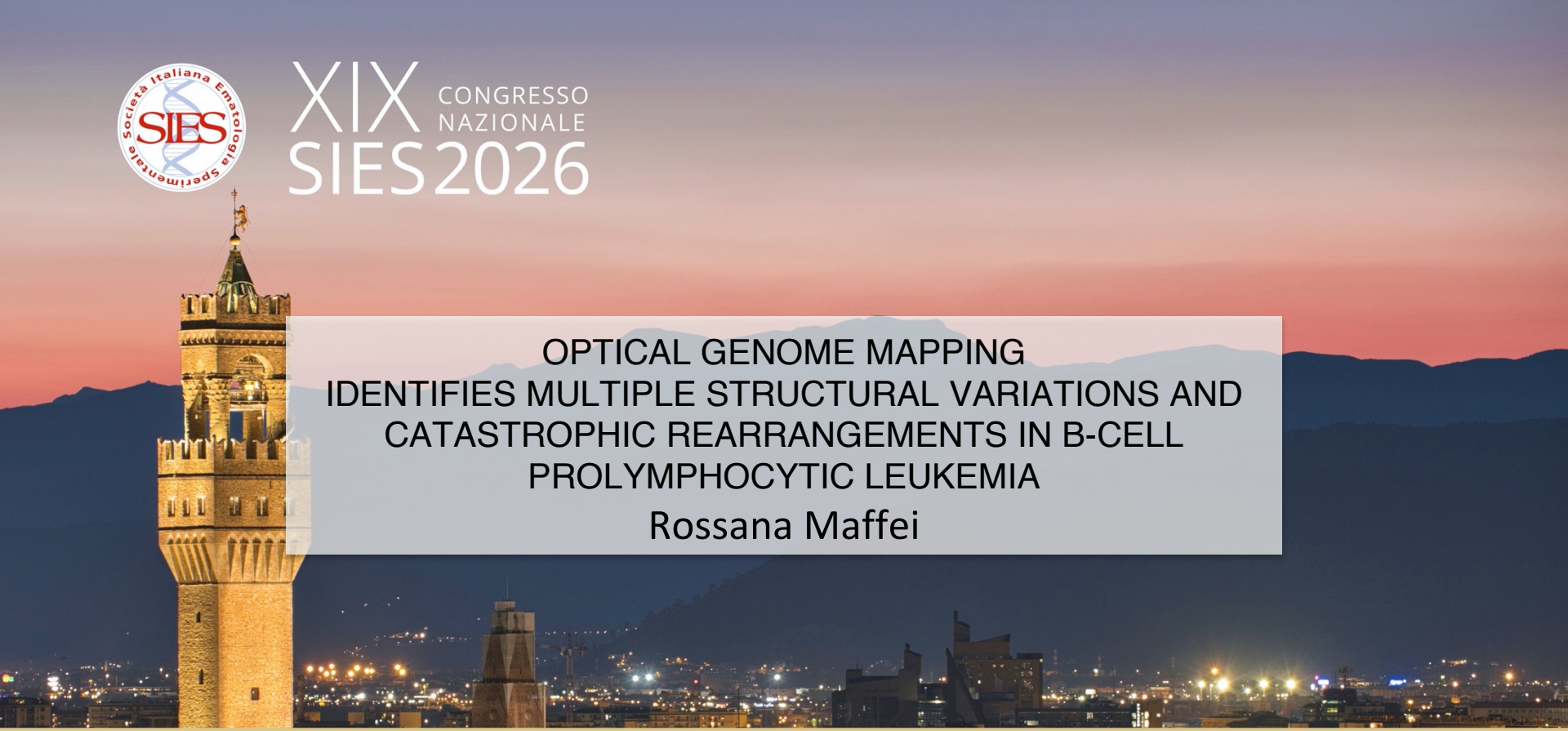

OPTICAL GENOME MAPPING IDENTIFIES MULTIPLE STRUCTURAL VARIATIONS AND CATASTROPHIC REARRANGEMENTS IN B-CELL PROLYMPHOCYTIC LEUKEMIA

