World Journal of *Clinical Cases*

World J Clin Cases 2022 December 26; 10(36): 13148-13469





Published by Baishideng Publishing Group Inc

W J C C World Journal of Clinical Cases

Contents

Thrice Monthly Volume 10 Number 36 December 26, 2022

MINIREVIEWS

13148 Liver injury in COVID-19: Holds ferritinophagy-mediated ferroptosis accountable Jia FJ. Han J 13157 Amebic liver abscess by Entamoeba histolytica

Usuda D, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Takano H, Shimozawa S, Hotchi Y, Tokunaga S, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M

Living with liver disease in the era of COVID-19-the impact of the epidemic and the threat to high-risk 13167 populations

Barve P, Choday P, Nguyen A, Ly T, Samreen I, Jhooty S, Umeh CA, Chaudhuri S

Cortical bone trajectory screws in the treatment of lumbar degenerative disc disease in patients with 13179 osteoporosis

Guo S, Zhu K, Yan MJ, Li XH, Tan J

13189 Probiotics for preventing gestational diabetes in overweight or obese pregnant women: A review Deng YF, Wu LP, Liu YP

ORIGINAL ARTICLE

Retrospective Cohort Study

13200 Effectiveness of microwave endometrial ablation combined with hysteroscopic transcervical resection in treating submucous uterine myomas

Kakinuma T, Kakinuma K, Shimizu A, Kaneko A, Kagimoto M, Okusa T, Suizu E, Saito K, Matsuda Y, Yanagida K, Takeshima N, Ohwada M

13208 Antibody and complement levels in patients with hypersplenism associated with cirrhotic portal hypertension and therapeutic principles

Zhang K, Zeng M, Li YJ, Wu HF, Wu JC, Zhang ZS, Zheng JF, Lv YF

Retrospective Study

- 13216 Case series in Indonesia: B.1.617.2 (delta) variant of SARS-CoV-2 infection after a second dose of vaccine Karuniawati A, Syam AF, Achmadsyah A, Ibrahim F, Rosa Y, Sudarmono P, Fadilah F, Rasmin M
- 13227 Endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic lymphadenopathy with extrathoracic malignancy

Li SJ, Wu Q

13239 Analysis of the clinical efficacy of two-stage revision surgery in the treatment of periprosthetic joint infection in the knee: A retrospective study

Qiao YJ, Li F, Zhang LD, Yu XY, Zhang HQ, Yang WB, Song XY, Xu RL, Zhou SH



World Journal of Clinical Cases		
Contents Thrice Monthly Volume 10 Number 36 December 26, 2022		
13250	Prognostic factors for disease-free survival in postoperative patients with hepatocellular carcinoma and construction of a nomogram model	
	Luo PQ, Ye ZH, Zhang LX, Song ED, Wei ZJ, Xu AM, Lu Z	
13264	Oral higher dose prednisolone to prevent stenosis after endoscopic submucosal dissection for early esophageal cancer	
	Zhan SG, Wu BH, Li DF, Yao J, Xu ZL, Zhang DG, Shi RY, Tian YH, Wang LS	
13274	Predictive value of the unplanned extubation risk assessment scale in hospitalized patients with tubes	
	Liu K, Liu Z, Li LQ, Zhang M, Deng XX, Zhu H	
13284	Classification of rectal cancer according to recurrence types - comparison of Japanese guidelines and Western guidelines	
	Miyakita H, Kamei Y, Chan LF, Okada K, Kayano H, Yamamoto S	
13293	Risk of critical limb ischemia in long-term uterine cancer survivors: A population-based study	
	Chen MC, Chang JJ, Chen MF, Wang TY, Huang CE, Lee KD, Chen CY	
13304	Serum Spondin-2 expression, tumor invasion, and antitumor immune response in patients with cervical cancer	
	Zhang LL, Lin S, Zhang Y, Yao DM, Du X	
13313	Thoracic para-aortic lymph node recurrence in patients with esophageal squamous cell carcinoma: A propensity score-matching analysis	
	Li XY, Huang LS, Yu SH, Xie D	
13321	Anastomotic leakage in rectal cancer surgery: Retrospective analysis of risk factors	
	Brisinda G, Chiarello MM, Pepe G, Cariati M, Fico V, Mirco P, Bianchi V	
	META-ANALYSIS	
13337	Successful outcomes of unilateral <i>vs</i> bilateral pedicle screw fixation for lumbar interbody fusion: A meta- analysis with evidence grading	
	Sun L, Tian AX, Ma JX, Ma XL	
	CASE REPORT	
13349	Pregnancy-induced leukocytosis: A case report	
	Wang X, Zhang YY, Xu Y	
13356	Acute moderate to severe ulcerative colitis treated by traditional Chinese medicine: A case report	
	Wu B	
13364	Solitary hyoid plasmacytoma with unicentric Castleman disease: A case report and review of literature	
	Zhang YH, He YF, Yue H, Zhang YN, Shi L, Jin B, Dong P	
13373	Recurrence of intratendinous ganglion due to incomplete excision of satellite lesion in the extensor digitorum brevis tendon: A case report	
	Park JJ, Seok HG, Yan H, Park CH	



