Genomic aberrations were detected in over 80% of CLL cases. These common chromosomal abnormalities include 13q, 11q, 17p and 7q deletions, and trisomy 12. The 13q14 deletion represents the most common CLL aberration reported in ~50% of all cases (mostly in indolent CLL), on the other hand, ~10– 20% of CLL cases do not show chromosomal aberrations.

B-CLL — **Characterized by a gradual accumulation of small, mature B cells with typical B-cell markers CD5, CD19, CD23, and CD20**

Abnormalities types

HGNC-ID	Approved name	Synonyms	Chromosomal location	Chromosome - Gene alteration	Gene / miR expression	Protein level / modification	Role in apoptosis / proliferation of the anomalies	Basic signaling mechanism	Notes	PubMed / data-bases source
CDKN2A	cyclin-dependent kinase inhibitor 2A	CDK4I, p16, INK4a, MTS1, CMM2, ARF, p19, p14, INK4, p16INK4a, p19Arf	9p21	Mutation						
KRAS	Kirsten rat sarcoma viral oncogene homolog	KRAS1	12p12.1	Mutation						
NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog	N-ras	1p13.2	Mutation						COSMIC data-base
PTEN	phosphatase and tensin homolog	MMAC1, TEP1, PTEN1	10q23	Locus deletion	Reduced/NO expression	Reduced/NO expression	anti-apoptosis		Tumor suppressor	
SF3B1	splicing factor 3b, subunit 1, 155kDa	SAP155, SF3b155, PRPF10, Prp10, Hsh155	2q33.1	Mutation			tumor cell proliferation and survival			
AKT1	v-akt murine thymoma viral oncogene homolog 1	RAC, PKB, PRKBA, AKT	14q32.32-q32.33	Not studied	Not studied	Phsophorylated	anti-apoptosis	BAD phosphorylation and inhibition; NFkB1 activation		
ATM	ataxia telangiectasia mutated	TEL1, TELO1	11q22-q23	Deletion	Deletion	Decreased	anti-apoptosis	TP53 activation		
BCL2	B-cell CLL/lymphoma 2	Bcl-2, PPP1R50	18q21.3	Mutation in P1	Increased expression	Increased	anti-apoptosis			
BAG1	BCL2-associated athanogene		9p12		Increased expression	Increased	anti-apoptosis			
MCL1	myeloid cell leukemia 1	BCL2L3, Mcl-1	1q21		Increased expression	Increased	anti-apoptosis			
BAX	BCL2-associated X protein	BCL2L4	19q13.3-q13.4		Decrease	Decreased	anti-apoptosis	Binds and inhibits BCL2		
DAPK1	death-associated protein kinase 1	DAPK	9q21.33			Decreased	anti-apoptosis			
EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2	PKR, EIF2AK1	2p22-p21	Not detected	Not detected	Reduced activity in 75% of patients	anti-apoptosis	Activated by Caspase and by viral ds RNA and bacterial RNA; phosphorylated by JAKs. Cells expressing mutated PKR are not insensitive to dsRNA-induced apoptosis and completely resistant to apoptosis induced by either Fas ligand or TNF	It is unknown if the p53 and PKR pathways overlap	
MDM2	MDM2 oncogene, E3 ubiquitin protein ligase	HDM2, HDMX, MGC5370	12q13-q14	Trisomy	Increased copy numbers	Increased	anti-apoptosis (MDM2 inhibits TP53)			
MMP9	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)		20q12-q13	Not studied	Not studied	Increased	increase of survival by stroma	MMP-9 is regulated by the chemokine CCL21 and its receptor CCR7 via the ERK1/2 pathway.		
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	KBF1, p105, NFKB-p50, p50, NF-kappaB, NFkappaB, NF-kB1	4q24	Not studied	Increased expression	Increased	anti-apoptosis	Increased expression of BCL2	NF-kB activation is critical in CLL development	
PIK3C2A	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	PI3K-C2alpha	11p15.5-p14	Not studied	Not studied	Phsophorylated	increase of survival	AKT1 activation		
PIK3C2B	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 beta	C2-PI3K, PI3K-C2beta	1q32	Not studied	Not studied	Phsophorylated	increase of survival	AKT1 activation		
