

Familial Multiple Lipomatosis: Report of a New Family

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GOAL

To understand familial multiple lipomatosis (FML) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the differences between FML and multiple symmetric lipomatosis.
2. Discuss karyotypic analysis of lipomas.
3. Identify clinical characteristics of lipomas in FML.

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Familial multiple lipomatosis (FML) is a rare entity. We report a family with this disease. Karyotypic analysis was performed on tissue isolated from excised lipomas and peripheral blood. No chromosomal abnormalities were found. This is the first report of karyotypic analysis of lipomas removed from a patient with FML. The finding of a normal karyotype is important because approximately 25% of spontaneous lipomas will have abnormal karyotypes; therefore, we felt there was

a significant probability that familial lipomas in FML would have abnormal karyotypes.

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The lipoma is the most common type of soft tissue tumor. With an annual incidence of 0.21% in the general population, lipomas comprise approximately one half of all benign soft tissue tumors.^{1,2} Although most lipomas are sporadic, 2 rare distinct familial types of lipomatosis have been identified: familial multiple lipomatosis (FML) and multiple symmetric lipomatosis (MSL)(also known as Madelung disease). Clinically, the most prominent difference between these 2 types of lipomatosis is that FML is marked by discrete lipomas that predominate on the extremities and generally are absent from the neck and shoulders, and MSL is distinguished by

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Comparison of Familial Multiple Lipomatosis and Multiple Symmetric Lipomatosis

	Familial Multiple Lipomatosis	Multiple Symmetric Lipomatosis
Age of onset	Usually third to fifth decades	Middle age
Sex	Controversial, with possible male predominance	Male-female ratio is 4:1
Heredity	Always hereditary; usually autosomal dominant	Usually not hereditary; some familial cases
Distribution	Forearms, thighs, trunk; spares neck and shoulders	Shoulders, neck, head, proximal upper extremity
Tumor morphology	Discrete, mobile, fibrous capsule	Nonencapsulated, diffuse, may infiltrate deep tissue
Associated conditions	None consistent	Alcoholism

Data from Gorlin.³

nonencapsulated diffuse lipomatous infiltration of underlying tissue that often is most prominent in the neck and shoulder regions (Table).³

Historically, Brodie⁴ first reported *lipomatose circumscribe multiple*, currently known as FML, in 1846. In a 1937 case study, Murchinson,⁵ described symptoms of what would later be recognized as FML. In 1891, Blaschko⁶ noted the hereditary aspect of the disease and initially proposed that males were more prone to the disease than females.

Madelung⁷ was the first to describe the symptoms of MSL in 1888 by studying the disease in men who worked in a brewery. He noted the nonencapsulated nature of his variation of familial lipomas. In 1898, Launois and Bensusade⁸ first used the term MSL to describe the vague characteristics of Madelung disease. In 1970, Das Gupta⁹ definitively divided benign fatty tumors into 3 main categories: solitary/ sporadic lipomas, FML, and MSL.

Case Reports

We present a family with FML with 7 affected members in 4 generations (Figure 1). Two of the affected family members are alive today and were examined at the University of Pittsburgh Department of Dermatology. The information about the other 5 members was collected by anamnestic family reports and photographs.

The proband was an otherwise healthy 47-year-old man with a medical history significant for ulcerative colitis and hypothyroidism. He recalled developing his first lipoma in his late 20s

on his forearm, and lipomas later developed symmetrically on his upper arm, trunk, and thighs. The man did not smoke or drink alcohol. A review of systems was otherwise unremarkable.

The proband's mother was a healthy 69-year-old woman with a medical history significant for hypertension, hyperthyroidism (treated with ablation and now requiring thyroid replacement), and multiple uterine leiomyomas leading to a hysterectomy when she was 41 years old. She recalled developing her first lipoma on her forearm when she was 22 years old, and lipomas later developed on the upper arm, trunk, and thighs. The woman did not smoke or drink alcohol. A review of systems was otherwise unremarkable.

Findings from a physical examination revealed that both patients were well-nourished white individuals with multiple lipomas on their upper and lower arms, trunk, and thighs. The neck and shoulders were spared in both patients. The lipomas ranged from pea sized to approximately 5 cm in diameter and were clinically typical for lipomas (Figure 2).

Three lipomas were removed from the proband and bisected. One half of each lipoma was sent for routine histologic testing to confirm the clinical diagnosis of lipoma. The other half was submitted for cytogenetic analysis.

