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► **To cite this version:**

Hippolyte Dupuis, Madleen Lemaitre, Arnaud Jannin, Claire Douillard, Espiard Stephanie, et al.. Lipomatoses. *Annales d'Endocrinologie = Annals of Endocrinology*, 2024, *Ann Endocrinol (Paris)*, 85 (3), pp.231-247. 10.1016/j.ando.2024.05.003 . hal-04636490

HAL Id: hal-04636490

<https://hal.univ-lille.fr/hal-04636490>

Submitted on 5 Jul 2024

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Original article

Lipomatoses

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INFO ARTICLE

Keywords :

Lipomatosis
Lipomas
Dercum disease
Madelung disease
Launois-Bensaude
Angiolipomatosis
Lipedema
Hibernoma
Proteus and Cowden syndromes
LMNA
MEN1
PIK3CA
MERFF
NF1

Mots clés :

Lipomatoses
Lipomes
Maladie de Dercum
Maladie de Madelung
Launois-Bensaude
Angiolipomatose
Lipoedeme
Hibernome
Syndrome de Protée
Syndrome de Cowden
LMNA
MEN1
PIK3CA
MERFF
NF1

ABSTRACT

Lipomatoses are benign proliferation of adipose tissue. Lipomas (benign fat tumors) are the most common component of lipomatosis. They may be unique or multiple, encapsulated or not, subcutaneous or sometimes visceral. In some cases, they form large areas of non-encapsulated fat hypertrophy, with a variable degree of fibrosis. They can develop despite the absence of obesity. They may be familial or acquired. At difference with lipodystrophy syndromes, they are not associated with lipoatrophy areas, except in some rare cases such as type 2 familial partial lipodystrophy syndromes (FPLD2). Their metabolic impact is variable in part depending on associated obesity. They may have functional or aesthetic consequences. Lipomatosis may be isolated, be part of a syndrome, or may be visceral. Isolated lipomatoses include multiple symmetrical lipomatosis (Madelung disease or Launois-Bensaude syndrome), familial multiple lipomatosis, the painful Dercum's disease also called Adiposis Dolorosa or Ander syndrome, mesosomatic lipomatosis also called Roch-Leri lipomatosis, familial angiolipomatosis, lipedema and hibernomas. Syndromic lipomatoses include *PIK3CA*-related disorders, Cowden/*PTEN* hamartomas-tumor syndrome, some lipodystrophy syndromes, and mitochondrial diseases, especially MERRF, multiple endocrine neoplasia type 1, neurofibromatosis type 1, Wilson disease, Pai or Haberland syndromes. Finally, visceral lipomatoses have been reported in numerous organs and sites: pancreatic, adrenal, abdominal, epidural, mediastinal, epicardial... The aim of this review is to present the main types of lipomatosis and their physiopathological component, when it is known.

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1. Introduction

Lipomatoses are characterized by abnormal localized fat hypertrophy, without lipoatrophy, usually benign and with most of the time, typical distribution patterns. Lipomas (benign fat tumors, from Greek *lipos* = fat and *-oma* = tumor) are the most common component of lipomatoses but are sometimes considered a different

entity when they are circumscribed [1]. Indeed, lipomatosis develop diffusely and are not surrounded by a fibrous pseudo-capsule, forming in some cases large areas of fat hypertrophy, whereas lipomas may be encapsulated or not. They can grow despite the lack of obesity. Because of the absence of lipoatrophy, lipomatoses are generally distinguished from lipodystrophy syndromes, which are characterized by limited capacity of subcutaneous adipose tis-

Abbreviations: ALT/WDLs, atypical lipomatous tumor/well differentiated lipo-

sarcoma

<https://doi.org/10.1016/j.ando.2024.05.003>

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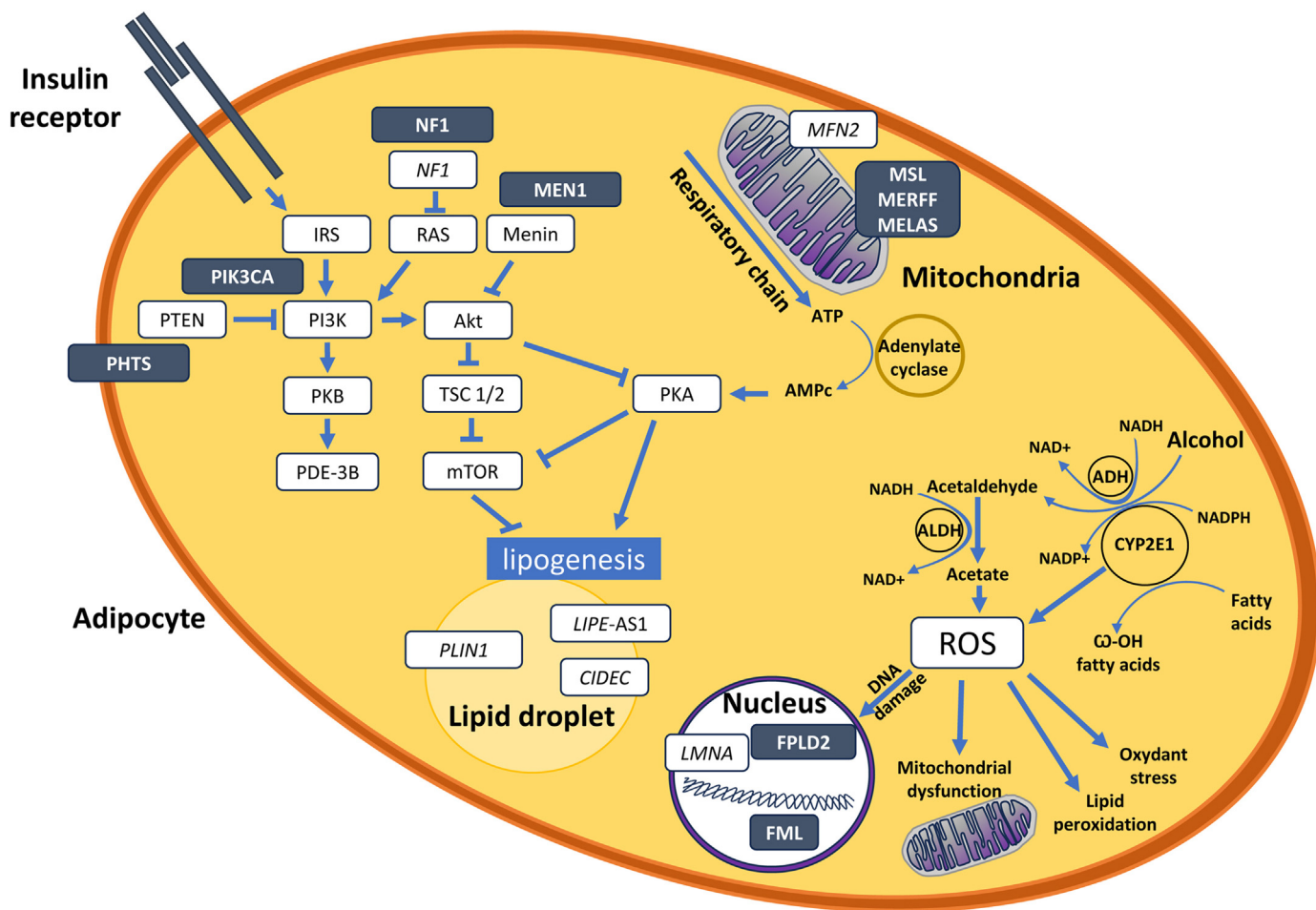


Fig. 1. Main physiopathological pathways involved in lipomatoses.

sue to store triglycerides causing notable metabolic abnormalities (insulin-resistance with diabetes, hypertriglyceridemia, fatty liver disease. . .) [2–4]. The degree of insulin resistance in lipomatosis is

- CFRD, cystic fibrosis related diabetes
- CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
- DC, Dercum’s disease
- ECCL, encephalocraniocutaneous lipomatosis
- FAO, fibroadipose hyperplasia or overgrowth
- FIB4, fibrosis 4 score
- FIL, fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis
- FML, familial multiple lipomatosis
- FPLD, familial partial lipodystrophy syndrome
- HHML, hemihyperplasia multiple lipomatosis
- KTS, Klippel-Trenaunay syndrome
- LIPE, lipase E
- LON, lipomatosis of nerve
- MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
- MEN1, multiple endocrine neoplasia type 1
- MERRF, myoclonus epilepsy with ragged-red fibers syndrome
- MRI, magnetic resonance imaging
- MSL, multiple symmetrical lipomatosis
- NF1, neurofibromatosis type 1
- PNDS, Programme National de Diagnostic et de Soins meaning National Program for Diagnosis and Care
- PHTS, PTEN hamartoma tumor syndrome
- VFA/TFA, visceral abdominal fat/total abdominal fat.

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generally moderate, since there is no lipotrophy, so no limitation of fat storage. Most of the time, metabolic syndrome is correlated to the degree of associated obesity. The impact of lipomatosis on quality of life is variable: lipomas may remain unnoticed, or induce functional discomfort to move, to dress or even to breathe, besides aesthetic and social consequences. Lipomatosis and their frontiers with obesity and lipodystrophy syndromes are sometimes difficult to define.

