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Presence of high-risk HLA genotype is the most important individual risk factor for coeliac disease among at-risk relatives

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Summary

Background: Family screening has been advocated as a means to reduce the major underdiagnosis of coeliac disease. However, the precise risk of the disease in relatives and the impact of patient- and relative-related individual factors remain obscure.

Aims: To investigate the individual risk of coeliac disease among patients' relatives.

Methods: Altogether 2943 relatives of 624 index patients were assessed for the presence of previous coeliac disease diagnosis, or were screened for the disease. Coeliac disease-associated human leucocyte antigen (HLA) genotype was determined from all participants. The association between individual factors and new screening positivity was assessed by logistic regression.

Results: There were 229 previously diagnosed non-index relatives with coeliac disease and 2714 non-affected (2067 first-degree, 647 more distant) relatives. Of these 2714 relatives, 129 (4.8%) were screening-positive (first-degree 5.1%, second-degree 3.6%, more distant 3.5%). The combined prevalence of the previously diagnosed and now detected cases in relatives was 12.2% (6.3% clinically detected, 5.9% screen-detected). In univariate analysis, age <18 years at diagnosis (odds ratio 1.60, 95% CI 1.04-2.45) in index, and age 41-60 years (1.73, 1.10-2.73), being a sibling (1.65, 1.06-2.59) and having the high-risk genotype (3.22, 2.01-5.15 DQ2.5/2.5 or DQ2.5/2.2 vs other risk alleles) in relatives were associated with screening positivity. Only high-risk HLA remained significant (2.94, 1.80-4.78) in multivariable analysis.

Conclusions: Unrecognised coeliac disease was common among at-risk relatives even in a country with an active case-finding policy, and also in relatives more distant than first-degree. The presence of a high-risk genotype was the most important predictor for screening positivity. ClinicalTrials.gov identifier NCT03136731.

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1 | INTRODUCTION

Coeliac disease is a gluten-driven chronic gastrointestinal condition affecting individuals with a predisposing human leucocyte antigen HLA-DQ2 and/or HLA-DQ8 haplogenotype.[1] Estimated prevalence of the disease is up to 1%-3% in general population, but currently, most of the affected patients remain unrecognised.[2-5] This substantial underdiagnosis could be improved by active testing of either specific at-risk groups or even the whole population with serum coeliac autoantibodies. At present, most authorities do not recommend untargeted screening mainly because of inconsistent data on the prognosis of unrecognised coeliac disease at the population level.[6-9] However, particularly, the first-degree (FDR) and, sometimes, also second-degree (SDR) relatives of patients are often considered to have a sufficiently high disease risk to justify screening.[9-13]

Selecting an optimal screening strategy is complicated by a wide variation in the reported family risk[14-16] possibly due to different poorly defined patient- and relative-related individual factors, such as age at screening, gender, HLA haplogenotype and degree of consanquinity.[1,16-23] Limited data on these factors make optimal timing of screening, testing of other than FDRs, and the benefits of genetic risk stratification debatable.[13,15,16,23] The heterogenous and often small study cohorts and different diagnostic outcomes in earlier studies further hamper the interpretation of the results and emphasise the need for additional evidence.[14] Besides optimised implementation of the screenings, better understanding of the individual risk factors could provide novel insights into pathogenesis. In fact, precise risk stratification in coeliac disease is becoming increasingly important as we may be entering the era of primary preventions.[24,25]

Here we aimed to study the impact of various index patient- and relative-related factors on the risk of coeliac disease. This was established by serological and genetic testing of a large and well-defined cohort of relatives of previously diagnosed coeliac disease patients.

