U.S.A. **86**, 2498 (1989); J. Zachary, J. Gil, W. Lehman, J. Sinnett-Smith, *ibid.* **88**, 4577 (1991); T. Force, J. M. Kyriakis, J. Avruch, J. V. Bonventre, *J. Biol. Chem.* **266**, 6650 (1991); L. M. T. Leeb-Lundberg and X.-H. Song *ibid.* **266**, 7746 (1991); S. J. Shattil and J. S. Brugge, *Curr. Opin. Cell Biol.*, in press.
94. B. F. O'Dowd, R. J. Lefkowitz, M. G. Caron, *Annu. Rev. Neurosci.* **12**, 67 (1989); J. Ramachandran, E. G. Peralta, A. Ashkenazi, J. W. Winslow, D. J. Capon, *Bioessays* **10**, 54 (1989); H. Y. Lin, E. H. Kaji, G. K. Winkel, H. E. Ives, H. F. Lodish, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 3185 (1991).
95. T. R. Jackson, L. A. Blair, J. Marshall, M. Goedert, M. R. Hanley, *Nature* **335**, 440 (1988).
96. D. Julius, T. J. Livelli, T. M. Jessell, R. Axel, *Science* **244**, 1057 (1989).
97. F. Cuttitta *et al.*, *Nature* **316**, 823 (1985).
98. J. L. Mulshine *et al.*, *Ann. N.Y. Acad. Sci.* **547**, 360 (1988).
99. C. A. Landis *et al.*, *Nature* **340**, 692 (1989); J. Lyons *et al.*, *Science* **249**, 655 (1990).
100. J. S. Gutkind, E. A. Novotny, M. R. Brann, K. C. Robbins, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 4703 (1991).
101. T. Miki *et al.*, *ibid.* **88**, 5167 (1991).
102. A. A. Donjacour and G. R. Cunha, *Cancer Treat. Res.* **53**, 335 (1991); M. E. Lippman, and R. B. Dickson, *J. Steroid Biochem.* **34**, 107 (1989).
103. S. Sukumar, *Cancer Cells* **2**, 199 (1990); C. A. Perez *et al.*, in *Principles and Practice of Oncology*, V. T. De Vita, S. R. Hallman, S. A. Rosenberg, Eds. (Lippincott, New York, 1989), pp. 1023–1058.
104. R. J. Coburn, *Cancer of the Skin* (Saunders, Philadelphia, 1976), pp. 939–949; S. Preston-Martin, M. C. Pike, R. K. Ross, P. A. Jones, B. E. Henderson, *Cancer Res.* **50**, 7415 (1990); R. H. Collins, Jr., M. Feldman, J. S. Fordtran, *N. Engl. J. Med.* **316**, 1654 (1987).
105. B. N. Ames and L. S. Gold, *Science* **249**, 970 (1990); N. R. Drinkwater, *Cancer Cells* **2**, 8 (1990).
106. Y. Tsujimoto, L. R. Finger, J. Yunis, P. C. Nowell, C. M. Croce, *Science* **226**, 1097 (1984); Y. Tsujimoto *et al. ibid.* **228**, 1440 (1985).
107. D. L. Vaux, S. Cory, J. M. Adams, *Nature* **335**, 440 (1988); D. Hockenbery, G. Nunez, C. Millman, R. D. Schreiber, S. J. Korsmeyer, *ibid.* **348**, 334 (1990).
108. J. C. Reed *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 3660 (1990).
109. P. W. Finch, J. S. Rubin, T. Miki, D. Ron, S. A. Aaronson, *Science* **245**, 752 (1989).
110. K. Miyazawa *et al.*, *Biochem. Biophys. Res. Commun.* **163**, 967 (1989); T. Nakamura *et al.*, *Nature* **342**, 440 (1989); J. S. Rubin *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 415 (1991).
111. T. Nakamura, K. Nawa, A. Ichihara, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 6489 (1986); E. Gohda *et al.*, *J. Clin. Invest.* **81**, 414 (1988); R. Zarnegar and G. Michalopoulous, *Cancer Res.* **49**, 3314 (1989).
112. E. Gherardi and M. Stoker, *Nature* **346**, 228 (1990).
113. K. M. Weidner *et al. J. Cell Biol.* **111**, 2097 (1990).
114. L. Liotta, P. S. Steeg, W. G. Stetler-Stevenson, *Cell* **64**, 327 (1991).
115. G. P. Dotto *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 6389 (1988); M. Bignami, S. Rosa, S. A. La Rocca, G. Falcone, F. Tato, *Oncogene* **2**, 509 (1988); A. W. Stoker, C. Hatier, M. J. Bissell, *J. Cell Biol.* **111**, 217 (1990).
116. S. H. Friend *et al.*, *Nature* **323**, 643 (1986); W. H. Lee *et al.*, *Science* **235**, 1394 (1987); Y. K. Fung, *ibid.* **236**, 1547 (1987).
117. A. J. Levine, *Nature* **351**, 453 (1991).
118. J. A. DeCaprio *et al.*, *Cell* **58**, 1085 (1989).
119. M. Laiho, J. A. DeCaprio, J. W. Ludlow, D. M. Livingston, J. Massague, *ibid.* **62**, 175 (1990).
120. R. A. Weinberg, *Trends Biochem. Sci.* **15**, 199 (1990); W. F. Benedict, H. J. Xu, R. Takahashi, *Cancer Invest.* **8**, 535 (1990); H. L. Moses, E. Y. Yang, J. A. Pietenpol, *Ciba Found. Symp.* **157**, 66 (1991).
121. S. Sell, *Clin. Lab. Med.* **10**, 1–37 (1990).
122. D. J. Slamon *et al.*, *Science* **244**, 707 (1989).
123. G. M. Brodeur, R. C. Seeger, M. Schwab, H. E. Varmus, J. M. Bishop, *ibid.* **224**, 1121 (1984).
124. J. Crawford *et al.*, *N. Eng. J. Med.* **325**, 164 (1991).
125. J. J. Mule and S. A. Rosenberg, *Important Adv. Oncol.* (1989), p. 99.
126. M. C. Lill and D. W. Golde, *Blood* **4**, 238 (1990).
127. Editorial, *Euro. J. Clin. Invest.* **17**, 281 (1987); A. V. Schally, *Cancer Res.* **48**, 6977 (1988); A. V. Schally *et al.*, *Proc. Soc. Exp. Biol. Med.* **175**, 259 (1984); J. J. Shepherd and G. B. Senator, *Lancet* ii, 574 (1986).
128. K. Y. Ho, A. J. Weissberger, P. Marbach, L. Lazarus, *Ann. Int. Med.* **112**, 173 (1990); S. W. J. Lamberts, *Acta. Endocrinol. (Copenhagen)* **286**, 54 (1987).
129. R. Kumar, H. M. Shepard, J. Mendelsohn, *Mol. Cell. Biol.* **11**, 979 (1991); J. A. Drebin, V. C. Link, D. F. Stern, R. A. Weinberg, M. I. Greene, *Cell* **41**, 697 (1985); R. M. Hudziak *et al.*, *Mol. Cell. Biol.* **9**, 1165 (1989).
130. I. Pastan (see accompanying article).
131. A. M. Umezawa *et al.*, *J. Antibiotics* **39**, 170 (1986).
132. P. Yaish, A. Gazit, C. Gilan, A. Levitzki, *Science* **242**, 933 (1988).
133. W. R. Schafer *et al.*, *ibid.* **245**, 379 (1989); W. A. Maltese and K. M. Sheridan, *J. Cell Physiol.* **133**, 471 (1987).
134. Y. Reiss, J. L. Goldstein, M. C. Seabra, P. J. Casey, M. S. Brown, *Cell* **62**, 81 (1990).
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Chromosome Aberrations and Cancer

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Cancer may be defined as a progressive series of genetic events that occur in a single clone of cells because of alterations in a limited number of specific genes: the oncogenes and tumor suppressor genes. The association of consistent chromosome aberrations with particular types of cancer has led to the identification of some of these genes and the elucidation of their mechanisms of action. Consistent chromosome aberrations are observed not only in rare tumor types but also in the relatively common lung, colon, and breast cancers. Identification of additional mutated genes through other chromosomal abnormalities will lead to a more complete molecular description of oncogenesis.

CANCER IS THE RESULT OF THE ACCUMULATION OF MULtiple genetic changes (*1*). Each alteration, whether an initiating or a progression-associated event, may be mediated through a gross chromosomal change and therefore has the potential to be cytogenetically visible. A corollary of this idea is that the molecular characterization of chromosomal rearrangements will lead to the identification of genes involved in cancer. This review will focus on those chromosomal aberrations for which the affected genes have been cloned and characterized. Readers interested in the burgeoning cancer cytogenetics literature are referred to other reviews (*2*).

