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MUTATION UPDATE

Mutations of the Human PTEN Gene

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PTEN (phosphatase and tensin homolog deleted on chromosome ten), a recently discovered tumor suppressor gene, appears to negatively control the phosphoinositide 3-kinase signaling pathway for regulation of cell proliferation and cell survival by dephosphorylating the phosphatidylinositol 3,4,5-triphosphate. To date, 110 germline PTEN mutations have been reported in patients affected with two tumor predisposing syndromes, each having overlapping clinical features: Cowden disease and Bannayan-Riley-Ruvalcaba syndrome. These germline mutations are scattered along the length of the gene, with the exception of exon 9 (no mutation reported) and exon 1 (only two mutations reported). A mutational hot spot is found in exon 5, which encodes the phosphatase catalytic core motif, and recurrent mutations are also found at CpG dinucleotides suggesting deamination-induced mutations. PTEN has also been found to be defective in a large number of sporadic human tumors. In this article, 332 somatic point mutations of PTEN, occurring in primary tumors or metastasis, have been reviewed. Somatic PTEN mutations are more particularly involved in two types of human cancers: endometrial carcinomas and glioblastomas. In most cases, these somatic mutations result in protein inactivation and, as with germline mutations, recurrent somatic mutations are found in CpG dinucleotides. A mutagenesis by insertion-deletion in repetitive elements is however specifically observed in endometrial carcinomas. Hum Mutat 16:109–122, 2000.

KEY WORDS: PTEN; tumor suppressor; Cowden disease; CD; Bannayan-Riley-Ruvalcaba syndrome; BRR; somatic mutations; germline mutations

DATABASES:
PTEN – OMIM:601728, 158350 (CD), 153480 (BRR); GDB:6022948; HGMD:PTEN

INTRODUCTION

PTEN (phosphatase and tensin homolog deleted on chromosome ten) (MIM# 601728), has been isolated by mapping homozygous deletions in tumor cell lines and xenografts as this gene is the target of 10q22-25 deletions which are frequently involved in prostate cancer, breast cancer, and glioblastoma [Li et al., 1997]. The same gene was independently isolated by Steck et al. [1997] who referred to it as MMAC1 for "mutated in multiple advanced cancer," and by Li and Sun [1997] who named it TEP1 for "TGFβ regulated and epithelial cell enriched phosphatase." Subsequently, germline PTEN mutations were detected in Cowden disease (CD; MIM# 158350) [Liaw et al., 1997], an autosomal dominant inherited cancer syndrome previously mapped at 10q23 [Nelen et al., 1996] and in Bannayan-Riley-Ruvalcaba syndrome (BRR; MIM# 153480) [Marsh et al., 1997]. Given that bi-allelic inactivation of the gene was observed in several tumor types, and inactivating germline mutations were responsible for a cancer prone syndrome, PTEN was expected to be a tumor suppressor gene. Indeed, anti-invasive and anti-proliferative effects of PTEN were documented in several cell models [Furnari et al., 1997; Cheney et al., 1998; Tamura et al., 1998]. PTEN encodes a protein with homology to tensin and auxilin, two cytoskeletal proteins, but it also contains, in exon 5, the catalytic signature motif (HCXXGXXRS/T) of the dual specificity protein

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phosphatases which dephosphorylate serine, threonine, and tyrosine residues. This fact is important because a large number of protein tyrosine kinases have been implicated as oncogenes, and the existence of such a phosphatase acting as a tumor suppressor gene had long been predicted. Biochemical studies revealed, however, that recombinant PTEN poorly dephosphorylated a number of artificial substrates [Myers et al., 1997] but was able to catalyze the dephosphorylation of phosphatidylinositol 3,4,5-triphosphate (PIP-3), specifically at position 3 on the inositol ring [Maehama and Dixon, 1998]. PTEN appears therefore to be a negative regulator of the second messenger PIP-3 and, thus, to negatively control the phosphoinositide 3-kinase (PI3K)/protein-serine/threonine kinase B (PKB-AKT) signaling pathway which is involved in cell survival and cell cycle entry [Myers et al., 1998; Wu et al., 1998; Furnari et al., 1998]. In fact, it has been shown that the wild type PTEN is able to block the G1 progression of the cell cycle [Li and Sun, 1998; Furnari et al., 1998; Ramaswamy et al., 1999; Cheney et al., 1999] and to induce apoptosis [Li et al., 1998] or anoikis [Davies et al., 1999] Moreover, it is possible that both effects are successively produced [Weng et al., 1999]. This paper summarizes the 110 germline and 332 somatic mutations in PTEN which have been reported to date in literature.

PTEN GERMLINE MUTATIONS

To date, 82 different germline mutations in PTEN and two gross deletions of the gene have been reported (Table 1). These mutations have been found in a total number of 110 unrelated patients or families (108 intragenic mutations and two gross deletions); 11 mutations have been reported twice or more.

Clinical Phenotype Associated With Germline PTEN Mutations

The clinical phenotype observed in patients with germline mutation in PTEN is summarized in Table 1. Germline mutations in PTEN have been detected mainly in patients affected with Cowden disease (CD) (N=7, 64.5%) and Bannayan-Riley-Ruvalcaba (BRR) syndrome (N=26, 23.6%). CD is a rare autosomal dominant familial cancer prone syndrome also known as multiple hamartoma syndrome. The diagnosis of CD requires a combination of criteria defined by the International Cowden Consortium [Nelen et al., 1996]. Pathognomonic criteria include trichilemmomas (benign tumors of the hair follicle infundibulum), acral keratoses, papillomatous lesions, and mucosal lesions. Macrocephaly (>97th centile), breast cancer, non-medullary thyroid cancer, and dysplastic gangliocytoma of the cerebellum known as Lhermitte-Duclos (LD) disease are considered as major criteria. Benign thyroid tumors (multinodular goiter and adenomas), fibrocystic breast disease, gastrointestinal hamartomatous polyps, lipomas, fibromas, genitourinary tumors or malformations, and mental retardation (QI<75) are considered as minor criteria. BRR is also a tumor predisposing syndrome which includes macrocephaly, multiple lipomas, intestinal hamartomatous polyps, haemangiomas, and pigmented macules of the glans penis [Fargnoli et al., 1996; Longy et al., 1998]. There is a considerable clinical overlap between CD and BRR but it is of note that speckled penis has been very rarely reported in CD [Fargnoli et al., 1996] and that the increased risk of cancer for patients affected with BRR is not formally documented. Interestingly, however, nine germline mutations of PTEN (8.2 %) have been evidenced in families where individuals affected either with CD or BRR coexist. Conversely, a mutation in PTEN was found in a family where affected individuals did not fulfill the diagnosis criteria for either CD or BRR [Marsh et al., 1998b]. This particular phenotype has been named Cowden-like [Marsh et al., 1998b]. Three mutations (2.8%) have been reported in patients affected with juvenile polyposis syndrome (JPS) without any other clinical manifestation of either CD or BRR [Olschwang et al., 1998]. However, the fact that isolated JPS is due to germline mutation in PTEN is controversial [Eng et al., 1998], and clinical stigmata of Cowden disease must be carefully searched for in patients apparently affected with isolated juvenile polyposis [Kurose et al., 1999]. Moreover, several studies have actually demonstrated that SMAD4 is the gene responsible for familial JPS [Howe et al., 1998].

