Celiac disease in patients with sporadic and inherited cardiomyopathies and in their relatives

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\textbf{Aims} To investigate celiac disease (CD) and related co-morbidity in patients with familial and sporadic cardiomyopathy and in their relatives.

\textbf{Methods and results} We screened anti-human-tissue-transglutaminase (IgA and IgG anti-h-tTG) and anti-endomysial antibodies (AEAs) in 238 consecutive adult patients with inherited or sporadic dilated cardiomyopathy (DCM), 418 relatives, and 2000 healthy blood donors. HLADQ2-DQ8 was tested in tTG-positive subjects. The IgA-tTG-positive patients with cardiomyopathy underwent duodenal biopsy. Twenty-six subjects were tTG-positive: five DCM patients (2.1%), two of 28 (7.1%) and three of 390 (0.7%) relatives with and without echocardiographic abnormalities respectively, and 16 controls (0.8%). Twenty-two of 26 subjects were AEA-positive, and 25 HLA-positive. Of the five patients with cardiomyopathy and biopsy-proven CD, four suffered iron-deficiency anaemia. Two CD-positive DCM patients and two tTG-positive relatives were from families with inherited disease in which CD did not co-segregate with DCM.

\textbf{Conclusions} The higher prevalence of CD in patients with sporadic or inherited DCM, and of tTG-positive serology in relatives with echocardiographic abnormalities, suggests that immune-mediated mechanisms are active in subsets of patients/families. However, gluten intolerance cannot be considered causative since CD seems to be associated but not co-segregated with DCM in familial cases.

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\textbf{KEYWORDS}
Celiac disease; Dilated cardiomyopathy; Tissue-transglutaminase

\textbf{Introduction}
Recent reports indicate an increased prevalence of celiac disease (CD) among patients with autoimmune diseases and their first-degree relatives.\textsuperscript{1,2} Familial aggregation is clear, with an approximately 10% prevalence of CD among first-degree relatives,\textsuperscript{3} but a single gene hypothesis has been excluded.\textsuperscript{4} Familial aggregation is explained by common genetic determinants related to some HLA alleles.\textsuperscript{5} Over 95% of the patients express the HLA-DQ (a1*0501,b1*0201; a1*0301,b1*0302) heterodimers (HLA-DQ2/DQ8). However, autoimmunity is not simply genetically controlled, and there is clear evidence
of gluten-dependent autoimmune disorders. It has recently been shown that the longer celiac subjects encounter gluten, the greater the chance that they will develop severe extra-intestinal autoimmune diseases. Although the data on time of gluten-exposure are still debated, and other series suggest age-related picks of phenotypical expression of extraintestinal autoimmune diseases, the possibility that a gluten-free diet improves the quality of life and clinical evolution of extraintestinal diseases raises new hopes for outcome control. If gluten plays a causative role in even a small subgroup of patients, the clinical implications would extend to screening and prevention strategies.

Bearing in mind the above data, Curione et al., found an increased prevalence of CD among patients with idiopathic dilated cardiomyopathy (DCM) (3/52 patients, 5.7% vs 0.4% in the general population), a severe chronic disease in which autoimmune mechanisms may play a part. The association between CD and cardiomyopathy was further confirmed in the Danish National Registry of patients. More recently, a smaller percentage of patients entering the waiting list for heart transplantation for end-stage cardiomyopathy (12/642, 1.9%) were found to be endomyosal antibody positive as against 0.35% of healthy controls (34/9729). Although to different extents both of these series confirm that CD is more prevalent in DCM patients than the control population.

The aetiological setting of cardiomyopathies is extremely complex and heterogeneous: hypertrophic cardiomyopathies (HCM) are monogenic disorders mainly inherited as autosomal dominant traits, whereas only 25% of idiopathic DCM cases are inherited. The full phenotypical expression of the disease can be preceded by echo- or electro-cardiographic changes such as left ventricular dilatation, decreased fractional shortening, left bundle branch block or atrio-ventricular block.

