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HLA ANTIGENS IN YUGOSLAV PATIENTS WITH PALMOPLANTAR KERATODERMA, TYPE UNNA-THOST: A FAMILY STUDY

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Abstract. In the present study we have analysed families of patients with palmoplantar keratoderma, type Unna-Thost (PPK-UT), regarding segregation of the PPK-UT gene and for linkage between the PPK-UT gene and HLA haplotypes. The results confirm the autosomal dominant mode of inheritance of the PPK-UT, with strong penetrance. No linkage was found between the PPK-UT gene and HLA haplotypes on the 6th autosomal chromosome.

Key words: Palmoplantar keratoderma Unna-Thost; HLA antigens; Segregation; Linkage; Lod score

Palmoplantar keratoderma (PPK) is a frequently encountered genodermatosis in humans. The main symptoms are: 1) a thickened horny layer on the palms and soles; 2) an intense hyperhydrosis of the involved areas, producing an unpleasant smell; 3) other anomalies of keratinization, e.g. hyperkeratosis of the knees, elbows and/or other areas of the skin, and a follicular hyperkeratosis or thickened nails; 4) anomalies of teeth and eyes as well as of other organs may be expressed. According to the clinical manifestations and the mode of inheritance, various types of PPK are described in the literature as separate nosologic entities, e.g. diffuse PPK (type Unna-Thost) (1), PPK with pachyonychia (type Jadassohn-Lewandowsky) (3), PPK with paradontopathia (type Papillon-Lefevre) (8), PPKof the Mljet type (type Mal de Meleda), as well as others (2).

A systematic clinical and genetic study of PPK cases in the western part of Yugoslavia, Slovenia (1.8 million inhabitants) has been carried out over the last few years (1, 3, 4, 5, 8). It was established that PPK of the Unna-Thost type (PPK-UT) is by far the most frequent in the group of keratodermas (5). According to the data obtained by Kansky and co-workers the incidence of this condition in Slovenia is 1 : 12 000, which is 3.3 times as high as in Northern Ireland 1 : 40 000 (2). Detailed epidemiological data on PPK-UT in Slovenia are being prepared for publication.

The main clinical features of PPK-UT are: (*a*) a diffusely thickened horny layer on the palms and soles, with deep furrows and rhagadae; (*b*) hyperhydrosis of the palms and soles; (*c*) inheritance is determined by an autosomal dominant gene with strong penetrance (12).

Because of the unknown pathogenesis and familial aggregation of PPK-UT it seemed to us of interest to investigate the HLA system in a group of patients and their relatives. The HLA system is known to be the most polymorphic of all genetic systems and it plays a major role in determining susceptibility to a great number of hereditary diseases (9, 10).

We have therefore analysed the families of patients regarding segregation of the PPK-UT gene and for linkage between the PPK-UT gene and HLA haplotypes.

The results of our study confirmed the autosomal dominant mode of inheritance of the PPK-UT gene, with strong penetrance, but revealed no linkage between the PPK-UT gene and HLA haplotypes on the 6th autosomal chromosome.

PATIENTS AND METHODS

The PPK-UT patients were detected by looking at clinical files and by routine clinical procedures at dermatological clinics all over Slovenia (Ljubljana, Maribor, Novo Mesto, Celje, Koper). When a patient was diagnosed as having PPK-UT, his family was invited for clinical investigation. In most cases, however, the patients and their relatives had to be visited at their homes on Sundays or holidays. This method of approach enabled the authors to draw up the genealogical trees and to detect patients with less obvious symptoms (doubtfully affected) which would