PTEN Germline Mutation Spectrum

The spectrum of the germline mutations in PTEN is shown in Figure 1 and in Table 1. The germline mutations in PTEN are scattered along the whole gene, with the exception of exon 9, and include point missense mutations (n=26), point stop mutations (n=35), small deletions, insertions and insertion-deletions (n=34), splice site mutations (n=13), and two gross deletions of the gene. A great number (n = 35, 31.5%) of the mutations are found in exon 5, which encodes for the phosphatase core motif. More particularly, 16 out of the

TABLE 1. Germline Mutations of PTEN in 111 Unrelated Patients or Families

Exon[a]	Nucleotide change[b]	Codon	Mutation type[c]	Predicted protein or RNA change	Phenotype[d]	Reference
E1	c.68T->A	23	Nonsense	L23X	Cowden	Lynch et al., 1997
E1	c.70G->T	24	Missense	D24Y	BRR	Celebi et al., 1999a
E2	c.83insA	28	S. ins	Stop at 43	Cowden	Iida et al., 1998b
E2	c.97del3	33	S. del	I33del	Cowden	Nelen et al., 1999
E2	c.101C->A	34	Nonsense	A34D	BRR	Marsh et al., 1999
E2	c.104T->G	35	Missense	M35R	JPS	Olschwang et al., 1998
E2	c.137insCAA	46	S. ins	N46ins	Cowden	Tsou et al., 1997
E2	c.158insATAC	53	S. ins	S54ins	Cowden	Marsh et al., 1998a
E2	c.158delTA	53	S. del	Stop at 54	Cowden	Marsh et al., 1998a
E2	c.158insTTAC	53	S. ins	Stop at 63	Cowden	Nelen et al., 1997
I2	I2-2A->G	/	Splicing	/	Cowden	Marsh et al., 1998a
E3	c.200T->G	67	Missense	I67R	Cowden	Marsh et al., 1998a
E3	c.202T->C	68	Missense	Y68H	BRR	Marsh et al., 1998a
E3	c.202T->C	68	Missense	Y68H	Cowden	Tsou et al., 1998
E3	c.209T->C	70	Missense	L70P	Cowden like	Marsh et al., 1998b
I3	I3+1G->C	/	Splicing	/	Cowden	Nelen et al., 1999
I3	I3+1G->A	/	Splicing	/	BRR	Marsh et al., 1999
I3	I3+5G->A	/	Splicing	/	Cowden	Marsh et al., 1998a
I3	I3+5G->A	/	Splicing	/	BRR	Celebi et al., 1999a
E4	c.244insT	82	S. ins	Stop at 91	Cowden	Kohno et al., 1998a
I4	I4+1G->T	/	Splicing	/	Cowden	Nelen et al., 1997
E5	c.259C->T	87	Nonsense	Q87X	Cowden	Marsh et al., 1998a
E5	c.277C->T	93	Missense	H93Y	Cowden	Kohno et al., 1998a
E5	c.289C->T	97	Nonsense	Q97X	Cowden	Nelen et al., 1999
E5	c.302delTCAinsCC	101-102	S.indel	Stop at 112	Cowden	Marsh et al., 1998a
E5	c.304insT	102	S. ins	Stop at 106	Cowden	Marsh et al., 1998a
E5	c.314->A	105	Missense	C105Y	BRR	Marsh et al., 1999
E5	c.325delG	109	S. del	Stop at 112	BRR	Marsh et al., 1999
E5	c.328C->T	110	Nonsense	Q110X	Cowden	Lynch et al., 1997
E5	c.328C->T	110	Nonsense	Q110X	Cowden	Marsh et al., 1998a
E5	c328C->T	110	Nonsense	Q110X	BRR	Marsh et al., 1999
E5	c.335T->C	112	Missense	L112P	Cowden	Tsou et al., 1998
E5	c.335T->C	112	Missense	L112P	Cowden	Sutphen et al., 1999
E5	c.347del5	116-117	S. del	Stop at 123	Cowden	Marsh et al., 1998a
E5	c.368A->G	123	Missense	H123R	Cowden	Nelen et al., 1997
E5	c.370T->C	124	Missense	C124R	Cowden	Nelen et al., 1997
E5	c.370T->C	124	Missense	C124R	Cowden	Marsh et al., 1998a
E5	c.370T->C	124	Missense	C124R	Cowden	Marsh et al., 1998a
E5	c.386G->A	129	Missense	G129E	Cowden	Liaw et al., 1997
E5	c.386G->A	129	Missense	G129E	Cowden	Liaw et al., 1997
E5	c.388C->T	130	Nonsense	R130X	Cowden	Nelen et al., 1997
E5	c.388C->T	130	Nonsense	R130X	Cowden	Nelen et al., 1997
E5	c.388C->T	130	Nonsense	R130X	Cowden	Marsh et al., 1998a
E5	c.388C->T	130	Nonsense	R130X	Cowden	Marsh et al., 1998a
E5	c.388C->T	130	Nonsense	R130X	Cowden	Iida et al., 1998a
E5	c.388C->T	130	Nonsense	R130X	Cowden/BRR	Zori et al., 1998
E5	c.388C->T	130	Nonsense	R130X	Cowden/BRR	Marsh et al., 1999
E5	c.388C->T	130	Nonsense	R130X	BRR	Marsh et al., 1999
E5	c.389G->T	130	Missense	R130L	Cowden	Marsh et al., 1998a
E5	c.389G->A	130	Missense	R130Q	Cowden	Kurose et al., 1999
E5	c.403A->G	135	Missense	I135V	BRR	Marsh et al., 1999
E5	c.407G->A	136	Missense	C136Y	Cowden	Scala et al., 1998
E5	c.416T->G	139	Nonsense	L139X	Cowden	Raizis et al., 1998
E5	c441insAdelGG	147-148	S. indel	Stop at 152	Cowden/BRR	Marsh et al., 1999
E5	c.469G->T	157	Nonsense	E157X	Cowden	Liaw et al., 1997
E5	c.469G->T	157	Nonsense	E157X	Cowden	Nelen et al., 1997
E6	c.494G->T	165	Missense	G165V	Cowden	Marsh et al., 1998a
E6	c.494G->A	165	Missense	G165E	Cowden	Nelen et al., 1999
E6	c.510T->A	170	Missense	S170R	BRR	Marsh et al., 1997
E6	c.520del25	174-182	G. del	Stop at 174	BRR	Marsh et al., 1998a
E6	c.330delAT	177	S. del	Stop at 178	Cowden	Kohno et al., 1998a
E6	c.534delTAinsAT	178	S. indel	Y178X	BRR	Longy et al., 1998
E6	c.545insA	183	S. ins	Stop at 189	Cowden	Nelen et al., 1997
E6	c.565A->T	189	Nonsense	R189X	Cowden	Lynch et al., 1997
E6	c.565delA	189	S. del	Stop at 198	Cowden	Marsh et al., 1998a

(*continued*)

TABLE 1. (*Continued*)

