ABSTRACT

Genetic linkage has been recently documented between a centromeric region of chromosome 10 and familial multiple endocrine neoplasia type II (MEN II). Medullary thyroid carcinoma consists of initial thyroid C-cell and adrenal chromaffin cell hyperplasia which result in multifocal medullary thyroid carcinomas and bilateral adrenal pheochromocytomas. Other hereditary cancers, such as retinoblastoma, appear to result from a series of genetic events involving, first the inheritance of a germ line abnormality, and subsequent loss of chromosome loci opposite this initial defect. In these cancers, this loss of the normal alleles in both familial and sporadic cases, is frequently manifest as a reduction to homozygosity for polymorphic DNA markers near the involved locus. It might then be expected that chromosome 10 regions would be lost with high frequency in tumor DNA from patients with MEN II and sporadic medullary thyroid carcinoma (MTC). We now demonstrate that only two of 16 MTC tumors studied by analysis of restriction fragment length polymorphisms for multiple regions of the short and long arms of chromosome 10 showed loci reduced to homozygosity. One of these tumors was from a patient with MEN II and the other from a patient with nonfamilial MTC. Importantly, no such chromosome 10 changes were noted in pheochromocytomas from the patient with MEN II or his sister. These findings strongly suggest that the sequence of genetic events for familial MTC is either different from that for retinoblastoma or that loss of normal alleles opposite the germ line genetic defect occurs by mechanisms other than gross loss of chromosomal material in MTC. A model is proposed suggesting that the mechanism involving loss of alleles opposite one another is operative in hereditary tumors, such as retinoblastoma, which do not arise within a setting of initial polyclonal cellular hyperplasia. In contrast, in tumors such as familial MTC and polyposis coli which arise as individual clones of neoplastic cells from a setting of preexistent polyclonal hyperplasia, the first genetic event may underlie hyperplasia, and additional events, frequently at other chromosomal loci, may cause individual clonal neoplasms.

INTRODUCTION

MTC is an endocrine cancer which is important in the study of mechanisms of tumor formation in humans. This tumor of the thyroid C-cell either can occur sporadically or can be inherited as an autosomal dominant trait. In the latter setting, MTC occurs as part of a MEN II or III syndrome (1, 2) which also involves adrenal pheochromocytomas and parathyroid adenomas (MEN II), or pheochromocytomas and neuromas (MEN III). Recently, restriction fragment length polymorphism linkage studies have demonstrated that the inherited genetic lesions for both MEN II (3, 4) and MEN III (5) are located near the centromere of human chromosome 10. In several heritable cancers, including retinoblastoma (6), bilateral acoustic neurofibromatosis (7, 8), and multiple endocrine neoplasia type I (9), the genetic locus linked to the disease is lost from the opposite normal allele in the tumors from patients with both the familial and sporadic forms of disease. This reduction to homozygosity has been explained by a two-hit theory of carcinogenesis (10, 11), in which both copies of a tumor suppressor gene must be inactivated before involved cells manifest any phenotypic abnormalities (reviewed in Refs. 11–14). In familial cancers, the initially inactive allele is carried as a germline defect, while the second, normal allele is inactivated in a somatic cell.

The course of development of MTC in the MEN II syndrome suggests that this tumor suppressor model may not be operative in MTC. In this syndrome, virtually all of the thyroid C-cells initially become hyperplastic (15), although only a few progress to form multifocal tumors, each of which arises from a different clone of cells (16, 17). The hyperplastic C-cells must then still be polyclonal, indicating that selection for a second rare event has not yet occurred in these cells. The hyperplasia of this entire C-cell population suggests that the germline defect on chromosome 10 in MEN II and MEN III is sufficient to dominantly confer an abnormal growth potential upon the C-cell. Subsequent genetic events necessary for frank neoplasm formation could involve the opposite normal allele or, as recent evidence has indicated in Wilms’ tumor (18, 19), other genetic loci.