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Tumor Cytogenetics

The common tumor chromosome aberrations are generally classified as structural or numerical. Structural alterations include translocations,

inversions, deletions, insertions, and amplifications, whereas numerical abnormalities are losses or duplications of whole chromosomes (Fig. 1). Tumors analyzed for chromosome aberrations are broadly classified by cytogeneticists as hematological, which include leukemias and lympho mas, or solid, which include carcinomas and sarcomas. For technical reasons, hematological malignancies have in the past been easier to analyze and, as a result, their analysis occupies roughly 80% of the tumor cytogenetics literature although these tumors represent only about 10% of the total (*3*). The result is that our understanding of these malignancies in molecular, if not biological terms, has emerged sooner than our understanding of the solid tumors. Many of the difficulties with solid tumors have now been overcome, and literature on these tumors is expanding rapidly.

Oncogenes and Tumor Suppressor Genes

Two classes of genes are implicated in cancer. Some cellular genes (the proto-oncogenes) can be activated by dominant mutations. A proto-oncogene can be converted from a normal cellular gene to an oncogene by a variety of submicroscopic events including point mutations, small insertions and deletions, and juxtaposition to other chromosome sequences. This last event can be visualized cytogenetically as a translocation or inversion; this observation led to the realization that it was likely that proto-oncogenes might be involved in structural rearrangements. At least three oncogenes, *MYC, ABL*, and *REL* (see below) are rearranged in this way.

The second type of tumor genes, often referred to as tumor suppressor genes (*4*), has been isolated to date only from solid tumors. Like oncogenes, these are also normal cellular genes; however, tumor suppressor genes contribute to oncogenicity through their loss rather than through their activation. Their behavior is recessive, and both copies must be inactivated for tumor formation to occur. Again, there are a variety of submicroscopic mutational mechanisms by which this can occur. These are detectable at the DNA level as loss of constitutional heterozygosity in tumor DNA. Loss of the entire gene, the region of the chromosome, or even the entire chromosome will also achieve this end, and in the case of a tumor suppressor gene, these chromosomal deletions and losses are detected cytogenetically.

In general terms, structural rearrangements that consistently juxtapose two different chromosomal regions are thought to contain dominantly acting oncogenic sequences. Deletions or monosomies are believed to be the site of recessive tumor suppressor genes.

Human Gene Mapping

The advances in the molecular understanding of chromosome aberrations probably owe the greatest debt to the continuing expansion of the human gene map. The first translocations to be analyzed at a molecular level, the translocation between chromosomes 8 and 14 [t(8;14)] of Burkitt lymphoma (BL) and t(9;22) of chronic myelogenous leukemia (CML), were both cloned on the basis of the assignment of genes to the breakpoint regions of the translocation chromosomes. Similarly, and perhaps more remarkably, the analysis of solid tumors is now possible because of the enormous numbers of random DNA sequences precisely located on the map. Small regions of chromosomes deleted in some tumors can now be detected submicroscopically by the use of anonymous DNA probes. The cloning of tumor suppressor genes from these regions has depended on the mapping of probes in these regions.

Translocations and Inversions

Specific reciprocal translocations are the cytogenetic hallmarks of leukemias and lymphomas. These translocations, together with the scarcer translocations seen in solid tumors, are found in 3% of all tumors (*5*). More than 100 recurrent translocations, extracted from available information on more than 14,000 neoplasms with karyotypic abnormalities (*2*), have been described (*6*). The consistent association of specific translocations with particular disease types, particularly when present as the sole chromosomal abnormality, has led to the realization that these rearrangements identify significant steps in the oncogenic process. Although almost all leukemias are thought to carry a karyotypic abnormality of one type or another, molecular insights have been provided mainly by the study of highly consistent reciprocal translocations (7).

The first consistent chromosome aberration observed in human neoplasia was the Philadelphia chromosome in CML in 1960 (*8*). The proof that the Philadelphia chromosome did indeed represent a translocation, rather than a deletion, had to wait until improved chromosome banding techniques became available in 1973 (*9*). The full description of the rearrangement as a reciprocal translocation between the long arm (q) of chromosome 9, band 34, and band q11 of chromosome 22 [t(9;22)(q34;q11)] and the subsequent molecular dissection of the disease loci it identified heralded the arrival of a productive era for cytogenetics. The realization that particular genes lie at the translocation breakpoints and that these rearranged genes contribute directly to the transformed phenotype has become the paradigm for all recurrent translocations seen in both hematological malignancies and solid tumors.

Translocations (and inversions) can pinpoint oncogenes, but, in order to characterize these genes, a breakpoint clone must be identified from among the 5 to 10 million base pairs suggested by the cytogenetic assignment. The translocations for which there is some molecular knowledge of the causative genes are presented in Table 1. The inclusion of more hematological neoplasms reflects the more advanced understanding of these diseases over the cytogenetics of solid tumors (Table 2).

The rearrangements shown in Table 1 are divided according to the molecular consequence of their translocations. Translocations have one of two effects. They may lead to the deregulation (overexpression) of oncogenes by their juxtaposition to enhancer or promoter sequences that are active in the cell type from which the tumor arises, particularly the immunoglobulin (Ig) and T cell receptor (TCR) enhancers. Thus, in BL *MYC* is deregulated by the Ig heavy chain enhancer or light chain λ or κ enhancer (*10*). Walking from the Ig or TCR genes has identified more than ten similarly deregulated oncogenes (Table 1, A and B). Examples of deregulation unconnected with the Ig and TCR enhancers have also been found (Table 1C). In parathyroid adenomas, a rearrangement, most probably an inversion between the short and long arms of chromosome 11, leads to the juxtaposition of the parathyroid hormone regulatory elements and the *PRAD1* putative oncogene (*11*), resulting in dramatic *PRAD1* overexpression. Furthermore, *PRAD1* may be the elusive *BCL1* locus because these two genes have a close physical linkage (*12*). *BCL1* was originally defined through its rearrangement with the IgH locus in B-cell chronic lymphocytic leukemia (B-CLL), diffuse B cell lymphoma, and multiple myeloma (*13*), but a transcription unit has proved difficult to find. *PRAD1* encodes a cyclin-like protein (*14*). Similarly, the t(8;12)(q24;q22) translocation in B-CLL rearranges *MYC*, not with an Ig enhancer, but rather with a locus termed *BTG1* on chromosome 12 that presumably deregulates *MYC* (*15*).

The alternative molecular consequence of translocation is gene fusion, which results in a chimeric oncoprotein whose transforming

ability is drawn from both partners. The t(9;22) of CML leads to a *BCR-ABL* fusion message and protein (*16*). The tyrosine kinase activity of ABL is unmasked by fusion to BCR sequences (*17*). The normal *BCR* encodes a guanosine triphosphatase (GTPase)–activating protein (GAP) for a Ras-related guanosine triphosphate (GTP)–binding protein, $p21^{rac}$ (*18*). In CML, the BCR-ABL fusion p210 is usually found, whereas in individuals with Philadelphia-positive acute lymphocytic leukemia (ALL) a variant p185 fusion protein is seen in approximately half of the cases. This is due to breakage in a different *BCR* intron and leads to a more potent transforming protein. Four other examples of chromosomal rearrangements leading to fusion proteins have been described (Table 1D).

Functions of genes at translocation breakpoints. Proto-oncogenes exert their effects at many points in the cascade of information that flows from a messenger outside a cell to the nuclear transcription factors that ultimately determine the stage of cell cycle and degree of differentiation. The genes identified at translocation breakpoints act throughout this same cascade.

The proof that deregulation of growth factors or their receptors occurs in leukemia came with the cloning of the t(5;14)(q31;q32) breakpoint in pre–B-cell ALL (pre-B ALL). At this breakpoint, the interleukin-3 (IL-3) growth factor on chromosome 5 is positioned next to the IgH enhancer on chromosome 14 (Table 1A). The ensuing overproduction of IL-3 results in an autocrine loop that favors leukemogenesis (*19*). Both normal counterparts of the CML BCR-ABL fusion act further down the signal transduction pathway. Tyrosine kinases such as that encoded by *ABL* are widely implicated in cancer, as are GTPase-activating proteins such as the *BCR* product and the neurofibromatosis I gene product (*20*).

