

ORIGINAL ARTICLE

## Prevalence of Celiac Disease among Children in Finland

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### ABSTRACT

#### BACKGROUND

Wheat, rye, and barley proteins induce celiac disease, an autoimmune type of gastrointestinal disorder, in genetically susceptible persons. Because the disease may be underdiagnosed, we estimated the prevalence of the disease and tested the hypothesis that assays for serum autoantibodies can be used to detect untreated celiac disease and that positive findings correlate with specific HLA haplotypes.

#### METHODS

Serum samples were collected from 3654 students (age range, 7 to 16 years) in 1994 and screened in 2001 for endomysial and tissue transglutaminase antibodies. HLA typing was also performed on stored blood samples. All antibody-positive subjects were asked to undergo small-bowel biopsy in 2001.

#### RESULTS

Of the 3654 subjects, 56 (1.5 percent) had positive antibody tests, as determined in 2001. Results of the two antibody tests were highly concordant. As of 1994, none of the subjects had received a clinical diagnosis of celiac disease, but 10 who had positive tests for both antibodies in serum obtained in 1994 received the diagnosis between 1994 and 2001. Of the 36 other subjects with positive antibody assays who agreed to undergo biopsy in 2001, 27 had evidence of celiac disease on biopsy. Thus, the estimated biopsy-proved prevalence was 1 case in 99 children. All but two of the antibody-positive subjects had either the HLA-DQ2 or the HLA-DQ8 haplotype. The prevalence of the combination of antibody positivity and an HLA haplotype associated with celiac disease was 1 in 67.

#### CONCLUSIONS

The presence of serum tissue transglutaminase and endomysial autoantibodies is predictive of small-bowel abnormalities indicative of celiac disease. There is a good correlation between autoantibody positivity and specific HLA haplotypes. We estimate that the prevalence of celiac disease among Finnish schoolchildren is at least 1 case in 99 children.

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N Engl J Med 2003;348:2517-24.

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**C**ELIAC DISEASE IS A DISORDER INDUCED by wheat, rye, and barley proteins, and its classic form is characterized in children by malabsorption and failure to thrive. During the past two decades, however, the clinical picture of the disease has changed to include milder forms, thus resulting in an upward shift of the age at diagnosis. Screening for active celiac disease with the use of serum autoantibodies usually focuses on patients with mild gastrointestinal symptoms, isolated iron deficiency, atypical or extraintestinal manifestations, or autoimmune diseases or on the first-degree relatives of affected patients.<sup>1-3</sup> Screening programs within populations indicate that the disease is underdiagnosed,<sup>4-7</sup> but because of the rather small number of subjects studied, the confidence intervals for the true prevalence are wide. In the United States, the disease is extremely rare when the criteria for diagnosis rely on classic symptoms such as diarrhea and short stature.<sup>8</sup> By broadening the clinical indication, however, antibody screening seems to indicate that the prevalence in the United States is similar to that in Europe.<sup>9</sup>

Approximately 90 percent of patients with celiac disease carry the HLA-DQ2 heterodimer encoded by the HLA-DQA1\*05 and DQB1\*02 genes. Such patients have at least one copy of the extended HLA-DR3-DQ2 haplotype (encoding both the  $\alpha$  and  $\beta$  chains of the major histocompatibility complex [MHC]) common to many autoimmune diseases, or they are heterozygous for the HLA-DR5-DQ7 haplotype (encoding the  $\alpha$  chain of the MHC) and the HLA-DR7-DQ2 haplotype (encoding the  $\beta$  chain of the MHC), in which the heterodimer molecule is encoded in the *trans* position.<sup>10</sup> Most of the remaining 10 percent of patients have the HLA-DR4-DQ8 haplotype.

Evidence suggests that celiac disease is underdiagnosed in children. Serologic testing has the potential to detect otherwise undiagnosed disease. Evidence is also accumulating that daily ingestion of wheat, rye, and barley results in long-term extraintestinal sequelae in subjects with undiagnosed or untreated celiac disease.<sup>1,2</sup> Early detection of the disease and subsequent dietary elimination of gluten might be the appropriate method for averting complications later in life.