The prevalence of lipomas is estimated around 2 per 1000 people, but these tumors are likely underreported because they often are asymptomatic. Moreover, the definition of lipomatosis is larger than only lipomas. Considered as usually benign, and also due to their heterogeneity, lipomatosis have raised little scientific interest until recently (around 30 yearly references in Pubmed in 1975, 140 currently), whereas the number increased from 127 in 1975 to 551 in 2023 for “lipoma”.

Knowledge concerning their pathological mechanisms will be reviewed when known for each entity, followed by a synthesis in section VII (Fig. 1).

The treatment, which will not be fully detailed, remains symptomatic in most cases (plastic surgery, liposuction, lipolysis, cryotherapy, analgesic therapy) associated to treatment of metabolic syndrome if present. Weight loss may improve symptoms especially in isolated lipomatosis but standard weight loss approaches, including lifestyle (diet, exercise), pharmacologic therapy, and even bariatric surgery, may be a failure due to tissue fibrosis. When an underlying mechanism has been identified, targeted treatments are indicated for each entity in the next sections.

Table 1
Classification of lipomatoses.

Isolated lipomatosis	Syndromic lipomatosis	Visceral lipomatosis
<ul style="list-style-type: none"> –Multiple symmetric lipomatosis or Madelung disease or Launois-Bensaude syndrome –Familial multiple lipomatosis –Dercum's disease or <i>Adiposis dolorosa</i> or Ander syndrome –Mesosomatic (Roch-Leri) lipomatosis 	<ul style="list-style-type: none"> –PIK3CA-related disorders (PRO, Proteus syndrome) –Cowden/PTEN hamartoma syndrome –Familial Partial lipodystrophy syndrome –Mitochondriopathies (MERRF, MELAS) 	<ul style="list-style-type: none"> –Pancreatic lipomatosis –Adrenal and abdominal myelolipomas –Abdominal lipomatosis –Mediastinal lipomatosis
<ul style="list-style-type: none"> –Angiolipomatosis 	<ul style="list-style-type: none"> –Multiple Endocrine Neoplasia type 1 	<ul style="list-style-type: none"> –Spinal epidural lipomatosis
<ul style="list-style-type: none"> –Lipedema –Hibernomas 	<ul style="list-style-type: none"> –Neurofibromatosis type 1 –Wilson's disease –Pai syndrome –Encephalocraniocutaneous lipomatosis or Haberland syndrome 	<ul style="list-style-type: none"> –Others (synovial...)

Lipomatous tumors may be classified into five different groups: simple lipomas, variant lipomas forms, heterotopic lipomas, infiltrating lipomas or lipomatosis, and finally hibernomas [5–8]. Nevertheless, we have chosen to rather classify lipomatosis according to the fact they are clinically isolated, syndromic, or visceral (Table 1).

Isolated lipomatoses include multiple symmetrical lipomatosis (Madelung or Launois-Bensaude disease; MSL), familial multiple lipomatosis (FML), the painful Dercum's disease (*Adiposis Dolorosa* or Ander syndrome), mesosomatic lipomatosis (Roch-Leri lipomatosis), lipedema, angiolipomatosis, and hibernomas.

Syndromic lipomatoses initially reported in Proteus, Cloves or Cowden syndromes, can benefit today from a molecular classification with variations in the *PIK3CA*, *LMNA*, *LIPE*, *MFN2*, mitochondrial genes such as MERRF syndrome, and some rarer genetic pathways such as *NF1*.

Finally, visceral lipomatosis has been reported in numerous sites: pancreatic, adrenal (myelolipoma), abdominal, epidural, mediastinal, epicardial, synovial and so on.

The aim of this work is to review the main types of isolated [7,8] and syndromic lipomatosis as well as visceral lipomatosis.

2. How to investigate lipomas and lipomatosis

2.1. Clinical diagnosis

Lipomas typically present as soft, solitary, painless, subcutaneous nodules that are mobile and not associated with epidermal change. A characteristic “slippage sign” may be elicited by gently sliding the fingers off the edge of the tumor (if the swelling does not slip under the palpating finger, it is rather a cyst than a lipoma; see <https://www.youtube.com/watch?v=C3f0056zPzI>). The lipoma may also become firmer if exposed to cold (“ice test”).

Schematically, lipomatoses may be diagnosed:

- on inquiry: familial or acquired, unique or multiple, painless, or painful.
- on examination: unique or multiple, symmetrical, or not, isolated, or syndromic, made of well limited or confluent lipomas, more or less fibrotic, with sometimes an angiomatous component, associated or not to obesity and various clinical features such as neuropathy. . .
- subcutaneous or visceral, this last diagnosis resulting of an imaging done purposely because of symptoms of compression or performed for another cause leading to an incidental discovery. whatever the localization the distribution of fat and lipomas should be analyzed.

- imaging and biopsy may show encapsulated or not encapsulated lipomas, while histological studies may argue for white or brown adipocytes.

2.2. Paraclinical investigations:

Ultrasound examination is the first line investigation to confirm the fatty nature and benign characteristics of subcutaneous nodules; lipomas appear as symmetrical, fatty deposits. It may even be used for the diagnosis of deep pancreatic lipomatosis, even if MRI is usually preferred in these situations. Combining high frequency ultrasound (HFUS) with clinical examination can generally improve the diagnostic accuracy, as well as contrast-enhanced ultrasound (CEUS) to differentiate between lipoma and atypical lipomatous tumors based on tumor perfusion [9,10].

Focal or whole-body magnetic resonance imaging (MRI) [11] allows to analyze the exact distribution of fat, its encapsulation if any, a qualitative assessment of the degree of inflammation, fibrosis or necrosis, and the muscle or bone associated involvement. Abdominal MRI may also help to quantify liver steatosis and whole and intra-abdominal fat distribution. Different techniques may be used:

- Traditional fat detection methods include inversion-recovery and chemically selective fat-suppression pulse sequences, with the former being less sensitive to field heterogeneity and less tissue specific than the latter.
- Chemical shift-based sequences, using the inherent resonance frequency difference between lipid and water to depict intracytoplasmic fat, is very useful for evaluating liver steatosis and lesions such as pancreatic focal lipomatosis.
- The signal from large amounts of fat can be suppressed by using a narrow radiofrequency pulse for selective excitation of fat protons (i.e., fat saturation imaging), a technique that increases image contrast resolution, and is especially useful for evaluating renal angiolipomas, adrenal myelolipomas, and liposarcomas.
- MR spectroscopy is a promising method for quantifying absolute liver fat concentration.
- New and evolving techniques include magnetization transfer and modified Dixon sequences.

Biphotonic absorptiometry and impedancemetry allow to quantify fat, muscle, water, and their distribution.

Multimodality imaging combining positron emission tomography with ¹⁸F-fluorodeoxyglucose, computed tomography, xenon-enhanced computed tomography, to non-invasively detect functional and structural changes associated with the browning process is emerging, although still in research [12].

Biopsy of fatty masses may be carried out, especially if a liposarcoma cannot be excluded.

2.3. Biological investigations

There are no specific recommendations. Nevertheless, looking for metabolic syndrome with fasting blood glucose, C-peptide or insulin, glycated hemoglobin, cholesterol HDL and LDL, triglycerides, oral glucose tolerance test, and measuring markers of adipose tissue (leptin, adiponectin), liver enzymes, (markers of liver steatosis), blood cell count, a biological fibrosis score such as FIB4, and CRP to screen for any inflammation, seem important.

2.4. Other investigations to look for complications

Lipomatoses are heterogeneous diseases and at difference with, for instance lipodystrophy syndromes, no recommendation to look for complications has been done. Nevertheless, screening for sleep apnea obstructive syndrome especially in Launois-Bensaude syndrome, may be of interest. Metabolic MRI can help to quantify liver steatosis and the relative distribution of visceral and total abdominal fat mass, a witness of insulin resistance. A non-invasive Fibroscan may indicate the level of liver fibrosis and the degree of steatosis. The presence or absence of metabolic syndrome will guide the cardiovascular assessment for its impact: thus, heart ultrasound and non-invasive heart ischemic screening may be indicated in metabolic syndrome. Excessive alcohol consumption or any specific complaints may also justify additional investigations. An electromyogram may be useful if a neuropathy is suspected.

3. Isolated lipomatosis

The main characteristics of isolated lipomatosis (MSL, FML, Dercum, mesosomatic, lipedema, angioliomatosis, and hibernomas) are summarized in [Table 2A](#).

3.1. Multiple symmetric lipomatosis (MSL; ORPHA #2398; OMIM#151800)

3.1.1. Diagnosis

All ethnic groups can be affected by MSL, generally between the third to sixth decade. MSL was first described as a “diffuse ruff-like fatty accumulation around the neck with grotesque distortion” followed by series reports of 33 to 65 cases. There are different subtypes of the disease, the most classical of which affecting the upper body and the nuchal region with a buffalo hump appearance ([Fig. 2](#)). A metabolic component with obesity is frequent. The disease progresses rapidly in the first few years, after which progression usually slows down or stabilizes. In contrast with what is currently admitted, it affects equally both sexes [13], even in Asian population, mainly in chronic alcohol abuse [14], and does not decrease with alcohol discontinuation. An excess of morbidity and mortality has been reported with sudden deaths without demonstrated coronary heart disease, possibly related to the toxic effect of alcohol on heart, or to unrecognized mitochondrial diseases which is another etiology. A neuropathy is frequent. Despite rare, malignant transformation into liposarcoma has been reported, supporting the need for a follow-up [15]. In addition to a frequent metabolic syndrome, neoplastic complications especially related to excessive alcohol and tobacco consumption should be screened as well as sleep apnea obstructive syndrome.

