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ORIGINAL ARTICLE

Differences Between Familial and Sporadic Celiac Disease

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Abstract

Background It is not known if genetic background, characteristics at diagnosis, physical and psychological well-being, and adherence to a gluten-free diet are comparable between patients with familial or sporadic celiac disease. These issues were investigated in a follow-up study.

Methods Altogether 1064 patients were analyzed for celiac disease-associated serology, predisposing HLA-DQ, and non-HLA genotypes. Medical data were collected from patient records and supplementary interviews. Current symptoms and quality of life were further evaluated with the Gastrointestinal Symptom Rating Scale (GSRS), the Psychological General Well-Being questionnaire (PGWB), and Short Form 36 (SF-36) questionnaires.

Results Familial and sporadic groups differed ($P<0.001$) in the reason for diagnosis and clinical presentation at diagnosis, familial patients being more often screen-detected (26% vs. 2%, $P<0.001$) and having less often gastrointestinal (49% vs. 69%) and severe symptoms (47% vs. 65%). The groups were comparable in terms of histological damage, frequency of malabsorption, comorbidities, childhood diagnoses, and short-term treatment response. At the time of the study, familial cases reported fewer symptoms (21% vs. 30%, $P=0.004$) and lower prevalence of all (78% vs. 86%, $P=0.007$), neurological (10% vs. 15%, $P=0.013$), and dermatological (9% vs. 17%, $P=0.001$) comorbidities. Dietary adherence and GSRS scores were comparable, but familial cases had better quality of life according to PGWB and SF-36. High-risk genotype HLA-DQ2.5/DQ2.5 was more frequent among familial cases, and four non-HLA SNPs were associated with familial celiac disease.

Conclusions Despite the greater proportion of high-risk genotypes, familial cases had milder symptoms at presentation than did sporadic cases. Worse experience of symptoms and poorer quality of life in sporadic disease indicate a need for intensified support.

Keywords Celiac disease · Familial · Sporadic · Symptoms · Quality of life · HLA

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Introduction

Celiac disease is a chronic immune-mediated disorder in which ingestion of dietary gluten typically causes inflammation and morphological damage in the small bowel mucosa. According to population-based screening studies, the true prevalence of this heavily underdiagnosed disease is approximately 1–3% [1–3]. In specific at-risk groups, such as relatives of patients and subjects with another autoimmune disease, prevalence may reach as high as 5–15% [4–8]. At the individual level, the risk of celiac disease is increased by several factors including gender, predisposing HLA-DQ genotype and, in the case of familial celiac disease, the degree of relatedness with the index patient [7–9].

HLA class II genes encoding HLA-DQ2 and DQ8 are required for the development of celiac disease. Approximately 90% of patients carry HLA-DQ2.5 (encoded by *HLA-DQA1*0501* and HLA-*DQB1*0201*; approximately 20% homozygotes) [10, 11]. The rest carry either HLA-DQ2.2 (*DQA1*0201/DQB1*0202*) or HLA-DQ8 (*DQA1*03/DQB1*0302*). In addition, more than 40 non-HLA loci may contribute to disease susceptibility [12–14]. Interestingly, the presentation of celiac disease varies widely and patients may suffer either gastrointestinal or extraintestinal symptoms, or be even completely asymptomatic [15]. In fact, the phenotype may even vary between identical twins [16], indicating a modifying effect of environmental factors. It is currently unclear whether familial risk, either in conjunction with or independently of the genotype, also affects the phenotype and treatment outcomes in celiac disease, as well as long-term coping with the gluten-free diet.

The aim of this study was to compare familial and sporadic celiac disease with regard to the clinical, histological, and serological presentation at diagnosis and physical and psychological well-being and treatment compliance after being on dietary treatment for several years. This was established by exploiting large and well-defined cohorts of patients with or without affected family members.

Materials and Methods

Patients and Study Design

The study was carried out at the Celiac Disease Research Center, Tampere University, and at Tampere University Hospital. Biopsy-proven celiac disease patients and their relatives were recruited by a nationwide search with the help of nationwide and local celiac societies and by means newspaper announcements. In order to ascertain whether the presence of family risk affects coping with a gluten-free diet, all voluntary adult study participants completed specific questionnaires eliciting symptoms and quality of life. Furthermore, they, or in the case of a child the guardian, were interviewed by a physician or a study nurse with expertise in celiac disease. All relevant medical data and diagnoses were confirmed from patient records as available. In addition, blood samples were drawn from both the patients and their relatives for further analyses of celiac disease-associated serology and genetics (Fig. 1).

