Chimeric protein identification of dystrophic, Pierson and other laminin polymerization residues.

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Abstract
Laminin polymerization is a key step of basement membrane self-assembly that depends on the binding of the three different N-terminal globular LN domains. Several mutations in the LN domains cause LAMA2-deficient muscular dystrophy and LAMB2-deficient Pierson syndrome. These mutations may affect polymerization. A novel approach to identify the amino acid residues required for polymerization has been applied to an analysis of these and other laminin LN mutations. The approach utilizes laminin-nidogen chimeric fusion proteins that bind to recombinant non-polymerizing laminins to provide a missing functional LN domain. Single amino acid substitutions introduced into these chimeras were tested to determine if polymerization activity and the ability to assemble on cell surfaces were lost. Several laminin α2 muscular dystrophy mutations, renal Pierson syndrome mutations, and Drosophila mutations causing defects of heart development were identified as ones causing loss of laminin polymerization. In addition, two novel residues required for polymerization were identified in the laminin γ1 LN domain.

KEYWORDS: Basement membrane; Chimeric proteins; Drosophila; LAMA2-md; LN domains; Pierson syndrome

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