Consider Cardiomyopathy in Subjects With Familial Partial Lipodystrophy

To the Editor:

Hegele1 excellently described the presence of premature coronary artery disease in 8 out of 23 adult subjects (aged above 35 years) with familial partial lipodystrophy (FPL) carrying LMNA mutations. His intriguing observations underline the striking similarity between FPL and the metabolic syndrome (also called syndrome X). The latter is known to result in premature coronary artery disease. In FPL, the phenotype of altered fatty tissue distribution and the prominence of the skeletal muscles, especially of the lower limbs, precedes the manifestation of dyslipidemia and diabetes mellitus. Dyslipidemia in turn seems to occur many years before diabetes mellitus may occur.2 However, it is remarkable, that Hegele reported on insulin resistance in all studied subjects, although 18/23 had dyslipidemia and 12/23 had diabetes mellitus. Does hyperinsulinemia and insulin resistance, respectively, precede dyslipidemia and diabetes mellitus in this selected cohort of patients? The observed coronary artery disease in FPL carrying LMNA mutations is presumably caused by the cardiovascular risk factors, which develop over time. At this point, there is no evidence that LMNA mutations result directly in atherogenesis.

Most of the currently reported mutations within LMNA result in peripheral and/or cardiac myopathy and/or arteriovenous conduction disease, but not in FPL.3 In contrast, mutations within LMNA causing FPL have not been observed to result in peripheral or cardiac muscle dystrophy. However, subjects with FPL present with prominent skeletal muscles with no adequate gain in muscular function. There is no detailed information on the heart in affected subjects.4 We identified an FPL family carrying the R482W mutation in respect to the genesis of cardiomyopathy. His intriguing observations underline the striking metabolic traits—potent risk factors—certainly led to the CHD in carriers.1-3 What is the cellular basis for these deleterious traits in carriers? Is the adipose repartitioning the inciting event in the cascade? These questions await resolution by other in vivo experiments.

Dr Schmidt next raised the issue of overlap between lipodystrophy and other disorders due to LMNA mutations, such as cardiomyopathy. In general, the association between the affected tissue type and the specific mutated LMNA residue is remarkably specific.4 For instance, lipodystrophy almost never occurs together with myopathy; none of the Canadian FPLD patients had either cardiomyopathy or conduction disturbances.3 The heart disease was clearly atherosclerotic, as indicated by coronary artery bypass graft surgery.1 However, some of us have seen rare patients, such as the one described by Dr Schmidt, with an overlap of lipodystrophy and cardiomyopathy. Elucidating the molecular mechanisms of these overlap syndromes will be most interesting.

Finally, Dr Schmidt suggested that gene-environment interactions could modulate the phenotype in carriers of mutant LMNA. This appears to be true for atherosclerosis susceptibility. For example, an elderly subject with definite FPLD and the LMNA R482W mutation escaped the development of diabetes, dyslipidemia, hypertension, and CHD.5 Her most obvious protective factor was a lifelong history of daily 5-km walks, suggesting that lifestyle could attenuate the metabolic complications. If confirmed, such observations could have therapeutic implications for FPLD mutation carriers who are identified early in the course of their disease.

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Response

Dr Schmidt’s letter raises several interesting points. First, what is the chain of metabolic events in Dunnigan-type familial partial lipodystrophy (FPLD) that begins with mutant LMNA and ends with premature atherosclerosis? The temporal sequence is suggested by observations from Canadian FPLD kindreds, in which relatively large numbers of mutation carriers were assessed at various ages and stages of disease progression.1,2 The initial metabolic abnormality is hyperinsulinemia, reflecting insulin resistance, although whether this precedes, overlaps with, or follows the adipose repartitioning is unclear. The next abnormality to present is dyslipidemia: elevated triglycerides and low HDL cholesterol. Hypertension presents next, although this is more variable. Finally, fasting hyperglycemia—frank diabetes—occurs many years later and most likely reflects pancreatic β-cell failure in the context of chronic insulin resistance. Dr Schmidt correctly states that LMNA mutations do not directly produce atherosclerosis; carriers with coronary heart disease (CHD) end points had hyperinsulinemia, dyslipidemia, hypertension, and diabetes.3 These intermediate metabolic traits—all potent risk factors—certainly led to the CHD in carriers.3 What is the cellular basis for these deleterious traits in carriers? Is the adipose repartitioning the inciting event in the cascade? These questions await resolution by other in vivo experiments.

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