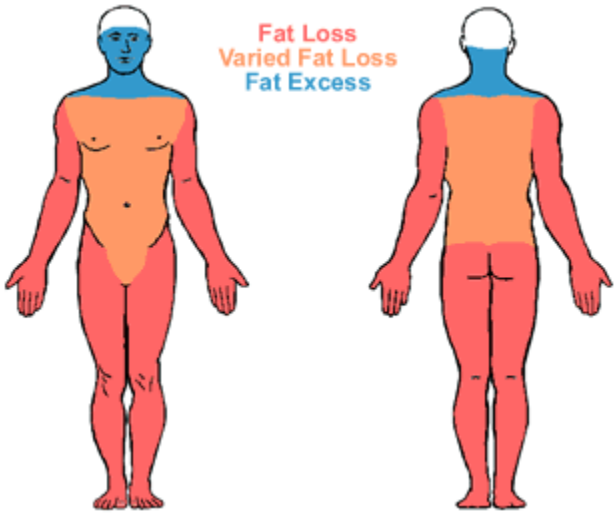
Inherited: Familial Partial - Dunnigan Variety (FPLD)



Familial partial lipodystrophy (FPL) is a rare autosomal dominant disorder which is characterized by variable loss of body fat from the extremities as well as from the truncal region. Individuals, both males and females, of several generations can be affected. The chance of transmission from an affected parent to offspring is 1:2 or 50%. Most of the patients have been of European origin; however, patients of African-American and Indian origin have been noted.

Familial partial lipodystrophy (FPL) is mostly inherited as an autosomal dominant condition caused by heterozygous mutations in genes. Three loci, lamin A/ C (*LMNA)*, peroxisome proliferator-activated receptor gamma (*PPARG)* and v-AKT murine thymoma oncogene homolog 2 (*AKT2*) have been identified for autosomal dominant types of FPL. Recently, a patient with autosomal recessive FPL has been identified with homozygous mutations in cell death –inducing Dffa-like effector C (*CIDEC*).

The most common FPL is the Dunnigan variety (FPLD) which is due to missense lamin A/ C (*LMNA)* mutations. It is also the most well characterized disorder. During childhood these patients do not show a lipodystrophy phenotype and have normal body fat distribution. The fat loss from the extremities and trunk occurs gradually at the time of puberty. Some patients at the same time .gain excess fat at the the face, chin ('double chin'), and neck ('Cushingoid appearance with buffalo hump'). Acanthosis nigricans and hepatomegaly is prominent, and in female patients hirsutism (increased body hair), menstrual abnormalities, and polycystic ovaries (enlarged ovaries) are observed infrequently. Women are more severely affected with metabolic complications such as diabetes, high levels of serum cholesterol and triglycerides and low levels of HDL cholesterol. Affected women with FPLD are more pre-disposed to coronary artery disease and other type of atherosclerotic vascular disease. Analysis of our research data also suggests similar symptoms.

Genetic Basis
FPL1locus- *LMNA*

LMNA gene for FPLD on the chromosome 1q21-22 was initially localized and identified by our lab. Subsequently, many missense mutations (alterations) have been identified in the Lamin A/C (LMNA) gene in patients with FPLD. LMNA encodes two major proteins, prelamin A, and lamin

C, and two minor proteins, by alternative splicing. Lamin A/C gene has 12 exons which by alternative splicing in exon 10 encodes lamin A (full form) or C (short form). Lamin A/C is a component of the nuclear lamina which is located between chromatin and the inner nuclear membrane. Thus, it is likely that missense mutations may affect nuclear function and may result in premature cell death of adipocytes (fat cells), thus causing lipodystrophy. Lamin A/C gene has 12 exons which by alternative splicing in exon 10 encodes lamin A (full form) or C (short form). Three-fourths of the FPLD patients have mutations at the codon position 482 where arginine is replaced by glutamine, leucine or tryptophan on exon 8. Some patients with mutations in exon 11 have been observed to have less severe form of lipodystrophy than those with exon 8 mutations. Rare patients with FPLD reveal mutations in exons 1and 3 and these patients develop cardiomyopathy (disease of heart muscles) which manifests as premature congestive heart failure and cardiac arrhythmias (rhythm disturbances), such as heart blocks and atrial fibrillation necessitating the use of cardiac pacemakers. Some of them had to undergo cardiac transplantation due to poor heart function. Lamins A and C are ubiquitously expressed proteins and therefore why specific mutations affect predominantly adipocytes and not other cells, remains unclear.

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