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p53 mutations in human lymphoid malignancies: Association with Burkitt lymphoma and chronic lymphocytic leukemia

(tumor suppressor genes)

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ABSTRACT **We have investigated the frequency of p53 mutations in B- and T-cell human lymphoid malignancies, including acute lymphoblastic leukemia, the major subtypes of non-Hodgkin lymphoma, and chronic lymphocytic leukemia. p53 exons 5–9 were studied by using genomic DNA from 197 primary tumors and 27 cell lines by single-strand conformation polymorphism analysis and by direct sequencing of PCR-amplified fragments. Mutations were found associated with (*i*) Burkitt lymphoma (9/27 biopsies; 17/27 cell lines) and its leukemic counterpart L_3-type B-cell acute lymphoblastic leukemia (5/9), both of which also carry activated c-*myc* oncogenes, and (*ii*) B-cell chronic lymphocytic leukemia (6/40) and, in particular, its stage of progression known as Richter's transformation (3/7). Mutations were not found at any significant frequency in other types of non-Hodgkin lymphoma or acute lymphoblastic leukemia. In many cases, only the mutated allele was detectable, implying loss of the normal allele. These results suggest that (*i*) significant differences in the frequency of p53 mutations are present among subtypes of neoplasms derived from the same tissue; (*ii*) p53 may play a role in tumor progression in B-cell chronic lymphocytic leukemia; (*iii*) the presence of both p53 loss/inactivation and c-*myc* oncogene activation may be important in the pathogenesis of Burkitt lymphoma and its leukemic form L_3-type B-cell acute lymphoblastic leukemia.**

Neoplasia involving the lymphoid system is characterized by marked biological and clinical heterogeneity including malignancies as distinct as acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and multiple myeloma. The pathogenesis of these malignancies is also heterogeneous, since distinct molecular lesions have been found associated with specific subtypes of lymphoid tumors (for review, see ref. 1). These lesions involve "dominantly acting" oncogenes activated either by chromosomal translocations, affecting c-*myc* in high-grade NHL and affecting *bcl-2* in low- and intermediate-grade NHL, or by point mutations, affecting N-*ras* in ALL and multiple myeloma (1). However, recent evidence has implied a role for "tumor suppressor genes" in tumorigenesis (reviewed in ref. 2), the disruption or loss of which is thought to relieve the cell from negative regulatory signals. While various studies (3–6) have shown that tumor suppressor genes—namely, Rb and p53—are the site of frequent lesions in multiple types of human tumors, their involvement in human lymphoid malignancies has not been comprehensively investigated.

The p53 gene (7) encodes a 53-kDa nuclear phosphoprotein that may be involved in the negative regulation of cell growth. Several lines of evidence support the notion that its loss or alteration may contribute to the deregulated growth characteristics of cancer cells. First, several types of human tumors display the monoallelic loss of variable portions of the short arm of chromosome 17 (5). In the case of colon cancer, it has been shown that the region 17p13.1, the site of the p53 locus (8), is consistently lost (4). Second, consistent with Knudson's model of tumor suppressor genes (9), it was found that the 17p13.1 loss was consistently associated with mutations of the residual p53 allele, which are thought to inactivate the remaining p53 function (4–6). Finally, functional evidence for the tumor suppressor role of p53 was achieved by showing that normal p53 can inhibit the transformation of rodent cells and can revert the malignant phenotype of human carcinoma cells *in vitro* (10–12). However, p53 may differ in some respects from the prototype of tumor suppressor genes, in that at least some p53 mutant alleles can behave as dominant oncogenes by transforming target cells *in vitro* and causing tumorigenesis in transgenic mice even in the presence of the normal allele (13, 14). Regardless of the exact mechanism involved, p53 mutations and allelic losses can now be considered as a relatively frequent pathogenetic feature of several types of human malignancies, including those of the colon, breast, lung, brain, and soft tissues (refs. 4–6; for review, see ref. 15).

Several lines of indirect evidence suggest that alterations of the p53 gene might be relevant to the development of lymphoid neoplasia in humans, including the development of lymphomas in transgenic mice carrying mutant p53 alleles (14), the presence of high levels of p53 expression, typical of tumors harboring p53 mutations, in lymphoproliferative disorders (16), and the presence of p53 mutations in a few T-ALL cell lines tested (17). These results have prompted our comprehensive analysis of the frequency of p53 mutations in a large panel of human lymphoid malignancies, including the most common types of B- and T-cell tumors. The results suggest that p53 mutations are associated with Burkitt lymphoma (BL), its leukemic counterpart L_3-type B-ALL, and the late stages of B-CLL.