Exon[a]	Nucleotide change[b]	Codon	Mutation type[c]	Predicted protein or RNA change	Phenotype[d]	Reference
E6	c.586delC	196	S. del	Stop at 198	Cowden/BRR	Longy et al., 1998
I6	I6+2T->G	/	Splicing	/	JPS	Olschwang et al., 1998
I6	I6+5G->T	/	Splicing	/	BRR	Marsh et al., 1999
I6	I6-1G->C	/	Splicing	/	Cowden/BRR	Marsh et al., 1999
E7	c.640C->T	214	Nonsense	Q214X	BRR	Longy et al., 1998
E7	c.697C->T	233	Nonsense	R233X	Cowden	Liaw et al., 1997
E7	c.697C->T	233	Nonsense	R233X	Cowden	Lynch et al., 1997
E7	c.697C->T	233	Nonsense	R233X	BRR	Marsh et al., 1997
E7	c.697C->T	233	Nonsense	R233X	Cowden	Marsh et al., 1998a
E7	c.697C->T	233	Nonsense	R233X	BRR	Marsh et al., 1999
E7	c.723insTT	241	S. ins	Stop at 256	Cowden	Marsh et al., 1998a
E7	c.733C->T	245	Nonsense	Q245X	Cowden	Marsh et al., 1998a
E7	c.737C->T	246	Missense	P246L	BRR	Marsh et al., 1999
E7	c.766G->T	256	Nonsense	E256X	BRR	Longy et al., 1998
E7	c.783delGA	261-262	S. del	Stop at 296	Cowden	Nelen et al., 1997
E7	791insAT	264	S. ins	Stop at 266	Cowden	Tsou et al., 1997
E7	c.798delA	266	S. del	Stop at 255	JPS	Olschwang et al., 1998
E7	c.800insA	266	S. ins	Stop at 297	Cowden	Marsh et al., 1998a
I7	I7+1G->T	/	Splicing	/	Cowden	Nelen et al., 1999
I7	I7+2T->G	/	Splicing	/	Cowden	Tsou et al., 1997
I7	I7-4insT	/	Splicing	/	Cowden/BRR	Marsh et al., 1999
E8	c.865A->G	289	Missense	K289E	Cowden	Chi et al., 1998
E8	c.866insCT	289	S. ins	Stop at 290	BRR	Marsh et al., 1999
E8	c.885insA	295	S. ins	Stop at 295	Cowden/BRR	Celebi et al., 1999a
E8	c.915del13	305	s. del	/	Cowden	Tsou et al., 1997
E8	c.937delA	313	S. del	Stop at 316	Cowden	Nelen et al., 1999
E8	c.945T->G	315	Nonsense	Y315X	Cowden	Marsh et al., 1998a
E8	c.950delTACT	317-318	S. del	Stop at 319	BRR	Marsh et al., 1999
E8	c.954delACTT	317-318	S. del	Stop at 319	Cowden	Rhei et al., 1997
E8	c.959T->A	320	Nonsense	L320X	Cowden	Nelen et al., 1999
E8	c.971insAT	324	S. ins	Stop at 344	Cowden	Marsh et al., 1998a
E8	c.981delA	327	S. del	Stop at 343	Cowden	Marsh et al., 1998a
E8	c.987delTAAA	329-330	S. del	Stop at 342	BRR	Celebi et al., 1999a
E8	c.987delTAAA	329-330	S. del	Stop at 342	Cowden/BRR	Marsh et al., 1999
E8	c.1003C->T	335	Nonsense	R335X	Cowden	Lynch et al., 1997
E8	c.1003C->T	335	Nonsense	R335X	Cowden	Lynch et al., 1997
E8	c.1003C->T	335	Nonsense	R335X	Cowden	Marsh et al., 1998a
E8	c.1003C->T	335	Nonsense	R335X	BRR	Celebi et al., 1999a
E8	c.1003C->T	335	Nonsense	R335X	Cowden/BRR	Celebi et al., 1999b
E8	c.1003C->T	335	Nonsense	R335X	Cowden/BRR	Marsh et al., 1999
E8	c.1007insA	336	S. ins	Stop at 336	Cowden	Marsh et al., 1998a
E8	c.1028T->A	343	Nonsense	V343E	Cowden	Lynch et al., 1997
I8	I8G->A	/	Splicing	/	BRR	Marsh et al., 1999
E1-E9	46XY,del10q23.2-q24.1	/	G. del	/	BRR	Arch et al., 1997
E1-E9	46XY,del10q23.2-q23.33	/	G. del	/	Cowden	Tsuchiya et al., 1998

[a]E, exon; I, intron.
[b]Mutations are designated according to the nomenclature of Beaudet and Tsui (1993) and Antonarakis et al., (1998). Numbering is according to the coding DNA starting at the A in the start codon.
[c]S. ins, small insertion; S. del, small deletion; G. del, gross deletion; S. indel, small insertion-deletion.
[d]BRR, Bannayan-Riley-Ruvalcaba syndrome; Cowden/BRR, patients affected either with Cowden disease or Bannayan-Riley-Ruvalcaba; JPS, juvenile polyposis syndrome.

35 mutations found in exon 5 directly affect the core motif which encompasses codons 123 to 131. Genotype–phenotype correlation analyses reveal that mutations in exon 5, including those affecting the core motif, significantly result more often in CD phenotype than in BRR ($p=0.06$). The majority of the germline mutations occurring in PTEN (n=85, 76%) result either in truncation, in abnormal RNA splicing, or in gross deletion of the gene, thus predicting inactivation of the protein and supporting haplo-insufficiency as an explanation of the clinical features of both CD and BRR.

Table 1 shows that 11 germline mutations occurred recurrently in PTEN. Eight of these recurrent mutations have been described only two or three times. Three mutations however, namely

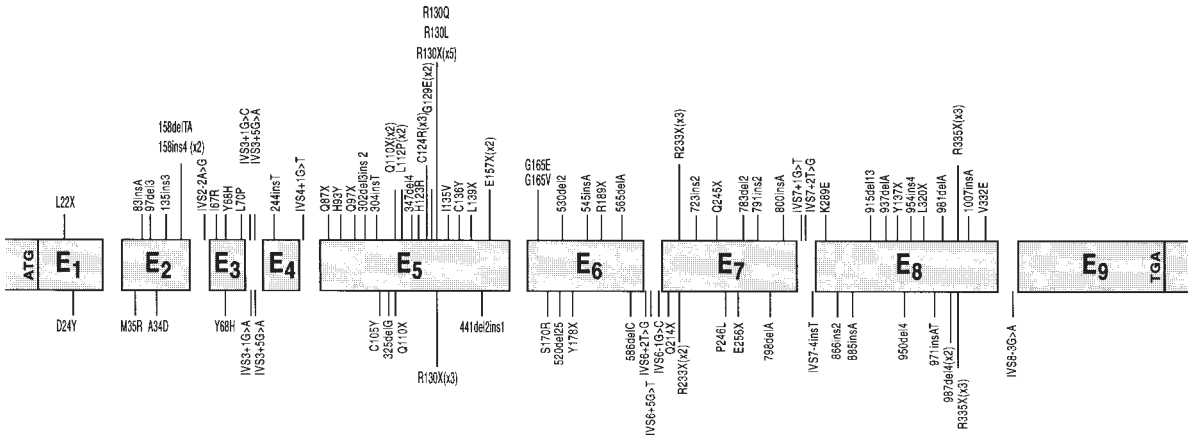

FIGURE 1. **Localization of germline PTEN mutations. Above: mutations observed in Cowden disease, below: mutations observed in Bannayan-Riley-Ruvalcaba-syndrome or in patients affected either with Cowden disease or Bannayan-Riley-Ruvalcaba syndrome within the same family. See Table 1 for references.**

R130X, R233X, and R335X, have been found in seven, five, and six unrelated affected individuals, respectively. Interestingly, all these mutations occurred in CpG dinucleotides. Including the non-recurrent mutation R130L, a proportion of 17.1% (n=19) of all germline mutations have occurred in codons 130, 233, and 235, which can therefore be regarded as mutational hot spots. Although the methylation status of the PTEN CpGs is currently unknown, these mutations, corresponding to a C→T/G→ A transition at dinucleotides CpG, are consistent with deamination-induced endogenous mutations.

PTEN SOMATIC MUTATIONS

A review of the literature (considering only the mutations found in tumoral specimens and not those found in cell lines or xenografts) provides 332 PTEN somatic point mutations occurring in various types of primary tumors or metastasis (Tables 2 and 3). These mutations have been found predominantly in endometrial carcinomas (n=118) and glioblastomas (n=110), or in histologically related tumors such as endometrial hyperplasia or anaplastic astrocytomas. Mutations of PTEN also have been detected, to a lesser extent, in other types of malignant tumors such as malignant lymphomas, prostate, breast, and thyroid carcinomas, or malignant melanomas.

The majority (70 %) of the somatic PTEN mutations are nonsense, frameshift, or splicing mutations resulting in a truncation of the protein. In addition, about half of the 100 missense mutations have been found in exon 5 coding for the phosphatase core motif, and are likely to alter the phosphatase activity of the protein. In 130 out of the 145 cases of informative tumors, bi-allelic inactivation of PTEN has been evidenced with both point mutations in one allele and deletions of the other allele resulting in loss of heterozygosity (LOH). This high rate of bi-allelic inactivation of PTEN is, however, misleading because the search of a point mutation in PTEN has often been undertaken in tumors after a LOH was first evidenced. Finally, 21 analysed tumors revealed two distinct somatic mutations of PTEN; it is unclear, however, if the mutations were affecting only one or both alleles in these cases.

