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Original Article

A novel compound heterozygous GAA mutation in a Chinese family with juvenile onset form of Pompe disease with cardiomyopathy

Lingling Xu[1*], Lidan Zhang[1*], Liangying Zhong[2], Xueqiong Huang[1], Suping Li[1], Yucai Cheng[1,4], Yujian Liang[1], Yuxin Pei[1], Huimin Huang[1], Wen Tang[1], Cheng Zhang[3]

Departments of [1]Pediatric Intensive Care Unit, [2]Laboratory Medicine, [3]Neurology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [4]Department of Pediatrics, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, China. [*]Co-first authors.

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Abstract: Pompe disease is an autosomal recessive disorder resulting from a deficiency of acid α-glucosidase (GAA). It is uncommon in the mainland of China, due to rare mutations in the *GAA* gene. The aim of this work was to elucidate the causative role of a novel compound heterozygous mutation of juvenile onset Pompe disease. In this study, clinical samples were obtained from two siblings with muscle weakness, recurrent airway infections, cardiomyopathy and respiratory insufficiency in a non-consanguineous Chinese family. The α-glucosidase activity in leukocytes of both children was low. Next-generation sequencing was performed on the 19 coding exons of *GAA* in both children, with confirmation by Sanger sequencing. Next-generation sequencing showed the same compound heterozygous *GAA* mutation (c.1216G>A p.Asp406Asn and c.1935C>A p.Asp645Glu) in both children. As this mutation is consistent with the clinical manifestations of juvenile onset Pompe disease and no other mutations were detected after scanning the gene sequence, we suggest that the Pompe disease phenotype is caused by compound heterozygosity for c.1216G>A and c.1935C>A. As c.1216G>A is not currently listed in the Pompe disease Mutation Database, this information about Pompe disease in a Chinese population is of particular interest.

Keywords: Pompe disease, juvenile onset, *GAA* mutation, c.1216G>A, c.1935C>A, Chinese family, cardiomyopathy

Introduction

Pompe disease (Glycogen storage disease type II, GSD II, acid maltase deficiency, OMIM #232300), an autosomal recessive disorder, is caused by a deficiency of acid alpha-1, 4-glucosidase (*GAA*; EC.3.2.10.20). Pompe disease is classified into infantile form (the classical and atypical infantile forms), and late onset form (juvenile and adult forms) based on the time of disease onset. The juvenile form usually presents with muscle weakness resembling that of progressive muscular dystrophy and is rarely associated with cardiomyopathy. The infantile form, originally described by Pompe, exhibits a rapidly progressive course characterized by prominent cardiomegaly, hepatomegaly, muscle weakness and hypotonia, and eventually death before the patient reaches 1 year of age. Adult-onset Pompe disease is characterized by slowly progressive limb-girdle sympathy presenting as late as the second to the sixth decade with or without respiratory insufficiency [1].

Pompe disease caused by mutations in the human gene *GAA* (OMIM #606800), and which is located on chromosome 17q25.2-25.3, is typically transcribed into three RNA forms encoding the same protein. The *GAA* gene is approximately 28 kb long and contains 20 exons (transcript variant 1, NM_000152) [2]. Molecular analysis of *GAA* in patients with Pompe disease has uncovered more than 558 different mutations which are listed in the Pompe disease mutation database (www.pompecenter.nl), updated on May 2016. In general, GAA activity correlates with the age at onset

Table 1. Summary of the clinical presentation of the family

Parameter	Patient 1 (P1)	Patient 2 (P2)	Sibling 3	Father	Mother
Sex-Age (years)	M-2	F-4	F-6	M-34	F-33
Type	Juvenile	Juvenile	-	-	-
Enzyme Activity*	1.45	1.03	-	-	-
Limb Weakness	+	+	-	-	-
Cardiac hypertrophy	+	+	-	-	-
Recurrent airway infections	+	+	-	-	-
Respiratory distress	+	-	-	-	-
Respiratory failure	+	-	-	-	-
Body weight (kg)	9	12	16	-	-
Body height (cm)	95	97	107	-	-
Proximal muscle strength	II-III	III-IV	V	V	V
Highest serum creatinekinase level (U/L)	1766	4116	Normal	Normal	Normal
Electromyography	Neurogenic changes in left rectus femoris muscle, left biceps, double tibialis anterior muscle and right gastrocnemius muscle	Neurogenic changes in left gastrocnemius, double biceps, double tibialis anterior muscle	-	-	-
Genotype#	c.1935C>A (ls), c.1216G>A (unknown)	c.1935C>A (ls), c.1216G>A (unknown)	?	c.1216G>A/-	c.1935C>A/-