Conton	<i>World Journal of Clinical Cases</i> ontents Thrice Monthly Volume 10 Number 36 December 26, 2022	
Conten		
13381	Two methods of lung biopsy for histological confirmation of acute fibrinous and organizing pneumonia: A case report	
	Liu WJ, Zhou S, Li YX	
13388	Application of 3D-printed prosthesis in revision surgery with large inflammatory pseudotumour and extensive bone defect: A case report	
	Wang HP, Wang MY, Lan YP, Tang ZD, Tao QF, Chen CY	
13396	Undetected traumatic cardiac herniation like playing hide-and-seek-delayed incidental findings during surgical stabilization of flail chest: A case report	
	Yoon SY, Ye JB, Seok J	
13402	Laparoscopic treatment of pyogenic liver abscess caused by fishbone puncture through the stomach wall and into the liver: A case report	
	Kadi A, Tuergan T, Abulaiti Y, Shalayiadang P, Tayier B, Abulizi A, Tuohuti M, Ahan A	
13408	Hepatic sinusoidal obstruction syndrome induced by tacrolimus following liver transplantation: Three case reports	
	Jiang JY, Fu Y, Ou YJ, Zhang LD	
13418	<i>Staphylococcus aureus</i> bacteremia and infective endocarditis in a patient with epidermolytic hyperkeratosis: A case report	
	Chen Y, Chen D, Liu H, Zhang CG, Song LL	
13426	Compound heterozygous p.L483P and p.S310G mutations in GBA1 cause type 1 adult Gaucher disease: A case report	
	Wen XL, Wang YZ, Zhang XL, Tu JQ, Zhang ZJ, Liu XX, Lu HY, Hao GP, Wang XH, Yang LH, Zhang RJ	
13435	Short-term prone positioning for severe acute respiratory distress syndrome after cardiopulmonary bypass: A case report and literature review	
	Yang JH, Wang S, Gan YX, Feng XY, Niu BL	
13443	Congenital nephrogenic diabetes insipidus arginine vasopressin receptor 2 gene mutation at new site: A case report	
	Yang LL, Xu Y, Qiu JL, Zhao QY, Li MM, Shi H	
13451	Development of dilated cardiomyopathy with a long latent period followed by viral fulminant myocarditis: A case report	
	Lee SD, Lee HJ, Kim HR, Kang MG, Kim K, Park JR	
13458	Hoffa's fracture in a five-year-old child diagnosed and treated with the assistance of arthroscopy: A case report	
	Chen ZH, Wang HF, Wang HY, Li F, Bai XF, Ni JL, Shi ZB	
	LETTER TO THE EDITOR	
13467	Precautions before starting tofacitinib in persons with rheumatoid arthritis	
	Swarnakar R, Yadav SL	

Contents

Thrice Monthly Volume 10 Number 36 December 26, 2022

ABOUT COVER

Editorial Board Member of World Journal of Clinical Cases, Janardhan Mydam, MD, Assistant Professor, Consultant Physician-Scientist, Statistician, Division of Neonatology, Department of Pediatrics, John H. Stroger, Jr. Hospital of Cook County1969 W. Ogden, Chicago, IL 60612, United States. mydamj@gmail.com

AIMS AND SCOPE

The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJCC as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The WJCC's CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ying-Yi Yuar; Production Department Director: Xu Guo; Editorial Office Director: Jin-Lei Wang,

NAME OF JOURNAL	INSTRUCTIONS TO AUTHORS
World Journal of Clinical Cases	https://www.wignet.com/bpg/gerinfo/204
ISSN	GUIDELINES FOR ETHICS DOCUMENTS
ISSN 2307-8960 (online)	https://www.wignet.com/bpg/GerInfo/287
LAUNCH DATE	GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
April 16, 2013	https://www.wignet.com/bpg/gerinfo/240
FREQUENCY	PUBLICATION ETHICS
Thrice Monthly	https://www.wjgnet.com/bpg/GerInfo/288
EDITORS-IN-CHIEF Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku	PUBLICATION MISCONDUCT https://www.wjgnet.com/bpg/gerinfo/208
EDITORIAL BOARD MEMBERS	ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/2307-8960/editorialboard.htm	https://www.wjgnet.com/bpg/gerinfo/242
PUBLICATION DATE December 26, 2022	STEPS FOR SUBMITTING MANUSCRIPTS https://www.wignet.com/bpg/GerInfo/239
COPYRIGHT	ONLINE SUBMISSION
© 2022 Baishideng Publishing Group Inc	https://www.f6publishing.com

© 2022 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com



W J C C World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 December 26; 10(36): 13426-13434

DOI: 10.12998/wjcc.v10.i36.13426

ISSN 2307-8960 (online)

CASE REPORT

Compound heterozygous p.L483P and p.S310G mutations in GBA1 cause type 1 adult Gaucher disease: A case report

Xiao-Ling Wen, Yao-Zi Wang, Xia-Lin Zhang, Jia-Qiang Tu, Zhi-Juan Zhang, Xia-Xia Liu, Hai-Yan Lu, Guo-Ping Hao, Xiao-Huan Wang, Lin-Hua Yang, Rui-Juan Zhang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A Grade B (Very good): 0 Grade C (Good): C Grade D (Fair): 0 Grade E (Poor): 0

