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EDITORIAL

- 5352 COVID-19: Considerations about immune suppression and biologicals at the time of SARS-CoV-2 pandemic
Costanzo G, Cordeddu W, Chessa L, Del Giacco S, Firinu D

REVIEW

- 5358 Obesity in people with diabetes in COVID-19 times: Important considerations and precautions to be taken
Alberti A, Schuelter-Trevisol F, Iser Betine PM, Traebert E, Freiberger V, Ventura L, Rezin GT, da Silva BB, Meneghetti Dallacosta F, Grigollo L, Dias P, Fin G, De Jesus JA, Pertille F, Rossoni C, Hur Soares B, Nodari Junior RJ, Comim CM
- 5372 Revisiting delayed appendectomy in patients with acute appendicitis
Li J

MINIREVIEWS

- 5391 Detection of short stature homeobox 2 and RAS-associated domain family 1 subtype A DNA methylation in interventional pulmonology
Wu J, Li P
- 5398 Borderline resectable pancreatic cancer and vascular resections in the era of neoadjuvant therapy
Mikulic D, Mrzljak A
- 5408 Esophageal manifestation in patients with scleroderma
Voulgaris TA, Karamanolis GP
- 5420 Exploration of transmission chain and prevention of the recurrence of coronavirus disease 2019 in Heilongjiang Province due to in-hospital transmission
Chen Q, Gao Y, Wang CS, Kang K, Yu H, Zhao MY, Yu KJ
- 5427 Role of gastrointestinal system on transmission and pathogenesis of SARS-CoV-2
Simsek C, Erul E, Balaban HY

ORIGINAL ARTICLE**Case Control Study**

- 5435 Effects of nursing care in fast-track surgery on postoperative pain, psychological state, and patient satisfaction with nursing for glioma
Deng YH, Yang YM, Ruan J, Mu L, Wang SQ

Retrospective Study

- 5442 Risk factors related to postoperative recurrence of dermatofibrosarcoma protuberans: A retrospective study and literature review
Xiong JX, Cai T, Hu L, Chen XL, Huang K, Chen AJ, Wang P

- 5453** Prediction of presence and severity of coronary artery disease using prediction for atherosclerotic cardiovascular disease risk in China scoring system

Hong XL, Chen H, Li Y, Teeroovengadum HD, Fu GS, Zhang WB

- 5462** Effects of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors on COVID-19

Li XL, Li T, Du QC, Yang L, He KL

- 5470** Prognostic factors and its predictive value in patients with metastatic spinal cancer

Gao QP, Yang DZ, Yuan ZB, Guo YX

Clinical Trials Study

- 5479** Prospective, randomized comparison of two supplemental oxygen methods during gastro-scopy with propofol mono-sedation in obese patients

Shao LJZ, Hong FX, Liu FK, Wan L, Xue FS

SYSTEMATIC REVIEWS

- 5490** Herb-induced liver injury: Systematic review and meta-analysis

Ballotin VR, Bigarella LG, Brandão ABM, Balbinot RA, Balbinot SS, Soldera J

META-ANALYSIS

- 5514** Type 2 diabetes mellitus increases liver transplant-free mortality in patients with cirrhosis: A systematic review and meta-analysis

Liu ZJ, Yan YJ, Weng HL, Ding HG

CASE REPORT

- 5526** Duplication of 19q (13.2-13.31) associated with comitant esotropia: A case report

Feng YL, Li ND

- 5535** Multiple left ventricular myxomas combined with severe rheumatic valvular lesions: A case report

Liu SZ, Hong Y, Huang KL, Li XP

- 5540** Complete pathological response in locally advanced non-small-cell lung cancer patient: A case report

Parisi E, Arpa D, Ghigi G, Micheletti S, Neri E, Tontini L, Pieri M, Romeo A

- 5547** Successful reversal of ostomy 13 years after Hartmann procedure in a patient with colon cancer: A case report

Huang W, Chen ZZ, Wei ZQ

- 5556** Delayed papillary muscle rupture after radiofrequency catheter ablation: A case report