MATERIALS AND METHODS

Pathologic Samples. Peripheral blood, bone marrow, or lymph node samples from 197 patients were collected during standard diagnostic procedures. For most cases, the fraction of malignant cells in the pathologic specimen was at least 60%, and for all cases it was at least 30%, as determined by cytofluorometric analysis of cell-surface markers, antigen-receptor gene rearrangement analysis, or both (18). DNA was

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Abbreviations: ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; BL, Burkitt lymphoma; SSCP, single strand conformation polymorphism.

purified by digestion with proteinase K, extraction with phenol/chloroform, and precipitation by ethanol (19).

Cell Lines. The following BL cell lines were used in the present study: CW678, MC116, KK125, JD38, As283A, EW36, Ramos, ST486, PA682, PP984, CA46, NAB9B, EB3, Daudi, Namalwa, Ag876, P3HR1, Mwika, BL2, BL37, BL47, BL104, BL84, BL99, BL49, BL60, and BL113 (20, 21). For four BL cases (GS 111, BL37, BL60, and BL113), DNA from nontumor cells from the same patients was obtained from three lymphoblastoid cell lines (IARC176A, IARC277, and IARC632, normal counterparts of BL37, BL60, and BL113, respectively) and a T-cell clone (normal counterpart of GS 111).

Oligonucleotide Primers. All of the oligonucleotides used for PCR amplification in this study were synthesized by the solid-phase triester method (22). Names and sequences of p53 primers derived from published sequences (23) are as follows: P5-5, 5′-TTCCTCTTCCTGCAGTACTC-3′ (nucleotides 911–930); P6-3, 5′-AGTTGCAAACCAGACCTCAG-3′ (nucleotides 1249–1268); P7-5, 5′-GTGTTGTCTCCTAGGTTGGC-3′ (nucleotides 1269–1288); P8-5, 5′-TATCCTGAGTAGTGGTAATC-3′ (nucleotides 1411–1430); P9-3, 5′-AAGACTTAGTACCTGAAGGGT-3′ (nucleotides 1654–1674). In addition, the following primers were used: P5-3, 5′-ACCCTGGGCAACCAGCCCTGT-3′, derived from intron 5 sequence (spanning nucleotides 26–46 3′ to the exon 5/intron 5 boundary); P6-5, 5′-ACAGGGCTGGTTGCCCAGGGT-3′, derived from intron 5 sequence (spanning nucleotides 26–46 3′ to the exon 5/intron 5 boundary); P7-3, 5′-GTCAGAGGCAAGCAGAGGCT-3′, derived from intron 7 sequence (G.G., unpublished observation; spanning nucleotides 46–65 3′ to exon 7/intron 7 boundary); P8-3, 5′-AAGTGAATCTGAGGCATAAC-3′, derived from intron 8 sequence (spanning nucleotides 45–64 3′ to exon 8/intron 8 boundary); P9-5, 5′-GCAGTTATGCCTCAGATTCAC-3′, derived from intron 8 sequence (spanning nucleotides 42–62 3′ to exon 8/intron 8 boundary).

Single-Strand Conformation Polymorphism (SSCP) Analysis. SSCP analysis was accomplished according to an adapted version of a previously reported method (24). Briefly, PCRs were performed with 100 ng of genomic DNA, 10 pmol of each primer, 2.5 μM dNTPs, 1 μCi of [α-^{32}P]dCTP (NEN; specific activity, 3000 Ci/mmol; 1 Ci = 37 GBq), 10 mM Tris·HCl (pH 8.8), 50 mM KCl, 1 mM $MgCl_2$, 0.01% gelatin, 0.5 unit of *Taq* polymerase (Cetus), in a final vol of 10 μl. Thirty cycles of denaturation (94°C), annealing (63°C for reactions amplifying exons 5, 6, 7, and 9; 58°C for exon 8), and extension (72°C) were done on an automated heat-block (DNA thermal cycler; Perkin–Elmer/Cetus). The reaction mixture (2 μl) was diluted 1:25 in 0.1% $NaDodSO_4$/10 mM EDTA and further mixed 1:1 with a sequencing stop solution (19) containing 20 mM NaOH. Samples were heated at 95°C for 5 min, chilled on ice, and immediately loaded (3 μl) onto a 6% acrylamide/TBE gel containing 10% (vol/vol) glycerol. Gels were run at 8 W for 12–15 h at room temperature. Autoradiography was performed with an intensifying screen for 6–72 h.