Family history of celiac disease was assessed by interview and from the medical records if reported. Furthermore, previously undiagnosed relatives with positive celiac antibodies in the present screening were referred to gastrointestinal endoscopy and the new confirmed cases were considered to be affected family members. Moreover, for the purposes of this study, relatives who refused the biopsy but had positive serum endomysium (EmA) and tissue transglutaminase antibodies (tTGab) were also regarded as affected family

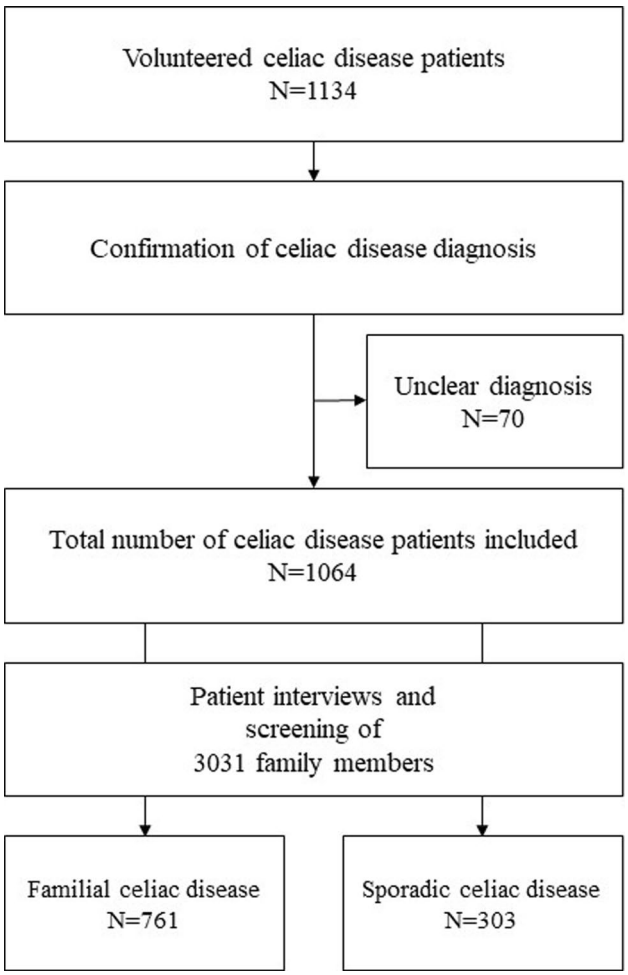

Fig. 1 Flowchart of the study

members based on the evidence that seropositivity for EmA and tTGab affords excellent specificity for celiac disease [5, 17]. Patients whose relatives had inconclusive serology and no biopsy were excluded from further analyses, as were those with unclear family history, non-celiac gluten sensitivity or only self-reported celiac disease.

The final study cohort included 1064 celiac disease patients, who were divided into "familial cases" ($n = 761$) with one or more affected relatives and "sporadic cases" ($n = 303$) with no diagnosed relatives (Fig. 1).

Clinical Data

Clinical information was gathered by patient interviews and supplemented from the patient records. In the case of children, the parents/guardians were interviewed. The data collected included demographic information, clinical presentation at diagnosis, and the main reason for suspicion of celiac disease, as well as celiac disease-associated (e.g., type 1 diabetes and autoimmune thyroidal disease) or other concomitant chronic illnesses. Moreover, data on adherence and capability to maintain a gluten-free diet, use of purified oats in the diet, and presence of any kind of (e.g., gastrointestinal and extraintestinal) recurrent self-reported symptoms and complications were recorded. Malabsorption was defined as weight loss and presence of characteristic laboratory abnormalities, such as anemia, hypoalbuminemia, low folate or low vitamin B12.

The main reason for suspecting celiac disease was further categorized into "gastrointestinal symptoms," "extraintestinal symptoms," and "screen-detected" and severity of symptoms before diagnosis as "none," "mild or moderate," and "severe" as previously defined [18]. Adherence to gluten-free diet was categorized as either "strict" or "occasional or frequent lapses" based on the dietary interview.

Serology

The results of celiac disease serology at the time of diagnosis were collected from the medical records. Only EmA titers were considered in this analysis, since some of the patients had been diagnosed before the introduction of tTGab tests. From serum samples collected at the time of the present study, tTGab values were tested by enzyme-linked immunosorbent assay (QUANTA Lite h-tTG IgA, INOVA Diagnostics, San Diego, CA; cutoff for positivity > 30 U/l) and EmA titers using indirect immunofluorescence with human umbilical cord as an antigen. Titers 1: ≥ 5 were considered positive for EmA, and positive samples were further diluted until negative to 1:50, 1:100, 1:200, 1:500, 1:1000, 1:2000, and 1:4000.