In this study, we screened for CD a consecutive series of index patients with DCM as well as their relatives with or without instrumental signs indicating myocardial alterations. We also evaluated how other autoimmune disorders in the study population are related to silent, unrecognized CD.

Methods

Patients and controls

The study included a consecutive series of 238 adult index patients with DCM (134 male, median age 42 years, range 18–63), and their 418 relatives (28 had instrumental cardiac abnormalities (16 male, median age 56 years, range 29–73)). All of the index patients and their relatives were diagnosed and followed up from 1995 to 2000 at the Department of Cardiology of the I.R.C.C.S. Policlinico San Matteo of Pavia.

The diagnosis of DCM was based on WHO criteria. All of the patients with DCM underwent endomyocardial biopsy. All of the male patients underwent dystrophin gene analysis, and all of the patients with familial disease underwent screening for known disease-causing genes. The informed and consenting relatives who accepted the screening underwent a clinical examination, 12-lead electrocardiography, echocardiography and serum creatine-phosphokinase determinations. Clinical and pathological records were obtained for deceased affected relatives.

The healthy control group consisted of 2000 informed and consent potential blood donors at their first test (1390 male, median age 35 years, range 18–60).

Study design

Serum samples positive for IgA-IgG anti-h-tTG were analysed for IgA anti-endomyosal antibodies (AEA) and the related CD class II HLA molecules: the DQ2 heterodimer encoded by the DQα1*0501/DQβ1*02 combination, or the HLA DQB8 heterodimer encoded by the DQα1*0301/DQβ1*0302 alleles. All of the subjects who were positive for both CD-related auto-antibodies and HLA DQ2-8 were recommended to undergo small intestine biopsies, which were classified according to a modified version of Marsh’s classification. The subjects with normal IgA and IgG anti-tTG antibody values were categorized as not having CD.

ELISA for anti-h-tTG

Serum IgA and IgG anti-h-tTG antibodies were determined as previously reported. Microtitre plates (EIA/RIA 2580, Costar) were coated by incubating 1 µg of h-tTG in 100 l of phosphate buffered saline (PBS) in each well overnight at 4 °C. The plates were washed three times with PBS, 0.05% Tween 20, and the wells were blocked by means of incubation with 100 µl of PBS, 0.1% Tween 20, for 20 min at room temperature (RT). Serum samples diluted 1:100 in PBS, 0.1% Tween 20, were incubated for 1 h at RT. The plates were washed and incubated for 1 h at RT with either 1:4000 phosphate-conjugated anti-human IgA (Sigma A-3062) or 1:2000 anti-human IgG (Sigma A-8542) diluted in PBS, bovine serum albumin 1%. The immune reaction was developed by adding a substrate solution and the absorbance was read in a microplate reader at 405 nm until the positive control serum reached an optical density value of 2 for IgA or 1.5 for IgG. The results were expressed as percentages of the positive control serum. Normal values were taken as <16% for IgA and <42% for IgG, which represented a value >2 SD above the mean of 400 healthy subjects (210 female, 190 male, median age 17 years, range 2–24).

Anti-endomysial antibody assay

Serum IgA anti-endomysial antibody (AEA) levels were measured by means of an indirect immunofluorescence assay using cryostat sections of human umbilical cord tissue, as previously described. Briefly, the sections were incubated for 30 min with the subject’s serum diluted 1:5. After washing, the sections were incubated with fluorescein-labelled goat anti-human IgA antibodies for 30 min. The slides were washed and examined by means of fluorescent microscopy. The immunological tests were performed by four operators (T.A., F.E., N.T., B.V.) unaware of the clinical and laboratory findings.

HLA-DQ typing

The known susceptibility alleles for CD were determined by means of polymerase chain reaction with allele-specific primers identifying DQ2 and DQ8, carried out using a Dynal Classic SSP DQ kit (Dynal A.S.). The genetic tests were performed by three operators (S.A., S.D., M.R.) unaware of the clinical and immunological findings.
Statistical analysis

The categorical variables were expressed as percentages and compared using the chi-square test. The continuous variables were expressed as mean values.

