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Connie Gan
Washington University in St. Louis

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Mentor: Brian N. Finck

Site-1 Protease (S1P) is a Golgi-resident enzyme required for activation and subsequent nuclear localization of several major transcription factors. A 24-year-old female patient with a *de novo* single point mutation in S1P presented with a complex phenotype of gut hypomotility, abnormal optic nerves, and polycystic ovarian syndrome. Furthermore, this patient suffers from phenotypes related to skeletal muscle dysfunction. This phenomenon has been described in the literature to manifest from myoedema and the breakdown of muscle that releases intracellular proteins into the blood, or rhabdomyolysis.

Exomic sequencing revealed a heterozygous amino acid substitution (P1003S) in the transmembrane domain of S1P. Previous research has shown that S1P plays an integral role in the activation of ATF6 and SREBP2, key transcription factors involved in the ER stress response and cholesterol biosynthetic pathway, respectively.

The goal of this study was to characterize the mutant S1P protein by assessing protein activity and localization. Over-expression of mutant S1P in a lipid and cholesterol auxotrophic S1P-null cell line rescued the dependence on exogenous lipids and sterols similar to null cells expressing wild-type S1P. Furthermore, induction of ER stress with tunicamycin showed a heightened expression of ATF6 target genes in mutant S1P patient fibroblasts relative to control patient cells. A similar elevated response in SREBP2 target genes was also observed when the SREBP2 pathway was stimulated in the mutant fibroblasts. In addition, EndoH sensitivity assays showed that localization of mutant S1P to the Golgi was not impaired. This initial characterization demonstrated that the *de novo* mutation produces a gain-of function phenotype and that the mutation does not disrupt proper localization of the protein. This is the first known case of S1P mutation in humans and it is unknown how many harbor similar mutations of the S1P protein, critical for sterol homeostasis.