Histology

The results of histological analysis of the small-bowel mucosal biopsies were collected from the pathology reports. In our clinical practice, a minimum of four duodenal biopsies are taken upon endoscopy from each patient with suspected celiac disease and during the repeat endoscopy while on a gluten-free diet. Severity of small intestinal mucosal damage is evaluated from several representative and well-orientated biopsy specimens, and the degree of diagnostic villous atrophy is classified as partial, subtotal, or total.

Questionnaires

Three structured and validated questionnaires were used to evaluate current gastrointestinal symptoms and quality of life. This was done with adult patients only since the questionnaires are not validated in subjects under 18 years of age.

The Gastrointestinal Symptom Rating Scale (GSRS) measures self-reported symptoms with 15 selected questions [19]. Each individual question is scored on a Likert scale from 1 to 7 points, with higher scores indicating more severe gastrointestinal symptoms. Total score is calculated as an average of the 15 individual scores. In addition, five separate sub-scores, including diarrhea, indigestion, constipation, abdominal pain, and reflux, can be calculated as an average of the relevant questions.

The Psychological General Well-Being questionnaire (PGWB) was used to evaluate quality of life and well-being [20, 21]. It consists of 22 questions covering anxiety, depression, well-being, self-control, general health, and vitality. Each question is scored from 1 to 6 points, higher values indicating better self-reported quality of life and well-being. The total score is reported as a sum of each question and each sub-score as a sum of the relevant sub-category questions.

The Short Form 36 (SF-36) was also used to evaluate quality of life and health [22]. The questionnaire consists of 36 items divided into eight sub-categories including physical functioning, physical role limitations, emotional role limitations, vitality, mental health, social functioning, bodily pain, and general health. Each question is scored from 0 to 100 points, with higher scores indicating a better result. The subcategory scores are calculated as averages of the relevant items. Physical functioning refers to an individual´s capacity to undertake daily activities such as doing dishes and cleaning, while physical role limitations elicit if health issues prevent the subject, e.g., from going to work or school.

Genetic Analysis

The genotypes corresponding to disease-associated HLA variants HLA-DQ2.5, HLA-DQ8, and HLA-DQ2.2 were

determined from the patients using commercial HLA typing kits (Olerup SSP low-resolution kit, Olerup SSP AB, Saltsjöbaden, Sweden, or DELFIA® Celiac Disease Hybridization Assay Kit, PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) or the TaqMan chemistry-based genotyping of the HLA tagging SNPs as previously described [23, 24].

A further 552 patients were genotyped with Illumina 610-Quad BeadChip array for 39 non-HLA SNPs previously associated with celiac disease risk as a part of the European Genome-wide Association Study [13]. Of these, 37 SNPs passed the quality control filters (Hardy–Weinberg Equilibrium test, $P \leq 0.05$) and were tested for association with familiar/sporadic celiac disease. Genotypes were stored on and quality checks and filtering performed with BC Genome platform, version 4.0 (BC Platforms Espoo, Finland). Single marker association analyses were performed using PLINK, version 1.07 [25]. Patients with unclear genotype were excluded and, in order to avoid false positive findings due to trait correlation between genetically related individuals, only one patient from each family was included.

Statistics

Statistical analyses were performed with SPSS Statistics version 23 (IBM Corp, New York, NY, USA). Continuous variables were presented as medians with range or with lower (25th percentile) and upper (75th percentile) quartiles, or as number of subjects, and tested for statistical significance by Mann–Whitney U test. Binominal and categorical variables were presented as percentages and tested by Chi-square test. P value < 0.05 was considered significant across all analyses. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the non-HLA SNPs in both study groups.

Results

At diagnosis of celiac disease, the median age of the familial cases was 39 (range 0–81) years and of the sporadic cases 41 (range 1–79) years ($P = 0.010$). Of the familial cases, 39% had one and 61% had two or more affected relatives and 92% of all familial cases had affected first- or second-degree relative(s). Affected relative(s) were more often from mother's (64%) than father's (31%) side of the family. In 5% of familial cases, both maternal and paternal relatives were affected.