*Enzyme activity in leukocytes (nmol/h/mg); Normal range: >14 nmol/h/mg; #Effect of the mutations: potentially less severe (ls) (see for details www. pompecenter.nl); + = Presence; - = Absence; F = Female; M = Male; ? = Unknown.

and severity of disease. Recently, isolation of GAA from peripheral blood leukocytes extracts has been developed for GAA activity assay [3].

The combined incidence of all forms of Pompe disease is approximately 1:40,000 [4]. The estimated frequency of Pompe disease in southern China and Taiwan newborns is 1 in 20,000-40,000 [5]. In Taiwanese populations, the c.1935C>A (p.Asp645Glu) mutation represents 36%-80% of mutations [6, 7]. Yet, very few cases of Pompe disease have been reported in Mainland China.

In the present study, we report the clinical features and a new heterozygous GAA compound gene mutation (c.1216G>A and c.1935C>A) of two siblings in a Mainland Chinese family with a juvenile onset form of Pompe disease. They were presented with clinical characteristics such as muscle weakness, recurrent airway infections and respiratory insufficiency. So, we herein elucidate the causative role of a novel compound heterozygous mutation (c.1216G>A and c.1935C>A) in the pathogenesis of a severe form of GAA with a review of previously reported cases.

Patients and methods

*Subjects (**Table 1**)*

The first patient (P1), a 2-year-old boy, born at term gestation by vaginal delivery weighed 4.7 kg at birth. He started walking 20 months after birth. His first visit to our clinic was when he was 2 years old. Respiratory problems (such as recurrent airway infections and respiratory distress) with progressive limb weakness were the first symptoms. He was admitted to our intensive care unit because of respiratory failure. Physical examination revealed malnutrition, with a body weight of 9 kg (-3 SD) and a height of 95 cm (0.2 SD) and a body weight for height value of -3.2 SD [8]. Neurological examination revealed a diffuse decrease of muscle mass in both the upper and lower extremities. Proximal muscle strength was II/III in the upper extremities and II in the lower extremities. Deep tendon reflexes were normal in upper extremities, and were absent in the patella and the Achilles tendons. Laboratory evaluation was unremarkable except for a mildly elevated creatine kinase level (range 201-1766 U/L; normal value 25-200 U/L). Left ventricular hypertrophy was observed during echocardiography (**Figure 1A**). Electromyography showed neurogenic changes in the left rectus femoris muscle, left biceps, double tibialis anterior muscle and right gastrocnemius muscle.

The second patient (P2), the sibling of P1, a 4-year-old girl, was born at term gestation by vaginal delivery and weighed 3.9 kg at birth. She started to walk 13 months after birth. Her first visit to our clinic was then that she was 4 years of age. She experienced recurrent airway