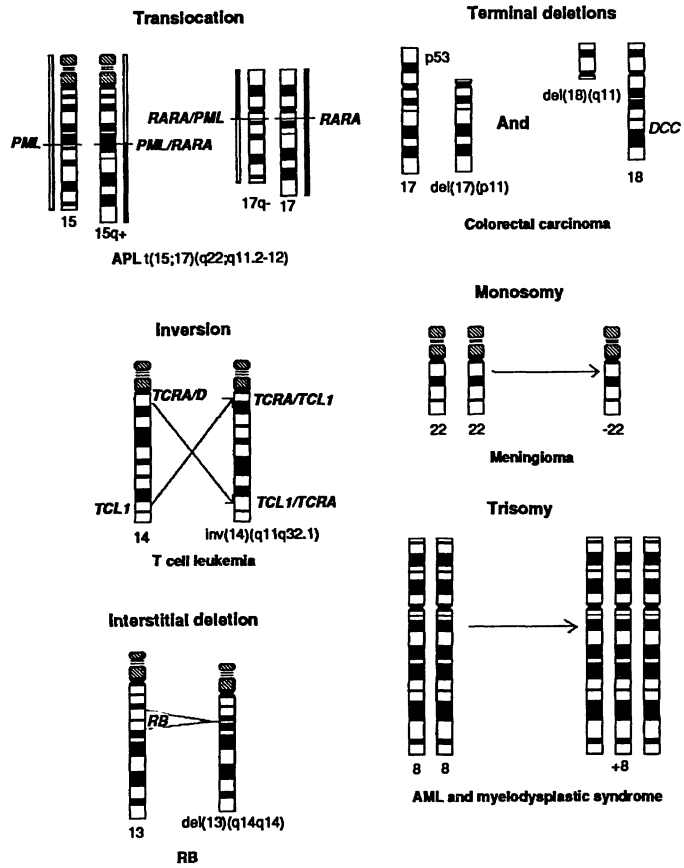

Fig. 1. Schematic representation of chromosomal aberrations observed in tumors. Shown are the t(15;17)(q22;q11.2-12) seen in APL; the inv(14)(q11q32.1) observed in T cell leukemia; the del(13)(q14q14) associated with RB; the terminal deletions of chromosomes 17p and 18q seen in colorectal carcinoma; monosomy 22 associated with meningioma; and trisomy 8 seen in AML and myelodysplastic syndrome.

Evidence for involvement of a ligand receptor in leukemogenesis comes from the rearrangement of a member of the steroid–thyroid hormone receptor superfamily, the retinoic acid receptor alpha (RARA), in the t(15;17)(q22;q11.2-12) of acute promyelocytic leukemia (APL) (Fig. 1 and Table 1D) (*21*). This translocation fuses the NH_2-terminus of a Zn finger protein PML to the COOH-terminus of the protein RARA that is encoded by a gene on chromosome 17 (*22*). The result is a chimeric transcription factor that retains the Zn fingers from both molecules and the ligand-binding domain of RARA. Transformation presumably results from the aberrant regulation of genes involved in myeloid differentiation that are normally regulated by PML or RARA. A second fusion protein derived from two transcription factors results from the t(1;19)(q23;p13) (p is the short arm of the chromosome) translocation in pre-B ALL (Table 1D). This translocation fuses *E2A* on chromosome 19, which encodes the helix-loop-helix (HLH) Ig enhancer binding proteins E12 and E47, with the homeobox *PBX* gene on chromosome 1 (*23*). The translocation switches the DNA binding domain of E2A with that of PBX, thus placing those genes usually regulated by PBX under the trans-activational control of E2A. Furthermore, because *PBX* is not normally transcribed in pre-B cells, the translocation results in ectopic expression of the PBX DNA binding domain.

The APL and pre-B ALL fusion proteins involve three different families of DNA binding proteins, those with Zn fingers, HLH domains, and homeobox domains (*21–23*). Rearrangements of a member of a fourth family, the *REL/NF-κB* family, occur in some cases of non–Hodgkin's lymphoma (NHL) as a consequence of an insertion on chromosome 2, ins(2;2)(p13;p11.2-14) (Table 1D). The molecular result of this insertion is the fusion of two genes in a manner similar to translocation fusions. The resultant REL-NRG fusion protein retains the NH_2-terminal DNA binding and transcriptional activation domains of REL but replaces its COOH-terminus with NRG sequences of unknown function (*24*).

The involvement of transcription factors at translocation breakpoints is a re-occurring theme. Two closely related HLH transcription factor genes *LYL1* (*25*) and *TCL5* (also called *TAL1* or *SCL*) (*26*) are rearranged in T cell ALL (T-ALL) (Table 1B). The translocation breakpoints fall within the 5′ or 3′ untranslated regions of these genes so that the coding potential remains unchanged. Although the t(1;14) that originally identified *TCL5* is infrequent in T-ALL, the same locus is activated by a cytogenetically undetectable 90-kb deletion in 25% of individuals with T-ALL. This leads to the production of a fusion complementary DNA (cDNA) (but not fusion protein) between an undefined locus, *SIL*, and *TCL5* (*27*). The HLH protein MYC is deregulated in both B and T cell–derived neoplasms. Finally, the *TCL3* locus identified in t(10;14)(q24;q11)–associated T-ALL has been shown to encode a homeobox protein, HOX11 (Table 1B) (*28*).

A different class of nuclear oncogene has been described in T-ALL with an associated t(11;14) (Table 1B). Walking from the TCRδ locus identified an overexpressed transcript (*RBNT1* or *TTG1*) (*29*) that proved to contain an LIM domain when sequence analysis was performed. LIM domains (*30*) are cysteine-rich motifs suggestive of metal-binding domains and are thought to mediate protein dimerization. A second LIM domain oncogene, *RBNT2* (Rhombotin 2), has been identified at another breakpoint in T-ALL (*31*). Although the protein encoded by *RBNT1*, Rhombotin 1, lacks a DNA binding motif, the occurrence of LIM domains in other proven transcription factors containing homeodomains suggests that Rhombotin 1 may interact with such factors and thereby modulate transcription. The dimerization of transcription regulators

Table 1. Molecularly characterized neoplastic rearrangements. (**A**) Oncogenes juxtaposed to Ig loci. (**B**) Oncogenes juxtaposed to TCR. (**C**) Oncogenes juxtaposed to other loci. (**D**) Fusion oncoproteins. Ref., reference; inv, inversion; deregs, deregulates; AML-M2, acute myeloblastic leukemia; and AML-M4, acute monomyelocytic leukemia.

Part	Disease	Rearrangement	Gene	Protein type	Ref.
A	BL	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	*MYC*	HLH domain	*10*
	B-CLL	t(11;14)(q13;q32)	*BCL1 (PRAD1?)*	PRAD1 is a G1 cyclin	*11, 12, 13, 14*
	Follicular lymphoma	t(14;18)(q32;q21)	*BCL2*	Inner mitochondrial membrane	*36, 37*
	B-CLL	t(14;19)(q32;q13)	*BCL3*	CDC10 motif	*35*
	Pre-B ALL	t(5;14)(q31;q32)	*IL-3*	Growth factor	*19*
B	T-ALL	t(8;14)(q24;q11)	*MYC*	HLH domain	*72*
	T-ALL	t(7;19)(q35;p13)	*LYL1*	HLH domain	*25*
	T-ALL	t(1;14)(p32;q11)	*TCL5 (TAL1, SCL)*	HLH domain	*26, 27*
	T-ALL	t(11;14)(p15;q11)	*RBNT1*	LIM domain	*29*
	T-ALL	t(11;14)(p13;q11)	*RBNT2*	LIM domain	*31*
	T-ALL	t(7;9)(q35;q34)	*TAN1 (TCL3)*	Notch homolog	*34, 73*
	T-ALL	t(10;14)(q24;q11)	*HOX11 (TCL3)*	Homeodomain	*28, 74*
C	Parathyroid adenoma	inv(11)(p15;q13)?	*PTH* deregs *PRAD1*	PRAD1 is a G1 cyclin	*11, 12, 13, 14*
	B-CLL	t(8;12)(q24;q22)	*BTG1* deregs *MYC*	MYC has an HLH	*15*
D	CML, B-ALL	t(9;22)(q34;q11)	*BCR-ABL*	BCR, GAP for $p21^{rac}$ ABL, tyrosine kinase	*16, 17* *18*
	APL	t(15;17)(q22;q11.2-12)	*PML-RARA*	PML, Zn finger RARA, Zn finger	*21, 22*
	AML-M2, AML-M4	t(6;9)(p23;q34)	*DEK-CAN*	DEK, nuclear CAN, cytoplasmic	*75*
	Pre-B ALL	t(1;19)(q23;p13)	*E2A-PBX*	E2A, HLH PBX, homeodomain	*23*
	NHL	ins(2;2)(p13;p11.2-14)	*REL-NRG*	REL, NF-κB family NRG, no homology	*24*

is not restricted to LIM domain proteins but is a widespread property of these factors (*32*).