Sun ZW, Wu BF, Ying X, Zhang BQ, Yao L, Zheng LR

- 5562** Temporary coronary sinus pacing to improve ventricular dyssynchrony with cardiogenic shock: A case report

Ju TR, Tseng H, Lin HT, Wang AL, Lee CC, Lai YC

- 5568** Hemoglobin Fukuoka caused unexpected hemoglobin A_{1c} results: A case report
Lin XP, Yuan QR, Niu SQ, Jiang X, Wu ZK, Luo ZF
- 5575** Giant androgen-producing adrenocortical carcinoma with atrial flutter: A case report and review of the literature
Costache MF, Arhirii RE, Mogos SJ, Lupascu-Ursulescu C, Litcanu CI, Ciuranghel AI, Cucu C, Ghiciuc CM, Petris AO, Danila N
- 5588** Can kissing cause paraquat poisoning: A case report and review of literature
Ly B, Han DF, Chen J, Zhao HB, Liu XL
- 5594** Spinal dural arteriovenous fistula 8 years after lumbar discectomy surgery: A case report and review of literature
Ouyang Y, Qu Y, Dong RP, Kang MY, Yu T, Cheng XL, Zhao JW
- 5605** Perianal superficial CD34-positive fibroblastic tumor: A case report
Long CY, Wang TL
- 5611** Low-dose clozapine-related seizure: A case report and literature review
Le DS, Su H, Liao ZL, Yu EY
- 5621** Rapid diagnosis of disseminated *Mycobacterium mucogenicum* infection in formalin-fixed, paraffin-embedded specimen using next-generation sequencing: A case report
Liu J, Lei ZY, Pang YH, Huang YX, Xu LJ, Zhu JY, Zheng JX, Yang XH, Lin BL, Gao ZL, Zhuo C
- 5631** Cytomegalovirus colitis induced segmental colonic hypoganglionosis in an immunocompetent patient: A case report
Kim BS, Park SY, Kim DH, Kim NI, Yoon JH, Ju JK, Park CH, Kim HS, Choi SK
- 5637** Primary extra-pancreatic pancreatic-type acinar cell carcinoma in the right perinephric space: A case report and review of literature
Wei YY, Li Y, Shi YJ, Li XT, Sun YS
- 5647** Muscular atrophy and weakness in the lower extremities in Behçet's disease: A case report and review of literature
Kim KW, Cho JH
- 5655** Novel technique of extracorporeal intrauterine morcellation after total laparoscopic hysterectomy: Three emblematic case reports
Macciò A, Sanna E, Lavra F, Calò P, Madeddu C
- 5661** Rare isolated extra-hepatic bile duct injury: A case report
Zhao J, Dang YL, Lin JM, Hu CH, Yu ZY
- 5668** Gelfoam embolization for distal, medium vessel injury during mechanical thrombectomy in acute stroke: A case report
Kang JY, Yi KS, Cha SH, Choi CH, Kim Y, Lee J, Cho BS

- 5675** Oncocytic adrenocortical tumor with uncertain malignant potential in pediatric population: A case report and review of literature
Chen XC, Tang YM, Mao Y, Qin DR
- 5683** Submucosal hematoma with a wide range of lesions, severe condition and atypical clinical symptoms: A case report
Liu L, Shen XJ, Xue LJ, Yao SK, Zhu JY
- 5689** Chorioamnionitis caused by *Serratia marcescens* in a healthcare worker: A case report
Park SY, Kim MJ, Park S, Kim NI, Oh HH, Kim J
- 5695** Endoscopic management of biliary ascariasis: A case report
Wang X, Lv YL, Cui SN, Zhu CH, Li Y, Pan YZ
- 5701** Role of ranulas in early diagnosis of Sjögren's syndrome: A case report
Chen N, Zeng DS, Su YT
- 5709** Sacral chondroblastoma — a rare location, a rare pathology: A case report and review of literature
Zheng BW, Niu HQ, Wang XB, Li J
- 5717** Primary liver actinomycosis in a pediatric patient: A case report and literature review
Liang ZJ, Liang JK, Chen YP, Chen Z, Wang Y
- 5724** Splenosis masquerading as gastric stromal tumor: A case report
Zheng HD, Xu JH, Sun YF
- 5730** Hemorrhagic transformation of ischemic cerebral proliferative angiopathy: A case report
Xia Y, Yu XF, Ma ZJ, Sun ZW
- 5737** Multidisciplinary team therapy for left giant adrenocortical carcinoma: A case report
Zhou Z, Luo HM, Tang J, Xu WJ, Wang BH, Peng XH, Tan H, Liu L, Long XY, Hong YD, Wu XB, Wang JP, Wang BQ, Xie HH, Fang Y, Luo Y, Li R, Wang Y
- 5744** Histopathology and immunophenotyping of late onset cutaneous manifestations of COVID-19 in elderly patients: Three case reports
Mazzitelli M, Dastoli S, Mignogna C, Bennardo L, Lio E, Pelle MC, Treccarichi EM, Pereira BI, Nisticò SP, Torti C

