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NON-HIV LIPODYSTROPHY: FOCUS ON INHERITED LIPODYSTROPHIES

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Lipodystrophies can be either inherited or acquired, and the different types can show substantial clinical differences. Because patients with inherited lipodystrophies have insulin resistance that progresses to type 2 diabetes, these disorders are considered to be monogenic model systems for the metabolic syndrome (MetS). Inherited lipodystrophies can involve a complete loss of fat from childhood, such as that seen in autosomal recessive Berardinelli-Seip congenital generalized lipodystrophy (CGL). CGL occurs in two molecular forms: CGL1 (MIM 608594) results from mutations in AGPAT2 (MIM 603100) encoding 1-acyl-*sn*-glycerol-3-phosphate acetyltransferase, and CGL2 (MIM 269700) results from homozygosity for mutations in GNG3LG (MIM 606158) encoding seipin. In contrast, familial partial lipodystrophy (FPLD) is characterized by fat loss from limbs and the gluteal region at puberty, with preservation of central, facial and visceral fat. FPLD also occurs in two molecular forms: FPLD2 (MIM 151660) results from heterozygosity for germline mutations in LMNA (MIM 150330), encoding nuclear lamin A/C, while FPLD3 (MIM 604367) results from mutations in PPARG (MIM 601487), encoding peroxisomal proliferator-activated receptor (PPAR) γ . FPLD is associated with increased risk of several medical complications, including abnormal serum lipids, hypertension and diabetes. FPLD is associated with increased risk of coronary heart disease, particularly in women. Since FPLD has later onset and is progressive, it may be an appropriate model for MetS and HIV-associated lipodystrophy. Careful systematic phenotypic analysis of subjects with FPLD2 and FPLD3, an approach called ‘phenomics’, has defined distinct stages in FPLD with particular clinical and biochemical attributes. Fat loss appears to be the inciting event, followed by increases in serum insulin and free fatty acids, then dyslipidaemia, then hypertension, then diabetes and finally vascular complications. Furthermore, fat loss is more extensive in FPLD2 than in FPLD3, but the metabolic complications are more severe in FPLD3 than in FPLD2. Molecular genetic characterization of FPLD2 has revealed that mechanisms related to the structure and

function of the nucleoskeleton can lead to lipodystrophy. Molecular genetic characterization of FPLD3 has confirmed that human PPAR γ deficiency affects adipose tissue and leads to insulin resistance, as expected from the mechanism of action of thiazolidinedione.

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