Research update: Generation of the mouse model of *Gbe1* intronic insertion/deletion and approaches to treatments

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The synthesis of glycogen is catalyzed by the sequential actions of two enzymes: (i) glycogen synthase, which attaches up to about 10 glucosyl units in alpha-1,4-glucosidic bonds to nascent linear chains of glycogen; and (ii) the branching enzyme, which attaches a short branch of approximately 4 glucosyl units to a linear chain in an alpha-1,6-glucosidic bond. Glycogen storage disease type IV (GSD IV) (OMIM 232500) is an autosomal recessive disorder caused by glycogen branching enzyme (GBE) deficiency and leading to the accumulation of an abnormal polysaccharide (polyglucosan, PG) in multiple tissues, including liver, heart, skeletal muscle, and the central nervous system. A late-onset clinical variant, known as adult PG body disease (APBD), causes a neurodegenerative disorder simulating amyotrophic lateral sclerosis (ALS). Most APBD patients are of Ashkenazi Jewish origin and harbor a c.986A>C change in GBE1. Although carriers do not develop the disease, a high number of manifesting heterozygous develop APBD. Onset and prognosis of APBD in these manifesting heterozygous patients are similar to homozygous patients. They have lower enzyme activity and are homozygous at mRNA level for c.986A>C, strongly suggesting the existence of a second mutation in the other allele. Recently, we have discovered this mutation in intron 15 of *GBE1*. This mutation is a complex deep intronic change, deleting 9 bp "GTGTGGTGG" of DNA sequence and replacing it with 19 bp "TGTTTTTTACATGACAGGT" DNA sequence. This sequence contains a strong splice acceptor site, which affects proper RNA synthesis. Unlike the common c.986A>C mutation, location and property of this intronic mutation allowed us to develop antisense oligonucleotide (ASO) treatment to recover the normal mRNA and enzyme synthesis from the affected allele.