If a second inactivating event at the germline locus is not necessary for formation of C-cell hyperplasia and MTC, one would predict that reduction to homozygosity for chromosome 10 might be rare in both sporadic and familial MTC. Previously, Mathew et al. (20) reported reduction to homozygosity for regions of the short arm of chromosome 1 in MTC. We now report that reduction to homozygosity for chromosome 10 regions, including those closely linked to MEN II and MEN III, in MTC tumor DNA from patients with MEN II, MEN III, and sporadic MTC is indeed an infrequent event. Furthermore, in the one MEN II patient whose MTC DNA did show reduction to homozygosity for chromosome 10, DNA from his pheochromocytoma and his affected sister’s pheochromocytoma did not have any evidence for such reduction to homozygosity. Taken together, these data support a model for development of familial MTC in which the initial germline lesion may cause C-cell hyperplasia, indicating that the mechanism for tumor development in this disease may be different from that of retinoblastoma and some other inherited cancers.

MATERIALS AND METHODS

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1 Supported by Grant PDT-207 from the American Cancer Society and funds from the Clayton Foundation.
2 To whom requests for reprints should be addressed, at The Johns Hopkins Oncology Center, 424 North Bond Street, Baltimore, MD 21231.
3 The abbreviations used are: MTC, medullary thyroid carcinoma; MEN, multiple endocrine neoplasia.
obtained and characterized as previously detailed (23–28). The polymorphisms used were: pMHZ15 (D10S17), Mspl (3.6 or 2.1 kilobases), and EcoRI (5.3 kilobases or 3.5 and 1.8 kilobases); cTBIQ4.34 (D10S34), TaqI (7.5 or 7.0 and 6.5 or 6.0 kilobases); pTBIQ163 (D10S22), Mspl (15.0, 12.0, or 8.0 kilobases); pTHH54 (D10S14), Mspl (3.7, 2.9, or 1.9 kilobases); pTHH 105.1 (D10S13), BglII (8.5 or 8.3 kilobases); pEFD75 (D10S25), TaqI (four alleles, 1.7–3.3 kilobases). For hybridizations, probes were labeled with [32P]dCTP either by nick translation or by the random priming procedure (29). Posthybridization washes were performed with 0.2× standard saline citrate (0.15 m sodium chloride:0.015 m sodium citrate, pH 7.4), 1% sodium dodecyl sulfate at 65°C and radioautograms were exposed for 1–4 days at −70°C.

RESULTS

We examined DNA from normal and MTC tissues from 16 individuals, using several previously described DNA probes, which have been localized on the short and long arms of chromosome 10 (28). We first noted reduction to homozygosity for probe pMHZ15 (D10S17), located distal to the MEN II locus in the middle of the short arm of the chromosome. Studies of a previously defined site-specific polymorphism for the enzyme Mspl, and a new polymorphism for EcoRI detected during this study (two alleles: 5.3 kilobases, or 3.5 and 1.8 kilobases; 70% and 30% incidence among a random Caucasian population, respectively) showed reduction to homozygosity in two of seven patients who were informative (heterozygous) for this locus in constitutional DNA (Fig. 1, Patients 1 and 2). One patient with this change had typical MEN II and died of widely disseminated MTC (Fig. 1, Patient 1), and one patient (Fig. 1, Patient 2) had the sporadic form of MEN II and died of widely disseminated MTC (Fig. 1, Patient 2). For Patient 2, three other chromosome 10 loci were informative, including cTBIQ7 (D10S28), which maps distal to pMHZ15, pTBIQ163 (D10S22) near the centromere and pEFD75 (D10S25) located near the telomere of the long arm. All showed reduction to homozygosity. The data are consistent with loss of all of one copy of chromosome 10 in tumor DNA from both individuals; since pMHZ15 appears to be present in two copies, this loss was probably accompanied by reduplication of the remaining copy of chromosome 10.