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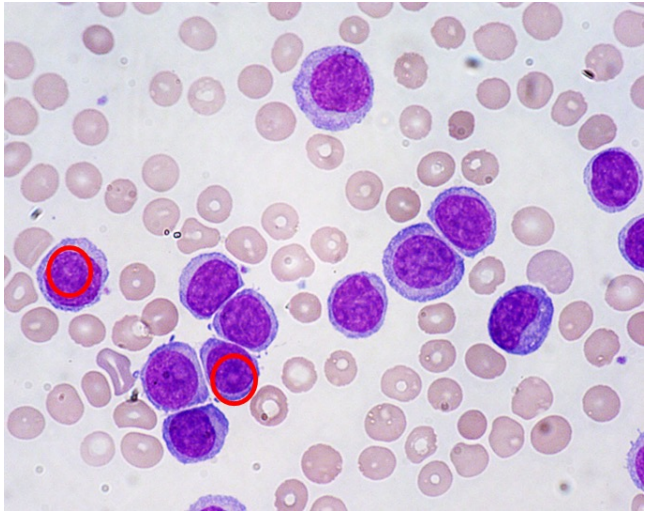
Palazzo degli Affari

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Background

1. B-cell prolymphocytic leukemia (B-PLL) is an extremely rare condition, accounting for less than 1% of all lymphoid leukemias
2. The identification of more than 55% of lymphocytes in the blood or bone marrow with prolymphocytic morphology is the hallmark feature of B-PLL
3. B-PLL is a poor-prognosis disease with a median overall survival (OS) of 3 years
4. Little is known about the true nature and underlying oncogenic events in B-PLL



Prolymphocyte:
- Two times the CLL lymphocyte
- Nucleus: cytoplasm < CLL lymphocyte
- Round nucleus, moderately condensed chromatin