CORRECTION

- 5752** Corrigendum to "Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases"
Sang LX

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Fan-Zheng Meng, MD, PhD, Director, Professor, Department of Pediatrics, The First hospital of Jilin University, Changchun 130021, Jilin Province, China. mengfanzheng1972@163.com

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Hemoglobin Fukuoka caused unexpected hemoglobin A_{1c} results: A case report

Xue-Ping Lin, Qiu-Rong Yuan, Shi-Qiong Niu, Xi Jiang, Zhi-Kun Wu, Zhao-Fan Luo

ORCID number: Xue-Ping Lin 0000-0002-0983-2343; Qiu-Rong Yuan 0000-0001-9508-9244; Shi-Qiong Niu 0000-0002-2052-5133; Xi Jiang 0000-0002-9688-6358; Zhi-Kun Wu 0000-0003-0832-9786; Zhao-Fan Luo 0000-0002-4874-7993.

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Xue-Ping Lin, Qiu-Rong Yuan, Shi-Qiong Niu, Xi Jiang, Zhi-Kun Wu, Zhao-Fan Luo, Department of Clinical Medical Laboratory, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen 518107, Guangdong Province, China

Corresponding author: Zhao-Fan Luo, PhD, Professor, Department of Clinical Medical Laboratory, The Seventh Affiliated Hospital of Sun Yat-sen University, No. 628 Zhenyuan Road, Guangming District, Shenzhen 518107, Guangdong Province, China.
luozhaofan@qq.com

Abstract

BACKGROUND

Glycated hemoglobin (Hb) (HbA_{1c}) is an indicator that is used to diagnose and monitor the treatment of diabetes. Many factors can affect the detection of HbA_{1c}. One of the most important of these factors is the Hb variant. Here, we report a rare Hb variant and evaluate its effect on HbA_{1c}.

CASE SUMMARY

A 35-year-old man was suspected of harboring an Hb variant following the measurement of HbA_{1c} with the Variant II Turbo 2.0 Hb detection system during a routine examination. Subsequently, we used the Arkray HA-8160 and ARCHITECT c4000 system to reanalyze HbA_{1c}. Finally, the Hb variant was detected with a Capillary2FP analyzer that operates on the principle of capillary electrophoresis. We also used gene sequencing to investigate the mutation site. The value of HbA_{1c} detected with the Variant II Turbo 2.0 system was 52.7%. However, the Arkray HA-8160 system did not display a result while the ARCHITECT c16000 system showed a result of 5.4%. The Capillary2FP analyzer did not reveal any abnormal Hb zones. However, gene sequencing identified the presence of a mutation in the Hb β2 chain [CD2(CAC>TAC), His>Tyr, *HBB*: c.7C>T]; the genotype was Hb Fukuoka.

CONCLUSION

Hb variants could cause abnormal HbA_{1c} results. For patients with Hb variants, different methods should be used to detect HbA_{1c}.

