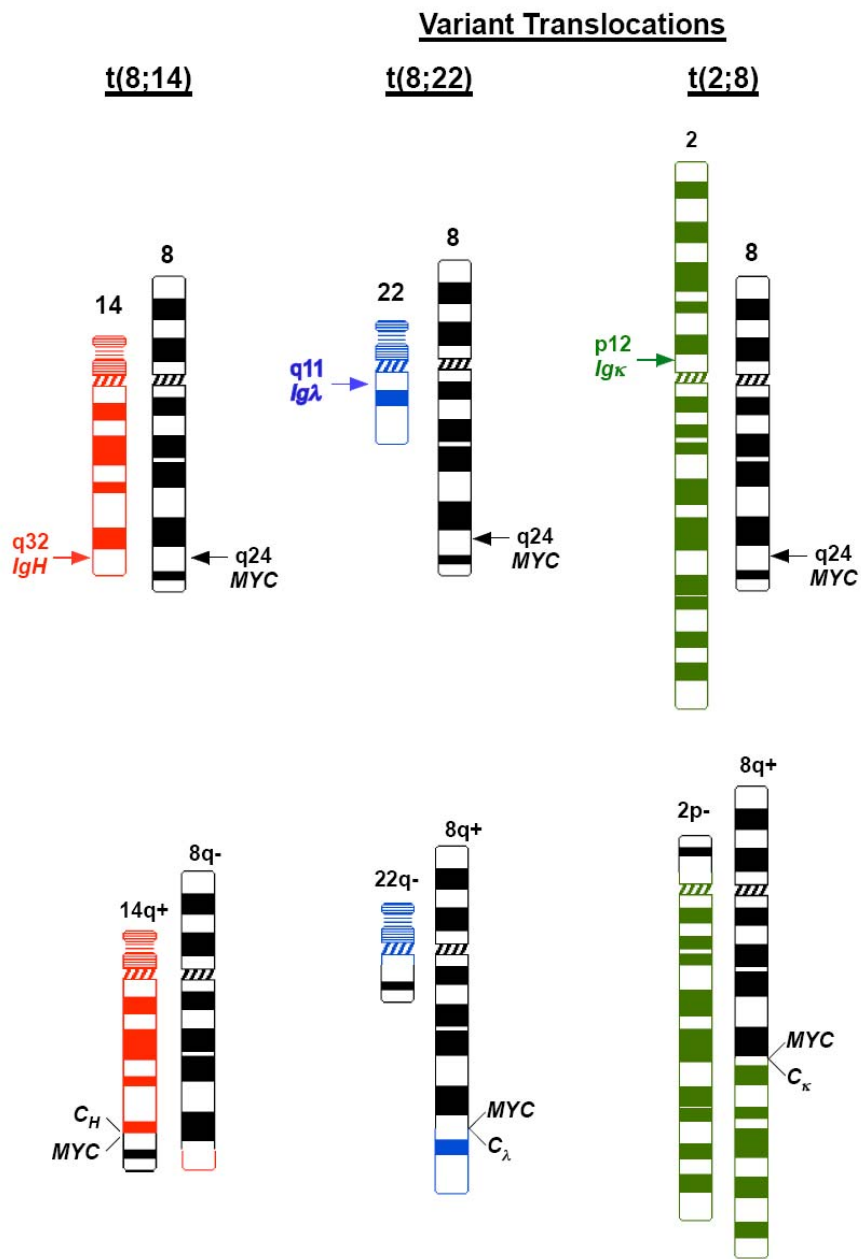


Supplementary Appendix

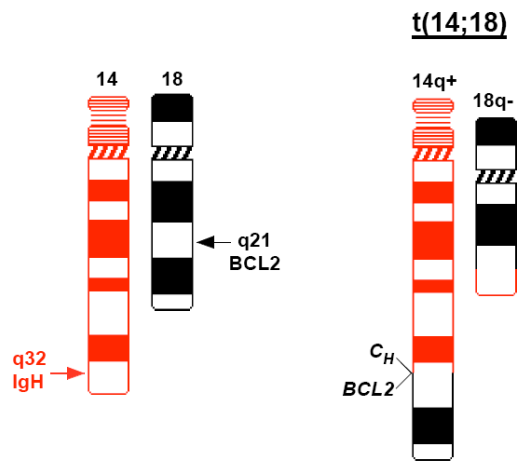
This appendix has been provided by the author to give readers additional information about his work.

