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Case Report

Analysis of *GBE1* mutations via protein expression studies in glycogen storage disease type IV: A report on a non-progressive form with a literature review

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ABSTRACT

Background: Glycogen storage disease type IV (GSD IV), caused by *GBE1* mutations, has a quite wide phenotypic variation. While the classic hepatic form and the perinatal/neonatal neuromuscular forms result in early mortality, milder manifestations include non-progressive form (NP-GSD IV) and adult polyglucosan body disease (APBD). Thus far, only one clinical case of a patient with compound heterozygous mutations has been reported for the molecular analysis of NP-GSD IV. This study aimed to elucidate the molecular basis in a NP-GSD IV patient via protein expression analysis and to obtain a clearer genotype-phenotype relationship in GSD IV.

Case presentation: A Japanese boy presented hepatosplenomegaly at 2 years of age. Developmental delay, neurological symptoms, and cardiac dysfunction were not apparent. Observation of hepatocytes with periodic acid-Schiff-positive materials resistant to diastase, coupled with resolution of hepatosplenomegaly at 8 years of age, yielded a diagnosis of NP-GSD IV. Glycogen branching enzyme activity was decreased in erythrocytes. At 13 years of age, he developed epilepsy, which was successfully controlled by carbamazepine.

Molecular analysis: In this study, we identified compound heterozygous *GBE1* mutations (p.Gln46Pro and p.Glu609Lys). The branching activities of the mutant proteins expressed using *E. coli* were examined in a reaction with starch. The result showed that both mutants had approximately 50% activity of the wild type protein.

Conclusion: This is the second clinical report of a NP-GSD IV patient with a definite molecular elucidation. Based on the clinical and genotypic overlapping between NP-GSD IV and APBD, we suggest both are in a continuum.

1. Introduction

Glycogen storage disease type IV (GSD IV; Andersen disease [1]; OMIM #232500) is a rare autosomal recessive metabolic disorder caused by a deficiency of amylo-(1,4 to 1,6)-transglucosidase (EC 2.4.1.18, 1,4-alpha-glucan-branching enzyme, GBE). It is characterized by the accumulation of an amylopectin-like glycogen (polyglucosan) in multiple organs, such as the liver, muscle, heart, and the central and peripheral nervous systems [2]. Several phenotypic categories have been reported for GSD IV [3]. The classic hepatic form is the most common, wherein patients progress rapidly to cirrhosis and tend to die no later than 5 years of age, unless liver transplantation is attempted [1,4–8]. Meanwhile, patients with the non-progressive form (NP-GSD IV) display hepatosplenomegaly and elevated transaminase levels, which regress spontaneously without any features of cirrhotic, neurologic, muscular, or cardiac involvement [4,9]. In addition, a neuromuscular form has been reported, which is further sub-divided in accordance with the age at onset (perinatal, neonatal, juvenile, or adult). Patients with the perinatal form present in utero fetal akinesia deformation sequence, polyhydramnios, fetal hydrops, arthrogryposis,

Abbreviations: APBD, adult polyglucosan body disease; GBE, 1,4-alpha-glucan-branching enzyme; GSD IV, glycogen storage disease type IV; NP-GSD IV, non-progressive form of glycogen storage disease type IV; RT-PCR, reverse transcriptase-polymerase chain reaction; WT, wild type

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and perinatal death [5,10–19]. Those with the neonatal form present hypotonia, muscular atrophy, and cardiomyopathy immediately postpartum, and usually die in the neonatal period [4–6,16,18,20–24]. The juvenile form is dominated by myopathy or cardiomyopathy with pubertal or young adult onset [5,25]. The adult form, also known as adult polyglucosan body disease (APBD), is characterized by adult-onset multisystem disorder including myopathy or neurological involvement such as neurogenic bladder, seizure, or spastic paraplegia with vibration loss and numbness [26–32].

The aforementioned various manifestations in GSD IV result from mutations in a single responsible gene, *GBE1* (*607839). *GBE1* is located on chromosome 3p14, consists of 16 exons, and encodes a protein of 702 amino acid residues [33]. Thus far, 52 different *GBE1* mutations have been reported, including missense, nonsense, deleterious, insertional, and splice-site mutations (Fig. 1). To our knowledge, however, only two mutations (p.Leu224Pro and p.Tyr329Ser) in a single patient have been identified in NP-GSD IV [4]. Interestingly, one of these mutations (p.Tyr329Ser) is a founder mutation of APBD among individuals of Ashkenazi-Jewish descent [27,31]. In addition, functional protein expression analysis has been performed in only one study [4].

Herein, we describe a case of NP-GSD IV caused by novel missense *GBE1* mutations and present a review of the literature to obtain a clearer genotype-phenotype relationship in GSD IV.