We sought to determine the prevalence of celiac disease in Finland and specifically to test the hypothesis that celiac disease can be identified by serologic testing in children who have not previously received a clinical diagnosis. We used two serologic

tests simultaneously — endomysial and tissue transglutaminase autoantibody tests — to screen a geographically defined, unselected population of schoolchildren. We also assessed whether positivity for disease-specific autoantibodies correlates with the HLA haplotypes associated with celiac disease.

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## METHODS

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### SUBJECTS

We tested serum samples collected in 1994 as part of a study of risk factors for type 1 diabetes among schoolchildren.<sup>11</sup> All 4280 schoolchildren who were 7 to 16 years old and who lived in five municipalities in northern Finland were invited to participate in the study. The cohort represents 8 percent of the area's school population. Whole blood for HLA typing and serum were obtained from 3662 subjects (85.6 percent), and the samples were stored at  $-20^{\circ}\text{C}$  until studied. Eight subjects were excluded because the volume of their serum samples was not sufficient for analyses. The median age of the remaining study cohort of 3654 subjects (1826 of whom were boys) was 12 years (range, 7 to 16) at the time of initial sampling.

The ethics committee of the Faculty of Medicine, University of Oulu, approved the original study protocol to screen for risk factors associated with type 1 diabetes and for the collection of blood samples in 1994. Written informed consent was also obtained from the subjects, their parents, or both. In 2001 the new protocol, which included serologic screening, upper gastrointestinal endoscopy, and mucosal biopsies, was evaluated and approved by the same committee. A new informed-consent document regarding blood testing and small-bowel biopsies was signed by the subjects, their parents, or both.

### STUDY PROTOCOL

The cohort was screened for endomysial and tissue transglutaminase antibodies in blood samples obtained in 1994, and all subjects with a positive result who had not previously received a diagnosis of celiac disease were asked to undergo upper gastrointestinal endoscopy in 2001. At the visit for endoscopy, a second serum sample was obtained for antibody testing. Serum testing began on August 31, 2000, and the last biopsy specimen was obtained on December 14, 2001. Clinical symptoms were assessed with use of a semistructured questionnaire completed at the visit with the study clinician in 2001. A clinical dietitian assessed the diet of the subjects.

**SERUM ANTIBODY TESTS**

The serum samples from all 3654 schoolchildren were simultaneously assessed in a blinded fashion in two different laboratories: tests for endomysial antibodies were conducted in Tampere, Finland, and tests for tissue transglutaminase antibodies were performed in Freiburg, Germany. Serum IgA- and IgG-class endomysial antibodies were determined by an indirect immunofluorescence method as previously described.<sup>3,12</sup> Determinations of IgA-class tissue transglutaminase antibodies were carried out with a Celikey assay (Pharmacia Diagnostics) in accordance with the manufacturer's instructions. The limit of detection of the assay was 0.1 U per milliliter, and we chose 5 U per milliliter as the cutoff point for positivity. Serum samples with IgA-class tissue transglutaminase antibody levels below the limit of detection were further tested for the determination of IgG-class tissue transglutaminase antibodies with an enzyme-linked immunosorbent assay (Pharmacia Diagnostics), as previously described.<sup>13</sup> The same microplates and test procedure used for IgA-class antibodies (Celikey) were used in this subgroup of serum samples. Values above 5 U per milliliter were considered positive.

In subjects who were positive for IgG-class tissue transglutaminase antibodies, an IgG-class endomysial antibody test was performed.<sup>12</sup> In such subjects, the total serum IgA was determined nephelometrically, and serum levels below 0.05 g per liter were considered indicative of selective IgA deficiency.

**ENDOSCOPY**

Upper gastrointestinal endoscopy was performed with an Olympus endoscope (model GIF-IT140) at the Department of Pediatrics, Oulu University Hospital. During the procedure, multiple duodenal-biopsy samples were obtained for routine histologic analysis. One sample was prepared for immunohistochemical staining.

**DIAGNOSIS OF CELIAC DISEASE**

Formalin-fixed biopsy specimens stained with hematoxylin and eosin were studied with the use of light microscopy and morphometric techniques. Villous height and crypt depth were measured, and the ratio of villous height to crypt depth was calculated. A ratio of less than 2 was considered to be indicative of celiac disease (i.e., villous atrophy with crypt hyperplasia).