Similarly to germline mutations, a great number (22.9%) of somatic mutations occur in exon 5, and the same mutational hot spots are found at arginins 130, 233, and 335. Interestingly, however, there is a significant difference between the location of the mutations involved in glioblastomas and those involved in endometrial carcinomas. In glioblastomas, a high proportion of mutations are found in exon 6 (27.3%), whereas few mutations are found in exons 7 and 8 (8.2% and 12.7%, respectively). By contrast, in endometrial carcinomas, few mutations are found in exon 6 (5.9%), whereas a high proportion of mutations occur in exons 7 and 8 (19.9% and 29.4%, respectively). This discrepancy may be explained by the types of mutation which are specifically and recurrently evidenced in exons 7 and 8 in endometrial carcinomas. These mutations are either an insertion/deletion of a single nucleotide within a poly A/T sequence (795delA, 962insA, and 963delA), or a four base pair deletion in a duplicated motif (deletion of 4 bases in codons 950 to 956). This type of mutation must be related to the high frequency of microsatellite instability (MIN) observed in endometrial carcino-

TABLE 2. Somatic Mutations of PTEN

Exon	Nucleotide change[a]	Mutation type[b]	Predicted protein or RNA change	Tumor type[c]	2nd hit[d]	Reference
E1	c.3del11	Frameshift	M1del	N.H.M.L.	?	Nakahara et al., 1998
E1	c.28del3	In-f. del	S10del	G.C.G.	?	Peraud et al., 1999
E1	c.29G->A	Missense	S10N	N.H.M.L.	?	Grønbæk et al., 1998
E1	c.36insA	Frameshift	Stop at 43	E.C.	No LOH	Kurose et al., 1998
E1	c.37A->G	Missense	L13E	Glb.	?	Duerr et al., 1998
E1	c.37delA	Frameshift	Stop at 23	E.C.	?	Risinger et al., 1997
E1	c.45A->C	Missense	R15S	Glb.	LOH	Steck et al., 1997
E1	c.45insGA	Frameshift	Stop at 24	Glb.	LOH	Li J et al., 1997
E1	c.46insA	Nonsense	Y16X	Glb.	LOH	Fults et al., 1998
E1	c.47A->G	Missense	Y16C	N.H.M.L.	?	Sakai et al., 1998
E1	c.49C->T	Nonsense	Q17X	E.C.	LOH	Simpkins et al., 1998
E1	c.49C->T	Nonsense	Q17X	N.H.M.L.	?	Dahia et al., 1999
E1	c.54delGGAT	Frameshift	Stop at 23	E.C.	Dble mut	Risinger et al., 1998
E1	c.59G->A	Missense	G20E	E.C.	LOH	Lin et al., 1998
E1	c.69A->C	Missense	L23F	Glb.	LOH	Liu et al., 1997
E1	c.69del6	In-f. del	D24,L25del	Glb.	LOH	Zhou et al., 1999
E1	c.69insA	Frameshift	Stop at 43	Glb.	LOH	Liu et al., 1997
E1	c.70G->A	Missense	D24N	E.C.	LOH	Tashiro et al., 1997
E1	c.70insC	Frameshift	Stop at 43	E.C.	LOH	Simpkins et al., 1998
E2	c.80A->C	Ms. lik. spl.	Y27S	Glb.	LOH	Davies et al., 1999
E2	c.80delAT	Frameshift	Stop at 42	E.C.	?	Risinger et al., 1997
E2	c.89delC	Frameshift	Stop at 53	E.C.	?	Risinger et al., 1998
E2	c.94delATT	In-f. del	I32del	E.C.	Dble mut	Kong et al., 1997
E2	c.95delT	Frameshift	Stop at 53	E.C.	MIN	Kong et al., 1997
E2	c.96delT	Frameshift	Stop at 53	E.C.	?	Risinger et al., 1998
E2	c.97del3	In-f. del	I33del	E.C.	LOH	Kurose et al., 1998
E2	c.97delA	Frameshift	Stop at 53	E.C.	No LOH	Lin et al., 1998
E2	c.97delATTG	Frameshift	Stop at 53	E.C.	?	Risinger et al., 1998
E2	c.98T->G	Missense	I33S	E.C.	No LOH	Kong et al., 1997
E2	c.104T->G	Missense	M35R	Glb.	LOH	Fults et al., 1998
E2	c.107delG	Frameshift	Stop at 53	P.C.	No LOH	Gray et al., 1998
E2	c.112delCCinsTT	Missense	P38F	M.M.	LOH	Teng et al., 1997
E2	c.118G->T	Nonsense	E40X	E.C.	?	Risinger et al., 1997
E2	c.125T->C	Missense	L42P	Glb.	LOH	Davies et al., 1999
E2	c.127delG	Frameshift	Stop at 53	Glb.	LOH	Fults et al., 1998
E2	c.131del6ins8	Frameshift	Stop at 54	P.C.	LOH	Gray et al., 1998
E2	c.131G->A	Missense	G44D	Odg.	?	Duerr et al., 1998
I2	IVS2-2A->C	Splicing		Glb.	LOH	Chiariello et al., 1998
I2	IVS2-1G->T	Splicing		E.C.	LOH	Simpkins et al., 1998
I2	IVS2-1G->T	Splicing		P.G.	LOH	Teng et al., 1997
E3	c.170T->G	Missense	L57W	Glb.	LOH	Steck et al., 1997
E3	c.171G->T	Missense	D58Y	Glb.	LOH	Chiariello et al., 1998
E3	c.171ins38	Frameshift	Stop at 98	E.C.	Dble mut	Tashiro et al., 1997
E3	c.175T->C	Missense	S59P	B.C.	?	Ueda et al., 1998
E3	c.176C->A	Nonsense	S59X	E.C.	LOH	Tashiro et al., 1997
E3	c.180ins25	Frameshift	Stop at 70	B.C.	LOH	Steck et al., 1997
E3	c.182A->G	Missense	H61R	Glb.	LOH	Fults et al., 1998
E3	c.182A->G	Missense	H61R	Glb.	LOH	Zhou et al., 1999
E3	c.184delA	Frameshift	Stop at 98	E.C.	Dble mut	Risinger et al., 1997
E3	c.184delA	Frameshift	Stop at 98	E.C.	Dble mut	Tashiro et al., 1997
E3	c.195C->A	Nonsense	Y65X	Glb.	LOH	Zhou et al., 1999
E3	c.197ins14	Frameshift	Stop at 103	G.C.G.	?	Duerr et al., 1998
E3	c.202delTA	Frameshift	Stop at 72	E.C.	LOH	Lin et al., 1998
E3	c.202insTAT	Frameshift	Stop at 74	E.C.	?	Risinger et al., 1997
E3	c.202T->C	Missense	Y68H	A.E.H.	?	Levine et al., 1998
E3	c.202T->C	Missense	Y68H	Glb.	LOH	Chiariello et al., 1998
E3	c.211delTG	Frameshift	Stop at 72	M.O.C.	Dble mut	Obata et al., 1998
I3	IVS3?del4	Splicing		E.C.	Dble mut	Kong et al., 1997
I3	IVS3?del4	Splicing		P.C.	LOH	Cairns et al., 1997
I3	IVS3?insT	Splicing		Glb.	LOH	Liu et al., 1997
I3	IVS3+1del20	Splicing		Glb.	?	Duerr et al., 1998
I3	IVS3+4delAGTA	Splicing		Glb.	?	Duerr et al., 1998
I3	IVS3+5G->A	Splicing		Glb.	LOH	Davies et al., 1999
I3	IVS3+5G->T	Splicing		Glb.	?	Duerr et al., 1998
I3	IVS3-7delCTTT	Splicing		N.H.M.L.	No LOH	Butler et al., 1999