P-Reviewer: Hakimi T, Afghanistan; Jovandaric M, Serbia

Received: September 18, 2022 Peer-review started: September 18, 2022

First decision: October 12, 2022 Revised: October 20, 2022 Accepted: November 30, 2022 Article in press: November 30, 2022 Published online: December 26, 2022



Xiao-Ling Wen, Jia-Qiang Tu, Department of Hematology, The First People's Hospital of Yibin, Yibin 644000, Sichuan Province, China

Xiao-Ling Wen, Yao-Zi Wang, Zhi-Juan Zhang, Xia-Xia Liu, Lin-Hua Yang, Department of Hematology, The Second Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, China

Xia-Lin Zhang, Rui-Juan Zhang, Department of Hematology, The Third Hospital of Shanxi Medical University, The Shanxi Bethune Hospital, The Shanxi Academy of Medical Sciences, The Tongji Shanxi Hospital, The Shanxi Medical University, Taiyuan 030032, Shanxi Province, China

Hai-Yan Lu, Guo-Ping Hao, Xiao-Huan Wang, Department of Hematology, The Children's Hospital of Shanxi, Taiyuan 030006, Shanxi Province, China

Corresponding author: Rui-Juan Zhang, MD, Chief Physician, Department of Hematology, The Third Hospital of Shanxi Medical University, The Shanxi Bethune Hospital, The Shanxi Academy of Medical Sciences, The Tongji Shanxi Hospital, The Shanxi Medical University, No. 99 Longcheng Street, Xiaodian District, Taiyuan 030032, Shanxi Province, China. 13593169668@163.com

Abstract

BACKGROUND

Gaucher disease (GD) is caused by a GBA1 gene mutation that leads to decreased acid β -glucosidase activity [glucocerebrosidase (GCase)]. This study aimed to identify and characterise compound heterozygous mutations in *GBA1* in a patient with type 1 GD.

CASE SUMMARY

Here, we report a rare adult-onset type 1 GD in a 46-year-old female patient with clinical manifestations of giant spleen, thrombocytopenia, and bone pain, diagnosed by enzymatic and genetic testing. Enzymology and whole exome sequencing revealed heterozygous missense mutations in exon 10 c.1448T>C (p.L483P) and exon 7 c.928A>G (p.S310G) of GBA1. The latter was first reported in patients with GD. Structural modelling showed that p.S310G and p.L483P were distant from the GCase active site. The p.S310G mutation in domain 1 may decrease stability between the a2 and a3 helices of GBA1. The p.L483P mutation in domain 2 reduced the van der Waals force of the side chain and disrupted the C-



WJCC | https://www.wjgnet.com

terminal β -sheet. The patient was treated with imiglucerase replacement therapy, and her condition was stable.

CONCLUSION

The p.L483P/p.S310G novel compound heterozygous mutation underlies type 1 GD and likely affects GCase protein function. This is the first description of p.S310G being associated with mild type 1 GD in the context of a coinherited p.L483P mutation.

Key Words: Gaucher disease; Parkinson's disease; Lipid metabolism; Molecular mechanism; Case report

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: We report a rare adult-onset type 1 GD patient in a 46-year-old female with clinical manifestations of giant spleen, thrombocytopenia, and bone pain, diagnosed by enzymatic and genetic testing. Using enzymology and whole exome sequencing, it is indicated that heterozygous missense mutations in exon 10 c.1448T>C (p.L483P) and exon 7 c.928A>G (p.S310G) of GBA1. The latter was first reported in GD. Structural modeling showed that p.S310G and p.L483P are far away from the glucocerebrosidase active site. The p.S310G mutation in domain 1 could cause decreased stability between the $\alpha 2$ and $\alpha 3$ helices of GBA1. The p.L483P mutation in domain 2 could reduce the van der Waals force of the side chain and disrupt the C-terminal-sheet. The patient was treated with imiglucerase replacement therapy, and her condition was basically stable.

Citation: Wen XL, Wang YZ, Zhang XL, Tu JQ, Zhang ZJ, Liu XX, Lu HY, Hao GP, Wang XH, Yang LH, Zhang RJ. Compound heterozygous p.L483P and p.S310G mutations in GBA1 cause type 1 adult Gaucher disease: A case report. *World J Clin Cases* 2022; 10(36): 13426-13434 URL: https://www.wjgnet.com/2307-8960/full/v10/i36/13426.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i36.13426

INTRODUCTION

Gaucher disease (GD) is a rare autosomal recessive hereditary lysosomal storage disease with a global incidence of approximately 0.4/100000-5.8/100000[1]. It arises from *GBA1* gene mutations, resulting in the accumulation of glucosylceramide in the reticuloendothelial system, leading to anaemia, low platelet counts, and damage to the liver and spleen. *GBA1* (RefSeq: NG_009783.1) located at chromosome 1q21, spans 7.6 kb with 11 exons. There are 459 reported *GBA1* mutations, including point mutations, splicing, insertions and deletions, frameshift mutations, and recombination alleles; however, not all are pathogenic[2]. GD is heterogeneous and is classified into three types based on neurological severity[3, 4]. In type 1, neuronal features are not observed, and patients can be asymptomatic and present at any age[5]. Both type 2 and 3 GD have neurological involvement and are present in infancy, but only type 2 GD results in early death.

