Disorders of Erythropoiesis

First detection of the splice donor site IVS-I-2 (T→C) β-thalassemia mutation in a Chinese patient

We present the first description of a Chinese family with a rare β-thalassemia mutation commonly observed in black Americans. This mutation is a splice donor site mutation, and is associated with a phenotype of β^0-thalassemia.

haematologica 2005; 90:1695
(*http://www.haematologica.org/journal/2005/12/1695.html*)

β-thalassemia is a common hereditary anemia caused by mutations that reduce or abolish expression from the β-globin genes. Over 200 different β-thalassemia mutations have now been characterized worldwide.[1] Relatively small numbers of common β-thalassemia mutations can be found for each high-risk population. For example, in the Chinese population, five mutations, of the 30 known, account for more than 90% of all cases.[2] Here we describe a rare β-thalassemia splice donor site mutation previously unreported in the Chinese.

The family was from Nanning city of Guangxi province in south China. Both parents had classic β-thalassemia trait (Table 1). Their first son with severe homozygous β-thalassemia had been diagnosed at 6 months of age and had been regularly transfused. This child had died at 3 years of age. At 20 weeks of gestation in the next pregnancy, the couple was referred to our center for prenatal diagnosis.

Reverse dot blots (RDB) were employed to investigate the 18 known types of Chinese β-thalassemia mutations. This analysis identified an IVS-II-654 (C→T) mutation in the mother, but failed to identify any of the known mutations in the father. Considering these results, cordocentesis was performed instead of amniocentesis for prenatal diagnosis. The cord blood was analyzed by automated high-performance liquid chromatography,[3] and it was found that the Hb A level was 0%, indicating that the fetus had homozygous β^0-thalassemia. The pregnancy was terminated at 21 weeks of gestation by the parents' request. The β-globin gene was amplified by polymerase chain reaction (PCR) and the PCR product was analyzed by direct nucleotide sequencing using the BigDye™ terminator Cycle Sequencing Kit and the ABI PRISM™ 310 genetic analyzer. Sequence analysis of the entire β-globin gene revealed that the father and the fetus were heterozygous for an IVS-I-2 (T→C) mutation (Figure 1). This mutation is a splice donor site mutation reported to be common among black Americans, and is associated with a phenotype of β^0-thalassemia.[4] Nevertheless, it has not been reported among Chinese, and can now be added to the more than 30 different β-thalassemia mutations that have been identified among the Chinese population so far.

Table 1. Summary of hematological findings of both parents.

Case	RBC ($x10^{12}$/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Hb (g/dL)	Hemoglobin electrophoresis	β-globin genotype
Father	6.10	59.1	19.3	32.7	11.8	A_2 5.9 A 94.1	$\beta^{IVS-I-2\ (T\to C)}/\beta^N$
Mother	5.64	62.4	23.8	35.1	12.5	A_2 5.7 A 94.3	$\beta^{IVS-II-654\ (C\to T)}/\beta^N$

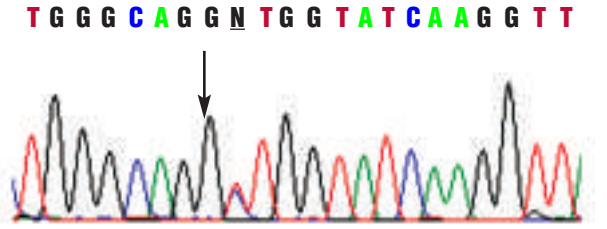

Figure 1. Sequence analysis of the β-globin gene amplified from the father. The arrow indicates the heterozygosity for the T→C substitution at position IVS-I-2 of the β-globin gene.

Can Liao, Jian Li, Yining Huang, Dongzhi Li
Prenatal Diagnostic Center, Guangzhou Maternal & Neonatal Hospital, Guangzhou Medical College, Guangzhou, Guangdong, China

Key words: β-thalassemia, splice mutation, β-globin gene.

Correspondence: Dongzhi Li, MD, Prenatal Diagnostic Center, Guangzhou Maternal & Neonatal Hospital, Guangzhou Medical College, Renminzhong Road 402, Guangzhou, Guangdong 510180, China. Phone: international +86.20.81854671. Fax: international +86.20.81854671. E-mail: dongzhi3@yahoo.com.cn

References

1. Weatherall DJ, Clegg JB. The Thalassemia Syndromes. 4th ed. Oxford, England: Blackwell Science. 2001.
2. Ko TM, Xu X. Molecular study and prenatal diagnosis of α- and β-thalassemias in Chinese. J Formos Med Assoc 1998; 97:5–15.
3. Tongsong T, Wanapirak C, Sirivatanapa P, Sanguansermsri T, Sirichotiyakul S, Piyamongkol W, et al. Prenatal control of severe thalassaemia: Chiang Mai strategy. Prenat Diagn 2000;20:229-34.
4. Goncalves J, Faustino P, Lavinha J, Rosado L, Peres MJ, Martins MC. An African origin for an "American black" β^0-thalassemia mutation? Am J Hematol 1994;46:373-4.