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CLINICAL REPORT

No Human Leukocyte Antigen-A, -B or -DR Association in Swedish Patients with Hidradenitis Suppurativa

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Hidradenitis suppurativa (HS) is a cicatrizing, inflammatory and recurrent disease restricted to inverse skin, such as that of the axilla and groin of younger adults. In a previous study, using serological tissue-typing techniques, no significant increases in the human leukocyte antigen (HLA)-A and -B specificities were found in patients with HS. The aim of this study was to determine the frequencies of HLA-A, -B and, for the first time, HLA-DR alleles, using genomic tissue-typing methods in patients with HS. Forty-two unrelated Swedish patients with HS were included and compared with 250 controls. According to clinical staging adopted from Hurley all of the patients had stage II HS, i.e. recurrent abscesses with tract formation and cicatrization and single or multiple widely separated lesions. No association with HLA-A, -B or -DRB1 alleles was found in patients with HS. Genetic factors associated with the HLA class I or II regions do not appear to contribute significantly to the possible genetic susceptibility of HS. ***Key words: hidradenitis suppurativa; genetic susceptibility; human leukocyte antigen.***

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Hidradenitis suppurativa (HS; syn. acne inversa) (1) is a cicatrizing, inflammatory and recurrent disease. It is characterized by progression from uninflamed nodules to painful, round, deep-seated inflamed lesions with subsequent scarring and chronic suppuration, restricted to inverse skin areas rich in genital terminal hair follicles and apocrine sweat glands, e.g. the axilla and groin of younger adults. The condition ranges from a few recalcitrant suppurating lesions to advanced widespread and disabling disease. The aetiology is obscure but follicular obstruction, bacterial infections and hormones are among the factors that have been discussed. An association with acne has been suggested (1). An underlying genetic predisposition seems likely as a result of the occurrence of clusters of cases in families (2–5).

HLA (human leukocyte antigen) molecules are polymorphic membrane glycoproteins found on the surface of almost all nucleated cells (HLA class I molecules) and cells mainly involved in the immune response (HLA class II molecules). The HLA molecules serve as markers for self during the thymic maturation of T-cells and these cells always recognize foreign antigenic peptides in the context of self HLA molecules. More diseases have been shown to be associated with alleles of the HLA region than with any other genetic region, the first described and commonest being the HLA-B27 association in ankylosing spondylitis (6).

Conventional serological and cellular typing methods permit identification of the HLA class I and II specificities. However, in many cases reliable assignment of class I and II alleles is impossible due to the small number or poor quality of T- or B-cells or reduced expression of HLA molecules on the cell surface. Genomic HLA typing, using restriction fragment length polymorphism (RFLP) analysis or various polymerase chain reaction (PCR)-based typing methods, is accurate for HLA association studies (7). The polymorphism detected with RFLP analysis and PCR-based typing methods of HLA class II genes, especially DR and DQ, correlates well with the polymorphism recognized by serology and cellular typing (8, 9) and, more importantly, more biologically relevant polymorphism can be detected with DNA-based tissue typing than with serology.

In a previous study using serological tissue-typing techniques, no significant increases in the HLA-A and -B specificities were found in 27 Irish patients with HS (10).

The aim of this study was to determine the frequencies of HLA-A and -B alleles using genomic tissue-typing methods in Swedish patients with HS. DR typing was also included, for the first time to our knowledge, in order to assess HLA class II locus association in HS.

MATERIALS AND METHODS

Study subjects

Forty-two unrelated Swedish patients (mean age 44 years; range 26–62 years; 40 women; 2 men), with a history of HS were included in this study. All patients were stage II cases, according to clinical staging adapted from Hurley, i.e. recurrent abscesses with tract formation and cicatrization and single or multiple widely separated lesions. We included no cases of concurrent diseases with fistulizing tendencies, such as regional enterocolitis, ulcerous colitis or rheumatoid arthritis. The patients were otherwise healthy. A group of 250 healthy, randomly selected Swedish people was used for comparison. All subjects gave their informed consent and the study was approved by the local Ethics Committee at Karolinska Institutet.

DNA extraction

Whole EDTA-peripheral blood samples (5 ml) were drawn and deep frozen (– 70°C) pending analysis. High-molecular-weight DNA was extracted by salting-out in mini-scale (11, 12).