Surprisingly, *in vitro* expression experiments have demonstrated that these *GBA1* mutations are relatively stable and active[6,7]. *In vivo*, glucocerebrosidase (GCase) is synthesised in the rough endoplasmic reticulum (ER) and then transported to the lysosome. *GBA1* mutations cause GCase to exit the ER and are destroyed by the ubiquitin-proteasome system[8]. Thus, GD patients have reduced amounts of acid β -glucosidase (GCase) in their lysosomes.

The current study examined the aetiology of type 1 GD in an adult female patient and found double heterozygosity for c.1448T>C (p.L483P) and c.928A>G (p.S310G) mutations in *GBA1*. The p.L483P mutation is common in Asian populations, and homozygous p.L483P mutations result in a severe GD phenotype with neurological manifestations and early death[9]. The patient with the heterozygous mutation p.L483P/p.S310G had a milder phenotype and did not have clinical GD symptoms until adulthood. The p.S310G mutation has only been reported in Parkinson's disease (PD)[10]. However, its molecular pathogenesis remains unclear. In the current study, the effects of p.L483P/p.S310G on the clinical manifestations of GCase and GD were preliminarily explored through gene diagnosis and protein structure analysis.

Zaishideng® WJCC | https://www.wjgnet.com

CASE PRESENTATION

Chief complaints

A 46-year-old Chinese woman was admitted to the hospital in December 2019 because of progressive enlargement of the spleen for more than 3 years and a progressive decrease in platelet count for more than 9 mo.

History of present illness

The patient presented with asymptomatic splenomegaly (ultrasound: Spleen length, 154 mm; width, 41 mm) in December 2016. In December 2018, the patient complained of persistent right hip joint pain without mobility problems. Radiographic studies did not reveal significant hip joint or femoral abnormalities. In March 2019, a review ultrasound revealed an enlarged spleen (length, 153 mm; width, 57 mm) and thrombocytopenia (52×10^{9} /L). In November 2019, another ultrasound showed continuous spleen enlargement (length, 249 mm; width, approximately 66 mm) and further decreased platelet count $(40 \times 10^9/L)$.

History of past illness

She was hepatitis B surface antigen-positive in December 2016.

Personal and family history

Except for her mother's PD diagnosis, her family history was insignificant.

Physical examination

Megasplenomegaly was noted 18 cm below the ribs, the liver was not palpable under the ribs, and the nervous system examination was normal.

Laboratory examinations

Complete blood counts showed white blood cells 3.59×10^{9} /L [normal: (4-10) × 10^{9} /L], haemoglobin 102 g/L (normal: 110-160 g/L), and platelets 34×10^{9} /L [normal: (100-300) × 10^{9} /L]. Bone marrow cytomorphological examination revealed that Gaucher-like cells accounted for 4.4% (Figure 1). The GCase activity of the peripheral blood leukocytes was 3.8 nmol/(mg h) (reference range: 10-25 nmol/mg · h). The GBA1 gene test showed heterozygous mutations c.1448T>C (p.L483P)/c.928A>G (p.S310G) (Figures 2 and 3). The patient was diagnosed with GD (type 1). The father was a p.L483P heterozygous carrier, and the mother was a p.S310G heterozygous carrier. The younger sister did not harbor any mutations. Predictions made by PolyPhen-2, SIFT, and MutationTaster suggested that the p.L483P and p.S310G mutations might be pathogenic. According to the American College of Medical Genetics and Genomics guidelines[11], p.L483P was evaluated as a pathogenic variant, and p.S310G was probably a pathogenic variant.

Imaging examinations

Bone mineral density testing of the thoracolumbar and bilateral hip joints revealed decreased bone mineral density; computed tomography showed bilateral hip joint changes; and magnetic resonance imaging showed an abnormal signal in the medullary cavity of the lower segment of the right femur, bone infarction, and abnormal signal in the medullary cavity of the left lower femur.

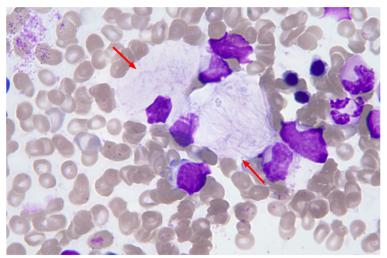
Protein structure analysis

GCase belongs to the GH30 family of glycoside hydrolases. In contrast to the traditional three-domain classification method, domains I and II were reclassified as domain 2, and domain III was classified as domain 1[12,13]. The GCase protein contains two domains, in which the active sites, E274 and E379, are located in the β -folded plates β 4 and β 7 of domain 1. The mutation point p.S310G was located in α -helix α4. However, it appears to be closer to E274 in the secondary structure. In the three-dimensional structure, p.S310G was located at the bottom of $\alpha 4$ and E274 at the top of $\beta 4$. The distance between the two was relatively large. The mutation point p.L483P was located at the β -pleated-sheet β s6 in domain 2, which was far away from the two active centres. Therefore, being far away from the GCase active centres, the mutation points p.S310G and p.L483P were predicted not to have a significant impact on the catalytic properties of the protein.