- Prominent nucleolus

LYMPHOID NEOPLASIA

CME Article

Genetic characterization of B-cell prolymphocytic leukemia: a prognostic model involving *MYC* and *TP53*

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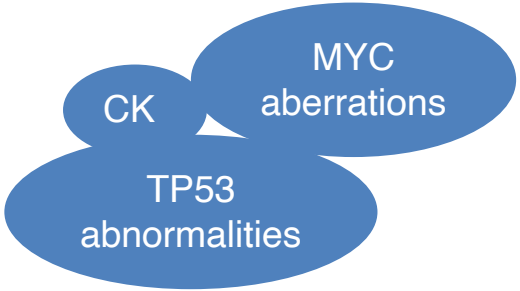


The majority of the cases (26 of 34 [76%]) had an **MYC abnormality**, MYC translocation and MYC gain being mutually exclusive.

The other frequent chromosomal aberrations were:

- **deletion (del)17p including the TP53 gene** (13 of 34 [38%])
- trisomy (tri) 18/18q (10 of 33 [30%])
- del13q (10 of 34 [29%])
- tri3 (8 of 33 [24%])
- tri12 (8 of 34 [24%])
- del8p (7 of 31 [23%])

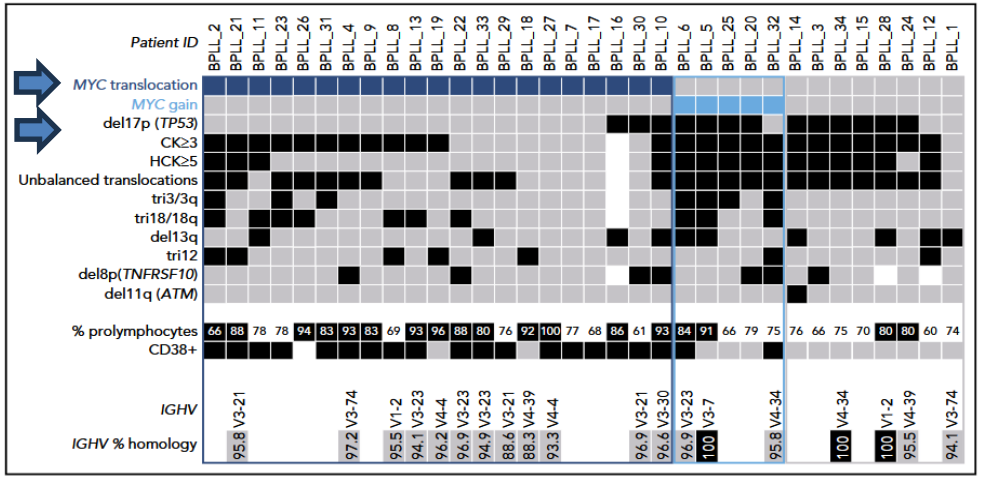
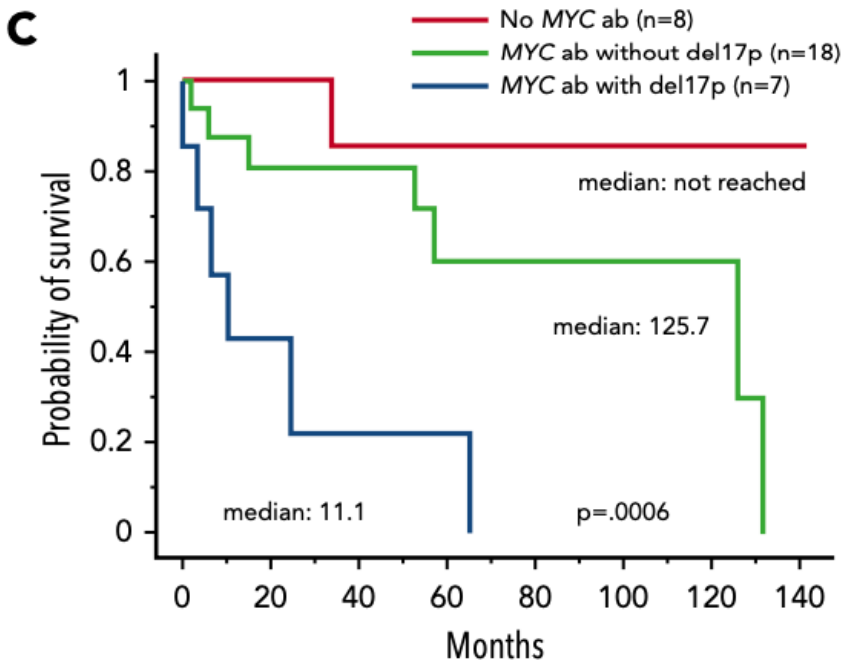


