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HLA antigens in bullous epidermolysis, congenital ichthyosis and ectodermal dysplasia

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HLA–ABC antigen typing was carried out in 4 homozygous patients and 10 family members from three families with bullous epidermolysis, 7 homozygous patients and 19 family members of six families with ichthyosis, and 4 homozygous patients and 8 family members of 4 families with ectodermal dysplasia. The type of heredity was established on the basis of genetical evidence and the clinical picture.

In bullous epidermolysis cases autosomal recessive heredity was detected in two families with congenital bullous epidermolysis, and autosomal heredity in two families with dystrophic bullous epidermolysis. The HLA–Aw 24, B5 combination, which was thought to be significant in epidermolysis bullosa, was found in one, B5 alone in two, out of the four families.

In congenital ichthyosis autosomal recessive heredity was detected in two families out of five. In one, X-linked recessive heredity was found, and in two families X-linked recessive heredity could be supposed. In three families out of the five with congenital ichthyosis, the A2, B18 antigen combination was found.

In a family where two infants died from the most severe form of ichthyosis, epidermolysis and psoriasis also occurred. In this family two grandfathers were brothers, and one of the two was a carrier of the Aw24, B5 combination.

In the case of ectodermal dysplasia, in one out of four families X-linked recessive heredity, in another autosomal recessive heredity was detected. In two families X-linked recessive heredity could be supposed as only the male children were affected and also on the basis of data in the literature. The HLA–A26, B38 antigen combination occurred in three of these four families.

The reports on HLA antigens in skin diseases have revealed an increased frequency of Al, B8, Dw3 and DR3 in dermatitis herpetiformis, B13, B17, B27 and B38 in psoriasis, of A10 in pemphigus [13], and of A32 in porphyria cutanea tarda [7]. In a family suffering from dominantly inherited epidermolysis bullosa dystrophica, identical HLA-haplotypes (Aw24, B5) were found in 71.6% of the patients [10].

In the present paper we report on the results of HLA typing in three skin diseases of genetic origin, bullous epidermolysis, congenital ichthyosis and ectodermal dysplasia, and also on their type of heredity, since we could

TABLE I

HLA pheno- and genotypes in bullous epidermolysis congenital ichthyosis and ectodermal dysplasia

Bullous epidermolysis

	HLA phenotypes	Possible genotypes
P.S. (patient)	A 2, 3; B 5, 18; Cw1, 6	A 2, B 5, Cw1/A 3, B18, Cw6
P.M. (sister)	A 2, 3; B 5, 18; Cw1, 6	A 2, B 5, Cw1/A 3, B18, Cw6
P.S. (father)	A 1, 3; B 8, 18; Cw6	A 1, B 8, Cwx/A 3, B18, Cw6
Mrs P. (mother)	A 1, 2; B 5, Cw1	A 2, B 5, Cw1/A 1, B 5, Cw2
Mrs A. (maternal grandmother)	A 1, 2; B 5, 39; Cw1, 6	A 2, B 5, Cw1/A 1, B39, Cw6
L.Sz. (patient)	A 1, 2; B 8, 17; Cw6	A 2, B17, Cw6/A 1, B 8, Cw6?
L.J. (patient)	A 1, 2; B17, 35; Cw6	A 2, B17, Cw6/A 1, B35, Cw6?
L.J. (father)	A 2, 28; B17, 41; Cw6	A 2, B17, Cw6/A28, B41, Cw6?
Mrs L. (mother)	A 1, ; B 8, 35; Cw6	A 1, B 8, Cw6/A1 , B35, Cw6?
P.J. (patient)	A 3, 24; B 5, 7; Cw6	A 3, B 7, Cw6/Aw24, B5, Cwx?
P.J. (father+patient)	A 2, 3; B 5, 7; Cw6	A 3, B 7, Cw6/A 2, B5, Cwx
P.J. (paternal grandfather, patient)	A 3, 25; B 7, 18; Cw6	A 3, B 7, Cw6/A25, B18, Cwx
P.L. (uncle, patient)	A 2, 3; B 7, 40; Cw2, 6	A 3, B 7, Cw6/A 2, B40, Cw2
Sz.Gy. (patient)	A 1, 3; Bw15, 35; C–	