**IMMUNOHISTOCHEMICAL STAINING**

Frozen biopsy samples of the small intestine were stained for intraepithelial lymphocytes bearing  $\gamma/\delta$  T-cell receptors, and cell densities were determined as previously described.<sup>14</sup> The biopsy specimens were also stained for HLA class II molecules, and the expression of HLA-DR was considered to be enhanced when epithelial staining was strong or was confined to crypt cells.<sup>14</sup>

**HLA TYPING**

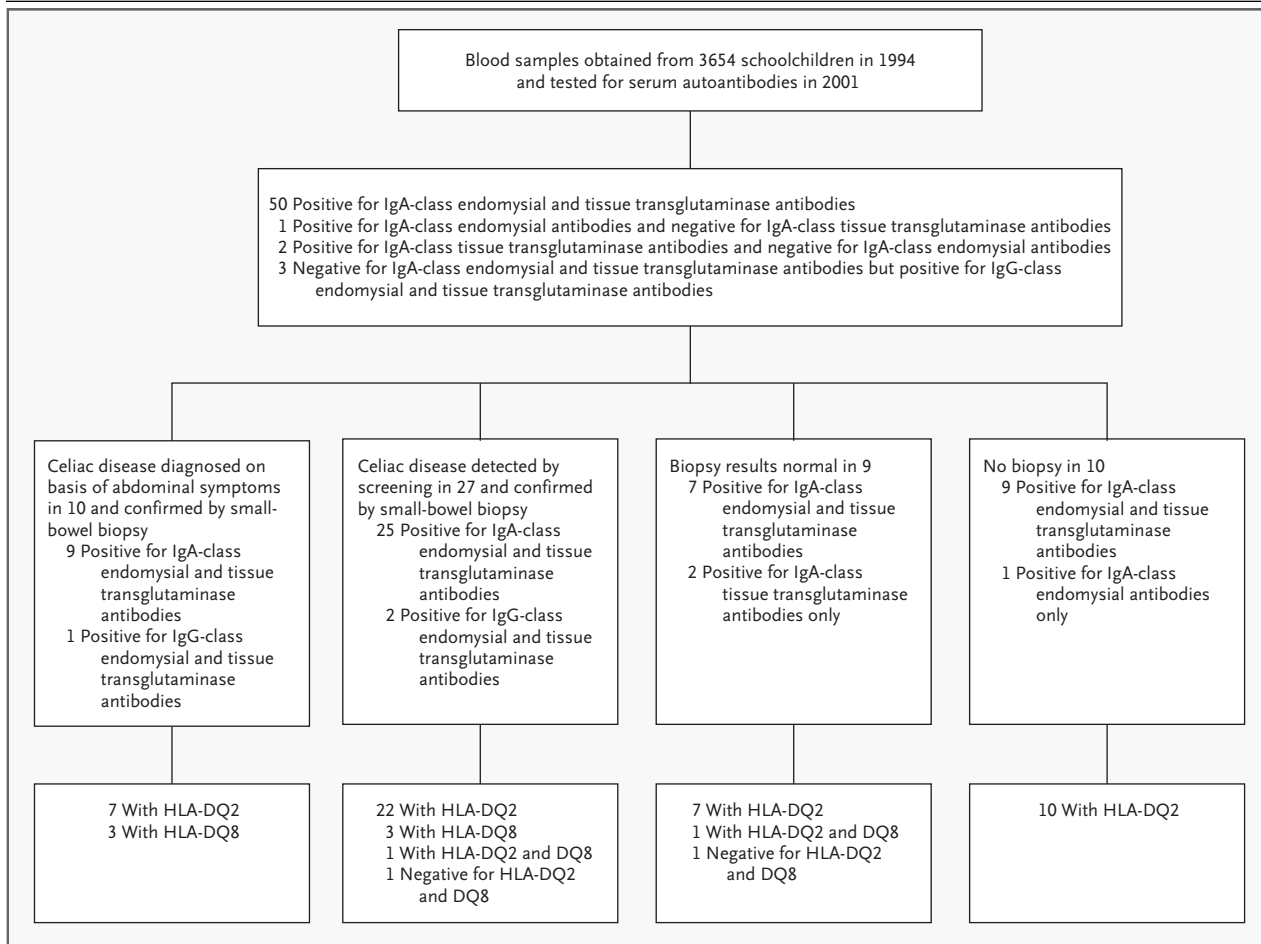
HLA typing was performed with the use of a screening test developed to detect alleles associated with an increased risk of type 1 diabetes and those associated with protection against it.<sup>15</sup> Samples were analyzed for selected HLA-DQB1 alleles, including DQB1\*02 and DQB1\*0302, and samples that were positive for the HLA-DQB1\*02 allele were further analyzed for the presence of associated alleles: HLA-DQA1\*0201 and DQA1\*05.

