAIN OF ADDITIONAL ABERRATIONS AT RECURRENCE



Gene	Freq, %
TET2	41
SGK1	17.5
GNA13	4.8



Gene	Freq, %
JAK2	38.1
FBXW7	31.5
ATM	24.8
KMT2D	19.4
TET2	16.6

Gene	Freq primary, %	Freq relapse, %
KMT2D	45.1	32.9
PTEN	44.4	32.7
TET2	42.2	32.2
KMT2D	3.8	6.1

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