Cytogenetic analysis was performed using the standard protocol at our institution. Briefly, minced tumor tissue was dissociated with trypsin and

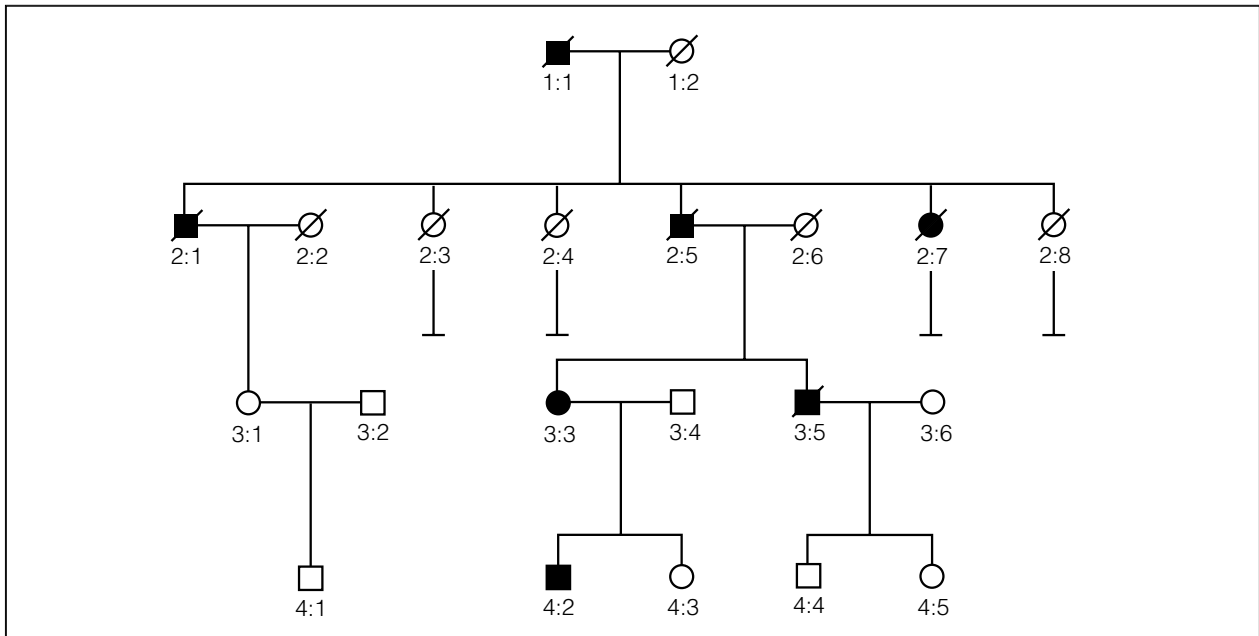


Figure 1. Pedigree of a family with familial multiple lipomatosis. Individuals 2:3, 2:4, and 2:8 were killed in war before reaching the fifth decade of life, prior to when lipomas are definitely expected in FML, and it is therefore unknown if they were affected. Individual 4:2 is the proband, and karyotypic analysis was performed on lipoma tissue and peripheral blood collected from this patient. Karyotypic analysis also was performed on blood collected from individual 3:3. Strikethrough indicates deceased; ■, affected male; ○, unaffected female; ●, affected female; □, unaffected male.

collagenase. The dissociated cells were cultured on coverslips for 5 to 6 days and harvested for chromosome analysis. In addition, peripheral blood samples from the proband and the proband's mother were set up for chromosome analysis to get the constitutional karyotypes. Metaphase cells were arrested with Colcemid[®], treated with a hypotonic solution of 0.07 mol/L potassium chloride, and fixed with a glacial acetic acid-methanol solution. G band metaphases were analyzed using an image analysis system.

Both peripheral blood and all 3 lipomas removed from the proband yielded normal 46,XY identical karyotypes. Peripheral blood from the proband's mother yielded a normal 46,XX karyotype. Routine histologic findings supported the clinical diagnosis of lipoma.

Comment

We report the first karyotypic analysis of lipomas removed from a patient with FML. No karyotypic abnormalities were detected, which is significant because karyotypic abnormalities are common in sporadic lipomas, and information about karyotypic abnormalities in familial lipomas has been lacking.

Appearing in 0.002% of the general population (1:50,000), FML is a rare disease. In fact, in 1933, Cockayne¹⁰ could find no more than a dozen reported families with FML.

The number, distribution, and clinical appearance of the lipomas in FML do not allow distinction from sporadic multiple lipomas in a single patient. Instead, eliciting a family history consistent with autosomal-dominant inheritance is the key step in separating this entity from multiple sporadic lipomas.

