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LETTER TO THE EDITOR

Severe hemolytic anemia due to combined α thalassemia and de novo Hemoglobin Sabine

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Dear Editor,

Hb Sabine has been reported in eight individuals with severe hemolytic anemia so far [1–7], and these affected patients are all Caucasian origin. Here, we reported a new case of de novo Hb Sabine in a 4-year-old boy of Chinese nationality, who simultaneously carried an α thalassemia deletion. The child was first referred to the hospital because of severe influenza-like illness in June 2013 when he was 4 months old. He also had been presenting with pallor as well as fatigue since birth. Bone marrow cell morphology showed significantly hyperplastic erythropoiesis. Hematological tests were performed by using SysmexXN-1000 Hematology System. The hematological data of the proband are shown in Fig. 1**a**. We noted that the child's mother had a history of mild anemia and thus hypothesized that the child might be a typical patient with thalassemia. DNA was extracted from peripheral blood samples of the proband and his parents. Genetic analysis of thalassemia was performed by using combined Gap-PCR and PCR-RDB. The results showed that the proband carried a common α globin gene deletion − α3.7. The deletion was inherited from his mother. In general, carriers with − α3.7 deletion are generally asymptomatic or mild anemia and do not need any treatment. However, this child showed unexplainable severe hemolytic anemia and required red blood cell transfusion every month. In August 2017, re-examinations showed serve anemia as well as enlargement of liver and spleen. Based on these abnormal clinical manifestations, we hypothesized that an unknown additional mutation together with − − α3.7 deletion might be the cause of the serve hemolytic anemia in this child. Combined Gap-PCR and NGS was carried out. As a result, an additional β globin gene point mutation at codon 91(T > C), which was corresponding to Hb Sabine, was identified in the child, while it was not found in either of his parents. This suggests the Hb Sabine mutation was a de novo mutation. This was confirmed by Sanger sequencing (Fig. 1**b**). In addition, standard triplet parentage testing was also conducted by detecting 24 short tandem repeats (STRs) in order to confirm the paternity (data not shown). To further characterize the abnormal hemoglobin, hemoglobin analysis was performed by using high performance capillary electrophoresis. Peripheral venous blood sample of the proband was obtained prior to blood transfusion. Three hemoglobin peaks presumed to be Hb A(Z9), Hb A2(Z3), and Hb X(Z11) were observed with concentrations of 95.3%, 2.9%, and 1.8% respectively. The hemoglobin peak at Z11 was considered to be Hb Sabine (Fig. 1**c**). The concentration might be affected because of the transfusions that were given previously at approximately one monthly intervals. The samples of the proband's parents were also analyzed and the level of Hb Sabine was not detected (Fig. 1**a**).

In our case, the patient showed more severe clinical phenotypes than those of other reported cases and required transfusion treatment monthly. We speculated that there might be two reasons. First, the Hb F level which can improve patients' clinical severity was undetectable in our patient. Second, the total hemoglobin level of our patient was further decreased in

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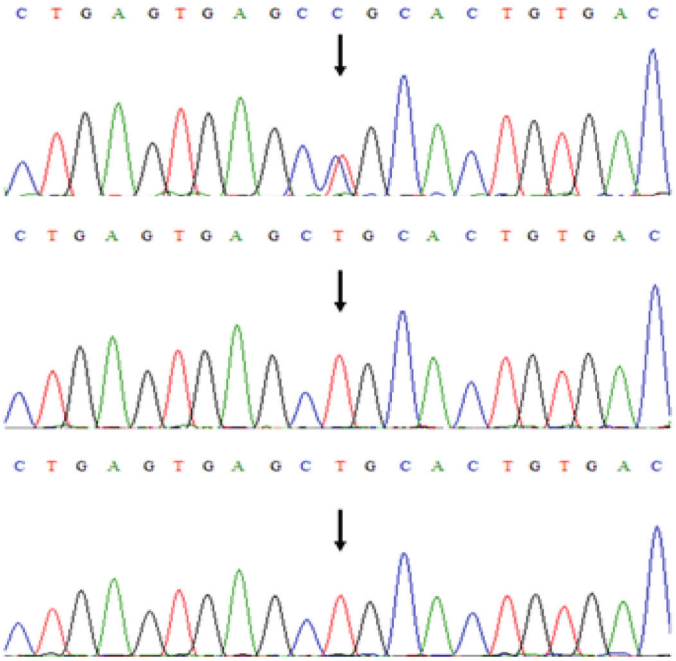
a