(*continued*)

TABLE 2. (*Continued*)

Exon	Nucleotide change[a]	Mutation type[b]	Predicted protein or RNA change	Tumor type[c]	2nd hit[d]	Reference
I3	IVS3-1G->T	Splicing		Glb.	?	Duerr et al., 1998
E4	c.218delAA	Frameshift	Stop at 76	E.C.	MIN	Tashiro et al., 1997
E4	c.223insA	Frameshift	Stop at 77	E.C.	MIN	Tashiro et al., 1997
E4	c.226delTAT	In-f. del	Y76del	A.A.	LOH	Davies et al., 1999
E4	c.227delAT	Nonsense	Y76X	E.C.	LOH	Simpkins et al., 1998
E4	c.235G->A	Missense	A79T	Odg.	?	Duerr et al., 1998
E4	c.238A->G	Missense	K80E	Glb.	LOH	Zhou et al., 1999
E4	c.240A->T	Missense	K80N	Glb.	LOH	Rasheed et al., 1997
I4	IVS4+1G->A	Splicing		E.C.	MIN	Kong et al., 1997
I4	IVS4+1G->A	Splicing		E.C.	MIN	Kong et al., 1997
I4	IVS4+1G->A	Splicing		Glb.	LOH	Fults et al., 1998
I4	IVS4+5del6	Splicing		Glb.	?	Boström et al., 1998
I4	IVS4+5G->T	Splicing		Glb.	?	Boström et al., 1998
I4	IVS4-3C->A	Splicing		Glb.	LOH	Zhou et al., 1999
I4	IVS4-2insA	Splicing		Glb.	?	Thoma et al., 1998
E5	c.267delT	Frameshift	Stop at 86	E.C.	Dble mut	Tashiro et al., 1997
E5	c.269T->C	Missense	F90S	E.C.	Dble mut	Tashiro et al., 1997
E5	c.271G->C	Missense	E91Q	P.C.(met)	No LOH	Suzuki et al., 1998
E5	c.275A->G	Missense	D92G	E.C.	LOH	Kurose et al., 1998
E5	c.277C->G	Missense	H93D	E.C.	MIN	Tashiro et al., 1997
E5	c.277C->T	Missense	H93Y	E.C.	MIN	Kong et al., 1997
E5	c.277C->T	Missense	H93Y	E.C.	MIN	Kurose et al., 1998
E5	c.279T->G	Missense	H93Q	Glb.	LOH	Liu et al., 1997
E5	c.284C->T	Missense	P95L	A.E.H.	MIN	Levine et al., 1998
E5	c.284C->T	Missense	P95L	E.C.	MIN	Tashiro et al., 1997
E5	c.287C->t	Missense	P96L	Glb.	LOH	Rasheed et al., 1997
E5	c.296insTA	Frameshift	Stop at 112	E.C.	?	Risinger et al., 1998
E5	c.302T->C	Missense	I101T	Glb.	LOH	Liu et al., 1997
E5	c.309insT	Frameshift	Stop at 106	E.C.	?	Risinger et al., 1997
E5	c.319G->T	Missense	D107Y	E.C.	?	Risinger et al., 1998
E5	c.348delC	Frameshift	Stop at 133	Glb.	?	Tohma et al., 1998
E5	c.356T->A	Missense	V119D	E.C.	Dble mut	Risinger et al., 1998
E5	c.360del75	In-f. del		E.C.	MIN	Rashiro et al., 1997
E5	c.361G->C	Missense	A121P	Glb.	?	Duerr et al., 1998
E5	c.364del1	Frameshift	Stop at 133	G.C.G.	?	Peraud et al., 1999
E5	c.364del5	Frameshift	Stop at 123	Glb.	?	Liu et al., 1997
E5	c.367C->T	Missense	H123Y	E.C.	MIN	Tashiro et al., 1997
E5	c.370delT	Frameshift	Stop at 133	Glb.	?	Liu et al., 1997
E5	c.370T->A	Missense	C124S	E.C.	?	Kurose et al., 1998
E5	c.376G->A	Missense	A126T	Glb.	LOH	Liu et al., 1997
E5	c.376G->C	Missense	A126P	A.A.	LOH	Rasheed et al., 1997
E5	c.377C->T	Missense	A126L	E.O.C.	LOH	Obata et al., 1998
E5	c.380G->A	Missense	G127E	M.M.(met)	?	Guldberg et al., 1997
E5	c.382del14	Frameshift	Stop at 159	A.E.H.	?	Maxwell et al., 1998
E5	c.384G->A	Missense	G132s	Glb.	?	Rasheed et al., 1997
E5	c.385G->A	Missense	G129R	Glb.	LOH	Li J et al., 1997
E5	c.386G->A	Missense	G129E	E.C.	?	Risinger et al., 1997
E5	c.387delA	Frameshift	Stop at 133	E.C.	?	Risinger et al., 1997
E5	c.388C->G	Missense	R130G	E.O.C.	LOH	Obata et al., 1998
E5	c.388C->G	Missense	R130G	E.O.C.	LOH	Obata et al., 1998
E5	c.388C->G	Missense	R130G	E.C.	?	Risinger et al., 1997
E5	c.388C->G	Missense	R130G	E.C.	Dble mut	Tashiro et al., 1997
E5	c.388C->G	Missense	R130G	E.C.	MIN	Kong et al., 1997
E5	c.388C->T	Nonsense	R130X	A.A.	?	Tohma et al., 1998
E5	c.388C->T	Nonsense	R130X	A.A.	LOH	Rasheed et al., 1997
E5	c.388C->T	Nonsense	R130X	E.O.C.	LOH	Obata et al., 1998
E5	c.388C->T	Nonsense	R130X	E.C.	?	Risinger et al., 1998
E5	c.388C->T	Nonsense	R130X	E.C.	MIN	Kong et al., 1997
E5	c.388C->T	Nonsense	R130X	E.H.	Dble mut	Maxwell et al., 1998
E5	c.388C->T	Nonsense	R130X	Glb.	LOH	Steck et al., 1997
E5	c.388C->T	Nonsense	R130X	Mdb.	?	Rasheed et al., 1997
E5	c.388C->T	Nonsense	R130X	M.O.C.	Dble mut	Obata et al., 1998
E5	c.388C->T	Nonsense	R130X	P.G.	LOH	Teng et al., 1997
E5	c.388C->T	Nonsense	R130X	P.C.	LOH	Suzuki et al., 1998
E5	c.389del7	Frameshift	Stop at 131	A.E.H.	?	Maxwell et al., 1998

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TABLE 2. (*Continued*)