Familial cases were more often screen-detected and EmA positive and had less often gastrointestinal presentation, dermatitis herpetiformis, and severe symptoms at diagnosis (Table 1). There were no significant differences between the study groups in the prevalence of childhood diagnoses and malabsorption, or severity of small-bowel mucosal damage (Table 1). The groups also achieved comparable recovery of the mucosal morphology after 1 year on a gluten-free diet (full recovery of the villi in 59.3% and 60.3%, respectively, $P = 0.956$).

At present follow-up evaluation, the median age was 50 (range 2–89) years in the familial cases and 52 (6–84) years in the sporadic cases. The former group had been on gluten-free diet significantly longer (median 8 [range 4–15] vs. 7 [range 3–13] years, respectively; $P = 0.005$). Familial cases reported overall symptoms less often but were more often EmA positive on a gluten-free diet (Table 2). They also had less often regular follow-up with borderline significance, whereas the groups were comparable in current adherence and capability to manage a gluten-free diet, use of gluten-free oats, and frequency of tTGab positivity (Table 2). In addition, the groups did not differ in gastrointestinal

Table 1 Clinical, serological, and histological characteristics at diagnosis in 1064 patients with familial or sporadic celiac disease

	Familial n = 761		Sporadic n = 303		*P*
	N	%	N	%	
Females	554	72.8	229	75.6	0.353
Celiac disease diagnosis in childhood	143	18.8	44	14.5	0.088
Main reason for the diagnosis					**< 0.001***
Screening	200	26.3	7	2.3	
Extraintestinal symptoms[a]	187	24.6	88	29.1	
Gastrointestinal symptoms[b]	374	49.1	207	68.5	
Other common symptoms					
Malabsorption	270	35.7	107	35.5	0.971
Dermatitis herpetiformis	102	13.5	64	21.3	**0.002**
Severity of symptoms at diagnosis[c]					**< 0.001***
No symptoms	60	10.2	3	1.4	
Mild or moderate	251	42.8	71	33.3	
Severe	275	46.9	139	65.3	
Seropositivity[d] at diagnosis[e]	358	88.6	112	81.8	**0.040**
Severity of villous atrophy at diagnosis[f]					0.147
Partial	192	32.9	97	39.8	
Subtotal	233	39.9	91	37.3	
Total	159	27.2	56	23.0	

Bold values indicate statistically significant difference with *P* value < 0.05

[a]For example, dermatitis herpetiformis, arthralgia, rash, swelling, fatigue [18]

[b]For example, diarrhea, constipation, abdominal pain, flatulence, loose stools, mouth ulcers [18]

[d]Endomysium or antireticulin antibodies

Data were available in > 90% of the cases except [c]586 and 213; [e]404 and 137; and [f]584 and 244, respectively

*Calculated across all three variables

Table 2 Follow-up characteristics in 1064 celiac patients with familial or sporadic celiac disease

	Familial, $n=761$		Sporadic, $n=303$		P
	N	%	N	%	
Self-reported adherence to gluten-free diet					0.202
Strict	704	96.6	291	97.7	
Occasional or frequent lapses	29	3.4	7	2.3	
Capable to manage the diet	673	94.4	274	93.8	0.732
Use of purified oats	611	83.2	253	85.5	0.378
Current symptoms[a]	152	21.1	85	29.5	**0.004**
Follow-up serology[b]					
Positive endomysium antibodies	108	15.2	18	6.6	**< 0.001**
Positive tTGab	182	24.0	57	18.9	0.077
Regular follow-up	189	29.4	96	36.0	0.052

Bold values indicate statistically significant difference with P value < 0.05

tTGab tissue transglutaminase antibodies

[a]Any type of recurrent gastrointestinal and extraintestinal symptoms

[b]Only samples taken ≥ 2 years after diagnosis were counted

symptoms as measured by GSRS, but familial cases had better median PGWB general health score and SF-36 total, physical functioning, vitality, and mental health scores (Table 3).

Regarding concomitant chronic conditions, there were no differences between the groups in frequency of fractures, but familial cases were more often completely free from other conditions and had less often neurological and dermatological diseases (Supplementary Table 1).

Celiac disease-associated HLA haplotypes were available (one case per family) from 330 familial and 222 sporadic cases. The overall HLA-DQ distribution differed significantly between the two groups (Table 4). Homozygosity for HLA-DQ2.5 was also more common among the familial cases, while HLA-DQ2.2/DQ2.2 or HLA-DQ2.2/DQX, HLA-DQ8/DQ8, and HLA-DQX/DQX haplotypes were more common among sporadic cases (Table 4).