**STATISTICAL ANALYSIS**

We calculated 95 percent confidence intervals for prevalence rates and odds ratios.<sup>16</sup> The odds ratio was calculated with use of the equation  $(a \times d) \div (b \times c)$ , and the positive predictive value was calculated with use of the equation  $a \div (a + c) \times 100$ . In these equations a and c represent the numbers of subjects with genotypic risk factors with and without celiac disease-specific autoantibodies, respectively, and b and d represent the numbers of subjects without genotypic risk factors who do and do not have autoantibodies, respectively.

**RESULTS****SEROLOGIC TESTS**

The correlation between the results of the two methodologically different autoantibody tests was almost perfect: 3651 of 3654 results were concordant. Fifty subjects were positive for both IgA-class endomysial antibodies (median titer, 1:500; range, 1:5 to 1:4000) and IgA-class tissue transglutaminase antibodies (median titer, 70.3 U per milliliter; range, 8.8 to 680), and 3601 were negative for both tests (Fig. 1). One subject who was negative for tissue transglutaminase antibodies (titer, 4.8 U per milliliter) was positive for IgA-class endomysial antibodies at the lowest titer, 1:5. Two subjects who were negative for IgA-class endomysial antibodies



**Figure 1. Results of Screening for Autoantibodies Associated with Celiac Disease in a Population of Finnish Schoolchildren.**

Blood samples obtained in 1994 were tested for serum endomysial antibodies and tissue transglutaminase antibodies in 2001. Subjects with positive results who had not previously been given a diagnosis of celiac disease were invited to undergo upper gastrointestinal endoscopy. The results of small-bowel biopsy and typing for HLA-DQ2 and DQ8 are shown. The overall prevalence of biopsy-proven celiac disease in the cohort was 1 case in 99 children.

were positive for IgA-class tissue transglutaminase antibodies, with titers of 5.7 and 7.0 U per milliliter.

Seventeen subjects had undetectable serum levels of IgA-class tissue transglutaminase antibodies (less than 0.1 U per milliliter). Fourteen were negative for IgG-class tissue transglutaminase antibodies, with a median titer of 1.2 U per milliliter (range, 0.8 to 3.1), and three were clearly positive, with serum titers of 160.6, 148.2, and 26.4 U per milliliter (Fig. 1). All three proved to have IgA deficiency.

**CELIAC DISEASE DETECTED ON THE BASIS OF SYMPTOMS**

As of 1994, no cases of celiac disease had been identified in this cohort. Between 1994 and 2001,

10 cases were detected on the basis of abdominal symptoms and confirmed by biopsy (median age, 16 years; range, 14 to 20) (Fig. 1). Nine of the subjects were positive for both serum IgA-class endomysial antibodies (median titer, 1:1000; range, 1:500 to 1:4000) and IgA-class tissue transglutaminase antibodies (median titer, 119 U per milliliter; range, 37.9 to 634.4), and 1 had IgA deficiency but was positive for IgG-class endomysial antibodies (titer, 1:2000) and IgG-class transglutaminase antibodies (26.4 U per milliliter). The antibody results were obtained retrospectively from tests of serum samples obtained in 1994, before the clinical diagnosis had been made.

**CELIAC DISEASE DETECTED BY SCREENING**

In 2001 the remaining 46 antibody-positive subjects who had not previously received a diagnosis of celiac disease were invited to undergo small-bowel biopsy and antibody testing. Thirty-six (78.3 percent) agreed to undergo biopsy, and 27 had mucosal villous atrophy with crypt hyperplasia typical of celiac disease. Morphometric studies revealed a mean ratio of villous height to crypt depth of 0.87 (range, 0.11 to 1.68; a ratio of less than 2 is indicative of celiac disease). In addition, the intraepithelial densities of  $\gamma/\delta$  T-cell receptor-bearing lymphocytes exceeded the threshold for positivity (3.5 cells per millimeter), with a mean of 20 cells per millimeter (range, 3.5 to 71.6). Aberrant up-regulation of the expression of HLA-DR was seen in 25 of 27 mucosal specimens.