Results

Prevalence of tTG-positive cases among patients and relatives (Fig. 1)

Five patients with DCM (5 males, 1 female) (5/238, 2.1%) and five of 418 relatives (1.19%) were anti-tTG positive. All five relatives came from unrelated families with DCM: two were healthy but with echocardiographic abnormalities (2/28, 7.14%, 1 male, 1 female), and three were healthy with normal instrumental and biochemical findings (3/390, 0.77%). Of the 2000 blood donors, 16 (0.8%) were positive for anti-tTG antibodies (9 male, 7 female; median age 24 years, range 18–48), 15 of whom were also positive for AEAs. All 16 carried the known susceptibility HLA alleles for CD, but none underwent intestinal biopsy.

The prevalence of tTG positivity was significantly higher ($P=0.04$) in patients than in normal controls while the difference between prevalence of tTG in all relatives versus the normal control population was higher but did not reach significant values ($P=0.4$). In the subgroup of relatives with echocardiographic abnormalities the prevalence of tTG positivity was significantly higher than that recorded in normal control population ($P=0.0004$).

Diagnostic work-up for CD (Fig. 1, Table 1)

Out of the five tTG-positive patients four were also AEA-positive. All five carried the DQ2 heterodimer. They all underwent intestinal biopsies, which showed total villous flattening (type 3c) in three cases, and marked villous flattening (type 3b) in two. Of the two relatives who were anti-h-tTG positive and had echocardiographic abnormalities, one was AEA-positive and one carried the HLA DQ2. One of these relatives agreed to undergo intestinal biopsy (B8, Table 1), which showed features consistent with CD (marked villous flattening). In the case of the three healthy CD-positive relatives without echocardiographic abnormalities, a specific educational programme has been started and they will undergo intestinal biopsy at their convenience once having accepted the test.

Intestinal and extra-intestinal manifestations (Table 1)

None of the CD-positive subjects complained of classical intestinal symptoms. None of the five CD-positive DCM patients had lymphocyte myocarditis. Of the 238 DCM patients, two had biopsy-proven acute myocarditis and tested negative for anti-tTG antibodies.