Lipomas in FML begin to appear during the third decade of life and may continue to develop through the fifth decade of life. Lipomas generally are restricted to the arms, lower trunk, and thighs, and are asymptomatic. Patient concerns with FML usually are cosmetic.

Although generally considered to be an autosomal-dominant inherited disease, the manner of FML inheritance has been highly disputed. Many authors have reported that FML is inherited in an autosomal-dominant pattern through a single gene and rarely is present in a particular family for more than 3 generations.^{1,3,11-14} However, many other authors disagree. Humphrey and Kingsley,¹⁵ for example, asserted that FML is passed through 2 distinct autosomal-dominant genes.⁶ Similarly, Rabbiosi et al¹⁶ proposed that FML is polygenic in origin, with no single mode of hereditary transmission. Finally, Ersek et al¹⁷ stated that FML is not passed through simple dominant or recessive genes, and the authors entertained the possibility of it being a sex-linked disease, affected by numerous ancillary



Figure 2. Representative lipomas on the right forearm of the proband's mother (A) and the left forearm of the proband (B).

variables. The pedigree of the family reported in our case is consistent with simple autosomal-dominant transmission.

Many authors state that the male-female ratio of FML is 2:1.^{1,13,15,16,18,19} Some of these statements are based on previous papers and are not supported by independent data. The validity of this ratio remains unknown.¹⁵ Other authors question the validity of the 2:1 ratio and report no gender prevalence in their case studies.^{11,12,20}

In general, lipoma tissue differs from ordinary adipose tissue in that higher citrate levels result in the loss of inhibition of lipoma phosphofructokinase, leading to continued lipid storage within the lipomas, regardless of the metabolic state of the individual.²¹ Thus, emaciated patients will note that even though they abstain from eating food, and even starve, the lipomas continue to grow.²¹ The pattern of growth usually encompasses a period of rapid developmental growth, finally stabilizing at the maximal mature size.

Genetics—Several cytogenetic studies have demonstrated a nonrandom association between

rearrangements of bands 12q13-15 or 6p21 and a variety of benign tumors, mainly of mesenchymal origin, including lipomas.²²⁻³⁰ Chromosome 12, in fact, is the most commonly abnormal chromosome on karyotypic analyses of sporadic lipomas, with up to 25% of lipomas showing aberrations.²² These data suggest that genes playing critical roles in these tumors are located in 12q13-15 and 6p21, and these genes have since been identified as the high-mobility group A2 (*HMGA2*) gene and the *HMGA1* family of genes, respectively. Multiple lines of evidence have demonstrated that truncations in *HMGA2* and *HMGA1* genes are sufficient to cause lipoma development.³¹⁻³³ Alternatively, the *CHOP* gene, which maps to the same region in 12q13-15, is not affected in benign tumors but is frequently rearranged in myxoid liposarcoma.^{22,34,35}

The *HMGA1* and *HMGA2* proteins both contain AT-rich DNA-binding domains and an acidic C-terminal domain. These proteins are involved in binding and modifying DNA structure to allow recruitment of transcription factors and binding of other proteins, thus facilitating DNA-protein

interactions.^{22,36,37} HMGA gene products are important during growth and development and are mainly expressed in undifferentiated and proliferating cells. HMGA2 truncation, in fact, has been reported to cause multiple anomalies, among which multiple lipomas are included.³⁸

Although the results of many studies have shown translocations that involve the aforementioned regions and genes in sporadic lipomas,²²⁻²⁹ there has been no evidence that these regions are involved in FML. We performed karyotypic analysis of the current family to determine if any of the common karyotypic abnormalities found in sporadic lipomas were reproducibly found in the lipomas of the proband. We did not detect any karyotypic abnormalities.

Conclusion

FML is a rare autosomal-dominant inherited disease. Although much is known of the genetic abnormalities of sporadic lipomas, the specific germ line genetic abnormality responsible for FML is unknown. It also is not known if the same genetic abnormality is present in all families affected by FML or if different genetic abnormalities produce the same phenotype in different families. We had anticipated that there may have been a consistent karyotypic abnormality in all of the lipomas of a given patient affected with FML; however, this was not the case in our patient because the 3 lipomas removed had normal karyotypes. Future work, including sequencing of the 12q13-15 and 6p21 regions in families affected with FML hopefully will allow further characterization of the specific responsible genetic lesion or lesions.

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