Congenital ichthyosis

D.J. (patient)	A 1, 3; B 5, 18; C—	
D.F. (patient)	A 2, w23; B18, ; Cw6	A 2, B18, Cw6/Aw23, B18?, Cwx
D.K. (sister)	A 2, w24; B18, 40; Cw3, 6	A 2, B18, Cw6/Aw24, B40, Cw3
Mrs D. (mother)	A 2, 11; B 5, 18; Cw2, 6	A 2, B18, Cw6/A11, B 5, Cw2
Mrs T. (maternal grandmother)	A 2, 11; B 7, 18; Cw6	A 2, B18, Cw6/A11, B 7, Cw6
T.L. (uncle)	A11, ; B 5, 7; Cw2, 6	A11, B 5, Cw2/A11, B 7, Cw6
T.E. (cousin)	A11, 26; B 7, 38; Cw6	A26, B38, Cwx/A11, B 7, Cw6
T.E. (nephew)	A11, 26; B 5, 14; Cw2	A26, B14, Cwx/A11, B 5, Cw2
B.G. (patient)	A 1, w31; Bw15, 35; Cw4, 6	A 1, B35, Cw4/Aw31, Bw15, Cw6
B.M. (sister)	A 1, w31; Bw15, 35; Cw4, 6	A 1, B35, Cw4/Aw31, Bw15, Cw6
B.É. (sister)	A 1, 2; B 8, w50; Cw6	A 1, B 8, Cw6/A 2, Bw50, Cwx
B.M. (father)	A 1, 2; B 35, w50; Cw4	A 1, B35, Cw4/A 2, Bw50, Cwx
Mrs B. (mother)	A 1, w31; B 8, w15; Cw6	A 1, B 8, Cw6/Aw31, Bw15, Cw6

Congenital ichthyosis

	HLA phenotypes	Possible genotypes
D.B. (patient)	A 2, 28; B 5, 15; Cw3	A 2, B 5, Cwx/A28, Bw15, Cw3
Mrs D (mother)	A 2, ; B 5, 12; C–	A 2, B 5, Cwx/A20, B 12, Cwx
V.I. (maternal)	A 2, ; B 5, w50; C–	A 2, B 5, Cwx/A20, Bw50, Cwx
Mrs V. (grandparents)	A 2, 11; B 12, 18; C–	A 2, B12, Cwx/A11, B 18, Cwx
D.I. (paternal)	A 11, 28; B 38, 40; Cw2, 3	
Mrs. D (grandparents)	A 2, 28; Bw15, 27; Cw2, 3	A 2, B27, Cw2/A28, Bw15, Cw3

Congenital ichthyosis

	HLA phenotypes	Possible genotypes
M.S. (father)	A 2, 28; B 7, 35; Cw4	
Mrs S. (mother)	Aw24, 32; B 5, 27; Cw2	Aw24, B 5, Cwx/A32, B 27, Cw2
L.P. (grand-	A 2, w24; B 5, 17; C–	Aw24, B 5, Cwx/A 2, B 17, Cwx
Mrs L. parents)	Aw23, 32; B 13, 27; Cw2	Aw23, B13, Cwx/A32, B 27, Cw2
L.S. (aunt)	A 2, w23; B 13, 17; C–	Aw24, B13, Cwx/A 2, B 17, Cwx
D.P. (patient)	A 2, 3; B 18, 35; C–	A 2, B35/A 3, B18
D.J. (patient)	A 1, 2; B 8, 35; C–	A 2, B35/A 1, B 8
Mrs D. (mother)	A 2, 28; B 27, 35; C–	A 2, B35/A28, B27
	Ectodermal dysplasia	
O.Gy. (patient)	A 1, 2; B 35, w50; Cw4	A 1, B35, Cw4/A 2, Bw50, Cxw
Mrs O. (mother)	A 1, 26; B 35, 38; Cw4	A 1, B35, Cw4/A26, B 38, Cwx
Mrs K. (maternal grandmother)	A 1, 2; B 12, 35; Cw4	A 1, B35, Cw4/A 2, B 12, Cwx
D.Zs. (patient)	A 2, w33; V 13, 39; C–	A 2, B39/Aw33, B13
D.L. (father)	A 2, w33; B 13, 18; C–	A 2, B18/Aw33, B13
Mrs D. (mother)	A 2, ; Bw15, 39; C–	A 2, B39/A20, Bw15
Mrs I. (aunt)	A 1, 32; B 8, 39; C–	
B.L. (patient)	A 25, 26; B 38, 40; Cw2	
Mrs B. (mother)	Aw24, 25; B 38, 40; Cw2	
N.E. (patient)	A 2, 26; B 7, 38; C–	A 2, B 7/A26, B38
Mrs N. (mother)	A 2, 3; B 7 C–	A 2, B 7/A 3, B7
N.L. (father)	A 11, 26; B 38, 37; C–	A 26, B38/A11, 37

find no literary data concerning the question or else they awaited confirmation [10].