2. Case report

A Japanese boy was referred to our hospital at 2 years of age because of elevated serum transaminases. He was born after an uneventful pregnancy and had no significant family history. At the time of admission, his height and weight were 80.9 cm (−1.5 SD) and 10.54 kg (−0.9 SD), respectively. He had hepatosplenomegaly (liver 6 cm below the right costal margin and spleen 1.5 cm below the left costal margin). His developmental milestones were normal, and he did not present any neurologic symptoms. Laboratory data indicated an elevation of serum transaminases (AST 221 IU/l and ALT 124 IU/l), without any other

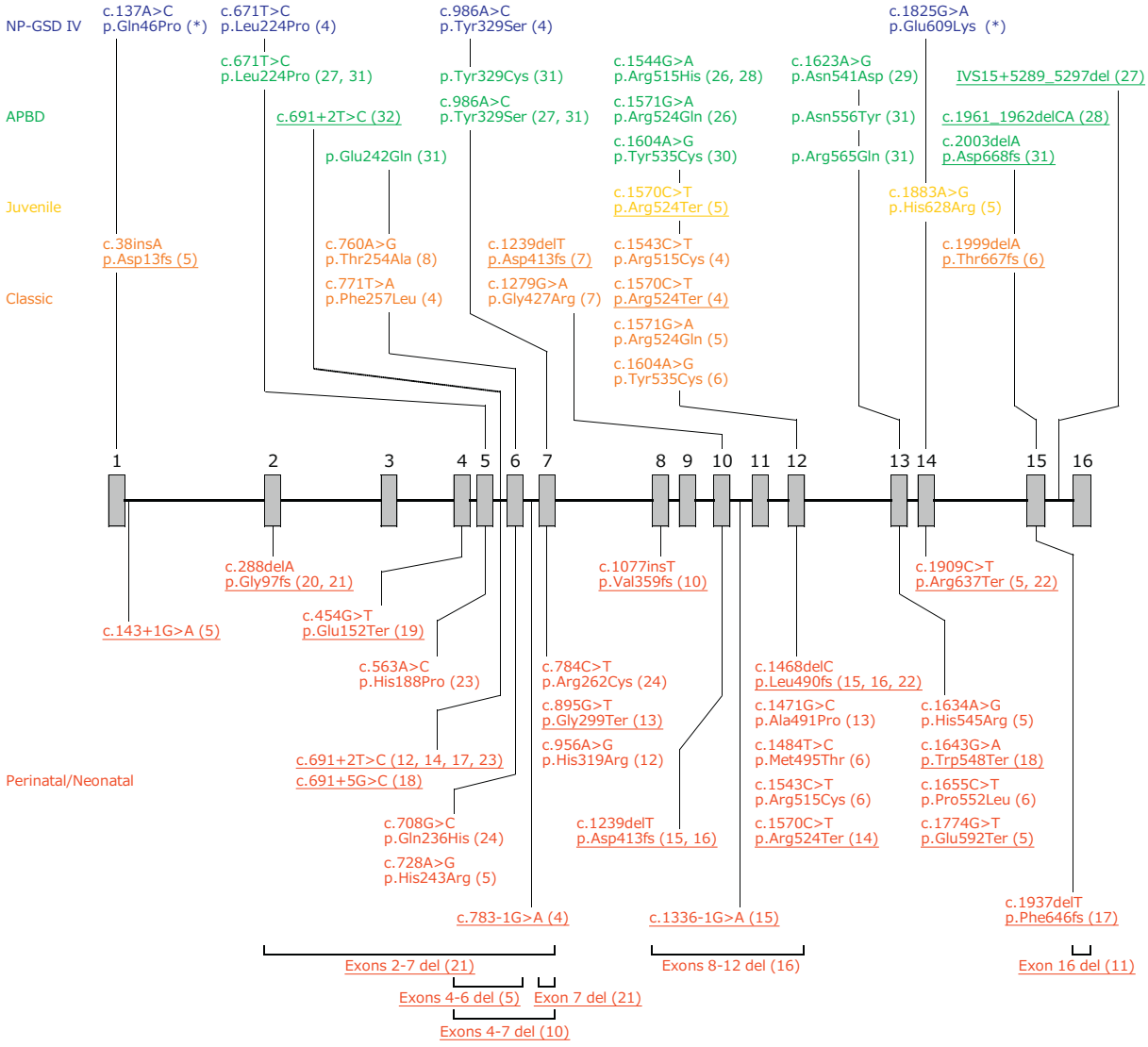

Fig. 1. Organization of the *GBE1* gene, and disease-associated mutations hitherto reported.
The number above each box indicates the exon number. References are denoted in parentheses. The mutations identified in our patient are indicated by an asterisk. Null mutations such as intragenic deleterious, nonsense, frameshift, and splice-site mutations are underlined. Herein, we gathered neonatal and perinatal forms in a mass because their diagnostic criteria are not strictly determined and clinical outcomes in these forms do not differ significantly. Null mutations, except for those located in exons 15 and 16, tend to associate with more severe forms of glycogen storage disease type IV (GSD IV), such as classic hepatic form or perinatal/neonatal neuromuscular forms. The same mutations are often reported in unrelated patients with milder forms, such as non-progressive-GSD IV (NP-GSD IV) and adult polyglucosan body disease (APBD).