Abstract Title: A gene editing based pluripotent stem cell model for Pompe disease

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Abstract: Pompe's disease (PD) is an inherited lysosomal storage disorder (LSD) with a global prevalence of 1 in 40,000. PD is caused by mutations affecting the enzymatic function of acid α-glucosidase (GAA) encoding gene. GAA is a hydrolase that breaks down glycogen within lysosomes and in PD, its reduced or complete loss of function causes glycogen accumulation in cells. This causes a progressive dysregulation of functions associated with heart, skeletal and the respiratory system. Enzyme replacement therapy (ERT), which involves administrating recombinant functional GAA enzyme remains the primary treatment for PD patients. The current ERT is inefficient in rescuing skeletal muscle defects and also comes with a heavy cost burden. Induced pluripotent stem cells (iPSCs) derived from PD patients have demonstrated to display the hallmarks of the disease and can be effectively used to study PD pathology. In this present study, we have successfully utilised CRISPR-Cas9 based gene editing approach to generate a PD embryonic stem cell line that carries mutations that are prevalent in India. The cell line is a homozygous GAA mutant with negligible enzyme activity and maintained all the functions of pluripotency. As skeletal muscles are severely affected in PD, we have also established protocols for deriving them. Further, we also show that the stem cell model can recapitulate PD pathogenesis demonstrating it's potential to be used in testing biotherapeutics and disease modelling studies.

Area of expertise: Human pluripotent stem cells and genome editing