The p.S310G mutation is located in α -helix α 4. In the wild type, the C- β atom of the side chain of the Ser residue formed a van der Waals force with the C- γ 2 atom of the Val253 side chain and the C atom of the Leu307 main chain. In addition, the N atom of the Ser residue main chain formed a hydrogen bond with a length of 3.5 Å and 3.2 Å with the O atom of the Thr306 and Leu307 main chains, respectively; the O atom of the main chain formed a hydrogen bond with a length of 3.3 Å with the N atom of the His313 main chain. After Ser310 was mutated to Gly310, the hydrogen bond of the main chain remained, while the van der Waals force formed by the side chain and surrounding residues disappeared. The p.S310G mutation weakened the force between this point and Val253, which is located

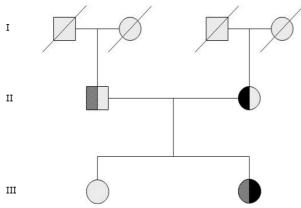


WJCC | https://www.wjgnet.com



DOI: 10.12998/wjcc.v10.i36.13426 Copyright ©The Author(s) 2022





DOI: 10.12998/wjcc.v10.i36.13426 Copyright ©The Author(s) 2022.

Figure 2 Family pedigree of the proband. The first-generation members have no information. The second generation is the father of proband is heterozygous for exon 10 c.1448T>C (p.L483P) mutation, and the mother is heterozygous for exon 7 c.928A>G (p.S310G) mutation. The third generation is the proband who was compound heterozygous for p.L483P/p.S310G. Her sister was normal and did not carry either mutation.

above the α helix α 3, therefore might affect the stability between α 2 and α 3 (Figure 4).

p.L483P was located in the loop region connecting β s5 and β s6 (near β s6). In the wild type, the side chain of Leu483 formed abundant van der Waals forces with the surrounding residues. The C-51 atom of its side chain could form van der Waals forces with the C- $\delta 2$ atom of Leu104, C- $\gamma 1$ atom of Val499, Cy1 atom of Val507, and C-82 atom of Leu509, and the C-82 atom could form van der Waals forces with C- γ atom of Asn501 and C- β atom of Ser523. Those van der Waals forces were formed because of the interactions between the side chains. When Leu483 mutated into Pro483, the N-C α rotation of Pro was bound by the pyrrolidine ring in its structure, thereby having less conformational freedom. This structure limited the diversity of its spatial conformation, especially in the loop region. The existence of Proline could help stabilise the loop region, which was originally more flexible. Therefore, theoretically, the p.L483P mutation located in the loop region should have enhanced the stability of this region. However, owing to side chain changes, the original 6 van der Waals forces were reduced to 3, and the retained van der Waals forces were formed between C- γ of Pro483 and C- δ 2 of Leu104 and C- γ 1 of Val507 and one between C- β and C- γ 1 of Val499. Thus, it can be seen that the introduction of Pro stabilised the conformation of the loop region, but the reduced van der Waals forces of the side chain might also affect the function of the protein structure (Figure 5).

FINAL DIAGNOSIS

GD (type 1).



WJCC | https://www.wjgnet.com

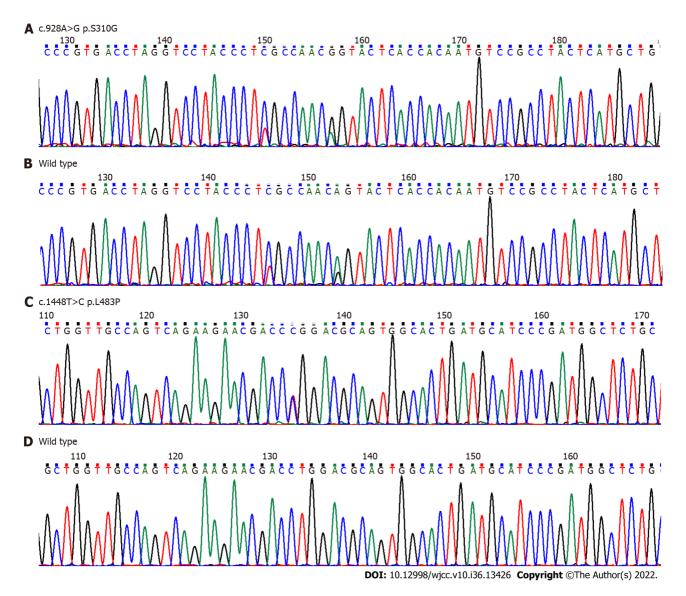


Figure 3 DNA sequencing analysis of glucocerebrosidase gene. A and B: Exon 7 c.928A>G (p.S310G) novel heterozygous missense mutation compared to the corresponding wild-type sequence; C and D: Exon 10 c.1448T>C (p.L483P) heterozygous mutation compared to the corresponding wild-type sequence.

TREATMENT

In January 2020, imiglucerase was administered intravenously (45 U/Kg, once every 2 wk).

OUTCOME AND FOLLOW-UP

The bone pain was relieved, the blood routine was rechecked several times, and the platelet count was continuously lower than 30×10^9 /L. No significant improvement was observed in the spleen size.

DISCUSSION

GD is a rare inborn metabolic error secondary to *GBA1* gene mutations that leads to reduced GCase activity. The substrate glucocerebroside (also known as glucose ceramide) accumulates in the macrophage lysosomes to form Gaucher cells. Gaucher cells accumulate widely in the liver, spleen, bones, lungs, brain, and other tissues and organs, resulting in the progressive worsening of dysfunction. Based on different clinical manifestations, GD can be divided into three types, of which type 1 (non-neuropathic) is the most common, accounting for approximately 95% of cases[4]. GD can occur at all ages with widely varying clinical manifestations. No primary central nervous system involvement is found in type 1 GD, and enzyme replacement therapy is the main treatment.



