



Differences Between Familial and Sporadic Celiac Disease

Laura Airaksinen¹ · Lauri Myllymäki¹ · Katri Kaukinen^{1,2} · Päivi Saavalainen³ · Heini Huhtala⁴ · Katri Lindfors¹ · Kalle Kurppa^{5,6,7}

Received: 4 March 2020 / Accepted: 11 July 2020 / Published online: 23 July 2020
© The Author(s) 2020

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

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10620-020-06490-1>) contains supplementary material, which is available to authorized users.

✉ Kalle Kurppa
kalle.kurppa@tuni.fi

Laura Airaksinen
laura.airaksinen@tuni.fi

Lauri Myllymäki
lauri.myllymaki@tuni.fi

Katri Kaukinen
katri.kaukinen@tuni.fi

Päivi Saavalainen
paivi.saavalainen@helsinki.fi

Heini Huhtala
heini.huhtala@tuni.fi

Katri Lindfors
katri.lindfors@tuni.fi

¹ Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, PO BOX 100, 33014 Tampere, Finland

² Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

³ Research Programs Unit, Immunobiology and Department of Medical and Clinical Genetics, University of Helsinki, Helsinki, Finland

⁴ Faculty of Social Sciences, Tampere University, Tampere, Finland

⁵ Centre for Child Health Research, Tampere University Hospital and Tampere University, Tampere, Finland

⁶ Department of Pediatrics, Seinäjoki University Hospital, Seinäjoki, Finland

⁷ University Consortium of Seinäjoki, Seinäjoki, Finland

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

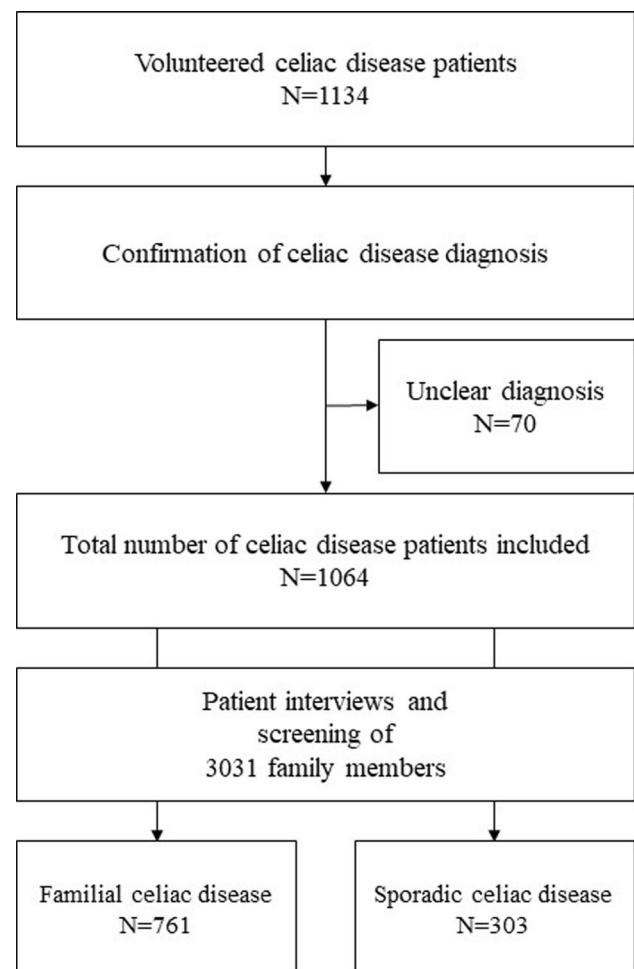


Fig. 1 Flowchart of the study

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 $1: \geq 5$ 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 sub-category 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 Clinical, serological, and histological characteristics at diagnosis in 1064 patients with familial or sporadic celiac disease

	Familial n = 761		Sporadic n = 303		<i>P</i>
	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

^aFor example, dermatitis herpetiformis, arthralgia, rash, swelling, fatigue [18]

^bFor example, diarrhea, constipation, abdominal pain, flatulence, loose stools, mouth ulcers [18]

^dEndomysium or antireticulin antibodies

Data were available in $> 90\%$ of the cases except ^e586 and 213; ^e404 and 137; and ^f584 and 244, respectively

*Calculated across all three variables

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

	Familial, <i>n</i> = 761		Sporadic, <i>n</i> = 303		<i>P</i>
	<i>N</i>	%	<i>N</i>	%	
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

^aAny type of recurrent gastrointestinal and extraintestinal symptoms

^bOnly 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

Q₁, lower (25th percentile) quartile; Q₃, 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

familial 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

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				
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

^aCalculated between all haplotypes by Pearson Chi-square test

^bDQX defines haplotype other than listed here

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.