Exon	Nucleotide change[a]	Mutation type[b]	Predicted protein or RNA change	Tumor type[c]	2nd hit[d]	Reference
E5	c.389del9	In-f. del		E.C.	?	Risinger et al., 1998
E5	c.389G->A	Missense	R130Q	A.A.	LOH	Rasheed et al., 1997
E5	c.389G->A	Missense	R130Q	E.C.	LOH	Simpkins et al., 1998
E5	c.389G->A	Missense	R130Q	E.C.	LOH	Simpkins et al., 1998
E5	c.389G->T	Missense	R130Q	A.E.H.	?	Levine et al., 1998
E5	c.389G->T	Missense	R130L	A.E.H.	?	Maxwell et al., 1998
E5	c.389G->T	Missense	R130L	E.C.	?	Risinger et al., 1998
E5	c.392C->T	Missense	T131N	A.A.	LOH	Davies et al., 1999
E5	c.395G->T	Missense	G132V	Glb.	LOH	Zhou et al., 1999
E5	c.397G->A	Missense	V133I	E.C.	LOH	Kurose et al., 1998
E5	c.397G->A	Missense	V133I	E.C.	LOH	Kurose et al., 1998
E5	c404delT	Frameshift	Stop at 146	Glb.	?	Boström et al., 1998
E5	c.404insA	Frameshift	Stop at 179	Glb.	LOH	Wang et al., 1997
E5	c.404T->A	Missense	I135K	Glb.	?	Liu et al., 1997
E5	c.405insA	Frameshift	Stop at 179	E.C.	Dble mut	Kong et al., 1997
E5	c.406T->C	Missense	C136R	Glb.	?	Duerr et al., 1998
E5	c.407G->T	Missense	C136F	Glb.	LOH	Zhou et al., 1999
E5	c.415delTT	Frameshift	Stop at 178	E.H.	?	Maxwell et al., 1998
E5	c.416T->G	Nonsense	L139X	E.H.	?	Maxwell et al., 1998
E5	c.416T->G	Nonsense	L139X	M.M.(met)	?	Guldberg et al., 1997
E5	c.424C->T	Missense	R142W	G.C.G.	Dble mut	Peraud et al., 1999
E5	c.454C->G	Missense	L152V	Glb.	LOH	Fults et al., 1998
E5	c.463T->C	Missense	Y155H	Glb.	?	Duerr et al., 1998
E5	c.473insT	Frameshift	Stop at 179	P.C.	LOH	Gray et al., 1998
E5	c.486insA	Frameshift	Stop at 166	E.C.	Dble mut	Tashiro et al., 1997
I5	IVS5+2delT	Splicing		E.C.	LOH	Simpkins et al., 1998
I5	IVS5-2A->G	Splicing		Glb.	LOH	Liu et al., 1997
E6	c.493G->A	ms. lik. spl.	G165R	Glb.	?	Tohma et al., 1998
E6	c.493G->A	ms. lik. spl.	G165R	Glb.	LOH	Chiariello et al., 1998
E6	c.506C->A	Missense	P169H	Glb.	?	Tohma et al., 1998
E6	c.509G->A	Missense	S170N	E.C.	?	Kurose et al., 1998
E6	c.509G->A	Missense	S170N	G.C.G.	?	Peraud et al., 1999
E6	c.509G->A	Missense	S170N	Glb.	LOH	Zhou et al., 1999
E6	c.509G->T	Missense	S170I	Glb.	LOH	Liu et al., 1997
E6	c.509G->T	Missense	S170I	Glb.	LOH	Chiariello et al., 1998
E6	c.511C->T	Nonsense	Q171X	Glb.	LOH	Davies et al., 1999
E6	c.511C->T	Nonsense	Q171X	Glb.	LOH	Rasheed et al., 1997
E6	c.512A->C	Missense	Q171P	Glb.	LOH	Liu et al., 1997
E6	c.513G->C	Missense	Q171H	Glb.	?	Duerr et al., 1998
E6	c.514del19	Frameshift	Stop at 176	R.C.C.	LOH	Steck et al., 1997
E6	c.517C->T	Missense	R173C	A.E.H.	?	Maxwell et al., 1998
E6	c.517C->T	Missense	R173C	E.C.	?	Risinger et al., 1998
E6	c.517C->T	Missense	R173C	E.C.	LOH	Simpkins et al., 1998
E6	c.517C->T	Missense	R173C	Glb.	?	Duerr et al., 1998
E6	c.571C->T	Missense	R173C	Glb.	LOH	Boström et al., 1998
E6	c.571C->T	Missense	R173C	Glb.	LOH	Fults et al., 1998
E6	c.571C->T	Missense	R173C	Glb.	LOH	Rasheed et al., 1997
E6	c.517C->T	Missense	R173C	Glb.	LOH	Rasheed et al., 1997
E6	c.517delC	Frameshift	Stop at 182	Glb.	LOH	Liu et al., 1997
E6	c.518G->A	Missense	R173H	A.A.	LOH	Davies et al., 1999
E6	c.518G->A	Missense	R173H	G.C.G.	Dble mut	Peraud et al., 1999
E6	c.518G->A	Missense	R173H	Glb.	?	Tohma et al., 1998
E6	c.518G->A	Missense	R173H	Glb.	?	Duerr et al., 1998
E6	c.520T->A	Missense	Y174N	P.C.	LOH	Feilotter et al., 1998
E6	c.526delTAT	In-f. del	Y176del	Glb.	?	Duerr et al., 1998
E6	c.527T->G	Nonsense	Y176X	E.C.	Dble mut	Tashiro et al., 1997
E6	c.530delATTAT	Frameshift	Stop at 178	E.C.	Dble mut	Risinger et al., 1998
E6	c.545insA	Frameshift	Stop at 189	E.C.	MIN	Gurin et al., 1999
E6	c.546del4	Frameshift	Stop at 199	Glb.	?	Tohma et al., 1998
E6	c.557delT	Frameshift	Stop at 198	Glb.	?	Duerr et al., 1998
E6	c.564T->A	Nonsense	Y188X	P.C.	LOH	Cairns et al., 1997
E6	c.572T->C	Missense	V191A	E.H.	?	Maxwell et al., 1998
E6	c.573del11	Frameshift	Stop at 197	Glb.	?	Boström et al., 1998
E6	c.577del3	In-f. del	L193del	Glb.	LOH	Rasheed et al., 1997
E6	c.594delATG	In-f. del	M199del	Glb.	?	Boström et al., 1998

(*continued*)

TABLE 2. (*Continued*)

