Prognostic Significance of Genomic Alterations in Mantle Cell Lymphoma

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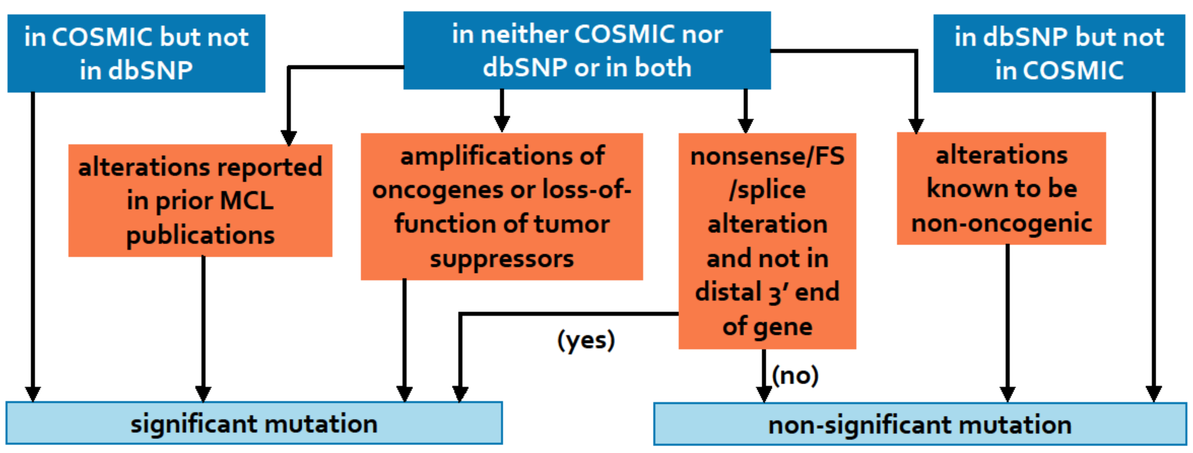
Introduction

- Whole genome, exome, and targeted sequencing have identified various genomic alterations in mantle cell lymphoma (MCL)
- We describe genomic alterations in MCL using an MSK targeted sequencing platform, HEMEPACT, and correlate with outcome
- HEMEPACT can be performed on formalin-fixed paraffin-embedded (FFPE) tissue and detect rare variants due to extensive depth of sequencing coverage

Methods

- Genomic DNA was isolated from FFPE specimens from 23 cases of MCL
- Mutations were identified using the HEMEPACT targeted sequencing platform without matched normals as controls
- Adaptor ligated sequencing libraries were captured by solution hybridization using two custom bait sets targeting 579 biologically significant cancer-related genes for DNA-Seq
- Captured libraries sequenced to a high depth (Illumina HiSeq), avg. >300x
- Significant non-synonymous variants were identified as mutations from the COSMIC database, amplifications of established oncogenes, or homozygous deletions and/or clear loss-of-function mutations of known tumor suppressors.
- Overall survival analyses were performed using the Kaplan-Meier and log-rank tests and associations assessed using the 2-sided Fisher's exact test.

