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Case Report

# Interpretation of acid α-glucosidase activity in creatine kinase elevation: A case of Becker muscular dystrophy

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**Abstract**

*Background:* Diagnosis of Pompe disease is sometimes challenging because it exhibits clinical similarities to muscular dystrophy.

*Case:* We describe a case of Becker muscular dystrophy (BMD) with a remarkable reduction in activity of the acid α-glucosidase (GAA) enzyme, caused by a combination of pathogenic mutation and polymorphism variants resulting in pseudodeficiency in *GAA*. The three-year-old boy demonstrated asymptomatic creatine kinase elevation. Neither exon deletion nor duplication was detected on multiplex ligation-dependent probe amplification (MLPA) of *DMD*. GAA enzyme activity in both dried blood spots and lymphocytes was low, at 11.7% and 7.7% of normal, respectively. However, genetic analysis of *GAA* detected only heterozygosity for a nonsense mutation (c.118C > T, p.Arg40*). Muscle pathology showed no glycogen deposits and no high acid phosphatase activity. Hematoxylin-eosin staining detected scattered regenerating fibers; the fibers were faint and patchy on immunochemistry staining of dystrophin. The amount of dystrophin protein was reduced to 11.8% of normal, on Western blotting analysis. Direct sequencing analysis of *DMD* revealed hemizygosity for a nonsense mutation (c.72G > A, p.Trp24*). The boy was diagnosed with BMD, despite remarkable reduction in GAA activity; further, he demonstrated heterozygosity for [p.Gly576Ser; p.Glu689Lys] polymorphism variants that indicated pseudodeficiency on another allele in *GAA*.

*Conclusions:* Pseudodeficiency alleles are detected in approximately 4% of the Asian population; these demonstrate low activity of acid α-glucosidase (GAA), similar to levels found in Pompe disease. Clinicians should be careful in their interpretations of pseudodeficiency alleles that complicate diagnosis in cases of elevated creatine kinase.
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*Keywords:* Acid α-glucosidase (GAA); Pseudodeficiency; Becker muscular dystrophy (BMD); Dystrophin; Creatine kinase

## 1. Introduction

Neuromuscular diseases are considered in some children who repeatedly exhibit elevated creatine kinase. A variety of glycogen storage diseases are included in differential diagnosis, such as Pompe disease, which can

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be treated with enzyme replacement therapy. Pompe disease is diagnosed through assessment of acid α-glucosidase (GAA) in lymphocytes and fibroblasts, as well as genetic analysis and muscle biopsy [1]. Recently, neonatal screening has included dried blood spots for earlier diagnosis and administration of enzyme replacement therapy [2,3]. However, there are pseudodeficiency polymorphism variants; these do not result in disease, even when low GAA enzyme activity is found [3–5].

A boy with incidentally-detected elevated creatine kinase was initially suspected of Pompe disease because of his low GAA enzyme activity; however, he was ultimately diagnosed with Becker muscular dystrophy (BMD). We present this instructive case regarding interpretation of GAA enzyme activity.

## 2. Case report

The patient was the third child of unrelated, healthy Japanese parents. He was born at 38 weeks of gestational age and weighed 3566 g. There was no family history of muscular dystrophy or creatine kinase elevation. His motor and mental milestones were not delayed. His blood was tested when he presented at the hospital for constipation at the age of three years old. Elevated creatine kinase was recognized repeatedly, ranging from 2421 to 5257 U/L. Multiplex ligation-dependent probe amplification (MLPA) of *DMD* revealed neither exon deletion nor duplication. GAA enzyme activity in dried blood spots was reduced, at 2.50 pmol/punch/h (normal: 21.38 pmol/punch/h), 11.7% of normal activity; this was accompanied by low GAA enzyme activity in lymphocytes, at 2.35 nmol/mg protein/h (normal range: 30.7 ± 10.3 nmol/mg protein/h, patient with Pompe disease: 1.48 ± 0.87 nmol/mg protein/h), 7.7% of normal activity (Table 1). Genetic analysis of *GAA* (NM_000152.4) detected heterozygosity for a nonsense mutation, c.118C > T (p.Arg40*), which was previously reported as disease-causing [6], and thirteen polymorphism variants, including c.1726G > A, p.Gly576Ser used by Sanger sequence (Table 2). The enzyme activity assay and genetic analyses were performed as published by Oda et al. [7].

Table 2
List of polymorphism variants in this case.

| | |
|---|---|
| c.547-4C > G | c.1551 + 49A>C |
| c.596G > A, p.Arg199His | c.1726G > A, p.Gly576Ser |
| c.668A > G, p.His223Arg | c.1888 + 21G>A |
| c.858 + 8G>A | c.2065G > A, p.Glu689Lys |
| c.858 + 24ins7 | c.2113A > G, p.Thr711Thr |
| c.858 + 30 T>C | c.2553A > G, p.Gly851Gly |
| c.1203A > G, p.Gln401Gln | |

The variants are classified as functionally benign, except for p.Gly576Ser and p.Glu689Lys (ClinVar).

At four years old, he was admitted to our hospital, suspected of Pompe disease. He exhibited no muscle weakness and hypertrophy of calf muscles. Blood tests showed AST 68 U/L, ALT 54 U/L, creatine kinase 4298 U/L, and aldolase 37.8 U/L. Muscle MRI showed negligible fatty infiltration of the gluteus maximus. Needle electromyography demonstrated myogenic change. Skeletal muscle biopsy was performed from the rectus femoris. Hematoxylin-eosin staining showed mild variation in fiber size and scattered regenerating fibers (Fig. 1A). However, Periodic acid-Schiff staining found no deposits of glycogen; acid phosphatase staining revealed no increased activity, as well as acid-phosphatase-positive global cytoplasmic inclusions [8]. These findings were not suggestive of Pompe disease. Additionally, immunochemistry staining for dystrophin showed faint, patchy expression on muscular fibers (Fig. 1B). The amount of dystrophin protein was significantly reduced, 11.8% of normal mean, on Western blotting analysis. Direct sequencing of *dystrophin* revealed hemizygosity for a nonsense mutation, (NM_004006.2: c.72G > A (p.Trp24*)). These findings supported the diagnosis of BMD. Analysis of *GAA* from his parents showed that one parent had a nonsense mutation and the other parent had p.Gly576Ser polymorphism (Table 1). The patient demonstrated the pathogenic mutation on one allele and the pseudodeficiency variant on the other allele.

Table 1
Comparison of GAA enzyme activity and *GAA* variants between proband and parents.

| | GAA enzyme activity in lymphocytes nmol/mg protein/h (% of normal mean) | *GAA* variants | |
|---|---|---|---|
| Proband | 2.35 (7.7) | c.118C > T, p.Arg40* | c.1726G > A, p.Gly576Ser<br>c.2065G > A, p.Glu689Lys |
| Parent A | 9.26 (30.2) | c.118C > T, p.Arg40* | |
| Parent B | 6.15 (20.0) | | c.1726G > A, p.Gly576Ser<br>(c.2065G > A, p.Glu689Lys) |

GAA enzyme activity in lymphocytes; Normal range: 30.7 ± 10.3 nmol/mg protein/h, patient with Pompe disease: 1.48 ± 0.87 nmol/mg protein/h. The substrate used for measuring GAA enzyme activity was 4-methylumbelliferyl α-D-glucopyranoside. In Parent B, the presence of only the p.Gly576Ser variant was confirmed, whereas no analysis was performed for p.Glu689Lys. However, pGly576Ser does not exist in isolation; it is always accompanied by p.Glu689Lys [5]. Parent B appears to have both p.Gly576Ser and p.Glu689Lys.

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