Material and Methods

Four families with bullous epidermolysis, 7 homozygous patients in 6 families with congenital ichthyosis as well as 4 homozygous children from 4 families with ectodermal dysplasia were typed for HLA–ABC antigens, using the NIH lymphocytotoxicity test [15]. The pedigrees were recorded on the basis of the clinical picture and the genetic history.

Results

The HLA pheno- and genotypes are shown in Table I.

Bullous epidermolysis

The pathological condition of baby P.S. was diagnosed in newborn age; his mother had had a similar dermatological abnormality in her babyhood and infancy. The patient is a male child (Fig. 1. III/1) who had the haplotype HLA–A2, B5, Cw1 in common with the gene-carrier mother

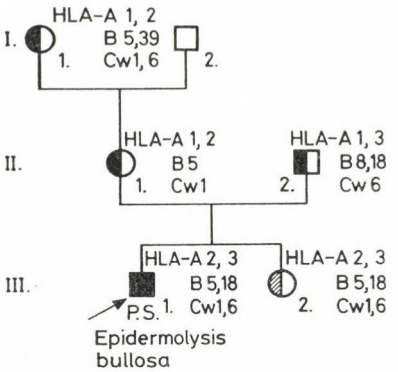


FIG. 1

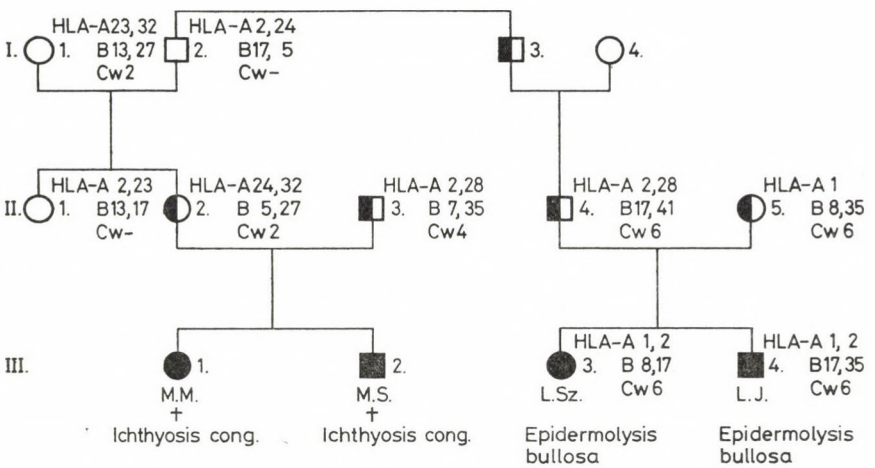


FIG. 2

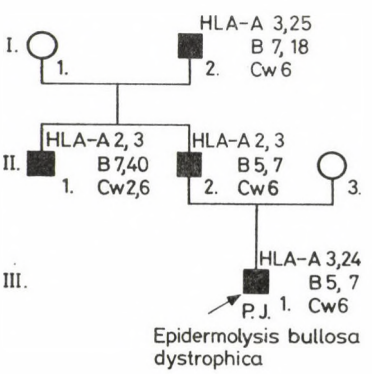


FIG. 3

and maternal grandmother. The genotype of the gene-carrier father is A1, B8, Cwx/A3, B18, Cw6, of which the combination A3, B18, Cw6 was represented in both of his children. On the basis of these common haplo-types and of the HLA-identity of the children, the sister III/2 may also be considered a gene carrier. The disease gene transfer in the family was of the autosomal recessive type.

In family L. heredity was also of the autosomal recessive type (Fig. 2). The common HLA haplotype of the two homozygous children (III/3, III/4) was A2, B17, Cw6. The single common antigen of the obligate gene-carrier parents is Cw6.

