An inflammatory, familial, inclusion body myositis with autoimmune features and a phenotype identical to sporadic inclusion body myositis

Studies in three families

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Summary
We describe the occurrence of an inflammatory inclusion body myositis in siblings of a single generation in three separate families. The disease in this total of seven patients was characterized by selective and early involvement of forearm and finger flexors, confirmed by MRI, and weakness of the quadriceps, triceps and foot extensors. Muscle biopsies in at least two members from each family showed endomysial inflammation, red-rimmed vacuoles, intracellular amyloid deposition and 15–18-nm tubulofilaments within the vacuolated muscle fibres. Immunocytochemistry on serial muscle biopsy sections demonstrated an abundance of CD8+ cells invading non-necrotic, MHC-I-expressing muscle fibres. Immunogenetic studies showed the presence of the DR3 allele (DRB1*0301/0302) in all seven patients. The combination of the clinical, histological, immunopathological and immunogenetic features indicate that these patients have a disease identical to sporadic inclusion body myositis (s-IBM). We conclude that the classic, inflammatory, s-IBM can also occur in families (familial inclusion body myositis), in a pattern analogous to the familial occurrence of other autoimmune neurological diseases such as myasthenia gravis and multiple sclerosis. These observations strengthen the view that s-IBM behaves like other autoimmune diseases and has disease susceptibility linked to the DR3 allele.

Keywords: myositis, HLA antigens; autoimmune disease; inclusion body myositis; inherited susceptibility

Abbreviations: CK = creatine kinase; f-IBM = familial inclusion body myositis; h-IBM = hereditary inclusion body myopathy; HLA = histocompatibility leukocyte antigen; MHC = major histocompatibility complex; s-IBM = sporadic inclusion body myositis; TNF-α = tumour necrosis factor-α

Introduction
Sporadic inclusion body myositis (s-IBM) is a chronic, acquired, inflammatory myopathy that (i) usually begins after the age of 50 years, (ii) affects proximal and distal muscle groups with a characteristic early involvement of finger flexors and quadriceps muscles and (iii) has characteristic histological features of red-rimmed vacuoles containing 15–18-nm tubulofilaments, small intracellular amyloid deposits, and primary endomysial inflammation with CD8+ cells and macrophages invading non-necrotic muscle fibres (Lotz et al., 1989; Dalakas, 1991; Sekul and Dalakas, 1993; Griggs et al., 1995). In contrast, hereditary inclusion body myopathies (h-IBMs) comprise a heterogeneous group of non-inflammatory, red-rimmed vacuolar myopathies that represent various clinical phenotypes which are always distinct from the typical clinical picture of s-IBM (Cole et al., 1988; Klingman and Gibbs, 1991; Neville et al., 1992; Sadeh et al., 1993; Sivakumar and Dalakas, 1996).

We now describe three separate families in which the classic clinicohistological picture of s-IBM was observed in a total of seven siblings. In all families, the disease [familial inclusion body myositis (f-IBM)] affected only one generation.
Patients and methods

**Family A**
Two brothers, aged 78 and 73 years and born in the Midwest of the USA, developed symptoms of proximal and distal muscle weakness in the lower extremities and frequent falls due to knee-buckling, at the age of 73 and 69 years, respectively. The older brother also developed weakness of the forearm flexors and swallowing difficulties. A muscle biopsy was diagnostic of IBM (Lotz et al., 1989) and both patients were referred to the NIH (National Institutes of Health). None of the other family members (Fig. 1) had symptoms of a myopathy. On admission, neurological examination revealed, in both brothers, wasting and weakness of the quadriceps muscles (Fig. 2), atrophy and weakness of the finger flexors and weakness of foot extensors, as classically seen in s-IBM (Dalakas, 1991; Sekul et al., 1994). There was no history of myotoxic drug use, infections or any systemic disease. The serum creatine kinase (CK) level was 167 and 426 U/l (normal; 52–386 U/l). An elevated CK level of 608 (normal: 55–283 U/l) was documented prior to the NIH admission in the older brother. Repeated muscle biopsies in both patients revealed histological, immunopathological and electron microscopic features typical of s-IBM, as described below.