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PCR amplification primers

Sets of sequence-specific primers (SSP) and appropriate control primers were designed in our laboratory to identify the presently known HLA-A, -B and -DRB1 alleles using the PCR-SSP technique (13).

PCR procedure

A detailed description of the PCR procedure has been published previously (12, 13). In brief, each PCR reaction mixture contained 2–3 allele- or group-specific primers and an internal positive control primer pair. Thirty amplification cycles were performed in a GeneAmp PCR System 9600 (Perkin-Elmer Cetus Instruments). The absence or presence of PCR products was visualized by agarose gel electrophoresis. Gels were examined under UV illumination and documented photographically.

Statistics

Data were analysed using the χ^2 test or with Fisher's exact test in cases where small numbers of samples were expected.

RESULTS

Patients and controls were studied for the frequencies of HLA-A, -B and -DR specificities using PCR amplification with SSP. The distributions of all presently known alleles for HLA-A, -B and -DR were similar in patients with HS and controls (Table I). Moreover, normal frequencies of the HLA-A1 and -B8 types were found in patients with HS.

DISCUSSION

The distribution of HLA class I alleles in patients with HS has been determined in a previous study. O'Loughlin et al. (10) found that 7 of 27 patients with moderate or severe clinical disease had a marked reduction in peripheral T lymphocytes (i.e. $\leq$43%) and an increased frequency of the HLA antigens A1 and B8; however, the differences were not significant. They speculated that T lymphocytes may play a role in the pathogenesis of HS and that HLA-A1 and -B8 may predispose the patients to more severe disease. However, the above-mentioned associations of O'Loughlin et al. were not significant, due to the small number of cases, and must be regarded as questionable from a statistical point of view. In favour of our findings is the fact that this is the first study utilizing highly accurate and high-resolution genomic tissue-typing techniques in patients with HS.

All cases in our study were graded as stage II according to the Hurley classification of clinical severity (14). It is uncertain whether inclusion of Hurley stage I (less severe than ours) and stage III cases (more severe) would have affected our results.

In the present study, the high degree of allelic polymorphism of HLA-A, -B and -DR genes was determined by PCR amplification with SSP. The distributions of HLA-A, -B and -DRB1 alleles were remarkably similar in the patients and controls (Table I). A review of the literature shows that our study is the first on phenotype frequencies of HLA-DRB1 allele groups in patients with HS and controls.

A familial form of HS with autosomal dominant inheritance was described in the UK in the 1980s (2–4), but was not confirmed by others. In a recent follow-up of the original studies by Von Der Werth et al. (5) on 132 family members, including additional clinical analysis of newly affected members of the same families studied before, the findings supported the concept of a familial form of HS with autosomal dominant inheritance. Whether one or several genes are involved in this form of HS remains to be proven. Furthermore, little is known about the clinical severity of this familial form of HS, as staging according to Hurley was not included in the HS family genetic study (5).

Another interesting finding in the literature on patients with HS or acne conglobata suggests an autoimmune association with the disease. In a high proportion of cases, patients with HS also have associated arthritis (15, 16). However, most of these patients are HLA-B27-negative (15, 17, 18), unlike those with ankylosing spondylitis who are usually HLA-B27-positive.

In conclusion, no HLA association was observed in Swedish patients with HS. Thus the notion that specific HLA antigens might confer genetic susceptibility to HS was not supported and remains questionable.

Table I. *Phenotype frequencies (%) of HLA-A, -B and -DRB1 alleles in patients with hidradenitis supurativa* (n= *42), compared to healthy controls* (n= *250). Frequencies <5% in patients or controls are not shown*

HLA-A	Patients	Controls	HLA-B	Patients	Controls	HLA-DRB1	Patients	Controls
*01	29	27	*07	33	30	*01	17	18
*02	57	59	*08	17	21	*15	29	30
*03	29	24	*15	19	22	*03	21	17
*11	7	8	*18	7	9	*04	36	37
*24	21	18	*27	10	12	*11	14	14
*26	7	8	*35	12	18	*12	2	6
*30	5	3	*40	21	20	*13	31	29
*31	2	5	*41	5	2	*14	10	6
*32	10	9	*44	31	28	*07	14	11
*68	5	11	*51	5	8	*08	5	9
			*56	7	1	*09	6	4
			*57	7	8			

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