The comorbidities in the five celiac patients discovered during the present screening included iron-deficiency anaemia in four cases, as well as a series of other conditions potentially associated with CD (Table 1). Of the five CD-positive relatives, one had iron-deficiency...
<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>CMP</th>
<th>Familial</th>
<th>Duodenal biopsy</th>
<th>LVEF (%)</th>
<th>LVEDD (mm)</th>
<th>LVFS (%)</th>
<th>sCPK (mU/ml)</th>
<th>AVB</th>
<th>LBBB</th>
<th>NYHA class</th>
<th>Comorbidity</th>
<th>tTG</th>
<th>AEA</th>
<th>HLA DQ2-DQ8</th>
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<tr>
<td><strong>Index patients</strong></td>
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<tr>
<td>A1</td>
<td>24</td>
<td>M</td>
<td>X-linked +</td>
<td>+</td>
<td>18</td>
<td>70</td>
<td>Increased</td>
<td>−</td>
<td>+</td>
<td>IV</td>
<td>Iron-deficiency anaemia; Paroxysmal haemoglobinuria</td>
<td>152%–158%</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>47</td>
<td>M</td>
<td>DCM</td>
<td>AD</td>
<td>+</td>
<td>23</td>
<td>71</td>
<td>Normal</td>
<td>−</td>
<td>+</td>
<td>II</td>
<td>Hiatus hernia, Iron-deficiency anaemia, Non-HP gastritis</td>
<td>81%–32%</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>A3</td>
<td>46</td>
<td>F</td>
<td>DCM</td>
<td>−</td>
<td>+</td>
<td>25</td>
<td>67</td>
<td>Normal</td>
<td>−</td>
<td>+</td>
<td>II</td>
<td>Non-HP gastritis</td>
<td>148%–132%</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>A4</td>
<td>24</td>
<td>M</td>
<td>DCM</td>
<td>−</td>
<td>+</td>
<td>30</td>
<td>64</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>II</td>
<td>Acute myeloid leukaemia 16 years before (chemotherapy), Iron-deficiency anaemia, Hepatic enzyme increase</td>
<td>25%–23%</td>
<td>−</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>A5</td>
<td>49</td>
<td>F</td>
<td>DCM</td>
<td>−</td>
<td>+</td>
<td>30</td>
<td>56</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>II</td>
<td>Iron-deficiency anaemia, Spontaneous abortions (n=2), Cholelithiasis and bilirubin</td>
<td>36%–45%</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Healthy relatives with (B7 and B8) and without (C9, C10 and C11) echocardiographic abnormalities</strong></td>
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<tr>
<td>B7 (Aunt)</td>
<td>66</td>
<td>F</td>
<td>AD</td>
<td></td>
<td>60</td>
<td>57</td>
<td>42</td>
<td>92</td>
<td>−</td>
<td>−</td>
<td>Recent carotid thromboendoarteriectomy</td>
<td>50%–24%</td>
<td>−</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index patient of B7</td>
<td>41</td>
<td>M</td>
<td>DCM</td>
<td>AD</td>
<td>30</td>
<td>67</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>I–II</td>
<td>Dyslipidaemia</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td></td>
<td></td>
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<tr>
<td>B8 (Nephew)</td>
<td>29</td>
<td>M</td>
<td>AD</td>
<td>+</td>
<td>54</td>
<td>18</td>
<td>239</td>
<td>−</td>
<td>−</td>
<td>II</td>
<td>Iron-deficiency anaemia</td>
<td>105%–44%</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>Index patient of B8</td>
<td>55</td>
<td>M</td>
<td>DCM</td>
<td>AD</td>
<td>20</td>
<td>74</td>
<td>Normal</td>
<td>I ‘</td>
<td>+</td>
<td>III</td>
<td>Gout, Duodenal diverticulum, Liver steatosis, Gastroesophageal reflux</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td></td>
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<tr>
<td>C9 (Nephew)</td>
<td>17</td>
<td>M</td>
<td>−</td>
<td></td>
<td>68</td>
<td>41</td>
<td>32</td>
<td>141</td>
<td>−</td>
<td>−</td>
<td>Healthy; two bone fractures</td>
<td>81%–21%</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Index patient of C9</td>
<td>50</td>
<td>M</td>
<td>DCM</td>
<td>−</td>
<td>10</td>
<td>71</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>IV</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td></td>
<td></td>
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<tr>
<td>C10 (Daughter)</td>
<td>14</td>
<td>F</td>
<td>−</td>
<td></td>
<td>60</td>
<td>44</td>
<td>32</td>
<td>65</td>
<td>−</td>
<td>−</td>
<td>Healthy</td>
<td>25%–11%</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index patient of C10</td>
<td>38</td>
<td>M</td>
<td>DCM</td>
<td>−</td>
<td>30</td>
<td>71</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>III</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>C11 (Daughter)</td>
<td>24</td>
<td>F</td>
<td>−</td>
<td></td>
<td>75</td>
<td>44</td>
<td>36</td>
<td>150</td>
<td>−</td>
<td>−</td>
<td>Healthy</td>
<td>34%–15%</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>Index patient of C11</td>
<td>44</td>
<td>M</td>
<td>DCM</td>
<td>−</td>
<td>28</td>
<td>78</td>
<td>Normal</td>
<td>−</td>
<td>+</td>
<td>III</td>
<td>−</td>
<td>−</td>
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CMP: cardiomyopathy; LVEF: left ventricular ejection fraction (normal value: >50%); LVEDD: left ventricular end-diastolic diameter [the predicted LVEDD, corrected for age and BSA, was calculated with the formula of Henry et al. 1980: LVEDD (predicted)=45.3+BSA0.3−0.03×age−7.2; the measured LVEDD was expressed as a percentage ratio: LVEDD%=LVEDD/LVEDD (predicted); LVEDD% ≥112% was chosen as the upper limit for normality]; LVFS: left ventricular fractional shortening (normal value: >25%); sCPK: serum creatin-phosphokinase (normal value: <180 mU/ml); AVB: atrio-ventricular block; LBBB: left bundle branch block; NYHA: New York Heart Association; tTG: tissue transglutaminase; (normal values: <16% for IgA and <42% for IgG); AEA: anti-endomysial antibodies; HLA: human leukocyte antigen; M: male; F: female; DCM: dilated cardiomyopathy; AD: autosomal dominant; ND: not done.