Supplement to: Croce CM. Oncogenes and cancer. N Engl J Med 2008;358:502-11.

Supplementary **FIGURE 1.**



Supplementary **FIGURE 2.**



Legends to Figures

Supplementary Fig.1 Chromosome translocations observed in Burkitt lymphomas (BL). Upper: chromosomes included in the translocations. Lower: translocated chromosomes. Similar translocations have been observed in a fraction of human B-ALLs. In every case of BL the MYC oncogene is juxtaposed to enhancers present in the human immunoglobulin loci.

Supplementary Fig. 2 The t(14;18) reciprocal chromosome translocation characteristic of human follicular lymphoma, one of the most common human lymphomas. The translocation juxtaposes the BCL2 gene to enhancer element of the immunoglobulin heavy chain locus causing deregulation of expression of oncogene BCL2.

Supplementary Table 1. Oncogenes

Oncogene	Chromosome	Method of Identification	Neoplasm	Mechanism of Activation	Protein Function
Transcription factors					
<i>v-myc</i>	8q24.1 (MYC)	Viral homologue	Carcinoma myelocytomatosis	Deregulated activity	Transcription factor
<i>N-MYC</i>	2p24	DNA amplification	Neuroblastoma:lung carcinoma	Deregulated activity	Transcription factor
<i>L-MYC</i>	1p32	DNA amplification	Carcinoma of lung	Deregulated activity	Transcription factor
<i>v-myb</i>	6q22-24	Viral homologue	Myeloblastosis	Deregulated activity	Transcription factor
<i>v-fos</i>					Transcription factor
	14q21-22	Viral homologue	Osteosarcoma	Deregulated activity	API
<i>v-jun</i>					Transcription factor
	P31-32	Viral homologue	Sarcoma	Deregulated activity	API
<i>v-ski</i>	1q22-24	Viral homologue	Carcinoma	Deregulated activity	Transcription factor
<i>v-rel</i>	2p12-14	Viral homologue	Lymphatic leukemia	Deregulated activity	Mutant NFKappa B
<i>v-ets-1</i>	11p23-24	Viral homologue	Erythroblastosis	Deregulated activity	Transcription factor
<i>v-ets-2</i>	21q24.3	Viral homologue	Erythroblastosis	Deregulated activity	Transcription factor
<i>v-erbA1</i>					T3 Transcription
	17-p11-21	Viral homologue	Erythroblastosis	Deregulated activity	factor
<i>v-erbA2</i>					T3 Transcription
	3p22-24.1	Viral homologue	Erythroblastosis	Deregulated activity	factor
Inhibitors of apoptosis and others					
<i>BCL2</i>	18q21.3	Chromosomal translocation	B-cell lymphomas	Deregulated activity	Antiapoptotic protein
				Gene amplification/ increased	
<i>MDM2</i>	12q14	DNA amplification	Sarcomas	protein	Complexes with p53
Chromatin modifiers					
<i>ALL1(MLL)</i>	11q23	Chromosome translocation	ALL or AML	Gene fusion	Chromatin modifier
<i>(This gene can fuse with >50 genes)</i>					