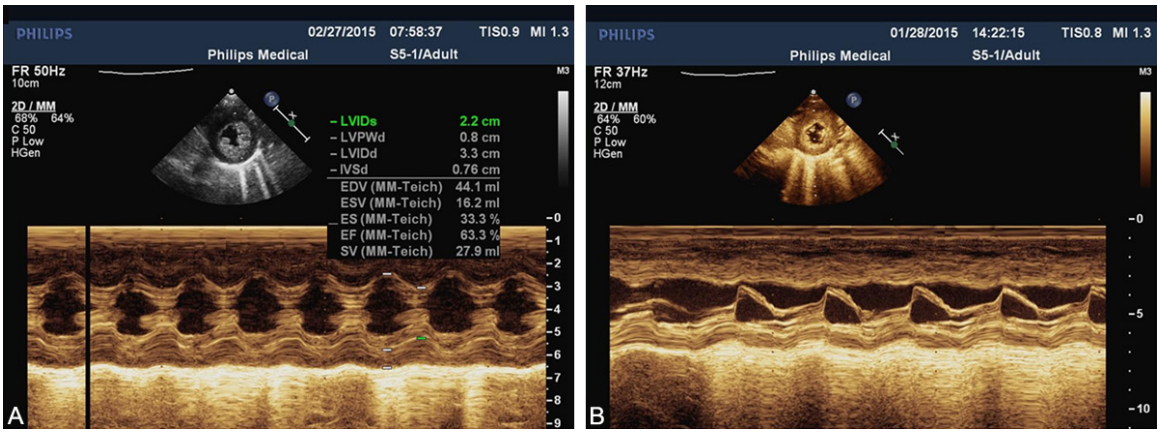


Figure 1. Echocardiogram images. A. The patient 1's interventricular septum thickness (8 mm). B. The patient 2's interventricular septum thickness (8 mm).

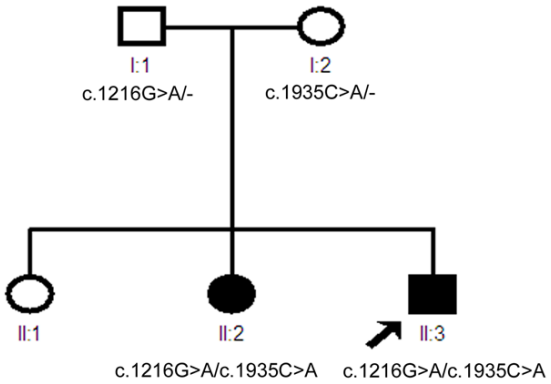


Figure 2. Family pedigree: the patient 1 is indicated by an arrow (II:3). The patient 2 is II:2.

infections and respiratory distress with progressive limb weakness and one month later she was admitted to our intensive care unit because of respiratory failure. Physical examination revealed malnutrition, with a body weight of 12 kg (-3.5 SD) and a height of 97 cm (-2 SD) and a body weight for height value of -2.2 SD. Neurological examination revealed a diffuse decrease in muscle mass in both the upper and lower extremities. Proximal muscle strength was II/III in the upper extremities and II in the lower extremities. Deep tendon reflexes were normal in the upper extremities, but were decreased in the patellas, and the Achilles tendons. Laboratory evaluation revealed a mildly elevated creatine kinase level (range 237-4116 U/L; normal value 25-200 U/L). Echocardiography revealed a left ventricular hypertrophy (**Figure 1B**). Electromyography showed neurogenic changes in the left gastrocnemius, double biceps, and double tibialis anterior muscle.

We herein describe two mainland Chinese siblings with clinical features of juvenile onset Pompe disease including recurrent airway infections and respiratory distress and muscular weakness that were mainly associated with neuromuscular disorders. Ultimately the diagnosis of Pompe disease was confirmed via the acid a-glucosidase deficiency and the presence of new compound heterozygous mutation in GAA gene.

The family comprised five individuals spanning two generations, coming from southern China (south of the Yangtze River) (**Figure 2**). The healthy non-consanguineous parents had no personal or family history of Pompe disease, following a healthy pregnancy with no prenatal complications. They have three children. The eldest sister is healthy. The other two children had pompe disease.

Ethical approval was obtained for this study from the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). All data were collected with informed consent of the parents.

Both children needed mechanical ventilatory support during the early phase of their hospital stay. They were treated with low tidal volume ventilation, anti-infection, regular mobilization on the bed, back patting and sputum suction. We also administered drugs to protect the heart and liver function as well as nourish the nerve. Both children quickly underwent smooth ventilator weaning (maybe you should state how long it took), without alglucosidasealfa (Myozyme®) enzyme replacement therapy.