2 | METHODS

2.1 | Patients and study design

The study was conducted in Tampere University and Tampere University Hospital. The participants were enrolled by inviting children and adults with previously diagnosed coeliac disease and their close relatives to a voluntary family screening via newspaper announcements and local coeliac societies. The aim was to recruit particularly FDRs and SDRs of the index patients, although more distant relatives could also participate. All subjects reporting coeliac disease, or in the case of children, their parents/caregivers were interviewed systemically by a study nurse or a physician (File S1). Patient records were obtained with participants' permission in order to confirm the original diagnosis and other relevant medical data. Patients with lacking medical records or unclear diagnoses were excluded. Blood samples were collected from all study participants for the determination of coeliac disease serology and HLA type.

The first family member diagnosed was defined as the index if there was more than one coeliac disease patient in the same family. The degree of consanguinity between index patients and relatives was documented based on self-report by the participant or caregivers. The non-index family members were further divided into FDRs (siblings, parents and offspring), SDRs (grandparents, grandchildren, aunts, uncles, nieces, nephews and half-siblings) and more distant (first- and second-degree cousins, great-grandchildren, great-grandparents, great-uncles and great-aunts).[26] The screened relatives were considered to belong to a multiple-case family if they had ≥1 FDR or SDR in addition to the index previously diagnosed with coeliac disease. Families with neither confirmed index patient nor any non-coeliac relatives to screen were excluded, as were individuals found to be unrelated to or having an unclear relation to the index patient.

2.2 | Ethics

The study design and recruitment of the participants were approved by the Ethics Committee of Pirkanmaa Hospital District. The Declaration of Helsinki was followed. The participants were informed in advance of the purpose of the study and the significance of the screening results. All participants/caregivers provided written informed consent. The study is registered in ClinicalTrials.gov, identifier number NCT03136731.

2.3 | Clinical data

Demographic information was collected from all participants. In addition, age at diagnosis, severity of small-bowel mucosal damage[27] (partial-, subtotal- and total villous atrophy) as reported by the pathologists and the presence of dermatitis herpetiformis or possible autoimmune co-morbidity (eg type 1 diabetes, Sjögren's syndrome, Addison's disease) were recorded from the previously diagnosed coeliac disease patients. Possible symptoms preceding the diagnosis or screening were assessed from the previously diagnosed coeliac disease patients and new screening-positive relatives.

2.4 | Serological testing, genetics and diagnostic outcome

Serum endomysial (EmA) and tissue transglutaminase antibodies (TGA) were tested from all relatives without previous coeliac disease diagnoses. EmAs were measured by indirect immunofluorescence using the human umbilical cord as an antigen and considering titres 1: ≥5 positive.[28] An enzyme-linked immunosorbent assay (QUANTA Lite h-tTG IgA; INOVA Diagnostics) was used to test TGA, applying a cut-off >20 U/L for seropositivity.[29] IgG-class EmA and TGA were used only if IgA deficiency was suspected based on abnormal EmA staining pattern and low TGA.[30]

Genotyping for the coeliac disease-associated HLA alleles was performed using the SSPTM DQB1 low-resolution kit (Olerup SSP AB), DELFIA® Coeliac Disease Hybridization Assay Kit (PerkinElmer Life and Analytical Sciences, Wallac Oy) or tagging SNP approach.[31] The genotypes were categorised based on predisposing alleles for coeliac disease to high risk (A1*05-B1*0201/A1*05-B1*0201 [DQ2.5/2.5] or A1*05-B1*0201/A1*02-B1*0202 [DQ2.5/2.2]), intermediate risk (A1*05-B1*0201/X [DQ2.5/X], A1*05-B1*0201/A1*03-B1*0302 [DQ2.5/8], A1*02-B1*0202 [DQ2.2/2.2 and DQ2.2/X], A1*02-B1*0202/A1*03-B1*0302 [DQ2.2/8] and A1*03-B1*0302 [DQ8/8 and DQ8/X]) and low risk (DQ2/DQ8 negative).[32]

The main diagnostic outcome—considered to signify coeliac disease in the present study—was positivity for both TGA and EmA and the presence of the disease-associated HLA DQ2 and/or DQ8 haplotype.[23] The possible new seropositive family members were either recruited for prospective studies or received a referral to health care for possible additional investigations or follow-up outside the study protocol.