The role of regulators of the cell cycle in neoplasia has been emphasized by the elucidation of the function of the retinoblastoma (RB) gene product. In addition, the t(11;14) in B-CLL affects the *BCL1* oncogene, now possibly equated with the G1 cyclin-like *PRAD1* (*14*). Disruption of the cell cycle after overproduction of a cyclin may lead to diseases as diverse as B-CLL and parathyroid adenoma (Table 1). The deregulation of the *BCL3* gene found at a t(14;19) in B-CLL may also deregulate the cell cycle (Table 1A) (*33*). *BCL3* encodes seven tandem copies of the CDC10 motif, a motif found in only two classes of protein. One class, including the three yeast genes *CDC10, SW14*, and *SW16*, functions in the initiation of the cell cycle. The second class, including the *Drosophila melanogaster* gene *Notch*, encodes proteins involved in cell lineage determination. It has yet to be determined which class *BCL3* more closely resembles. The human homolog of the *Notch* gene, *TAN1*, is disrupted in the t(7;9) in T-ALL (Table 1B) (*34*).

Table 2. Translocations in solid tumors.

Tumor	Translocation	Ref.
Breast adenocarcinoma	t(1)(q21-23)	*76, 76a*
Glioma	t(19)(q13)	*77*
Ewing's sarcoma	t(11;22)(q24;q12)	*78*
Leiomyoma (uterus)	t(12;14)(q13-15;q23-24)	*79*
Lipoma	t(3;12)(q27-28;q13-15) t(6)(p22-23) t(12)(q13-15)	*80*
Liposarcoma (myxoid)	t(12;16)(q13;p11)	*81*
Melanoma	t(1)(q11-q12) t(1;6)(q11-12;q15-21) t(1;19)(q12;p13) t(6)(p11-q11) t(7)(q11)	*82*
Myxoid chondrosarcoma	t(9;22)(q22;q11.2)	*83*
Malignant histiocytosis	t(2;5)(p23;q35)	*84*
Ovarian adenocarcinoma	t(6;14)(q21;q24)	*85*
Pleomorphic adenoma	t(3;8)(p21;q12) t(9;12)(p13-22;q13-15) t(12)(q13-15)	*86*
Renal cell carcinoma	t(3;8)(p21;q24)	*54*
Rhabdomyosarcoma (alveolar)	t(2;13)(q35-37;q14)	*87*
Synovial sarcoma	t(X;18)(p11;q11)	*88*

The one translocation-identified oncogene that does not obviously fit into the signal transduction cascade is *BCL2* (Table 1A). *BCL2* is consistently deregulated by the IgH μ enhancer in the t(14;18) of follicular lymphoma (*35*). BCL2 is localized on the inner mitochondrial membrane and has been shown to prolong cell survival by blocking apoptosis (programmed cell death) (*36*).

Mechanisms of oncogene deregulation. Oncogenes are activated either by fusion or overexpression at translocation or inversion breakpoints. However, overexpression of a gene induced by Ig or TCR enhancers may not be the only mechanism by which genes are deregulated. The discovery of further Ig enhancers in the mouse (*37*) suggests that, at least in BL, an enhancer is consistently associated with the derivative chromosome carrying *MYC*, although the distances between the enhancer and *MYC* may be greater than 100 kb. The debate over BL has therefore focused on the necessity for somatic mutations in the 5′ noncoding and 5′ coding regions. In particular, mutations in the first *MYC* exon may alleviate a block to transcriptional elongation (*38*). For other translocations involving TCR enhancers, it appears that the oncogene is left on the derivative chromosome, which lacks any known enhancer. This is the case for *RBNT1, RBNT2*, and occasionally *TCL5*. Two explanations are possible: either the enhancer responsible remains to be discovered, or deregulation occurs as a consequence of the removal of silencer or promoter sequences or because of exon deletion. In these latter scenarios, the TCR would still provide the heptamer-nonamer sequences required for the VDJ recombinase. The VDJ recombinase, normally

required for antigen receptor rearrangement, is thought to mediate the illegitimate rearrangements between the Ig-TCR loci and the genes these loci deregulate.

The causality of recurrent translocations for their respective neoplasias is now ironclad, but their ability to function alone is debatable. BL and adult T cell leukemia are associated with the Epstein-Barr virus and human T cell leukemia virus, respectively. The viruses may serve to expand the cell population so a mutation, such as a translocation, can occur as a secondary event. Furthermore, karyotypes frequently develop further abnormalities as the disease progresses, presumably reflecting further mutations that increase growth potential. Another line of evidence is provided by data from mice made transgenic with constructs that mimic translocation rearrangements (*39*). Each trans-oncogene engenders a pathology similar but not identical to the human disease counterpart. Again, tumorigenesis requires additional mutations to complement the transgene (*40*). However, the best evidence for the insufficiency of translocations alone to cause cancer is provided by ataxia telangiectasia, an inherited disorder affecting multiple systems, in which individuals have an increased likelihood of developing leukemia. In these individuals, pre-leukemic clonal expansions of T lymphocytes carrying translocations are observed that may not progress to full leukemia for several years (*41*). Additionally, there is evidence for *BCL2* rearrangement in benign follicular hyperplasia (*42*).

Chromosomal Deletions and Monosomies

The cytogenetic rearrangements observed in solid tumors fall into three broad categories based on the mechanisms through which they promote malignant growth: (i) translocation, insertion, and inversion (Table 2); (ii) interstitial deletion and chromosome monosomy (Table 3); and (iii) amplification (trisomies, isochromosomes, double-minute chromosomes, and homogeneously staining regions). As discussed above, translocations, insertions, and inversions affect genes within a limited distance of the translocation breakpoint and can result in the deregulation of normal cellular genes or the formation of oncogenic chimeric genes. So far none of the translocations consistently observed in solid tumors have been molecularly cloned. Numerical changes, visible deletions, and amplification cause alterations in the dosage of large blocks of genes, and therefore the specific gene or genes responsible for inducing phenotypic changes in the cell are more difficult to identify.

Deletion of genomic material is usually suggestive of a gene whose loss of function is important in the initiation or progression of malignancy. More than 20 solid tumors (Table 3) and the myelodysplastic syndromes have been shown to have karyotypic aberrations that implicate loss of specific chromosomal material. An understanding of the roles gene inactivation plays in the etiology of neoplasia requires identification of the genes that are targets of this form of mutagenesis during the malignant process. Consistent and specific chromosomal deletions in tumors are a powerful tool in delineating regions of the genome harboring tumor suppressor genes and have led to the cloning of a number of these loci.

Tumor-specific chromosome deletion. A number of chromosome deletions are specific to a single tumor type. The del(13)(q14q14) deletion, for example, is observed only in RB (Fig. 1) and 11p13 deletions are restricted to Wilms tumor (WT) (Table 3). The kinetics of RB and WT development and the association of predisposition to RB or WT with specific congenital chromosomal deletions and translocations affecting 13q14 and 11p13, respectively (*43, 44*), led to the hypothesis that these embryonic tumors arise as the result of inactivation of normal diploid suppressor loci (*4, 45*). Because only a minute proportion of the predisposed cells develop into tumors, the predisposing lesions were proposed to be recessive loss-of-function mutations. In predisposed cells, the single normal allele is sufficient for the maintenance of a normal phenotype and a second mutation inactivating the remaining normal allele is required to initiate malignant growth. Loss of a chromosome, chromosome arm, or subchromosomal band is considered to be a cytogenetic hallmark of this mechanism. The loss of one allele of a specific gene by a chromosomal mechanism is coupled with a second mutational event, such as a point mutation, insertion, translocation, or submicroscopic deletion, so that both alleles of the tumor suppressor are inactivated or deleted.

Careful comparison of tumor DNA samples with normal DNA from the same individuals by means of restriction fragment length polymorphisms (RFLPs) provided molecular confirmation of the involvement of recessive inactivating mutations in cellular transformation. Loss of constitutional heterozygosity detected by RFLPs in the same regions indicated by chromosomal deletions and monosomies has revealed that loss of genetic information also occurs by cytogenetically invisible mechanisms. In RB, the use of RFLPs revealed that tumors lacking obvious chromosome aberrations lost allelic variation in the same region of 13q as was lost by interstitial chromosome deletion in a subset of individuals. Loss of heterozygosity has confirmed the location of suppressor

Table 3. Deletion and loss of heterozygosity in solid tumors. NT, not tested.

Tumor	Chromosomal deletion in tumor	Allele loss	Ref.
	Cloned		
RB	13q14	13q	*89*
Colorectal carcinoma	17p 18q	5q; 17p; 18q	*90*
WT	11p13	11p	*91*
	Noted		
Bladder adenocarcinoma	1q21-23 Monosomy 9	9q; 11p; 17	*92*
Breast adenocarcinoma	1p11-13 3p11-13 3q11-13	1p; 1q; 3p; 11p; 13q; 16q; 17p; 17q; 18q	*93*
Glioma	1p32-36 6p15-q27 7q22-q34 8p21-23 9p24-p13	17	*94*
Leiomyosarcoma (intestine)	1p12-12	NT	*95*
Leiomyoma (uterus)	6p21 7q21-31	NT	*96*
Lipoma	13q12-13	NT	*97*
Lung adenocarcinoma	3p13-23	3p; 13q; 17p	*98*
Lung small cell carcinoma	3p13-23	3p; 13q; 17p	*99*
Mesothelioma	3p21-25	NT	*100*
Mesothelioma (pleura)	1p11-13	NT	*100*
Malignant fibrous histiocytoma	1q11	NT	*101*
Melanoma	1p11-22 6q11-27	1p	*82* *102*
Meningioma	Monosomy 22 22q12-13	22q12-qter	*103*
Neuroblastoma	1p32-36	1p	*104*
Ovarian adenocarcinoma	3p13-21 6q15-23	3p; 6q; 11p; 17q	*105*
Prostatic adenocarcinoma	7q22 10q24	10; 16	*106*
Renal cell carcinoma	3p13-21	3p	*107*
Uterine adenocarcinoma	1q21-23	3p	*108*

loci originally detected by chromosomal aberration in a number of different cancers (Table 3).