TCL1A	T-cell leukemia/lymphoma 1A	TCL1	14q32.1	Not studied	Increased expression (90% of patients)	Increased (90% of patients)	increase of survival	Tcl1 interacts with and activates AKT1 by interaction with AKT1 PH domain.However, Tcl1 may also activate NF-kB activity 2~4 fold by a mechanism independent of Akt1. Tcl1 also physically interacts with AP-1 complex (c-Jun + c-Fos) and functions as an AP-1 inhibitor	Correlates with aggressive CLL phenotype. In T-cells, Tc1 activates Akt, this leads to increased proliferation, inhibition of apoptosis and T-cell transformation. In B cells, Tc1 functions as transcriptional regulator, it activates NF-kB and inhibits AP-1). This leads to defects in apoptosis, increase in cell survival, and CLL pathogenesis.	Cancer Biol Ther. 2008 Feb;7(2):174-9. Epub 2007 Nov 3. Molecular basis of pathogenesis, prognosis and therapy in chronic lymphocytic leukaemia. Chen JT, McMillan NA. PMID: 18059180;
TERT	telomerase reverse transcriptase	TRT, TP2, TCS1, hEST2, EST2	5p15.33	Not studied	Not studied	increased				
TNFSF13	tumor necrosis factor (ligand) superfamily, member 13	APRIL ("a proliferation-inducing ligand"), CD256	17p13.1	Not studied	Not studied	increased	increase of survival by stroma	NFKB1 upregulation	APRIL binds with high affinity to two receptors, BCMA (B-cell maturation antigen) and TACI, both are members of TNF receptor superfamily; BCMA is mostly expressed in mature B- and T-cells, while TACI is detected in activated T-cells and subpopulations of B-cells. They stimulate NF- kB pathway by interaction with various TRAFs.	
TNFSF13B	tumor necrosis factor (ligand) superfamily, member 13b	BAFF, THANK, BLYS, TALL-1, TALL1, CD257	13q32-q34	Not studied	Not studied	increased	increase of survival by stroma	NFKB1 upregulation		
TP53	tumor protein p53	p53, LFS1	17p13.1	Deletion and mutation	Decrease	Decrease or loss of function	anti-apoptosis	Promotes apotposis	It is unknown if the p53 and PKR pathways overlap. Associated to poor survival	
ZAP70	zeta-chain (TCR) associated protein kinase 70kDa	ZAP-70, STD	2q11-q13	Not studied	Increased expression	Increased	increase of survival		Correlates with aggressive CLL phenotype. The expression of ZAP 70 is 3.24-fold higher in the subgroup with unmutated IgVH than mutated.	
DLEU7	deleted in lymphocytic leukemia, 7	FLJ44882	13q14.3	Locus deletion (66% of patients)	Decrease	Decreased	anti-apoptosis	Dleu7 expression inhibits NF-kB activation by BCMA and TAC1 by over 4-5 folds. Moreover, Dleu7 inhibits by ~8 fold the ability of BCMA and TAC1 to induce *NFAT* mediated transactivation. Thus, Dleu7 functions as NF-kB and NFAT inhibitor.	DLEU7 is methylated and in essence is not expressed in CLL	Pekarsky Y, Zanesi N, Croce CM. Molecular basis of CLL. Semin Cancer Biol. 2010 Dec;20(6):370-6.
DLEU1	deleted in lymphocytic leukemia 1 (non-protein coding)	BCMS; DLB1; LEU1; LEU2; XTP6; DLEU2; LINC00021; NCRNA00021	13q14.3	Locus deletion (50-60% of patients)	Decrease					
DLEU2	deleted in lymphocytic leukemia 2 (non-protein coding)	184; DLB2; LEU2; BCMSUN; RFP2OS; MIR15AHG; TRIM13OS; LINC00022; NCRNA00022	13q14.3	Locus deletion (50-60% of patients)	Decrease			The *DLEU2* locus generates a long non-coding RNA that has only one known function: to serve as the primary RNA from which the mature miR-15a/miR-16a microRNAs are processed		
NOTCH1	"Notch (Drosophila) homolog 1 (translocation-associated)", "Notch homolog 1, translocation-associated (Drosophila)	hN1; TAN1	9q34.3	Mutation (One recurrent mutation (c.7544_7545delCT) accounts for approximately 80% of all NOTCH1 mutations)		activation	Constitutively expressed in CLL; the precise role of *NOTCH1* activation in CLL pathogenesis is still under scrutiny	NOTCH1 encodes a ligand-activated transcription factor that regulates several down-stream pathways important for cell growth control and is affected by activating mutations in 60% of T-lineage acute lymphoblastic leukemias	*NOTCH1* mutations identify a high-risk subgroup of patients showing poor survival comparable to that associated with TP53 abnormalities. NOTCH1 directly regulates c-MYC and activates a feed-forward- loop transcriptional network promoting leukemic cell growth.	