Of the 37 tested celiac disease-associated non-HLA SNPs, rs3748816 (OR 1.39, 95% CI 1.03–1.90; $P=0.034$), rs2816316 (OR 1.75, 95% CI 1.10–2.79; $P=0.017$), and rs2762051 (OR 1.48, CI 1.03–2.13; $P=0.035$) were associated with increased risk and rs10903122 (OR 0.71, 95% CI 0.53–0.96; $P=0.026$) with decreased risk for familial celiac disease (Supplementary Table 2).

Discussion

Patients with familial and sporadic celiac disease were found to have mostly comparable characteristics at diagnosis, except that the former were more often screen-detected and had milder symptoms. The minor differences in diagnostic approach and symptoms are probably attributable to the active screening of at-risk groups recommended in our national guidelines [17]. While there are no earlier studies with similar design, there are reports of a high frequency of undiagnosed celiac disease among family members of patients [26–29]. Altogether, there seems to be a gradual shift in the typical presentation of celiac disease toward a milder form [30, 31]. Interestingly, despite the greater proportion of asymptomatic/mildly symptomatic cases among the familial patients, the degree of histological damage was comparable between the groups. This concurs with reports showing a weak correlation between clinical presentation and severity of the mucosal lesions [28, 32–34], the ultimate reasons for which remain unclear.

The study groups were also found to have similar adherence to gluten-free diet, which is somewhat surprising as maintaining the diet could be expected to be less challenging in subjects with a family history of celiac disease. The excellent adherence in both groups is likely attributable to several factors, including the widespread availability and labeling of gluten-free products as well as the generally high awareness of the disease in Finnish food stores and restaurants, along with the former (now discontinued) governmentally granted financial reimbursement for officially diagnosed patients. Interestingly, despite equal dietary adherence, a greater proportion of sporadic patients reported having current self-perceived overall symptoms according to the interview. This experience is unlikely to be explained the minor difference in the duration of the gluten-free diet, since the symptoms generally diminish quite rapidly on treatment [35–37]. It must be mentioned that in spite of the equal self-reported dietary adherence, there was higher proportion of EmA positivity in the familial group on gluten-free diet. This may reflect their higher frequency of seropositivity already at diagnosis, since normalization of the autoantibodies may take longer than 2 years [38]. However, the possibility of

Table 3 Current symptoms and quality of life as measured by validated questionnaires in 627 adult* celiac patients with familial or sporadic celiac disease

	Familial, $n=420$		Sporadic, $n=207$		P
	Median	Q_1, Q_3	Median	Q_1, Q_3	
Gastrointestinal Symptom Rating Scale[a]					
Total score	1.9	1.5, 2.5	1.9	1.5, 2.6	0.379
Diarrhea	1.3	1.0, 2.3	1.7	1.0, 2.0	0.791
Indigestion	2.3	1.8, 3.3	2.3	1.8, 3.3	0.348
Constipation	1.7	1.0, 2.7	1.7	1.3, 2.7	0.282
Pain	2.0	1.3, 2.3	1.7	1.3, 2.5	0.875
Reflux	1.5	1.0, 2.0	1.5	1.0, 2.0	0.906
Psychological General Well-Being[b]					
Total score	107	95, 116	105	93, 115	0.171
Anxiety	25	21, 27	24	22, 27	0.688
Depression	17	15, 18	17	15, 18	0.283
Well-being	18	15, 20	17	15, 19	0.235
Self-control	16	14, 17	16	14, 17	0.707
General health	14	11, 15	13	10, 15	**0.028**
Vitality	18	16, 20	18	16, 20	0.410
Short Form 36[c,d]					
Total score	81	67, 89	78	63, 86	**0.011**
Physical functioning	95	80, 100	90	80, 98	0.126
Physical role functioning	100	50, 100	75	25, 100	**0.027**
Emotional role functioning	100	67, 100	100	67, 100	0.708
Vitality, energy	73	55, 85	70	50, 80	**0.015**
Mental health	84	72, 92	80	71, 88	**0.040**
Social role functioning	88	75, 100	88	75, 100	0.209
Bodily pain	78	58, 90	68	55, 90	0.216
General health perceptions	65	50, 80	60	40, 75	0.084

Data were available in >90% of cases in each category except in[d] only from 376 familial cases

Bold values indicate statistically significant difference with P value < 0.05

Q_1, lower (25th percentile) quartile; Q_3, upper (75th percentile) quartile

*Children were excluded since the questionnaires are validated for adults only

Higher scores indicate either more severe symptoms[a], better well-being[b] or better functioning[c]