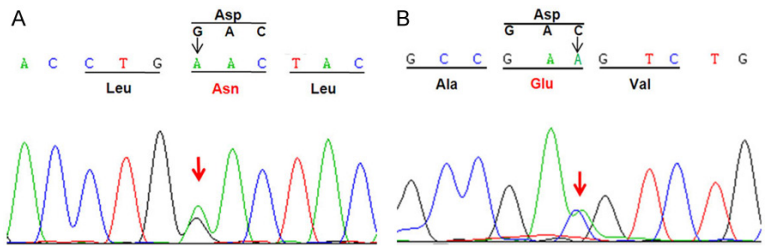


Figure 3. The chromatograms showing mutations identified in this study. A. In patients single base change from G to A at position c.1216 produced the substitution of aspartic acid at position p.406 to asparagusate. B. Amino acid aspartic acid at position p.645 is substituted to glutamic acid by the single base change from C to A at position c.1935 in patients.

GAA enzyme assay

The GAA activity was obtained from peripheral blood leukocytes.

GAA mutation analysis

5 ml of peripheral blood was obtained by venipuncture from the patients and their parents, and Genomic DNA was extracted from peripheral blood leukocytes with the QIAamp Blood DNA Mini Kit (Qiagen, American). The coding region (exon 2-exon 20) of GAA was amplified with PCR from genomic DNA. Primers for 19 exons and exon-intron boundaries of GAA were designed using Primer 5.0. PCR amplification was performed in a conventional PCR machine (ABI Gene AmpPCR System 9700, Life Technologies, USA) with 2 × Red Dye PCR master mixes. PCR products were analyzed using a 3500 Genetic DNA analyzer, ABI Prism (Life technology, USA). NG_009822.1 and NM_000152.3 were used as the reference sequence for the coding regions to find a mutation.

The pathogenicity prediction of the missense mutation

The assessment of the damaging effect of missense mutation was performed using PolyPhen-2 software (http://genetics.bwh.harvard.edu/pph2/). This software calculates the probability that a given mutation is damaging and reports both possible false positive rates (the chance that the mutation is classified as damaging when it is in fact non damaging) and true positive rates (the chance that the mutation is classified as damaging when it is indeed damaging). Our results showed PolyPhen-2 achieved true positive prediction rates of 92% and 73% on HumDiv and HumVar datasets, respectively [9]. The probability of a false positive rate was 20%.

Results

The diagnosis of late-onset Pompe disease was confirmed by an abnormal low acid alpha glucosidase activity. The α-glucosidase activity in white blood cells of the elder sister (P2) was 1.03 nmol/h/mg and the younger brother (P1) was 1.45 nmol/h/mg (>14 nmol/h/mg).

The capture and sequencing of genomic DNA indicated that both siblings had the same mutations in the *GAA* gene. Sanger sequencing confirmed that both siblings carried the same compound heterozygous mutation (c.1216G>A and c.1935C>A) in *GAA*. Furthermore, sequencing of the parental DNA showed that the c.1216G>A mutation was inherited from the father (**Figure 3A**). Whereas the c.1935C>A mutation was inherited from the mother (**Figure 3B**). Molecular analysis of the healthy elder sister was not done due to non-consent of the parents.

The pathogenicity prediction of the c.1216G>A mutation

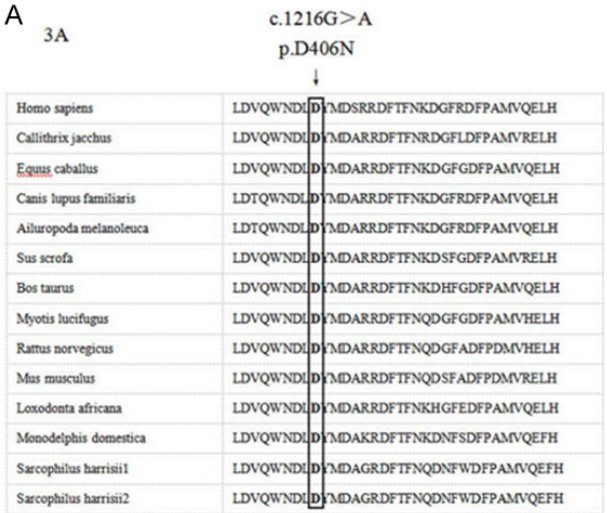
Multiple sequence alignments of GAA homologous sequences in different species are shown (**Figure 4A**). Poly-Phen-2 analysis predicted that this variant is probably damaging with score of 1.000 and 0.998 on HumDiv and HumVar models, respectively (**Figure 4B**).