Direct Sequencing of PCR Products. PCR was performed with 500 ng of genomic DNA, 20 pmol of each primer, 200 μM dNTPs, 10 mM Tris·HCl (pH 8.8), 50 mM KCl, 1 mM $MgCl_2$, 0.01% gelatin, and 2.5 units of *Taq* polymerase. The number and conditions of amplification cycles were as described above. Direct sequencing of the amplified product was performed as described (25).

RESULTS

Experimental Plan. We selected 197 cases, representative of the spectrum of human lymphoid malignancies (Table 1), from our collection of pathologic specimens based on unequivocal diagnosis and a high percentage of malignant cells. In addition, 27 BL cell lines and 4 germ-line control tissues, obtained from the corresponding tumor patients, were included in this study.

Table 1. Frequency of p53 mutations in lymphoid malignancies

Diagnosis	Positive/tested
B-cell tumors	
ALL	
Precursor B	2/25
B-ALL (L_3)	5/9
NHL	
Small lymphocytic	0/9
Follicular*	0/20
Diffuse†	0/14
Burkitt	
Biopsies‡	9/27
Cell lines§	17/27
B-CLL	6/40
Richter's transformation	3/7
HCL	1/8
PLL	0/2
T-cell tumors	
T-ALL	0/7
T-CLL	0/9
CTCL	0/8
PTCL	1/12

HCL, hairy cell leukemia; PLL, prolymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; PTCL, peripheral T-cell lymphoma.
*Follicular small cleaved (13 cases) and follicular mixed (7 cases).
†Diffuse mixed (5 cases) and diffuse large cell (9 cases).
‡Sporadic Burkitt lymphoma (13 cases) and endemic Burkitt lymphoma (14 cases).
§Sporadic Burkitt lymphoma (19 cell lines) and endemic Burkitt lymphoma (8 cell lines).

A two-step experimental approach was devised. By SSCP analysis (24), all samples were analyzed for mutations within exons 5–9 of the p53 gene, which are the regions most frequently affected by mutations in other types of human tumors (4–6). Under our experimental conditions, the SSCP method is sensitive at the level of at least 1% and it is specific, as evaluated by the 100% concordance between the results obtained by direct sequencing versus SSCP analysis of 69 distinct PCR-amplified fragments (50 negative/19 positive for mutations) representative of p53 exons 5–9 from BL cell lines (data not shown). Fragments displaying an altered electrophoretic mobility by SSCP analysis were subsequently reamplified in a separate reaction and analyzed by direct sequencing to confirm and characterize the nature of the mutations.

Frequency of p53 Mutations in Lymphoid Neoplasia. The results of the SSCP analysis are summarized in Table 1, while representative results are shown in Fig. 1. The overall frequency of p53 mutated samples among the primary lymphoid malignancies studied is 13.7% (27/197); however, mutations do not follow a random distribution among the different subtypes of lymphoid tumors, but instead cluster into two main groups: (*i*) BL, in which 9/27 (33%) biopsies and 17/27 (63%) cell lines are mutated, and its leukemic equivalent L_3-type B-ALL, in which 5/9 (55%) cases are mutated; and (*ii*) B-CLL, in which 6/40 (15%) cases are mutated; interestingly, a higher percentage of mutations is observed in the B-CLL stage of progression known as Richter's transformation (3/7; 42%). Occasional positive cases were found in hairy cell leukemia, precursor B-ALL, and peripheral T-cell lymphoma, while other types of malignancies—e.g., low- and intermediate-grade NHL—were found completely negative for p53 mutations.