We also examined DNA from a pheochromocytoma from Patient 1, which developed as part of his MEN II syndrome. Importantly, this pheochromocytoma did not demonstrate the same reduction to homozygosity of any of the informative loci on chromosome 10 as did the patient’s MTC (Fig. 1B, lane 1). Similarly, a clonally derived pheochromocytoma from the patient’s sister also failed to show reduction to homozygosity for chromosome 10 (Fig. 1B, lanes 2–3). Since MTC and pheochromocytoma in the MEN II syndrome are related to the same germ line defect, this suggests that loss of the entire chromosome 10 was not required for MEN II-related tumor development in these two family members.

DISCUSSION

We have now shown that only a small percentage of patients with MTC of both the familial and sporadic forms have a loss of one copy or regional losses of chromosome 10 in tumor DNA. In the published cytogenetic studies of MTC, consisting of one MTC cell line (30) and two MTC tumors (31), one of four tumors were found to have a reduction to homozygosity for a chromosome 10 region. We have also verified the previously reported low incidence of other apparent chromosomal changes (except for chromosome 10) in MTC (20) by failing to find evidence for reduction to homozygosity in tumor DNA with probes for chromosomes 2, 6, 7, 12, 15, 17, and 22 (data not shown).

In the two patients whose MTC DNA showed reduction to homozygosity for locus D10S17 (Fig. 1, Patients 1 and 2), studies of other chromosome 10 regions indicated that an entire chromosome 10 was missing in each tumor (Table 1; examples are shown in Fig. 2). For Patient 1, two additional loci were informative. One, cTBIQ4.34 (D10S34), is near the centromere on the short arm of chromosome 10 which is tightly linked to familial MTC, and the other, pTHH54 (D10S13), is in the middle of the long arm. For Patient 2, three other chromosome 10 loci were informative, including cTBIQ7 (D10S28), which maps distal to pMHZ15, pTBIQ163 (D10S22) near the centromere and pEFD75 (D10S25) located near the telomere of the long arm. All showed reduction to homozygosity. The data are consistent with loss of all of one copy of chromosome 10 in tumor DNA from both individuals; since pMHZ15 appears to be present in two copies, this was probably accompanied by reduplication of the remaining copy of chromosome 10.

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Fig. 1. A, loss of heterozygosity for probe pMHZ15 in DNA from MTC tumor tissue from two patients with MTC. Hybridization patterns for DNA from normal lymphocytes (N) and MTC tumor (T) from seven informative patients are shown. Lanes 1, 2, Patient 1; lanes 3, 4, 16, 17, Patient 2; lanes 5, 6, Patient 5; lanes 7, 8, Patient 6; lanes 9, 10, Patient 8; lanes 11, 12, Patient 12; lanes 13, 14, Patient 13; lane 15, established MTC cell line derived from Patient 7. Lanes 1–15, Mspl restriction; lanes 16, 17, EcoRI restriction. Each of these patients is heterozygous, in the normal constitutional DNA, for an Mspl polymorphism, having both the 3.6- and 2.1-kilobase Mspl alleles. Note loss of the 2.1-kilobase allele in tumor DNA from Patient 1, and of the 3.6-kilobase allele in tumor DNA from Patient 2. Patient 2 is also heterozygous in constitutional DNA for an EcoRI polymorphism found during this study, having both a 5.3-kilobase allele and a 3.5- and 1.8-kilobase allele (lane 16). The 5.3-kilobase allele is lost in tumor DNA (lane 17). B, no loss of heterozygosity for probe pMHZ15 in DNA from pheochromocytoma tissue from Patient 1 (lane 1) and his sister (lanes 2, 3). Normal lymphocyte DNA restriction pattern for Patient 1 is shown in A, lane 1. Mspl restriction is shown. N, normal lymphocyte DNA; P, pheochromocytoma DNA.
Table 1  Summary of RFLP studies of chromosome 10 probes in normal and tumor DNA from patients with MTC

