36.2 *Molecular aspects of thalassemias*

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The thalassemias (α and ß) is a group of inherited anaemia affecting 1-20% of the population in various regions of S. E. Asia. a thalassemia (thal) is mainly due to gene deletion and the loss of 1 or 2 genes (a thal-2 and a thal-1 respectively) does not manifest any clinical symptoms, while loss of 3 genes (Hb H disease) gives rise to moderate anaemia and a thal intermedia picture and complete deletion of all 4 α genes (homozygous α thal-1, Hb Barts Hydrops fetalis) is incompatible with late intrauterine or neonatal life without transfusion. Various deletions of both α genes in cis, resulting in α thal-1, occurred in different ethnic groups and the commonest deletion in S. E. Asians is ~22 kb extending from 3' of the ψζ gene to 4 kb 3' of the θ1 gene. Complete deletion of the ζ-α cluster also occurs. Non-deletion α thal accounts for 3% of cases locally and 4 common variants have been defined: α Constant Spring, α Quong Sze, α NSW and α LYC. Co-inheritance of α thal-1 or ζ-α thal-1 with any of these non-deletion defects results in a more severe Hb H disease phenotype than with coinheritance of a single leftward or rightward α gene deletion. With the last two non-deletion variants, α NSW and α LYC, the fetus is severely anaemic in utero, causing Hb H hydrops fetalis and death. β thal are mainly due to point mutation, minor addition or deletion. Over 80 different defects have been characterized but only 4-5 common defects account for the majority of cases in each ethnic group. In Southern Chinese, there are 12 known mutations and the 4 commonest, accounting for 85% of cases, are: Codon 41/42 (ΔTCTT), IVS2-nt 654 (C→T), Codon 17 (A→T) and nt -28 (A→G). Dominant forms of β thal have been defined and are mostly due to mutations in the third exon of the β gene resulting in unstable β chains. Rarely, β thal results from mutations at the hypersensitive sites (HS) 5' upstream of the ε-β gene cluster. The understanding of the molecular genetics of thal is applicable to other single gene disorders. Prenatal diagnosis for pregnancies at risk for homozygous α or β thal has been available for over 15 yrs. Recent efforts have centered on non-invasive techniques for fetal cell procurement. The use of a few numbers or even single fetal cell for diagnosis is possible with polymerase chain reaction (PCR) amplification of α or β genes. The diagnosis of homozygous α thal 1 is possible by amplification of the α thal 1 chromosome and for β thal major, fluorescent allele-specific PCR of the mutations allows rapid and accurate prenatal testing to be made.

36.3 β-Thalassaemia: from hospital to the community

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There are currently over 300 patients with transfusion dependent thalassaemia in Hong Kong. Majorities are thalassaemia major while a small proportion had clinical picture of thalassaemia intermedia. Five different mutations involving the ß-globin gene account for over 90% of the genotype. It is however interesting to correlate the genotypes and phenotypes in the both the "major" and "intermedia" groups.

The outcome has substantially improved with implementation of regular transfusion and chelation regimen more than 15 years ago. Complications related to transfusion and iron overloading still occurred albeit with lower incidence. Improvements were made in recent years regarding the provision of safer blood products, more accurate assessment of iron overload, and intensified chelation. Haemopoietic stem cell transplant is a treatment option, which enables cure. Cord blood transplant, which is a new innovative strategy, has been successfully performed locally. The benefits or feasibility of alternative treatment e.g. oral chelator or gene therapy are still not definite.

A large-scale screening program has shown a carrier rate of 3% for ß-thalassaemia. New patients with thalasaemia major were still seen despite availability of antenatal screening in some obstetrics units. The reasons why these patients were born are due to no screening, late presentation or cross-border deliveries. Unsatisfactory public awareness of the condition is reflected in a survey among secondary school students. To prevent further occurrence of the condition, public education through media and school is worth undertaking. It remains controversial as regards to what is the best screening strategy for the community.