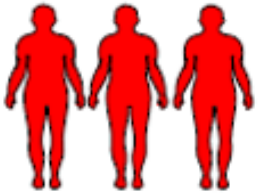
Figure 1. Distribution of chromosomal abnormalities detected in 34 patients with B-PLL with 3 cytogenetic subgroups of patients: *MYC* translocation, *MYC* gain, and no *MYC* aberration. Each column represents 1 patient, and each row 1 particular genetic or laboratory parameter. Color code: black or blue, presence; gray, absence; white, not available. CK, ≥3 chromosomal abnormalities; HCK, ≥5 chromosomal abnormalities. The percentages of prolymphocytes (indicated in black boxes) correspond to above-median values, relative to the cohort as a whole.

Chapiro E. et al. Blood. 2019

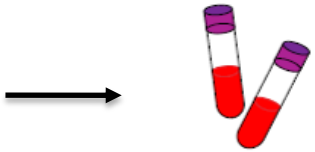
Prognostic impact of genetic lesions



Our study



n=3 B-PLL



Conventional cytogenetics

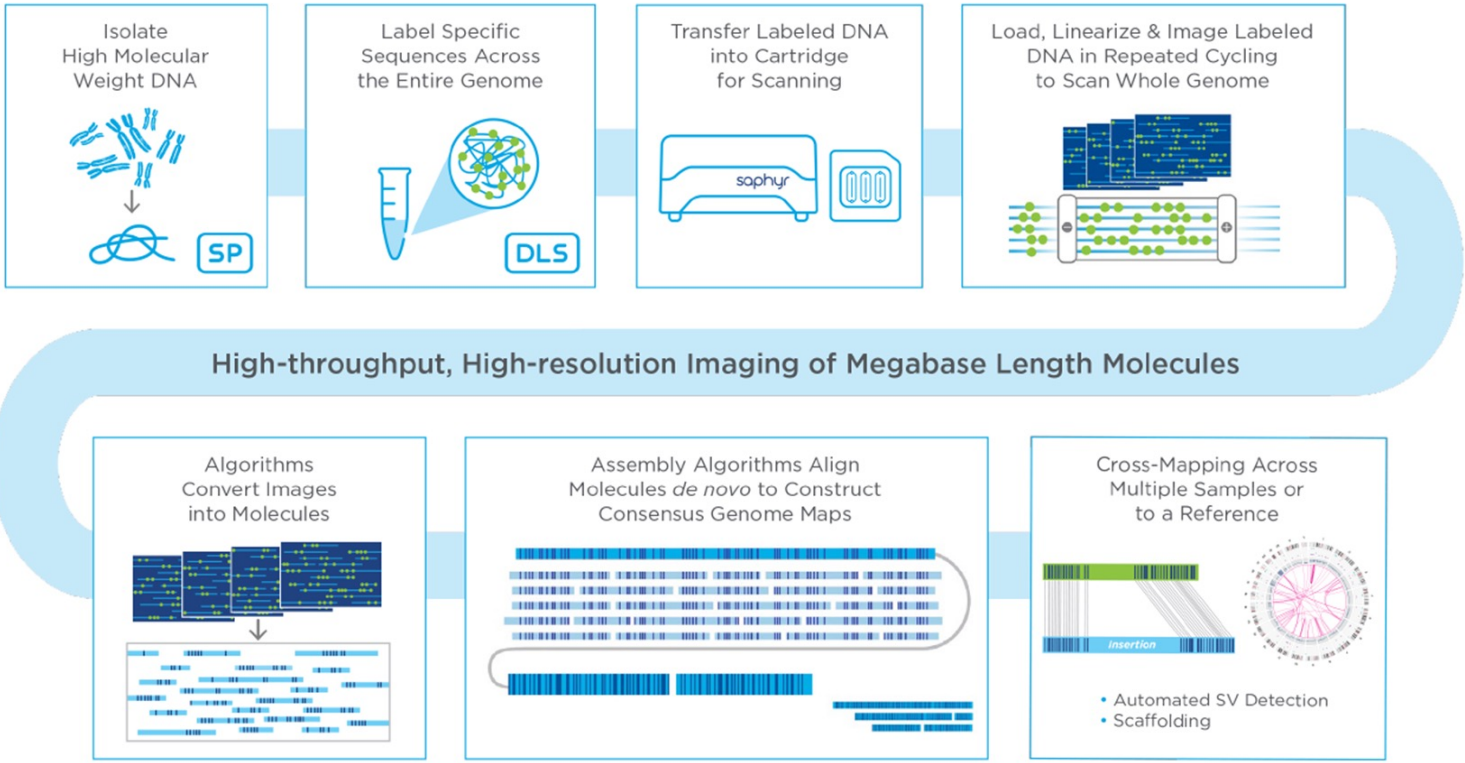
Next-generation sequencing

NGS CLL Community Panel

Optical Genome mapping

Patient	gender	Age at diagnosis	WBC (x10^9/L)	Lymphocytes (x10^9/L)	Hb(g/dL)	PTL (x10^9/L)	Splenomegaly	lymphoadenopathy	First-line treatment	Response	Follow-up
case1	male	84	116.2	104.0	10.8	202	present	absent	Zanubrutinib (160 mg BID)	**PR**	**14 months**
case2	male	87	125.5	117.5	12.9	137	present	minimal	Zanubrutinib (160 mg BID)	**PR**	**32 months**
case3	female	80	30.5	28.8	6.2	56	present	absent	Zanubrutinib (160 mg BID)	**PR**	**26 months**

Optical genome mapping



Case#3 B-PLL

gene	Sequenza di riferimento	esone	c.DNA	proteina	Tipo di variante	VAF (%)
TP53	NM_000546	5	c.518T>C	p.(Val173Ala)	missense	48,3
CXCR4	NM_003467	2	c.1013_1023del	p.(Ser338Tyrfs*2)	frameshift	2,3