Status is given only for probes detecting a heterozygous pattern in germ line DNA.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Type of MTC</th>
<th>Clinical status</th>
<th>cTBQ7 10p</th>
<th>pMHZ15 10p</th>
<th>cTB 14.34 10 cen</th>
<th>pTB10.163 10 cen</th>
<th>pTHH54 10q</th>
<th>pTHH105.1 10q</th>
<th>pEFD75 10q ter</th>
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<tr>
<td>1</td>
<td>Familial MEN II</td>
<td>Died, disseminated tumor</td>
<td>Homozygous*</td>
<td>Homozygous*</td>
<td>Homozygous*</td>
<td>Homozygous*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sporadic</td>
<td>Mediastinal extension</td>
<td>Homozygous*</td>
<td>Homozygous*</td>
<td>Homozygous*</td>
<td>Homozygous*</td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Familial MEN II</td>
<td>Localized</td>
<td>Heterozygous</td>
<td>Heterozygous</td>
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<td>Heterozygous</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>Familial MEN II</td>
<td>Local extension</td>
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<td>Heterozygous</td>
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<tr>
<td>5</td>
<td>Familial MTC only</td>
<td>Localized</td>
<td>Heterozygous</td>
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<tr>
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<tr>
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<td>Heterozygous</td>
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<tr>
<td>8</td>
<td>MEN III</td>
<td>Alive, distant metastases</td>
<td>Heterozygous</td>
<td>Heterozygous</td>
<td>Heterozygous</td>
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<tr>
<td>9</td>
<td>MEN III</td>
<td>Died, disseminated tumor</td>
<td>Heterozygous</td>
<td>Heterozygous</td>
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<tr>
<td>10</td>
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<tr>
<td>11</td>
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<tr>
<td>13</td>
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<tr>
<td>16</td>
<td>Unknown</td>
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<td></td>
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* Region closest to MEN II locus.
* Loci reduced to homozygosity in tumor DNA.
† TT cell line (32) of MTC.

Fig. 2. Loss of heterozygosity in DNA from MTC tumor tissue from Patients 1 and 2 for additional chromosome 10 probes. Lanes 1, 2, Patient 1, probe cTB14.34; lanes 3, 4, Patient 2, probe cTBQ7; lanes 5, 6, Patient 2, probe pTB10.163; N, normal; T, tumor.

the tumors (31) appears to have an abnormality of chromosome 10, possibly involving loss of the entire chromosome. Our data now confirm, at the molecular level, that this event does occasionally occur in MTC.

Contamination of tumor tissue with normal tissue can confound results of the type of DNA studies being conducted and suggest a falsely low incidence of reduction to homozygosity for chromosomal regions in tumors. Several lines of evidence indicate that such contamination is not responsible for the low incidence of the reduction to homozygosity described above. First, save for large amounts of acellular stromal tissue, MTC and pheochromocytoma are relatively homogeneous neoplasms with respect to the neoplastic cell content. We have previously shown this to be the case in enzymatic (glucose-6-phosphate dehydrogenase) studies of tumor clonality, which include one of the pheochromocytomas analyzed in this study (16), and in recent DNA methylation studies of MTC (22). The tumor DNA samples used in the current studies have readily demonstrable hypomethylation of the calcitonin gene, relative to DNA from control normal tissues (22); we estimate that ≤20% contamination with normal cell DNA in these samples would have been evident. Second, the DNA for Patient 7 was extracted from a well-characterized cell line of MTC (32) established from a patient with very aggressive, sporadic tumor. The DNA in this cell line is clearly heterozygous for multiple loci on chromosome 10 (Fig. 1, lane 15, and Table 1, Patient 7), indicating retention of both copies of chromosome 10 in the tumor cells. Therefore, it is likely that the low incidence of only 12.5% for
reduction to homozygosity in the present study represents the fact that a structural loss of the chromosome 10 regions studied is infrequent in MTC.