Growth factors

<i>v-sis</i>	22q12.3-13.1	Sequence homology	Glioma/fibrosarcoma	Constitutive production	B chain PDGF
<i>int2</i>	11q13	Proviral insertion	Mammary carcinoma	Constitutive production	Member of FGF family
<i>KS3</i>	11q13.3	DNA transfection	Kaposi's sarcoma	Constitutive production	Member of FGF family
<i>HST</i>	11q13.3	DNA transfection	Stomach carcinoma	Constitutive production	Member of FGF family

Growth factor receptors

Tyrosine kinases:integral membrane proteins

<i>EGFR</i>	7P1.1-1.3	DNA amplification/DNA sequencing	Squamous cell carcinoma Non-small cell lung cancer	Gene amplification/protein/point mutation	EFG receptor
<i>v-fms</i>	5q33-34 (FMS)	Viral homologue	Sarcoma	Constitutive activation	CSF1 receptor
<i>v-KIT</i>	4q11-21 (KIT)	Viral homologue/DNA sequencing	Sarcoma/GIST	Constitutive activation/ point mutation	Stem cell factor receptor
<i>v-ros</i>	6q22 (ROS)	Viral homologue	Sarcoma	Constitutive activation	?
<i>MET</i>	7p31	DNA transfection	MNNG-treated human osteocarcinoma cell line	DNA rearrangement/ ligand-independent constitutive activation (fusion proteins)	HGF/SF receptor
<i>TRK</i>	1a32-41	DNA transfection	Colon/thyroid carcinomas	DNA rearrangement/ligand-independent constitutive activation (fusion proteins)	NGF receptor
<i>NEU</i>	17q11.2-12	Point mutation/DNA amplification	Neuroblastoma/breast carcinoma/NSCLC	Gene amplification/point mutation	?
<i>RET</i>	10q11.2	DNA transfection	Carcinomas of thyroid Men 2A. Men 2B	DNA rearrangement/point mutation (ligand-indepen- dent constitutive	GFNG/NTT/ART/PSF receptor

activation/ fusion proteins)

Receptors lacking protein kinase activity

<i>mas</i>	6q24-27	DNA transfection	Epidermoid carcinoma	Rearrangement of 5' non-coding region	Angiotensin receptor
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Signal transducers

Cytoplasmic tyrosine kinases

<i>SRC</i>	20-12-13	Viral homologue	Colon carcinoma	Constitutive activation	Protein tyrosine kinase
<i>v-yes</i>	18q21-3 (YES)	Viral homologue	Sarcoma	Constitutive activation	Protein tyrosine kinase
<i>v-fgr</i>	1p36.1-36.2 (FES)	Viral homologue	Sarcoma	Constitutive activation	Protein tyrosine kinase
<i>v-fes</i>	15q25-26 (FES)	Viral homologue	Sarcoma	Constitutive activation	Protein tyrosine kinase
<i>ABL</i>	9q34.1	Chromosome translocation	CML	DNA rearrangement (constitutive activation/fusion proteins)	Protein tyrosine kinase

Membrane-associated G proteins

<i>H-RAS</i>	11p15.5	Viral homologue/DNA transfection	Colon, lung, pancreas carcinomas	Point mutation	GTPase
<i>K-RAS</i>	12p11.1-12.1	Viral homologue/DNA transfection	AML, thyroid carcinoma, melanoma/colon/lung	Point mutation	GTPase
<i>N-RAS</i>	1p11-13	DNA transfection	Carcinoma, melanoma	Point mutation	GTPase
<i>BRAF</i>	6	DNA sequencing	Melanoma, thyroid, colon, ovary	Point mutation	Ser/Thr kinase
<i>gsp</i>	20	DNA sequencing	Adenomas of thyroid	Point mutation	Gs alpha
<i>gip</i>	3	DNA sequencing	Ovary, adrenal carcinoma	Point mutation	Gi alpha

