BRIEF COMMUNICATION

Positive association of HLA-DRB1*15 with Dupuytren’s disease in Caucasians

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Abstract
Dupuytren’s disease (DD) is a permanent nodular condition affecting the palms and digits of the hands, leading to progressive shortening and contractures of the digits often resulting in diminished function and severe deformity of the hand (Figure 1). The disorder is progressive and irreversible with a high rate of recurrence after surgical excision (1). There is an increased familial predisposition to the disease, which most often affects Northern European Caucasians. There have also been reports of the presence of DD in identical twins (2). More than 25% of men older than 60 years and of Celtic ancestry show evidence of DD (3). The disorder is thought to be one of the most common hereditary connective tissue disorders in Caucasians (4). Autosomal dominance with variable penetrance, autosomal recessive and maternal transmission have been proposed as likely modes of inheritance (2, 5). Despite the suspected genetic predisposition to the development of this disease, no susceptibility genes have yet been fully associated with DD. In addition, it is uncertain whether DD is a simple monogenic Mendelian disorder or a complex oligogenic condition.

An ideal approach to unravelling the hereditary component of this common disease would be to identify susceptibility gene loci. Identification of susceptible gene loci would provide an ideal approach to discovering the hereditary component of this disease in affected individuals. Identifying a polymorphic genetic marker associated with the disease would be extremely useful for identifying individuals at risk.
Several studies aimed at identifying genes associated with DD have been conducted; these include transforming growth factor (TGF)-β1 (6), TGF-β2 (7) and TGF-β receptor genes (8). In all cases, the associations were negative, although a positive association was identified with Zf9 transcription factor gene and a mitochondrial mutation in a maternally transmitted cohort of cases (9).

The most polymorphic genetic system in all vertebrates is the major histocompatibility complex (MHC) also known as the human leukocyte antigens (HLA) system. Since the discovery of the MHC, numerous associations with a variety of disease conditions have been established. Several of these conditions are autoimmune disorders involving cellular and humoral immune responses directed against the affected tissue. Neumuller et al. investigated the prevalence of HLA-DR3 and autoantibodies to connective tissue in Dupuytren’s contracture (10). Their results strongly support the hypothesis of an immunogenic component to DD, although no specific MHC alleles were identified.

To date, there has been no report of an association between a specific MHC allele and a risk for development of DD. The aim of our study was therefore to investigate the potential association of HLA-DRB1 in DD pathogenesis.

All patients with DD were assessed by the senior author, who took a full medical history and examined both hands in each patient. All patients had confirmed diagnoses of DD preoperatively, with the presence of characteristic Dupuytren’s nodules in the palm of the hand and/or digits and with contracture of the digits at the metacarpophalangeal or proximal interphalangeal joints. Only patients with advanced DD were selected for this study. Those having early-stage DD with only the presence of nodules and no contractures were excluded from the study. A total of 67 patients with DD were enrolled in the study (60 males and 7 females) with an age range of 37–81 years. A total of 28 patients had a family history of DD. All patients were unrelated and of Caucasian ethnicity from the northwest of England. The successive DD cases were identified through operative records from the South Manchester University Hospital Trust, Manchester, UK. The local and hospital ethical committees gave approval for the study and written consent was obtained from all individuals.

A total of 537 UK Caucasian controls were available for comparison. These originated from three sources: 118 were from general practice registers as comparative subjects for the Norfolk Arthritis Register, the second group comprised 159 individuals from the same region of England collected as part of a population-based survey identifying possible risk factors for cancer and the third group was a cohort of 260 UK blood donors collected as controls for disease studies (11). The age range of patients in the control group was 45–74 years, with 45.7% males and 54.3% females.

Each patient had a 5-ml venous blood sample taken using a standard venesection technique. Blood was collected in ethylenediaminetetraacetic acid-coated bottles and kept frozen until DNA was extracted from the peripheral blood cells, using a commercially available DNA extraction kit (Qiagen, West Sussex, UK). The DNA concentrations were then measured and diluted using sterile Tris-EDTA (TE) buffer (Qiagen) to 100 ng/μl.