The delineation of cytogenetically small regions of the genome defines a rather large area in molecular terms. However, this has been sufficient to lead to the identification and cloning of tumor suppressor genes implicated in the initiation of RB and WT (*46*) and in the initiation and progression of colorectal carcinoma (Fig. 1). The gene whose inactivation predisposes to RB, *RB1*, encodes a ubiquitously expressed nuclear phosphoprotein that appears to be involved in both transcriptional regulation and cell cycle control (*47*). *WT1*, on the other hand, is a highly tissue-specific and developmentally regulated gene encoding a protein with a structure suggestive of a transcription factor (*48*). The association of WT with Beckwith-Weidmann syndrome and rearrangements of 11p15 (*49*) and the lack of linkage of some cases of familial WT with chromosome 11 (*50*) implicate two additional loci in the etiology of WT.

Visible deletions of 5q are observed in a number of hematological conditions (refractory anemias, acute nonlymphocytic leukemia, treatment-induced leukemias, lymphoproliferative disorders, and chronic myeloproliferative disorders) but are almost never seen in solid tumors (*51*). The region commonly deleted includes 5q21-31, a region rich in genes encoding growth factors and growth factor receptors (*52*), some of which have been implicated in myeloid lineage development. Loss of one allele of a critical growth factor or receptor may be sufficient to perturb normal development and lead to malignant growth, or alternatively interstitial deletion may be accompanied by a cytogenetically invisible alteration inactivating a key suppressor locus.

Chromosome deletions shared by multiple tumors. Certain chromosomal aberrations are common to tumors of different cellular origin. For example, the 3p13-23 region is commonly affected by deletions in small cell carcinoma and adenocarcinoma of the lung, renal cell carcinoma, and ovarian adenocarcinoma (Table 3). Unfortunately, because of the limitations of cytogenetic resolution, it has not been possible to determine if these interstitial deletions are identical or if they represent distinct molecular locations, but the observation that all these tumors show loss of heterozygosity in the region of 3p21 suggests that functional inactivation of the same suppressor gene might be involved in the etiology of these malignant epithelial tumors. Although no tumor suppressor gene has yet been identified in this region, a potential candidate gene *PTPG*, encoding a receptor protein with tyrosine phosphatase activity, has been mapped to the smallest region of allele loss observed in lung carcinomas in the 3p21 region (*53*). Two tumors of neuroectodermal origin, neuroblastoma and glioma, both show deletions of the 1p32-36 region (Table 3), implicating a common regulatory locus that must be inactivated for neuroectodermal tumors to develop.

Four other chromosomal regions are the targets of deletions in tumors of multiple histological types (Table 3). Melanoma, breast adenocarcinoma, intestinal leiomyosarcoma, pleural mesothelioma, and malignant fibrous histiocytoma are all affected by deletion of the 1p11-22 region. The 1q21-23 region is deleted in uterine and bladder adenocarcinomas and is the target for translocation in breast adenocarcinoma; deletions of 6q11-27 are observed in melanoma, glioma, and adenocarcinoma of the ovary; and the 7q21-34 region is commonly lost in uterine leiomyoma, adenocarcinoma of the prostate, glioma, acute myeloid leukemia (AML), and myelodysplastic syndrome. Tumor suppressors in these regions must function to regulate growth in a number of tissues, and their inactivation must therefore be required in the development of multiple tumor types.

Germ line chromosomal aberrations in familial cancer. It is difficult to differentiate between the primary initiating events in the malignant process and the secondary progression-associated changes. However, a number of tumor-specific aberrations have been identified as initiating events through the observation of similar rearrangements in somatic cells of individuals with a congenital predisposition to cancer and sporadic cases of the same tumor. Deletions and translocations of 13q14 in familial RB (*43*), deletions and translocations of 11p13 in familial WT (*44*), and translocations involving 3p21 in inherited renal cell carcinoma (Table 2) (*54*) support the identification of these mutations as early rate-limiting steps in the evolution of each tumor.

Inherited colorectal carcinoma (familial adenomatous polyposis) associated with constitutional deletion of the long arm of chromosome 5 has been observed, and although this 5q is not visibly deleted in sporadic cases, the 5q22 region is affected by molecular events resulting in allelic loss (*55*) and presumably inactivation of a suppressor locus in early stages of colorectal carcinoma development (*56*). Two candidate tumor suppressor genes, *MCC* (mutated in colorectal carcinoma) and *APC* (adenomatous polyposis coli), have been isolated from this region (*57, 58*). Mutations in *APC* have been observed in both sporadic and familial colorectal carcinomas (*57, 59*), whereas *MCC* mutations have only been observed in sporadic cases (*57, 59*), suggesting that although both genes may be involved in the development of colorectal carcinoma, only germ line mutations of *APC* predispose individuals to the disease.

Although tumor-specific chromosomal abnormalities have not been detected in neurofibromatosis type I (NF1)–associated tumors, possibly because of the polyclonal nature of these tumors, the characterization of translocations involving 17q11.2 (*60*) in the somatic cells of two individuals with NF1 proved instrumental in isolating the gene responsible (*61*). The *NF1* gene product shows significant homology to GTPase-activating proteins (*20*), suggesting a role in signal transduction.

Tumor progression and chromosomal alterations. Some chromosomal aberrations appear to correlate with later stages of malignancy. Structural rearrangements of chromosome 1 are observed in a range of tumors including RB, WT, colorectal carcinoma, ovarian adenocarcinoma, uterine adenocarcinoma, bladder adenocarcinoma, and breast adenocarcinoma (*5*). It is likely that a gene located on chromosome 1 is important in the acquisition of a more aggressive or metastatic growth potential. Another chromosomal change involved in progression is the i(6p) (two short arms of chromosome 6 fused at the centromere) isochromosome frequently seen in RB and also observed in melanoma, acute lymphoblastic leukemia, and malignant lymphoma (*62*).

Progression-associated events in colorectal carcinoma have been well characterized because the development of normal colonic epithelium into a carcinoma proceeds through a series of well-defined stages (*56*). Two cytogenetic abnormalities associated with later stages are the 17p− and 18q− chromosome deletions (Fig. 1 and Table 3). The chromosomal regions important for progression were localized further through allelic loss studies to 17p13 and 18q21-qter (qter indicates the terminus of arm q). The *DCC* gene (deleted in colorectal carcinoma) on chromosome 18 was isolated on the basis of this knowledge. *DCC* encodes a protein with homology to the Ig superfamily in general and to the neural cell adhesion molecules (N-CAMs) in particular (*63*). Loss of *DCC* function at a late stage in colon cancer may reflect the requirement for escape from normal cell-cell contact regulation mediated through N-CAMs, especially at the transition from the benign state to a fully malignant carcinoma with metastatic ability. Involvement of the well-characterized tumor suppressor gene p53 in colorectal carcinoma was suggested by the 17p− abnormality

and allele loss affecting 17p in over 75% of colon carcinomas (*64*). Inactivation of p53, a protein involved in the cell cycle and potentially in apoptosis (*65*), could mediate the transition from adenoma to carcinoma. Initial mutation of one p53 allele could reduce functional protein amounts much more than 50% through proposed dominant-negative interactions between normal and mutant proteins (*66*). The loss of the remaining normal allele as the adenoma progresses into a carcinoma would eliminate the remaining wild-type p53 activity.

Amplification

Low-level and high-level gene amplification may result in functionally distinct physiological effects. Minor changes in gene dosage brought on by the acquisition of one or two extra copies of a chromosome or chromosome arm will affect hundreds or thousands of genes. Increased dosage of one or more loci may be involved or the balance between the gene product of a locus present in three or four copies relative to another present in the diploid state may be important. Low-level amplification could alternatively be linked to parental imprinting, representing a mechanism for increasing the dosage of blocks of genes expressed in low amounts or not at all because of a parentally programmed suppression of expression. Hematological malignancies are associated with low-level amplification. In solid tumors, greatly increased copy numbers of much smaller chromosomal regions are more frequent; the increased copy number and enhanced expression of cellular oncogenes appear to correlate with more advanced and aggressive stages of malignancy.

