

### Two thalassemia intermedia patients with $\delta\beta/\beta$ -thalassemia and a deletional type $\alpha$ -thalassemia

We report two cases of thalassemia (thal) intermedia in Chinese adolescents caused by  $\delta\beta/\beta$ -thal and a deletional type  $\alpha$ -thal. This is the first report of thal intermedia cases with genotype  $\delta\beta/\beta$ -thal and  $\alpha$ -thal in the Chinese population. The relationship between its phenotype and genotype is discussed.

Thalassemia (thal) intermedia, whose molecular basis is quite heterogeneous, is a clinical definition ranging in severity from  $\beta$ -thal carrier state to transfusion-dependent thal major.<sup>1-3</sup> Here we report two thal intermedia Chinese patients with delta  $\beta/\beta$ -thal and  $\alpha$ -thal of Southeast Asia (SEA) deletional type. The two probands were a 13-year old boy (proband #1) and a 14-year old girl (proband #2), who presented with a history of easy fatigability, excessive sweating and somnolence for years. Though with normal growth and development, they both had moderate anemia, jaundice, hepatosplenomegaly and some facial bone alteration. They were not, however, blood transfusion dependent. The results of laboratory examinations of both families are listed in Table 1.

Microcythemia and hypochromia were obvious in both probands while anemia was moderate. The extremely high level of HbF was distributed among circulating red cells heterocellularly with  $\gamma/(\gamma+Ag)$  higher than the normal range. Though with normal hemoglobin (Hb) concentration, all parents showed microcythemia and hypochromia. One side of both couples had significantly high levels of HbF with heterocellular distribution in red cells, whereas the other side only had increased level of HbA<sub>2</sub> or a slightly increased HbF.

Gene analysis showed both probands were compound heterozygotes for  $\beta$ -thal/Chinese  $\gamma/(\gamma+Ag)$ -thal, with concurrent SEA  $\alpha$ -thal. The  $\beta$ -thal mutations were  $\beta$ -28 (A→G) and IVS-II-654 (C→T) respectively. The father of proband 1 was a compound heterozygote for  $\beta$ -28 (A→G)/SEA  $\alpha$ -thal, and the father of proband 2 was a compound heterozygote for Chinese  $\gamma/(\gamma+Ag)$ -thal/SEA  $\alpha$ -thal; their wives were carriers of Chinese  $\gamma/(\gamma+Ag)$ -thal or  $\beta$  IVS-II-654 (C→T).

The phenotype of compound heterozygotes for  $\beta$ -thal/ $\delta\beta$ -thal can range from mild thal intermedia to thal major,<sup>4</sup> in relation to many factors. These are the nature of  $\beta$ -thal mutation, the range of gene deletion, the coexisting  $\alpha$ -thal, and other genetic fac-

tors that can elevate  $\gamma$ -chain production. Chinese  $\gamma/(\gamma+Ag)$ -thal involves a long-segment deletion of more than 80 kilobases with its 5' breakpoint in intron II of  $\gamma$ -globin gene and the 3' breakpoint far downstream to the  $\beta$ -globin gene, including an enhancer downstream to  $\beta$ -gene.<sup>5-7</sup> Therefore, compound heterozygosity of this defect with other  $\beta$ -thal mutations may result in severe  $\beta$ -thal. However, when  $\alpha$ -thal is coinherited, the clinical condition will be improved. Recently we found a Chinese adolescent who was a compound heterozygote for this  $\delta\beta$ -thal/ $\beta$  IVS-II-654 (C→T) but did not have  $\alpha$ -thal. Although within the spectrum of thal intermedia, she had more severe clinical symptoms (Hb 59.4 g/L, transfusion imperative occasionally). Moreover, proband #1's sister had suffered from anemia and jaundice for years, but for the lack of an exact diagnosis and proper therapy in time, she died at the age of 14. We infer her molecular defect was the same as her brother's, but without the  $\alpha$ -thal coinherited to alleviate the imbalance of the  $\alpha$ -non- $\alpha$  chains.

Chinese  $\gamma/(\gamma+Ag)$ -thal is one of the most common  $\delta\beta$ -thal in China,<sup>8</sup> consequently, it is not unusual that compound heterozygotes of this mutation match with  $\beta$ -thal. To sum up, we should be more careful in making decisions during prenatal diagnosis or when giving genetic counselling to such families.

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Key words: thalassemia intermedia, genotype, phenotype

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Table 1. Results of hematologic analysis of two thal intermedia patients and their parents.

	Proband1	Father1	Mother1	Proband2	Father2	Mother2
Sex	M	M	F	F	M	F
Age	13	38	36	15	45	45
Hb (g/L)	75	140	104	73	146	111
Hct (%)	23.7		32.1	24.4		37.6
MCV (fL)	66.2	70.5	66.6	60.5	72.3	67.4
MCH (pg)	20.9	21.8	21.6	18.1	22.1	19.9
RDW (%)	32.4	16.8	19.1	42.4	16.2	17.4
HbA (%)	21.3	90.3	94.3	19.9	87.7	95.8
HbA2 (%)	2.4	5.2	2.7	3.9	2.9	4.2
HbF (%)	76.3	4.3	13.0	76.2	9.4	LD
$\gamma/(\gamma+Ag)$	0.717	-	1.000	0.861	1.00	-

Abbreviations. M: male; F: female; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; RDW: red distribution width.