Algorithm for Determining Significant Mutations



HEMEPACT Genes

AAMP	BLM	CKS1B	EPHB1	FH	HIST1H3B	LATS1	MYCL1	PDCD1	RAD54L	SMAD3	TNFAIP3
ABL1	BMPR1A	CPS1	ERBB2	FHIT	HLA-A	LATS2	MYCN	PDCD1LG2	RAF1	SMAD4	TNFRSF11A
ABL2	BRAF	CRBN	ERBB3	FLCN	HLA-B	LEF1	MYD88	PDGFRA	RARA	SMARCA1	TNFRSF14
ACTB	BRCA1	CREBBP	ERBB4	FLT1	HMGA2	LMO1	MYO18A	PDGFRB	RASA1	SMARCA4	TNFRSF17
AKT1	BRCA2	CRKL	ERCC2	FLT3	HNF1A	LRP1B	MYOD1	PDK1	RASGEF1A	SMARCB1	TNFRSF6
AKT2	BRD4	CRLF2	ERCC3	FLT4	HRAS	LRRK2	MYST3	PDPK1	RB1	SMARCD1	TNFSF9
AKT3	BRIP1	CSF1R	ERCC4	FLYWCH1	HSP90AA1	MAF	NBN	PDS5B	RBM10	SMC1A	TOP1
ALK	BRSK1	CSF3R	ERCC5	FOXA1	ICK	MAFB	NCOR1	PHF6	RECQL4	SMC3	TOX
ALOX12B	BTG1	CTCF	ERG	FOXL2	ICOSLG	MAGED1	NCOR2	PHOX2B	REL	SMO	TP53
APC	BTG2	CTLA4	ESCO1	FOXO1	ID3	MALT1	NCSTN	PIK3C2G	RELN	SOCS1	TP63
APCDD1	BTK	CTNNA1	ESCO2	FOXO3	IDH1	MAP2K1	NF1	PIK3C3	RET	SOCS2	TRAF2
APH1A	BTLA	CTNNB1	ESR1	FOXP1	IDH2	MAP2K2	NF2	PIK3CA	RFWD2	SOCS3	TRAF3
AR	C17orf39	CUL3	ETS1	FRS2	IFNGR1	MAP2K4	NFE2L2	PIK3CB	RHOA	SOX10	TRAF5
ARAF	CAD	CUL4A	ETV1	FUBP1	IGF1	MAP3K1	NFKB1	PIK3CD	RHOH	SOX17	TRAF7
ARFRP1	CARD11	CUL4B	ETV6	FYN	IGF1R	MAP3K13	NFKB2	PIK3CG	RICTOR	SOX2	TRRAP
ARHGAP26	CASP8	CUX1	EXOSC6	GADD45B	IGF2	MAP3K14	NFKBIA	PIK3R1	RIT1	SOX9	TSC1
ARID1A	CBFB	CXCR4	EZH2	GATA1	IKBKE	MAP3K6	NKX2-1	PIK3R2	RMRP	SPEN	TSC2
ARID1B	CBL	CYLD	FAF1	GATA2	IKZF1	MAP3K7	NKX3-1	PIK3R3	RNF43	SPOP	TSHR
ARID2	CCND1	CYP17A1	FAM123B	GATA3	IKZF2	MAPK1	NOD1	PIM1	ROS1	SRC	TUSC3
ARID5B	CCND2	D2HGDH	FAM175A	GLI1	IKZF3	MAX	NOTCH1	PLCG2	RPA1	SRSF2	TYK2
ASMTL	CCND3	DAXX	FAM46C	GNA11	IL10	MCL1	NOTCH2	PLK2	RPL11	STAG1	U2AF1
ASXL1	CCNE1	DCUN1D1	FANCA	GNA12	IL7R	MDC1	NOTCH3	PMAIP1	RPL13	STAG2	U2AF2
ASXL2	CCT6B	DDR2	FANCC	GNA13	INHBA	MDM2	NOTCH4	PMS1	RPL15	STAT3	VHL
ASXL3	CD22	DDX3X	FANCD2	GNAQ	INPP4A	MDM4	NPM1	PMS2	RPL35A	STAT4	VTCN1