GTPase exchange factor (GEF)						
<i>Dbl</i>	Xq27	DNA transfection		Diffuse B-cell lymphoma	DNA rearrangement	GEF for Rho and Cdc42Hs
<i>Vav</i>	19p13.2	DNA transfection		Hematopoietic cells	DNA rearrangement	GEF for Ras ?
Serine/threonine kinases : cytoplasmic						
<i>v-mos</i>	8q11 (MOS)	Viral homologue		Sarcoma	Constitutive activation	Protein kinase (ser/thr)
<i>v-raf</i>	3p25 (Raf-1)	Viral homologue		Sarcoma	Constitutive activation	Protein kinase (ser/thr)
<i>pim-1</i>	6p21 (PIM-)	Insertional mutagenesis		T-cell lymphoma	Constitutive activation	Protein kinase (ser/thr)
Cytoplasmic regulators						
<i>v-crk</i>	17q13 (CRK)	Viral homologue			Constitutive tyrosine phosphorylation of cellular substrates (eg, paxillin)	SH-2/SH-3 adaptor
ALL – acute lymphoblastic leukemia ; AML= acute myeloid leukemia ; CML=chronic myelogenous leukemia ; GTPase- guanosine triphosphatase ; PDGF=platelet-derived growth factor.						

Supplementary Table 2. Consistent Chromosome Translocations in Human Cancers

Affected Gene	Rearrangements	Disease	Protein Type
<i>Oncogenes juxtaposed with IG loci</i>			
c-MYC	t(8:14) (q24:q32)	BurKITt's lymphoma;BL-ALL	HLH domain
	t(2:8) (p12:q24)		

	t(8:22) (q24;q11)		
BCL1 (Cyclin D1)	t(11:14) (q13;q32)	B-cell chronic lymphocyte leukemia	PRADI-GI Cyclin D1
BCL-2	t(14:18) (q32;q21)	Follicular lymphoma	Inner mitochondrial membrane
BCL-3	t(14:19) (q32;q13.1)	Chronic B-cell leukemia	CDC10 motif
IL-3	t(5:14) (q31;q32)	Acute pre-B-cell leukemia	Growth factor
<i>Oncogenes juxtaposed with TRC loci</i>			
c-MYC	t(8:14) (q24;q11)	Acute T-cell leukemia	HLH domain
LYLA	t(7:19) (q35;p13)	Acute T-cell leukemia	HLH domain
TAL1/SCL/TCL-5	t(1:14) (q32;q11)	Acute T-cell leukemia	HLH domain
TAL-2	t(7:9) (q35;q34)	Acute T-cell leukemia	HLH domain
Rhombotin 1/Ttg-1	t(11:14) (p15;q11)	Acute T-cell leukemia	LIM domain
Rhombotin 2/Ttg-2	t(11:14) (p13;q11)	Acute T-cell leukemia	LIM domain
	t(7:11) (q35;p13)		
HOX 11	t(10:14) (q24;q11)	Acute T-cell leukemia	Homeodomain
	t(7:10) (q35;q24)		
TAN-1	t(7:9) (q34;q34.3)	Acute T-cell leukemia	Notch homologue
TCL-1	T(14;14) q11;q32.1 or t(7q35-14q32.1)	T-cell prolymphocytic leukemia	

or inv14(q11;q32.1)

Hematopotetic tumor

Gene fusion

c-ABL (9q34)	t(9:22) (q34;q11)	Chronic myelogenous leukemia and acute leukemia	Tyrosine kinase activated by BCR
BCR (22q11)			
PBX-1 (1q23)	t(1:19) (q23;p13.3)	Acute pre-B-cell leukemia	Homeodomain
E2A(19p13.3)			HLH
PML(15q21)	t(15:27) (q21;q11-22)	Acute promyelocytic leukemia	Zn finger
RAR(17q21)			
CAN(6-23)	t(6:9) (P23;q34)	Acute myeloid leukemia	No homology
DEK(9q34)			
REL	ins(2:12) (p11.2-14)	Non-Hodgkin's lymphoma	NF-κB family
ALL1(MLL)*	11q23	ALL and AML	Chromatin modifier