Funding This study was supported by the Academy of Finland, the Finnish Medical Foundation, the Sohlberg Foundation, the Paulo Foundation, the Sigrid Juselius Foundation, the Foundation for Pediatric Research, and the Competitive State Research Financing of the Expert Area of Tampere University Hospital.

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.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

- Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med*. 2003;348:2517–2524.
- Myléus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr*. 2009;49:170–176.
- Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16:e2.
- Pittschieler K, Gentili L, Niederhofer H. Onset of coeliac disease: a prospective longitudinal study. *Acta Paediatr*. 2007;92:1149–1152.
- Kurppa K, Salminen J, Ukkola A, et al. Utility of the new ESPGHAN criteria for the diagnosis of celiac disease in at-risk groups. *J Pediatr Gastroenterol Nutr*. 2012;54:387–391.
- Oliveira A, Trindade E, Tavares M, Lima R, Terra M, Dias JA. Celiac disease in first degree relatives of celiac children. *Arq Gastroenterol*. 2012;49:204–207.
- Singh P, Arora S, Lal S, Strand TA, Makharia GK. Risk of celiac disease in the first- and second-degree relatives of patients with celiac disease: a systematic review and meta-analysis. *Am J Gastroenterol*. 2015;110:1539–1548.
- Wessels MMS, de Rooij N, Roovers L, Verhage J, de Vries W, Mearin ML. Towards an individual screening strategy for first-degree relatives of celiac patients. *Eur J Pediatr*. 2018;177:1585–1592.
- Bourgey M, Calcagno G, Tinto N, et al. HLA related genetic risk for coeliac disease. *Gut*. 2007;56:1054–1059.
- Kårhus LL, Thuesen BH, Skaaby T, Rumessen JJ, Linneberg A. The distribution of HLA DQ2 and DQ8 haplotypes and their association with health indicators in a general Danish population. *United Eur Gastroenterol J*. 2018;6:866–878.
- Liu E, Dong F, Barón AE, et al. High incidence of celiac disease in a long-term study of adolescents with susceptibility genotypes. *Gastroenterology*. 2017;152:e1.
- Dubois PCA, Trynka G, Franke L, et al. Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet*. 2010;42:295–302.
- Trynka G, Hunt KA, Bockett NA, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet*. 2011;43:1193–1201.
- Gutierrez-Achury J, Zorro MM, Ricaño-Ponce I, et al. Functional implications of disease-specific variants in loci jointly associated with coeliac disease and rheumatoid arthritis. *Hum Mol Genet*. 2016;25:180–190.