NGS

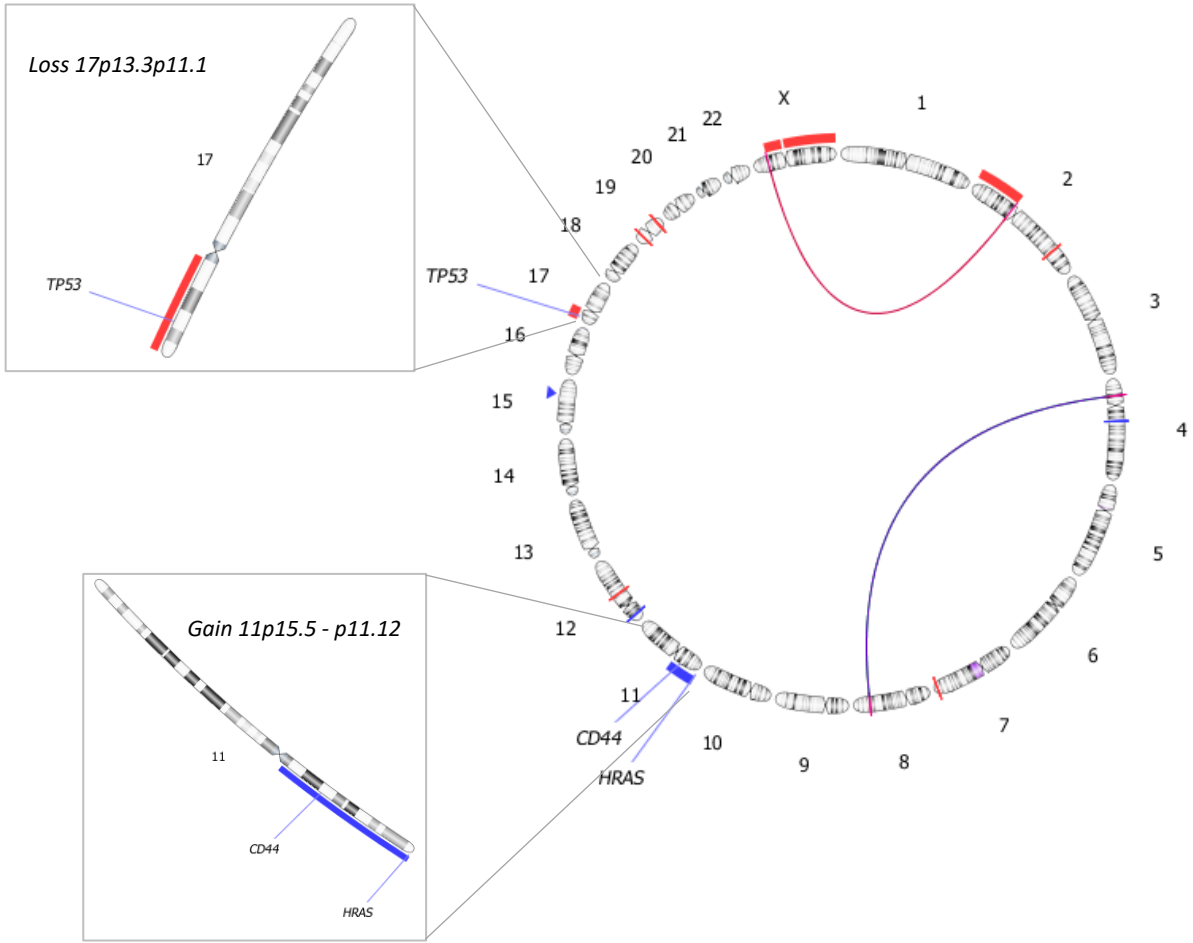
Gene	genoma	cromosoma	posizione cromosomica-inizio	posizione cromosomica-termine	Tipo di variante	Copie alleliche (CNV)	Alterazione
XPO1	hg19	chr2	61719054	61719633	CNV	1.3	loss Chr 2
TP53	hg19	chr17	7571530	7591021	CNV	1.4	del 17p

Patient	clonotype	IGHV identity (%)	Functionality	Junction
case3	IGHJ6*02 - IGHD1-14*01 - IGHV1-46*01	100	Productive	CARAEPSGAGGMDVW

Cytogenetics

patients	karyotype	FISH
case3	44-46, X,-X, del(2)(p21),-2, del(6)(q22),der(9)t(2;9)(q21;p21), +der(11)t(11;17)(q13;q21), +1-2mar[cp20]	**del(17p13) 92%**

Case#3: Optical genome mapping



Case#1 B-PLL

NGS

gene	Sequenza di riferimento	esone	c.DNA	proteina	Tipo di variante	VAF (%)
TP53	NM_000546	7	c.687_695del	p.(Thr230_Ile232del)	inframe_9	81,3
TP53	NM_000546	6	c.578A>T	p.(His193Leu)	missense	4,4