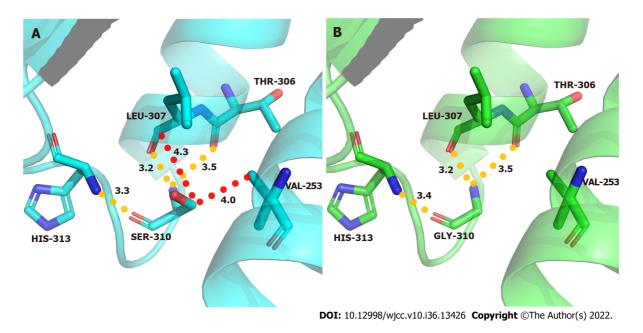


Figure 4 Molecular contacts of residue 310. A: Wild-type acid β-glucosidase protein; B: Mutant type.

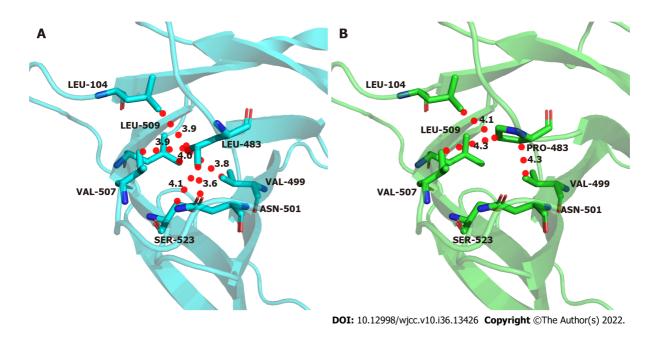


Figure 5 Molecular contacts of residue 483. A: Wild-type acid β-glucosidase protein; B: Mutant type.

A previous study suggested that GBA1 mutations are closely associated with PD[14]. Carriers of *GBA1* gene mutations, such as p.N370S and p.L483P, were found to increase the risk of PD disease by 2.16 times, with the characteristics of early-onset age and declined cognitive ability. A possible pathogenic mechanism is that these mutations increase α -synaptic nucleoprotein aggregation[15-18]. The coexistence of p.L483P with recombinant alleles, splice variants, or known severe missense alleles, such as p.D488H and p.R159W, has been reported to commonly lead to neuronopathic GD. When coexisting with mild mutations, such as p.N409S and p.P305A, it manifests as non-neuronopathic GD[9, 19]. p.L483P has long been considered a serious pathogenic mutation; however, p.L483P has been reported to be associated with delayed onset of neurological symptoms in type 3 patients with Japanese patients^[20], which may be related to the possible genetic heterogeneity among different ethnic groups. Enzyme replacement therapy can significantly improve haematological and other systemic symptoms in patients with type I GD, but its efficacy in patients with type 3 GD remains controversial. It has been reported in the literature that some type 3 patients developed symptoms of nervous system involvement after a median treatment period of 7.6 years[21]. In this study, the patient was treated with imiglucerase for 2 years, the platelet count continued to fail to recover, and the splenomegaly did not improve significantly. The proband with type 3 GD is the most common pathogenic mutation, p.L483P, and her



mother carries the p.S310G mutation, which has been confirmed to be a patient with PD. Therefore, this proband is a high-risk patient for PD and should be aware of the combination of neurological symptoms. The p.S310G mutation has only been reported in PD, and to the best of our knowledge, this is the first report of this mutation in patients with GD. However, its molecular mechanism of action and significance in GD remain unclear. In our patient with type 1 GD, the p.L483P mutation alone was not sufficient to result in the GD phenotype, suggesting that the p.S310G mutation contributed to the manifestation of type 1 disease.

In this study, to further understand the significance of p.L483P/p.S310G compound heterozygous mutations in GD, GCase protein structure analysis was conducted to probe the pathogenic characteristics of p.L483P/p.S310G mutations at the protein level. GCase belongs to the glycoside hydrolases GH30 family. The GH30 protein structure was first defined in 2010[13]. Based on the overall characteristics of GH30 family proteins, this study divided the GCase protein into two domains. GBA1 mutations can significantly influence the structure and function of the protein, including reducing the stability of domain III, premature termination of translation, and interference with catalytic activity[22-24]. Protein structure simulation revealed that p.L483P and p.S310G mutation points were far from the GCase active centre, suggesting that they should have little effect on the catalytic properties of the GCase protein. This also conformed to the patient's late-onset age with a mild clinical phenotype. Located in domain 2, the p.L483P mutation is believed to affect the structure and function of the protein by reducing van der Waals forces of the side chain. Earlier studies have suggested that the p.L483P mutation could lead to decreased enzymatic activity [25], affect the catalytic activity of GCase[26], disrupt the hydrophobic core and domain folding[17], or alter protein stability by reducing intramolecular hydrogen bonding[22]. Our study is different from the previous study, which further enriches the understanding of the impact of the p.L483P mutation on the protein structure. In this study, we demonstrated the first observed influence of the p.S310G mutation on the GCase protein. The p.S310G mutation in domain 1 could decrease the stability between $\alpha 2$ and $\alpha 3$ of the α -helix of the GCase protein, thus affecting the function of the GCase protein.

