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Genodermatoses; Clinical and Molecular Aspects

Kazuo Nomura, M.D.

Department of Dermatology,
Hirosaki University School of Medicine
Hirosaki, Japan

Introduction

Recent progress of molecular analysis in genodermatoses brings us new insight for pathogenesis, classification and diagnosis of the disease. In this paper, some interesting cases of genodermatoses were described, and the importance of clinical observation as well as molecular ananlysis was discussed, because correlations between phenotype and genotype are more complex than originally suspected.

Moreover, the necessity of genetic counseling was proposed.

Dystrophic epidermolysis bullosa (EB) and type VII collagen gene mutation

Dystrophic EB result from structural abnormalities of anchoring fibrils (decreased in number, rudimentary, or defective, et etc) at the basal lamina in the cutaneous basement membrane, Type VII collagen is the major component of anchoring fibrils. Recent molecular coning of type VII collagen and subsequent analyzes revealed many type VII collagen gene mutations in dystrophic EB. Among them, type VII collagen gene mutation in a large family with dominant dystrophic EB of Cockayne Touraine (Gly2076Asp) and Pasini (Gly2034-Arg) were demonstrated (Kon A, 1997 Nomura K, 1998).

Molecular-based differentiation in a sporadic case of dystrophic EB.

In dystrophic EB, dominant and recessive forms must be distinguished for deciding management, commenting on prognosis and intiating genetic counseling. But, in a sporadic case, it is very difficult to differentiate because of striking clinical and histological similarities. Therefore, we attempt to differenticate them by molecular analysis. Briefly, if a type VII collagene gene mutation in at least one allele is identified in the affected child, and if an unaffected parent has the same mutant allele with affected child, , then the case is judged as recessive. In a sporadic case of 2 year old boy, we succeeded in determining his mode of inheritance as a recessive one by this procedure.

Atrichia congenita and genetic counseling

Atrichia with papular lesions is a rare autosomal recessively inherited skin dis-

order characterized by congenital atrichia of the whole body with numerous papular lesions. The patient was 27-year-old woman who had normal scalp hair at birth, but this was shed at six months of age and thereafter no further growth occurred. The patient has been married two years previously. Because of worry that she might have a baby with the same skin problem, she had undergone induced abortion four times. At her request, genetic counseling was carried out. On the basis of the incidence of carriers in the general population estimated by the Hardy-Weinberg law, we explained to the patient that the risk of having an affected child was approximately from 0.001 to 0.002, and suggested that reproduction avoidance was unnecessary. However, the final decision was left to the discretion of the patient. She accepted our advice and finally deciced to have a baby. As a result, she became pregnant and was able to have an unaffected child. Our client was overanxious that her baby will have the same skin problem. Genetic counseling may help to overcime patients' misunderstanding or ignorance about genetic skin diseases (Nomura K *et al*, 1998).

Genetic and clinical mosaicism in bullous congenital ichthhyosiform erythroderma (BCIE)

A son with severe generalized BCIE born to a mither with mild form of BCIE was described. This phenotypic heterogenecity in this family was probably due to a genetic and clinical mosaicism (Nomura K *et al*, 1998). The proband (son) was a 19-year old son who had extensive erythroderma, ichthyosiform skin with scales and hyperkeratosis. Palms and soles were prominent hyperkeratosis with contractures of digits. Histological examination showed an epidermolytic hyperkeratosis. The proband's 46-year-old mother exhibited brown granular papules scattering on her nape, cubital, inguinal, back and abdominal region as well as severe palmoplantar hyperkeratosis. But, her remaining body was covered with normal skin. In the proband, a keratin K1 gene mutation was identified in a highly-conserved 1A domain (Asp187Ser). In the mother, however, the same mutation was detected in the DNA only from the lesional skin. These redults suggest that midly-affected mother is a somatic mosaicissm for keratin gene mutation. The probable presence of somatic cell mosaicism in the mother has implications for other probands and families with BCIE. Particularly, in genetic counseling, patients with mild form of BCIE should be informed about the risk of transmission of BCIE with a generalized severe skin involvement to the next generation.

Searching for c-KIT gene mutation in piebaldism

Piebaldism is a rare autosomal dominant genetic pimentary disorder, characterized by congenital white hair and patches. In the region of the white patches, melanocytes are almost totally lacking, and therefore pievaldism is thought to be due to defective proliferation or migration of melanocytes during development. Recent studies have revealed that piebaldism result from mutations of the KIT proto-

oncogene, which encodes the cellular receptor transmembrane tyrosine kinase for mast/stem cell growth factor. The proband was a 5-year-old girl who had a depigmented fleck in the middle of the forehead, and various-sized depigmented patches on the abdomen and anterior bilateral legs. The patient's 30-year-old mother exhibited similar, but somewhat less severe symptoms. In this family, we identified c-Kit mutation in the highky conserved cytoplasmic tyrosine kinase domain (Thr847-Pro) (Paller AS *et al*, 1994). Such a missenscmutation within the tyrosine kinase domain produces a severe phenotype.

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