Discussion

The *GAA* genetic mutation analysis revealed a previously unreported compound heterozygous mutation (c.1216G>A and c.1935C>A). Normative population databases (e.g., 1000 Genomes SNP Database and HapMap) were used for comparison, and this same mutation has not been previously observed in Pompe disease patients. The mutation identified in this study is associated with the clinical manifestations of Pompe disease, and no other mutation was detected after scanning the gene sequence.

In our study, the siblings inherited a novel c.1216G>A (p.Asp406Asn) missense mutation from their father and a c.1935C>A (p.Asp645Glu) missense mutation from their mother. Their parents both in heterozygosis were asy-

A



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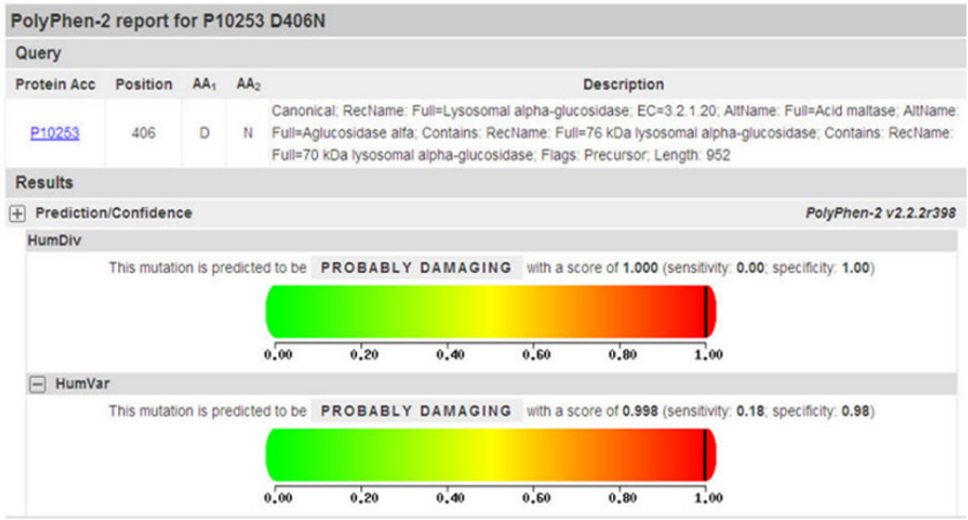

Figure 4. A. Multiple sequence alignments of *GAA* homologous sequences in different species are shown. Missense mutation reported in this study is highlighted by a black rectangle, illustrating that the p.D406N (p.Asp406Asn) mutation is in a highly conserved region. B. Results of the PolyPhen-2 analysis predicting the pathogenicity the c.1216G>A substitution on GAA protein.

mptomatic. GAA mutations have been reported to cluster in three critical regions: exon 2 which contains the start codon, exon 10 and 11 which contain the enzyme catalytic site, and exon 14, which encodes a highly conserved region of the protein [10]. Genetic heterogeneity is a characteristic of Pompe disease. Missense mutations have been reported to be involved with impaired enzyme synthesis, transport, post-translational modification and function [11, 12]. The missense mutation c.1935C>A (p.Asp645Glu), located in exon 14, has frequently been identified in Taiwanese Pompe disease patients [13, 14], and the presence of a "potentially less severe" mutation (http://www.pompecenter.nl/). Also, c.1935C>A mutation has also been identified in mainland Chinese patients with infantile and late onset Pompe disease [15]. The other missense mutation c.1216G>A, located in exon 8, has not been elsewhere reported.