Exon	Nucleotide change[a]	Mutation type[b]	Predicted protein or RNA change	Tumor type[c]	2nd hit[d]	Reference
E6	c.597G->A	Frameshift	Stop at 220	Glb.	?	Tohma et al., 1998
E6	c.602delA	Frameshift	Stop at 217	Glb.	LOH	Steck et al.,1997
E6	c.610C->T	Missense	P204S	Glb.	LOH	Zhou et al., 1999
I6	IVS6+1G->T	Splicing		E.C.	LOH	Simpkins et al., 1998
I6	IVS6+2delT,insA	Splicing		Glb.	?	Tohma et al., 1998
I6	IVS6+4A->G	Splicing		Glb.	LOH	Fults et al., 1998
I6	IVS6–1G->T	Splicing		E.C.	MIN	Gurin et al., 1999
E7	c.640C->T	Nonsense	Q214X	E.C.	?	Risinger et al., 1997
E7	c.640C->T	Nonsense	Q214X	E.C.	?	Risinger et al., 1998
E7	c.640C->T	Nonsense	Q214X	E.C.	LOH	Kong et al., 1997
E7	c.640C->T	Nonsense	Q214X	E.C.	MIN	Gurin et al., 1999
E7	c.640C->T	Nonsense	Q214X	Glb.	LOH	Rasheed et al., 1997
E7	c.646G->A	Missense	V216M	E.C.	LOH	Lin et al., 1998
E7	c.654C->A	Nonsense	C218X	E.C.	Dble mut	Kong et al., 1997
E7	c.655C->T	Nonsense	Q219X	Glb.	?	Duerr et al., 1998
E7	c.655C->T	Nonsense	Q219X	P.A.	?	Duerr et al., 1998
E7	c.670insA	Frameshift	Stop at 242	P.C.(met	LOH	Suzuki et al., 1998
E7	c.670insA	Frameshift	Stop at 242	P.C.(met)	MIN	Suzuki et al., 1998
E7	c.675insTA	Frameshift	Stop at 256	M.M.(met)	?	Guldberg et al., 1997
E7	c.686C->G	Nonsense	S229X	Glb.	LOH	Fults et al., 1998
E7	c.697C->T	Nonsense	R233X	E.O.C.	LOH	Obata et al., 1998
E7	c.697C->T	Nonsense	R233X	E.C.	Dble mut	Kong et al., 1997
E7	c.697C->T	Nonsense	R233X	E.C.	Dble mut	Tashiro et al., 1997
E7	c.697C->T	Nonsense	R233X	E.C.	Dble mut	Tashiro et al., 1997
E7	c.697C->T	Nonsense	R233X	Glb.	?	Duerr et al., 1998
E7	c.697C->T	Nonsense	R233X	Glb.	LOH	Zhou et al., 1999
E7	c.697C->T	Nonsense	R233X	Gls.	?	Duerr et al., 1998
E7	c.703G->T	Missense	E235X	E.C.	LOH	Simpkins et al., 1998
E7	c.703G->T	Nonsense	E235X	N.S.C.L.C.	?	Kohno et al., 1998b
E7	c.703ins20	Frameshift	Stop at 260	T.C.L.	?	Dahia et al., 1999
E7	c.704delA	Frameshift	Stop at 255	B.C.	LOH	Teng et al., 1997
E7	c.710del9	In-f. del		B.C.	LOH	Steck et al., 1997
E7	c.710insAA	Frameshift	Stop at 242	E.C.	LOH	Simpkins et al., 1998
E7	c.711delG	Frameshift	Stop at 255	SCLC(met.)	LOH	Kohno et al., 1998b
E7	c.721delT	Frameshift	Stop at 255	E.C.	LOH	Tashiro et al., 1997
E7	c.727del13	Frameshift	Stop at 251	E.C.	?	Risinger et al., 1997
E7	c.729delC	Frameshift	Stop at 255	P.C.	LOH	Pesche et al., 1998
E7	c.733C->T	Nonsense	Q245X	E.C.	Dble mut	Tashiro et al., 1997
E7	c.733C->T	Nonsense	Q245X	H.N.C.	LOH	Okami et al., 1998
E7	c.733del8insA	Frameshift	Stop at 253	E.C.	No LOH	Kurose et al., 1998
E7	c.737C->T	Missense	P246L	Glb.	LOH	Liu et al., 1997
E7	c.737insGT	Frameshift	Stop at 256	A.E.H.	?	Levine et al., 1998
E7	c.738delG	Frameshift	Stop at 255	E.C.	MIN	Kong et al., 1997
E7	c.740insA	Frameshift	Stop at 252	Glb.	LOH	Zhou et al., 1999
E7	c.740insA	Frameshift	Stop at 242	Glb.	LOH	Rasheed et al., 1997
E7	c.750T->A	Nonsense	C250X	E.C.	Dble mut	Kong et al., 1997
E7	c.754G->T	Missense	D252Y	Glb.	LOH	Liu et al., 1997
E7	c.758T->A	Missense	I253N	A.A.	MIN	Zhou et al., 1999
E7	c.760del5	Frameshift	Stop at 295	Glb.	No LOH	Liu et al., 1997
E7	c.761dlAAGTA	Frameshift	Stop at 295	F.T.C.	LOH	Halachmi et al., 1998
E7	c.761delAAGTA	Frameshift	Stop at 295	P.C.	LOH	Cairns et al., 1997
E7	c.762del14	Frameshift	Stop at 298	E.C.	?	Risinger et al., 1998
E7	c.792del13	Frameshift	Stop at 271	E.C.	No LOH	Lin et al., 1998
E7	c.795delA	Frameshift	Stop at 275	E.C.	?	Risinger et al., 1997
E7	c.795delA	Frameshift	Stop at 275	E.C.	?	Risinger et al., 1998
E7	c.795delA	Frameshift	Stop at 275	E.C.	Dble mut	Kong et al., 1997
E7	c.795delA	Frameshift	Stop at 275	E.C.	Dble mut	Risinger et al., 1997
E7	c.795delA	Frameshift	Stop at 275	E.C.	Dble mut	Risinger et al., 1998
E7	c.795delA	Frameshift	Stop at 275	E.C.	Dble mut	Tashiro et al., 1997
E7	c.795delA	Frameshift	Stop at 275	E.C.	LOH	Lin et al., 1998
E7	c.795delA	Frameshift	Stop at 275	E.C.	MIN	Kurose et al., 1998
E7	c.799delAA	Frameshift	Stop at 296	E.C.	Dble mut	Risinger et al., 1998
E7	c.802ins171	Frameshift		E.C.	?	Risinger et al., 1997
I7	IVS7+1G->T	Splicing		E.C.	LOH	Kurose et al., 1998
E8	c.863delA	Frameshift	Stop at 290	E.C.	Dble mut	Tashiro et al., 1997

(*continued*)

TABLE 2. (*Continued*)

