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Characterization of somatic mutations in the pathogenesis of lipedema

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Abstract

Background. Lipedema, a complex and enigmatic adipose tissue disorder, remains poorly understood despite its significant impact on the patients' quality of life. Genetic investigations have uncovered potential contributors to its pathogenesis, including somatic mutations, which are nonheritable genetic alterations that can play a pivotal role in the development of this disease.

AIM. This review aims to elucidate the role of somatic mutations in the etiology of lipedema by examining their implications in adipose tissue biology, inflammation, and metabolic dysfunction.

Results. Studies focusing on leukocyte clones, genetic alterations like TET2 and DNMT3A, and the intricate interplay between adipose tissue and other organs have shed light on the underlying mechanisms driving lipedema. From the study of the scientific literature, mutations to genes correlated to three main pathways could be involved in the somatic development of lipedema: genes related to mitochondrial activity, genes related to localized disorders of subcutaneous adipose tissue, and genes of leukocyte clones.

Conclusions. The insights gained from these diverse studies converge to highlight the complex genetic underpinnings of lipedema and offer potential avenues for therapeutic interventions targeting somatic mutations to alleviate the burden of this condition on affected individuals. ***Clin Ter 2023; 174 Suppl. 2 (6):249-255 doi: 10.7417/CT.2023.2495***

Key words: *Lipedema, Adipose Tissue, Somatic Mutations, Leukocyte Clones, Mitochondrial Activity, SAT, Localized Disorders of SAT*

Introduction

The exploration of human genetics has unveiled the pivotal role of somatic mutations in the genesis of various diseases, particularly those involving adipose tissue, as exemplified by the enigmatic disorder lipedema (1). Lipedema, primarily affecting women, manifests as an anomalous and symmetrical accumulation of subcutaneous adipose tissue (SAT) in the limbs (2). The peculiar cyto- and histomorphological features of adipocytes involved in lipedema are the subject of recent and extensive studies. In particular, more dysplastic or metaplastic/dysplastic features are emerging with increasing evidence alongside the well-known hyperplastic and hypertrophic aspects. Unlike obesity, lipedema induces distinctive symptoms—such as pain and vascular vulnerability—and remains unresponsive to conventional weight loss methods (3,4). Despite its perceived rarity, studies propose an incidence of 8% to 17% among adult women, indicating a quite prevalent presence (4). The onset of lipedema often coincides with puberty and can intensify during hormonal transitions like pregnancy and menopause, hinting at potential estrogenic involvement (3,5). While genetic predisposition is suggested, with a reported positive family history of lipedema in 64% of affected women, the inheritance pattern remains ambiguous, oscillating between X-chromosome-linked dominance and autosomal dominance with sex restriction (5).

Initiating the landscape of molecular exploration, the first gene implicated in lipedema pathogenesis was Aldo-Keto Reductase 1C1 (AKR1C1), demonstrated to be mutated in a familial context (5). This spotlight on progesterone metabolism hints at hormone-mediated pathways that might underlie the development of this condition (6). The aim of

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this review is to increase our understanding of the intricate molecular origins of lipedema, facilitating the formulation of novel preventive, diagnostic, and therapeutic strategies, which is crucial for managing such a complex disease. This endeavor employs a specific approach, aiming to unveil potential somatic mutations within the aberrant adipose tissue of lipedema patients, thereby unearthing latent non-germinal genetic triggers for the disorder's emergence (7).

Exploring Hormonal Influence: AKR1C1 Mutation and Hormones

Investigations into the genetic aspects of lipedema have uncovered mutations within affected families, notably highlighting the involvement of AKR1C1 in progesterone metabolism. Notably, this marks the first gene to be correlated with lipedema (8). This observation suggests the potential influence of hormonal factors in the development of lipedema, which aligns with its worsening during hormonal fluctuations like pregnancy and menopause (9). This interplay between genetic susceptibility and hormonal changes adds intricacy to our understanding of the origins of lipedema (2). For instance, a study by Steckelbroeck et al. revealed AKR1Cs' ability to catalyze the reduction of DHT into both 3alpha- and 3beta-Diol, shedding light on its role in steroid metabolism (10). Lewis et al. explored enzyme activity differences in tumorous and non-tumorous breast tissues in relation to progesterone metabolizing enzyme gene expression (6). They used semi-quantitative RT-PCR to assess mRNA expression ratios of various enzymes, including AKR1C1, in breast tissues.