2.5 | Statistics

The results are given either as number of cases, percentages, medians with lower and upper quartiles or as odds ratios (OR) with 95% CIs. The FDRs were analysed both as a whole group and also separately (offspring, siblings, parents) and SDRs and more distant relatives as whole groups. Statistical significance of categorical variables was assessed by chi-square test and that of continuous variables by Mann-Whitney test, considering P values <0.05 significant. The association between index-related factors and positive screening outcomes was studied by setting the properties of the index as variables for each screened relative. The ORs for new seropositivity were then evaluated by binary logistic regression first in univariate analysis. The reference category was defined as the group with the greatest number of subjects. Next, statistically significant independent risk predictors were determined by multivariable binary logistic regression for characteristics significant in the univariate analysis. Three different models were applied for the multivariable analysis as follows: *Model 1* notifies the significant characteristics of the screened relative excluding HLA, *Model 2* the significant characteristics of both relative and index excluding HLA and *Model 3* the characteristics of *Model 2* and high- vs intermediate-risk HLA of the screened relative. Statistical analyses were performed using either SPSS Statistics for Windows (IBM Corp.) or Confidence Interval Analysis Program[33] as appropriate.

3 | RESULTS

Altogether 4155 subjects were enrolled (Figure 1). White North European origin was the only ethnic background reported. After applying the exclusion criteria, 624 index patients with coeliac disease and 2943 of their relatives were included. Among the relatives, there were altogether 229 previously diagnosed non-index coeliac disease patients in 152 multiple-case families (Figure 1), including 45 who were screen-detected. The characteristics of the index and non-index coeliac disease patients are shown in Table S1. The median age of the 2714 relatives without previous coeliac disease diagnosis was 36 (range 1-91) years and 55.5% were females. Altogether 2067 (76.2%) were FDRs (30.1% offspring, 28.9% siblings, 17.2% parents), 534 (19.7%) SDRs and 113 (4.2%) more distant relatives. The distribution of HLA risk alleles did not differ significantly either between men and women or between FDRs, SDRs and more distant relatives (data not shown).

Altogether 129 (4.8%) of the 2714 screened relatives without previously diagnosed coeliac disease were screening-positive (Figure 1), the prevalence being 5.1% in FDRs (siblings 6.5%, parents 4.7%, offspring 4.0%), 3.6% in SDRs and 3.5% in other relatives. The combined prevalence of the newly detected relatives and previous coeliac disease in non-index relatives was 12.2% (6.3% clinically detected, 5.9% screen-detected) as a whole and 12.5% in FDRs, 10.9% in SDRs and 12.8% in more distant relatives (Figure 1). Of the 2714 screened relatives, three had IgA deficiency and one EmA positive subject had negative (19 U/L) TGA. High-risk HLA haplogenotypes were more frequent in the newly detected screening-positive relatives than in screening-negative relatives, whereas the groups were comparable in demographic data, prevalence of multiple-case families and relation with the index (Table 1). The presence of screening positivity was not affected by sex (FDR: sisters 6.2% vs brothers 6.9%, $P = 0.670$; mothers 5.1% vs fathers 4.1%, $P = 0.591$; daughters 4.1% vs sons 4.3%, $P = 0.766$; SDR: women 4.1% vs men 2.9%, $P = 0.430$; more distant relatives: women 3.0% vs men 4.3%, $P = 1.000$). Clinical data were available from 87 of the new screening-positive relatives, of whom 62.1% reported experiencing possible coeliac disease-related symptoms before the study.