Key Words: Hemoglobin Fukuoka; Hemoglobin A_{1c}; Hemoglobin variant; High-performance liquid chromatography; Enzymatic method; Case report

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Core Tip: Hemoglobin A_{1c} (HbA_{1c}) is an indicator of diabetes diagnosis and blood glucose monitoring. Therefore, the accuracy of HbA_{1c} results is of great significance to clinical diagnosis and treatment. This case had an abnormal HbA_{1c} result and traced back to a rare hemoglobin variant. Hemoglobin variants are one of the important factors affecting the accuracy of HbA_{1c} results. In this case, different methods were used to detect HbA_{1c}, which can provide reference evidence for subsequent cases and reduce false results reports.

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INTRODUCTION

Hemoglobin A_{1c} (HbA_{1c}) is the main indicator recommended by the American Diabetes Association and the World Health Organization for the diagnosis of diabetes[1]. HbA_{1c} is a stable compound that covalently bonds glucose and hemoglobin (Hb) β-chain N-terminal valine residues in human blood. It reflects the average blood glucose concentration over the previous 2 mo to 3 mo. However, the results of the HbA_{1c} are affected by a wide range of factors, including Hb variants, severe hemolytic anemia, and severe liver disease, *etc.* The most common factors that interfere with HbA_{1c} tests are Hb variants[2,3]. In this paper, we report a case with abnormal HbA_{1c} values, which was eventually diagnosed as a rare Hb mutation.

CASE PRESENTATION

Chief complaints

A 35-year-old man arrived at our hospital for a physical examination in November 2018.

History of past illness

The patient had no special past history.

Personal and family history

The patient had no special personal and family history.

Physical examination

Normal physical examination without any obvious signs of abnormality.

Laboratory examinations

The HbA_{1c} result of 52.7% was out of the expected detection range (Figure 1A). The HbA_{1c} of the patient was remarkably elevated in comparison to the reference range (4.0%-6.4%). Data arising from routine blood analyses are shown in Table 1. The patient had normal liver function, normal fasting glucose, and no previous history of diabetes. The HbA_{1c} test was performed using the Biorad Variant II Turbo 2.0 automatic glycosylated Hb analyzer (Biorad, United States); the HbA_{1c} value was abnormally elevated, although the patient had no history of diabetes. Therefore, we suspected that the patient possessed Hb variants that interfered with the results of the HbA_{1c} test.

Further investigations for Hb variants

We attempted to confirm the HbA_{1c} value by using the Arkray HA-8160 automatic glycosylated Hb analyzer (Acolai, Japan), which features high-performance liquid chromatography (HPLC), and the ARCHITECT c4000 system (Abbott, United States), which operates by enzymatic methods. The Arkray HA-8160 system returned no result; the instrument showed that the HbA_{1c} peak did not appear, and there was an

Table 1 Routine blood data

	Results	Reference range
Red blood cells ($\times 10^{12}/L$)	5.6	4.3-5.8
Hemoglobin (g/L)	161	130-175
Mean erythrocyte volume (fL)	91	82-100
Mean erythrocyte hemoglobin volume (pg)	29	27-34
Mean erythrocyte hemoglobin concentration (g/L)	315	316-354
Erythrocyte distribution width (%)	13	12-15
Total protein (g/L)	79.3	65.0-85.0
Albumin (g/L)	46.1	32.0-45.0
Alanine aminotransferase (U/L)	19	0-55
Aspartate transferase (U/L)	22	15-40
Blood creatinine ($\mu\text{mol}/L$)	76	64-104
Blood urea nitrogen (mmol/L)	4.8	3.2-7.4
Fasting glucose (mmol/L)	4.71	3.90-6.10

abnormal protruding peak on the left of peak A₀ (Figure 1B). The ARCHITECT c16000 enzyme assay returned a result of 5.4%.

Next, we used the Capillary2FP automated Hb analyzer (Sebia, France) to find the presence of abnormal Hb. Capillary electrophoresis showed no abnormal Hb bands (Figure 2).