*a*Non-ACTC, -desmin, -LMNA gene defects.

*b*Likely AD with incomplete penetrance.

*c*Age at onset of DCM=24 years.
anaemia and a 17-year-old healthy boy has a recent history of two bone fractures.

**Clinical and genetic basis of the cardiomyopathies and co-morbidities (Fig. 2)**

Of the five CD-positive DCM patients, one had familial autosomal dominant disease and one X-linked recessive dystrophin defect-related disease (in-frame deletion of exon 48). A third patient (24 years old) had a history of acute myeloid leukaemia treated with anthracyclines at the age of 6 years. The two remaining DCM patients had sporadic disease.

Both the CD- and tTG-positive healthy relatives with echocardiographic abnormalities belong to families DCM (one autosomal dominant and one with four affected siblings), but the corresponding probands and the other affected members of their families were tested negative for tTG.

**Discussion**

This study documents a prevalence of CD in patients with sporadic or inherited DCM and in relatives with echocardiographic abnormalities higher than that recorded in control populations. The results confirm the increased prevalence of CD recently reported by Prati et al. in candidates for heart transplantation: 1.9% vs 0.37% in normal controls,\(^\text{13}\) as well as the data originally reported by Curione et al.\(^\text{10}\) and by Fonager et al.\(^\text{12}\), although to a lesser extent. DCM shows a relevant association with CD, and the relatives of DCM patients (in particular those with echocardiographic abnormalities) are at higher risk of CD than the normal control population (\(P=0.0004\)) regardless of whether their corresponding proband/index patient has CD. Very recent studies on prevalence of positive tTG in normal population is around one of 100: in USA healthy adult citizens one of 111.\(^\text{23}\)

Our data emphasise the diagnostic value of anti-h-tTG antibodies, which were able to identify one biopsy
proven celiac subject missed by AEA assay (patient no. A4). The present finding confirms previous studies and our own experience in which human recombinant tTG based ELISA has higher sensitivity (98% vs 90%) and specificity (99% vs 100%) and positive predictive value (97% vs 100%) of the standard AEA test.24

The non-causative role of CD in the cardiomyopathy is proved by the inheritance of DCM in 2/5 cases: one had X-linked DCM caused by the in-frame deletion of exons 48 of the dystrophin gene, and the other autosomal dominant DCM (more than one living member of the family is proven to be affected) without any within-family co-segregation of CD with the cardiac phenotype. Furthermore, one of the three sporadic DCM cases has a history of acute myeloid leukaemia treated with anthracyclines at the age of 6 years. Myocardial toxicity by anthracyclines is a proven cause of DCM.25 Unrecognized CD may have a facilitated DCM, when a genetic or drug-related cofactor is present. Further support for the non-causative role of CD emerges from the non-segregation of the cardiac phenotype with CD in the families with inherited DCM both autosomal dominant and with four affected siblings, in which the tTG-positive members had echocardiographic abnormalities but did not meet the full diagnostic criteria for DCM and the corresponding probands are tTG-negative (cases no. 7, no. 8; Table 1).