When the newly detected screening-positive FDRs (n = 106) and SDRs (n = 19) were compared, the former were older (median 42 vs 29 years, $P = 0.007$) and less often below 18 years of age (17.9% vs 44.4%, $P = 0.026$) and members of multiple-case families (20.8% vs 47.4%, $P = 0.020$), whereas there were no significant differences between the FDRs and SDRs in sex or distribution of HLA risk alleles (data not shown).

The highest frequencies of both previously diagnosed coeliac disease and screening positivity detected in the present study were seen in subjects aged between 41 and 50 years of age and the lowest frequencies in those older than 60 years (Figure 2). The overall prevalence among relatives was highest in siblings, and there was a trend for decreasing frequency of new screening positivity from siblings to more distant relatives, while the prevalence was distributed more equally among the previously diagnosed patients (Figure 3).

Age below 18 years at diagnosis in index patients and age between 41 and 60 years at screening, being a sibling, and carrying high-risk HLA alleles in relatives were significantly associated with

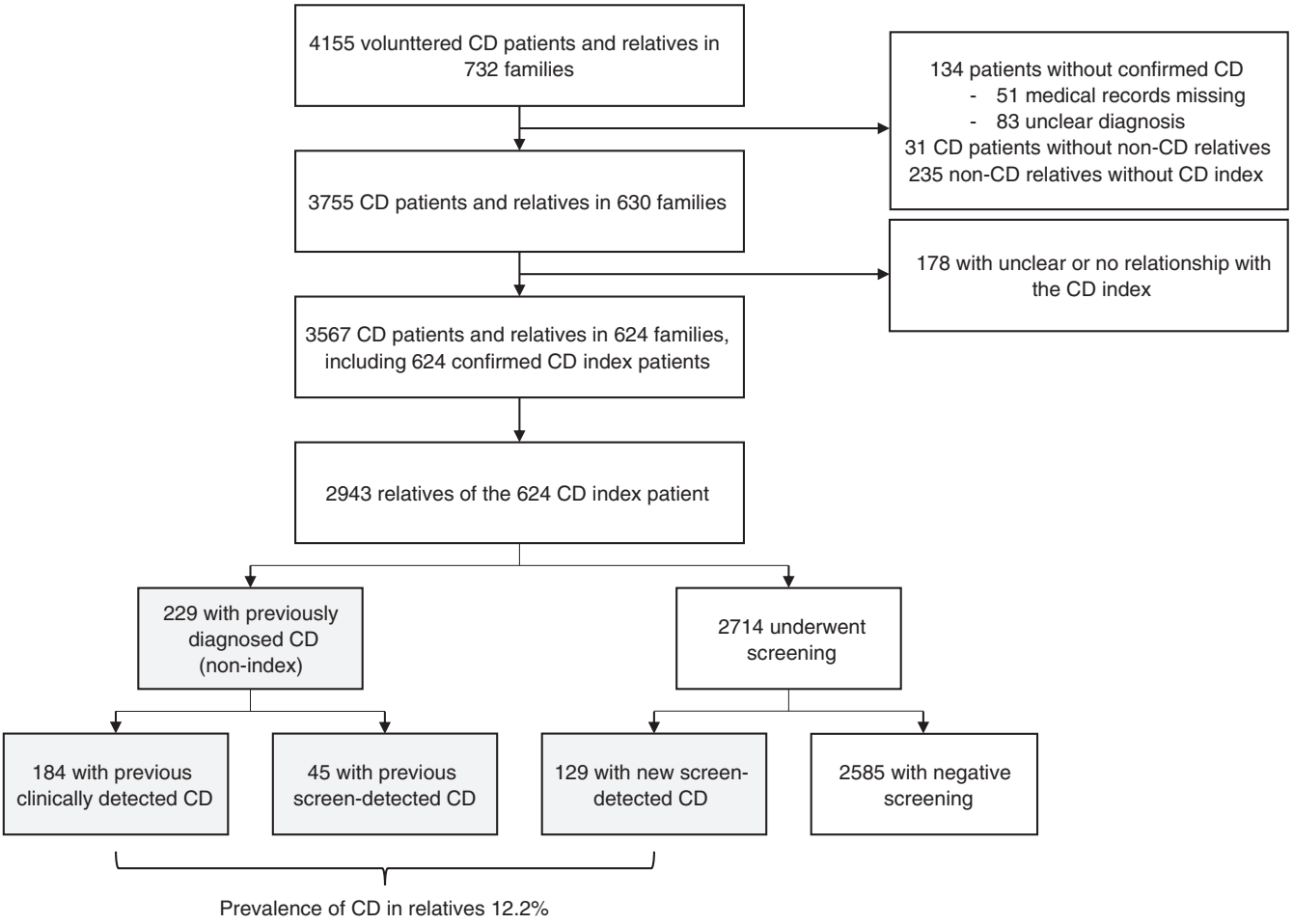


FIGURE 1 Flowchart of the study. CD, coeliac disease

screening positivity in univariate regression analysis (Table 2). In multivariable analysis, a significant association was observed with being a sibling in *Model 1* (notifying consanguinity and age at screening) and with the presence of high-risk HLA group in *Model 3* (notifying all characteristics significant in univariate analysis) (Table 2).

4 | DISCUSSION

We found unrecognised coeliac disease to be common (4.8%) among the index patients' relatives despite a high rate of previously diagnosed family members. The combined prevalence of all relatives detected either by clinical suspicion (6.3%) or by present and earlier screening (5.9%) was 12.2%, which is approximately five times our population-based estimate.