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Review

# Genetic syndromes with localized subcutaneous fat tissue accumulation

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**Summary.** Syndromes with localized accumulation of subcutaneous fatty tissue belong to a group of genetically and phenotypically heterogeneous disorders. These diseases may show some common signs, such as nodular fat, symmetrical fat masses, obesity, fatigue, lymphedema and symmetrical lipomas (painful or otherwise). Other symptoms may be specific for the different clinical entities, enabling correct differential diagnosis. Disorders belonging to this spectrum are lipedema, generalized diffuse or nodular forms of Dercum disease, localized nodular Dercum disease and multiple symmetric lipomatosis. Here we summarize the genes involved in syndromes with localized accumulation of subcutaneous fat and the test we use for genetic analysis. (www.actabiomedica.it)

**Key words:** lipedema, Dercum disease, lipomatosis

Lipedema is an underdiagnosed chronic debilitating disease characterized by bruising, pain and excess subcutaneous fat affecting the lower and/or upper limbs of women during or after periods of hormonal change, especially puberty (1). The first guidelines on lipedema were proposed in Germany in 2015, and again in 2017 using the international classification of function, disability and health (2-4). Lipedema can easily be confused with obesity, but is distinguished by primarily affecting the lower limbs and upper extremities; the fat deposits do not reduce with a low-calorie diet and body mass index is normal (5). Lipedema can also be confused with lymphedema, but is always bilateral, whereas lymphedema can be unilateral or bilateral; pain and bruising are absent in lymphedema while lipedema patients are negative for Stemmer sign (6). The prevalence of lipedema has been reported to be 1-9/100,000 (7). Lipedema can be considered a component of a spectrum of diseases characterized by dysregulated proliferation of adipose tissue and pain: generalized diffuse form of Dercum disease (painful pearl-sized nodular subcutaneous adipose tissue throughout the body); generalized nodular form of Dercum disease (large painful nodules on the arms, trunk, and thighs); lipedema (localized form of painful fat with pearl-sized nodular fat and larger masses on the limbs); localized nodular form of Dercum disease (localized around joints); Madelung disease or multiple symmetric lipomatosis (nodular fat and lipomas on the upper part of the body (8,9). Genetic testing that includes all genes known to be involved in syndromes with localized accumulation of subcutaneous fat is useful for confirming diagnosis, and for differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation (10).

Syndromes with localized subcutaneous fat accumulation can have autosomal dominant or autosomal recessive inheritance (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the genes listed in Table 1.

**Table 1.** Genes associated with various forms of localized accumulation of subcutaneous fat

| .Gene | OMIM gene | Disease | OMIM disease | Inheritance | Function |
|---|---|---|---|---|---|
| *POU1F1* | 173110 | Combined pituitary hormone deficiency 1 (1 family with lipedema) | 613038 | AD | Regulation of expression of growth hormone, prolactin, thyroid-stimulating hormone |
| *NSD1* | 606681 | Sotos syndrome 1 (1 case with lipedema) | 117550 | AD | Androgen receptor transactivation |
| *ALDH18A1* | 138250 | Cutis laxa, type III (abnormal fat pad, buttocks, upper thighs (some patients) | 616603, 219150 | AD, AR | De novo biosynthesis of proline, ornithine, arginine |
| *PALB2* | 610355 | Multiple subcutaneous familial lipomatosis (1 case) | / | AD | DNA repair |
| *TBL1XR1* | 608628 | Pierpont syndrome | 602342 | AD | Essential transcription activation mediated by nuclear receptors |
| *MFN2* | 608507 | Madelung disease | 151800 | AR | Mitochondrial membrane protein necessary for mitochondrial fusion and maintenance of mitochondrial network |
| *LMNA* | 150330 | FPLD2 | 151660 | AD | Nuclear assembly, chromatin organization, nuclear membrane and telomere dynamics |
| *PPARG* | 601487 | FPLD3 | 604367 | AD | Master regulator of adipocyte differentiation |
| *PLIN1* | 170290 | FPLD4 | 613877 | AD | Coating of lipid storage droplets in adipocytes |
| *CIDEC* | 612120 | FPLD5 | 615238 | AR | Regulation of lipid droplet enlargement by restricting lipolysis, favoring storage |
| *LIPE* | 151750 | FPLD6 | 615980 | AR | Hydrolysis of stored triglycerides to free fatty acids |
| *AKT2* | 164731 | FPLD | / | AD | Key-mediator of insulin receptor |
| *ADRA2A* | 104210 | Atypical FPLD | / | AD | Fundamental for regulation of neurotransmitter release from sympathetic nerves and adrenergic neurons in CNS |

FPLD=familial partial lipodystrophy; AD=autosomal dominant; AR=autosomal recessive; CNS = central nervous system.

## Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with localized accumulation of subcutaneous fat. When this suspects is present we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of ≥99% (coverage depth ≥10x).

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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