A second blood sample was obtained at the time of biopsy in 2001. Altogether 24 of 27 patients with celiac disease detected by screening had both IgA-class endomysial antibodies (median titer, 1:1000; range, 1:50 to 1:4000) and IgA-class tissue transglutaminase antibodies (median titer, 37.8; range, 6.8 to 624). Both antibody tests were negative in one subject. Two subjects had IgA deficiency but were

positive for IgG-class antibodies alone. A gluten-free diet was prescribed for all 27 subjects with newly diagnosed celiac disease, and 25 agreed to follow the diet.

**NORMAL MUCOSAL MORPHOLOGY**

Table 1 summarizes the findings in the nine subjects with normal mucosal architecture on small-bowel biopsy. Five subjects who were initially antibody-positive were negative for antibodies during follow-up in 2001. All but one of them had an increased density of  $\gamma/\delta$  T-cell receptor-bearing lymphocytes, and all had enhanced expression of HLA-DR, indicating ongoing mucosal inflammation in the morphologically normal mucosa. Two subjects who were initially negative for endomysial antibodies but who had low levels of tissue transglutaminase antibodies had negative tests for both types of antibodies in 2001. Eight of the nine subjects were positive for HLA-DQ2.

**ANTIBODY-POSITIVE SUBJECTS WHO DECLINED TO UNDERGO BIOPSY**

Ten of the antibody-positive subjects declined to undergo small-bowel biopsy. In the 1994 serum

**Table 1. Results of Serum Antibody Tests and Small-Bowel Biopsy in Nine Subjects with Normal Mucosal Architecture on Small-Bowel Biopsy.\***

Subject No.	1994 Serum Sample		2001 Serum Sample		Morphometric Findings on Biopsy			Immunohistochemical Findings on Biopsy		HLA Haplotype
	EMA titer	tTG† U/ml	EMA titer	tTG† U/ml	VH $\mu$ m	CrD	VH:CrD‡	Density of $\gamma/\delta$ T-Cell Receptor-Bearing Lymphocytes§	Expression of HLA-DR¶	
1	1:200	13.7	1:500	20.3	430	140	3.07	12.5	Enhanced	DR3-DQ2
2	1:200	28.9	1:100	5.6	430	200	2.15	3.2	Enhanced	DR3-DQ2
3	1:100	13.4	1:<5	0.5	550	180	3.06	5.6	Enhanced	DR3-DQ2 and DR4-DQ8
4	1:100	14.8	1:<5	1.5	480	160	3.00	34.4	Enhanced	DR3-DQ2
5	1:50	76.6	1:<5	0.6	460	190	2.42	9.1	Enhanced	DR3-DQ2
6	1:200	16.6	1:<5	1.4	450	170	2.65	0	Enhanced	DR3-DQ2
7	1:500	51.0	1:<5	2.3	430	190	2.26	12.7	Enhanced	DR3-DQ2
8	1:<5	7.0	1:<5	0.5	550	200	2.75	1.4	Enhanced	DR3-DQ2
9	1:<5	5.7	1:<5	4.1	500	200	2.50	0.7	Normal	Neither DR3-DQ2 nor DR4-DQ8

\* EMA denotes IgA-class endomysial antibodies, tTG IgA-class tissue transglutaminase antibodies, VH villous height, and CrD crypt depth.

† A value above 5 U per milliliter was considered positive.

‡ A ratio of less than 2 is considered to indicate celiac disease.

§ The normal value is fewer than 3.5 cells per millimeter of epithelial tissue.

¶ The expression of HLA-DR is considered to be enhanced if it is expressed only in crypt cells or is expressed strongly in epithelium.



samples, the median endomysial antibody titer was 1:200 (range, 1:5 to 1:4000), and the median level of tissue transglutaminase antibodies was 70.6 U per milliliter (range, 4.8 to 169.7). Four subjects agreed to provide a second blood sample in 2001, and all four had increased levels of IgA-class endomysial antibodies (1:1000, 1:2000, 1:2000, and 1:4000) and IgA-class tissue transglutaminase antibodies (66.7, 89.0, 91.1, and 101 U per milliliter, respectively).