In addition, the patient's genomic DNA was extracted using a Genomic DNA Isolation Kit (Kaipu, China) and the *HBA1*, *HBA2*, and *HBB* genes were amplified with specific forward/reverse primers and sequenced on an ABI3500 sequencer. *HBA1* forward primer was 5'-CGCGCCAGCCAATGAGC-3' and *HBA1* reverse primer was 5'-ACACACA TGGCTAGAACCTCTCTG-3'. *HBA2* forward primer was 5'-GGGCT CCGCGCCAGCCAA-3' and *HBA2* reverse primer was 5'-CAAGGACCTCTCT GCAGCT-3'. *HBB* forward primer was 5'-TACGGCTGTCATCACTTAG-3' and *HBB* reverse primer was 5'-GCCACACTGAGTGAGCTGCACT-3'. We extracted a sample of whole blood from the patient and extracted genomic DNA. This was used as a template to amplify the *Hb* gene. Polymerase chain reaction amplicons were then sequenced. No thalassemia mutation types were found in the sequencing range for $\alpha 1$ and $\alpha 2$. However, the β -globin gene possessed a histidine > tyrosine (CAC >TAC) mutation in the 7th amino acid, C>T (Figure 3). Next, we searched the HbA_{1c} variant library website (<http://globin.bx.psu.edu/hbvar/menu.html>), which revealed that the Hb genotype was Hb Fukuoka (*HBB*:c.7C>T). Finally, the patient was confirmed to possess a heterozygous Hb Fukuoka mutation.

FINAL DIAGNOSIS

Finally, the patient was confirmed to possess a heterozygous Hb Fukuoka mutation.

TREATMENT

The patient was not treated.

OUTCOME AND FOLLOW-UP

For patients with Hb variants, we recommend the use of an assay that is not affected by interference caused by Hb variants.

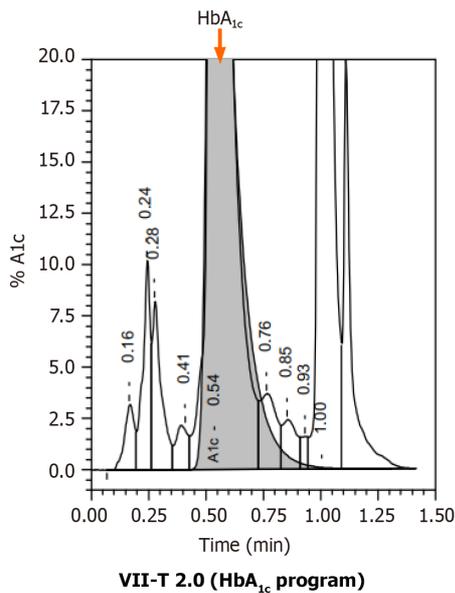
A

Peak Name	NGSP %	Area %	Retention Time (min)	Peak Area
A1a	-	1.2	0.165	26419
A1b	-	3.0	0.240	66059
F	-	2.8	0.275	62211
LA1c	-	1.3	0.408	28427
A1c	52.7*	-	0.538	1004703
P3	-	2.3	0.764	50501
P4	-	1.3	0.854	28995
Unknown	-	0.4	0.930	8266
Ao	-	41.6	1.004	910068

*Values outside of expected ranges

Total Area: 2185649

HbA_{1c} (NGSP) = 52.7* %



B

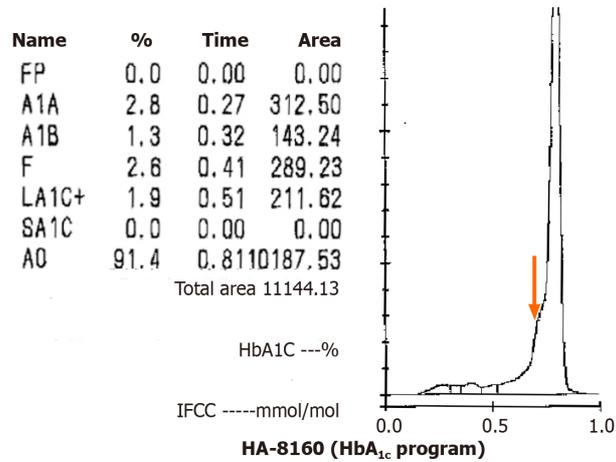


Figure 1 Detection of hemoglobin A_{1c} with a Variant II Turbo 2.0 system and an Arkray HA-8160 system. A: The peak of hemoglobin A_{1c} (HbA_{1c}) was abnormally elevated (orange arrow); B: The HbA_{1c} peak did not appear, and there was an abnormal protruding peak on the left of peak A₀ (orange arrow). HbA_{1c}: Hemoglobin A_{1c}.

