Structural instability of lamin A tail domain modulates its assembly and higher order function in Emery-Dreifuss muscular dystrophy.

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Abstract

The C-terminal Ig-domain of lamin A plays critical roles in cell function via interaction with proteins, DNA, and chromatin. Mutations in this domain are known to cause various diseases including Emery-Dreifuss muscular dystrophy (EDMD) and familial partial lipodystrophy (FPLD). Here we examined the biophysical and biochemical properties of mutant Ig-domains identified in patients with EDMD and FPLD. EDMD-related mutant Ig-domain showed decreased stability to heat and denaturant. This result was also confirmed by experiments using full-length mutant lamin A, although the decrease in melting temperature was much less than that of the mutant Ig-domain alone. The unstable EDMD Ig-domain disrupted the proper assembly of lamin A, resulting in abnormal paracrystal formation and decreased viscosity. In contrast, FPLD-related mutant Ig-domains were thermally stable, although they lost DNA binding function. Alanine substitution experiments revealed a functional domain of DNA binding in the Ig-domain. Thus, the overall biophysical property of Ig-domains is closely associated with clinical phenotype.

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KEYWORDS: Ig-domain; Lamin A; Laminopathy; Thermal stability

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