3.1.2. Physiopathology

Environmental factors such as alcohol, and genetic factors in some rare cases, seem mainly involved. Hazardous alcohol may act on liver and adipose tissue especially through modifications

of microbiota, lipid metabolism, oxidative stress, inflammation, mitochondrial dysfunction, epigenetics, adipokines, enzymes and transporters, such as cytochrome P450 related to acetaldehyde accumulation [7]. A few familial forms of MSL have also been identified, generally associating besides the neuropathy, a myopathy in the context of mitochondrial diseases such as MERFF syndrome [16,17]. Other mendelian genetic causes have been reported, mainly involving the *MFN2* and *LIFE* genes through null variants in less than 15 families for each gene. They will be detailed in the syndromic chapter IV.3 and IV.4. The differential diagnosis may be challenging [16,17].

3.1.3. Treatment

Plastic surgery may improve quality of life, but recurrence is favored by resumption of alcohol consumption.

In summary, multiple symmetrical lipomatosis occurs preferentially in people who are alcohol abuser. Rare genetic forms have been reported. In contrast to Dercum's disease, there is no pain component. The pathophysiology of MSL remains poorly understood but seems related to a mitochondrial dysfunction either acquired, especially through toxicity of the alcohol byproduct acetaldehyde, or genetically determined.

3.2. Familial multiple lipomatosis (FML; ORPHA #199276; OMIM#151900)

3.2.1. Diagnosis

Familial multiple lipomatosis is characterized by the presence of painless, multiple encapsulated lipomas (from a few lipomas to hundreds) in the subcutaneous fat usually located on the trunk, lower back, arms, and thighs. Only 200 FML cases have been reported in Pubmed, with no longitudinal study [7].

At difference with most lipodystrophy disorders, FML is not associated with a metabolic syndrome. Most of the time, lipomatosis appears in the third decade but may occur at any age even in children. Confusion with MSL is common.

3.2.2. Pathophysiology

Inheritance is frequently autosomal dominant, with variable penetrance. Different genetic abnormalities (*HMGA2* [High Mobility Group At-Hook 2], a gene involved in the genesis of adipose tissue, and *PALB2* [Partner and Localizer of BRCA2]) are associated with the disease, without being considered as the cause. Recently, a variant of a zinc-finger encoding domain of the *PRDM10* gene was shown in a novel disorder overlapping with Birt-Hogg-Dubé syndrome associating skin and mucosal lesions, renal cell carcinomas and extensive familial lipomatosis. Further studies are needed to understand the precise mechanisms linking these genes with FML [18].

To summarize, FML has been little described since the first report in 1846. Rather associated with insulin sensitivity, it is considered autosomal dominant with variable penetrance, but no gene has been identified yet.

3.3. Dercum's disease (ORPHA #36397; OMIM#103200)

3.3.1. Diagnosis

Dercum's disease is a very rare disease characterized by multiple, painful subcutaneous lipomas, occurring mainly on the trunk, and the proximal part of the arms and legs [8,19,20] ([Fig. 3](#) left). The disease is often associated with obesity, asthenia, and various neurological disorders, including depression and epilepsy. Nevertheless, it is not certain that these disorders are related to the disease itself. In addition to other lipomatosis and obesity, the differential diagnosis includes fibromyalgia and lipedema.

Table 2A
Characteristics of the main isolated lipomatosis.

Lipomatosis type	Mechanism	Classical presentation	Comorbidities	Treatment
Isolated lipomatosis				
Multiple symmetric lipomatosis or Madelung disease or Launois Bensaude syndrome	<ul style="list-style-type: none"> –Alcohol abuse –Genetic factors (figuring in Table 2B and MERFF, MFN2, LIPE... see Table 2B) –Mitochondrial dysfunction? 	<ul style="list-style-type: none"> –30-60 years – Location: neck, upper body, grotesque distortion 	<ul style="list-style-type: none"> Higher morbidity and mortality – Coronary disease – Neoplasia related to alcohol – Sleep apnea obstructive syndrome – Rare malignant transformation 	<ul style="list-style-type: none"> –Plastic surgery –Reoccurrence if resumption of alcohol abuse
Familial multiple lipomatosis	<ul style="list-style-type: none"> –Autosomal dominant disease without identified gene (<i>HMG2?</i> <i>PALB2?</i> <i>PRDM10?</i>) 	<ul style="list-style-type: none"> –30 years –Location: trunk, lower back, arms and thighs 	<ul style="list-style-type: none"> No metabolic syndrome 	<ul style="list-style-type: none"> –Possible surgical resection
Dercum's disease or <i>Adiposis dolorosa</i> or Ander syndrome	<ul style="list-style-type: none"> –Unknown: Lipid alteration? Previous infections? Lymphatic disorder? Basophil activation? 	<ul style="list-style-type: none"> –Women –Painful deep subcutaneous lipomas located on the trunk and proximal members. –Three main subtypes: Type I: neck, shoulder girdle, upper arms Type II: hips, bottom, and upper legs, and Type III: general distribution skipping head, forearms, and lower legs 	<ul style="list-style-type: none"> – Obesity – Neurological disorders (epilepsy, depression) 	<ul style="list-style-type: none"> – Histamine 1/2 receptor blockers – Non-steroidal anti-inflammatory – Flavonoids (quercetin, pycnogenol) – immunosuppressants (suni-, tofaci-, ima-tinib... used in mastocyte disorders) –Pain reoccurs after surgery
Mesosomatic (or Roch-Leri) lipomatosis	<ul style="list-style-type: none"> –Unknown –Sometimes familial –Adaptive immunity disorder? 	<ul style="list-style-type: none"> –Painless, multiple, small (2–5 cm) lipomas located between “breast and knees”. 	<ul style="list-style-type: none"> – Obesity – Metabolic syndrome – Autoimmune diseases? 	<ul style="list-style-type: none"> Weight loss? Surgical resection?
Angiolipomatosis	<ul style="list-style-type: none"> –Sporadic > inherited (no identified gene) –Microthrombi? 	<ul style="list-style-type: none"> –Men- sometimes painful –Unique or multiple nodules located on the arms and trunk with angiomatous component 		<ul style="list-style-type: none"> Tricyclic antidepressant?
Lipedema or <i>Lipohyperplasia dolorosa</i>	<ul style="list-style-type: none"> –Unknown: Polygenic susceptibility? Hormonal disorders? Lymphatic or microvascular? 	<ul style="list-style-type: none"> –Women (almost exclusively) –BMI most of the time > 35 –Disproportionate ± painful limbs (butt, thighs, calves; never feet and hands) 	<ul style="list-style-type: none"> –Psychological distress 	<ul style="list-style-type: none"> Weight loss? Plastic surgery?
Hibernomas	<ul style="list-style-type: none"> –4 types according to the proportion of brown fat (UCP1) –Reciprocal translocations of chromosome 11q 	<ul style="list-style-type: none"> –Mean age: 38 –Thigh, shoulder, and back –Sometimes atypical location (bone, breast...) FDG-PET uptake 	<ul style="list-style-type: none"> –May be association with MEN1 	<ul style="list-style-type: none"> Surgery



Fig. 2. Multiple symmetric lipomatosis: top: most frequent form affecting the upper part of the body; bottom: affecting only the neck.



Fig. 3. Left: Dercum disease; right: Roch-Leri or mesosomatic lipomatosis.

3.3.2. Physiopathology

The pathophysiology of Dercum's disease remains unknown although various mechanisms have been suggested, such as autoimmunity, lipid alterations, previous infections, or abnormal lymphatic tissue. Most reported cases are sporadic, but a few apparently autosomal dominant familial cases have been described. Recently, a study comparing metabolic and immunohematology characteristics in 9 cases of Dercum disease, 11 Roch and Leri lipomatoses, 18 lean and 8 obese controls, showed a common background of obesity and metabolic phenotype, but a distinct immune-hematological profile in Dercum and Roch-Leri lipomatoses. The Dercum's group was characterized by increased levels of leukocytes and platelets, already reported in metabolic syndrome, and a specific increase of basophils on the one hand, with a lower

number of Natural Killer (NK) cells on the other hand, compared with lean, but also obese controls. Basophil cells, very similar to mast cell, may expand inflammation, in association with T helper 2 (Th2) immune responses [21]. Both cell types contain serotonin, increase of which is associated with obesity [22,23]. Besides, the decrease of NK cells, which are usually dedicated to the removal of unhealthy adipocytes with a stimulation of proliferation, could participate in a low adipose tissue remodelling, favouring inflammation and insulin resistance.

3.3.3. Treatment

Treatment is currently symptomatic, and mainly analgesic. Recurrence of lipomas after surgical removal is common. but targeting mast cells and serotonin synthesis could deserve a trial.



Fig. 4. Angioliipomatosis.