**Family B**
Two brothers (Fig. 1), aged 69 and 63 years, developed weakness and wasting of the quadriceps muscle and the flexor compartment of the forearm in their mid-fifties. In the older brother, the symptoms began in the lower extremities with frequent falls and weakness in ambulation; in the younger brother the symptoms began in the upper extremities with weakness of the grip. Subsequently, both brothers developed the classic features of s-IBM with severe involvement of the quadriceps, forearm flexors, triceps and foot extensors. No bulbar or respiratory symptoms were noted. By the time the patients were seen at the NIH,
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Fig. 2 Photographs of anterior thighs in siblings with inflammatory IBM. Two brothers from Family A demonstrate the selective atrophy of the quadriceps muscle, as typically seen in s-IBM.

the older brother was wheelchair-bound but the younger brother was still ambulatory. Their CK levels were 522 and 980 U/l, respectively. Muscle biopsy in both patients had all the histological and immunopathological features of s-IBM, as described below.

Family C
Three siblings of an African-American family (Fig. 1), two men aged 73 and 69 years and a woman aged 77 years, developed a myopathy with an identical pattern of muscle involvement. The two men developed proximal lower extremity weakness, quadriceps wasting and frequent falls in their early sixties, followed, a few years later, by weakness in the distal muscles of the upper extremities. Muscle biopsy in both male patients showed the typical histological features of s-IBM. Their sister (CI) developed weakness in the lower extremities at the age of 48 years, and developed slowly thereafter weakness and wasting in the proximal and distal muscles of the upper and lower extremities. None of the other members of the family had symptoms of muscle disease.

On admission and examination at the NIH, all three patients had wasting and weakness of the quadriceps and foot extensors. A varying degree of weakness and wasting in the finger flexors (forearm flexor compartment) was present in all three siblings but was more prominent in the older brother and sister who both had difficulty making a fist (Fig. 3). Overall, in the upper extremities, the weakness was predominantly distal but both the proximal and the distal muscles were equally affected in the lower extremities. Mild facial- and neck-flexor weakness were present in all three patients. When seen at the NIH, the older brother (CII) had also developed dysphagia. CK levels were 359 and 434 in the men and 124 U/l in the woman. As described below, the previous and repeated biopsies in the two brothers revealed features identical to those seen in patients with s-IBM.

Special studies
(i) T1-weighted MRIs of the thigh muscles were performed in Family C, to confirm the selective and prominent involvement of the knee extensor muscles. The MRIs of the quadriceps were compared with the studies previously performed in patients with s-IBM and h-IBM (Sivakumar and Dalakas, 1996).
(ii) Open muscle biopsies were performed and processed for muscle-enzyme histochemistry and Congo-red staining.
Glutaradehyde-fixed and Epon-embedded tissue as well as frozen sections (Askanas et al., 1991) were used for electron microscopy. In addition, immunocytochemistry was performed on serial, 5-µm sections, of the muscle biopsy specimens, utilizing monoclonal antibodies directed against major histocompatibility complex (MHC) class I antigen, CD8+ cells, macrophages, CD4+ cells and Natural Killer cells (Leu 19) in an immunoperoxidase technique, as described by Illa et al. (1992). Disease control biopsies, run concurrently with the above sections, included muscle specimens from a patient with typical histological features of s-IBM and a patient with the autosomal dominant form of h-IBM (Sivakumar and Dalakas, 1996).

(iii) Histocompatibility leukocyte antigen (HLA) Class II genotyping was performed using PCR (polymerase chain reaction) amplification with sequence-specific primers (Park and Tonai, 1992) to determine if the predominance of DR3 haplotype, seen in patients with s-IBM (Garlepp et al., 1994), was also present in the studied patients.

(iv) Complete haematological, biochemical and serological studies were performed including a search for anti-nuclear antibodies, and antibodies against double-stranded DNA, ribonuleoprotein, Jo-1, SS-A and SS-B.