ATM	CD274	DICER1	FANCE	GNAS	INPP4B	MED12	NRAS	PNRC1	RPS14	STAT5A	WDR90
ATR	CD276	DIS3	FANCF	GPR124	INPP5D	MEF2B	NSD1	POLE	RPS19	STAT5B	WHSC1
ATRX	CD36	DKC1	FANCG	GRAF	INSR	MEF2C	NT5C2	POT1	RPS26	STAT6	WISP3
AURKA	CD58	DNM2	FANCI	GREM1	IRF1	MEN1	NTRK1	PPP2R1A	RPS6KA4	STK11	WT1
AURKB	CD70	DNMT1	FANCL	GRIN2A	IRF4	MET	NTRK2	PRDM1	RPS6KB2	STK40	WWOX
AXIN1	CD79A	DNMT3A	FANCM	GSK3B	IRF8	MIB1	NTRK3	PRKAR1A	RPTOR	SUFU	XBP1
AXIN2	CD79B	DNMT3B	FAS	GTSE1	IRS1	MIR17HG	NUP93	PRKDC	RUNX1	SUZ12	XIAP
AXL	CDC73	DOT1L	FAT1	H3F3C	IRS2	MITF	NUP98	PRSS8	RUNX1T1	SYK	XPO1
B2M	CDH1	DTX1	FAT3	HDAC1	JAK1	MKI67	P2RY8	PTCH1	RYBP	TAF1	XRCC3
BACH1	CDK12	DUSP2	FBXO11	HDAC4	JAK2	MLH1	PAG1	PTEN	S1PR2	TBL1XR1	YAP1
BAP1	CDK4	DUSP9	FBXO31	HDAC7	JAK3	MLL	PAK1	PTPN11	SBDS	TBX3	YES1
BARD1	CDK6	E2F3	FBXW7	HGF	JARID2	MLL2	PAK3	PTPN2	SDHA	TCF3	YY1AP1
BBC3	CDK8	EBF1	FGF10	HIF1A	JUN	MLL3	PAK7	PTPN6	SDHAF2	TCL1A	ZMYM3
BCL10	CDKN1A	ECT2L	FGF12	HIST1H1C	KDM2B	MPL	PALB2	PTPRD	SDHB	TERT	ZNF217
BCL11B	CDKN1B	EED	FGF14	HIST1H1D	KDM4C	MRE11A	PARK2	PTPRO	SDHC	TET1	ZNF24
BCL2	CDKN2A	EGFL7	FGF19	HIST1H1E	KDM5A	MSH2	PARP1	PTPRS	SDHD	TET2	ZNF703
BCL2L1	CDKN2B	EGFR	FGF23	HIST1H2AC	KDM5C	MSH3	PARP2	RAC1	SERP2	TET3	ZRSR2
BCL2L11	CDKN2C	EIF1AX	FGF3	HIST1H2AG	KDM6A	MSH6	PARP3	RAD21	SETBP1	TGFBR1	
BCL2L2	CEBPA	ELP2	FGF4	HIST1H2AL	KDR	MSI1	PARP4	RAD50	SETD2	TGFBR2	
BCL6	CHD2	EMSY	FGF6	HIST1H2AM	KEAP1	MSI2	PASK	RAD51	SF3B1	TIPARP	
BCL7A	CHEK1	EP300	FGF7	HIST1H2BC	KIT	MTAP	PAX5	RAD51B	SGK1	TLL2	
BCOR	CHEK2	EPCAM	FGFR1	HIST1H2BD	KLF4	MTOR	PBRM1	RAD51C	SH2B3	TMEM127	
BCORL1	CHUK	EPHA3	FGFR2	HIST1H2BJ	KLHL6	MUTYH	PC	RAD51D	SH2D1A	TMEM30A	
BIRC2	CIC	EPHA5	FGFR3	HIST1H2BK	KMT2C	MYB	PCBP1	RAD52	SHQ1	TMPRSS2	
BIRC3	CIITA	EPHA7	FGFR4	HIST1H2BO	KRAS	MYC	PCLO		SMAD2	TMSL3	

