Hong Kong J. Dermatol. Venereol. (2006) **14**, 119

Editorial

Diagnosis of genetic disease in the post-genomic era

There are various ways of diagnosing genetic diseases. We can diagnose genetic diseases based on clinical criteria, radiological features, biochemical changes, and DNA sequence changes. DNA-based diagnosis of genetic disease is the preferred method because the fundamental abnormalities in genetic diseases are DNA sequence changes-the genotypes. Approximately half of the disease-causing mutations, such as frameshift mutations (insertion, deletion, and indel), initiation codon mutations, transcription start site mutations, promoter mutations, splicing mutations, lariat branch point mutations, stop codon mutations, mutations at polyadenylation sites, cryptic splice site mutations, DNA rearrangement, DNA duplication, actually affect the (genomic or complementary DNA or both) DNA sequences rather than affecting the function, stability or cellular trafficking of the gene products-the encoded proteins. Virtually all these mutations will mostly produce a null phenotype. Additionally, non-DNA diagnostic testing may involve invasive procedures and the corresponding assays may be only available in few (research) laboratories worldwide, e.g. DNA repair diseases.

For most genetic testing, few millilitres of EDTA whole blood (or less) are usually sufficient for analysis. In the past decade, we have performed mutational analysis of a number of genes related to heritable skin diseases, namely Fabry disease,[1] variegate porphyria,[2] xeroderma pigmenotosum type C,[3] steatocystoma multiplex, Darier disease, and Hailey-Hailey disease. In all these studies, a direct mutation detection and identification was employed. A diagnostic method based on direct detection of genetic mutation is: 1) fundamental, definitive, objective, ultimate, and predictive; 2) 100% sensitivity and 100% specificity in distinguishing heterozygotes from normal individuals; 3) 100% sensitivity and 100% specificity in identification of presymptomatic family members; 4) crucial for reproductive and genetic counselling. If the disease-causing gene is known for a heritable disease, simply giving the chance of 0.25 for recurrence of an autsosomal recessive disease probably cannot satisfy our patients in the post-genomic era. For autosomal dominant disease, the chance of recurrence is 0.5, and this figure is too high to be accepted by most parents or patients. For clinicians, DNA-based testing of genetic disease can prevent misdiagnosis and increase our confidence in diagnosing the rare diseases.

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