It should be noted that the disease was relatively more severe in P1 than in P2. The relative severity of the disease in our patients were not determined by the low enzyme activity [16], but Wens et al. reported genotype, other factors such as epigenetic and environmental effects influence the clinical presentation and disease course [17]. The genotype-phenotype relationship for the c.1216G>A mutation in Pompe disease is not clear. The c.1216G>A mutation is likely pathogenic in several reasons. First, in multiple alignment analysis, both amino acids are highly conserved between several species of mammals and reside in the conserved regions of amino acid sequences. The highly conservation of the amino acid at the position 1216 (**Figure 4A**) suggests that the replacement within the aspartic acid may change the tertiary structure of GAA. Second, consequently, the D406N (Asp406Asn) substitution caused by our mutation may affect the function and the stability of GAA protein (**Figure 4B**). The mutation is likely to produce a conformational change in protein structure since the charged amino acid Aspartic acid has been substituted into an uncharged amino acid Asparagine. Most of the reported mutations associated with late onset Pompe disease are missense mutations producing a single amino acid change as in patients [18]. Another characteristic of mutations found in Pompe disease is that many of the GAA mutations show ethnic specificity [19, 20]. For example, c.-32-13T>G is the most common mutation in Caucasian patients with a frequency as high as 34-47% [21-26]. Conversely, c.1935C>A (p.D645E) and c.2238G>C (p.W746C) are common in Taiwanese patients (include probability rate) [13, 15, 27], while it is not among Japanese (include probability rate) [19, 28]. Mutations in the GAA gene that cause Pompe disease have been sporadically identified in mainland Chinese patients. Fu L et al. examined a total of 18 Chinese children with infantile-onset Pompe disease and found 6 novel mutations (c.1356delC, c.378G>A, c.18-27C>G, c.859-2A>T, c.1551+2T>G, and c.14-65G>T) in mainland China [15]. Now, we identified one novel missense mutation c.1216G>A (p.Asp406Asn) in mainland patients with late onset Pompe disease.

Respiratory difficulty is a consistent feature in juvenile onset Pompe disease, and often precedes ambulatory failure in many patients [29]. Previous studies have suggested that a smaller proportion of patients with late onset (juvenile and adult onset) Pompe disease (<10%) have cardiovascular involvement, including electrophysiological abnormalities and myocardial hypertrophy [30-32]. We herein report two siblings diagnosed with a juvenile onset form Pompe disease with both having skeletal and cardiac muscle involvement. P1 had hypertrophic myocardiopathy, while P2 had ventricular hypertrophy. This may be the clinical characteristics of the compound heterozygous mutation (c.1216G>A and c.1935C>A).

Enzyme-replacement therapy (ERT) is currently being evaluated in the treatment of the severe infantile form [33] as well as late-onset [34] patients, but is not widely available yet in Mainland China.

In summary, we diagnosed two siblings Mainland Chinese patients with Pompe disease using biochemical and molecular genetic analyses and discovered a novel GAA mutation. This is significant in that mutation could be specific for patients with late onset form of the disease.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wen Tang, Department of Pediatric Intensive Care Unit, The First Affiliated Hospital of Sun Yat-sen University, Zhongshan Er Lu, Guangzhou 510080, China. Tel: (0086) 13688893116; E-mail: tangwen@mail.sysu.edu.cn

References

[1] Maggi L, Salerno F, Bragato C, Saredi S, Blasevich F, Maccagnano E, Pasanisi B, Danesino C, Mora M, Morandi L. Familial adult-onset Pompe disease associated with unusual clinical and histological features. Acta Myol 2013; 32: 85-90.

[2] Martiniuk F, Bodkin M, Tzall S, Hirschhorn R. Isolation and partial characterization of the structural gene for human acid alpha glucosidase. DNA Cell Biol 1991; 10: 283-92.

[3] Okumiya T, Keulemans JL, Kroos MA, Van der Beek NM, Boer MA, Takeuchi H, Van Diggelen OP, Reuser AJ. A new diagnostic assay for glycogen storage disease type II in mixed leukocytes. Mol Genet Metab 2006; 88: 22-8.

[4] Martiniuk F, Chen A, Mack A, Arvanitopoulos E, Chen Y, Rom WN, Codd WJ, Hanna B, Alcabes P, Raben N, Plotz P. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. Am J Med Genet 1998; 79: 69-72.

[5] Lin CY, Shieh JJ. Molecular study on the infantile form of Pompe disease in Chinese in Taiwan. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1996; 37: 115-21.

[6] Ko TM, Hwu WL, Lin YW, Tseng LH, Hwa HL, Wang TR, Chuang SM. Molecular genetic study of Pompe disease in Chinese patients in Taiwan. Hum Mutat 1999; 13: 380-4.