The low incidence for reduction to homozygosity for chromosome 10 in MTC tissues is similar to recent data for familial polyposis. This inherited disorder involves the formation of multiple clonal colonic polyps with an extremely high predisposition to malignant transformation. Restriction fragment length polymorphism studies show linkage of familial polyposis to chromosome 5 (33). However, reduction to homozygosity for these chromosome 5 regions in DNA from small adenomas in patients with familial polyposis was not observed, although in DNA from latter stage colonic cancers deriving directly from familial polyps, or from sporadic colonic carcinoma, this reduction to homozygosity could be shown in 20–36% of the neoplasms (34, 35).

In familial MTC, and in familial polyposis, as opposed to retinoblastoma, the failure to find a high incidence for structural alterations in the chromosome regions directly linked to germ line abnormalities could relate to alternative proposed mechanisms of multihit carcinogenesis, two of which we discuss here and diagram in Fig. 3.

As one alternative, the low incidence of reduction to homozygosity we have observed in MTC may still be consistent with a mechanism similar to the recessive tumor gene loss (Fig. 3A) proposed for other hereditary cancers not involving hyperplasia, such as retinoblastoma (10–12). This recessive oncogene hypothesis assumes that the germ line event involves inactivation of expression of one allele of a tumor suppressor gene, and phenotypic abnormalities are not manifest until a structural alteration occurs in the opposite allele via chromosome loss, deletion, recombination events, or other mechanisms (Fig. 3A).

We have not found, in the present study, frequent evidence for such structural changes of the germ line locus for MTC. Perhaps, loss of the opposite normal allele occurs by means not involving structural alterations of large regions of chromosome 10. Particularly since the MEN II germ line lesion has been mapped to a region near the centromere of chromosome 10, it may be difficult to delete this locus without losing the entire chromosome. Moreover, if two copies of another locus on chromosome 10 were necessary for cell survival, then loss of a copy of the MEN II locus by either recombination or nondisjunction, scoring as reduction to homozygosity, would be a rare event. The second event for gene inactivation in MTC might instead involve mechanisms other than mitotic nondisjunction, loss/reduplication, or large deletions which are readily detectable as a reduction to homozygosity. Small deletions or point mutations, which are difficult or impossible to detect by this means, may be the mechanisms commonly responsible for gene inactivation of the region allelic to the germ line defect on chromosome 10, in the majority of patients with MTC. Only occasionally, as in the two cases we describe, might the change involve an alteration which is large enough, such as the loss of the whole chromosome, that the currently available probes easily detect the structural change.

An alternative explanation for our findings should be given serious consideration (Fig. 3B). The recessive nature of the germ line defect proposed for hereditary human tumors such as retinoblastoma and bilateral acoustic neurofibromatosis (Fig. 3A) might not be operative in MTC and polyposis coli. Instead, in familial polyposis (14, 33, 35), it has been hypothesized that the first germ line chromosomal abnormality may have phenotypic consequences such as hyperplastic growth (Fig. 3B). Indeed, the colonic epithelium of familial polyposis patients does often exhibit widespread mitotic abnormalities (36, 37) and it also has uniform metabolic abnormalities including increased levels of ornithine decarboxylase, an enzyme associated with increased growth potential (38). The subsequent events which result in formation of clonal colonic polyps (35, 39) and/or the full malignant phenotype would then not involve the second copy of the inherited tumor gene, and this would explain failure to find, in tumor DNA, a high incidence of reduction to homozygosity for the chromosome 5 locus closely linked to familial polyposis coli, or the chromosome 10 locus linked to familial MTC.