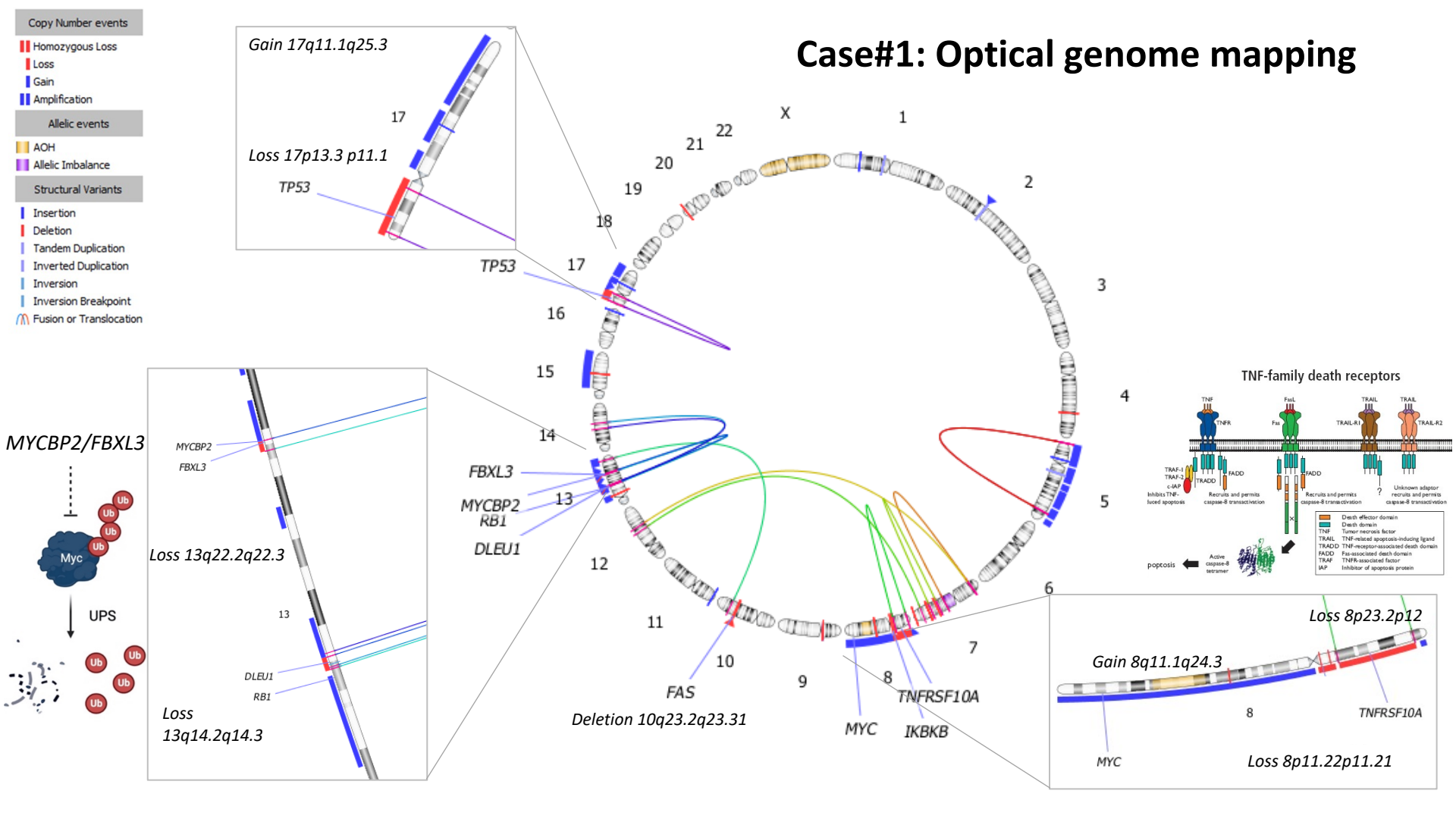
Gene	genoma	cromosoma	posizione cromosomica-inizio	posizione cromosomica-termine	Tipo di variante	Copie alleliche (CNV)	Alterazione
DLEU1	hg19	chr13	50656194	51102890	CNV	1.3	del 13q
TP53	hg19	chr17	7571530	7591021	CNV	1.1	del 17p

Patient	clonotype	IGHV identity (%)	Functionality	Junction
Case#1	IGHJ4*02 - IGHD3-22*01 - IGHV3-30*18,IGHV3-30-5*01	100	Productive	CAKDQDYYDSSGYWRGY YFDYW
	IGHJ4*02 - IGHD1-26*01 - IGHV4-39*01	100	Productive	CARQSGSYVKDFDYW

Cytogenetics

patients	karyotype	FISH
Case#1	43-49, XY, -7,-10,?12,-14**, +15**,i(15)(q10),add(17)(p12), +der(22)t(14;22)(q?21;q?13),+1-3mar[cp15]/46,XY[5]	**del(17p13) 87%**

Case#1: Optical genome mapping



Case#2 B-PLL

gene	Sequenza di riferimento	esone	c.DNA	proteina	Tipo di variante	VAF (%)
TP53	NM_000546	7	c.713G>T	p.(Cys238Phe)	missense	87,4