Solid tumors

Gene Fusions in sarcomas

FLI1,EWS	t(11:22) (q24;q12)	Ewing's sarcoma	Ets transcription factor family
ERG,EWS	t(21:22) (q22;q12)	Ewing's sarcoma	Ets transcription factor

			family
ATV1,EWS	t(7:21) (q22;q12)	Ewing's sarcoma	Ets transcription factor
			family
ATF1,EWS	t(12:22) (q13;q12)	Soft-tissue clear cell sarcoma	Transcription factor
CHN,EWS	t(9:22) (q22 31;q12)	Myxoid chondrosarcoma	Steroid receptor family
WT1,EWS	t(11:22) (p13;q12)	Desmoplastic small round cell tumor	Wilms' tumor gene
SSX1,SSX2,SYT	t(X18) (p11.2;q11.2)	Synovial sarcoma	HLH domain
PAX3,FKHR	t(2:13) (q37;q14)	Alveolar	Homeobox homologue
PAX7,FKHR	t(1:13) (q36;q14)	Rhabdomyosarcoma	Homeobox homologue
CHOP,TLS	t(12:16) (q13;p11)	Myxoid liposarcoma	Transcription factor
var,HMG1-C	t(var:12) (var:q13- 15)	Lipomas	HMG DNA-binding protein
HMG2-C?	t(12:14) (q13;q15)	Leiomyomas	HMG DNA-binding protein
Gene fusions in thyroid carcinomas			
RET/ptc1	inv(10) (q11.2;q2.1)	Papillary thyroid carcinomas	Tyrosine kinase activated by H4
RET/ptc2	t(1:17) (q11.2;q23)	Papillary thyroid carcinomas	Tyrosine kinase activated by RIa(PKA)

RET/ptc3		inv(10) (q11.2)	Papillary thyroid carcinomas	Tyrosine kinase activated by ELE1
TRK		inv(1) (q31;q22-23)	Papillary thyroid carcinomas	Tyrosine kinase activated by TPM3
TRK-T1(T2)		inv(1) (q31;q25)	Papillary thyroid carcinomas	Tyrosine kinase activated by TPR
TRK-T3		t(1q31:3)	Papillary thyroid carcinomas	Tyrosine kinase activated by TFG
<i>Gene fusions in prostate cancer</i>				
TMPR552	ERG or ETV1	t(21q22;21q22.3 or 7p21.2)	Prostate carcinoma	Ets transcription factor family activated by TMPR552
<i>Deregulation of oncogenes</i>				
Parathyroid tumors				
PTH deregulates PRAD1 (Cyclin D1)		inv(11)(P15q;q13)	Parathyroid adenoma	PRADI/Cyclin D1

*ALL1 can fuse with more than 50 different genes. More frequently it fuses with AF4 in ALL and AF9 in AML

Supplementary Table 3. Oncogene Amplification in Human Cancers

Tumor Type	Gene Amplified	Percent of Tumors
Neuroblastoma	MYCN	~20
Small cell lung cancer	MYC	~15
Glioblastoma	ERBB1 (EGFR)	~30
Breast cancer	MYC	~20
	EGFR2	~20
	FGFR1	~10
	FGFR2	~10
	CCND1 (Cyclin D1)	15-20
Esophageal cancer	MYC	~35
	CCND1 (Cyclin D1)	25
Gastric cancer	KRAS	10
	CCNE (Cyclin E)	15
Hepatocellular cancer	CCND1 (Cyclin D1)	~15

Sarcoma	MDM2	10-30
	CDK4	~10
Cervical cancer	MYC	25-50
Ovarian cancer	MYC	20-30
	ERBB2 (EGFR2)	15-30
	AKT2	~10
Head and neck cancer	MYC	~10
	ERB B2 (EGFR2)	10
	CCND (Cyclin D1)	~50
Colorectal cancer	MYB	15-20
	HRAS	29
	KRAS	22