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HLA Genotypes in a Family with a Case of Homozygous C2 Deficiency and Discoid Lupus Erythematosus

LASSE R. BRAATHEN,[1] ANNE BRATLIE[2] and PER TEISBERG[3]

[1]*Department of Dermatology,* [2]*Institute of Transplantation Immunology and* [3]*Department of Internal Medicine, Institute of Forensic Medicine, Rikshospitalet, The National Hospital, University of Oslo, Oslo, Norway*

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A fifty-year-old man with a history of recurrent bronchial and renal infections, and rheumatoid arthritis was admitted with a sunexposure-induced discoid lupus erythematosus. Complement levels and HLA typing of the patient and his family revealed a homozygous C2 deficiency in the patient and his HLA-identical healthy younger sister. The C2 deficiency gene was associated with HLA-A10, B18, DR2, C4A4B2, BfS on one chromosome and with HLA-A2, B7, DR2, C4A4B2, BfS on the other. *Key words: Complement deficiency; C2; HLA-antigens; Rheumatoid arthritis; Infections.* (Received April 16, 1986.)

L. R. Braathen, Department of Dermatology, Rikshospitalet, Pilestredet 32, 0027 Oslo 1, Norway.

Although inherited complement deficiences are rare in unselected populations, examination of patients with autoimmune diseases and certain bacterial infections, demonstrates a substantial frequency. It seems that inherited deficiences of complement predispose for the development of these diseases.

We here report a case of homozygous C2-deficiency associated with discoid lupus erythematosus, recurrent bronchitis and pyelonephritis, and sero-positive rheumatoid arthritis.

CASE REPORT

A 50-year-old carpenter was admitted with plaques of erythema with atrophy, teleangiectasias and vesicles/bullae in the skin of the face, neck, ventral and dorsal part of thorax and both arms. The skin changes were induced by intense sun-exposure.

He had suffered form recurrent bronchitis for many years, and the last year he had three episodes of pyelonephritis, as well as arthritis of finger-joints and the left knee. Skin-biopsy demonstrated findings compatible with lupus erythematosus.

Immunofluorescence microscopy of skin-lesions: pos. Lupus band. No band in non-lesional skin. ANA: neg. LE-test: neg. Anti-DNA (native): neg. Anti-DNA (denaturated): neg. Waaler's test: pos. 256. Latex test: pos. 3+. Complement factors: CH50<20 U/ml. Cl-esteraseinhibitor 100%. Immunoglobulins g/l: IgG 10.0, IgA 2.6, IgM 1.4, IgD<0.03, IgE 40 U/ml. Cryoglobulins and coldagglutinins: neg. ECG: normal.

Other laboratory tests: Hgb: 13.9, SR 30, WBC 8800. Diff. counts: normal. Se-creatinine, urea, uric acid, alk. phosphatase, ALAT, ASAT, bilirubin, total protein, se-electrophoresis, Na, K, Cl: all normal. Urine: normal.

In order to investigate his low CH50 further the patient and his family were typed with regard to the genetic polymorphisms C4, C2, factor B and HLA. C4 typing was performed by immunofixation agarose gel electrophoresis on desialised plasma samples. The C2 typing procedure included isoelectric focusing in polyacrylamid gel slabs, iodine treatment of gels, and visuliazation of C2 bands by overlay of agarose-containing sensitised red blood cells and C2 deficient human serum. The BF typing was performed by immunofixation electrophoresis. HLA typing was performed as described earlier (1). The results are presented in Fig. 1.

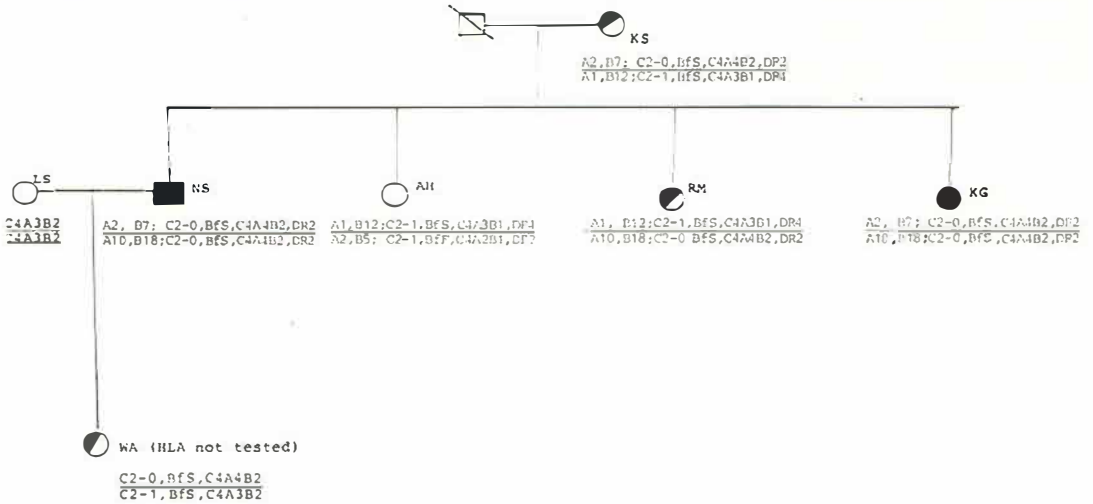

Fig. 1. Chromosome 6 haplotypes in family members. Filled symbols: homozygous C2 deficient individuals. Half-filled symbols: obligate heterozygous C2 deficient individuals.