NGS

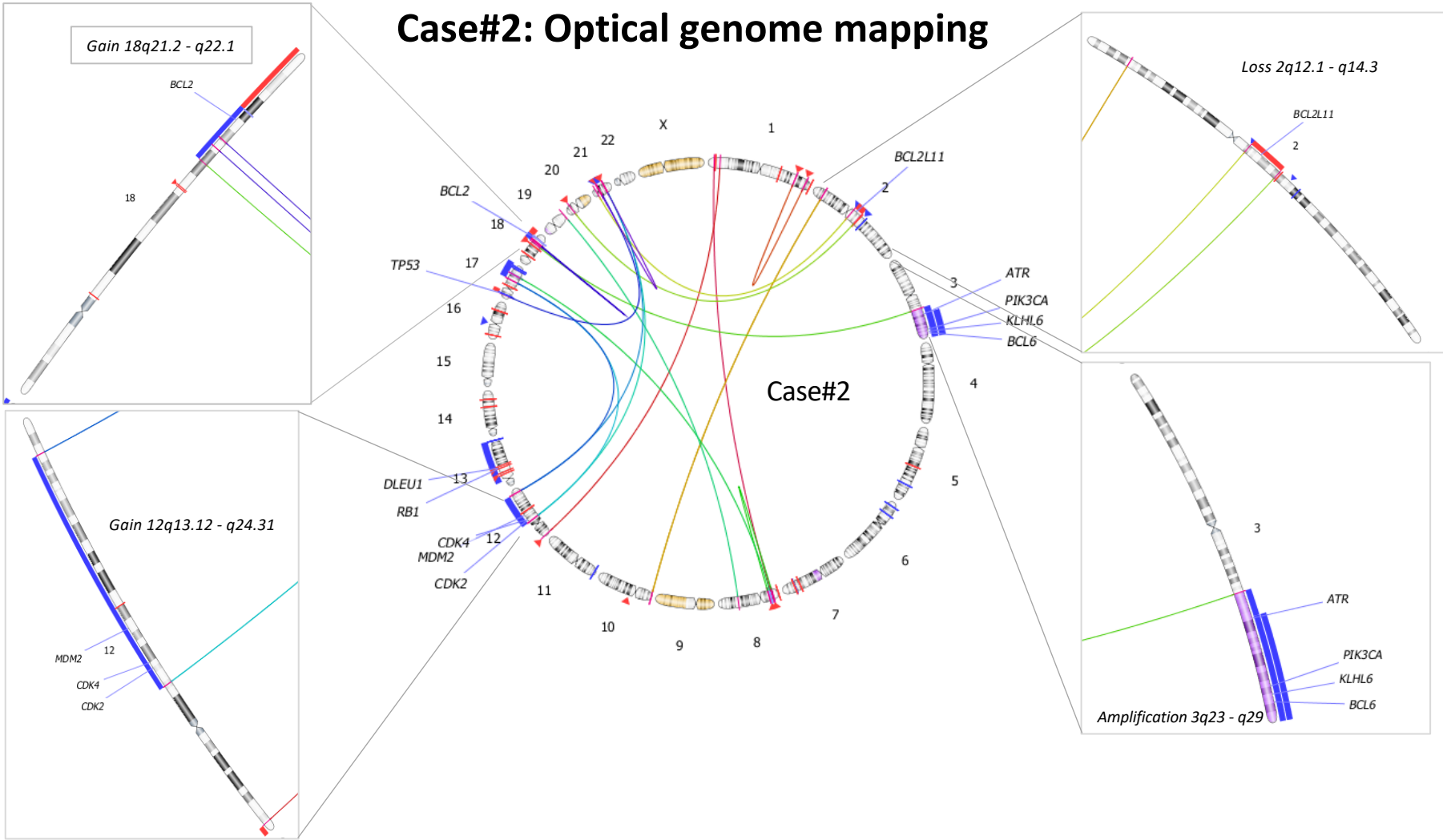
Gene	genoma	cromosoma	posizione cromosomica-inizio	posizione cromosomica-termine	Tipo di variante	Copie alleliche (CNV)	Alterazione
RB1	hg19	chr13	48877935	49054327	CNV	1.1	LOSS CHR 13
DLEU1	hg19	chr13	50656194	51102890	CNV	1.1	LOSS CHR 13
KLF5	hg19	chr13	73633355	73650114	CNV	2.9	GAIN CHR 13
PROZ	hg19	chr13	113812863	113826529	CNV	2.9	GAIN CHR 13
CUL4A	hg19	chr13	113862976	113883943	CNV	2.9	GAIN CHR 13
TP53	hg19	chr17	7571530	7591021	CNV	1.1	DEL 17P
BCL2	hg19	chr18	60795748	60986010	CNV	3	GAIN CHR 18