Case	HGB(g/dL)	MCV(fl)	MCH(pg)	HbA(%)	HbA2(%)	HbF(%)	HbX(%)
Father	15.9	92.9	30.8	97.4	2.6	0	0
Mother	10.5	75.9	23.2	97.7	2.3	0	0
Proband-1[a]	8.1	103.5	28.2	-	-	-	-
Proband-4[b]	8.9	93.4	27.8	95.3	2.9	0	1.8

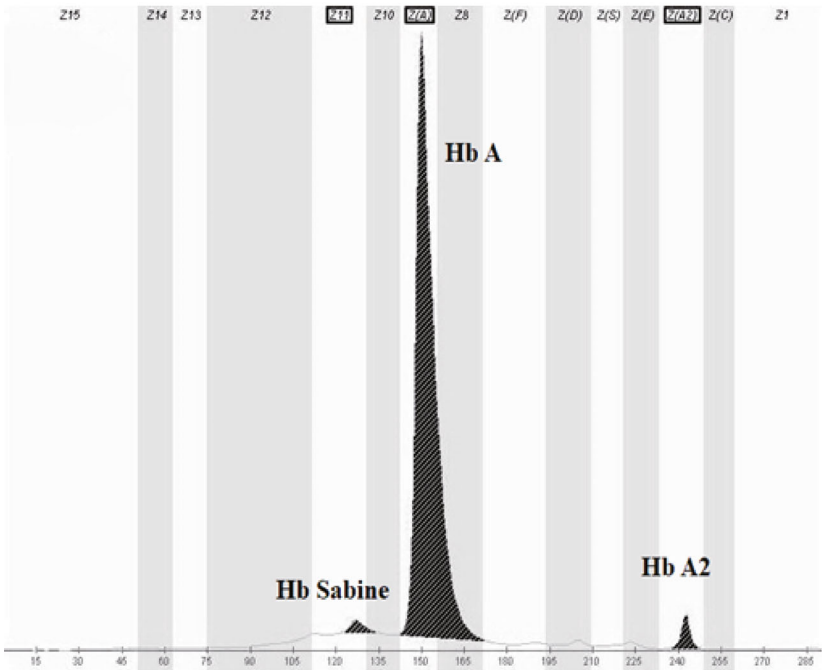
a Hematological analysis at age 1 in June 2013

b Hematological analysis at age 4 in August 2017

b



c



◀ **Fig. 1** **a** Hematological data from proband and proband's parents. **b** Sequence analysis of HBB in the study family. Top: heterozygous c.275T>C substitution in the affected proband. Medium-bottom: normal sequences of proband's parents. The arrows show the position of the mutation. **c** Patterns of hemoglobin separation using capillary electrophoresis

the presence of a thalassemia. The Hb level is generally 8–12 g/dL in other Hb Sabine carriers, whereas the Hb level fluctuated between 8 and 9 g/dL prior to transfusion in our case. Notably, our report demonstrates the efficiency and power of NGS for identifying rare hemoglobin variants and emphasizes the importance of an accurate molecular characterization of hemoglobinopathies in the prevention and treatment of hemoglobinopathies.

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Compliance with ethical standards

Informed consent was obtained from the parents of the patient.

Conflict of interest The authors declare that they have no conflicts of interest.

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