

## Research Article

# Cystic Fibrosis and Celiac Disease: Mere Coincidence?

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**Abstract**

**Aim:** An increased prevalence of celiac disease (CD) in cystic fibrosis (CF) has been discussed. The aim of this survey was to determine the prevalence of a genetic predisposition to CD in CF-patients compared to the general population.

**Methods:** Celiac serology and HLA-DQ2/-DQ8 screening was performed in 190 CF-patients at the CF-Center Cologne, Germany. Informed consent was obtained from all patients or caregivers.

**Results:** 62 (32.6 %) carried HLA-DQ2 and 41 (21.6 %) HLA-DQ8 compared to 32% HLA-DQ2 and 17 % HLA-DQ8 in the German population. 5 (2.6%) carried both and 82 (43.2 %) carried neither HLA-DQ2 nor -DQ8. Six CF-patients (3.1%) showed elevated anti-tTG-IgA and two were diagnosed with CD (1.1 %) (both HLA-DQ2 positive).

**Conclusion:** There is a higher prevalence of elevated CD serology in CF-patients (3.1% with elevated anti-tTG-IgA compared to 0.8 % in the general German population). The frequency of CD in our CF-population is 1.1 %, which is elevated to the general population. However, the frequency of HLA-DQ2 and -DQ8 is similar to the general German population. Therefore, CF could be a risk factor for elevated celiac serology and CD and could contribute to the development of CD.

**KEYNOTE**

In a CF-population 3.1 % had elevated anti-tTG-IgA compared to 0.8 % in the general German population and 1.1 % of the CF patients were diagnosed with CD. The prevalence of HLA-DQ2 and -DQ8 is similar in CF-patients compared to the general population. Therefore, CF could be a risk factor for elevated celiac serology and HLA-typing helps to discriminate mere positive serology from celiac disease.

**ABBREVIATIONS**

CD: Celiac Disease; CF: Cystic Fibrosis; Anti-DGP: Anti-Deamidated Gliadin Peptide; EMA: Endomysial Antibodies; HLA: Human Leukocyte Antigen; Anti-Ttg: Anti-Tissue Transglutaminase

**INTRODUCTION**

Cystic Fibrosis (CF) is the most common chronic genetic disease in Caucasians with a global prevalence of 0.74/10000 [1]. Current life expectancy has risen to an average of 38 years [2] and continues to rise.

Celiac disease (CD) is one of the most common lifelong disorders on a worldwide basis, and it is still underdiagnosed

[3]. A high prevalence in the general population (1 %) has been reported in Finland thought to be due to nutritional and environmental factors [4]. Using celiac screening with anti-TG-IgA Anderson et al. could even increase the prevalence of CD in an Australian population to 1.2 % in men and 1.9 % in women [5]. In the USA studies have shown that CD has a prevalence of approximately 0.8 % [5,6]. In the KiGGS study in Germany (12751 children between 1 and 17 years) 0.8 % showed elevated tTG-IgA and/ or tTG-IgG and the prevalence of CD (clinically and serologically, but no histologically) is reported to be 0.9 % [7]. It has also been shown that the prevalence of CD is substantially increasing [4].

Both CF and CD cause intestinal malabsorption in the majority of cases making it difficult to identify CD in CF patients [8]. The co-existence of both CF and CD has been published numerously [9,10]. Valletta et al. calculated a prevalence of 0.45 % of CD in 1100 Italian CF patients [11]. Fluge et al. performed systematic screening for CD in a Scandinavian cohort of 790 CF patients, calculating a prevalence of 1.2 % [12]. A recent study reported an incidence of even 2.13 % of CD among 230 Polish CF patients [8].

The diagnosis of CD is based on the presence of gluten-dependent symptoms, CD specific antibodies, HLA-DQ2 or

-DQ8 haplotypes and histological features [13]. Screening serum antibody tests, such as the anti-tissue transglutaminase (anti-tTG)-IgA, endomysial antibody (EMA)-IgA or the anti-deamidated gliadin peptide (anti-DGP)-IgA or -IgG tests, have excellent sensitivity and specificity rates. However, duodenal biopsies classified according to the Marsh criteria (intraepithelial lymphocyte infiltration, crypt cell hyperplasia and villous atrophy) are still the gold standard to confirm the diagnosis [13,14].