Results
MRI findings
MRI performed in one family showed that the extensor compartment of the thighs was more significantly involved than the flexor compartment (Fig. 4), as typically seen in s-IBM (Sekul and Dalakas, 1993). The same pattern was seen clinically as marked wasting of the quadriceps muscle in the other two families (Fig. 2). In Patient II of Family C, who had advanced disease, the flexor compartment was also involved (Fig. 4).

Histology
The muscle biopsies on all patients showed a myopathy with variation of fibre size, hypertrophic and small fibres, and increased connective tissue. Red-rimmed vacuoles, intramyofibre amyloid deposits, ragged-red fibres and primary inflammation with lymphocytic infiltrates invading non-necrotic muscle fibres were seen in all affected members of Families A and B, and in the two siblings (CII and CIII) of Family C (Fig. 5). Patient CII had two muscle biopsies, one from the least affected deltoid muscle that showed non-specific myopathic features and another from the more affected quadriceps muscle that showed all the diagnostic features of an inflammatory inclusion body myositis, as noted above. In Patient CI, who had the same typical phenotype of s-IBM as her two brothers (Figs 3 and 4), muscle biopsy performed from the least affected deltoid muscle revealed non-specific myopathic features, similar to the deltoid muscle biopsy of her brother (CII) (probable IBM). However, she did not receive any further biopsies. By electron microscopy, 15–18 nm diameter tubulofilaments were observed in the muscle biopsy of at least one representative member (AI, AII, BII and CIII) from each family (Fig. 5).

Immunocytochemistry
The predominant endomysial cells were CD8+ cells which surrounded or invaded non-necrotic and MHC-I antigen-
expressing muscle fibres (Fig. 6). The other cells were macrophages and CD4+ cells. Natural killer cells were not detected. The MHC class I antigen was expressed in most fibres, even in areas without inflammation (Fig. 6B), in a pattern identical to the one seen in s-IBM (Engel and Arahata, 1984). In contrast, in the concurrently stained sections of a patient with h-IBM, MHC class I antigen was not expressed (Fig. 7A and B), as previously described (Sivakumar and Dalakas, 1996).

**Immunogenetic studies.**

The DRB1*0301/0302 allele corresponding to the DR3 haplotype was seen in all affected members (Table 1). No
autoantibodies were detected, except for a positive antinuclear antibody titre (1:160), with a speckled pattern, observed in the older brother of Family A (Patient A1).

Discussion
At least two siblings in three different families had the typical clinical phenotype and the radiological, histological, ultrastructural and inflammatory features of s-IBM with prominent endomysial CD8+ cytotoxic T cells invading MHC class I antigen-expressing non-necrotic muscle fibres. These observations indicate that the typical s-IBM, with immunopathological features of an autoimmune process, can be also familial, affecting more than one sibling of a generation.

The observed familial occurrence of an inflammatory, and probably autoimmune, inclusion body myositis (f-IBM) needs to be distinguished from the hereditary inclusion body myopathies (h-IBM), a heterogenous group of vacuolar myopathies without inflammatory or immunopathological features that often occur in more than one generation of a family, or have predilection for certain ethnic groups (Askanas...
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Fig. 7 Expression of MHC class I antigen in low-magnification field in the muscle biopsies of patients with f-IBM (A) compared with h-IBM (B). Muscle biopsy of Patient CIII immunostained for MHC-I (A) demonstrates the ubiquitous expression of the MHC-I antigen in many fibres. Several foci of inflammatory cells invading these fibres are also noted (×270). In a concurrently immunostained section from a control patient with h-IBM (B), no MHC-I-stained fibres are seen (×350).

and Engel, 1995; Sivakumar and Dalakas, 1996). Although the phenotype of patients with h-IBM is variable (Sivakumar and Dalakas, 1996), these patients do not have the selective pattern of involvement of the quadriceps and the long finger flexor muscles, as typically seen in s-IBM.

