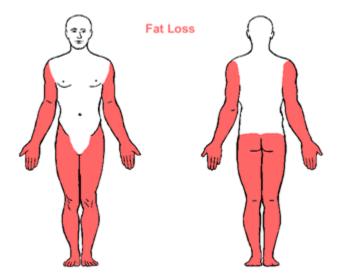
# Inherited: Familial Partial Lipodystrophies, other Types



# Familial Partial Lipodystrophy- PPAR gamma (Peroxisome Proliferator Activated Receptor- $\boldsymbol{\gamma}$ ) gene mutations

Only about twenty patients with FPL due to heterozygous mutation in PPARG have been reported so far. It is either much less common than FPL, Dunnigan variety or is less recognized likely due to milder phenotype. We recently reported heterozygous mutation (Arg397Cys) of peroxisome proliferator-activated receptor gamma (PPARG) gene (involved in the differentiation of body fat) in a patient who did not appear to have Dunnigan variety of lipodystrophy. This patient had diabetes mellitus, high levels of serum triglycerides, hirsutism and had loss of fat from the extremities and face at the age of 50. The loss of fat was more prominent in the forearms and calves than in the upper arms and thighs. Thus, *PPARG* gene mutation could be the molecular basis for one of the variety of familial partial lipodystrophy. Since our report, two other groups have reported additional FPL families with PPARG missense mutations (pro467Leu, Val290Met and Phe388Leu).

# FPL2 locus: PPARG

*PPARG is* a nuclear receptor protein. It is highly expressed in the adipose tissue. PPAR-γ protein is a nuclear transcription factor and plays an important role in adipogenesis (generation of new fat cells from precursor cells). It is suggested that missense mutation in the gene which is located on the chromosome 3p25 may cause FPL by affecting adipogenesis. Thus, these dominant negative mutations may impair adipocyte differentiation resulting in fat loss. However, why loss of fat is restricted to some areas of the body and not others remains unclear.

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#### Familial Partial Lipodystrophy due to v-AKT murine thymoma oncogene homolog 2 (AKT2) gene mutations

Recently, a heterozygous missense mutation, Arg274His, in AKT2 gene was reported in several members of a family who had insulin resistance and diabetes mellitus. One of them was a 35year-old white female who developed diabetes mellitus at age 30 years, whereas her mother and grandmother harboring the same mutation developed diabetes during late thirties and a maternal uncle, a middle-aged person, had no diabetes but had hyperinsulinemia. Three of the four affected subjects had hypertension. The 35 year-old lady also had reduced body fat and partial lipodystrophy affecting mainly her extremities however, in depth evaluation of body fat distribution has not been conducted.

# FPL3 locus: AKT2

AKT2, also know as protein kinase B (PKB), is a phosphoinositol dedependent serine/threonine kinase and is involved in post-receptor insulin signaling. It is located on the chromosome 19q13.2. The three isoforms of AKT share more than 80% amino acid identity. Whereas, AKT1 is expressed almost everywhere, AKT2 is predominantly expressed in insulin sensitive tissues and AKT3 in the testes and brain. The mutant form of ATK2 has reduced lipid accumulating capacity. Previously, a knock-out mouse model has shown features of lipodystrophy, insulin resistance and diabetes with increasing age. Thus, loss of adipose tissue in patients with heterozygous mutations in AKT2 may either be due to reduced adipocyte differentiation or dysfunctional post receptor signaling.

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