Patient	clonotype	IGHV identity (%)	Functionality	Junction
Case#2	IGHJ5*02 - IGHD2-8*02 - IGHV4-39*01,IGHV4-39*08	93.47	Productive	CARHSCTGISCYLAGWFDPW

Cytogenetics

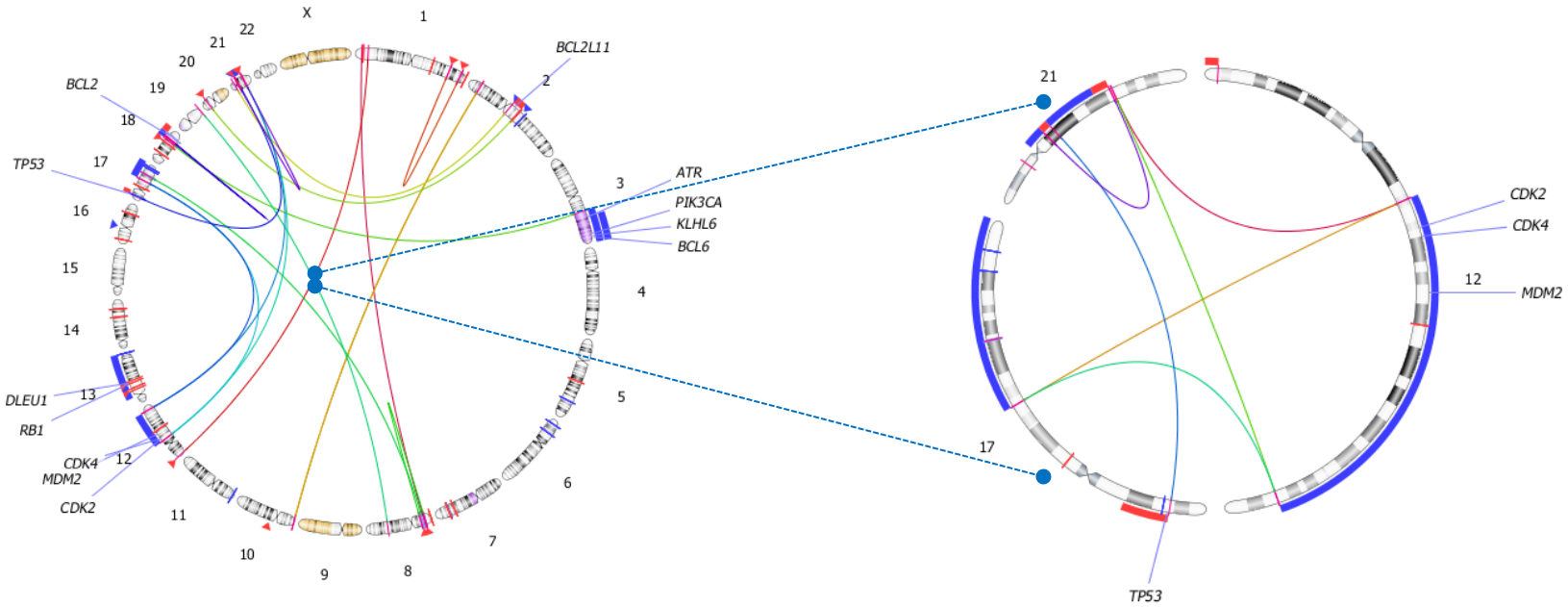
patients	karyotype	FISH
Case#2	42-46, XY,-2,-5,-6,-7,i(7)(q10),+der(8)add(8)(q24),add(9)(p24),-10,add(12)(p13),-13, der(18)t(13;18)(q14;q23),add(19)(q13),-20,-21,-22,+2-5mar[cp20]	**del(17p13) 94%, del(13q14) 93%**

Case#2: Optical genome mapping



Chromoanagenesis

Multiple chained translocations in chromosomes 12,17 and 21 with features typical of catastrophic genomic events, collectively referred to as chromoanagenesis, and specifically resembling chromoplexy



Conclusion

- ✓ When integrated with NGS, OGM reveals convergent, multi-hit genomic alterations affecting both intrinsic and extrinsic apoptotic pathways (TP53, TNFRSF10, FAS, BCL2, BCL2L11, MDM2) as well as key regulators of cell-cycle control (CDK2, CDK4, RB1), expanding the genomic spectrum of B-PLL beyond the established MYC/TP53 prognostic model

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