

# Multiple Endocrine Neoplasia Type I and Lipomas

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**M**ultiple endocrine neoplasia type 1 (MEN 1) is characterized by the frequent occurrence of parathyroid and pancreatic islet cell tumors and the less frequent occurrence of tumors of the anterior pituitary gland.<sup>1</sup> Other neoplasms, such as carcinoid tumors, also can occur in patients with familial MEN 1, but even less frequently than do pituitary tumors.<sup>1</sup> Patients with MEN 1 exhibit a variety of cutaneous findings, including multiple facial angiofibromas, collagenomas, café au lait macules, confetti-like hypopigmentation, multiple gingival papules, and lipomas.<sup>2</sup> Lipomas, both cutaneous and visceral, have been noted to occur in a relatively high proportion of patients with MEN 1.<sup>3,4</sup>

This article explores the relationship between lipomas and MEN 1. First, the history and genetic basis of MEN 1 and the epidemiology of lipomas are discussed. A subsequent literature review considers whether the occurrence of lipomas has any genetic link to MEN 1 and any relationship to the loss of the wild-type allele observed in the disorder. A review of the existing literature on MEN 1 and lipomas will be presented to help elucidate the latter points.

## HISTORY AND GENETIC BASIS OF MEN 1

MEN 1 is an autosomal dominant disorder in which tumors characteristically develop in the parathyroid glands, endocrine pancreas, and anterior pituitary gland.<sup>1,5</sup> In 1903, Erdheim<sup>6</sup> was the first to report an association between tumors of the pituitary and parathyroid glands. Cushing and Davidoff<sup>7</sup> later described a patient who, in addition to tumors of these glands, also had a pancreatic islet cell tumor. In 1954, Wermer<sup>8</sup> recognized that the disorder causing such tumors was familial in origin and was transmitted in an autosomal dominant fashion, with high penetrance.

In 1988, Larsson and colleagues<sup>9</sup> used genetic linkage analysis to localize the MEN 1 gene (*MEN1*) to chromosome 11, specifically to band 11q13. Genetic linkage analysis exploits the tendency of genes that lie close together on a chromosome to be associated in inheri-

tance. *MEN1*, which shows tight linkage with the human muscle phosphorylase gene, has recently been cloned.<sup>10</sup> Identified by positional cloning, *MEN1* contains 10 exons and encodes a ubiquitously expressed 2.8 kilobase transcript. The 610 amino acid protein product is termed *menin*,<sup>10</sup> although its function is still unknown.

Gene deletions have been implicated as the ultimate event in oncogenesis of inherited neoplasia. According to the 2-mutation model, an inherited tumor results from the unmasking of a recessive mutation at the disease locus. In such a circumstance, affected persons have inherited an altered copy of the causative gene from an affected parent, but the resultant tumors have lost the remaining copy (the wild-type allele) as a somatic event. Thus, the inheritance pattern is dominant, but the mechanism of tumorigenesis is recessive. The first mutation is carried in the germline and predisposes to neoplasia, whereas a second somatic event serves to eliminate the remaining wild-type allele at this locus, a process termed *loss of heterozygosity* (LOH). The occurrence of 2 somatic mutations or deletions at the same locus results in a sporadic tumor. The mutations can take many forms (eg, frameshift, nonsense, missense, deletion). The vast majority of, if not all, tumors in patients with MEN 1 are characterized by 2 genetic hits (consistent with the retinoblastoma 2-hit model for tumor suppressor genes<sup>11</sup>): a germline mutation of the MEN 1 tumor suppressor gene combines with an allelic deletion of the corresponding wild-type allele.<sup>10</sup>

MEN 1 typically involves germline mutation of chromosome 11, and LOH at chromosome band 11q13 involving the wild-type allele leads to the phenotypic manifestations of the syndrome. The extent of chromosome loss at band 11q13 associated with LOH can vary in different tumors from the same patient.<sup>12,13</sup> This variation

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**Table 1.** Published Incidence of Lipomas in Patients with Familial Multiple Endocrine Neoplasia Type 1

Source	Incidence (%)	Number of Patients Studied
Darling et al <sup>2</sup>	34	32
Metz et al <sup>1*</sup>	20	NA
Ballard et al <sup>3</sup>	13	85
Yoshimoto et al <sup>4</sup>	5	106

NA = not available.

\*Secondary source.

is consistent with tumorigenesis, reflecting independent somatic events in separate lesions from the same patient.<sup>14</sup>

Beckers and colleagues<sup>12</sup> performed LOH studies of chromosome 11 in different pathologic tissues of a patient with MEN 1. Allelic loss of chromosome 11 was detected in several tumors, but the chromosomal regions of LOH were different, suggesting that different somatic mutational events are involved in the pathogenesis of these tumors. Allelic loss of chromosome 11 has also been shown to occur in sporadic tumors related to familial MEN 1.<sup>15,16</sup> Thus, based on the LOH for polymorphic markers at chromosome band 11q13 in typical MEN 1 tumors from pancreatic islet cells<sup>9,15,17-20</sup> and parathyroid glands,<sup>12,16-18,21,22</sup> *MEN1* is thought to be a tumor suppressor gene.