The most commonly observed trisomy is that of chromosome 8 (Fig. 1) in myelodysplastic syndrome, myeloproliferative disease, AML, and ALL. Trisomy 21 occurs to a lesser extent in these same conditions. Also, trisomy 9 is seen in myeloproliferative disorders, trisomy 12 is associated mainly with chronic lymphoproliferative disorders, malignant lymphoma, and benign mesothelial tumors, and trisomy 3 is associated with malignant lymphoma. Among solid tumors, the only commonly observed trisomy is that of chromosome 7 in benign and malignant epithelial tumors and malignant neurogenic tumors (*62*).

Isochromosome formation is another mechanism through which low-level amplification (two- to threefold) is achieved. In many cases, the presence of a specific isochromosome is observed in a number of malignancies of different histological type, suggesting the isochromosomes provide a rather non–tissue-specific growth advantage. The exception is i(12p), which is specific to germ-cell tumors and is the only consistently observed abnormality in these tumors (*67*).

High levels of gene amplification manifest cytogenetically as homogeneously staining regions and double-minute chromosomes and often result in 10- to 100-fold or greater amplification of a small number of genes, usually only one of which is believed to contribute in a dominant manner to the malignant phenotype. Few of the amplification units reported have been repeatedly observed in primary tumors at clinical presentation. The oncogene *MYCN* is amplified in stage III and IV neuroblastomas, where amplification is associated with a poorer prognosis, and is occasionally amplified in RBs (*68*). Amplification of the epidermal growth factor receptor gene has been seen in brain tumors of glial origin and a related gene *ERBB2* (*HER-2/NEU*) is amplified in the more advanced stages of adenocarcinoma of the breast and ovary (*69*). The region of 11p encompassing *INT2, HST1*, and *PRAD1* is also amplified in 15 to 20% of breast carcinomas, squamous cell tumors, and melanomas (*70*).

Conclusions

Studies of the chromosomal rearrangements in cancer have served to reinforce the view that cancer is caused by a progressive series of genetic changes. Cloning of the disease loci suggested by cytogenetic analyses has led to the isolation of a host of new oncogenes and tumor suppressor genes, as well as implicating previously characterized genes whose contribution to tumorigenesis had before been unrecognized. The molecular characterization of rearranged genes suggests new therapies (for example, the treatment of t(5;14) positive pre-B ALL individuals with IL-3 antagonists) or helps explain the molecular basis of previous empirically administered treatments (for example, differentiation therapy with retinoic acid in acute promyelocytic leukemia). Lastly, the consistency of some rearrangements with particular disease states has led to the use of that abnormality for improved diagnosis, as illustrated by the polymerase chain reaction detection of the *BCR-ABL* fusion message in CML (*71*).

REFERENCES AND NOTES

1. P. Armitage and R. Doll, *Br. J. Cancer* **8**, 1 (1954).
2. F. Mitelman, *Catalogue of Chromosomal Aberrations in Cancer* (Wiley-Liss, New York, ed. 4, 1991).
3. S. Heim and F. Mitelman, *Adv. Cancer Res.* **52**, 1 (1989).
4. A. G. Knudson, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 820 (1971).
5. J. J. Yunis, in *UCLA Symposium: Recent Advances in Leukaemia and Lymphoma*, Schering Corp., Keystone, CO, 25 to 31 January 1987, R. P. Gale and D. W. Golde, Eds. (Liss, New York, 1987), pp. 3–21.
6. F. Mitelman, Y. Kanedo, J. M. Trent, *Cytogenet. Cell Genet.* **55**, 358 (1990).
7. J. J. Yunis, *Adv. Pathol.* **2**, 147 (1989); J. D. Rowley, *Cancer Res.* **50**, 3816 (1990); T. H. Rabbitts and T. Boehm, *Adv. Immunol.* **50**, 119 (1991); C. L. Sawyers, C. T. Denny, O. N. Witte, *Cell* **64**, 337 (1991).
8. P. C. Nowell and D. A. Hungerford, *Science* **132**, 1497 (1960).
9. J. D. Rowley, *Nature* **343**, 290 (1973).
10. P. Leder *et al.*, *Science* **222**, 765 (1983).
11. A. Arnold *et al.*, *J. Clin. Invest.* **83**, 2034 (1989); E. Friedman *et al.*, *J. Clin. Endocrinol. Metab.* **71**, 293 (1990); C. L. Rosenberg, H. G. Kim, T. B. Shows, H. M. Kronenberg, A. Arnold, *Oncogene* **6**, 449 (1991).
12. G. A. Lammie, *Oncogene* **6**, 439 (1991).
13. Y. Tsujimoto *et al.*, *Science* **224**, 1403 (1984).
14. T. Motokura *et al.*, *Nature* **350**, 512 (1991).
15. R. Rimokh *et al.*, *Genes Chromosomes Cancer* **3**, 24 (1991).
16. R. Kurzrock, J. U. Gutterman, M. Talpaz, *N. Engl. J. Med.* **319**, 990 (1988).
17. J. B. Konopka, S. M. Watanabe, O. N. Witte, *Cell* **37**, 1035 (1984).
18. D. Diekman *et al.*, *Nature* **351**, 400 (1991).
19. J. C. Grimaldi and T. C. Meeker, *Blood* **73**, 2081 (1989); T. C. Meeker, D. Hardy, C. Willman, T. Hogan, J. Abrams, *ibid.* **76**, 285 (1990).
20. R. Ballester *et al.*, *Cell* **63**, 851 (1990); A. M. Buchberg, L. S. Cleveland, N. A. Jenkins, N. G. Copeland, *Nature* **347**, 291 (1990).
21. J. Borrow, A. D. Goddard, D. Sheer, E. Solomon, *Science* **249**, 1577 (1990); H. de The *et al.*, *Nature* **347**, 558 (1990).
22. A. D. Goddard, J. Borrow, P. S. Freemont, E. Solomon, *Science*, in press; A. Kakizuka *et al.*, *Cell* **66**, 663 (1991); H. de The *et al.*, *ibid.*, p. 675; P. P. Pandolfi *et al.*, *Oncogene* **6**, 1285 (1991).
23. M. P. Kamps, C. Murre, X.-H. Sun, D. Baltimore, *Cell* **60**, 547 (1990); J. Nourse *et al.*, *ibid.*, p. 535.
24. D. Lu *et al.*, *Oncogene* **6**, 1235 (1991).
25. J. D. Mellentin, S. D. Smith, M. L. Cleary, *Cell* **58**, 77 (1989).
26. C. G. Begley *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 2031 (1989); C. R. Finger *et al.*, *ibid.*, p. 5039; B. Q. Chen *et al.*, *EMBO J.* **9**, 415 (1990).
27. P. D. Aplan *et al.*, *Science* **250**, 1426 (1990); B. Q. Chen *et al.*, *J. Exp. Med.* **172**, 1403 (1990); O. L. Brown *et al.*, *EMBO J.* **9**, 33 (1990).
28. M. Hatano, C. W. M. Roberts, M. Minden, W. M. Crist, S. J. Korsmeyer, *Science* **253**, 79 (1991); I. Dube *et al.*, *Blood*, in press; M. A. Kennedy *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 8900 (1991).
29. T. Boehm *et al.*, *EMBO J.* 7, 385 (1988); E. A. McGuire *et al.*, *Mol. Cell. Biol.* **9**, 2124 (1989); T. Boehm *et al.*, *EMBO J.* **9**, 857 (1990).
30. G. Freyd, S. K. Kim, H. R. Horvitz, *Nature* **344**, 876 (1990); O. Karlsson, S. Thor, T. Norberg, H. Ohlsson, T. Edlund, *ibid.*, p. 879; T. Boehm, L. Foroni, M. Kennedy, T. H. Rabbitts, *Oncogene* **5**, 1103 (1990).
31. T. Boehm, L. Foroni, Y. Kaneko, M. F. Perutz, T. H. Rabbitts, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 4367 (1991).
32. N. Jones, *Cell* **61**, 9 (1990).
33. T. W. McKeithan, J. D. Rowley, T. B. Shows, M. O. Diaz, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 9257 (1987); H. Ohno *et al.*, *Cell* **60**, 991 (1990).
34. L. W. Ellisen *et al.*, *Cell* **66**, 649 (1991).
35. Y. Haupt, W. S. Alexander, G. Barri, S. P. Klinken, J. M. Adams, *ibid.* **65**, 753 (1991); M. Van Lohuizen *et al.*, *ibid.*, p. 737.