Furthermore, Michelini et al. reported on a family with sex-limited autosomal dominant nonsyndromic lipedema, reinforcing the genetic basis of the condition and its potential inheritance patterns (8). Child et al. proposed that the genetic nature of lipedema could involve X-linked dominant or autosomal dominant inheritance with sex limitation (11). This exploration of genetics forms the foundation of a continuing education activity, aimed at equipping healthcare professionals with the knowledge to better manage lipedema patients—including strategies for diagnosis, pathophysiology, and treatment (12). In parallel, research on AKR enzymes sheds light on their roles in adipocyte functions and metabolic pathways. Notably, human aflatoxin B(1) aldehyde reductase (AKR7A2), aldehyde reductase (AKR1A1), aldose reductase (AKR1B1), dihydrodiol dehydrogenase 1 (AKR1C1), and chlordecone reductase (AKR1C4) have been extensively studied, revealing distinct catalytic abilities and tissue distributions (13). These enzymes, as part of the aldo-keto reductase (AKR) superfamily, play key roles in fat deposition and hormone metabolism, with AKR1C's heightened activity linked to subcutaneous fat accumulation and altered steroid metabolism.

Moreover, genetic studies have identified a missense variant in AKR1C1 through whole exome sequencing in lipedema patients, potentially influencing reduced progesterone metabolism and contributing to subcutaneous fat depositionc(14). This implicates AKR1C1 as a candidate gene for nonsyndromic lipedema. Recognizing the limitations of standard weight loss methods for lipedema patients, research explored the benefits of a modified Mediterranean diet (mMeD), revealing substantial weight loss and improved quality of life for both lipedema patients and controls, suggesting its potential as an effective treatment approach (15).

Overall, the intricate relationship between genetics, hormones, and metabolism continues to uncover new insights into lipedema, influencing both diagnosis and treatment strategies.

Mitochondrial Dynamics in Lipedema, Obesity, and Metabolic Dysfunction

Somatic mutations, which accumulate over an individual's lifetime, have recently taken center stage in understanding the pathogenesis of lipedema, with implications extending to mitochondrial function and activity (16). Mitochondria, recognized as pivotal regulators of metabolic processes and adipose tissue dynamics, have been implicated in the interplay between somatic mutations, obesity, and metabolic activity (2). A significant study underscored how mitochondrial DNA methylation patterns exhibit tenuous connections with obesity severity, potentially influencing mitochondrial copy number and key gene expressions (like NRF1)(17).

Delving further, investigations into mitochondrial DNA copy number (mtDNAcn) variations and methylation within mitochondrial DNA, particularly the D-Loop, shed light on the intricate interplay between nuclear and mitochondrial genetic elements within the context of obesity (18). Notably, the study's insights elucidate a complex correlation between D-Loop and LINE-1 methylation, further strengthening the case for an integrated role of nuclear-mitochondrial dynamics in obesity (18). Shifting the focus to metabolic-associated fatty liver disease (MAFLD), the interplay between mitochondrial DNA methylation and hepatic lipid accumulation becomes evident. Findings suggest that altered mtDNA methylation could potentially drive mitochondrial dysfunction and aberrant lipid metabolism in the context of MAFLD (19). Transitioning to cardiovascular health, a pioneering investigation is emerging, studying platelet mtDNA methylation as a predictive marker for future cardiovascular disease (CVD) risk among individuals with obesity. Highlighting specific mtDNA loci (MT-CO1 nt6807, MT-CO3 nt9444, and MT-TL1 nt3254), this study presents a novel approach to enhance CVD risk prediction independently of conventional risk factors (20). As these studies collectively unravel the intricate relationships between somatic mutations, mitochondrial dynamics, obesity, and associated metabolic dysregulations, a compelling hypothesis emerges: somatic mutations might contribute to lipedema development through their impact on abnormal adipose tissue proliferation, urging further exploration of the multifaceted ties between mitochondrial function and lipedema manifestations.

