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P140. Occult alpha globin gene mutations are the commonest causes of red cell microcytosis unexplained by phenotypic testing

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Aim

Hypochromic microcytic anaemia is the hallmark phenotype of thalassaemia. Current phenotypic tests do not provide a diagnosis in a small proportion of patients with red cell microcytosis. We investigated the genetic basis of microcytosis in a cohort of such subjects.

Method

We identified from a large cohort of 1684 unselected requests for thalassaemia testing 25 Chinese subjects who had unexplained microcytosis after phenotypic haemoglobin studies. Extensive genotypic analysis of the α and β globin gene cluster was performed in 20 of these subjects who had adequate DNA. Techniques employed included gap-polymerase chain reaction, amplification-refractory mutation system, Sanger sequencing and multiplex ligation-dependent amplification.

Result

Occult single and double alpha globin gene (HBA1, HBA2) deletions and α thalassaemic haemoglobinopathies (Haemoglobin Quong Sze, Haemoglobin Constant Spring) are the genetic basis for the microcytosis. Occult β globin gene (HBB) mutations, and δ globin gene (HBD) abnormalities masking β thalassaemia are not seen. A cost-effective genotyping approach for the detection of these occult globin gene mutations is proposed (Figure).

Conclusion

Occult alpha globin gene mutations are the commonest causes of red cell microcytosis unexplained by phenotypic testing. These occult mutations can produce diseases with significant morbidities if they occur together with common thalassaemia mutations. Identification of these occult mutations is important not only for making a diagnosis but also for the provision of accurate genetic counselling.