Reducing the burden of mast cells may involve histamine 1 and/or 2 receptor blockers, montelukast, non-steroidal anti-inflammatory drugs, antihistaminergic bioflavonoids such as quercetin or pycnogenol, and possibly powerful immunosuppressive drugs such as sunitinib (used for mastocytosis), or tofacitinib or imatinib (used for mast cell activation syndrome). Note that these last suggestions have not been tested in a randomized study and may show serious side effects.

To summarize, Dercum disease shows a background of obesity and metabolic phenotype, with a distinct immunohematological profile characterized by a low level of NK cells, favouring basophil activation, chronic subclinical Th2 inflammation and recurrent painful lipomas which may correspond to inflammatory foci of adipose tissue. These findings could offer specific therapeutic opportunities.

3.4. Mesosomatic (Roch-Leri) lipomatosis (ORPHA#529)

3.4.1. Diagnosis

Roch-Leri lipomatosis, characterized by the presence of generally painless, multiple, small lipomas, 2–5 cm in diameter, in the middle third of the body (forearms, trunk, thighs), has raised little scientific interest because it is considered harmless (Fig. 3 right).

3.4.2. Physiopathology

Autosomal dominant cases have been reported but no gene has been identified and sporadic cases seem to be the most common [8]. In a recent study [19], Roch-Leri lipomatosis was associated to the same metabolic phenotype as in the Dercum's group, but in contrast to lean and Dercum controls, Roch-Leri lipomatosis was characterized by a significant decrease of blood CD3⁺ T cells, and to a lesser extent of CD4⁺ T helper/regulatory T cells and cytotoxic CD8⁺ T cells, a profile already reported in overweight subjects [24]. Also, this immune profile seems associated with a relatively high proportion of Roch-Leri patients with autoimmune disease (a type of disease also reported to be associated with lymphopenia). Nevertheless, due to the low number of patients studied, the results

need to be regarded with caution, although a low-grade deficit of adaptive immunity could be considered.

To summarize, as for Dercum disease, mesosomatic lipomatosis shows a background of obesity and metabolic phenotype, but a distinct immune-hematological profile characterized by T lymphocyte depletion, and a relative high proportion of auto-immune diseases.

3.5. Angioliipomatosis (ORPHA #199279; OMIM #206550)

3.5.1. Diagnosis

Angioliipomatosis is a rare disease with unknown prevalence, most of the time sporadic, rarely inherited on an autosomal dominant or recessive mode, without identified genes [25]. Angioliipomas usually present as solitary nodules or as multiple subcutaneous nodules, typically on the arms and trunk of men (Fig. 4). They may be painful, sometimes with a dissociation between the lesion and a strong complaint.

3.5.2. Physiopathology and histology

Angioliipomas arise from highly innervated fascia, especially on puberty (hormonal influence) or after repeated traumatism. They associate intermingled adipocytes and vessels. Microthrombi could lead to painful necrosis of blood vessels and adipocytes leading to inflammation. It is not known if angioliipomatosis is a specific disease, a vascular subtype of FML, or a phenotypic expression of other entities such as Cowden syndrome. Some angioliipomas could be neoplastic due to microdeletion of chromosome 13, a region containing the retinoblastoma gene, a tumor suppressor gene. Pseudoangiomatic spindle cell lipoma is a rare pattern within the spindle cell lipoma spectrum exhibiting a special histological pattern similar to vascular lesions, creating a pseudoangiomatic appearance [26]. Approximately 20 to 30 reports have been described in the literature.

3.5.3. Treatment

Resection of angioliipomas may be complicated with painful recurrent inflammation. Tricyclic antidepressant, which also inhibits serotonin and adrenalin reuptake with antihistaminergic



Fig. 5. Leg lipedema.

effects, may control the release of mast cell mediators, with a potential good therapeutic effect.

3.6. Lipedema (OMIM #614103)

3.6.1. Diagnosis

Lipedema, still named *Lipohyperplasia dolorosa*, is a chronic progressive disease characterized by abnormal fat distribution resulting in disproportionate, painful limbs, especially butt, thighs and calves, more rarely hips or upper arms (Fig. 5). It doesn't affect hands or feet. It almost exclusively affects women, generally leading to considerable disability and psychosocial distress. Literature shows both scarce and conflicting data regarding its prevalence. Lipedema is considered a rare entity but may be a more frequent condition than thought.

Features for lipedema have been defined using ultrasound (increased subcutaneous adipose tissue), lymphoscintigraphy (slowing of the lymphatic flow and a frequent asymmetry between the lower extremities), computed tomography (symmetrical bilateral soft tissue enlargement without either skin thickening or subcutaneous edema), MRI (increased subcutaneous adipose tissue), MR lymphangiography (enlarged lymphatic vessels up to a diameter of 2 mm), and dual-energy X-ray absorptiometry (fat mass in the legs adjusted for body mass index (BMI) ≥ 0.46 or fat mass in the legs adjusted for total fat mass ≥ 0.38) [27].

3.6.2. Physiopathology

Polygenic susceptibility combined with hormonal, microvascular, and lymphatic disorders may be partly responsible for its development, but indeed lipedema pathophysiology remains unknown, and an etiological treatment is not yet available.

3.6.3. Treatment

Weight loss measures exhibit minimal effect on the abnormal body fat distribution, resulting in eating disorders, increased obesity risk, and psychological consequences. Surgical techniques, such as liposuction and excisional lipectomy, represent therapeutic options in selected cases [28,29].

3.7. Hibernomas

3.7.1. Diagnosis

In contrast with previous lipomatosis which are mainly made of white fat cells, hibernomas are uncommon benign neoplasms of brown adipose tissue, coined about the presence of brown fat

in hibernating animals [30,31]. Described by Merkel in 1906, these tumors are similar to (and often mistaken with) lipomas or liposarcomas, slow growing, painless, but have unique imaging and histopathologic feature. Hibernomas generally present in young adults with a mean age of 38, in the thigh, shoulder, and back (regions rich in brown adipose tissue). They are often warm to touch owing to their vascularity; otherwise, the physical exam features of these neoplasms are nonspecific.

Commonly used imaging modalities include ultrasonography showing well-defined borders and high-echoic lesions with abundant blood flow signals, computed tomography (CT) demonstrating well-circumscribed, lobulated soft tissue masses, with sometimes internal septations. On T1- and T2-weighted MRI images, hibernomas appear isointense or slightly hyperintense with fat-suppressed sequences showing high signal intensity (Fig. 6), with heterogeneous enhancement patterns. Due to the high metabolic activity and abundance of mitochondria in brown adipomas, they exhibit elevated FDG uptake on PET-CT and may raise issues to differentiate from malignancies [30].

Differential diagnosis with liposarcoma requires histological diagnosis.

3.7.2. Physiopathology and histology

Histopathological features suggest an origin from fetal brown fat tissue, but these tumors rarely occur in infants, and possibly represent an altered differentiation pathway of brown fat. Reciprocal translocations of chromosome 11q have been implicated especially in the regions involving tumor suppressor genes *MEN1* and *AIP*. Also, hibernomas may be associated with multiple endocrine neoplasia type 1. Hibernomas can have variable histopathologic composition depending on their histological subtypes and the amount of brown fat cells resulting in 4 classes 1) typical (> 70% of brown adipocytes), 2) lipoma-like (containing white adipocytes), 3) myxoid, and 4) spindle cell variants. These 2 last less common variants are most often located in the posterior neck and shoulder. The brown fat marker gene *UCP1* a mitochondrial protein transporter, is consistently expressed in hibernoma. Hibernoma may also contain fat cells resembling lipoblasts, which makes it difficult to distinguish it from atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLs). Although nuclear expressions of murine double minute 2 (*MDM2*) and cyclin-dependent kinase 4 (*CDK4*) are widely used as immunohistochemical surrogate markers for ALT/WDLs, nuclear expression of *MDM2*, *USP7* and p 53 are also expressed in most hibernoma at difference with *CDK4* [31].

3.7.3. Atypical localization

Some localization are very rare such as breast hibernoma [32] or intraosseous hibernoma [33], most often detected in the spine and pelvis of older adults. Intraosseous hibernomas are generally small, sclerotic, and frequently found incidentally and can raise concern for metastasis. Whether or not these tumors are related to soft tissue hibernomas is uncertain. Finally, an increased potential for hibernomas to arise as spontaneous neoplasms in some animal models such as Sprague–Dawley mice has important implications in studies involving peroxisome proliferators-activated receptor (PPAR) drugs, lipophilic environmental chemicals (e.g., polychlorinated biphenyls), and other molecules (e.g., beta-adrenergic stimulation) that may target brown fat adipocytes [34].

3.7.4. Treatment

Most of the time, a surgical resection is proposed.