Type and Position of p53 Mutations. The characteristics of the p53 mutations detected by SSCP analysis were further

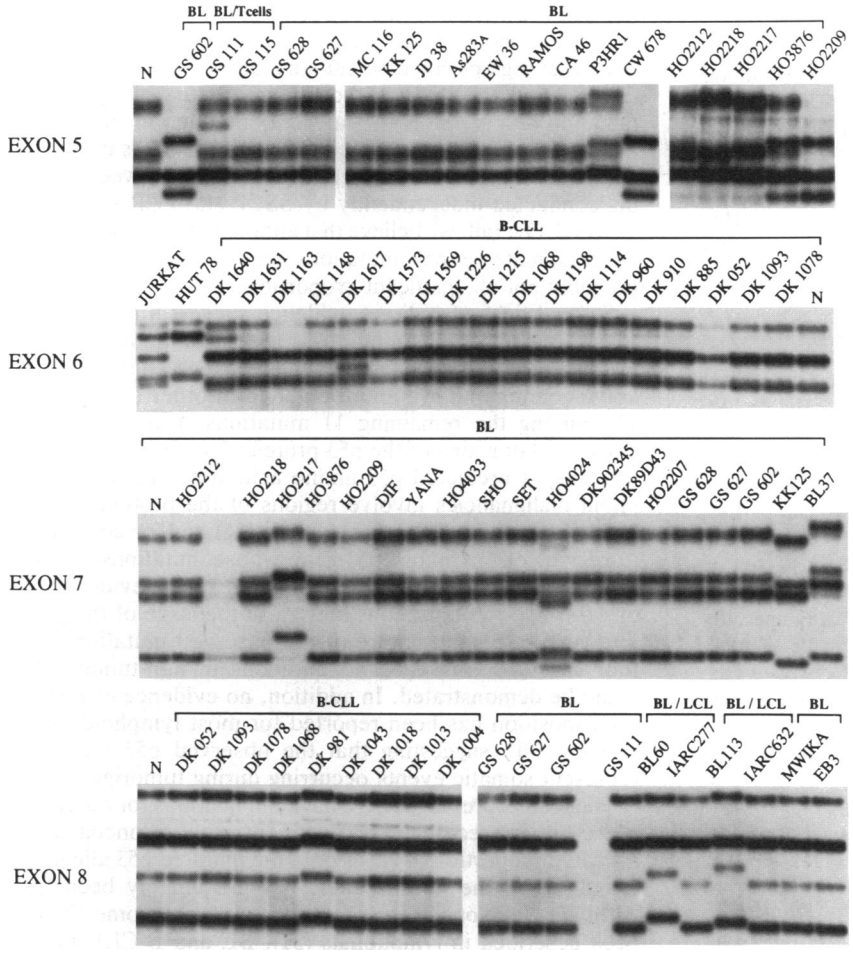

FIG. 1. SSCP analysis of p53 mutations in lymphoid malignancies. PCR-amplified fragments corresponding to individual exons 5–9 were amplified from genomic DNA in the presence of [α-^{32}P]dCTP, denatured by heat and alkaline treatment, and run on a 6% acrylamide gel containing 10% glycerol. Representative samples are shown for exons 5–8. Although three main bands (corresponding to the residual undenatured fragment and the two single-stranded fragments) are expected in this assay for wild-type samples, an additional band, probably representing a different conformer of the fragment, was consistently observed (see ref. 24). Samples were scored positive for mutations when bands different from the normal control (N) were detectable. GS 111/GS 115 (exon 5) and BL60/IARC277 and BL113/IARC632 (exon 8) represent pairs of neoplastic and normal tissue DNAs obtained from the same patient. LCL, lymphoblastoid cell line.

examined by direct sequencing of the PCR-amplified exons (see Table 2 for summary and Fig. 2 for representative results). In the vast majority of samples (41/44), p53 mutations were represented by single nucleotide changes, most frequently missense mutations (39 events), and occasionally nonsense mutations (4 events), point deletions (2 events), or point insertions (2 events). Mutations occurred more frequently (48.8% of cases) at CpG dinucleotides, in the form of C to T or G to A transitions, although 12 transitions (mainly G to A or A to G) not occurring at CpGs and 10 transversions were also detected. The high frequency of mutations at CpGs is in accordance with previous data from various human tumors (5), with the exception of lung carcinomas, where G to T transversions are most frequently detected (15). Three samples (RDF 378, L3-4, DK 1361) displayed gross rearrangements, which could also be detected as a shift in the size of the band following electrophoresis in 1.8% agarose gels (data not shown; see Table 2).

The location of mutations affecting the p53 gene has been reported to correspond to regions of the gene displaying high homology among different species (26). Thirty-five point mutations fell into these regions or their immediate boundaries, while 12 were located at other sites, mainly between codons 205 and 216.