36. Y. Tsujimoto, J. Gorham, J. Cossman, E. Jaffe, C. M. Croce, *Science* **229**, 1390 (1985); A. Bakhshi *et al.*, *Cell* **41**, 899 (1985); M. L. Cleary and J. Sklar, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 7439 (1985).
37. D. Hockenbery, G. Nunez, C. Milliman, R. D. Schreiber, J. Korsmeyer, *Nature* **348**, 334 (1990).
38. K. B. Meyer and M. S. Neuberger, *EMBO J.* **8**, 1959 (1989); S. Pettersson *et al.*, *Nature* **344**, 165 (1990).
39. E. Cesarman, R. Dalla-Favera, D. Bentley, M. Groudine, *Science* **238**, 1272 (1987).
40. G. Q. Daley, R. A. Van Etten, D. Baltimore, *ibid.* **247**, 824 (1990); N. Heisterkamp *et al.*, *Nature* **344**, 251 (1990).
41. A. M. R. Taylor and S. V. Butterworth, *Cancer* **37**, 511 (1986); G. Russo *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 602 (1989).
42. J. Limpens *et al.*, *Oncogene*, in press.
43. E. Yunis, R. Zuniga, E. Ramirez, *Hum. Genet.* **56**, 283 (1981).
44. V. M. Riccardi, E. Sujansky, A. C. Smith, U. Franke, *Pediatrics* **61**, 604 (1978); U. Franke, L. M. Holmes, L. Atkins, V. M. Riccardi, *Cytogenet. Cell Genet.* **24**, 185 (1979).
45. A. G. Knudson and L. C. Strong, *J. Natl. Cancer Inst.* **48**, 313 (1972).
46. S. H. Friend *et al.*, *Nature* **323**, 643 (1986); K. M. Call *et al.*, *Cell* **16**, 509 (1990); M. Gessler *et al.*, *Nature* **343**, 774 (1990); L. Bonetta *et al.*, *Science* **250**, 994 (1990).
47. S. Wagner and M. R. Green, *Nature* **352**, 189 (1991).
48. K. Pritchard-Jones *et al.*, *ibid.* **346**, 194 (1990); A. Huang *et al.*, *Science* **250**, 991 (1990); K. M. Call *et al.*, *Cell* **16**, 509 (1990).
49. C. Sotelo-Avila and W. M. Gooch, *Perspect. Pediatr. Pathol.* **3**, 255 (1976).
50. P. A. Grundy *et al.*, *Nature* **336**, 374 (1988); V. Huff *et al.*, *ibid.*, p. 377.
51. H. Van den Berghe, K. Vermaelen, C. Mecucci, D. Barbieri, G. Tricot, *Cancer Genet. Cytogenet.* **17**, 189 (1985).
52. J. J. Wasmuth, C. Park, R. E. Ferrell, *Cytogenet. Cell Genet.* **51**, 137 (1989); D. T. Bishop and C. Westbrook, *ibid.* **55**, 111 (1990).
53. S. LaForgia *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 5036 (1991).
54. N. Wang and K. L. Perkins, *Cancer Genet. Cytogenet.* **11**, 479 (1984).
55. L. Herrara, S. Kakati, L. Gigas, E. Pietrak, A. A. Sandberg, *Am. J. Med. Genet.* **25**, 473 (1981); E. Solomon *et al.*, *Nature* **322**, 616 (1987).
56. B. Vogelstein *et al.*, *N. Engl. J. Med.* **319**, 525 (1988).
57. K. W. Kinzler *et al.*, *Science* **251**, 1366 (1991).
58. K. W. Kinzler *et al.*, *ibid.* **253**, 661 (1991); G. Joslyn *et al.*, *Cell* **66**, 601 (1991).
59. I. Nishisho *et al.*, *Science* **253**, 665 (1991); J. Groden *et al.*, *Cell* **66**, 589 (1991).
60. M. A. Schnidt, V. V. Michels, G. W. Dewald, *Am. J. Med. Genet.* **28**, 771 (1987); D. H. Ledbetter, D. C. Rich, O. O'Connell, M. Leppert, J. C. Carey, *Am. J. Hum. Genet.* **44**, 20 (1989).
61. D. Viskochil *et al.*, *Cell* **62**, 187 (1990); M. R. Wallace *et al.*, *Science* **249**, 181 (1990).
62. F. Mitelman, Y. Kaneko, J. M. Trent, *Cytogenet. Cell Genet.* **55**, 358 (1990).
63. E. R. Fearon *et al.*, *Science* **247**, 49 (1990).
64. S. J. Baker *et al.*, *ibid.* **244**, 217 (1989).
65. E. Yonis-Rouach *et al.*, *Nature* **352**, 345 (1991).
66. I. Herskowitz, *ibid.* **329**, 219 (1987).
67. N. B. Atkin and M. C. Baker, *Cancer Genet. Cytogenet.* **10**, 199 (1983).
68. N. E. Khol *et al.*, *Cell* **35**, 359 (1983); G. M. Brodeur, R. C. Seeger, M. Schwab, H. E. Varmus, J. M. Bishop, *Science* **224**, 1121 (1984); R. C. Seeger *et al.*, *N. Engl. J. Med.* **313**, 1111 (1985); W. H. Lee, A. C. Murphree, W. F. Benedict, *Nature* **309**, 458 (1984).
69. T. A. Liberman *et al.*, *Nature* **313**, 144 (1985); D. J. Slamon *et al.*, *Science* **235**, 177 (1987); D. Zhou, H. Battifora, J. Yokota, T. Yamamoto, M. J. Cline, *Cancer Res.* **47**, 6123 (1987); D. J. Slamon *et al.*, *Science* **244**, 707 (1989).
70. J. Adelaide *et al.*, *Oncogene* **2**, 413 (1988); T. Tsuda *et al.*, *Jpn. J. Cancer Res. (Gann)* **79**, 584 (1988); I. Ali, G. Merlo, R. Callahan, R. Lidereau, *Oncogene* **4**, 89 (1989); J. R. Berenson, J. Yang, R. A. Mickel, *ibid.*, p. 1111; V. Fanti *et al.*, *Eur. J. Cancer* **26**, 423 (1990); C. Theillet *et al.*, *Oncogene* **5**, 147 (1990).
71. E. S. Kawasaki *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 5698 (1988); M.-S. Lee *et al.*, *Blood* **72**, 893 (1988); A. Dobrovic *et al.*, *ibid.*, p. 2063.
72. E. A. Shima *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 3439 (1986); T. W. McKeithan *et al.*, *ibid.*, p. 6636; L. R. Finger, R. C. Harvey, R. C. A. Moore, L. C. Showe, C. M. Croce, *Science* **234**, 982 (1986).
73. T. C. Reynolds, S. D. Smith, J. Sklar, *Cell* **50**, 107 (1987).
74. J. Kagan *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 4161 (1989); M. Zutter *et al.*, *ibid.* **87**, 3161 (1990).
75. M. von Lindern *et al.*, *Mol. Cell. Biol.* **10**, 4016 (1990).
76. G. Kovacs, *Int. J. Cancer* **21**, 688 (1978); *Cancer Genet. Cytogenet.* **3**, 125 (1981); C. S. Rodgers, S. M. Hill, H. A. Hulten, *ibid.* **13**, 95 (1984).
76a. E. Gebhart *et al.*, *Breast Cancer Res. Treat.* **8**, 125 (1986); J. M. Trent *et al.*, in *Oncogenes and Hormones in Breast Cancer*, M. Sluyser, Ed. (Ellis Horwood, Amsterdam, 1987).
77. S. H. Bigner *et al.*, *Cancer Res.* **48**, 405 (1988); R. B. Jenkins *et al.*, *Cytogenet. Cell Genet.* **51**, 1019 (1989); R. B. Jenkins *et al.*, *Cancer Genet. Cytogenet.* **39**, 253 (1989).
78. C. Turc-Carel, I. Philips, M.-P. Berger, T. Philip, G. M. Lenoir, *Cancer Genet. Cytogenet.* **12**, 1 (1984); A. Aurias, C. Rimbaut, D. Buffer, J. M. Zucker, A. Mazabraud, *ibid.*, p. 21.
79. S. Heim *et al.*, *ibid.* **32**, 13 (1988).
80. N. Mandahl *et al.*, *Int. J. Cancer* **39**, 685 (1987).
81. C. Turc-Carel *et al.*, *Cancer Genet. Cytogenet.* **23**, 291 (1986); F. Mertens *et al.*, *ibid.* **28**, 191 (1987).
