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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Familial steatocystoma multiplex: HLA, Gm, Km genotyping and chromosomal analysis in two unrelated families

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Steatocystoma Multiplex (S.M.) is an inherited condition characterized by the appearance of cysts during the first or second decade of life. Familial cases have occasionally been reported. We studied 13 patients affected by S.M. from two unrelated families, focusing our attention on HLA, Gm and Km genotypes and on chromosomal analyses. Although we failed to correlate the syndrome with a particular HLA, Gm or Km haplotype, we report some peculiarities and differences between these two families and the healthy Italian population.

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Key words: autosomal dominant inheritance; chromosomal analysis; HLA histoglobulins; Ig allotypes; steatocystoma multiplex.

Steatocystoma Multiplex (S.M.) is a rare but distinct condition characterized by the formation of numerous cysts (called steatomas, steatocystomas, or sebocytes). Clinically the lesions are cysts involving the face, the trunk, the arms and especially the chest; the cysts are always multiple and vary from 0.1 to 2 cm in diameter; they are commonly elevated and movable; the overlying skin is usually normal (Fig. 1). The age of onset of lesions is usually in early childhood or adolescence.

Although individual cases are not exceedingly rare (Egbert et al. 1979, Cole 1976, Anderson 1950), familial cases have seldom been described (Noogin & Reynolds 1948). Hereditary S.M. has an autosomal dominant transmission (Touraine 1955) and males and females are equally affected. We recently observed 13 patients affected by S.M. from two unrelated families (Brazzelli et al. 1987). The familial occurrence of this disease induced us to study genetic markers (of the 6th, 14th and 2nd chromosome) in the patients and their relatives in order to correlate the disease with a specific genetic profile. The distribution of HLA, Gm and Km genotypes was studied in these two families, both of which had more than one affected sibling in successive generations, and a correlation between the inheritance of this disease and patterns of segregation of genetic markers was investigated.

Material and Methods
The study was carried out on two unrelated families originating from Piedmont (Family A) and Sicily (Family B). There are 4 people in Family A, two of whom, the father and the daughter, are affected by S.M., and 21 people in Family B, 11 of whom are affected by S.M., this disease occurring in all 4 generations. The clinical diagnosis of S.M. was confirmed by histological analysis in both affected subjects from Family A and 7 subjects from Family B, belonging to three different generations. In these subjects and their relatives, chromosomal analyses, HLA, Gm and Km typing were carried out using the following techniques.

HLA Polymorphisms
~ HLA typing for class I and II histoglobulins, coded by genes at A, C, B, DR and DQ loci on the short arm of chromosome

Fig. 1. Patient 3 (III generation) from Family B affected on the back and on the shoulders.
Short Communication

Familial S.M. and Genetic Markers

Stomatoma multiplex: HLA, and chromosomal related families

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Introduction. characterized by the appearance of only cases have occasionally been reported in unrelated families, focusing our attention on mal analyses. Although we failed to correlate haplotype, we report some peculiarities and peculiarities of the Italian population.

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Fig. 1. Patient 3 (III generation) from Family B affected by Stomatocystoma Multiplex. Several cysts are present on the back and on the shoulders.

Recently observed 13 patients affected by Stomatoma, from two unrelated families (Brazzelli et al. 1987). The familial occurrence of this disease induced us to study genetic markers of the 6th, 14th and 2nd chromosome in the patients and their relatives in order to correlate the disease with a specific genetic profile. The distribution of HLA, Gm and Km genotypes was studied in these two families, both of which had more than one affected sibling in successive generations, and correlation between the inheritance of this disease and patterns of segregation of genetic markers was investigated.

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HLA Polymorphisms

- HLA typing for class I and II histocomponents, coded by genes at A, C, B, DR and DQ loci on the short arm of chromosome 6, was performed using the microlymphocyte-toxicity test on T and B enriched lymphocyte suspensions. The typing reagents consisted of the core-set of antisera available from the Xth International Histocompatibility Workshop (New York, November 1987).

- Typing of HLA class III polymorphisms (Bf, C4A and C4B serum complement proteins) was performed by electrophoresis on agarose gels and immunofixation with goat anti-human Bf and C4 antisera (Alper et al. 1972, Awdeh & Alper 1980).

Gm and Km Typing

Serum samples were typed for IgG heavy-chains (Gm) and K light-chains (Km) allotypes by means of a hemagglutination-in-
Results and Discussion

The pedigrees of Family A and Family B are summarized in Fig. 2 and 3, respectively. The affected subjects are indicated by an arrow and HLA, Gm and Km haplotypes are fully reported in the figure legends. We detected two HLA-identical siblings in Family B (IV:3 and 4) and two HLA haploidentical siblings in Family A (II:1 and 2) one affected and the other healthy. Two affected brothers in Family B (III:4 and 5) were HLA haploidentical.