HLA-DRB1 alleles were determined in all cases and controls using a commercially available semi-automated reverse hybridisation polymerase chain reaction–sequence-specific oligonucleotide probes typing system according to the manufacturer’s instructions (Invitrogen, Paisley, UK). The phenotype frequency of HLA-DRB1 alleles were calculated for controls and DD cases. Identical phenotype frequencies were observed for each of the three control groups used and therefore the control cohorts were grouped together for statistical analysis. Phenotype frequencies were compared between all DD cases and controls using the chi-square test and associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The main focus of this study was to investigate HLA association with DD. All statistical analyses were carried out using Stata (Stata Corporation, College Station, TX).

The HLA-DRB1 phenotype frequencies in both DD patients and controls are summarised in Table 1. For the
majority of HLA-DRB1 alleles, frequencies were similar between both groups with no significant differences were seen. However the frequency of DRB1*15 was significantly higher in Dupuytren’s patients (37.3%) compared with controls (20.9%). This achieved statistical significance ($P = 0.0029$), which remained significant after correction for multiple testing ($P = 0.029$). HLA-DRB1*15 status was associated with a 2.3 times increased risk (OR: 2.26, 95% CI) of developing DD. Further analysis suggests that HLA-DRB1*11 frequency was lower in DD cases (4.5%) compared with controls (11.4%), although this did not achieve statistical significance after correction for multiple testing ($P = 0.56$). Interestingly, HLA-DRB1*08 occurred at a frequency of 6.9% in the controls and was absent from the DD cohort.

This study has shown a statistically significant genetic association between the HLA-DRB1*15 status and the risk of developing DD in Caucasians of Northern European extraction. This is potentially of great interest as despite the strong familial element in DD, no genetic study has detected a positive association between an HLA gene and the pathogenesis of DD (12). The suggestion of an autoimmune component in DD was proposed as early as 1972 (13) and subsequent studies confirmed the presence of serum antibodies to collagen in patients with DD (14, 15). Neumuller et al. investigated the potential role of HLA class I, HLA-DR class II and autoantibodies to types I-IV collagen in Dupuytren’s contracture (10). HLA-DR3 was shown to be significantly associated with DD ($P = < 0.05$), with a relative risk of 2.94, although no specific HLA-DR alleles were identified. Spencer and Walsh investigated MHC antigen patterns in 37 patients with DD (16). HLA-A, B and DR locus antigens were investigated using mixed lymphocyte cytotoxicity screening. This study supported the findings of Tait (1982) by showing a higher incidence of DR4 in DD patients, although statistical significance was not achieved.

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haemophiliac patients (40). Goodpasture’s disease has very
strong associations with MHC class II loci, with more than
80% of patients carrying DRB1*1501, compared with only
25% in control populations, giving an OR for disease of 8.5
(41). In contrast to Goodpasture’s disease aetiology, HLA-
DRB1*15 is protective in rheumatoid arthritis (42).
In the UK Caucasoid population, HLA-DRB1*1501
accounts for nearly all alleles within the broader DRB1*15
(DR2) group, and all the HLA-DRB1*15 positive Cauca-
soid DD cases detected in our study were specifically HLA-
DRB1*1501.
HLA-DRB1*1501 has been shown to be associated with
a susceptibility to *Mycobacterium leprae* infection (43). A
common characteristic of leprosy patients is deformity of the
digits. The infiltration of the peripheral nerves by *M. leprae*
initiates a series of destructive events that result in intra-
nodal oedema and destruction of Schwann cells and axons in
a CD4+ T-cell-mediated granulomatous process (44). Whether
or not a CD4+ T-cell-mediated response is the catalyst for DD
is currently unknown. HLA-DRB1*08 occurred at a frequency of 6.9%
in the control group and was absent from the DD cohort. This
deviation is statistically significant (*P* = 0.026) and may confer
a protective status against the development of DD. However, HLA
typing in a larger cohort is required to confirm this observation.

Within the MHC, extensive linkage disequilibrium exists
between genes, thus making it difficult to determine whether
HLA genes directly determine disease susceptibility/resis-
tance or whether the association is because of other genes
within the MHC. Furthermore, the high density of immune
response genes in this region makes identifying specific gene
effects difficult (45). Our data are in keeping with the
involvement of an immunogenic component to DD, although
the exact mechanisms involved in MHC-driven DD require
further investigation.

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