[7] Shieh JJ, Wang LY, Lin CY. Point mutation in Pompe disease in Chinese. J Inherit Metab Dis 1994; 17: 145-8.

[8] Li H, Ji CY, Zong XN, Zhang YQ. [Height and weight standardized growth charts for Chinese children and adolescents aged 0 to 18 years]. Zhonghua Er Ke Za Zhi 2009; 47: 487-92.

[9] Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR. A method and server for predicting damaging missense mutations. Nat Methods 2010; 7: 248-9.

[10] Fernandez-Hojas R, Huie ML, Navarro C, Dominguez C, Roig M, Lopez-Coronas D, Teijeira S, Anyane-Yeboa K, Hirschhorn R. Identification of six novel mutations in the acid alpha-glucosidase gene in three Spanish patients with infantile onset glycogen storage disease type II (Pompe disease). Neuromuscul Disord 2002; 12: 159-66.

[11] Reuser AJ, Kroos MA, Hermans MM, Bijvoet AG, Verbeet MP, Van Diggelen OP, Kleijer WJ, Van der Ploeg AT. Glycogenosis type II (acid maltase deficiency). Muscle Nerve Suppl 1995; 3: S61-9.

[12] Hermans MM, De Graaff E, Kroos MA, Mohkamsing S, Eussen BJ, Joosse M, Willemsen R, Kleijer WJ, Oostra BA, Reuser AJ. The effect of a single base pair deletion (delta T525) and a C1634T missense mutation (pro545leu) on the expression of lysosomal alpha-glucosidase in patients with glycogen storage disease type II. Hum Mol Genet 1994; 3: 2213-8.

[13] Yang CC, Chien YH, Lee NC, Chiang SC, Lin SP, Kuo YT, Chen SS, Jong YJ, Hwu WL. Rapid progressive course of later-onset Pompe disease in Chinese patients. Mol Genet Metab 2011; 104: 284-8.

[14] Amarinthnukrowh P, Tongkobpetch S, Kongpatanayothin A, Suphapeetiporn K, Shotelersuk V. p.D645E of acid alpha-glucosidase is the most common mutation in Thai patients with infantile-onset pompe disease. Genet Test Mol Bioma 2010; 14: 835-7.

[15] Fu L, Qiu W, Yu Y, Guo Y, Zhao P, Zhang X, Liu C, Li F, Huang H, Huang M, Chen S. Clinical and molecular genetic study of infantile-onset Pompe disease in Chinese patients: identification of 6 novel mutations. Gene 2014; 535: 53-9.

[16] Remiche G, Ronchi D, Magri F, Lamperti C, Bordoni A, Moggio M, Bresolin N, Comi GP. Extended phenotype description and new molecular findings in late onset glycogen storage disease type II: a northern Italy population study and review of the literature. J Neurol 2014; 261: 83-97.

[17] Wens SC, van Gelder CM, Kruijshaar ME, de Vries JM, van der Beek NA, Reuser AJ, van Doorn PA, van der Ploeg AT, Brusse E. Phenotypical variation within 22 families with Pompe disease. Orphanet J Rare Dis 2013; 8: 182.

[18] Pittis MG, Montalvo AL, Miocic S, Martini C, Deganuto M, Candusso M, Ciana G, Bembi B. Identification of four novel mutations in the alpha glucosidase gene in five Italian patients with infantile onset glycogen storage disease type II. Am J Med Genet A 2003; 121A: 225-30.

[19] Raben N, Plotz P, Byrne BJ. Acid alpha-glucosidase deficiency (glycogenosis type II, Pompe disease). Curr Mol Med 2002; 2: 145-66.

[20] Huie ML, Anyane-Yeboa K, Guzman E, Hirschhorn R. Homozygosity for multiple contiguous single-nucleotide polymorphisms as an indicator of large heterozygous deletions: identifica-

tion of a novel heterozygous 8-kb intragenic deletion (IVS7-19 to IVS15-17) in a patient with glycogen storage disease type II. Am J Hum Genet 2002; 70: 1054-7.

[21] Huie ML, Chen AS, Tsujino S, Shanske S, DiMauro S, Engel AG, Hirschhorn R. Aberrant splicing in adult onset glycogen storage disease type II (GSDII): molecular identification of an IVS1 (-13T-->G) mutation in a majority of patients and a novel IVS10 (+1GT-->CT) mutation. Hum Mol Genet 1994; 3: 2231-6.