Mutated Somatic Clones and Adipose Tissue Growth: A Closer Look

Considering the complex genetic basis of lipedema, somatic mutations can be one of the cause of excessive and

anoumalous adipose tissue growth, such as in PIK3CA-related hyperplasia syndrome (PROS) (21). These somatic mosaic mutations, characterized by their diverse genetic alterations, intricately disrupt endocrine balance and metabolic regulation, significantly impacting adipose tissue dynamics (22). Notably, studies have delineated how PIK3CA mutations disrupt GLUT4 membrane dynamics, subsequently perturbing insulin secretion and metabolic equilibrium (23). The convergence of these somatic mutations with lipedema's unique pathology offers a novel perspective on potential genetic triggers driving the condition's manifestation, thus unveiling multifaceted molecular mechanisms that underlie its enigmatic nature.

Ladraa et al. studied PIK3CA-related overgrowth syndrome (PROS), which results from somatic mosaic gain-of-function mutations in PIK3CA, leading to various clinical manifestations and disruptions in endocrine function. Notably, their investigation on mouse model closely recapitulated the patient phenotype, revealing underlying mechanisms such as GLUT4 membrane accumulation, alterations in the insulin feedback loop, liver IGFBP1 synthesis, and metabolic reprogramming. Importantly, the use of Alpelisib effectively counteracts adipose tissue overgrowth driven by PIK3CA mutations, and restores metabolomic abnormalities in both animal models and affected patients (24). Exploring somatic mutations in genes like AKT, PIK3CA, and PIT-1 provides intriguing insights into their roles in regulating adipose tissue mass, metabolic pathways, and associated disorders. Investigating these mutations can uncover critical mechanisms underlying conditions such as lipodystrophy and overgrowth syndromes, offering potential therapeutic avenues for these complex disorders. The regulation of adipose depot mass is crucial for maintaining energy homeostasis, with AKT playing a pivotal role in adipogenesis. Deleting adipocyte AKT in mice resulted in severe lipodystrophy, insulin resistance, fatty liver, and hepatomegaly, underscoring the significance of AKT in preserving adipose tissue mass and insulin signaling (25). Furthermore, the PI3K-AKT signaling pathway is essential for cell growth and metabolism. Researchers have identified cancer-associated mutations in the PIK3CA gene, specifically p.His1047Leu and p.His1047Arg, in individuals with congenital progressive segmental overgrowth syndromes affecting fibrous, adipose, and bone tissues. These mutations lead to heightened PI3K signaling, highlighting a potential therapeutic target for this distinctive overgrowth syndrome (26). In a separate case, a 23-year-old male diagnosed with idiopathic isolated growth hormone deficiency was found to carry a PIT-1 mutation (P24L), associated with inherited combined pituitary deficiency. This case shows a unique combination of Pit-1 mutation and lipedema within the family, shedding light on potential interactions between growth hormone and sex steroids that influence fat distribution during puberty (27). Mice lacking the Cav1 gene exhibit adipocyte abnormalities and insulin resistance. A frameshift mutation (I134fsdelA-X137) in CAV1 was found in patients with atypical lipodystrophy and hypertriglyceridemia, causing partial lipodystrophy (with fat loss affecting specific body areas) and hyperlipoproteinemia, along with additional atypical features (28). This review highlights their differences and commonalities to guide future research (29). The interaction between MMP-14 and caveolin 1 (CAV1) in adipocytes could lead to abnormal matrix processing, contributing to the enlargement of subcutaneous adipose tissue (SAT) (30). Progressive resistance training enhances insulin sensitivity and promotes the balance of adrenergic alpha 2A (ADRA2) and beta pathways within subcutaneous adipose tissue in obese individuals (31).