4. Syndromic lipomatosis

The classification of syndromic lipomatoses initially reported in Proteus, Cloves, or Cowden syndromes, have been deeply modified

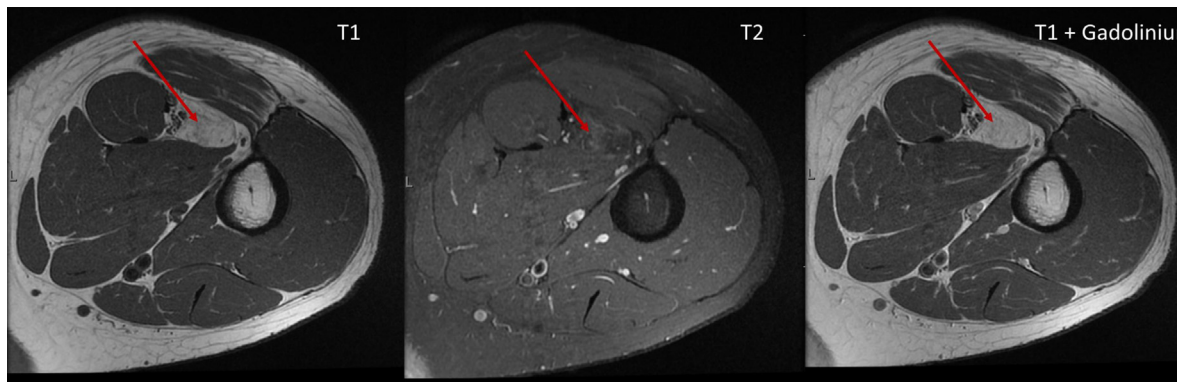


Fig. 6. MRI imaging of a hibernoma located on the right medium gluteal muscle in a MEN1 patient.

with advances in genetic knowledge. As of today, mutations in the *PIK3CA*, *LMNA*, *MEN1* genes, mitochondrial genes such as *MERRF*, and some rarer genetic pathways have allowed a new genetic classification. Other genetic conditions such as MEN1 or NF1 have been associated with lipomatosis (Table 2B).

4.1. *PIK3CA*-related disorders (ORPHA #530313)

Currently identified *PIK3CA*-related disorders presented in Fig. 7 [35] are classified according to the association with 1. an overgrowth syndrome (PROS), 2. vascular, or 3. non-vascular malformations. *PIK3CA*-related PROS disorders include some lipomatoses figuring in Table 2B, and in bold italic in Fig. 7. Mosaic gain-of-function mutation in *PIK3CA* gene leads to abnormal Akt-mTOR pathway activation which results in abnormal tissue growth. Diagnosis is complicated by the variability and overlap in phenotypes associated with *PIK3CA*-related disorders [36–38]. Inhibitors of mTOR such as sirolimus (=rapamycin) have been proposed in treatment, but more recently alpelisib, a PI3K α -selective inhibitor, has proven its effectiveness and safety in the management of PROS [39]. Phenotypic variants of PROS such as Proteus syndrome, first reported by Cohen and Hayden, had been described before the identification of *PI3KCA* mutations, as a sporadic hamarto-neoplastic syndrome characterized by an asymmetric, disproportionate overgrowth of any connective tissues, such as bone, fat (large subcutaneous or internal lipomas), or epidermal nevi, in a mosaic or patchy pattern [40]. The prevalence is about 1/1,000,000 live births. Proteus syndrome is also caused by mutations in components of the PI3K-AKT signaling cascade, the most common mosaic gene alterations being in *AKT1* gene [41]. AKT1 inhibitor miransertib may be proposed in this setting.

4.2. Cowden syndrome/*PTEN* (ORPHA #201; OMIM#158350)

4.2.1. Diagnosis

PTEN hamartoma-tumor syndrome (PHTS) is a rare autosomal dominantly inherited condition caused by germline mutations of *PTEN* gene, associated with multiple hamartomatous lesions occurring in various tissues, including the gastrointestinal tract, skin, mucous membranes, breast, thyroid, endometrium, and brain (Table 3) [42]. Lipomas, if ≥ 3 , are a minor criteria of diagnosis.

4.2.2. Physiopathology

PTEN (phosphatase and tensin homolog) gene, encodes a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase protein, containing a tensin-like domain and a tyrosine phosphatase catalytic domain. Unlike most of tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates and negatively regulates intracellular levels of phosphatidylinositol-

3,4,5-trisphosphate. It functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway.

4.2.3. Treatment

Early screening of cancers associated to the syndrome is required especially for breast, thyroid, colorectal, endometrial, and renal cancers.

4.3. Familial partial lipodystrophy syndrome

4.3.1. *LMNA* (ORPHA #280365; OMIM#150330)

Lipodystrophy syndromes are usually defined by a limited capacity of subcutaneous adipose tissue to store triglycerides causing metabolic abnormalities (insulin resistance, hypertriglyceridemia, fatty liver disease, cardiovascular and gynaecological complications [2–4]). Familial partial lipodystrophy syndrome especially related to mutation R482 of the *LMNA* gene (*FPLD2*) are characterized by cervico-facial fat distribution and may be associated with small lipomas of the abdominal wall despite the body subcutaneous lipodystrophy [43]. In lipomas, the adipogenic machinery is impaired in lipodystrophic fat coming from lipoatrophic regions, although the histological phenotype is near-normal, exhibiting low-grade inflammatory features [44].

4.3.2. *LIPE* (ORPHA #435660; OMIM #615980)

Other recessive types of lipodystrophy syndromes such as *LIPE* or *CIDEA* variants may be associated with lipomatosis [45,46]. A phenotype of myopathy and lipodystrophy syndrome (facio-truncular MSL-like lipomatosis with relative lipoatrophy from the lower extremities), has been reported associated with a homozygous Lipase E gene (*LIPE*) mutation [45,46]. *LIPE* gene encodes the hormone sensitive lipase, a key enzyme for triglyceride metabolism, expressed in adipocytes and neurological tissue.

4.3.3. *CIDEA*

Otherwise, *Cidea* and *Cidec* are lipid droplet-associated proteins that promote lipid storage in brown and white adipose tissue. *CIDEA* gene variants could favor familial thigh lipomatosis mimicking the classical “saddlebag” phenotype. *CIDEA* genes participate in the regulation of energy expenditure among lipid droplets, peroxisomes, and mitochondria through the *CIDE-ATGL-PPAR α* pathway in adipocytes [47]. Other genes such as Calcyphosine-like (*CAPSL*) have also been involved.

4.3.4. *MFN2*

Mutations in the *MFN2* nuclear gene coding for mitofusin 2, has been reported in autosomal recessive MSL associated with lipoatrophy of non-lipomatous areas with the same pathogenic

Table 2B
Characteristics of the main syndromic lipomatoses.

Lipomatosis type	Mechanism	Classical presentation	Comorbidities	Treatment
Syndromic lipomatosis PIK3CA-related overgrowth syndrome (PROs disorders) (including Proteus syndrome)	– Mosaic gain-of-function variants of PIK3CA – Activation of Akt-mTOR pathway	Lipomatosis sometimes included in: – CLOVES syndrome (<i>Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal naevi, Scoliosis</i>) – Fibroadipose hyperplasia or overgrowth – Hemihyperplasia multiple lipomatosis – Fibroadipose infiltrating lipomatosis – Facial infiltrating lipomatosis – Klippel-Trenaunay syndrome – Lipomatosis of nerve		Inhibitors of: – mTOR (sirolimus = rapamycin) – PI3Kalpha (alpelisib) – AKT1 (miransertib)
Cowden/ <i>PTEN</i> hamartoma syndrome	– <i>PTEN</i> variants, tumor suppressor negatively regulating AKT/PKB – Autosomal dominant	– Lipomas (≥ 3) = minor criteria – Hamartomatous lesion (stomach, skin, breast, thyroid, endometrium, brain...)	– Macrocephaly, mucocutaneous lesions, gastrointestinal polyps, autism spectrum disorders, intellectual disability – Neoplasia (thyroid, colorectal, endometrial, renal)	– Early cancer screening
Familial partial lipodystrophy syndrome	Variants of: – <i>LMNA</i> (FPLD2) Autosomal dominant – <i>LIPE</i> (FPLD6), <i>-CIDEA</i> (FPLD5) & <i>MFN2</i> Autosomal recessive	– FPLD2: cervico-facial fat distribution with body subcutaneous lipodystrophy – FPLD6: facio-truncular MSL-like – FPLD5: familial thigh lipomatosis? FPLD6 & MFN2: sometimes classified as pseudolipomatous because of limbs (FPLD6) or non-lipomatous areas (MFN2) lipodystrophy Lipomas: 1.7% Frequent diabetes, deafness	– Metabolic syndrome (insulin resistance ++) – Fatty liver disease – Cardiovascular complication (coronary, rhythmic) especially for FPLD2	– Metformin – Gliflozines – GLP1 analogs, – metreleptin if low leptin
Mitochondrial disorders (MERRF, MELAS)	Mitochondrial DNA – <i>MT-TK</i> : MERRF, – <i>MT-TI</i> , <i>UUR</i> : MELAS	Lipomas: 1.7% Frequent diabetes, deafness	MERRF: myoclonus, epilepsy, ragged-red fibers MELAS: Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, & Stroke-like episodes	
Multiple endocrine neoplasia type 1	<i>MEN1</i> gene variants Autosomal dominant	Lipomas, hibernomas and leiomyomas	Primary hyperparathyroidism, Pituitary adenoma Neuroendocrine pancreatic and lung tumors...	Surgery of hibernomas
Neurofibromatosis type 1	<i>NF1</i> gene variants Autosomal dominant RASopathy	Associated lipomas (6%)	Neurofibroma (skin, CNS, peripheral nerves), Ophthalmic lesions, pheochromocytoma Neoplasia (glioma, peripheral nerves, breast, blood)	–
Wilson disease	<i>ATP7B</i> gene variants Copper accumulation Autosomal recessive	Limb & trunk subcutaneous lipoma (25%)	Liver and neurological disorders	– no effect of decoppering
Pai syndrome Encephalocraniocutaneous lipomatosis (Haberland syndrome)	Unknown Postzygotic <i>FGFR1</i> variant?	Midline CNS lipomas, mostly corpus callosum Intraspinal or intracerebral lipomas	Polyps (facial, nasal mucosa) Hairless fatty tissue nevus (scalp) Choristomas (eye)	– –

Table 2C
characteristics of the main visceral lipomatosis (excluding liver steatosis).

