LMNA missense mutations causing familial partial lipodystrophy do not lead to an accumulation of prelamin A.

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Abstract

A variety of missense mutations in LMNA (the gene for lamin C and prelamin A) cause familial partial lipodystrophy (FPLD), a disease associated with reduced adipose tissue, particularly in the limbs. Several studies have reported that fibroblasts from FPLD subjects have an accumulation of prelamin A. Those findings were intriguing but also perplexing because many of the LMNA missense mutations associated with lipodystrophy are located in sequences distant from the sequences required for the farnesylation of prelamin A and ZMPSTE24-mediated conversion of prelamin A to mature lamin A. Here, we revisited the issue of prelamin A accumulation in the setting of FPLD mutations. We used western blots with lamin A/C antibodies and prelamin A-specific monoclonal antibodies to assess prelamin A levels in wild-type fibroblasts and fibroblasts carrying LMNA mutations associated with lipodystrophy (R482W, I299V, C591F, T528M). None of the mutant fibroblasts exhibited an accumulation of prelamin A. Also, the amount of prelamin A accumulation in response to lopinavir (an inhibitor of ZMPSTE24) was similar in wild-type and mutant fibroblasts. Thus, the LMNA lipodystrophy mutations that we examined did not lead to prelamin A accumulation, nor did they render those cells more susceptible to prelamin A accumulation when ZMPSTE24 was inhibited by lopinavir.

KEYWORDS: lamin A/C; laminopathy; lipodystrophy; prelamin A; progeria

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