[22] Joshi PR, Glaser D, Schmidt S, Vorgerd M, Winterholler M, Eger K, Zierz S, Deschauer M. Molecular diagnosis of German patients with late-onset glycogen storage disease type II. J Inherit Metab Dis 2008; 31 Suppl 2: S261-5.

[23] Gort L, Coll MJ, Chabas A. Glycogen storage disease type II in Spanish patients: high frequency of c.1076-1G>C mutation. Mol Genet Metab 2007; 92: 183-7.

[24] Montalvo AL, Bembi B, Donnarumma M, Filocamo M, Parenti G, Rossi M, Merlini L, Buratti E, De Filippi P, Dardis A, Stroppiano M, Ciana G, Pittis MG. Mutation profile of the GAA gene in 40 Italian patients with late onset glycogen storage disease type II. Hum Mutat 2006; 27: 999-1006.

[25] Laforet P, Nicolino M, Eymard PB, Puech JP, Caillaud C, Poenaru L, Fardeau M. Juvenile and adult-onset acid maltase deficiency in France: genotype-phenotype correlation. Neurology 2000; 55: 1122-8.

[26] Kroos MA, Van der Kraan M, Van Diggelen OP, Kleijer WJ, Reuser AJ, Van den Boogaard MJ, Ausems MG, Ploos van Amstel HK, Poenaru L, Nicolino M, et al. Glycogen storage disease type II: frequency of three common mutant alleles and their associated clinical phenotypes studied in 121 patients. J Med Genet 1995; 32: 836-7.

[27] Liu X, Wang Z, Jin W, Lv H, Zhang W, Que C, Huang Y, Yuan Y. Clinical and GAA gene mutation analysis in mainland Chinese patients with late-onset Pompe disease: identifying c.2238G > C as the most common mutation. BMC Med Genet 2014; 15: 141.

[28] Tsujino S, Huie M, Kanazawa N, Sugie H, Goto Y, Kawai M, Nonaka I, Hirschhorn R, Sakuragawa N. Frequent mutations in Japanese patients with acid maltase deficiency. Neuromuscul Disord 2000; 10: 599-603.

[29] Pipo JR, Feng JH, Yamamoto T, Ohsaki Y, Nanba E, Tsujino S, Sakuragawa N, Martiniuk F, Ninomiya H, Oka A, Ohno K. New GAA mutations in Japanese patients with GSDII (Pompe disease). Pediatr Neurol 2003; 29: 284-7.

[30] van der Beek NA, Soliman OI, van Capelle CI, Geleijnse ML, Vletter WB, Kroos MA, Reuser AJ, Frohn-Mulder IM, van Doorn PA, van der Ploeg AT. Cardiac evaluation in children and adults with Pompe disease sharing the common c.-32-13T>G genotype rarely reveals abnormalities. J Neurol Sci 2008; 275: 46-50.

[31] Muller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, Pongratz D, Walter MC, Baethmann M, Schlotter-Weigel B, Lochmüller H, Schoser B. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007; 17: 698-706.

[32] Soliman OI, van der Beek NA, van Doorn PA, Vletter WB, Nemes A, Van Dalen BM, ten Cate FJ, van der Ploeg AT, Geleijnse ML. Cardiac involvement in adults with Pompe disease. J Intern Med 2008; 264: 333-9.

[33] Berrier KL, Kazi ZB, Prater SN, Bali DS, Goldstein J, Stefanescu MC, Rehder CW, Botha EG, Ellaway C, Bhattacharya K, Tylki-Szymanska A, Karabul N, Rosenberg AS, Kishnani PS. Corrigendum: CRIM-negative infantile Pompe disease: characterization of immune responses in patients treated with ERT monotherapy. Genet Med 2015; 17: 596.

[34] Qiu JJ, Wei M, Zhang WM, Shi HP. [Clinical and molecular genetic study on two patients of the juvenile form of Pompe disease in China]. Zhonghua Er Ke Za Zhi 2007; 45: 760-4.