**HLA TYPING**

The distribution of the HLA genotypes associated with celiac disease in the 3627 subjects who underwent genotyping is shown in Table 2. Altogether 655 schoolchildren (18.1 percent) carried the HLA-DQA1\*05-DQB1\*02 (HLA-DR3-DQ2) haplotype, and 1411 (39 percent) carried either the HLA-DR3-DQ2 or the HLA-DQ-A1\*03-DQB1\*0302 (HLA-DR4-DQ8) haplotype. All but two of the antibody-positive subjects were positive for one or both of these haplotypes, irrespective of the findings on small-bowel biopsy (Fig. 1). The majority (85.7 percent) carried the HLA-DR3-DQ2 haplotype. There was no correlation between the various haplotypes and the severity of mucosal abnormalities.

**CLINICAL ASPECTS OF CELIAC DISEASE DETECTED BY SCREENING**

All 27 subjects with newly diagnosed, biopsy-proved celiac disease and the 9 subjects with normal muco-

sal architecture on small-bowel biopsy completed a questionnaire concerning symptoms related to celiac disease. None had another autoimmune disease. Four of the 27 patients with newly diagnosed celiac disease had an affected first-degree relative. When specifically asked, 11 reported recurrent abdominal pain and intermittent diarrhea or constipation, 1 reported tiredness, and 1 had skin symptoms. Ten subjects had clinically silent celiac disease. Two of the subjects with normal mucosal architecture on small-bowel biopsy reported abdominal pain.

**PREVALENCE OF CELIAC DISEASE**

Among the 3654 schoolchildren, 37 had biopsy-proven celiac disease, for a minimum prevalence of 1 case in 99 children (95 percent confidence interval, 1 in 146 to 1 in 75) (Fig. 1). The prevalence of subjects who were positive for both antibodies and HLA-DQ2 or DQ8 was 1 in 67 (95 percent confidence interval, 1 in 89 to 1 in 52).

**DISCUSSION**

This population-based screening study showed that celiac disease is underdiagnosed. Simple, noninvasive serologic tests detected celiac disease in schoolchildren who had not previously been given a diagnosis of the disease.

Clinical celiac disease represents the tip of the iceberg.<sup>17,18</sup> According to our findings, the prevalence of biopsy-proven celiac disease is at least

**Table 2. Prevalence of HLA-DR and DQ Genotypes Associated with Celiac Disease among the 3627 Schoolchildren Who Underwent Genotyping, Including the 56 Subjects Who Were Positive for Serum Endomysial or Tissue Transglutaminase Antibodies.**

HLA Genotype	All Children (N=3627)	Antibody-Positive Children (N=56)	Odds Ratio (95% CI)*	Positive Predictive Value†
	<i>no. (%)</i>			
DR3-DQ2 and any other haplotype except DR4-DQ8	575 (15.9)	46 (82.1)	26.45 (11.81-51.85)	8.00
DR4-DQ8 and any other haplotype except DR3-DQ2	756 (20.8)	6 (10.7)	0.45 (0.18-1.11)	0.79
DR3-DQ2 and DR4-DQ8	80 (2.2)	2 (3.6)	1.66 (0.02-7.03)	2.50
Other genotypes	2216 (61.1)	2 (3.6)‡	0.02 (0.01-0.09)	0.09

\* The odds ratio is the risk that a subject who carried a certain HLA genotype was positive for celiac disease-specific auto-antibodies. CI denotes confidence interval.

† The positive predictive value is the percentage of all subjects with a specific genotype who were positive for antibodies.

‡ One subject with confirmed celiac disease carried the HLA-DQB1\*02 allele (DR7 haplotype). The other was negative for both HLA-DQ2 and DQ8 (Subject 9 in Table 1).