CONCLUSION

The current study verified that the p.L483P/p.S310G novel compound heterozygous mutation was the cause of GD. This mutation caused the disease probably by interfering with the biological function of the GCase protein. A follow-up study will be performed to assess the risk of developing PD in patients with the p. L483P variant.

FOOTNOTES

Author contributions: Zhang RJ, Wen XL and Zhang XL designed the study. Zhang XL and Wen XL performed the experiments. Wen XL and Wang YZ drafted the manuscript; and all authors have contributed to the revision of the manuscript.

Supported by Shanxi Key Research and Development Project, No. 201903D321133; Shanxi Bethune Hospital's Talent Introduction Scientific Research Start-up Fund Project, No. 2021RC038 and 2021RC017.

Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and any accompanying images. This study was approved by the Ethics Committee of the Third Hospital of the Shanxi Medical University (approval no. SBQKL-2021-052) and in accordance with the principles of the Declaration of Helsinki.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is noncommercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Xiao-Ling Wen 0000-0001-7300-4027; Rui-Juan Zhang 0000-0001-7300-4027.

S-Editor: Wang JJ



L-Editor: A P-Editor: Wang JJ

REFERENCES

- 1 Nguyen Y, Stirnemann J, Belmatoug N. [Gaucher disease: A review]. Rev Med Interne 2019; 40: 313-322 [PMID: 30638965 DOI: 10.1016/j.revmed.2018.11.012]
- 2 Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, Abeysinghe S, Krawczak M, Cooper DN. Human Gene Mutation Database (HGMD): 2003 update. Hum Mutat 2003; 21: 577-581 [PMID: 12754702 DOI: 10.1002/humu.10212]
- Daykin EC, Ryan E, Sidransky E. Diagnosing neuronopathic Gaucher disease: New considerations and challenges in 3 assigning Gaucher phenotypes. Mol Genet Metab 2021; 132: 49-58 [PMID: 33483255 DOI: 10.1016/j.ymgme.2021.01.002]
- Biegstraaten M, Cox TM, Belmatoug N, Berger MG, Collin-Histed T, Vom Dahl S, Di Rocco M, Fraga C, Giona F, Giraldo P, Hasanhodzic M, Hughes DA, Iversen PO, Kiewiet AI, Lukina E, Machaczka M, Marinakis T, Mengel E, Pastores GM, Plöckinger U, Rosenbaum H, Serratrice C, Symeonidis A, Szer J, Timmerman J, Tylki-Szymańska A, Weisz Hubshman M, Zafeiriou DI, Zimran A, Hollak CEM. Management goals for type 1 Gaucher disease: An expert consensus document from the European working group on Gaucher disease. Blood Cells Mol Dis 2018; 68: 203-208 [PMID: 28274788 DOI: 10.1016/j.bcmd.2016.10.008]
- 5 Kalużna M, Trzeciak I, Ziemnicka K, Machaczka M, Ruchała M. Endocrine and metabolic disorders in patients with Gaucher disease type 1: a review. Orphanet J Rare Dis 2019; 14: 275 [PMID: 31791361 DOI: 10.1186/s13023-019-1211-5]
- 6 Alfonso P, Rodríguez-Rey JC, Gañán A, Pérez-Calvo JI, Giralt M, Giraldo P, Pocoví M. Expression and functional characterization of mutated glucocerebrosidase alleles causing Gaucher disease in Spanish patients. Blood Cells Mol Dis 2004; 32: 218-225 [PMID: 14757438 DOI: 10.1016/j.bcmd.2003.10.010]
- Liou B, Kazimierczuk A, Zhang M, Scott CR, Hegde RS, Grabowski GA. Analyses of variant acid beta-glucosidases: 7 effects of Gaucher disease mutations. J Biol Chem 2006; 281: 4242-4253 [PMID: 16293621 DOI: 10.1074/ibc.M511110200
- Schapira AH, Gegg ME. Glucocerebrosidase in the pathogenesis and treatment of Parkinson disease. Proc Natl Acad Sci U 8 SA 2013; 110: 3214-3215 [PMID: 23412333 DOI: 10.1073/pnas.1300822110]
- Phetthong T, Tim-Aroon T, Khongkraparn A, Noojarern S, Kuptanon C, Wichajarn K, Sathienkijkanchai A, Suphapeetiporn K, Charoenkwan P, Tantiworawit A, Noentong N, Wattanasirichaigoon D. Gaucher disease: clinical phenotypes and refining GBA mutational spectrum in Thai patients. Orphanet J Rare Dis 2021; 16: 519 [PMID: 34930372 DOI: 10.1186/s13023-021-02151-2]
- Nuytemans K, Rajabli F, Bussies PL, Celis K, Scott WK, Singer C, Luca CC, Vinuela A, Pericak-Vance MA, Vance JM. 10 Novel Variants in LRRK2 and GBA Identified in Latino Parkinson Disease Cohort Enriched for Caribbean Origin. Front Neurol 2020; 11: 573733 [PMID: 33281709 DOI: 10.3389/fneur.2020.573733]
- Rehder C, Bean LJH, Bick D, Chao E, Chung W, Das S, O'Daniel J, Rehm H, Shashi V, Vincent LM; ACMG Laboratory Quality Assurance Committee. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2021; 23: 1399-1415 [PMID: 33927380 DOI: 10.1038/s41436-021-01139-4]
- 12 Dvir H, Harel M, McCarthy AA, Toker L, Silman I, Futerman AH, Sussman JL. X-ray structure of human acid-betaglucosidase, the defective enzyme in Gaucher disease. EMBO Rep 2003; 4: 704-709 [PMID: 12792654 DOI: 10.1038/sj.embor.embor873]
- 13 St John FJ, González JM, Pozharski E. Consolidation of glycosyl hydrolase family 30: a dual domain 4/7 hydrolase family consisting of two structurally distinct groups. FEBS Lett 2010; 584: 4435-4441 [PMID: 20932833 DOI: 10.1016/j.febslet.2010.09.051]
- 14 Galper J, Balwani M, Fahn S, Waters C, Krohn L, Gan-Or Z, Dzamko N, Alcalay RN. Cytokines and Gaucher Biomarkers in Glucocerebrosidase Carriers with and Without Parkinson Disease. Mov Disord 2021; 36: 1451-1455 [PMID: 33570220 DOI: 10.1002/mds.28525]
- Behl T, Kaur G, Fratila O, Buhas C, Judea-Pusta CT, Negrut N, Bustea C, Bungau S. Cross-talks among GBA mutations, 15 glucocerebrosidase, and a-synuclein in GBA-associated Parkinson's disease and their targeted therapeutic approaches: a comprehensive review. Transl Neurodegener 2021; 10: 4 [PMID: 33446243 DOI: 10.1186/s40035-020-00226-x]
- 16 Creese B, Bell E, Johar I, Francis P, Ballard C, Aarsland D. Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. Am J Med Genet B Neuropsychiatr Genet 2018; 177: 232-241 [PMID: 28548708 DOI: 10.1002/ajmg.b.32549]
- Liu LY, Liu F, Du SC, Jiang SY, Wang HJ, Zhang J, Wang W, Ma D. A Novel Functional Missense Mutation p.T219A in 17 Type 1 Gaucher's Disease. Chin Med J (Engl) 2016; 129: 1072-1077 [PMID: 27098793 DOI: 10.4103/0366-6999.180523]
- Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol 2012; 11: 986-998 [PMID: 23079555 DOI: 10.1016/S1474-4422(12)70190-4]
- 19 Chiong MAD, Racoma MJC, Abacan MAR. Genetic and clinical characteristics of Filipino patients with Gaucher disease. Mol Genet Metab Rep 2018; 15: 110-115 [PMID: 30023299 DOI: 10.1016/j.ymgmr.2018.03.010]
- 20 Tajima A, Yokoi T, Ariga M, Ito T, Kaneshiro E, Eto Y, Ida H. Clinical and genetic study of Japanese patients with type 3 Gaucher disease. Mol Genet Metab 2009; 97: 272-277 [PMID: 19481486 DOI: 10.1016/j.ymgme.2009.05.001]
- Lee NC, Chien YH, Wong SL, Sheen JM, Tsai FJ, Peng SF, Leung JH, Chao MC, Shun CT, Hwu WL. Outcome of early-21 treated type III Gaucher disease patients. Blood Cells Mol Dis 2014; 53: 105-109 [PMID: 24984925 DOI: 10.1016/j.bcmd.2014.05.007



