Summary of Duke Pediatric Medical Genetics Glycogen Storage Disease Type IV (GSD IV) Research Program (2016)

Priya Kishnani
Duke University School of Medicine, Durham, North Carolina

1. ***A modified enzymatic method for measurement of glycogen content in GSD IV:*** Standard enzymatic method, used to quantify glycogen content in GSD IV tissues, causes significant loss of the polysaccharides during preparation of tissue lysates. We report a modified method including an extra boiling step to dissolve the insoluble glycogen, ultimately preserving the glycogen content in tissue homogenates from GSD IV mice. This study provides important information for improving disease diagnosis, monitoring disease progression, and evaluating treatment outcomes in both clinical and preclinical clinical settings for GSD IV.
2. ***Starch binding domain-containing protein 1 (stbd1) plays a dominant role in glycogen transport to lysosomes in liver:*** A small portion of cellular glycogen is transported to and degraded in lysosomes by acid alpha-glucosidase (GAA) in mammals, but the function and mechanism of this process remain unknown. Here we generated a GAA/Stbd1 double knockout mouse model and identified that Stbd1 is a major mediator for transporting glycogen to lysosomes in mouse liver. Our finding provides a potential novel therapeutic target for both lysosomal and cytoplasmic GSDs.
3. ***Alglucosidase alfa treatment alleviates liver disease in a mouse model of GSD IV:*** Patients with progressive hepatic form of GSD IV often die of liver failure in early childhood. We tested the feasibility of using recombinant human acid-α glucosidase (rhGAA) for treating GSD IV. Weekly intravenously injection of rhGAA at 40 mg/kg for 4 weeks significantly reduced hepatic glycogen accumulation, lowered liver/body weight ratio, and reduced plasma ALP and ALT activities in GSD IV mice. Our data suggests that rhGAA is a potential therapy for GSD IV.
4. ***Systemic correction of murine GSD IV by an AAV-mediated gene therapy:*** Deficiency of glycogen branching enzyme (GBE) in GSD IV results in deposition of polyglucosan bodies in multiple tissues. In this study we demonstrated that a single injection of an AAV-GBE vector into GSD IV (*Gbe1*$^{ys/ys}$) mice at a young age effectively prevented glycogen accumulation in all muscles and, to a lesser extent, in the liver and brain for up to 9 months of age. In addition, the AAV treatment resulted in an overall decrease in plasma activities of alanine transaminase, aspartate transaminase, and creatine kinase. Our data suggests a long-term benefit of AAV-mediated gene therapy for GSD IV.

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