Patient Characteristics

Characteristic	N = 23 (%)
Age years, median [range]	60 [24-76]
≥ 60	12 (52)
Gender	
Female	5 (22)
LDH > ULN, (N = 20)	6 (30)
Poor Performance Status (ECOG ≥ 2)	1 (4)
Ann Arbor Stage	
Stage I/II	1 (4)
Stage III/IV	22 (96)
Bone Marrow Involvement	14 (61)
Ki-67	
< 10%	3 (13)
10 – 29.9%	10 (43)
≥ 30%	10 (43)
MIPI, (N = 20)	
Low	12 (60)
Intermediate	6 (30)
High	2 (10)
Treatment	
Intensive Therapy (R-CHOP-14+(R)ICE+ASCT)	11 (48)
Radioimmunotherapy (Tositumomab + CHOP)	11 (48)
Rituximab	1 (4)

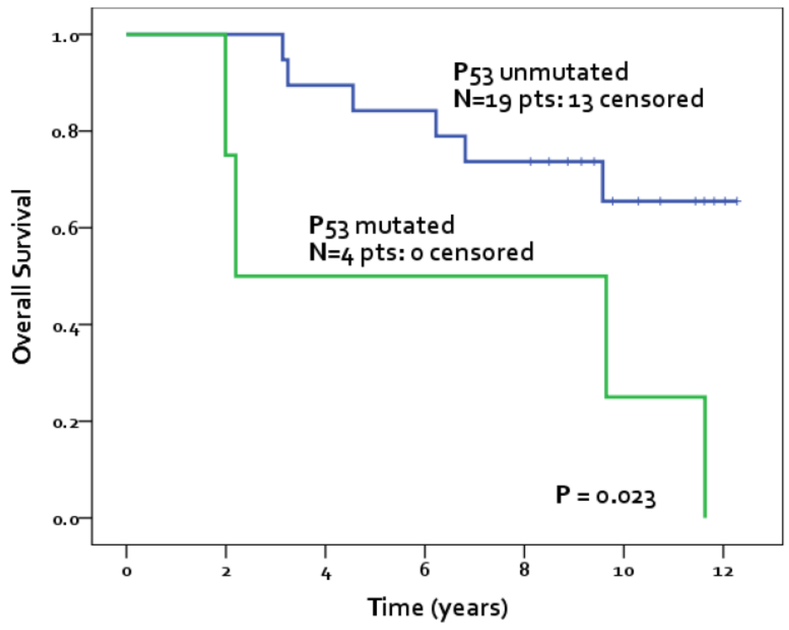
Results

- Genomic Alterations Identified:
  - ATM most frequently mutated (43%)
  - Driver mutations in MCL, p53 (17%) and *CCND1* (13%)
  - Alterations in chromatin modifying genes - e.g. *MLL2*, *SETD2*, *WHSC1* (30%)
  - Recurrent alterations in the Notch pathway - *NOTCH1/FBXW7* (17%)
  - Alterations in *BIRC3* (13%), in the alternative NF-κB pathway / apoptotic mediator
  - Alterations in APC (9%)

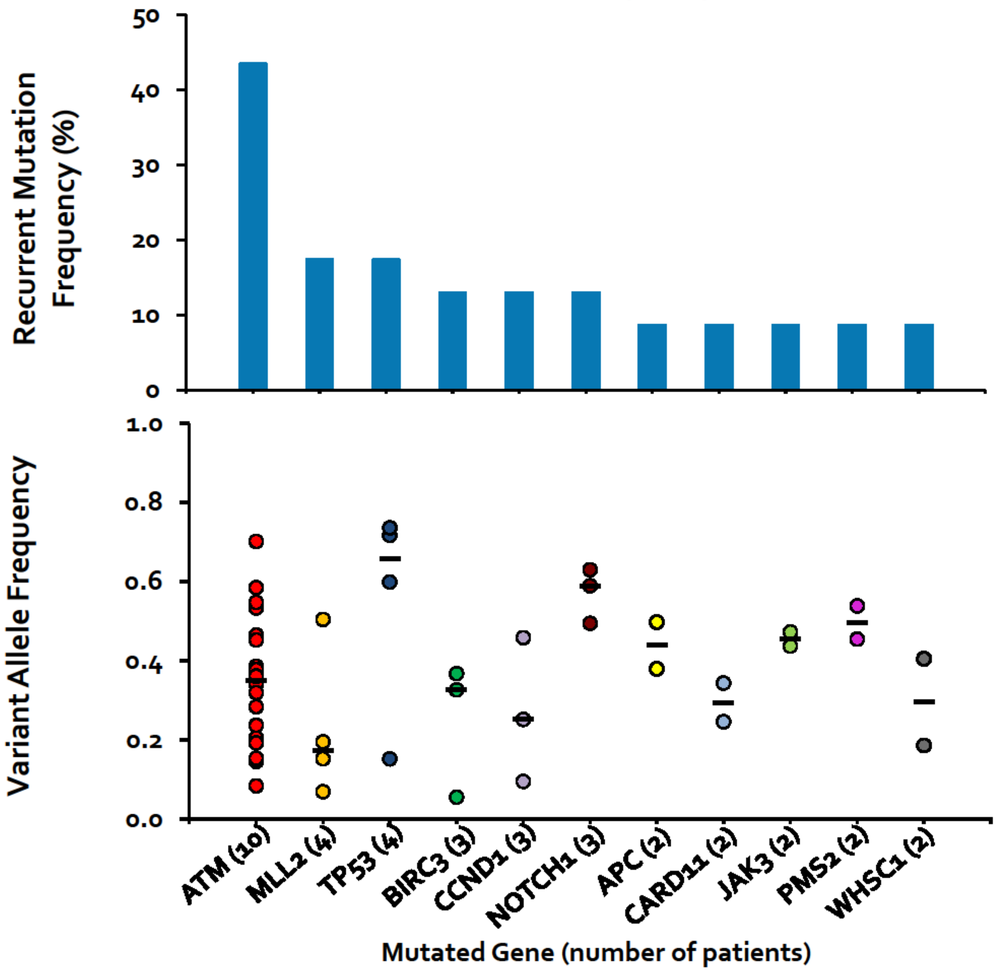
- Preliminary Outcome Analysis:
  - Mutations in p53 were significantly associated with inferior OS (p=0.023) and an elevated proliferative index (p=0.024).