In the case of family P. (Fig. 3) epidermolysis bullosa dystrophica of dominant heredity was observed. The common haplotype of the homozygous family members was A3, B7, Cw6. In patient P.J. also Aw24, B5 haplotype occurred which has been observed to be characteristic of bullous epidermolysis [10]. B5 alone occurred in the father, too. In the adult patient Sz. G., B35 was found as a shared antigen in the bullous epidermolysis family L.

Congenital ichthyosis

In family D. (Fig. 4) where four male individuals were affected, the heredity was X-linked recessive. In the two homozygous patients in the family who were HLA-typed, no common antigen was found. One common haplotype of the obligate heterozygous mother and grandmother, A2, B18, Cw6, could be found in one of the homozygous patients (IV/3) and in the supposed gene-carrier sister (IV/4).

Baby B. G. was born of the third pregnancy. Three of the four children of the maternal grandmother's brother died (Fig. 5) in early infancy, two of them of congenital hydrocephalus, and one of spina bifida. The common haplotype of the propositus, his sister, and of the mother was A31, B15, Cw6. The heredity is, according to literary evidence, X-linked recessive. We suppose that the sister (III/3) is a possible gene-carrier, on the basis of the HLA-haplotype shared with the gene-carrier mother.

In the family of the female infant D. B. (Fig. 6), no similar disease occurred excluding thus an autosomal dominant heredity. The sex of the child excluded an X-linked recessive heredity, therefore transmission of the gene may be qualified as autosomal recessive. The common haplotype of the mother, the maternal grandfather and of the female child is A2, B5.

In family D. (Fig. 7) the two male twins suffer from ichthyosiform congenital erythroderma. We must consider the mother to be an obligate gene-carrier. The heredity is, on the basis of the family data and the literature, X-linked recessive. The common haplotype of the two homozygous male children and the possible gene-carrier mother is HLA–A2, B35.

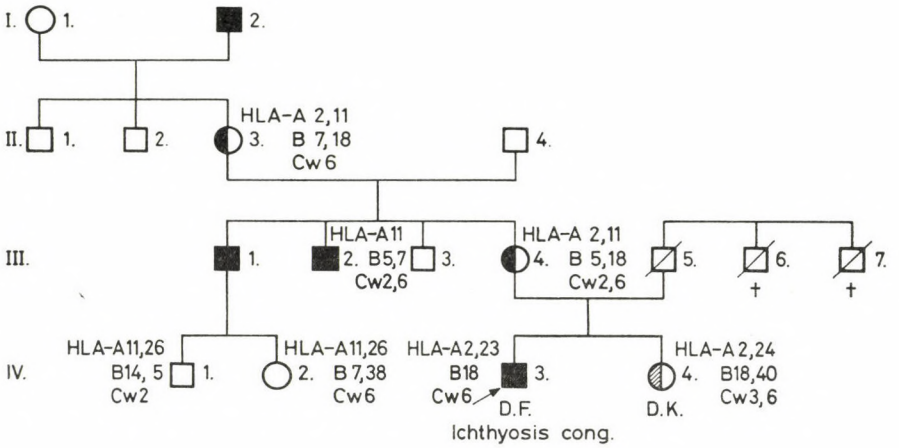
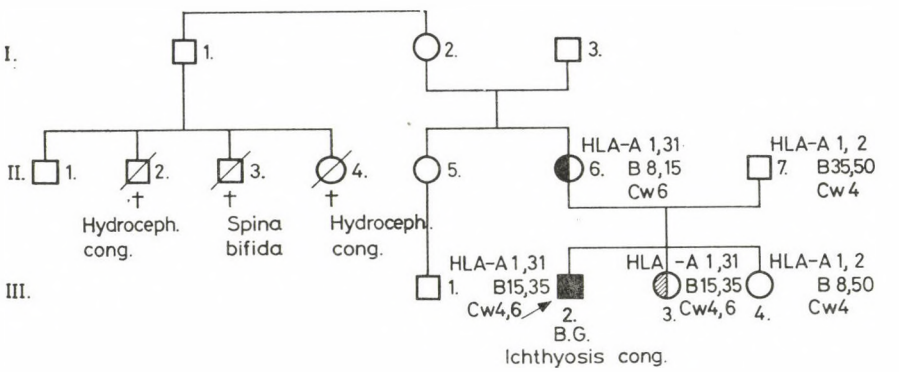