Leukocyte Clones and Inflammation: Impact on Lipedema

As the intricate genetic tapestry of lipedema unfolds, a notable emergence is the prominence of leukocyte clones and their inflammatory implications. The involvement of certain genes, such as TET2 and DNMT3A, marked by somatic inactivating mutations in hematopoietic cells, takes center stage (33). These mutations, exacerbating insulin resistance and triggering a surge of pro-inflammatory cytokines within white adipose tissue (33), align with a pivotal study illustrating how inactivating mutations in TET2 escalate age- and obesity-linked insulin resistance, coupled with heightened IL-1β expression in white adipose tissue (34). Given lipedema's strong association with inflammation, scrutinizing leukocyte clone contributions to this pro-inflammatory trend presents a promising avenue to unravel its etiology (35). To discern whether inherent cellular differences underpin metabolic variances between adipocyte subtypes, exploration shifts to human precursor stromal cells from diverse fat depots. This study highlights that, while gene expression and adiponectin secretion diversify, inherent metabolic characteristics endure during differentiation. Subcutaneous adipo-

Table 1. Genes correlated to adipose tissue disorders with somatic mutations.

Gene	Name	adipose tissue disorders	References
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	PIK3CA-related overgrowth syndrome (PROS)	(24, 32)
AKT1	AKT serine/threonine kinase 1	Lipodystrophy	(25)
AKT2	AKT serine/threonine kinase 2	PIK3CA-related overgrowth syndrome (PROS)	(24)
MMP-14	matrix metallopeptidase 14	Lipedema	(30)
CAV1	caveolin 1	Atypical lipodystrophy and hypertriglyceridemia	(28)
AKR1C1	aldo-keto reductase family 1 member C1	Lipedema	(8)
AKR1C2	aldo-keto reductase family 1 member C2	Nonsyndromic lipedema with AKR1C1 gene involvement	(15)

cytes showcase elevated C/EBPalpha, AP2, and adiponectin expression, whereas visceral counterparts exhibit amplified insulin-stimulated glucose uptake and signaling, affirming the retention of distinct metabolic traits through differentiation (36). The intricacies of adipose tissue expansion take on new dimensions in light of varying depot behaviors (37). Murine adipose tissue turnover rates and adipogenesis surge differently between visceral and subcutaneous depots. Adipocyte hypertrophy predominantly fuels adult fat mass expansion, accentuating adipose tissue's adaptive plasticity in metabolic equilibrium (37). Age-related somatic mutations in the hematopoietic system have been linked to clonal hematopoiesis, which is associated with an increased risk of cardiovascular disease and type 2 diabetes. Notably, inactivating mutations in the TET2 gene have been shown to exacerbate insulin resistance and metabolic dysfunction in mice, primarily driven by heightened IL-1β expression in white adipose tissue. However, this detrimental effect can be mitigated by inhibiting NLRP3 inflammasome-mediated IL-1β production (34). Moreover, research by Haring et al. has explored the intricate relationship between lifestyle, environmental factors, and clonal hematopoiesis of indeterminate potential (CHIP) as a cardiovascular risk factor. CHIP, often involving genes such as DNMT3A, TET2, JAK2, and ASXL1, has been associated with accelerated atherosclerosis and cardiovascular disease, and with underlying mechanisms tied to inflammation. While age remains a primary risk factor, emerging evidence suggests that factors like smoking, obesity/type 2 diabetes, and an unhealthy diet contribute to the occurrence of somatic mutations and the development of CHIP (38). Furthermore, investigations into adipocyte progenitors in heterozygous knockout mice that mimic TBRS phenotypes have unveiled the pivotal role of DNMT3A in regulating adipose tissue expansion, preadipocyte maturation, and inflammatory gene networks. This regulation has profound implications for energy storage and the development of obesity. Loss of DNMT3A leads to DNA hypomethylation, influencing the differentiation of adipocyte progenitors and underscoring its multifaceted role in weight regulation, as well as in preventing inflammatory obesity (39). Table 2 displays leukocyte clonal variations involved in lipedema.