82. S. Kakati, S. Y. Song, A. A. Sandberg, *Cancer* **40**, 1173 (1977); N. B. Atkin and M. C. Baker, *Hum. Genet.* **58**, 217 (1981); R. Becher, Z. Gibas, C. Karakousis, A. A. Sandberg, *Cancer Res.* **43**, 5010 (1983); G. Balaban *et al.*, *Cancer Genet. Cytogenet.* **3**, 243 (1984); J. M. Trent, F. H. Thompson, F. L. Meyskens, *Cancer Res.* **49**, 420 (1989); J. M. Cowan, R. Halaban, A. T. Lan, U. Franke, *Cancer Genet. Cytogenet.* **20**, 255 (1986); A. H. Parmiter, G. Balaban, M. Herlyn, W. H. Clark, P. C. Nowell, *Cancer Res.* **46**, 1526 (1986); M. I. Pendersen, J. W. Bennett, N. Wang, *Cancer Genet. Cytogenet.* **20**, 11 (1986).
83. S. H. Hinrichs *et al.*, *Cancer Genet. Cytogenet.* **14**, 219 (1985); C. Turc-Carel, P. D. Cin, U. Rao, C. Karakousis, A. A. Sandberg, *ibid.* **30**, 145 (1988).
84. R. Morgan, B. K. Hecht, A. A. Sandberg, F. Hecht, S. D. Smith, *N. Engl. J. Med.* **314**, 1322 (1986).
85. N. Wake *et al.*, *Cancer Res.* **40**, 4512 (1980).
86. J. Mark and R. Dahlenfors, *Anticancer Res.* **6**, 299 (1986).
87. C. Turc-Carel *et al.*, *Cancer Genet. Cytogenet.* **19**, 361 (1986).
88. C. Turc-Carel *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 1981 (1987).
89. G. Balaban, F. Gilbert, W. Nichols, A. T. Meadows, J. Shields, *Cancer Genet. Cytogenet.* **6**, 213 (1982); W. K. Cavenee *et al.*, *Nature* **305**, 779 (1983).
90. M. Muleris, R. J. Salmon, B. Zafrani, J. Girodet, B. Dutrillax, *Ann. Genet. (Paris)* **28**, 206 (1985); E. Solomon *et al.*, *Nature* **328**, 616 (1987); B. Vogelstein *et al.*, *Science* **244**, 207 (1989).
91. K. Kondo, R. R. Chilcote, H. S. Maurer, J. D. Rowley, *Cancer Res.* **44**, 5376 (1984); A. Koufos *et al.*, *Nature* **309**, 170 (1984); S. H. Orkin, D. S. Goldman, S. E. Sallan, *ibid.*, p. 172; A. E. Reeve *et al.*, *ibid.*, p. 174.
92. Z. Gibas, G. R. Prout, J. E. Pontes, J. G. Connolly, A. A. Sandberg, *Cancer Genet. Cytogenet.* **19**, 229 (1986); N. B. Atkins and M. C. Baker, *ibid.* **15**, 253 (1985); E. R. Fearon, A. P. Feinberg, S. H. Hamilton, B. Vogelstein, *Nature* **318**, 377 (1985); Y. C. Tsai *et al.*, *Cancer Res.* **50**, 44 (1990).
93. C. Theillet *et al.*, *Cancer Res.* **46**, 4776 (1986); I. U. Ali, R. Lidereau, C. Thiellet, R. Callahan, *Science* **238**, 185 (1987); T. Sato *et al.*, *Cancer Res.* **50**, 7184 (1990); P. Devilee, M. van Vliet, N. Kuipers-Dijkshoorn, P. L. Pearson, C. J. Cornelisse, *Oncogene* **6**, 311 (1991); T. Sato, F. Akiyama, G. Sakamoto, P. Kasumi, Y. Nakamura, *Cancer Res.* **51**, 5118 (1991); P. Devilee *et al.*, *Oncogene* **6**, 1705 (1991).
94. J. A. Rey, M. J. Bello, J. M. de Camps, M. E. Kusak, S. Moreno, *Cancer Genet. Cytogenet.* **29**, 223 (1987); S. H. Bigner, *Cancer Res.* **48**, 405 (1988); C. D. James *et al.*, *ibid.*, p. 5546; R. B. Jenkins *et al.*, *Cytogenet. Cell Genet.* **51**, 1019 (1988); R. B. Jenkins *et al.*, *Cancer Genet. Cytogenet.* **39**, 253 (1988).
95. S. N. J. Sait, P. Dal Cin, A. A. Sandberg, *Cancer Genet. Cytogenet.* **37**, 157 (1989); J. Mark, B. Wendell, R. Dahlenfors, G. Havel, *ibid.*, p. 215.
96. S. N. J. Sait, P. Dal Cin, A. A. Sandberg, *ibid.* **35**, 47 (1988); J. Mark, G. Havel, C. Grepp, R. Dahlenfors, B. Wendell, *ibid.* **44**, 1 (1990); M. Nilbert *et al.*, *Cytogenet. Cell Genet.* **49**, 300 (1988).
97. M. Mandahl *et al.*, *Hum. Genet.* **79**, 203 (1988); C. Sreekantaiah *et al.*, *Cancer Genet. Cytogenet.* **39**, 281 (1989).
98. J. A. Rey *et al.*, *Cancer Genet. Cytogenet.* **25**, 355 (1987); R. Lukeis, L. Irving, M. Garson, S. Hasthorpe, *Genes Chromosomes Cancer* **2**, 116 (1990); J. Yokota, M. Wada, Y. Shimosato, M. Terada, T. Sugimura, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 9252 (1987).
99. J. Whang-Peng *et al.*, *Science* **215**, 181 (1982); J. Whang-Peng *et al.*, *Cancer Genet. Cytogenet.* **6**, 119 (1982); S. L. Naylor, B. E. Johnson, J. D. Minna, A. Y. Sakaguchi, *Nature* **329**, 451 (1987); J. Yokota, M. Wada, Y. Shimosato, M. Terada, T. Sugimura, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 9252 (1987).
100. Z. Gibas *et al.*, *Cancer Genet. Cytogenet.* **20**, 191 (1986); G. Stenman, R. Olofsson, T. Mapsson, J. Hagmar, J. Mark, *Hereditas* **105**, 1233 (1986); M. Tiainen, L. Tammilehto, K. Maltson, S. Knuutila, *Cancer Genet. Cytogenet.* **33**, 251 (1988); M. Tiainen *et al.*, *Br. J. Cancer* **60**, 618 (1989).
101. M. Mandahl *et al.*, *Genes Chromosomes Cancer* **1**, 9 (1989); W. M. Molenaar *et al.*, *Lab. Invest.* **60**, 266 (1989).
102. N. C. Dracopoli *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 4614 (1989).
103. J. Mark, *Adv. Cancer Res.* **24**, 165 (1977); K. D. Zang, *Cancer Genet. Cytogenet.* **6**, 249 (1982); B. R. Seizinger, R. L. Martuza, J. F. Gusella, *Nature* **322**, 644 (1986); J. P. Dumanski, E. Carlbon, V. P. Collins, M. Nordenskjold, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 9275 (1987).
104. G. M. Brodeur *et al.*, *Cancer Res.* **41**, 4678 (1981); F. Gilbert, G. Balaban, P. Moorhead, N. Bianchi, H. Schelesinger, *Cancer Genet. Cytogenet.* **7**, 33 (1982); C. T. Fong *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 3753 (1989).
105. J. M. Trent and S. E. Salmon, *Cancer Genet. Cytogenet.* **3**, 279 (1981); C. J. Kusyk, J. C. Seski, W. V. Medlin, C. L. Edwards, *J. Natl. Cancer Inst.* **66**, 1021 (1981); J. Whang-Peng *et al.*, *Cancer Genet. Cytogenet.* **11**, 91 (1984); T. Ehlen and L. Dubeau, *Oncogene* **5**, 219 (1990); D. M. Eccles, G. Cranston, C. M. Steel, Y. Nakamura, R. C. F. Leonard, *ibid.*, p. 1599; S. E. H. Russell, G. I. Hickey, W. S. Lowry, P. White, R. J. Atkinson, *ibid.*, p. 1581; W. Foulkes, D. Black, E. Solomon, J. Trowsdale, *Lancet* **338**, 444 (1991).
106. N. B. Atkins and M. C. Baker, *N. Engl. J. Med.* **312**, 215 (1985); *Hum. Genet.* **70**, 359 (1985); R. Lundgren, U. Kristoffersson, S. Heim, N. Mandahl, F. Mitleman, *Cancer Genet. Cytogenet.* **35**, 103 (1988); B. S. Carter *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 8751 (1990).
107. M. A. Yoshida *et al.*, *Cancer Res.* **46**, 2139 (1986); G. Kovacs, S. Szucs, W. de Riese, H. Baumgartel, *Int. J. Cancer* **40**, 171 (1987); G. Kovacs *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 1571 (1988); B. Zbar, H. Brauch, C. Talmadge, M. Linehan, *Nature* **327**, 721 (1987).
108. N. B. Atkin and M. C. Baker, *Cancer Genet. Cytogenet.* **7**, 209 (1982); M. A. Yoshida, K. Ohyashiki, S. M. Piver, A. A. Sandberg, *ibid.* **20**, 159 (1986); J. Yotaka *et al.*, *Cancer Res.* **49**, 3598 (1989).

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