FIG. 4



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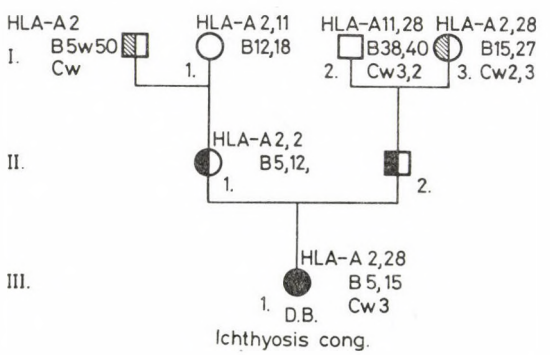

FIG. 6

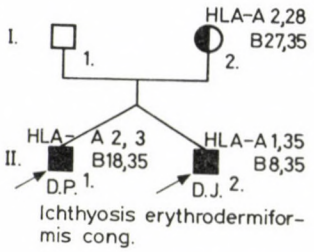

FIG. 7

In family M. (Fig. 2), on the basis of the affected infants of different sexes, gene transfer must have been of the recessive type. The two collodium babies (III/1, III/2) had died so that HLA-typing could not be done, therefore in Table I. only the HLA phenotypes of the obligate heterozygous parents are given.

Ectodermal dysplasia

The male infant O. G. was admitted as a newborn with anhydrotic ectodermal dysplasia (Fig. 8). The mother and the maternal grandmother have slight symptoms. The type of heredity is, according to the literature [13], X-linked recessive. The patient, the mother and the maternal grandmother share the HLA-A1, B35, Cw4 haplotype.

In the case of D. Zs. (Fig. 9) who is a male individual, X-linked recessive heredity may be suspected. Of the HLA-antigens of D.Zs., A2, B39 are shared with the gene-carrier mother. The mother's sister does not have these antigens.

The anhydrotic ectodermal dysplasia of the male child B.L. proved to be of X-linked recessive heredity, as there were three homozygous male children in the family (Fig. 10). Three sons of the mother's brother died in infancy; according to the history they have probably been also affected. The mother was found to

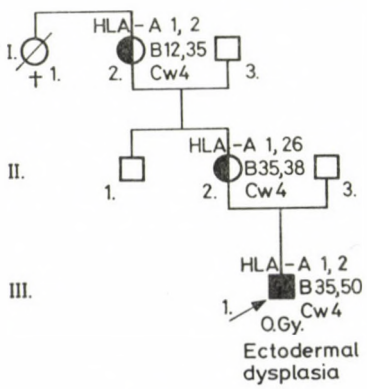

FIG. 8

have cystinuria. The affected male child and the gene-carrier probably had the common haplotype A25, B40.

The type of heredity of the female infant N.E. was, on the basis of her sex, autosomal recessive (Fig. 11). Her HLA antigens inherited from the