### EPIDEMIOLOGY OF LIPOMAS

Lipomas are the most frequent and ubiquitous benign mesenchymal tumor in the adult population.<sup>23-25</sup> In contrast, lipomas account for less than 10% of soft-tissue lesions in the first 2 decades of life.<sup>26,27</sup> Most lipomas become apparent in patients age 40 to 60 years. Statistics about gender incidence vary. Brasfield and DasGupta reported that approximately 90% of patients affected by ordinary lipomas are women.<sup>28</sup> Multiple lipomas, on the other hand, have a male preponderance of 3:1.<sup>29</sup> Moreover, 7% of patients with lipomas have multiple lesions.<sup>29</sup>

In addition to their widely recognized association with MEN 1, lipomas typically occur in conditions such as familial multiple lipomas, Madelung's disease, Dercum's disease, congenital lipomatosis, proteus syndrome, encephalocraniocutaneous lipomatosis, Bannayan-Riley-Ruvalcaba syndrome, Fröhlich's syndrome and Gardner's syndrome.<sup>23,30</sup> The lipomas in MEN 1 can occur anywhere, are often multiple, can be small or large, and are sometimes cosmetically disturb-

ing. When removed, lipomas typically do not recur. Large visceral lipomas are occasionally noted incidental to abdominal imaging or at laparotomy.

### LITERATURE REVIEW

A review of the existing literature indicates that not all patients with MEN 1 (or family members with the MEN 1 gene) have lipomas. Less clear is the actual number of MEN 1 patients who do have such tumors, with several studies reporting varying percentages (Table 1).

Another question that various studies have examined is whether genetic chromosomal abnormalities similar to those responsible for MEN 1 cause lipomas and other lipomatous tumors. In a published report from 1995 by the Chromosomes and Morphology Collaborative Study Group (Table 2), Fletcher and colleagues<sup>31</sup> identified clonal chromosomal abnormalities in 149 of 178 (84%) lipomatous neoplasms; to a large extent, the karyotype correlated with the morphologic diagnosis.

Vortmeyer and colleagues<sup>32</sup> extracted DNA of 2 lipoma patients with known MEN 1 gene germline mutation and compared it with normal cellular DNA. In the DNA of both patients, the authors revealed loss of the MEN 1 allele, confirming their findings by fluorescence in situ hybridization (FISH) analysis. They further investigated the role of the MEN 1 gene in sporadic lipomas. The DNA of 6 sporadic lipomas was analyzed; in 1 case they detected a 4-nucleotide deletion in exon 2 of the MEN 1 gene. This study concluded that MEN 1 gene mutation might play a role in the development of not only MEN 1-associated lipomas but also sporadic lipomas. Similar studies of patients with MEN 1 have demonstrated that these lipomas are affected by allelic loss on chromosome band 11q13 in 1 out of 6 lipomas,<sup>33</sup> 1 out of 2 lipomas,<sup>14</sup> and 1 out of 1 lipoma, respectively.<sup>34</sup> A very recent study published by Schulte et al<sup>35</sup> analyzed the DNA of 2 patients with lipomas by complete direct DNA sequencing of all coding exons and splice junctions of the MEN 1 gene. No mutation was identified in the coding exons of *MEN1*.

Gisselsson and colleagues<sup>36</sup> used metaphase FISH analysis to show aberrations of chromosome band 11q13 in 5 cases of hibernomas. They further argued that, although hibernomas and MEN 1-associated endocrine tumors show the same chromosomal patterns, they progress along separate routes of tumorigenesis.

### CONCLUSION

A review of the current literature suggests that clonal chromosomal abnormalities are the root cause of lipomatous tumors, but the genetic basis for the formation of multiple lipomas in patients with MEN 1 has yet

**Table 2.** Incidence of Chromosomal Abnormalities in Lipomatous Neoplasms

Type of Lipoma	Number of Abnormalities	Chromosomal Abnormality Present	Chromosomal Abnormality Absent	Chromosomal Aberration	Incidence (%)
All lipomas	178	149	29	Varied	84
Subcutaneous and intramuscular lipomas	93	74	19	Aberrations in 12q, 6p, 13q	80
Atypical lipomas	37*	29*	8	Ring chromosomes	78
Myxoid liposarcomas	27	26	1	t(12;16)	96
Spindle cell and pleomorphic lipomas	8	7	1	Loss of 16q13	87
Lipoblastomas	3	3	0	8q11→13	100
Hibernomas	2	2	0	11q13, 10q22	100

Data from Fletcher et al.<sup>31</sup>

\*Includes 5 dedifferentiated tumors.

to be conclusively established. Detection of LOH in chromosome band 11q13 in lipomas is consistent with these lesions being an integral feature of the MEN 1 phenotype and possibly also having a tumor suppressor gene pathogenesis. LOH has been observed in all patients studied who have lipomas; in those patients whose lipomas did not exhibit LOH, LOH involving the wild-type allele was seen in other lesions.

Because none of these studies has provided a final answer, the relationship between lipomas and MEN 1 remains a riddle. The possibility remains that the lesions could arise through a completely independent mechanism not involving the MEN 1 gene on chromosome band 11q13 and that their occurrence in patients with familial MEN 1 is purely coincidental. Further studies are necessary to solve the riddle once and for all. The new advances occurring in the world of genetics, especially the breakthroughs coming from the human genome project, may soon provide more answers. **HP**

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