Overall Survival:
Median follow-up was 8.5 years

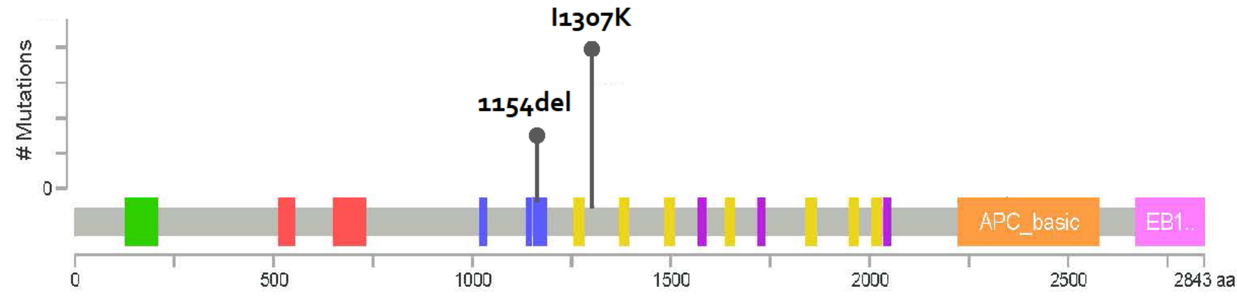
Presence of p53 mutations was associated with inferior OS: 8.5 year OS 74% (unmutated) vs. 50% (mutated)



Frequency of Recurrent Mutations and Variant Allele Frequency Identified in MCL Cases (at >5% frequency) n = 23



Alterations in APC Gene



- 2 alterations in APC gene
  - I1307K (n=1), non-synonymous single nucleotide variant, in COSMIC
  - 1154del (n=1), non-frameshift deletion, disrupts a motif critical for beta-catenin binding
  - Mutations in APC gene described in colorectal cancer, not previously identified in MCL.

Conclusion

- Analysis describes the genomic landscape in MCL prior to frontline therapy using a comprehensive targeted sequencing platform
- The study identifies potential targets for mechanism-based therapy
- This is the first report describing genetic alterations in the APC gene in MCL
- In future, we will analyze more cases to elucidate the biologic and clinical significance of these genetic alterations with the aim of developing biologically-targeted therapies in MCL

CONFLICT OF INTEREST DISCLOSURES: No conflict of interests; No financial disclosures

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Pathology and biology

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