BIRC3	baculoviral IAP repeat containing 3	AIP1; API2; MIHC; CIAP2; HAIP1; HIAP1; MALT2; RNF49; c-IAP2	11q22	Gere inactivation by mutation		Inhibition; (all BIRC3 mutations in CLL are predicted to disrupt the C-terminal RING domain)	anti-apoptosis	BIRC3 negatively regulates MAP3K14, an activator of the non-canonical pathway of NF-kB signaling; the C-terminal RING domain is essential for proteasomal degradation of MAP3K14 by BIRC3. Consistently, CLLs harboring BIRC3 disruption display constitutive NF-kB activation		J Clin Invest. Oct 1, 2012; 122(10): 3432–3438. Molecular pathogenesis of chronic lymphocytic leukemia Gianluca Gaidano, Robin Foà, and Riccardo Dalla-Favera
MYD88	myeloid differentiation primary response 88	MYD88D	3p22	Mutation (p.L265P mutation constitutes an activating mutation of this novel proto-oncogene)					MYD88 is a critical adaptor molecule of the TLR complex that is also mutated in other B cell malignancies, namely DLBCL and marginal zone lymphoma; timulation of interleukin-1 receptor or Toll-like recep- tors in MYD88-mutated CLL cells induced the secretion of 5-fold to 150-fold higher levels of interleukin 1 receptor antagonist (IL1RN, also known as IL1RA), interleukin 6 and chemokine (C-C motif) ligands 2, 3 and 4 (CCL2, CCL3 and CCL4), when compared to the secretion of these cytokines by MYD88-unmutated CLL	
XPO1	exportin 1	emb; CRM1; exp1	2p15	Mutation affects XPO1 activity. Notably, four cases with mutations in XPO1 belonged to the IGHV-unmutated subtype and two of them also had the p.P2515fs*4 mutation in NOTCH1, indicating that both muta-tions could have synergic effects in CLL development.					The protein encoded by this gene mediates leucine-rich nuclear export signal (NES)-dependent protein transport. Exportin 1 specifically inhibits the nuclear export of Rev and U snRNAs. It is involved in the control of several cellular processes by controlling the localization of cyclin B, MPAK, and MAPKAP kinase 2. This protein also regulates NFAT and AP-1.	Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia
ROR1	receptor tyrosine kinase-like orphan receptor 1	NTRKR1; dJ537F10.1	1p32-p31		Over-expression	Phsophorylated	anti-apoptosis		Various ROR1 isoforms were differentially expressed in non-progressive vs. progressive CLL patients and ROR1 was constitutively phosphorylated particularly in progressive CLL patients. Dephosphorylation of ROR1 preceded in vitro apoptosis induced by the anti-ROR1 mAbs.	The Tyrosine Kinase Receptor ROR1 Is Constitutively Phosphorylated in Chronic Lymphocytic Leukemia (CLL) Cells

MIRs

miR15a			13q14	Locus deletion (66% of patients)	Decrease	TCL1 increased expression; BCL2 increased expression; CCND1 increased expression; CCND3 increased expression; CDK6 increased expression	Increase of survival (TCL1); anti-apoptosis (BCL2)	Inhibits expression of TCL1, BCL2, CCND1, CCND3, CDK6	deletion of *MIR15A/MIR16A* abrogates the inhibitory effect and favors the constitutive cycling of B cells	
miR16a			13q14	Locus deletion (66% of patients)	Decrease	TCL1 increased expression; BCL2 increased expression; CCND1 increased expression; CCND3 increased expression; CDK6 increased expression	Increase of survival (TCL1); anti-apoptosis (BCL2)	Inhibits expression of TCL1, BCL2, CCND1, CCND3, CDK7	deletion of *MIR15A/MIR16A* abrogates the inhibitory effect and favors the constitutive cycling of B cells	
miR34b			11q22-23							
miR34c			11q22-24							
miR29b				Locus deletion		TCL1 increased expression	Increase of survival (TCL1)			
miR181b				Locus deletion		TCL1 increased expression	Increase of survival (TCL1)			