15. Lindfors K, Ciacci C, Kurppa K, et al. Coeliac disease. *Nat Rev Dis Prim.* 2019;5:3.
16. Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, Reunala T. Concordance of dermatitis herpetiformis and celiac disease in monozygous twins. *J Invest Dermatol.* 2000;115:990–993.
17. Celiac Disease. Current care guidelines, 2018. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society of Gastroenterology. <https://www.kaypahoito.fi>. Accessed February 28, 2020.
18. Kivelä L, Kaukinen K, Lähdeaho ML, et al. Presentation of celiac disease in Finnish children is no longer changing: a 50-year perspective. *J Pediatr.* 2015;167:e1.
19. Svedlund J, Sjödin I, Dotevall G. GSRS: a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci.* 1988;33:129–134. <https://doi.org/10.1007/252FBF01535722>.
20. Dupuy HJ. The psychological general well-being (PGWB) index. In: Wenger NK, Mattson ME, Furburg CD EJ, eds. *Assessment of quality of life in clinical trials of cardiovascular therapies*. New York: Le Jacq Publishing; 1984.
21. Dimenäs E, Carlsson G, Glise H, Israelsson B, Wiklund I. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. *Scand J Gastroenterol Suppl.* 1996;221:8–13.
22. McHorney CA, Ware JE, Rachel Lu JF, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care.* 1994;32:40–66.
23. Monsuur AJ, de Bakker PIW, Zhernakova A, et al. Effective detection of human leukocyte antigen risk alleles in celiac disease using tag single nucleotide polymorphisms. *PLoS ONE.* 2008;3:e2270.
24. Koskinen L, Romanos J, Kaukinen K, et al. Cost-effective HLA typing with tagging SNPs predicts celiac disease risk haplotypes in the Finnish, Hungarian, and Italian populations. *Immunogenetics.* 2009;61:247–256.
25. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet.* 2007;81:559–575.
26. Rubio-Tapia A, Van Dyke CT, Lahr BD, et al. Predictors of family risk for celiac disease: a population-based study. *Clin Gastroenterol Hepatol.* 2008;6:983–987.
27. Agardh D, Lee HS, Kurppa K, et al. Clinical features of celiac disease: a prospective birth cohort. *Pediatrics.* 2015;135:627–634.
28. Kivelä L, Kaukinen K, Huhtala H, Lähdeaho M-L, Mäki M, Kurppa K. At-risk screened children with celiac disease are comparable in disease severity and dietary adherence to those found because of clinical suspicion: a large cohort study. *J Pediatr.* 2017;183:e2.
29. Nellikall SS, Hafed Y, Larson JJ, Murray JA, Absah I. High prevalence of celiac disease among screened first-degree relatives. *Mayo Clin Proc.* 2019;94:1807–1813.
30. Brandimarte G, Tursi A, Giorgetti GM. Changing trends in clinical form of celiac disease. Which is now the main form of celiac disease in clinical practice? *Minerva Gastroenterol Dietol.* 2002;48:121–130.
31. Rampertab SD, Pooran N, Brar P, Singh P, Green PHR. Trends in the presentation of celiac disease. *Am J Med.* 2006;119:355.e9–355.e14.
32. Brar P, Kwon GY, Egbuna II, et al. Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. *Dig Liver Dis.* 2007;39:26–29.
33. Thomas HJ, Ahmad T, Rajaguru C, Barnardo M, Warren BF, Jewell DP. Contribution of histological, serological, and genetic factors to the clinical heterogeneity of adult-onset coeliac disease. *Scand J Gastroenterol.* 2009;44:1076–1083.
34. Taavela J, Koskinen O, Huhtala H, et al. Validation of morphometric analyses of small-intestinal biopsy readouts in celiac disease. *PLoS ONE.* 2013;8:e76163.
35. Murray JA, Watson T, Clearman B, Mitros F. Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. *Am J Clin Nutr.* 2004;79:669–673.
36. Zarkadas M, Cranney A, Case S, et al. The impact of a gluten-free diet on adults with coeliac disease: results of a national survey. *J Hum Nutr Diet.* 2006;19:41–49.
37. Pekki H, Kurppa K, Mäki M, et al. Predictors and significance of incomplete mucosal recovery in celiac disease after 1 year on a gluten-free diet. *Am J Gastroenterol.* 2015;110:1078–1085.
38. Gidrewicz D, Trevenen CL, Lyon M, Butzner JD. Normalization time of celiac serology in children on a gluten-free diet. *J Pediatr Gastroenterol Nutr.* 2017;64:362–367.
39. Plevinsky JM, Greenley RN, Fishman LN. Self-management in patients with inflammatory bowel disease: strategies, outcomes, and integration into clinical care. *Clin Exp Gastroenterol.* 2016;9:259–267.
40. Halpert A. Irritable bowel syndrome: patient-provider interaction and patient education. *J Clin Med.* 2018;7:3.
41. Paarlahti P, Kurppa K, Ukkola A, et al. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. *BMC Gastroenterol.* 2013;13:75.
42. Romanos J, van Diemen CC, Nolte IM, et al. Analysis of HLA and non-HLA alleles can identify individuals at high risk for celiac disease. *Gastroenterology.* 2009;137:e3.
43. Bajor J, Szakács Z, Farkas N, et al. Classical celiac disease is more frequent with a double dose of HLA-DQB102: a systematic review with meta-analysis. *PLoS ONE.* 2019;14:e0212329.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.