1 case in 99 children. One explanation for this high prevalence might be that the population studied may have had an unusually high genetic risk of celiac disease. However, the fact that the distribution of HLA genotypes in this population corresponds to that in the Finnish population in general suggests that the study population was representative of the Finnish population as a whole. The true prevalence of celiac disease is likely to be even higher than 1 in 99. Not all our antibody-positive subjects consented to undergo biopsy, and some may have had a mucosal lesion or gluten-induced disease despite the presence of morphologically normal mucosa.<sup>19-21</sup> The presence of gluten-induced autoantibodies in subjects with initially normal villous architecture on small-bowel biopsy who are eating normal amounts of gluten predicts subsequent mucosal deterioration and celiac disease.<sup>22,23</sup> Five subjects who were initially positive for such autoantibodies were negative on follow-up testing, despite the fact that they were eating a normal, gluten-containing, diet. This finding might point to a minor variant of the natural history of celiac disease, in which gluten sensitivity fluctuates over time.<sup>24</sup> We have previously observed that intolerance to cereals is not a specific sign of celiac disease, and only 10 percent of patients who spontaneously report abdominal symptoms after consuming cereals are found to have celiac disease.<sup>25</sup>

An important finding of this study is that most antibody-positive subjects carried the HLA-DQ2 or DQ8 molecules that are characteristic of celiac disease.<sup>10</sup> The HLA-dependency of the production of autoantibodies associated with celiac disease has been reported in a study of the first-degree relatives of patients with celiac disease.<sup>3,26</sup> We found that the risk associated with the HLA-DR3-DQ2 haplotype was much greater than that associated with the HLA-DR4-DQ8 haplotype, and it is striking that a compound heterozygote (one who carried both haplotypes) had a lower risk than a person who carried only the HLA-DR3-DQ2 haplotype.

We used the IgA-class serum endomysial antibody test, which has been validated in Europe,<sup>27</sup> to identify untreated celiac disease, but the drawback of this test remains its subjectivity. After the identification of tissue transglutaminase as the target of celiac disease-specific autoantibodies in both rodent and primate tissues,<sup>28</sup> a non-observer-dependent enzyme-linked immunosorbent assay was developed to detect the antibodies.<sup>29-31</sup> We found that

this assay was as reliable and sensitive as the endomysial antibody test, which is based on indirect immunofluorescence.

Our findings suggest that these assays are a reliable and simple means of screening children for clinically silent celiac disease and genetically inherited gluten intolerance before symptoms or signs of chronic malabsorption develop. The crucial question now is whether population-based screening should be considered outside research programs. In our study, one third of the subjects in whom celiac disease was detected by screening had no symptoms and did not have any risk factors for celiac disease. In other clinical settings, even those in which serologic testing for celiac disease is routine, prevalence figures similar to ours are not obtained.<sup>32</sup> Nonetheless, whether treatment benefits clinically silent celiac disease should be thoroughly assessed. Undetected celiac disease increases the risk of several complications, including osteoporosis.<sup>1,2,18</sup> On the other hand, the lifelong need to follow a gluten-free diet may be burdensome, especially if the patient is asymptomatic.<sup>33</sup> Further studies of the effect of asymptomatic celiac disease, including cost-effectiveness evaluations, are needed before population-based screening studies can be recommended. However, given our finding that celiac disease is underdiagnosed, clinicians should keep in mind the complex clinical picture of the disease and have a high index of suspicion and a low threshold for ordering serologic tests.

In summary, we found that celiac disease was highly prevalent in an unselected population of schoolchildren and adolescents. The results of serum endomysial and tissue transglutaminase antibody tests were highly correlated with the HLA genotype. The tissue transglutaminase antibody test offers an objective means of detecting celiac disease early, when it is clinically silent.

The Celiac Disease Study Group is supported by grants from the Päivikki and Sakari Sohlberg Foundation, the Foundation of the Friends of the University Children's Hospitals in Finland, the Medical Research Fund of Tampere University Hospital, and the Academy of Finland Research Council for Health (73489). The study was also funded by the Commission of the European Communities in the form of the Research and Technology Development programs "Quality of Life and Management of Living Resources" (QLRT-1999-00037) and "Evaluation of the Prevalence of Celiac Disease and its Genetic Components in the European Population." The study does not necessarily reflect the current views or future policies of the Commission of European Communities.

Dr. Höpfl, Dr. Hansson, and Ms. Dahlbom are employees of Pharmacia Diagnostics. Pharmacia did not sponsor the study but did provide the immunoassays for the detection of tissue transglutaminase antibodies.

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