Several aspects of the development of familial MTC suggest that the above hypothesis may be especially attractive. In patients with familial MTC, there is initially a well-described setting of generalized thyroid C-cell and adrenal chromaffin cell hyperplasia. This suggests that the precursors to the C-cells and adrenal chromaffin cells all may have sustained a growth-promoting lesion before formation of clonal neoplasms, and this lesion is very likely the inherited germ line defect on one allele on chromosome 10. This single allelic change, alone, could be responsible for the generalized thyroid C-cell and adrenal chromaffin cell hyperplasia. It is presumed that some of these cells subsequently give rise to MTC and pheochromocytomas. In such patients, the multifocal carcinomas that arise in the thyroid are clonal, but each tumor derives from a different cell clone (17). Similarly, the benign pheochromocytomas are clonal (16). These findings strongly suggest that the preceding hyperplasia is a polyclonal event and that further somatic changes are necessary for tumor development. These subsequent events could well be at loci other than chromosome 10, such as the frequently seen reduction to homozygosity for chromosome 1 (20), which may underly clonal evolution of MTC and pheochromocytoma.

If a single event at one germ line region may have the

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Fig. 3. Two models for "two hit" development of hereditary cancers. A, both hits occur at the same locus, inactivating a tumor suppressor gene. This model, reviewed in Refs. 11-14, predicts that the first-inactivated allele will have no phenotypic consequences as long as the second allele is active. Inactivation of the second allele results in clonal tumorigenesis. In familial cases, the first hit is carried as a germ line abnormality, while in sporadic cases, other hits occur in somatic cells. When the second hit results from loss of substantial chromosomal material, the tumor DNA will exhibit reduction to homozygosity at the genetically linked locus. B, the second hit(s) occurs at another locus. In this model, encompassing points made in Refs. 14, 33, and 35 and by our present data, the first hit, which can be carried as a germ line abnormality, dominantly results either in a predisposition to, or actual, hyperplastic growth of target tissue. The second hit(s) can either be a further dominant mutation at the other allele of the germ line defect or elsewhere, or it can be a recessive mutation elsewhere in the genome, resulting in inactivation of a tumor suppressor gene and development of a clonal tumor. If the second hit(s) represents a recessive mutation, it can be manifested as a reduction to homozygosity of a site disparate from the germ line defect. This model is proposed for MTC and is consistent with current data for Wilms' tumor and polyposis coli.
phenotypic consequence of hyperplastic growth, while subsequent events at the same or, commonly, at different chromosomal loci lead to frank neoplasia, then the above series of genetic events may also be operative in the development of some forms of Wilms' tumor. In Wilms' tumor, reduction to homozygosity is often found for markers near chromosome band 11p13 (40-43), but recently two groups have reported that the hereditary form of Wilms' tumor is not linked to this locus (18, 19). In some, although not all, cases of hereditary Wilms' tumor, there is a widespread hyperplasia of the kidney (44, 45) which may result directly from the initial germ line abnormality.

Two caveats must be considered to the above theory. First, another familial MEN syndrome, MEN I (tumors of pituitary, parathyroid, and pancreatic islet cells), which has a generalized hyperplastic phase (46), has been linked to chromosome 11 (9). In that study, the pancreatic tumors in three patients did show reduction to homozygosity for chromosome 11. Furthermore, it is mentioned in that study that one pancreatic islet hyperplasia tissue showed the same change. However, it is possible that, in MEN I, the second event may be a recessive change at a locus other than the germ line defect on chromosome 11. chromosome 11 frequently shows reduction to homozygosity (40-43, 47, 48) or cytogenetic changes (49, 50) in multiple types of human cancers and may be the site of a general tumor suppressor gene (51, 52). Also, much further study of all the lesions in MEN I and of islet cell hyperplasia is needed to comment fully on this syndrome.

Our current findings in MTC and those discussed above for other heritable tumors, emphasize the need to search for the multiple mechanisms which may underly neoplastic transformation. Further resolution of the precise interpretation of our other heritable tumors, emphasize the need to search for the multiple mechanisms which may underly neoplastic transformation. Further resolution of the precise interpretation of our and parathyroid disease. Ann. Intern. Med., 78:561-579, 1973.


CHROMOSOME 10 LOSS IN MTC

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Low Incidence of Loss of Chromosome 10 in Sporadic and Hereditary Human Medullary Thyroid Carcinoma

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