Mitochondrial activity and related somatic mutations that can alter adipose tissue biology

In recent studies, researchers have explored various intricate mitochondrial changes associated with many somatic changes that contribute to altering adipose architecture. Kim et al. studied mitochondrial changes in subcutaneous adipose tissue from HIV-infected patients with lipoatrophy and matched controls, revealing mtDNA depletion, compensated mtDNA-dependent activity, increased mitochondrial biogenesis, and apoptosis induction. While mtDNA content doesn't correlate with other mitochondrial parameters, preserved mtDNA-dependent functions persist despite severe depletion (40). Giralt et al. examined the expression of marker genes related to mitochondrial function, adipocyte differentiation and metabolism, and adipokines in subcutaneous adipose tissue from healthy controls, untreated HIV-1-infected patients, and those treated with HAART, with or without HALS. Their results revealed disruptions in adipose tissue gene expression in untreated HIV-1-infected patients, implying the role of HIV-1 infection itself in eliciting alterations exacerbated by HAART, ultimately leading to HALS (41). Vernochet et al. generated a mouse model with mitochondrial transcription factor A (TFAM) disruption in adipose tissue, to explore its impact on metabolism. TFAM-deleted adipose tissue displayed altered mitochondrial function, leading to increased energy expenditure and protection against obesity, insulin resistance, and hepatosteatosis, suggesting adipose tissue mitochondria as a potential therapeutic target for obesity treatment (42). Exposure to calorie-dense foods decreased mitofusin 2 (Mfn2) expression, known for promoting mitochondrial fusion, in white and brown fat of adult animals. Reduced Mfn2 mRNA was observed in obese humans too. Knockdown of Mfn2 in adipocytes led to increased adiposity, food intake, and glucose metabolism impairment, reflecting its role in systemic metabolic regulation. Transcriptional changes in adipose tissue indicated enhanced lipogenesis and adipocyte proliferation, influencing systemic glucose utilization content (43). Capel et al. investigated MFN2-associated multiple symmetric lipomatosis (MSL), a condition marked by lipomatous masses and lipodystrophy. Patients with a homozygous p.Arg707Trp MFN2 pathogenic variant showed both lipomatous masses and a lipodystrophic syndrome, along with varying severity of Charcot-Marie-Tooth neuropathy. Lipomatous tissue exhibited mitochondrial alterations and abnormal expression of adipokines, while elevated serum FGF21 and increased fat metabolic activity were observed (44).

Pace et al. assessed the impact of highly active antiretroviral therapy (HAART) on adipose tissue mitochondrial DNA (mtDNA) depletion, mitochondrial proliferation, and adipocyte differentiation markers. They analyzed adipose tissue samples from 31 HIV-infected individuals, comparing treatment-naive participants with those on HAART. Stavudine-based HAART led to mtDNA depletion, altered mitochondrial protein mass, and reduced expression of PPARgamma, UCP2, and UCP3 mRNA, while zidovudine-based HAART resulted in similar mtDNA effects, along with

Table 2. Genetic Contributions of somatic mutations to Leukocyte Clones in adipose tissue disorders.

Gene	Name	Leukocyte Clonal Variation	Role	Reference
TET2	Tet methylcytosine dioxygenase 2	Somatic inactivating mutations in hematopoietic cells	Exacerbate insulin resistance, trigger pro-inflammatory cytokines in white adipose tissue	(34)
DNMT3A	DNA methyltransferase 3 alpha	Clonal hematopoiesis and adipocyte progenitors	Various physiological and pathological processes	(38, 39)

increased UCP1 mRNA expression, particularly in non-stavudine, protease inhibitor-containing HAART (45). Kim et al. investigated mitochondrial alterations in lipoatrophy by analyzing DNA, RNA, and protein levels in abdominal subcutaneous adipose tissue from HIV-infected patients with lipoatrophy and controls. Despite mtDNA depletion and increased mitochondrial biogenesis indicators, normal cytochrome c oxidase activity and protein levels suggest compensation. Although mtDNA content didn't correlate with other mitochondrial parameters, severe mtDNA depletion coexisted with preserved mtDNA-dependent mitochondrial functions, and oxidative stress and apoptosis were present without correlation with mtDNA content (45). Multiple symmetric lipomatosis (MSL) is a rare disorder characterized by large subcutaneous fat masses in specific trunk regions. In patients with tRNALys mutations in mitochondrial DNA, lipomas within MSL originate from brown adipose cells, as evidenced by the expression of UCP-1 mRNA in these lipomas, which is not present in normal subcutaneous fat or lipomas with different tRNALys mutations (46).