DISCUSSION

The guidelines relating to diabetes mellitus that were published by the American Chemical Society in 2011 suggest that a patient should receive further research/investigation if HbA_{1c} > 15% or if the laboratory data are inconsistent with clinical manifestations. The guidelines also recommend the use of different test principles and methods so that the patient can be re-tested[4]. In this case, the patient's HbA_{1c} was 52.7%, significantly higher than 15%. The patient had no history of diabetes. Laboratory data were all within the normal quantitative range, including Hb, kidney and liver function parameters, and fasting blood glucose. Therefore, it was necessary to retest this patient and identify reasons that might underlie the abnormal HbA_{1c} result.

Biorad Variant II Turbo 2.0 and Arkray HA-8160 Glycation Hemoglobin analyzers are based on HPLC technology. Using this technology, it is possible to separate Hb fractions by differential affinity to the internal surface of the column or to the buffer. The greater the affinity to the buffer, the faster the elution, and the shorter the retention time. The greater the affinity to the analytical column, the slower the elution, and the longer the retention time. In this case, the Biorad Variant II Turbo 2.0 returned an HbA_{1c} result of 52.7%, and no result was detected by Arkray HA-8160. Therefore, we considered the possibility of interference caused by Hb variants. Hb variants can affect the separation of variants from HbA_{1c} or HbA by changing their charge, co-eluting with HbA_{1c}, and replacing glycosylation sites[5,6]. The NGSP website has declared that the common variants including S, C, D, and E have no effect on Biorad Variant II Turbo 2.0 (<http://ngsp.org/factors.asp>). However, some rare Hb variants

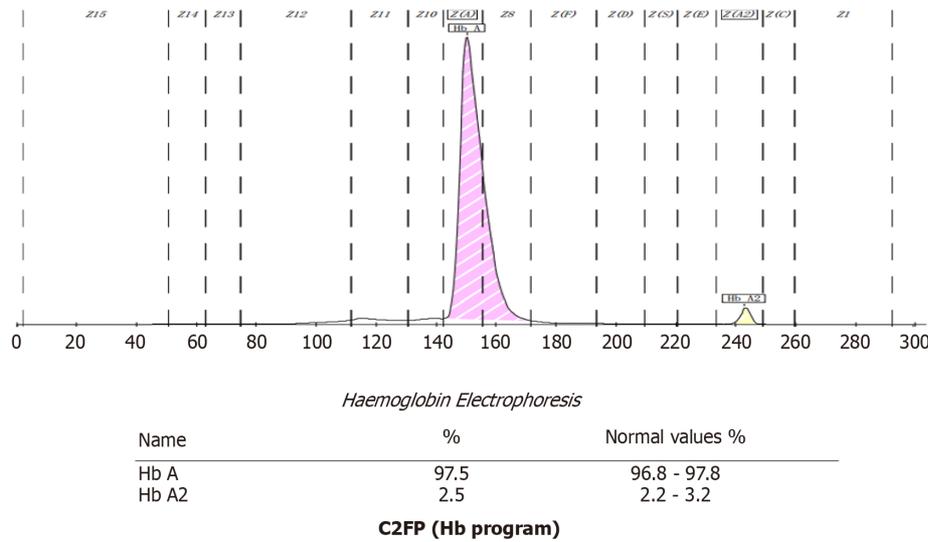


Figure 2 A Capillary2FP system was used to find the hemoglobin variant. Hb: Hemoglobin.