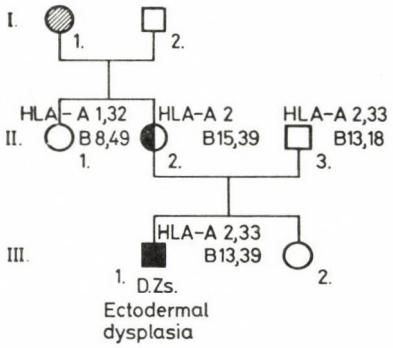

FIG. 9

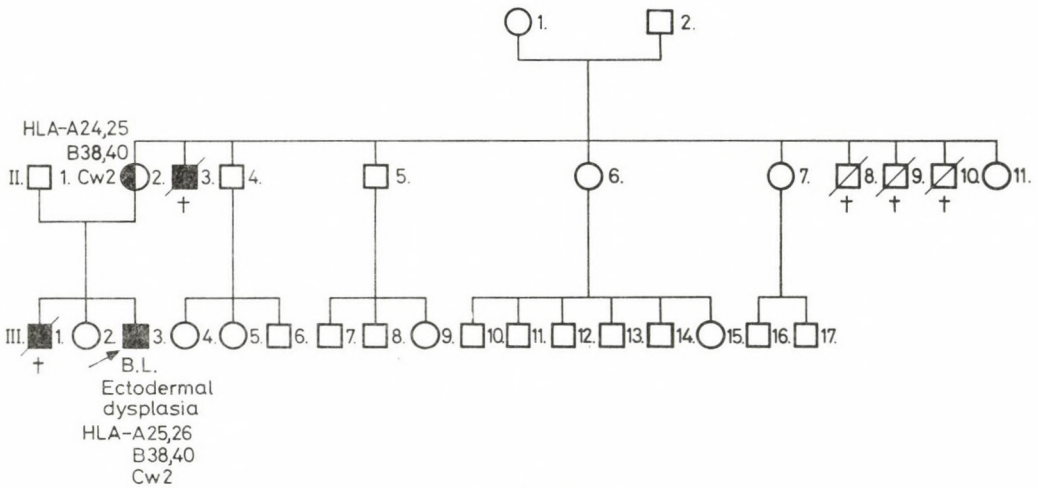

FIG. 10

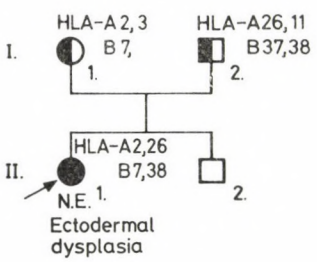

FIG. 11

mother were HLA–A2, B7, those inherited from her father, A26, B38.

The haplotype A26, B38 probably occurred in three of the four cases shown in the ectodermal dysplasia group.

Discussion

Bullous epidermolysis

On the basis of the clinical picture, the pathological findings and the prognosis, 8 types of bullous epidermolysis may be distinguished. I. Epidermolysis bullosa simplex (type Koebner) with autosomal dominant heredity; II. Weber–Cockayne syndrome with autosomal dominant heredity; III. epidermolysis bullosa lethalis (type Herlitz) of autosomal recessive heredity; IV. locally missing skin with blisters and dystrophy of the nails (Barty syndrome), with autosomal dominant gene transfer; V. epidermolysis bullosa dystrophica (autosomal dominant); VI. epidermolysis bullosa dystrophica (autosomal recessive); VII. Macular dystrophic epidermolysis bullosa (Mendes Da Costa syndrome) with X-linked recessive heredity; and VIII. epidermolysis bullosa dystrophica neuropathica which may be associated with deafness of the perceptive type [4].

In the two families L. and P. (Figs 1–2) the heredity of congenital epidermolysis was autosomal recessive and in a third family (P. J., Fig. 3), autosomal dominant in type. In the last case the clinical picture was somewhat different as it was a dystrophic bullous epidermolysis with the haplotype Aw24, B5. This might be characteristic of bullous epidermolysis [10] as we found it in a homozygous patient (P. J. Fig. 3) and B5 alone in his father. In the case of P.J. as well as in the one published by Ozawa et al [10], the gene transfer was of the autosomal dominant type. B5 alone was observed in addition in four members of Family P.S. (Fig. 1) with bullous epidermolysis of the autosomal recessive type.

In family P.S. A2, B5, Cw1 were demonstrated in the homozygous male child patient (III/1), in her sister, a suspected gene carrier (III/2), as well as in the gene-carrier mother and maternal grandmother. From the gene-carrier father both children received the haplotype A3, B18, Cw6.

In family L. (Fig. 2) the common haplotype of two homozygous children (III/3, III/4) was A2, B17, Cw6, and they were different in the antigens inherited from their mother.

In the case of the male patient Sz.Gy. who only shared a B35 with some members of the family L., the mother was affected, thus the heredity was autosomal dominant.

Congenital ichthyosis

Heredity is different in the different ichthyosiform dermatoses [4]. The heredity of ichthyosis vulgaris is autosomal dominant, the X-linked recessive ichthyosis also belongs to the group of normokinetic ichthyoses. In the group of hyperkinetic ichthyoses, epidermolytic hyperkeratosis has an

autosomal dominant, while lamellar ichthyosis an autosomal recessive heredity. To this last group belong the ichthyosiform erythrodermia, the Harlequin fetus, lamellar ichthyosis of infants, and the collodium baby.

Voigtländer et al [16] classified the hereditary ichthyoses as follows.