As a number of studies bear witness to the higher prevalence of CD among patients with DCM than in normal controls,10,13 the major clinical problem seems to be identifying this sub-population. If CD is found in both sporadic and inherited DCM, and the combination of the two conditions is not usual, specific clinical markers of the CD should be identified. The recent study by Frustaci et al.26 showing a higher prevalence of CD among patients with ‘idiopathic congestive heart failure’ and a biopsy-proven diagnosis of myocarditis suggests a potential link between inflammatory myocardial disease and autoimmunity. Thirteen of the 187 patients with biopsy-proven myocarditis had CD-related autoantibodies, nine of whom also had AEs (4.4%). In terms of myocarditis, our DCM series differs from that reported by Frustaci et al.26 in so far as all of them underwent endomyocardial biopsy but none of the CD-positive patients had myocarditis and none of those with biopsy-proven myocarditis had CD. The rationale for linking the two apparently unrelated disorders of CD and myocarditis is strong, especially in the case of sporadic forms of ‘idiopathic heart failure’. If confirmed in other series, myocardial inflammation may be a useful marker for CD screening in patients with idiopathic congestive heart failure.

The extra-intestinal manifestations of CD could also be helpful. All of the nine patients described by Frustaci et al.26, and four of our five DCM patients (as well as one of the relatives with echocardiographic abnormalities) had iron-deficiency anaemia. Iron-deficiency anaemia is the most common clinical presentation of CD in adults,27,28 and its presence may have a negative impact on the clinical outcome of DCM patients. It has recently been shown that anaemia is associated with worse symptoms, greater functional impairment, and a significant increase in mortality in patients with congestive heart failure.29 Other extra-intestinal manifestations that may be useful in CD screening include thyroiditis, type-1 diabetes mellitus, dermatitis herpetiformis, bone fractures, psychiatric and neurological syndromes, infertility and abortions. For example, one of our two female CD-positive DCM patients had experienced two spontaneous abortions. Furthermore, the 17-year-old CD-positive family member of our series had experienced two bone fractures that are known to recur more frequently in CD patients than in normal controls.30 In the practical clinical setting, patients with DCM and iron-refractory anaemia, or poli-abortivity, infertility, or evidence of bone fragility etc. could be elective candidates to CD screening. Alternatively, all DCM patients should undergo screening: the low costs of the tTG test would not be a major limit.

A potentially significant association between CD and DCM is highly suggestive, especially in the case of sporadic diseases. Mechanisms shared by CD and DCM could involve ubiquitary activation of metalloproteases,31 extramolecular epitope spreading,32 and non-tTG-related autoimmunity.33 Anti-tTG antibodies may have a shared affinity to antigen epitopes of different cells/tissues, or different antigens could mimic tTG epitopes. Cardiomyopathies may enter the list of atypical presentations of CD, but this hypothesis requires confirmation.

In conclusion, our study indicates a non-causal link between CD and DCM. This association seems to be unrelated to the aetiology: CD was diagnosed in autosomal dominant, X-linked, drug-toxicity and sporadic DCM. However, the higher prevalence of CD in DCM patients (confirming previous reports) and their relatives than in controls, and the extra-intestinal comorbidity data, suggest that CD may contribute to the cardiac phenotype either as a direct effect of the autoantibodies or by means of associated conditions that may worsen the DCM outcome. Furthermore, comorbidities such as iron-deficiency anaemia, could be useful markers for arousing the clinical suspicion of CD in patients with cardiomyopathy. Therefore, CD should be specifically looked for in patients diagnosed with DCM at least when co-morbidity signs potentially related to CD are present.

Appendix A

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The authors thank the informed and consenting patients and relatives who agreed to participate in the clinical programme of family screening, as well as all volunteers who accepted to enter the screening of the normal population.

Role of funding source

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Patient consent
The patients and relatives gave their informed consent; in addition to informative interviews that the clinicians had with the patients first, and then with their relatives, a booklet entitled ‘Informative path for patients diagnosed as having cardiomyopathies and their families’ was given to each family. The screening program on healthy subjects was approved by Ethical Committee of I.R.C.C.S. Burlo Garofolo, Trieste (Research Programs from 1997 up to #30/2000, updated 17/05/2000 and 21/12/2000). The Research Projects on ‘Familial Cardiomyopathies: non invasive screening of relatives’ and ‘Celiac Disease and Dilated Cardiomyopathy’ were approved by the Ethical Committee of the I.R.C.C.S. Policlinico San Matteo, Pavia (RC/1998 and RC/2000, confirmed 2002).

References