Table 4 Celiac disease-related human leukocyte antigen (HLA) genotypes in 552 patients with familial or sporadic celiac disease

	Familial, $n=330$		Sporadic, $n=222$		P[a]
	N	%	N	%	
HLA haplotype					**0.001**
DQ2.5/DQ2.5	69	20.9	26	11.7	
DQ2.5/DQ2.2	15	4.5	14	6.3	
DQ2.5/DQ8	27	8.2	19	8.6	
DQ2.5/DQX[b]	182	55.2	114	51.4	
DQ2.2/DQ2.2 or DQX[b]	7	2.1	17	7.7	
DQ8/DQ2.2 or DQX[b]	19	5.8	12	5.4	
DQ8/DQ8	3	0.9	6	2.7	
DQX[b]/DQX[b]	8	2.4	14	6.3	

Bold value indicates statistically significant difference with P value < 0.05

[a]Calculated between all haplotypes by Pearson Chi-square test

[b]DQX defines haplotype other than listed here

familiar cases actually having poorer dietary adherence cannot be fully excluded.

The sporadic patients had more often neurological and dermatological disorders, which could possibly explain the higher frequency of experienced symptoms as these complaints could be mistakenly attributed to celiac disease. Absence of peer support from family members with the disease might further hamper this assessment of causality and exacerbate the experience of symptoms [39, 40]. Alternatively, severe symptoms, more common among sporadic cases at diagnosis, may also predispose to persistent symptoms on a strict gluten-free diet [41], which could offer another explanation for the difference observed here. The experience of persistent symptoms, concomitant disorders, and lack of peer support may also explain the poorer quality of life as measured by PGWB and SF-36 scores in subjects with sporadic disease [40, 41]. These findings emphasize the importance of adequate guidance and support both at diagnosis and during the management of celiac disease.

There was also a significant difference in the HLA-DQ distribution between the groups. The high-risk genotype DQ2.5/DQ2.5 in particular was almost twice as frequent among familial cases, whereas the medium and low-risk genotypes [42] were, correspondingly, more common in sporadic disease. This is not surprising, since the predisposing risk alleles cluster within families with multiple affected members. In contrast to the findings of a recent meta-analysis [43], this was not reflected in a more severe and classic phenotype. However, the more active screening among familial cases complicates this issue, and further studies with larger numbers of cases are needed to confirm our findings. Besides the HLA genotypes, four SNPs were associated with familial celiac disease. Rs2762051 is located within the long non-coding RNA *DLEU1*, whereas the other three, rs3748816, rs2816316, and rs10903122, map to loci harboring genes *MMEL1/TNFRSF14*, *RGS1,* and *RUNX3*, respectively. These genes are all involved in immunological functions, and thus, the possible role of these non-HLA gene loci in familial celiac disease could be of interest in future studies.

The main strength of the present study is the carefully phenotyped cohort of patients with and without family history of celiac disease. Furthermore, a potential bias caused by undiagnosed disease among the relatives was reduced by serological screening of previously undiagnosed participants. One may criticize the fact that no biopsy was required for the diagnosis of these individuals, but this is no longer required in the Finnish diagnostic guidelines, and, in our opinion, it would be more biased to classify subjects with positive tTG and EmA as non-celiacs [5, 17]. As a limitation, it was not possible to recruit all the family members or to access comprehensive information on the family histories of all index patients, which may have impaired the detection of familial cases in the cohort. Moreover, the degree of familial relation to the index patient varied to some extent, since a minority of the familial cases had more distant than first- or second-degree relative(s) affected. Nor can it be fully excluded that even though not specifically reported here, the experienced symptoms and quality of life may in fact be attributable to confounding factors such as sporadic autoimmunity in close family members. In addition, although the study is clinically large, the groups were still small for purposes of genetic association analyses, and the systematic questionnaires used were validated only in adults.

To conclude, despite the greater proportion of high-risk genotypes among the subjects in the familial cohort, their clinical presentation was milder and other features comparable with those subjects with sporadic disease. The increased frequency of self-perceived symptoms and poorer health and quality of life scores in the questionnaires in sporadic cases underlines the need for physicians to pay special attention and possibly provide intensified support to this patient group.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the 1964 Helsinki Declaration and its later amendments. The study design, patient recruitment, and collection of patient record data were approved by the Regional Ethics Committee of Pirkanmaa Hospital District.

Informed consent Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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