Lipomatose type	Mechanism	Classical presentation	Comorbidities	Treatment
Visceral lipomatosis Pancreatic lipomatosis	<ul style="list-style-type: none"> – Acquired: obesity? alcohol hypercortisolemia, steroids – Genetic <i>CFTR</i>, <i>MODY 8 and 5</i> <i>SBDS</i>) 	<ul style="list-style-type: none"> – Common: obesity and metabolic syndrome – Cystic fibrosis especially with diabetes – Lean C-peptide positive maturity-onset diabetes of the young (<i>MODY 5 and 8</i>) – Shwachman-Diamond syndrome or congenital pancreatic lipomatosis: inherited bone marrow failure syndrome – Unilateral adrenal masse (95%) – More frequent in congenital adrenal hyperplasia (bilateral) – Other abdominal sites 	<ul style="list-style-type: none"> – Hepatic steatosis – Diabetes with exocrine pancreatic insufficiency Neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities 	
Adrenal and abdominal myelolipomas	Unknown	<ul style="list-style-type: none"> – Unilateral adrenal masse (95%) – More frequent in congenital adrenal hyperplasia (bilateral) – Other abdominal sites 	Adrenal hormone excess disorders sometimes associated	Surgery only if symptomatic (rare)
Abdominal lipomatosis	Unknown	<ul style="list-style-type: none"> Located on any abdominal structure – Fibrofatty mesenteric proliferation – Epiploic appendagitis or omental infarction – Mesenteric panniculitis: asymptomatic 50% – Juxtacaval – Abdominal or pelvic lipomatosis (FML) – Renal sinus lipomatosis 	<ul style="list-style-type: none"> – Crohn diseases in fibrofatty mesenteric proliferation) – 50% of cases: Abdominal pain, bloating/distention, diarrhea, constipation, vomiting, anorexia, weight loss, fever, malaise, and nausea – Differential diagnosis: lymphoma (PET-CT) 	<ul style="list-style-type: none"> Mesenteric panniculitis if symptomatic: – Prednisone – Tamoxifen – Surgery if recurrent bowel obstruction
Mediastinal lipomatosis	<ul style="list-style-type: none"> – Described in Bardet-Biedl syndrome, a ciliopathy – <i>BBS1</i> to <i>BBS12</i> gene variants – Autosomic recessive 	<ul style="list-style-type: none"> Bardet-Biedl syndrome – Polydactyly, retinitis pigmentosa, – Central obesity, hypogonadism, – Intellectual disability) 	Compressive pelvic renal lipomatosis with renal dysfunction	
Spinal epidural lipomatosis	<ul style="list-style-type: none"> – Unknown – Overweight – Glucocorticoid treatment? 	Obesity	Metabolic syndrome	<ul style="list-style-type: none"> – Weight loss – Surgery
Cardiac steatosis or lipomatosis cordis and epicardial lipomatosis	<ul style="list-style-type: none"> – Steatosis: fatty myocardium without fibrosis – Epicardial fat thickness > 7 mm (Heart US), therefore called lipomatosis 	<ul style="list-style-type: none"> Epicardial lipomatosis associated with – Obesity – Diabetes, metabolic syndrome – Atherosclerosis – Non-alcoholic liver steatosis 	<ul style="list-style-type: none"> – Coronary artery disease – Stroke – Heart failure – Electrical disorders (atrial fibrillation), via paracrine signaling and direct infiltration 	<ul style="list-style-type: none"> – Weight loss – Treatment of metabolic syndrome – Specific cardiac treatment

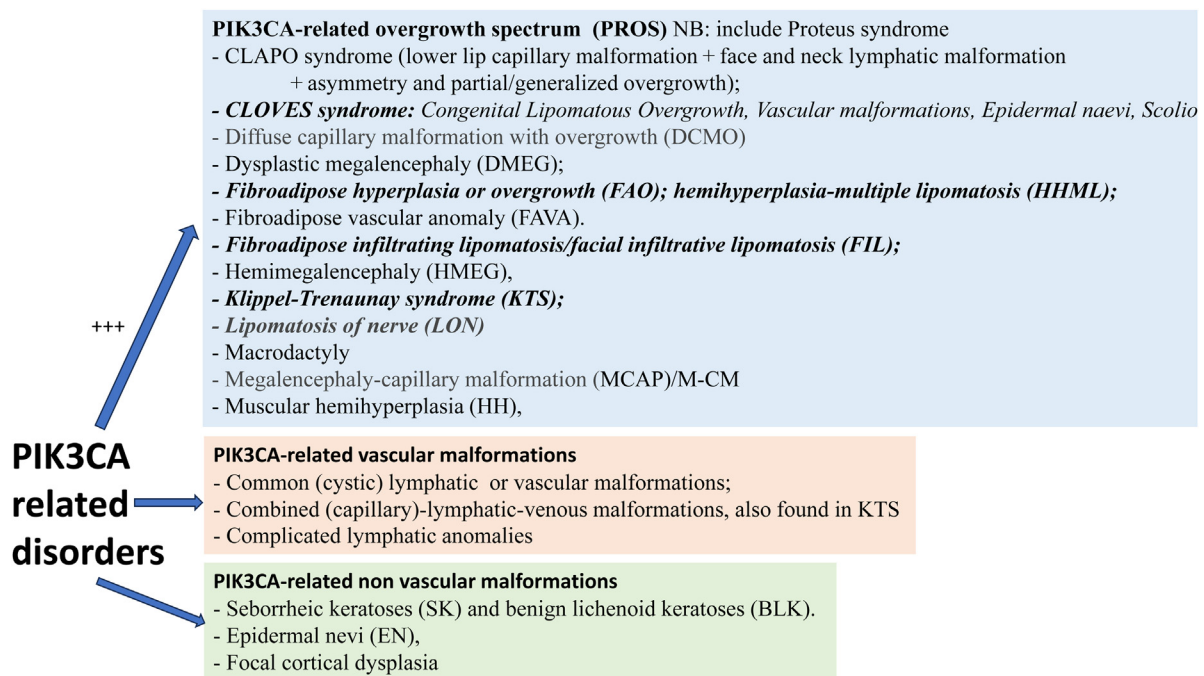


Fig. 7. Classifications of PIK3CA-related disorders.

variant, p.Arg707Trp, in the homozygous or composite heterozygous state. The gene codes for an enzyme on the outer mitochondrial membrane, participating in mitochondrial fusion and cell energy metabolism [48]. Involvement of this gene leads to emphasize the role of mitochondria in energy metabolism and to make a link with mitochondrial diseases.

4.4. Mitochondrial diseases.

4.4.1. MERFF (ORPHA #551; OMIM#545000)

Lipomas have often been associated with a maternally inherited multisystem mitochondrial disorder especially in patients with mutation in mitochondrial lysine tRNA (mitochondrial thymidine kinase or *MT-TK*) (A8344G mtDNA mutation) which is also the most frequent mutation associated with MERRF (myoclonus epilepsy with ragged-red fibers) [16,49–55]. In the Nation-wide Italian Collaborative Network of Mitochondrial Diseases including 1 300 patients, 1.7% (n=22) of them had lipomas. Among 18% of these 22 patients, MSL was the only clinical manifestation while 54% of patients showed a classical MERRF syndrome. Myopathy, alone or in association with other symptoms, was found in 27% of patients [56].

4.4.2. MELAS (ORPHA #550; OMIM #540000)

Besides A8344G mtDNA mutation, other mutations such as 4302 (4302A>G) of the tRNA(Ile) gene (*MTTI*) and 3243 (3243 A>G) of the tRNA(Leu(*UUR*)) causing Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) appear to be a “hot spot” for mtDNA mutations causing chronic progressive external ophthalmoplegia, with diabetes mellitus and multiple lipomas [57,58], while m.8357T>C transition (mitochondrial DNA) has also been involved.

4.4.3. To summarize

The wide phenotypic heterogeneity of mitochondrial diseases should lead to look for variants of mitochondrial genome, especially in lean C-peptide positive people with diabetes and sometimes maternal inheritance, deafness or non-awaited neuropathic, renal

or cardiac complications. MSL is often overlooked by clinicians but could be considered a red flag for mitochondrial disorders, even in patients with an apparently isolated MSL. Life -style intervention may be efficient [59].