[4] Most earlier studies have concentrated on FDRs, in whom prevalences have ranged from 1.3% to 44.1%.[14,34] This heterogeneity may be due to differences in the overall incidence of coeliac disease[1] and demographic features of the relatives. In fact, most earlier studies have been small and included only a few hundred screened FDRs.[14] Another salient factor may be the definition of screening positivity adopted. The seropositivity definition used here, providing that validated tests are used, may yield less biased results than duodenal biopsy, which is frequently declined, particularly by asymptomatic screening-positive subjects.[35,36] Serology is actually gaining a more important role in screening studies and even diagnosis, in spite of not yet being a universally accepted diagnostic criterion.[37-39] In the few relatively large studies with at least partially similar design, 4.2%-5.6% of FDRs have been screening-positive.[36,40,41] Closer to our findings, Rubio-Tapia et al[22] reported a prevalence of 16.4% in FDRs in which they—exceptionally—also counted the proportion (5.1%) of previous diagnoses in non-index family members.

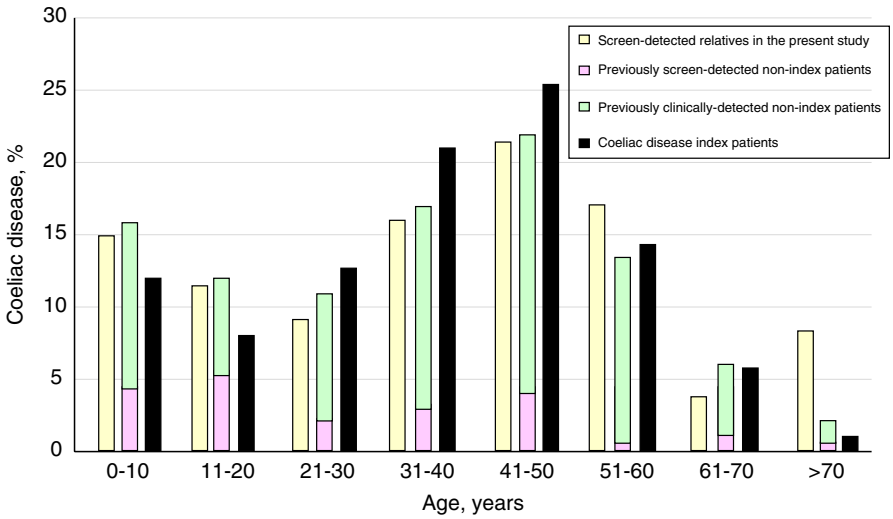
In detailed analysis, siblings had the highest frequency of seropositivity among the FDRs. Despite concurring with previous reports,[14] the differences between consanguinities were smaller here and not significant in multivariable analysis, possibly because confounding factors have not been similarly considered in earlier studies.[16,20] Likewise, although the SDRs and more distant relatives had less often newly detected seropositivity than the FDRs, the groups did not differ in either the combined prevalences or multivariable analysis. This might be due to similar HLA distribution within the groups and indicates that coeliac disease risk in other relatives than FDRs is higher than previously thought.[15,39,40] It must be noted, however, that seropositive SDRs belonged more often to multiple-case families than the FDRs, although this was not a significant risk