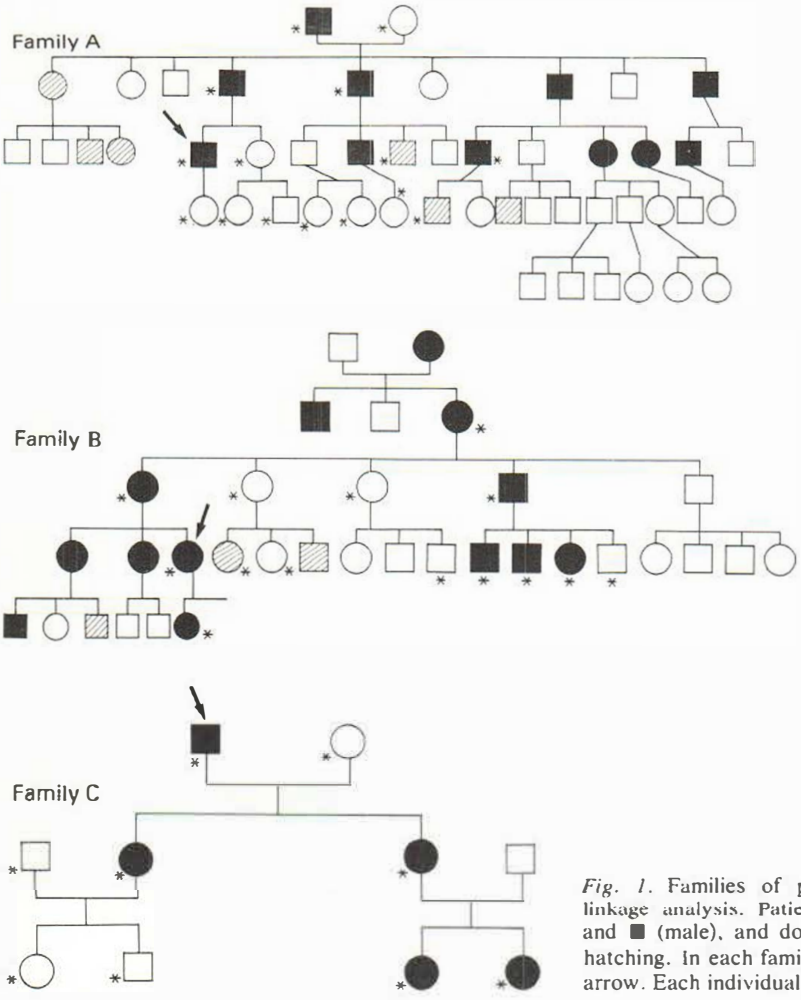

Fig. 1. Families of patients with PPK-UT used for linkage analysis. Patients are marked with ● (female) and ■ (male), and doubtfully affected individuals with hatching. In each family the proband is marked with an arrow. Each individual HLA typed is labelled with a star.

otherwise pass unrecognized. As there is so far no laboratory test by which diagnosis can be confirmed, the clinical symptoms and the patients' histories were the only criteria on which diagnosis of PPK-UT could be based.

Four families, two five-generation and two four-generation, with a total of 32 PPK-UT patients, 9 doubtfully affected and 58 unaffected members, were included in the present study. Of these, 19 patients, 3 latent cases and 19 unaffected sibs were studied regarding HLA-A and B antigens by using the two-stage microlymphocytotoxicity method of Terasaki & McCleland (11).

The segregation ratio of PPK-UT in families was followed and compared with the expected model in autosomal diseases. The probands and their affected parents and grandparents in each family were excluded from the analysis.

Finally, three large families (Fig. 1) were analysed as regards linkage between the PPK-UT gene and HLA-A,B haplotypes as markers. The estimates of the recombination fraction between the PPK-UT gene and HLA haplotypes were obtained by the standard method of maximum likelihood. The lod scores were computed using the LIPED computer program (7). A lod score of +3.0 is considered conclusive evidence of linkage and a lod score of −2.0 as evidence against it.

It was assumed that the recombination fraction is the same in both sexes. A dominant model with 100% pene-

Table I. *Dominant mode of inheritance of PPK-UT in multi-case families*

	Observed[a]	Expected[b] dominant model
Affected	22	26.5
Healthy	31	26.5
Total	53	53

[a/b] $\chi^2 = 1.53$, NS. Doubtfully affected individuals are excluded from the segregation analysis

Table II. *Lod scores for linkage between PPK-UT gene and HLA haplotypes*

Genetic model	Family	Recombination fraction				
		0.01	0.10	0.20	0.30	0.40
Dominant with 100% penetrance	A	−6.821	−2.714	−1.375	−0.670	−0.247
	B	−5.437	−1.642	−0.687	−0.256	−0.057
	C	−2.508	−0.632	−0.184	−0.005	0.044
Total		−14.77	−4.988	−2.245	−0.931	−0.260

trance was tested. The doubtfully affected individuals were considered as having a 50% chance of bearing the PPK-UT gene.

RESULTS

The segregation ratios of PPK-UT versus healthy sibs in four informative families studied fit perfectly with the expected segregation ratio in autosomal dominant diseases ($\chi^2=1.53$; $p=$NS) (Table I).

In four families studied, if we excluded doubtfully affected cases, the disease never skipped a generation, thus confiming the strong penetrance of the PPK-UT gene.

The estimates of the recombination fraction (θ), from 0.01 to 0.40 for a dominant model with 100% penetrance, gave a negative total lod score of −2.245 for a recombination fraction of 0.20 (Table II). We could therefore exclude linkage between PPK-UT and HLA haplotypes of closer than 20 map units.

DISCUSSION

The idea concerning association of PPK-UT and HLA antigens which motivated our present study, arose form the very similar features of PPK-UT and other hereditary diseases associated with HLA antigens. In the etiology of most of these diseases a strong immunogenetic background was postulated.

The possible lindage between the PPK-UT gene and HLA haplotypes ought to help us to locate the PPK-UT gene on the short arm of the sixth autosomal chromosome. In this case HLA antigens could be used as the marker of the disease.

The results of linkage analysis gave negative total lod scores for recombination fractions (θ) from 0.01 to 0.40, for the dominant model with 100% penetrance, and therefore exclude a linkage of the PPK-UT gene and HLA haplotypes of closer than 20 map units.

The incidence of the disease in the western part of Yugoslavia, Slovenia, is 3.3 times as high as in Northern Ireland (2).

Finally, we confirmed, once more, the autosomal dominant mode of inheritance of the PPK-UT gene with strong penetrance of the disease (12).

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