Juvenile-onset generalized lipodystrophy due to a novel heterozygous missense LMNA mutation affecting lamin C.

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Abstract
The LMNA gene contains 12 exons and encodes lamins A and C by alternative splicing within exon 10. While mutations in lamin A specific residues cause several diseases including lipodystrophy, progeria, muscular dystrophy, neuropathy, and cardiomyopathy, only three families with mutations in lamin C-specific residues are reported with cardiomyopathy, neuropathy, and muscular dystrophy so far. We now report two brothers with juvenile-onset generalized lipodystrophy due to a lamin C-specific mutation. The proband, a 23-year-old Caucasian male was reported to have generalized lipodystrophy at 3 weeks of age, developed diabetes, hypertriglyceridemia, hypertension and liver problems and died with complications of cirrhosis, and kidney failure. His younger brother, a 37-year-old Caucasian male developed generalized lipodystrophy around 2 years of age and was diagnosed with diabetes, hypertriglyceridemia, fatty liver, and hypertension at 36 years of age. Their father also died of end stage renal disease at age 52 years. Exome sequencing of the proband revealed an extremely rare missense heterozygous variant c.1711_1712CG>TC; p.(Arg571Ser) in LMNA which was confirmed by Sanger sequencing in both the patients. Interestingly, the mutation had no effect on mRNA splicing or relative expression of lamin A or C mRNA and protein in the lymphoblasts. Our observations suggest that mutant lamin C disrupts its interaction with other cellular proteins resulting in generalized lipodystrophy due to defective development and maintenance of adipose tissue.

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KEYWORDS: LMNA; diabetes mellitus; generalized lipodystrophy; hepatic steatosis; hypertension; lamin C

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