Pathogenic and Likely Pathogenic Variants

A heterozygous c.1444C>T (p.Arg482Trp) pathogenic variant in the LMNA (NM_170707.3) gene was detected in this individual, which was confirmed by Sanger sequencing. Defects in LMNA are associated with a spectrum of distinct and overlapping conditions collectively termed the laminopathies. Laminopathies include autosomal dominant Emery-Dreifuss muscular dystrophy type 2 (EDMD2), also known as limb-girdle muscular dystrophy type 1B (LGMD1B), congenital muscular dystrophy (CMD), and dilated cardiomyopathy (DCM), along with autosomal recessive Emery-Dreifuss muscular dystrophy type 3 (EDMD3). Laminopathies which primarily affect the peripheral nervous system include autosomal recessive Charcot-Marie-Tooth disease type 2B1 (CMT2B1). Syndromic laminopathies affecting multiple systems include autosomal dominant and recessive familial partial lipodystrophy and Hutchinson-Gilford progeria syndrome (HGPS). The c.1444C>T (p.Arg482Trp) variant in the LMNA gene has been reported in unrelated individuals with familial partial lipodystrophy and segregates in affected families (PMID: 10655060, 11344241, 26976018, 22938045, 22938045, 24002959). This variant is present in 1/251272 (0.000398%) alleles in the gnomAD population database and is predicted to be deleterious by REVEL. Other variants affecting this same position (p.Arg482Gln, p.Arg482Leu) have also been reported in affected individuals (PMID: 10655060, 10587585, 31194872). Experimental studies have shown that this variant affects the function of the LMNA protein (PMID: 11929849, 25524705). Therefore, the c.1444C>T (p.Arg482Trp) variant in the LMNA gene is classified as pathogenic.

Table : Details of Pathogenic and Likely Pathogenic Variants

Disease	Inheritance	Gene	Type	Variant	Zygosity	Interpretation	Notes
Laminopathies [MIM 150330]	Autosomal Dominant	LMNA	SNV/InDel	c.1444C>T (p.Arg482Trp) NM_170707.3	Heterozygous	Pathogenic	Confirmed by Sanger sequencing