4.5. Lipomatosis associated with other genetic conditions.

Multiple Endocrine Neoplasia type 1 (MEN1; ORPHA #652; OMIM#131100) caused by mutations of *MEN1* gene is characterized by a combination of several endocrine (hyperparathyroidism, neuroendocrine pancreatic and lung tumors, pituitary adenoma. . .) and non-endocrine manifestations, among which an increase frequency of neoplasms of the skin (angiofibromas, collagenomas, melanomas), adipose tissue (lipomas and hibernomas (Fig. 6)), and smooth muscle (leiomyomas), with not yet established causality [60–62]. Adrenal liposarcoma may reveal MEN 1 [63].

Neurofibromatosis type 1 (NF1; ORPHA #636; OMIM #162200)-like syndromes (or Legius syndrome) are classified according to the presence of *NF1* and *SPRED1* genes mutations. NF1 is a complex autosomal dominant disorder associated with germline mutations in the *NF1* tumor suppressor gene, belonging to RASopathies, caused by mutations in the Ras/mitogen-activated protein kinase pathway. Despite not mentioned in the French PNDs [64], an Italian review of more than 1000 cases of NF1 found a prevalence of lipomas of 6% besides Café-au-lait macules (96%), axillary and inguinal freckling (90%), neurofibromas (78%), nevus anemicus (3.9%), juvenile xanthogranuloma (3.2%), and melanoma (0.7%) [65,66]. An association between *NF1* gene variants and lipomas with often null phenotype (meaning non-functional allele) has also been reported [66,67].

Wilson disease (ORPHA #905; OMIM#277900) is an autosomal recessive disorder resulting in copper accumulation in the liver and the central nervous tissue. Subcutaneous lipomas were present in 26% of a series of 80 patients with Wilson disease, multiple in 75% of them, mainly found on the extremities and the trunk. Decoupling treatment did not influence the presence or course of lipomas [68].

Pai syndrome (ORPHA #1993; OMIM#155145) was originally described as the presence of a median cleft lip, cutaneous polyps of

Table 3
Diagnosis criteria for Cowden/*PTEN* hamartoma syndrome.

Major criteria	Minor criteria
1 - Breast Cancer	1 - Autism spectrum disorder
2 - Endometrial cancer	2 - Colorectal cancer
3 - Follicular carcinoma of thyroid gland	3 - Esophageal glycogenic acanthosis (≥ 3)
4 - Gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplastic polyps: ≥ 3)	4 - Lipomas (≥ 3)
5 - Adult-onset Lhermitte-Duclos disease	5 - Intellectual disability ($IQ \leq 75$)
6 - Macrocephaly ($> 97^{\text{th}}$ percentile: 58 cm F & 60 cm M)	6 - Renal cell carcinoma
7 - Macular pigmentation of the glans penis	7 - Testicular lipomatosis
8 - Multiple mucocutaneous lesions (trichilemmomas, acral keratoses, neuroma, oral papillomas)	8 - Thyroid cancer (papillary carcinoma or follicular variant of papillary carcinoma)
	9 - Thyroid lesions (adenoma, goiter...)
	10 - Vascular anomalies (venous)

Diagnostic is established if (1) ≥ 3 major criteria including macrocephaly, adult-onset Lhermitte-Duclos disease, or gastrointestinal hamartomas; (2) ≥ 2 major criteria associated with ≥ 3 minor criteria.

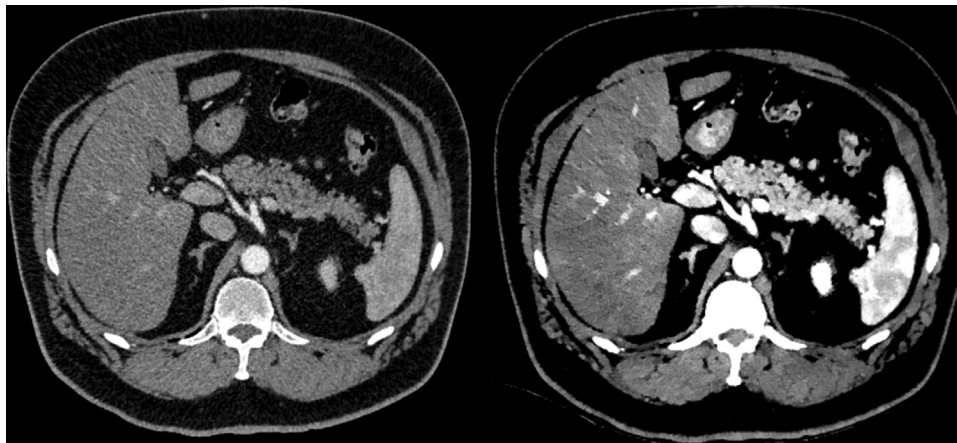


Fig. 8. MRI images of pancreatic steatosis.

the nasal mucosa and face, and midline lipomas of the central nervous system, mostly at the corpus callosum [69]. Exome and/or genome sequencing from blood DNA in 12 patients and from affected tissue in one patient failed to identify any replication in candidate gene, as of today.

Encephalocraniocutaneous lipomatosis (ECCL) or Haberland syndrome (ORPHA #2396; MIM #613001) is a rare congenital neurocutaneous disorder, characterized by unilateral ocular, cutaneous and central nervous system anomalies. Key clinical features include hairless fatty tissue nevus of the scalp, choristoma of the eye and intraspinal and intracerebral lipomas. ECCL is related to postzygotic *FGFR1* mutation and belongs to the Rasopathy group [70].

5. Visceral lipomatosis

Perivisceral depots of fat are sometimes called lipomatosis such as epidural or mesenteric lipomatosis. Nevertheless, lipomas have also been reported as encapsulated tumors in different organs such as adrenals and pancreas (Table 2C). Indeed, fat may be noted in a diffuse or focal manner in a variety of nonneoplastic conditions. The expansion of computed tomography or MRI along with the specific characteristic findings makes the diagnosis of these conditions relatively straightforward. Non-alcoholic liver steatosis will not be considered in this review.

5.1. Pancreatic lipomatosis

Some cases of “pancreatic lipomatosis” may culminate in steatopancreatitis (Fig. 8) and ultimately neoplastic transformations. So far, a fatty pancreas has been related to obesity and ageing, but genetic diseases (cystic fibrosis, Shwachman-Diamond syndrome, and Johanson-Blizzard syndrome), pancreatitis, especially hereditary and obstructive, metabolic and hormonal disorders (hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia and hypercortisolemia), alcohol overuse, drugs such as steroids, diseases of the liver and visceral adiposity may also favor lipomatosis.

5.1.1. Common pancreatic lipomatosis

As regards pancreatic lipomatosis resulting mainly from dyslipidemia and hyperglycemia, is sometimes named “nonalcoholic fatty pancreas disease” [71]. Pancreatic steatosis was also shown to be related to higher visceral fat (VFA), VFA/TFA (total abdominal fat) and hepatic steatosis in a study of living donors of liver, with a cut-off value of $VFA \geq 107 \text{ cm}^2$ predicting pancreatic steatosis [72].

5.1.2. Genetic causes

- Pancreatic lipomatosis is more frequent in subjects with cystic fibrosis-related diabetes (CFRD), as compared to patients without diabetes, and is related to exocrine pancreatic insuffi-

- ciency and to severe *CFTR* mutations (classes I to III). Pancreatic calcifications in pancreatic lipomatosis are specific of CFRD [73].
- Chronic pancreatitis with loss of acinar cells, acinar-to-ductal metaplasia, and lipomatosis, with impaired acinar cell regeneration and ductal cell deficiency characterized by shortened primary cilia has also been shown in a mouse model of *MODY 5* diabetes, in good correlation with human findings [74].
 - Also, CEL-related maturity-onset diabetes of the young (*CEL-MODY*, *MODY8*), a type of monogenetic diabetes caused by mutations in the carboxyl-ester lipase (*CEL*) gene, present with exocrine pancreatic dysfunction (e.g., chronic pancreatitis, pancreas atrophy and lipomatosis) followed by insulin-dependent diabetes, especially in frameshift mutations of exon 11. Hereditary chronic pancreatitis or diabetes may lead to screening for this mutation [75,76].
 - Shwachman-Diamond syndrome or congenital pancreatic lipomatosis (ORPHA #811; MIM#260400) is a rare inherited bone marrow failure syndrome characterized by neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities. In 10–30% of cases, transformation to a myeloid neoplasm occurs. Approximately 90% of patients have biallelic pathogenic variants in the *SBDS* gene located on human chromosome 7q11. Three other genes (*DNAJC21*, *EFL1*, and *SRP54*) have been identified to cause similar phenotypes [77].

5.2. Adrenal (or abdominal) myelolipomas

Adrenal myelolipomas are benign, lipomatous tumors with elements of myeloid cells, most of which present as adrenal incidentalomas and comprise 3.3 to 6.5% of all adrenal masses [78]. Adrenal myelolipomas are usually unilateral (in 95% of cases), variable in size, most often found during midlife, and affect both sexes almost equally. On imaging, adrenal myelolipomas show pathognomonic imaging features consistent with the presence of macroscopic fat. Large adrenal myelolipomas can cause symptoms of mass effect and can occasionally be complicated with hemorrhage. In the event of a concomitant adrenal cortical adenoma or hyperplasia with adrenal myelolipoma, adrenal hormone excess might be detected in patients. Patients with congenital adrenal hyperplasia exhibit a higher prevalence of adrenal myelolipomas than other patient groups and are at risk of developing large and bilateral lesions. Extra-adrenal myelolipoma may occur in different sites: perirenal, in the kidney sinus, presacral, spinal, in the chest, mediastinum, spleen, or pelvis. They are usually asymptomatic; however, in the presence of symptoms, significant growth, or complications, open surgical resection is indicated [78,79].

