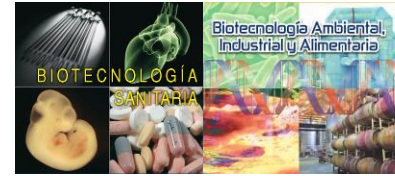


## Talk

# POGLUT1 mutation causes a muscular dystrophy with reduced Notch signaling and satellite cell loss



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**Keywords:** Distrofia muscular; células satélite; Notch; O-glucosiltransferasa

## ABSTRACT

**Motivation:** It is widely known that Notch signaling pathway plays critical roles in the highly coordinated muscle regenerative process, maintaining an appropriate population of satellite cells and preventing premature differentiation. Our previous work in *Drosophila* and mammalian cell lines has shown that addition of O-linked glucose to Notch receptors by protein O-glucosyltransferase 1 (POGLUT1; also known as Rumi) is required for Notch signaling. We describe a family with autosomal recessive limb-girdle muscular dystrophy, in which a homozygous missense D233E mutation in POGLUT1 dramatically reduces its enzymatic activity on Notch.

**Results:** We describe a family with autosomal recessive limb-girdle muscular dystrophy, in which a homozygous missense D233E mutation in POGLUT1 dramatically reduces its enzymatic activity on Notch. As a result, our family shows a defect in Notch signaling, with a significant depletion of satellite cells resulting in defective muscle regeneration, ultimately leading to muscle dystrophy. We show that the enzymatic activity of POGLUT1 is also essential for the formation of adult muscles by myoblasts in *Drosophila*. Moreover, cross-species overexpression studies in *Drosophila* indicate that the D233E mutation impairs the ability of human POGLUT1 in rescuing the muscle defects in flies lacking endogenous POGLUT1 activity. Together, these observations demonstrate that the POGLUT1 enzymatic activity plays an evolutionarily conserved role in muscle stem/progenitor cells.

An additional striking result in our family was the reduced  $\alpha$ -dystroglycan glycosylation and functional defect as a receptor, in muscle but not in fibroblasts from skin. This result suggests that the reduction in  $\alpha$ -dystroglycan glycosylation is related to defects in the satellite cells. According to previously reported by Goddeeris et al (Nature 2013), we propose the altered timing and dynamic of the muscle regenerative process in our patients can explain why  $\alpha$ -dystroglycan is hypoglycosylated only in muscle fibers and not in the skin.

**Conclusions:** These findings broadens the field of pathomechanisms in muscular dystrophy and identify a new class of O-linked glycosylation as an important player. Our findings demonstrate that D233E mutation in POGLUT1 causes autosomal recessive limb-girdle muscular dystrophy and implicate a primary defect in muscle progenitor cells as a novel pathomechanism for muscular dystrophy.

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