While gluten is a well known environmental factor, inherited genetic factors are also known for affecting disease susceptibility as seen in family and twin studies [15]. Among the genetic factors, the HLA genes have the greatest impact on the development of the disease [15]. Results from genetic linkage studies have shown that CD is strongly associated with HLA-DQ genes located on chromosome 6p21. The presence of genes coding for HLA-DQ2 (DQA1\*0501/DQB1\*0201) and -DQ8 (DQA1\*0301/DQB1\*0302) molecules of the HLA complex class II explains up to 40 % of the occurrence of CD in European populations [16]. It is hypothesized that HLA-DQ2 is more efficient than HLA-DQ8 in presenting gliadin to the immune system [17]. Therefore, the more severe forms of CD are marked by the HLA-DQ2 allele, especially in the homozygous condition [17]. The absence of these alleles is important for their high negative predictive value [18].

The aim of this survey was to evaluate the prevalence of elevated celiac serology and CD as well as the genotypes HLA-DQ2 and -DQ8 and to compare them to the general population in order to assess if CF is a risk factor for CD.

## PATIENTS AND METHODS

### Patients

HLA typing was performed and celiac serology was obtained in 190 CF patients aged between 0 and 68 years. The diagnosis CF was defined according to the CF guidelines [19]. The diagnosis of CD was established according to the guidelines of the ESPGHAN [13]. Informed consent was obtained from all patients or their caregivers.

### HLA-DQ2 and -DQ8 genotyping

All CF patients were genotyped for the expression of the HLA-DQ2 and -DQ8 heterodimers by DNA tests for the HLA-DQB1 and -DQA1\*0501 loci coded for the alpha and beta chain of the DQ molecule. Genomic DNA was extracted from whole blood (EZ1 DNA Blood 350 µl Kit, Qiagen Group). HLA genotyping was performed by the PCR-SSP-method (HLA-DQB1\*/DQA1\* Low Resolution CTS-PCR-SSP Tray Kit, Department of Transplantation Immunology, University Clinic Heidelberg, Germany).

### Serological tests

In all CF patients anti-tTG-IgA, anti-DGP-IgA and anti-DGP-IgG were measured by ELISA (anti-human-anti-tTG-IgA, anti-human-Gliadin (GAF-3X)-IgA and anti-human-Gliadin (GAF-3X)-IgG (Euroimmun AG, Luebeck, Germany). EMA-IgA was determined by indirect immunofluorescence using monkey liver as substrate (Euroimmun AG, Luebeck, Germany). Sera were diluted 1:10 in PBS-Tween, and the antigen-antibody complex was determined by fluorescein tagged anti-human-EMA-IgA (Euroimmun AG,

Luebeck, Germany) using fluorescence microscopy. Total IgA was determined by immunoturbidimetry using anti-human-IgA antibodies (Tinaquant IgA-2 test; Roche Diagnostics GmbH, Mannheim, Germany). The cut-off for anti-tTG-IgA was 20 RU/ml, for EMA-IgA >1:10, for anti-DGP-IgA and anti-DGP-IgG both 25 RU/ml. In case of an IgA-deficiency ( $\leq 0.3$  g/l below age 15,  $\leq 0.85$  g/l for women, and  $\leq 1$  g/l for men) anti-DGP-IgG testing was performed [13].

In patients with elevated anti-tTG-IgA an esophagogastroduodenoscopy was suggested. The histology of the duodenal biopsies (including the duodenal bulb) was classified according to the Marsh criteria [14].

## RESULTS

190 CF patients aged between 0 and 68 years (median 17 +/- 12 years) were examined. 100 (53 %) CF patients were female, 159 (84 %) were pancreatic insufficient. 62 (32,6 %) carry HLA-DQ2; 41 (21.6 %) HLA-DQ8 (cf. table 1). 82 (43,2%) carry neither HLA-DQ2 nor -DQ8 and 5 (2.6 %) carry both HLA-DQ2 and -DQ8.