To confirm the assumption that p53 mutations in BL represent a somatic event, we analyzed the DNA from three lymphoblastoid cell lines and one T-cell clone obtained from four corresponding BL patients that had been shown to harbor p53 mutations. In each case, the mutation was detected only in the tumor tissue, thus suggesting that it had arisen during the neoplastic process (Fig. 1).

In 24 cases (marked with asterisk in Table 2; 13/27 mutated biopsies; 11/17 mutated cell lines), the wild-type sequence at the mutation site was either not detectable or was present at low intensity, presumably reflecting the loss of the normal allele (Fig. 2; see below). In two BL primary tumors (HO4024 and HO3876) and two BL cell lines (P3HR1 and BL49), two mutations were observed at different codons, all in the presence of the wild-type band (Fig. 2); in two other cases (Ramos and Namalwa), one codon displayed two mutations. Whether these mutations reside on the same allele or on different chromosomes has not been assessed.

Finally, it is noteworthy that almost one-third (4/13) of cases displaying an abnormal SSCP migration pattern for exon 6 (i.e., 1.78% of all cases analyzed) contained a silent mutation at codon 213 when assayed by direct sequencing, suggesting the presence of a polymorphism.

DISCUSSION

Our data indicate that point mutations in the p53 gene do not represent a general lesion in lymphoid neoplasia but, rather, are specifically associated with certain subtypes of malignancies such as BL and B-CLL. Previously available data were limited to the analysis of a few T-ALL cell lines (17) in which mutations were detectable at a relatively high frequency. This observation, however, was not confirmed by our analysis of primary T-ALL samples. There may be multiple reasons for this discrepancy, but a higher frequency of mutations in cell lines versus primary samples is also observed in this study for BL (63% vs. 33%). While it remains possible that p53 mutations and deletions may frequently occur during *in vitro* establishment or culture (10, 27), it is also conceivable that those cases that carry p53 mutations/deletions may be more suitable for *in vitro* establishment as permanent cell lines. In general, these results suggest caution

Table 2. p53 mutations in lymphoid malignancies

Sample	Diagnosis	Codon	Mutation	Amino acid substitution
DK 428	Precursor B-ALL	273	CGT → TGT*	Arg → Cys
L3-1	B-ALL L_3	282	CGG → TGG*	Arg → Trp
L3-2	B-ALL L_3	175	CGC → CAC	Arg → His
L3-5	B-ALL L_3	205	TAT → TGT	Tyr → Cys
L3-8	B-ALL L_3	175	CGC → CAC	Arg → His
HO3931	sBL	213	CGA → TGA*	Arg → End
HO4024	sBL	236	TAC → TGC	Tyr → Cys
		239	AAC → AGC	Asn → Ser
GS 602	sBL	175	CGC → CAC*	Arg → His
GS 111	sBL	173	GTG → GGG	Val → Gly
IM 6	eBL	144	CAG → CCG	Gln → Pro
HO2218	eBL	133	ATG → AAG*	Met → Lys
HO2209	eBL	175	CGC → CAC*	Arg → His
HO3876	eBL	175	CGC → CAC	Arg → His
		216	GTG → GAG	Val → Glu
HO2217	eBL	258	GAA → AAA*	Glu → Lys
KK125	sBL cell line	248	CGG → CAG*	Arg → Gln
MC116	sBL cell line	238	TGT → TAT*	Cys → Tyr
JD38	sBL cell line	234	TAC → TGC*	Tyr → Cys
AS283A	sBL cell line	206	TTG → TΔG*	Frameshift
Ramos	sBL cell line	254	ATC → GAC*	Ile → Asp
CW678	sBL cell line	175	CGC → CAC*	Arg → His
ST486	sBL cell line	158	CGC → CAC	Arg → His
PP984	sBL cell line	273	CGT → TGT	Arg → Cys
BL37	sBL cell line	237	ATG → ATA*	Met → Ile
BL99	sBL cell line	213	CGA → TGA*	Arg → End
BL49	sBL cell line	176	TGC → TAC	Cys → Tyr
		248	CGG → TGG	Arg → Trp
P3HR1	eBL cell line	163	TAC → CAC	Tyr → His
		287	GAG → TAG	Glu → End
EB3	eBL cell line	206	TTG → TΔG*	Frameshift
Daudi	eBL cell line	213	CGA → TGA	Arg → End
Namalwa	eBL cell line	248	CGG → CAG	Arg → Gln
		248	CGG → TGG†	Arg → Trp
BL60	eBL cell line	282	CGG → TGG*	Arg → Trp
BL113	eBL cell line	273	CGT → TGT*	Arg → Cys
DK 1640	B-CLL	194	CTT → CGT	Leu → Arg
DK 1631	B-CLL	248	CGG → CAG	Arg → Gln
DK 1617	B-CLL	205	TAT → TGT	Tyr → Cys
DK 1198	B-CLL	152	CCG → CCCG* (inserted a C)	Frameshift
DK 885	B-CLL	232	ATC → AGC*	Ile → Ser
DK 981	B-CLL	275	TGT → TTGT* (inserted a T)	Frameshift
DK 1317	Richter's	282	CGG → TGG*	Arg → Trp
DK 1732	Richter's	237	ATG → ATA*	Met → Ile
DK 2042	Richter's	281	GAC → GAG	Asp → Glu
DK 490	PTLC	177	CCC → CGC	Pro → Arg
RDF 378	Precursor B-ALL		Δ976–990*	Frameshift
L3-4	B-ALL L_3	Exon 5	≈15-bp deletion‡	
DK 1361	HCL	Exon 8	≈25-bp insertion‡	