TABLE 1 Clinical characteristics and HLA distribution in 2714 at-risk relatives with positive[a] or negative screening outcome

	Positive screening, n = 129		Negative screening, n = 2585		
	n	%	n	%	*P* value
Age at screening, median (Q_1, Q_3), y	40 (20, 53)		36 (17, 55)		0.556
Age <18 y at screening	29	22.7	667	26.0	0.404
Women	72	55.8	1435	55.5	0.946
Member of multiple-case family[b]	35	27.1	631	24.4	0.483
Degree of consanguinity with index					
First-degree relatives	106	82.2	1961	75.9	0.260[c]
Sibling	51	48.1	732	37.3	0.073[d]
Offspring	33	31.1	783	39.9	
Parent	22	20.8	446	22.7	
Second-degree relatives[e]	19	14.7	515	19.9	
More distant relatives	4	3.1	109	4.2	
HLA risk group[f]					<0.001
High[g]	27	26.5	156	7.0	
Intermediate[h]	75	73.5	1394	62.3	
Low[i]	0	0	686	30.7	

[a]Positive endomysium and transglutaminase antibodies and presence of human leucocyte antigen (HLA) DQ2 and/or DQ8.
[b]At least two first- or second-degree relatives previously diagnosed with coeliac disease.
[c]First-degree vs second-degree vs more distant.
[d]Among first-degree relatives.
[e]Grandparent, grandchild, aunt, uncle, niece, nephew, half-sibling.
[f]Data missing from 376 screened relatives.
[g]DQ2.5 homozygotes and DQ2.5/2.2.
[h]DQ2.5 heterozygotes or DQ2.2 and/or DQ8 positive.
[i]DQ2 and DQ8 negative.

FIGURE 2 Age distribution at coeliac disease diagnosis in previously diagnosed index patients and non-index relatives with coeliac disease and current age of new screening-positive relatives



factor as such. However, the somewhat arbitrary classification of index in the multiple-case families according to the order of the coeliac disease diagnosis and the general homogeneity of Finnish population may have affected the analysis.[40] Of note, although evidence has been scant,[15] the American College of Gastroenterology recommends screening more distant relatives than FDRs,[13] and our findings give further support for this approach. However, additional studies on this issue are warranted.

Age at screening was not a significant factor associated with screening positivity in multivariable analysis, but the prevalence of affected cases increased from childhood to middle age, after which it decreased. The former is in line with the similar increase in the