The immunopathological features observed in the present familial cases are identical to those seen in s-IBM and in polymyositis where an autoimmune pathogenesis has been strongly considered (Engel and Arahata, 1984; Engel et al., 1994). s-IBM has been associated with other autoimmune conditions, e.g. Sjogrens disease, dermatitis herpetiformis, pernicious anaemia and common variable immunodeficiency, while other autoimmune diseases including autoimmune thyroiditis, myasthenia gravis and pernicious anaemia can occur in their relatives (Rugero et al., 1995). Some siblings or relatives of patients with neurological diseases of putative or definite autoimmune origin, e.g. multiple sclerosis, myasthenia gravis and polymyositis (Cook et al., 1963; Leukonia and Buxton, 1973), also demonstrate a variety of autoantibodies and develop an unrelated (or the same) autoimmune disease. The present observations that IBM with prominent inflammatory features can also occur in siblings,
are consistent with the pattern of familial occurrence noted in the other autoimmune neurological diseases, and suggest genetic susceptibility to the autoimmune process.

Many autoimmune diseases have been associated with a particular HLA antigen and the susceptibility to autoimmunity has been linked to various MHC-associated genes. In polymyositis and dermatomyositis, there is a high incidence (42%) of the DR3 phenotype (Love, 1989). A very significant (92%) incidence of the HLA DR3 phenotype, compared with 25% in the control population, has been found in s-IBM (Garlepp et al., 1994). We also found the same strong association with the DR3 phenotype (HLA DRB1*0301/0302 allele) in all affected members of the three families (Table 1), suggesting that the inflammatory f-IBM is not only phenotypically and histologically identical to the sporadic form; it is also linked to the same DR3 alleles. Because these rare alleles are seen in other inflammatory diseases, such as autoimmune hepatitis, agranulocytosis and inflammatory bowel disease (Satsangi et al., 1996), the noted association suggests that the sporadic and the familial forms of inflammatory IBM share the same inherited determinants of susceptibility to the inflammatory process.

Genes related to the MHC locus may alter the cell-mediated immunity, by affecting lymphocytes or cytokine regulatory function, and increase the susceptibility of individuals and their family members to develop an autoimmune disease. One such possibility may involve the higher tumour necrosis factor-α (TNF-α) secretory state related to the DR3 antigen. A genetically based propensity to produce high levels of TNF-α in association with the DR3 status, might contribute to muscle-fibre injury by triggering the recruitment of activated T cells or the accumulation of TNF-α at the sites of inflammation, in a mechanism analogous to that proposed for lupus (Jacob et al., 1990).

Based on the clinicopathological and immunogenetic features of our patients with f-IBM, which resemble the s-IBM, we have argued that the pathogenesis may be related to an increased genetic susceptibility to the autoimmune process. However, because of the possibility that members in the next generation may also develop the same late-onset disease, other modes of disease inheritance cannot be excluded.

The observed similarities between inflammatory f-IBM and s-IBM, prompted us to treat the f-IBM with the same therapeutic strategies used in s-IBM. One patient, from Family A, reported a subjective, transient benefit to steroids. Another patient, from Family B, noted a transient and objective, albeit mild, improvement in his arms after high-dose intravenous Ig, as reported for some patients with s-IBM (Dalakas et al., 1995).

### Table 1 Alleles in HLA II antigens seen in affected siblings of inflammatory f-IBM

<table>
<thead>
<tr>
<th>Patient</th>
<th>DRB1</th>
<th>DQB1</th>
<th>DRB3</th>
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<tr>
<td>AI</td>
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</tr>
<tr>
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<tr>
<td>B</td>
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<td>0201</td>
<td>0202</td>
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<td>0201, 0301</td>
<td>0202</td>
</tr>
<tr>
<td>CI</td>
<td>0301, 0302</td>
<td>04, 0201</td>
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<tr>
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<tr>
<td>CIII</td>
<td>0101, 0302</td>
<td>04, 0501</td>
<td>0101</td>
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</tbody>
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The DRB1*0301 and 0302 alleles correspond serologically to DR3 haplotypes.

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