14 CF patients (7.4 %) showed an abnormal celiac serology. Positive tTG-IgA was found in 6 CF patients (3.2 %); in 2 of them HLA-DQ2 and -DQ8 were negative and in 2 other patients duodenal histology was normal (Table 2). 2 CF patients were diagnosed with CD (Table 2); the frequency of CD in our CF population was 1:90 (1.1 %).

In 6 CF patients isolated elevated anti-DGP-IgA was detected (1 of them also had elevated anti-DGP-IgG). Since all patients were asymptomatic and 2 of them were HLA-DQ2/-DQ8 negative no duodenal biopsies were obtained (Table 2). One patient had isolated elevated EMA-IgA, but he remained asymptomatic and was HLA-DQ2/-DQ8 negative.

## DISCUSSION

We could demonstrate a higher prevalence of elevated celiac serology as well as a higher prevalence of CD in our CF-patient population compared to the general German population. 7.4 % of CF patients had abnormal celiac serology and 3.2 % of the CF-patients had elevated anti-tTG-IgA compared to 0.8 % in the general German population. 1.1 % or 1:90 of our CF patients were diagnosed with CD as the remaining CF patients did not show histological features of CD, were asymptomatic or HLA-DQ2/-DQ8 negative.

Prolonged delays in the diagnosis of CD are common as the symptoms of CD are difficult to differentiate from CF related malabsorption [3]. Therefore, we emphasize that serological screening for CD should be included in the initial diagnostic work-up of CF patients older than nine months of age or about three months after gluten has been introduced in the diet as well as in CF patients with persistent gastrointestinal symptoms [12]. As the prevalence of CD is steadily increasing [4] and as CD can develop later in life, it has been discussed that celiac serology should be tested on a regular basis. Anti-tTG-IgA is a sensitive screening test [20-22] and significantly correlates with histological a finding [23], which remains the gold standard to diagnose CD.

It has been discussed whether the co-existence of CF and CD

**Table 1:** Frequency of the distribution of HLA-DQ2 and -DQ8 in CF patients and in the general population (Germany) (www.allelefreqencies.net).

HLA-DQ allele	Number (percentage) in CF patients	Percentage in the general German population
2	62 (32.6 %)	32 %
8	41 (21.6 %)	17 %
2+8	5 (2.6 %)	
none	82 (43.2 %)	

**Abbreviations:** HLA: Human Leukocyte Antigen; CF: Cystic Fibrosis

**Table 2:** Characteristics of the CF-patients with elevated celiac serology.

Patient	CF-genotype	pancreatic status	anti-tTG-IgA (<20 RU/ml)	EMA-IgA (<1:10)	anti-DGP-IgA (<25 RU/ml)	anti-DGP-IgG (<25 RU/ml)	Marsh classification	HLA-DQ2	HLA-DQ8	other HLA-DQ
1	F508del/W1282X	PI	>200	-	>200	>200	IIIa	positive	negative	3
2	F508del/F508del	PI	>20000	1:10240	58	54	n.a.	positive	negative	7
3	F508del/F508del	PI	118	1:20	30	44	n.a.	<b>negative</b>	<b>negative</b>	7, 9
4	F508del/F508del	PI	44	1:10	41	57	0	positive	negative	n.a.
5	F508del/IVS12+1G>C	PI	44	1:10	negative	negative	0	negative	positive	n.a.
6	F508del/3849+10kBC>T	PS	80	negative	negative	negative	n.a.	<b>negative</b>	<b>negative</b>	5, 7
7	F508del/1677delTA	PI	negative	1:10	negative	negative	n.a.	<b>negative</b>	<b>negative</b>	5, 7
8	F508del/F508del	PI	negative	negative	55	negative	n.a.	positive	negative	5
9	F508del/G542X	PI	negative	negative	43	negative	n.a.	<b>negative</b>	<b>negative</b>	3, 6
10	F508del/F508del	PI	negative	negative	41	negative	n.a.	negative	positive	4
11	F508del/F508del	PI	negative	negative	39	negative	n.a.	positive	negative	6
12	F508del/F508del	PI	negative	negative	37	negative	n.a.	positive	positive	-
13	F508del/R1066C	PI	negative	negative	34	51	n.a.	<b>negative</b>	<b>negative</b>	5, 9
14	N1303K/Q220X	PI	negative	negative	33	negative	n.a.	<b>negative</b>	<b>negative</b>	n.a.