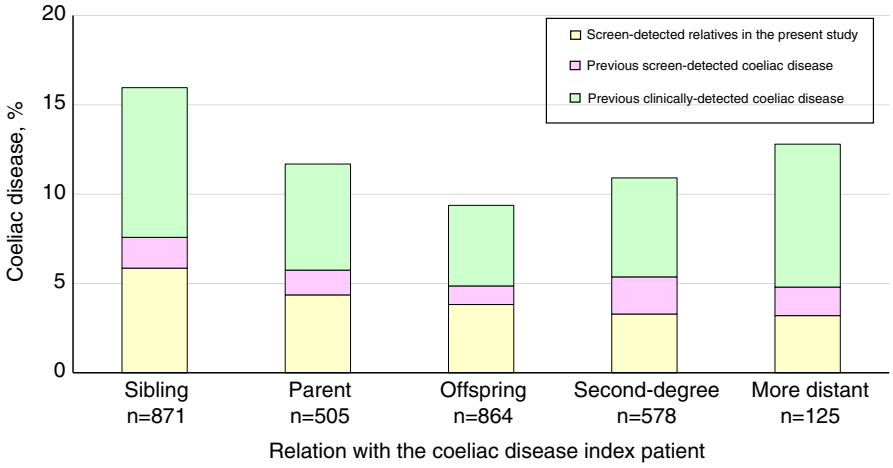


FIGURE 3 Percentage of coeliac disease in the relatives of index patients, divided according to degree of consanguinity and pathway leading to the diagnosis

TABLE 2 Logistic regression analysis of different index- and relative-related characteristics for positive screening outcome[a] in 2714 at-risk relatives

		Multivariable		
	Univariate	Model 1[b]	Model 2[c]	Model 3[d]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Index characteristics				
Age <18 y at diagnosis	1.60 (1.04-2.45)		1.34 (0.80-2.23)	1.41 (0.80-2.51)
Women	0.73 (0.49-1.07)			
High vs intermediate risk HLA	1.37 (0.89-2.12)			
Dermatitis herpetiformis	0.91 (0.55-1.52)			
Autoimmune co-morbidity	1.39 (0.86-2.23)			
TVA vs PVA/SVA	1.02 (0.68-1.62)			
Relative characteristics				
Age <18 y at screening	0.84 (0.55-1.28)			
Women	1.01 (0.71-1.45)			
High[e] vs intermediate[f] risk HLA	3.22 (2.01-5.15)			2.94 (1.80-4.78)
Consanguinity with index				
Offspring	1	1	1	1
Sibling	1.65 (1.06-2.59)	1.67 (1.00-2.79)	1.51 (0.88-2.58)	1.30 (0.71-2.35)
Parent	1.17 (0.67-2.03)	1.58 (0.82-3.05)	1.29 (0.61-2.72)	1.05 (0.45-2.44)
Second-degree relative	0.88 (0.49-1.57)	0.86 (0.48-1.55)	0.84 (0.46-1.52)	0.90 (0.46-1.76)
More distant relative	0.87 (0.30-2.51)	0.91 (0.31-2.62)	0.84 (0.29-1.27)	1.24 (0.41-3.76)
Multiple-case family	1.15 (0.77-1.72)			
Age at screening, years				
0-20	1	1	1	1
21-40	1.06 (0.65-1.74)	0.97 (0.58-1.61)	1.01 (0.60-1.69)	1.06 (0.59-1.91)
41-60	1.73 (1.10-2.73)	1.21 (0.71-2.07)	1.30 (0.75-2.26)	1.62 (0.88-2.97)
61-	0.70 (0.37-1.33)	0.48 (0.23-1.01)	0.57 (0.26-1.27)	0.51 (0.19-1.34)

Note: Characteristics notified in multivariable analysis were [b]consanguinity with the index and relative's age at screening; [c]model 1 and age of index <18 y at diagnosis; [d]model 2 and high vs intermediate risk HLA of relatives.

Abbreviations: OR, odds ratio; PVA, partial villous atrophy; SVA, subtotal villous atrophy; TVA, total villous atrophy.

[a]Positive endomysium and transglutaminase antibodies and presence of human leucocyte antigen (HLA) DQ2 and/or DQ8.

[e]DQ2.5 homozygotes and DQ2.5/2.2.