Obesity has been observed in Finnish patients with ataxia caused by mitochondrial DNA polymerase-γ mutations, and a deficient version of this polymerase has been linked to reduced subcutaneous white adipose tissue and somatic mtDNA mutations during aging (47). The decrease in mtDNA content coincides with compromised expression of adipocyte differentiation-associated genes (such as peroxisome proliferator-activated receptor-γ), lipid accumulation-related genes (including lipoprotein lipase and GLUT4), as well as adipokines like adiponectin (41,45,48). Deficient enzymatic activity of mitochondrial deoxyribonucleoside kinases (DGUOK or TK2) leads to mitochondrial DNA (mtDNA)-depletion syndromes in humans. A mouse model lacking Tk2 demonstrates growth retardation, mtDNA loss, and tissue-specific effects, highlighting Tk2's crucial role in mtDNA replication (49). In both models, there was a significant depletion of mtDNA levels in white and brown adipose tissue.

The orphan nuclear receptor estrogen-related receptor α (ERRα) is involved in fatty acid metabolism. ERRα-null (ERRα−/−) mice exhibit reduced body weight, peripheral fat deposits, and resistance to high-fat diet-induced obesity, with altered expression of genes related to lipid synthesis and metabolism, highlighting ERRα's role in metabolic regulation (50). DNMT3A and TET2 potentially impact atherosclerotic cardiovascular disease risk by modulating lipid and glucose metabolism pathways. These epigenetic regulators influence genes related to lipid homeostasis and glucose utilization, offering insights into strategies for managing and preventing cardiovascular diseases (51). Table 3 shows somatic variations involved in Lipedema.

Conclusions

In conclusion, this review underscores the significance of investigating somatic mutations in the context of lipedema. It is crucial to emphasize that genetic investigations of pathological mutations are essential not only for unraveling existing genetic factors but also for identifying novel genes associated with diseases (53-55). The genetic underpinnings of this condition present intriguing pathways for exploration, including mitochondrial activity, mutated somatic clones, and leukocyte clones. By investigating these mechanisms, we could move closer to unraveling the complex genetic factors contributing to the development of lipedema (56-58). Such understanding is pivotal for advancing targeted diagnostic and therapeutic approaches for this challenging condition.

Table 3. Genetic Variations, Molecular Roles, and Disease Associations of Key Genes related to Mitochondrial activity

Gene	Name	Adipose tissue disorders	Reference
TFAM	transcription factor A, mitochondrial	Lipodystrophy	(40)
NRF1	nuclear respiratory factor 1	Lipodystrophy	(40)
GABPA	GA binding protein transcription factor subunit alpha	Lipodystrophy	(40)
PPARGC1A	PPARG coactivator 1 alpha	Lipodystrophy and obesity	(40, 52)
PPARGC1B	PPARG coactivator 1 beta	Lipodystrophy and obesity	(40, 52)
PPRC1	PPARG related coactivator 1	Lipodystrophy and obesity	(40)
POLG	DNA polymerase gamma	Obesity	(52)
ERR	estrogen related receptor alpha	Obesity	(52)
LPL	lipoprotein lipase	Obesity	(52)
GLUT4	solute carrier family 2 member 4	Obesity	(52)
ADIPOQ	adiponectin	Obesity	(52)
UCP1	uncoupling protein 1	Lipoatrophy	(45)
UCP2	uncoupling protein 2	Lipoatrophy	(45)
UCP3	uncoupling protein 3	Lipoatrophy	(45)
DLK1 (Pref-1)	preadipocyte factor-1	HALS-HIV-Associated Lipodystrophy Syndrome	(41)
MFN2	mitofusin 2	Obesity and lipomatosis	(43, 44)

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Conflicts of interest statement

Authors declare no conflict of interest.

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