PTLC, peripheral T-cell lymphoma; HCL, hairy cell leukemia; sBL, sporadic BL; eBL, endemic BL; bp, base pair.

*Wild-type sequence at the mutation site could not be detected or was faintly visible.

†The observed mutations would lead to different amino acid substitutions if both mutations resided on the same allele.

‡The PCR amplified fragment displayed an abnormal size on agarose gel and the mutation was confirmed by PCR-SSCP technique; further analysis by PCR direct sequencing could not be informative because of the superimposition of the wild-type sequence.

in extrapolating the frequency of p53 mutations *in vivo* based on data derived from cell lines.

The results reported here may slightly underestimate the frequency of p53 mutations for two reasons. First, our analysis has been restricted to the p53 sites most often implicated in human tumors. Evidence from studies on solid tumors suggest that other regions could be mutated, albeit at lower frequency (28). Second, the SSCP method may not detect every possible mutation in a given DNA fragment, although in trial experiments performed on restricted panels of BL cases during this study, there has been a perfect concordance between screening conducted independently by SSCP and PCR sequencing analysis. Overall, we believe that although the possibility of an underestimate of p53 mutations must be recognized, it is probably not of significant proportions.

Several lines of indirect evidence suggest a pathogenetic role for the observed mutations. First, most mutations found in this study (32/43 missense and nonsense mutations) involve codons that are found mutated in other tumors (4–6, 15); among the remaining 11 mutations, 8 involve highly conserved domains of the p53 protein (26). Second, the vast majority of predicted p53 amino acid substitutions in lymphoid malignancies involve regions of the protein that are highly conserved through evolution (26) and/or correspond to regions of the mouse p53 gene whose mutations result in its oncogenic activation (10). Finally, the recent evidence (29) of germ-line p53 mutations may raise the issue of the germline versus somatic nature of the observed mutations. For four cases, the absence of mutations in non-tumor DNA could be demonstrated. In addition, no evidence of familiar predisposition has been reported for most lymphoid malignancies (30), suggesting that the observed p53 mutations represent somatic events occurring during tumorigenesis.

The results presented here have implications for the role of p53 as either a recessive or a dominant-negative oncogene. In a sizable proportion of cases only the mutated p53 allele was found, while the normal allele has presumably been lost. Although deletions of the short arm of chromosome 17 have been described in lymphomas (31), BL and B-CLL in particular are not frequently associated with cytogenetic alterations of region 17p (32, 33); we conclude that, in these two types of lymphoid malignancies, the loss of the normal p53 allele may reflect cytogenetically undetectable events such as small deletions within the 17p13 region or the loss of one chromosome and the duplication of the remaining mutated chromosome. In all these cases, however, it appears that mutated p53 alleles act as typical recessive oncogenes. Conversely, the interpretation of those cases in which both a normal and a mutated p53 allele are detectable is more difficult. In these cases we could not distinguish whether this finding reflects: (*i*) hemizygosity for the mutated allele, the normal one being present only in contaminating normal cells; or (*ii*) true p53 heterozygosity of the tumor cells, with the mutated allele acting as a dominant-negative oncogene; or (*iii*) "first step" p53 heterozygosity (possibly with no phenotypic effect), which may be followed by "second step" loss of the normal allele, allowing for the recessively acting action of the mutated allele. Further studies combining the analysis of p53 mutation and loss of heterozygosity along the 17p region in sequential tumor samples may help in addressing these issues.