Exon	Nucleotide change[a]	Mutation type[b]	Predicted protein or RNA change	Tumor type[c]	2nd hit[d]	Reference
E8	c.864del5	Frameshift	Stop at 295	E.C.	?	Risinger et al., 1997
E8	c.877G->T	Nonsense	G293X	E.C.	MIN	Kong et al., 1997
E8	c.883insT	Frameshift	Stop at 296	P.T.C.	No LOH	Dahia et al., 1997
E8	c.892C->T	Nonsense	Q298X	E.C.	LOH	Kurose et al., 1998
E8	c.901del10	Frameshift	Stop at 303	E.C.	No LOH	Tashiro et al., 1997
E8	c.923delG	Frameshift	Stop at 316	E.O.C.	?	Obata et al., 1998
E8	c.923delGT	Frameshift	Stop at 310	A.E.H.	?	Levine et al., 1998
E8	c.937delA	Frameshift	Stop at 315	E.C.	?	Risinger et al., 1997
E8	c.941delA	Frameshift	Stop at 316	Glb.	?	Duerr et al., 1998
E8	c.950del4	Frameshift	Stop at 319	E.O.C.	LOH	Obata et al., 1998
E8	c.950del4	Frameshift	Stop at 319	E.C.	Dble mut	Kong et al., 1997
E8	c.950del4	Frameshift	Stop at 319	E.C.	MIN	Kong et al., 1997
E8	c.950del4	Frameshift	Stop at 319	P.C.	LOH	Gray et al., 1998
E8	c.951delACTT	Frameshift	Stop at 319	Glb.	LOH	Chiariello et al., 1998
E8	c.951delACTT	Nonsense	T319X	Glb.	?	Duerr et al., 1998
E8	c.952delCTTA	Frameshift	Stop at 319	A.E.H.	?	Maxwell et al., 1998
E8	c.952delCTTA	Frameshift	Stop at 319	A.E.H.	?	Maxwell et al., 1998
E8	c.952delCTTA	Frameshift	Stop at 320	E.C.	Dble mut	Risinger et al., 1998
E8	c.952delCTTA	Frameshift	Stop at 319	E.C.	Dble mut	Maxwell et al., 1998
E8	c.953delTTAC	Frameshift	Stop at 319	A.E.H.	?	Levine et al., 1998
E8	c.954delTACT	Nonsense	T319X	Glb.	LOH	Zhou et al., 1999
E8	c.955delACT	In-f. del	L318del	Glb.	?	Duerr et al., 1998
E8	c.955delACT	In-f. del	T319del	Glb.	LOH	Steck et al., 1997
E8	c.955delACTT	Nonsense	T319X	E.C.	LOH	Kurose et al., 1998
E8	c.955delACTT	Nonsense	T319X	E.C.	MIN	Kurose et al., 1998
E8	c.955delACTT	Nonsense	T319X	E.C.	MIN	Lin et al., 1998
E8	c.956delCTTT	Frameshift	Stop at 342	E.C.	?	Risinger et al., 1998
E8	c.956delCTTT	Frameshift	Stop at 342	Glb.	LOH	Steck et al., 1997
E8	c.956delCTTT	Frameshift	Stop at 342	Glb.	LOH	Chiariello et al., 1998
E8	c.956insA	Frameshift	Stop at 324	E.C.	Dble mut	Risinger et al., 1997
E8	c.962insA	Frameshift	Stop at 324	E.C.	?	Kong et al., 1997
E8	c.962insA	Frameshift	Stop at 324	E.C.	?	Risinger et al., 1997
E8	c.962insA	Frameshift	Stop at 324	E.C.	Dble mut	Kong et al., 1997
E8	c.962insA	Frameshift	Stop at 324	E.C.	Dble mut	Risinger et al., 1997
E8	c.962insA	Frameshift	Stop at 324	E.C.	Dble mut	Risinger et al., 1997
E8	c.962insA	Frameshift	Stop at 324	E.C.	Dble mut	Risinger et al., 1998
E8	c.962insA	Frameshift	Stop at 324	E.C.	MIN	Gurin et al., 1999
E8	c.962insA	Frameshift	Stop at 324	E.C.	No LOH	Kong et al., 1997
E8	c.963delA	Frameshift	Stop at 343	E.C.	?	Risinger et al., 1997
E8	c.963delA	Frameshift	Stop at 343	E.C.	?	Risinger et al., 1998
E8	c.963delA	Frameshift	Stop at 343	E.C.	?	Risinger et al., 1998
E8	c.963delA	Frameshift	Stop at 343	E.C.	Dble mut	Risinger et al., 1998
E8	c.963delA	Frameshift	Stop at 343	E.C.	MIN	Kong et al., 1997
E8	c.963delA	Frameshift	Stop at 343	E.C.	No LOH	Kurose et al., 1998
E8	c.963delAA	Frameshift	Stop at 324	E.C.	?	Risinger et al., 1998
E8	c.966ins37	Nonsense	N323X	Glb.	?	Duerr et al., 1998
E8	c.968delA	Frameshift	Stop at 343	E.H.	?	Maxwell et al., 1998
E8	c.976del55	In-f.del+spl.		E.C.	Dble mut	Kong et al., 1997
E8	c.984del4	Frameshift	Stop at 343	E.C.	?	Risinger et al., 1997
E8	c.987del10	Frameshift	Stop at 343	B.C.	No LOH	Freihoff et al., 1999
E8	c.987del4	Frameshift	Stop at 343	E.C.	?	Risinger et al., 1997
E8	c.988delAA	Frameshift	Stop at 341	E.C.	?	Risinger et al., 1998
E8	c.992A->G	Missense	D331G	E.C.	No LOH	Lin et al., 1998
E8	c.1003C->T	Nonsense	R335X	E.C.	?	Risinger et al., 1997
E8	c.1003C->T	Nonsense	R335X	Glb.	LOH	Fults et al., 1998
E8	c.1003C->T	Nonsense	R335X	Glb.	LOH	Wang et al., 1997
E8	c.1003C->T	Nonsense	R335X	Glb.	LOH	Rasheed et al., 1997
E8	c.1004delGATA	Frameshift	Stop at 342	Glb.	?	Boström et al., 1998
E8	c.1008C->A	Nonsense	Y336X	E.C.	LOH	Kong et al., 1997
E8	c.1009delT	Frameshift	Stop at 343	E.C.	?	Risinger et al., 1997
E8	c.1011del4	Frameshift	Stop at 342	Glb.	LOH	Li J et al., 1997
E8	c.1026G->C	ms. lik. spl.	K342N	N.H.M.L.	?	Grønbæk et al., 1998
E9	c.1043C->T	Missense	T348I	A.E.H.	?	Maxwell et al., 1998
E9	c.1043insA	Frameshift	Stop at 360	E.C.	Dble mut	Risinger et al., 1997
E9	c.1121delC	Frameshift	Stop at 415	Glb.	LOH	Liu et al., 1997

(*continued*)

TABLE 2. (*Continued*)

Exon	Nucleotide change[a]	Mutation type[b]	Predicted protein or RNA change	Tumor type[c]	2nd hit[d]	Reference
E9	c.1129del4	Frameshift	Stop at 414	Glb.	LOH	Rasheed et al., 1997
E9	c.1129del4	Frameshift	Stop at 414	Glb.	LOH	Rasheed et al., 1997
E9	c.1133del4	Frameshift	Stop at 414	Glb.	LOH	Fults et al., 1998
E9	c.1154delCT	Nonsense	S385X	B.C.	?	Rhei et al., 1997
E9	c.1189C->T	Missense	H397X	G.C.G.	?	Peraud et al., 1999
E9	c.1211G->T	Ms. stop	X404L	Glb.	LOH	Zhou et al., 1999
E9	c.1212A->C	Ms. stop	X404C	Glb.	?	Tohma et al., 1998

[a]Mutations are designated according to the nomenclature of Beaudet and Tsui (1993) and Antonarakis et al. (1998). Numbering is according to the coding DNA starting at the A in the start codon.
[b]In-f. del, in frame deletion; ms.lik.spl, Missense likely Splicing; ms.stop, Missense mutation at a stop codon.
[c]A.A., anaplastic astrocytoma; A.E.H., atypical endometrial hyperplasia; B.C., breast carcinoma; F.O.C., endometrioid ovarian carcinoma; E.C., endometrial carcinoma; E.H., endometrial hyperplasia; F.T.C., follicular thyroid carcinoma; G.C.G., giant cell glioblastoma; Glb: glioblastoma; Gls, gliosarcoma; H.N.C., head and neck carcinoma; Mdb, medulloblastoma; met, metastasis; M.M., malignant melanoma; M.O.C., mucinous ovarian carcinoma; N.H.M.L., non Hodgkin Malignant Lymphoma; S.C.L.C., small cell lung; N.S.C.L.C., non small cells lung carcinoma; Odg, oligodendroglioma; P.T.C., papillary thyroid carcinoma; P.G., pediatric glioma; P.A., pilocytic astrocytoma; P.C., prostate carcinoma; R.C.C., renal cell carcinoma; T.C.L., T cell lymphoma.
[d]2nd hit, second allele status at the PTEN locus; LOH, Loss of heterozygosity; MIN, microsatellite instability; dble mut, two distinct point mutations found in the same tumor; ?, no information available.

mas in which a PTEN mutation has been found [Kong et al., 1997]. The specific defect of mismatch repair in MIN tumors is therefore likely to be responsible for the high rate of mutations found in repetitive motifs of PTEN exons 7 and 8.

CLINICAL RELEVANCE

Germline mutations of PTEN are responsible CD and BRR syndromes, two autosomal dominant conditions which share a number of clinical features such as macrocephaly and formation of multiple benign tumors that are mostly hamartoma. Affected patients are also at high risk of developing malignancies such as breast and non-medullary thyroid carcinoma, dysplastic gangliocytoma of the cerebellum, and endometrial carcinoma. It is therefore of importance to recognize individuals at risk in affected families and to recommend the surveillance for early detection of malignant tumors. Somatic PTEN mutations have been found in a large number of sporadic tumors and this gene therefore must be regarded as a particularly important tumor suppressor gene. PTEN mutations are found mainly in glioblastoma and endometrial carcinoma when the studies are restricted to tumoral tissue specimens. The question whether PTEN is inactivated by other mechanisms in tumors with low frequency of PTEN mutations remains unanswered.

TABLE 3. Tumor Types Associated With Somatic Mutations in PTEN

Tumor type	Number of cases
Endometrial carcinoma	118
Endometrial hyperplasia	18
Ovarian carcinoma	8
Mucinous type	2
Endometrioid	6
Glioblastoma	110
Giant cell glioblastoma	6
Astrocytoma	9
Anaplastic type	8
Pilocytic type	1
Other cerebral tumors	6
Prostate carcinoma	13
Breast carcinoma	6
Malignant melanoma	4
Malignant lymphoma	7
Other types of cancer	4
Total	309

FUTURE PROSPECTS

The many results obtained concerning PTEN highlight the significance of the Pi2-K/Akt pathway in embryonic development and carcinogenesis [Di Cristofano et al., 1998] which open interesting new prospects for cancer therapy research [Minaguchi et al., 1999].

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