- 22 Kim YM, Choi JH, Kim GH, Sohn YB, Ko JM, Lee BH, Cheon CK, Lim HH, Heo SH, Yoo HW. The GBA p.G85E mutation in Korean patients with non-neuronopathic Gaucher disease: founder and neuroprotective effects. Orphanet J Rare Dis 2020; 15: 318 [PMID: 33176831 DOI: 10.1186/s13023-020-01597-0]
- Riboldi GM, Di Fonzo AB. GBA, Gaucher Disease, and Parkinson's Disease: From Genetic to Clinic to New Therapeutic 23 Approaches. Cells 2019; 8 [PMID: 31010158 DOI: 10.3390/cells8040364]
- 24 Thirumal Kumar D, Eldous HG, Mahgoub ZA, George Priya Doss C, Zayed H. Computational modelling approaches as a potential platform to understand the molecular genetics association between Parkinson's and Gaucher diseases. Metab Brain Dis 2018; 33: 1835-1847 [PMID: 29978341 DOI: 10.1007/s11011-018-0286-3]
- Malini E, Grossi S, Deganuto M, Rosano C, Parini R, Dominisini S, Cariati R, Zampieri S, Bembi B, Filocamo M, Dardis 25 A. Functional analysis of 11 novel GBA alleles. Eur J Hum Genet 2014; 22: 511-516 [PMID: 24022302 DOI: 10.1038/ejhg.2013.182]
- 26 Fishbein I, Kuo YM, Giasson BI, Nussbaum RL. Augmentation of phenotype in a transgenic Parkinson mouse heterozygous for a Gaucher mutation. Brain 2014; 137: 3235-3247 [PMID: 25351739 DOI: 10.1093/brain/awu291]





Published by Baishideng Publishing Group Inc 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA Telephone: +1-925-3991568 E-mail: bpgoffice@wjgnet.com Help Desk: https://www.f6publishing.com/helpdesk https://www.wjgnet.com