The association between B-CLL and p53 mutation occurs at low frequency, yet it is noteworthy in view of the paucity of information regarding the involvement of either dominant or recessive oncogenes in this malignancy. On the other hand, a number of cytogenetic abnormalities, presumably reflecting unknown oncogene activation events, have been identified and shown to have prognostic significance in this disease (33). It may be interesting to note that, within the general B-CLL category, p53 mutations appear to be more frequent in Richter's syndrome, which represents the evolution of B-CLL into a highly aggressive malignancy. Further studies based on a larger number of cases will clarify whether

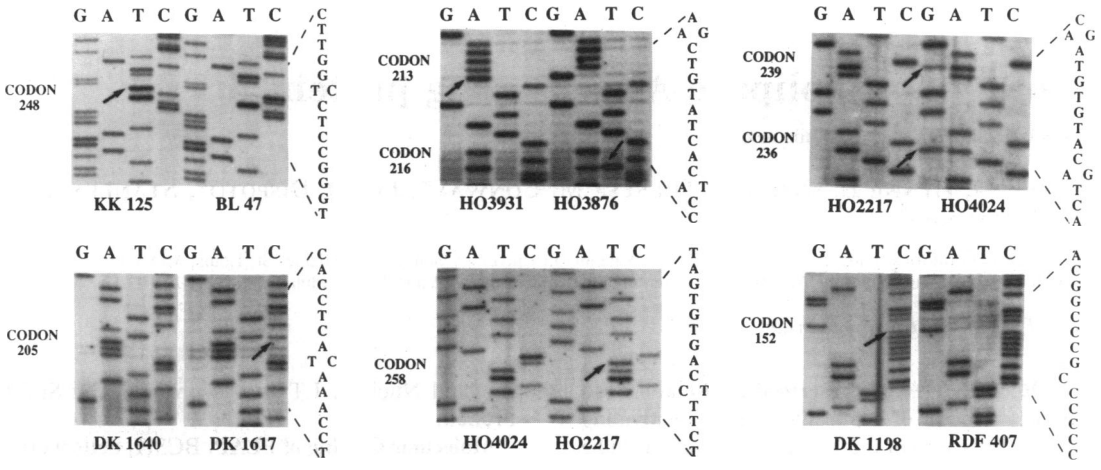

FIG. 2. p53 mutations detected by PCR-amplified fragments. Each mutation shown is matched to a control DNA. The codon at which the mutation occurs is indicated. Each sequence is shown 5′ (bottom) to 3′ (top). Coding strands are shown for cases HO2217/HO4024 (codons 236 and 239), DK 1198/RDF 407; noncoding strands are shown for cases KK125/BL47, HO3931/HO3876, DK 1640/DK 1617, HO4024/HO2217 (codon 258). Arrows point to bands corresponding to mutated base pairs.

p53 mutations significantly correlate with B-CLL neoplastic progression.

Among all types of lymphoid neoplasia, the most frequent targets for p53 mutations are BL and L_3-type B-ALL. BL includes two pathogenetically distinct forms—namely, the endemic African type characterized in virtually all cases by Epstein–Barr virus infection and the sporadic American type characterized by Epstein–Barr virus infection in only ≈30% of cases. The L_3-type B-ALL leukemic cells are morphologically similar to BL, suggesting that this tumor is a leukemic manifestation of BL. A common denominator among all these diseases is the consistent presence of chromosomal translocations leading to c-*myc* oncogene activation (reviewed in ref. 1). Interestingly, p53 mutations have also been found at high frequency in those cases of AIDS-associated lymphoma that carry an activated c-*myc* oncogene (P.B., G.G., G.I., J.Z.G., G. Saglio, D.M.K., and R.D.-F., unpublished data). Whether p53 mutation/loss and c-*myc* activation by chromosomal translocation act synergistically in the pathogenesis of the Burkitt type phenotype remains to be determined.

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