Detailed quantitative studies of complement were performed in the patient and the family members. Total haemolytic complement and the component C2 were determined by haemolytic plate technique as described in Lachmann et al. (4). Complement factors C4 and factor B were determined in all family members by the radial immuno-diffusion method with commercially obtained antisera. C5 and C8 were determined by the same method but in the patient only. Results of quantitative determinations are found in Table I. C5 and C8 levels in the patient are not given in the table, but were in the normal range.

As can be seen, the patient and one of his sisters (K. G.) with an identical set of HLA haplotypes HLA-A2, 10; B7, 18: and DR2 totally lacked C2. This sister had no history of previous disease and was healthy. Furthermore it can be seen that C2 levels in obligate heterozygotes were found to be higher than expected. This may be due to methodological inaccuracy.

DISCUSSION

The present report demonstrates a case of homozygous C2 deficiency associated with discoid lupus erythematosus, recurrent infections and seropositive rheumatoid arthritis. His HLA-identical healthy younger sister also demonstrated the same C2 deficiency.

Table I. *Complement factor levels in the family (in % of normal levels)*

	Total hemolytic complement[a]	C2[a]	C4[b]	Factor[b] B
N. S. (patient)	<10	<5	110	80
A. A. (sister)	100	130	120	110
R. M. (sister)	80	80	120	110
K. G. (sister)	<10	<5	70	100
K. S. (mother)	100	85	120	100
L. S. (wife)	160	100	110	120
W. A. (daughter)	85	80	110	100
Normal level	>60	70–130	60–140	75–125

[a] Hemolytic technique.
[b] Radial immuno-diffusion-technique.

Inherited deficiences of complement predispose for the development of autoimmune diseases and bacterial infections. Classical pathway component deficienses are mostly associated with autoimmune disease, 57–85 % of all homozygotes being affected with such diseases (8).

C2 deficiency is the most frequently reported complement deficiency and has the best documented association with autoimmune disease (8).

In a survey of 545 patients; 134 with rheumatoid arthritis, 274 with juvenile rheumatoid arthritis and 137 with systemic lupus erythematosus, several probable C2 deficient heterozygotes, but only one C2 deficient homozygote was discovered (2). Patients with systemic lupus erythematosus had the highest frequency (5.9%). Two studies report the same frequency of 1.2 % for C2 deficient heterozygotes in the general population (2, 9). Using this frequency for the C2-null gene the authors calculated that one in 28000 individuals would be expected to be homozygous for C2 deficiency.

The C2 locus on chromosome 6 is closely linked to the C4 and Bf loci. The three complement loci are situated within the HLA complex between HLA-B and the HLA-D regions. Our C2 deficient patient and his sister had identical HLA-types (Fig. 1) including HLA-A10, B18. In a previous study all C2-deficient heterozygotes had the HLA-A10, B18 haplotype, and persons with this haplotype were calculated to have a 62.5 % chance of being heterozygous for C2 deficiency (9).

The close linkage between the C2 locus and the other loci in the HLA region is reflected in the association between the C2 deficient gene and especially HLA B18 and HLA DR2. The majority of previously reported C2 deficiency genes show this association. However, there are several reports from other countries of C2 deficiency genes occurring with other HLA-B genes. In the present family one of the C2 def. genes occur on the typical chromosome carrying B18 and DR2. This chromosome also carries BfS and C4A4B2. The other C2 deficient gene also occurs together with BfS, C4A4B2 and HLA DR2. The HLA A and B genes are, however, not the typical 10.18 but 2.7. This shows that sometime in the past recombination has occurred between the C2 deficient gene and the HLA A, B region.

The evidence from this family and from other previously reported families indicate that the C2 deficient gene is fairly ancient. It most probably occurred on the HLA haplotype HLA A10, B18, DR2, BfS, C4A4B2. Recombinations have, however, occurred and a substantial number of C2 deficient genes now are found together with other HLA types. Recombinations between C2 deficiency and BfS, C4A4B2 have not been reported.

Recent reports of C2 deficient patients have emphasized recurrent pyogenic infections in these individuals (3, 10, 11). Our patient also had recurrent infections, but not his C2 deficient sister. Organisms that require classical pathway-mediated opsonization are not ingested by phagocytes in sera deficient in C2 (7, 10). In view of their adjacent loci on chromosome 6 and analogous roles in the classical and alternative pathways, it is interesting to note that in several cases of C2 deficiency, factor B levels have been notably low, but not absent (5).

This is probably an aquired abnormality and not a co-inherited trait (6). Our patient had a factor B level in the low normal range. In conclusion, complement deficiencies can be regarded as the nature's own experiments which give valuable insight into the etiology and pathogenesis of autoimmune and infectious diseases.

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