1. The group of ichthyosis vulgaris includes (i) autosomal dominant ichthyosis, (ii) X-linked recessive ichthyosis (iii), ichthyosis in Refsum syndrome.

2. The congenital ichthyosis group consists of (i) ichthyosis congenita gravis (Riecke I, Harlequin fetus), (ii) ichthyosis congenita mitis (Riecke II) and tarda (Riecke III), (iii) ichthyosis in the Sjögren–Larsson-syndrome, (iv) ichthyosis in the Rud-syndrome.

3. In the ichthyosis hystrix group (i) erythrodermia congenitalis ichthyosiformis bullosa and (ii) the four subtypes of ichthyosis hystrix gravior are to be found.

Palásty [11] observed in a gipsy family five collodium babies and supposed an autosomal recessive heredity, in agreement with Burgoon [3] and Lencz and Altman [6].

Mevorah et al [8] observed autosomal dominant and X-linked recessive variants of ichthyosis vulgaris within one family. Phenotypically the ichthyosis was of the dominant type in the mother, while it was dominant and X-linked recessive in her sons. Ultrastructural examination of the keratinization disorders in the ichthyoses of different hereditary types may provide important clues regarding the type of heredity [1].

Koppe et al [5] reported on cases of ichthyosis congenita vulgaris with X-linked heredity. They considered the decrease in arylsulphatase-C activity of the skin and the placenta to be the causative factor.

In two of our families with congenital ichthyosis we demonstrated an autosomal recessive heredity(M. and D.B., Fig. 2 and 6) and X-linked recessive heredity in one family (D.F., Fig. 4). In one case (family B., Fig. 5) we supposed an X-linked recessive gene-transfer on the basis of literary data.

In the case of family D.F. (Fig. 4) with X-linked recessive heredity the combination of HLA–A2, B18, Cw6 antigens could be demonstrated in four out of the eight family members, viz. in a homozygous male child and three obligate gene carriers. The similarly affected maternal uncle (III/1) totally differed in his HLA-antigens from the genetically affected nephew. Among his antigens A11, B5, and Cw2 agreed with those of some other family members, while in A11, B7, Cw6 he was identical with his daughter and the obligate heterozygous maternal grandmother (IV/2, II/3). The antigen combination A26, B38 in the daughter is apparently very frequent in our families with ectodermal dysplasia.

In the family of the collodium babies (Fig. 2) the HLA types of the two obligate heterozygous parents may be important. The phenotype of the father was A2.28; B7.35; Cw4, and that of the mother Aw24, B5, Cwx/A32, B27, Cw2. It is interesting

that she carried Aw24, B5 in one haplotype, an antigen combination which was thought to be significant in bullous epidermolysis [10]. As regards our own cases with bullous epidermolysis, we found this combination in one out of three families. It is assumed that Aw24 and B5 are markers of some sort of general sensitivity to certain dermatological disorders. It was remarkable that this antigen combination seemingly important in bullous epidermolysis should occur in a family where the grandfathers were brothers and in which one psoriasis and two collodium baby cases occurred. Only one of the two grandfathers was HLA-typed; he was healthy and a carrier of the Aw24, B5 combination. Another frequent antigen combination in this family, A2, B17, Cw6, was found in five out of ten persons and in a sixth case it was very probably present. B17, however, did not occur in some obligate ichthyosis gene-carriers (II/2, II/3).

Ectodermal dysplasia

Concerning the inheritance of ectodermal dysplasia, the anhydrotic form was reported to be an X-linked condition [13] while Bernard et al [2a] demonstrated an autosomal dominant heredity through three generations.

In one (family B.) out of four families with ectodermal dysplasia, the heredity was clearly X-linked recessive (Fig. 10). In two other families (D. and O.) (Figs 8, 9). owing to the genetic affection of the male persons and on the basis of literary data, heredity was considered to be X-linked. Finally, in the fourth family (Family N., Fig. 11) gene transfer was found to be autosomal recessive.

In three of these four families (see Table I) the combination of A26 and B38 was demonstrated and in the fourth family B39 occurred in another combination. Thus, the former Bw16 antigen (B37 and B38 together), which has a 9 % frequency in European populations, was present in four out of the four families with ectodermal dysplasia.

As regards prevention, odontological screening, detection of agenesis or hypoplasia of the teeth may also throw light upon gene transfer in ectodermal dysplasia [11].

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