Linkage analysis did not provide significant evidence against or in favor of a linkage between the susceptibility gene to S.M. and HLA (maximum negative lod score -0.0177 at theta = 0.4), Gm (lod scores = 0.0000 at every theta value), Km (maximum positive lod score = 0.2576 at theta = 0.05).

The father's and brother's chromosomal analysis (from Family A) showed a male karyotype with an inversion of the Y chromosome: 46, XY, inv (Y), p11, q11; all the other members of this family have normal karyotypes.

In Family B, all the members showed normal lymphocyte karyotypes, except for subject 3 (IV generation), a 15-year-old boy, with mental retardation and protogynism who has a fragile X; 46, XY, fra (X) (q28 in 7 out of 100 metaphases as detected in cultures with 199 medium. The fibroblasts culture of the cystic wall, carried out on only one patient (II:1) in Family A, was normal. The analysis of S.C.E., performed in Family A, revealed an average number of exchanges per mitosis within the normal range of our laboratory.
Results and Discussion

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Fig. 3. Pedigree of Family B. HLA haplotypes: a = A2; CX.B18; B15; C4A3; C4B1; DR5; DQW3
b = A2; CW4; B12(24); Bfn.d.; C4An.d.; C4Bn.d.; DR3; DQW2
c = A3; CW7; B7; Bfn.d.; C4An.d.; C4Bn.d.; DR5; DQW3
d = A9(24); CX.B18; B15; C4A3; C4B1; DRX; DQX
d' = A3; CX.B7; B15; C4A3; C4B1; DRX; DQX
b' = A1; CW2; B21; Bfn.d.; C4An.d.; C4Bn.d.; DR5; DQW3
c' = A11; CW4; B18; Bfn.d.; C4An.d.; C4Bn.d.; DR1; DQW1
d'' = A2; CX; BX; Bfn.d.; C4An.d.; C4Bn.d.; DRX; DQX

Gm haplotypes:
0 = 3; 23; 5; 10; 11; 13; 14
1 = 1; 7; 21; 28

Km alleles:
\( \Delta = 1 \)
\( \Delta = 3 \)

Our work is particularly extensive considering the rarity of family histories with this disease and the number of genetic polymorphisms studied.

We have examined genetic aspects of S.M., investigating different chromosomal markers: the short arm of chromosome 6 (HLA), the long arm of chromosome 14 (Gm), and the long arm of chromosome 2 (Km). We failed to detect any genetic linkage between this disease and a particular HLA, Gm or Km haplotype; in fact, the segmentation pattern of these genetic markers does not seem to correlate with the inheritance of the disease.

Nevertheless, Family A showed the HLA
haplotype B13;DR1, which is quite rare (2%) in the Italian population and inherited only by patients. The C4BQO homozygous condition, that we found in one patient in Family A (II:1), is also infrequent in our healthy population (1%). The rarity of haplotypes observed could not be irrelevant; on the contrary, this information might induce other investigators to look more closely at HLA types in familial cases of S.M.

Chromosomal analyses carried out on lymphocytes did not show any abnormalities as far as number or structure is concerned. The fragile X detected in Sibling 3 (IV generation of Family B) seems uncorrelated with S.M. (Gerald 1980, Optiz & Sutherland 1984). The inversion of the Y chromosome detected in the father and brother of Family A is considered a non-pathological karyotypic variant present in 1% of the male population (Zeuthen & Nielsen 1973). Karyotype analysis of fibroblasts surrounding the cystic wall was normal, but this does not imply that cell walls (of epidermal origin) do not have chromosomal aberrations.

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References


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Letters to

Holoprosencephaly, polydactyly pseudo-t

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Sirs,

Holoprosencephaly, premaxillary agenesis and polydactyly are usually associated with chromosome abnormalities, particularly trisomy 13. A recent report of a stillborn with these malformations and cardiac abnormalities (Young & Madders 1987) but normal chromosomes, was followed by two similar cases (Moerman & Fryns 1988, Shiota & Tanimura 1988). We present another instance.

This first pregnancy of a healthy, unrelated Caucasian couple (mother 28 years; father 45 years) was uncomplicated until a scan at 18 weeks demonstrated a midline facial cleft and no nose, the presence of midbrain, thalamus and cerebellum, but minimal forebrain tissue, the normal-sized cranium being occupied by fluid — apparently external hydrocephalus. The chromosomes were normal: 46,XY. Termination of pregnancy was requested.

The male fetus (Fig. 1) was of the expected size and stage of development. There was marked ocular hypotelorism, exophthalmia, no nose and total median clefting of the upper lip and palate. Postaxial polydactyly was present on all extremities. There was semilobar holoprosencephaly with absent olfactory lobes, optic chiasmata, pituitary stalk and gland. The malformed forebrain was small and occupied only the floor of