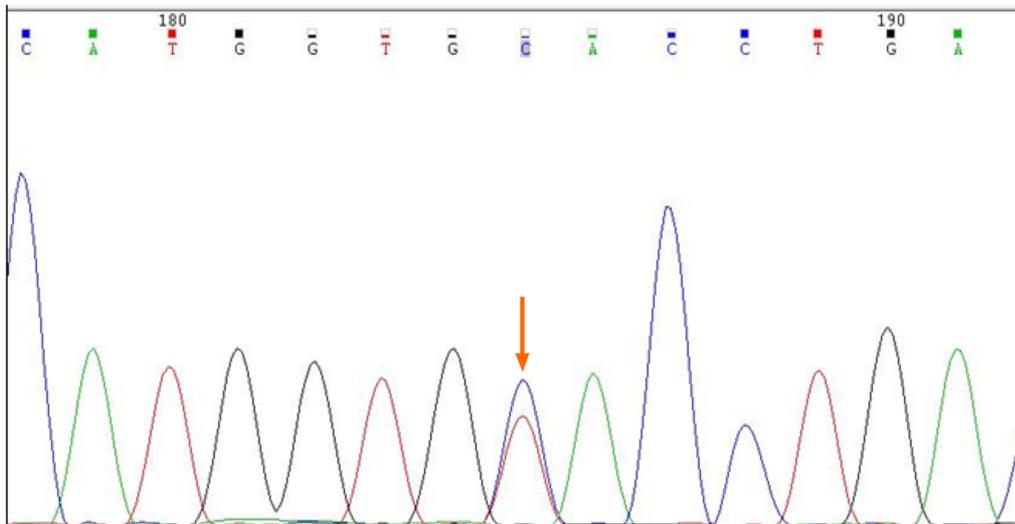


Figure 3 Gene sequencing results revealed a β chain mutation in the gene [CD2(CAC>TAC), His>Tyr, HBB:c.7C>T] (orange arrow).

can affect HbA_{1c} with HPLC[7,8]. The ARCHITECT c16000 uses enzymatic methods to detect HbA_{1c} values. By lysing the whole blood sample and performing extensive proteolytic digestion, the Hb β chain releases amino acids, especially the glycosylated N-terminal valine. The signal generated by the glycosylated valine in the subsequent color-based reaction can then be used to calculate the HbA_{1c}. At the analytical level, these methods are unaffected by the presence of Hb variants, such as HbC, HbD, HbE, and HbS. However, this method is unable to detect Hb variants[9]. Therefore, an HbA_{1c} result of 5.4% can accurately reflect the glycosylated Hb of the patient. The Capillary 2FP system operates on the principle of capillary electrophoresis and was used to investigate for the presence of an Hb variant. The Capillary 2FP system showed no abnormal Hb bands. Gene sequencing identified the variant as an Hb Fukuoka heterozygote. This variant was first reported in Japan in 1985, and subsequently reported by both Harano *et al*[10] and Farah *et al*[11]. Harano *et al*[10] found abnormal Hb peak in a diabetic patient's HbA_{1c} test in 1990, and identified that the patient had Hb Fukuoka. Furthermore, Farah *et al*[11] identified the presence of Hb Fukuoka by performing electrophoresis examinations in a patient with anemia. As far as we know, this case was the first case to be discovered in China.

Several methods can be used to detect glycosylated Hb, including electrophoresis, immunoturbidimetric assay (immunoassay), enzymatic assay, boronate affinity, ion-

exchange HPLC, or capillary electrophoresis. Laboratories should be aware of the limitations of their methods with respect to interference from other Hb variants and suggest alternative HbA_{1c} quantification methods[12,13]. For patients with Hb variants, we recommend the use of an assay that is not affected by interference caused by Hb variants; this strategy will help avoid erroneous results that can mislead data in clinical practice[14]. Glycated albumin and fructosamine are recommended as alternative indicators to monitor glycaemia when HbA_{1c} is disturbed[15].

CONCLUSION

The chromatographic pattern of abnormal Hb variants differs from that of normal samples, making it difficult for some instruments to determine accurate HbA_{1c} values. HbA_{1c} is an important indicator for the diagnosis, treatment, and monitoring of diabetes mellitus, and the accuracy of HbA_{1c} results is of paramount importance. But meanwhile, it is important for laboratory staff to be familiar with the factors that may cause interference, and to be able to communicate with clinicians in a timely manner to clarify the situation and make clinical suggestions. The ultimate goal is to ensure accurate and realistic test results so as to help clinical diagnosis.

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