[f]DQ2.5 heterozygotes and DQ2.2 and/or DQ8 positive.

overall prevalence of coeliac disease by age,[4,17,42] whereas the later decrease could be caused by a higher frequency of seronegative disease among the elderly.[43] Another explanation could be increased mortality in unrecognised diseases, but this is debatable.[44-47] Although interpretation is complicated by temporal changes in the recognition and true prevalence of coeliac disease,[4,48] our results suggest that age should not affect the implementation of family screening. A more challenging issue is the follow-up of the seronegative relatives.[16,41] Further evidence is needed, but a previously reported peak in the seroconversion rate in early life and possible risk of permanent complications in growing children could justify more frequent re-testing in childhood.[18,49,50] Of note, somewhat contrary to some earlier reports,[4,14] sex had no significant effect here. This finding should be interpreted with some caution due to the high proportion of women among the index and non-index patients and possible gender differences in healthcare-seeking behavior.[51] On the other hand, there are also previous reports consistent with our findings[36] and it is possible that stronger HLA risk in family members independent of sex factors might contribute. Unfortunately, we were not able to study the role of symptoms but based on previous evidence they are a poor predictor of coeliac disease in subjects undergoing screening.[52-54]

The presence of a high-risk haplotype was the only factor significantly affecting (OR ~3) the risk of newly identified screening positivity in multivariable analysis and clearly overrode the other hypothesised factors. Similar findings have been reported in a few smaller studies.[16,20] In light of these findings, and that the high-risk haplotype may even increase the risk for complications,[55] determination of the HLA genotype could be beneficial, as it would make it possible to target screening most actively at those with high genetic risk and even to omit testing of low-risk relatives. It must, however, be realised that most of the affected relatives still carry the much more frequent intermediate-risk haplotypes and the majority of cases would thus be missed if only high-risk subjects were included. Although more studies are needed, the role of HLA risk group determination may be more useful in re-screening of initially seronegative relatives, since making a distinction between the high- and intermediate-risk HLA might help to target the possible re-testing, as also suggested by Wessels et al.[16] In the future, improved genetic score considering the additional contribution of non-HLA coeliac disease risk variants to disease risk of, as well as more precise stratification of the HLA-DQ alleles, might enable more precise screening protocols.[56-58] In any case, before a more specific genetic risk score is validated, serological testing of at least all FDRs after an index patient is diagnosed likely remains the simplest and most effective approach for the initial screening.

4.1 | Strengths and limitations

The main strengths of our study were the exceptionally large and well-defined cohort of index patients and their relatives, the meticulously collected family trees and the knowledge of various individual factors. Furthermore, the screening was conducted with well-validated serological tests, although only IgA class assays were systematically used. As a limitation, we had no exact data on those refusing to participate in the study or the individual symptoms or gluten consumption of the relatives. Furthermore, although largely as a whole, the study may still have been too small to reveal all significant associations in the regression analysis, and the high proportion of previous diagnoses—a sign of active case finding and at-risk group screening—further complicates interpretation of the results. It must also be noted that our participants were ethnically very homogeneous which, although beneficial in association analyses, for example, may overestimate the coeliac disease risk of more distant relatives than FDRs and limit the generalisability of the study.

4.2 | Conclusions

The prevalence of unrecognised coeliac disease was high in all ages and also in more distant than FDRs despite a high rate of previously diagnosed non-index relatives. Moreover, further supporting more active screening, the diagnostic yield was suboptimal even in a country with high coeliac disease awareness and broad healthcare coverage. The presence of the high-risk genotype is the most important predictor for coeliac disease and HLA determination could thus be useful to target serological screening of at-risk relatives.

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AUTHORSHIP

Guarantor of the article: KKu.

Author contributions: SP, KL, LK, HH, KKa and KKu designed the study. SP and HH were responsible for statistical analyses. PS, RT, KKa and KKu collected the data. SP and KKu drafted the manuscript and SP wrote the final version. KL, JC, LK, HH, PS, RT, KKa and KKu reviewed the paper for important intellectual content. All authors interpreted the results and approved the final draft submitted.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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