

## Familial Partial Lipodystrophy (FPLD)

Familial partial lipodystrophy (FPLD), Dunnigan variety, is transmitted as an autosomal dominant trait. 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 origins have been noted.

This lipodystrophy is characterised by gradual loss of subcutaneous fat (fat under the skin) from the upper and lower extremities during puberty with normal appearance at birth. The arms and legs appear very muscular. Veins under the skin appear prominent. Variable amount of fat is lost from the trunk. The loss of subcutaneous truncal fat is more evident anteriorly. In women, lack of fat in the buttocks (gluteal regions) is striking and they complain of "no-hips" or "flat hips". In many patients (mostly women), excess fat may accumulate in the face, and neck at puberty or thereafter. Patients may develop a double chin, excess supraclavicular fat (fat above the clavicle) and a round face (cushingoid appearance). Acanthosis nigricans (dark velvety pigmentation of the skin), hirsutism (increased body hair), menstrual abnormalities, and polycystic ovaries (enlarged ovaries) are observed infrequently.

Patients usually have high levels of serum triglycerides that lead to recurrent episodes of acute pancreatitis and low levels of HDL cholesterol. Onset of glucose intolerance or diabetes mellitus usually occurs after age 20. Compared with affected men, women with FPLD are particularly predisposed to develop diabetes, high levels of triglycerides, low levels of HDL cholesterol and early onset coronary artery disease and other types of atherosclerotic vascular disease. Data analysis suggests that women with FPLD who have had multiple pregnancies and those with increased accumulation of fat in the non-lipodystrophic regions such as chin may be more predisposed to develop diabetes mellitus.

### Genetic basis Lamin A/C (LMNA) mutations

Initially the gene for FPLD was localized on the chromosome 1q21-22. Subsequently, many missense mutations (alterations) have been identified in the Lamin A/C ( LMNA ) gene in patients with FPLD. Lamin A/C is a component of the nuclear lamina which is located between chromatin and the inner nuclear membrane. It is likely that defective lamins A/C cause premature death of fat cells in the extremities. 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 a less severe form of lipodystrophy than those with exon 8 mutations. Rare patients with FPLD reveal mutations in exon 1 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.

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