5.3. Abdominal lipomatosis

In the intestinal tract, the “fat halo sign” usually arises in the context of subacute to chronic bowel wall inflammation. “Fibrofatty mesenteric proliferation” is a characteristic feature of Crohn disease.

In the setting of the acute abdomen, accurate diagnosis of fat-containing lesions (epiploic appendagitis or omental infarction) from other causes of the acute abdomen is critical.

Mesenteric panniculitis is one of the causes of the “misty mesentery”, usually corresponding to a benign chronic inflammation and fibrosis of adipose tissue mainly of the small bowel mesentery. They are commonly detected incidentally on cross-sectional imaging of the abdomen, are asymptomatic in up to 50% of patients, but may induce abdominal pain, bloating/distention, diarrhea, constipation, vomiting, anorexia, weight loss, fever, malaise, and nausea in the other half. On CT scan, mesenteric panniculitis is seen as a mass-like area of increased fat attenuation, usually located in the left upper quadrant of the abdomen, enveloping mesenteric vessels

with frequent lymph node making lymphoma the main differential diagnoses, justifying FDG-PET in some cases. In case of symptoms, prednisone and tamoxifen may be proposed, and surgery reserved in case of recurrent bowel obstruction [80].

Juxtacaval fat deposition is a benign process that has the potential to be confused with more serious conditions.

More diffuse fat deposition (abdominal or pelvic lipomatosis) has the potential to become symptomatic by causing mass effect upon the adjacent structures, for instance in stomach, duodenum, colon. They may also be associated with Familial Multiple Lipomatosis.

Excess fat in the renal sinus may occur with renal sinus lipomatosis or “replacement lipomatosis of the kidney”. Fat can also be seen in a variety of postoperative/iatrogenic conditions or abdominal wall/diaphragmatic hernias [81–84].

5.4. Spinal epidural lipomatosis

Spinal epidural lipomatosis is abnormal accumulation of normal fat in the epidural space with weight loss suggested as first-line therapy. It may be favored by glucocorticoid therapy [85,86]. Surgery may also improve quality of life in case of functional consequences.

5.5. Mediastinal lipomatosis

Mediastinal lipomatosis and compressive pelvic renal lipomatosis have been reported in Bardet-Biedl Syndrome a rare autosomal recessive disorder characterized by polydactyly, retinitis pigmentosa, obesity, hypogonadism and mental retardation [87–89].

5.6. Myocardial steatosis

V.6 Myocardial steatosis, also known as lipomatosis cordis, is characterized by adipose tissue within the myocardium without significant fibrosis. Besides, epicardial fat thickness may be highly protective for the myocardium through brown fat-like thermogenic function, but its thickness strongly correlates with diabetes, atherosclerosis, and coronary artery disease. It is easy to screen with echocardiography and considered abnormal if > 7 mm even if there is not absolute cut-off. It is frequently observed in obesity and non-alcoholic liver steatosis. Besides coronary artery disease, it increases the risk of stroke, heart failure and electrical disorders (atrial fibrillation), via paracrine signaling and direct infiltration [90,91].

5.7. Differential diagnosis

Diagnosis is mainly clinical for isolated and syndromic lipomatosis, or radiological for visceral lipomatosis. An unsightly aspect, pain, functional difficulty, metabolic syndrome are the main circumstances of diagnosis. Different diagnoses need, however, to be ruled out such as common obesity, Cushing’s syndrome, especially in MSL, fibromyalgia, lipodystrophy syndromes (which may also be an etiology), lymphoma, neurofibroma, venous malformation, other possible malignant tumors among which atypical lipomatous tumors and liposarcoma [92].

Myxoid liposarcoma, classified in the group of sarcomas with adipose differentiation, is the second most common group of sarcomas. The behavior and clinical course of these tumors can vary widely. A fatty/myxoid component below 50% in MRI are usually high-grade tumors. Also, some well differentiated liposarcoma may present as lipomas [93].

Finally, adult patients with HIV-1 infection on some anti-retrovirals, especially thymidine analogue nucleoside reverse transcriptase inhibitors, may present a lipodystrophy syndrome associating peripheral lipoatrophy, central fat accumulation, and

lipomatosis. However, an objective, validated definition of the disorder does not exist, and these patients may also present with MSL, multiple lipomas, isolated buffalo hump or epidural lipomatosis [94].

In addition, acquired partial lipodystrophy syndrome have been reported following bone marrow transplant or total body irradiation during childhood for hemopathy. The pathophysiology is unknown, may be induced by autoimmunity in some cases. [95].

5.8. Physiopathological synthesis

Adipose tissue is known to be highly heterogeneous. This heterogeneity depends on the various anatomical depots which differ according to developmental origin, proliferation ability, glucose and lipid metabolism, insulin sensitivity, hormonal regulation, endocrine secretion, thermogenesis, vascularization, genetic predisposition, environmental factors, gender and age. Individuals with central obesity are more susceptible to developing diabetes and cardiovascular complications, whereas those with peripheral obesity are more metabolically healthy [96].

Besides obesity (most of the time secondary to environmental factors) and lipodystrophy syndromes (most of the time related to genetic or sometimes auto-immune, or iatrogenic causes), lipomatosis is a third group of fat disorder. In this setting, environmental factors, especially excessive alcohol intake, or genetic causes, especially on the Ras-PI3K-PTEN-Akt-mTOR pathway, seem particularly critical.

Alcohol is metabolized in the body via different pathways by the catalytic activity of 3 different enzymes—alcohol dehydrogenase, cytochrome P450 2E1 (CYP2E1), and catalase. Chronic ethanol exposure induces CYP2E1 expression and causes oxidative stress and inflammation of adipose tissue, with alteration of immunity. In addition, lipolysis is increased leading to excess fatty acid release and hepatic steatosis [97,98]. CYP2E1 may also be induced by drugs such as anesthetics, nicotine, dexamethasone, solvents, or other environmental factors. Finally, all causes of chronic adipose tissue inflammation (including associated obesity) may induce alterations of immune balance and increase of serotonin through basophils and mast cells, favoring insulin resistance, obesity, low adipose tissue remodeling, inflammation, and immune alterations.

The Ras-PI3K-PTEN-Akt-mTOR pathway is involved in the regulation of metabolic processes, maintenance of the redox balance, and cell survival and growth. The mTOR pathway, highly conserved during evolution, integrates several environmental cues, such as growth factors, amino acids or glucose, regulates energy metabolism and lipid/protein synthesis, and influences cell survival and growth. Mutations of the *NF1* gene encodes neurofibromin which accelerates the conversion of Ras into an inactive form inducing a deregulation of PI3Kinase-Akt-mTOR pathway [99]. *PTEN* and *MEN 1* genes are tumor suppressor genes, both acting as negative regulator of AKT kinase activity [100]. Their mutations induce proliferation and anti-apoptosis in non-endocrine and endocrine cells.

Finally, genes involved in the function of adipocytes such as those important in nuclear function (*LMNA*), lipid droplets (*CIDEA*, *LIPE*), or mitochondrial function (*MFN2*, *MERFF*, *MELAS*) may also be participate to the occurrence of lipomatosis.

It is not known whether the occurrence of lipomatosis could induce as a consequence a metabolic syndrome. Improving knowledge in the field acknowledge the necessity of registry and networking around adipocyte physiopathology and diseases [101].

6. Conclusion

Lipomatosis are human diseases characterized by the accumulation of benign fat proliferations, associated in the case of Dercum's

disease and some angioliomatosis with a prominent pain complaint, and in some cases but not all (MSL, Dercum, Roch Leri. . .) with a moderate metabolic syndrome. Most of these lipomatosis have been discovered in the 19th century and have since been considered benign. There are currently no specific biological markers, and the differential diagnosis may be difficult especially because of some overlap between the different syndromes. Nevertheless, considerable physio-pathological advances have been made unveiling the role of environmental factors such as alcohol and genetic causes especially affecting pathways involved in energy metabolism (mitochondrial and lipid droplets genes) and those altering the Ras-PI3K-PTEN-Akt-mTOR impairing energy production, cell proliferation and immunity. A better understanding of the underlying pathophysiological mechanisms opens avenues on therapeutic research such as the treatments today available for *PI3KCA*-related disorders.

Authorship statement

All authors participated in the research. Hippolyte Dupuis, Madleen Lemaître and Marie-Christine Vantghem performed data analysis and wrote the manuscript. Stéphanie Espiard, Claire Douillard and Arnaud Jannin reviewed the manuscript.

Sources of support

This manuscript was supported by the PHRC 2009_09/094/Clin.gov2009-AO-1169-48.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

Lipodystrophy studies were supported by the French Ministry of Health (Clin.gov2009-AO-1169-48/PHRC-2009_09/094). We are indebted to Geraldine Lavergne and Anne-Sophie Vanceulebroek; the clinical staff of the Department of Endocrinology and Metabolism; the *Délégation à la Recherche Clinique et de l'Innovation* for their support.

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