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Cystic fibrosis: a HLA associated hereditary disease?

By

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Twelve homozygote patients and thirty-two heterozygote gene carriers from families with cystic fibrosis were HLA-typed. Diagnostic criteria were sweat electrolyte concentration, pancreatic enzyme levels from duodenal juice and stool, Szczepanski's bromide test in the group of homozygotes, and the latter only in the cases of heterozygotes.

In comparison with 130 healthy blood donors typed for 29 HLA antigens, B18 proved to be more frequent in the group of patients and gene carriers, with 50 and 31%, respectively, and 14% in the normal population. The association seems to be stronger in the homozygotes than in the heterozygotes ($p < 0.005$ and $p < 0.02$, respectively).

With growing knowledge concerning tissue antigens, a search has begun for their correlation with diseases [1, 2]. The first success was the demonstration of a correlation between the susceptibility to oncogenic viruses and H-2, the main histocompatibility system in mice, which corresponds to the HLA system in man [7]; and then their relation with human leukaemia [2].

The pioneer work was followed by many clinical observations [3, 6, 8, 10]. Some of the correlations between a disease and the presence of certain HLA antigen(s) are so strong, e. g. ankylosing spondylitis with B27 or gluten enteropathy with B8, that persons negative for these antigens are affected only exceptionally. There are now other examples, in which an association found with a HLA-B series antigen was followed by finding another, but stronger, association with a HLA-D antigen in linkage disequilibrium with the former, e. g. 7 and 7a (the present B7 and Dw2) in multiple sclerosis. (The nomenclature used in this paper corresponds to the latest decisions of the WHO-IUIS Terminology Committee, see ref. [12].) It seems certain that as soon as HLA-D typing becomes a routine procedure, further disease associations will be found.

The next step would be the elucidation of the mechanism through which these effects are brought about. It is, however, impossible to find a common explanation for the different malignancies, immunopathological diseases, or bacterial and viral in-

fections. The most plausible explanation for most disease groups is perhaps the theory that certain disease genes not localized as yet may be in linkage disequilibrium with some HLA antigens.

Cystic fibrosis (CF) has so far been involved in a single study and this brought a negative result, showing no deviation from normal HLA antigen frequencies [4, 5]. A slight association with B5 was considered insignificant [5].

Material and Results

Twelve homozygote patients and 32 heterozygote gene carriers from families with CF were HLA-typed. The diagnostic criteria were sweat electrolyte concentrations, pancreatic enzyme levels (lipase, amylase) from duodenal juice and stool, Szczepanski's bromide test [9] in the group of homozygotes, and the latter only in the cases of heterozygotes. Of the latter, 18 were parents of homozygous children, with a bromide index corresponding to the level of heterozygotes.

In comparison with 130 healthy blood donors typed with microlymphocytotoxicity test (by NIH technique) during the same period with the same typing sera for 29 HLA antigens, HLA-B18 proved to be more frequent in the group of homozygotes and heterozygous gene carriers (50 and 31%, respectively, and 14% in the normal control group (Table I)).

Discussion

Cystic fibrosis is a genetically well-defined condition with severe clinical consequences. To offer an explanation for the observed correlation with B18, which might hold true only if confirmed on a greater number of patients, we believe that linkage disequilibrium with the disease gene(s) should be assumed in this particular case too. There seems to be room for many genes in the region where those coding for the antigens of the main histocompatibility complex are situated [3, 6]. One or more of these genes might regulate a certain metabolism necessary to the normal development of cell membranes.

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Table I

Incidence of HLA-B18 in 44 CF patients

Patients	Number of cases	HLA-B18 positive per cent	Chi square	p	p (corrected)
Homozygotes	12	50	8.164	<0.005	0.116
Heterozygotes	32	31	5.440	<0.02	
Control blood donors	130	14			

References

1. Dausset, J.: Les systèmes d'histocompatibilité et la susceptibilité au cancer. Presse méd. **76,** 1397 (1968).
2. Dausset, J., Dupuy, J. M.: Coincidences or fundamental relationships between leukemogenesis and transplantation antigens. Nouv. Rev. franç. Hematol. **7,** 161 (1967).
3. Dausset, J., Degos, L., Hors, J.: The association of the HL-A antigens with diseases. Clin. Immunol. Immunopath. **3,** 127 (1974).
4. Götz, M., Ludwig, H., Polymenidis, Z.: H-L antigens in cystic fibrosis. Z. Kinderheilk. **117**, 183 (1974).
5. Polymenidis, Z., Ludwig, H., Götz, M.: Cystic fibrosis and HL-A antigens. Lancet **2**, 1452 (1973).
6. van Rood, J. J., van Hooff, J. P., Keuning, J. J.: Disease predisposition, immune responsiveness and the fine structure of the HL-A supergene. Transplant. Rev. **22,** 75 (1975).
7. Snell, G. D.: The H-2 locus of the mouse: observations and speculations concerning its comparative genetics and its polymorphism. Folia biol. **14,** 335 (1968).
8. Svejgaard, A., Platz, P., Ryder, L. P. Staub, N. L., Thomsen, M.: HL-A and disease associations. Transplant. Rev. **22,** 3 (1975).
9. Szczepanski, Z.: Sweat bromide test — a diagnostic tool for mucoviscidosis. A micromethod of bromide determination. Z. Kinderheilk. **113**, 297 (1972).
10. Woodrow, J. C.: HL-A and its association with clinical disease. Proc. roy. Soc. Med. **68**, 802 (1975).
11. WHO-IUSIS Terminology Committee: Nomenclature for factors of the HLA system. Europ. J. Immunol. **5,** 889 (1975).

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