**Abbreviations:** CF: Cystic Fibrosis; Anti-tTg: Anti-Tissue Transglutaminase; EMA: Endomysial Antibodies; Anti-DGP: Anti-Deamidated Gliadin Peptide; HLA: Human Leukocyte Antigen; PI: Pancreatic Insufficient; PS: Pancreatic Sufficient; N.A., Not Available At the Moment Of The Survey.

is more than a mere coincidence. Walkowiak et al. and Fluge et al. could show that the incidence of CD in CF patients is significantly higher than in the general Polish and Scandinavian population, respectively [8,12]. The CD prevalence in this CF patient survey is 1.1 % and thus mildly elevated compared to the serological and clinical prevalence of CD in a German population of 0.9 % [7].

HLA typing is suggested to be a useful tool to exclude CD or make the diagnosis unlikely in the case of a negative test result for both HLA-DQ2 and -DQ8 [13]. In children with a strong clinical suspicion of CD and high specific celiac antibodies it is suggested to perform HLA typing to strengthen the diagnosis if duodenal biopsies are not performed [11]. Furthermore, HLA typing may be offered in asymptomatic individuals with CD associated conditions to select them for further CD specific antibody testing [13]. We could show that the frequency of HLA-DQ2 and -DQ8 in our CF population is similar to the general German population (Table 1) (32,6% carry HLA-DQ2 and 21,6 % carry HLA-DQ8 versus 32 % and 17 %, respectively, in the general German population) (www.allelefreqencies.net). Walkowiak *et al.* could show similar results with the prevalence of HLA-DQ2 being 24.8 % in the CF patient cohort compared to 28.5 % in the general Polish population and a prevalence of 9.6 % HLA-DQ8 compared to 10,0 % in the general population [8] confirming the ethnic influence on HLA-DQ frequencies.

Interestingly, CF is not listed as CD associated condition such as type 1 diabetes, Down syndrome, Turner Syndrome, Williams Syndrome, autoimmune thyroid disease, autoimmune liver disease, selective IgA deficiency and first-degree relatives with CD [2,13]. Clinical signs of CD might be incorrectly attributed to CF making it difficult to identify CD in CF patients, especially when they have significant pulmonary or gastrointestinal disease associated with malabsorption or in case of nonadherence to enzyme replacement therapy. Therefore, it is helpful to identify CF patients at risk for developing CD, because early diagnosis and treatment of CD may positively influence the course of CF. Regular celiac serology testing is a very reliable method to screen for CD, however, as the absence of HLA-DQ2 or -DQ8 has a very high negative predictive value, 43,2 % of our CF patients do not need regular testing.

The complications of CD typically occur after many years of disease and usually are observed in adults not adhering to a gluten free diet. There is an increased risk for the classic CD associated lymphoma (enteropathy associated T-cell lymphoma [EATL]), for adenocarcinoma of the small intestine and for gastrointestinal carcinoma [3]. Therefore, it is of further importance having identified CF patients at risk for CD being able

to screen regularly and treat early in order to reduce the risk of developing malignancies.

CD is a complex disease in which genetic factors interact with environmental factors inducing the disease [24]. It has been shown that the introduction of complimentary foods containing gluten before the age of four months and after the age of seven months increases the risk of developing CD in a population at risk [25]. Various hypotheses for the co-morbidity of CF and CD have been discussed in the literature, from mere coincidence to a higher antigen load of undigested gluten proteins in the intestinal mucosa due to exocrine pancreatic insufficiency [26]. In addition, malnutrition might contribute to additional mucosal damage causing increased intestinal permeability, which leads to increased exposure to gluten in the diet [8]. Furthermore, intestinal inflammation could influence intestinal permeability causing higher gluten exposition [27]. It has been shown that CF patients have increased intestinal inflammatory markers, including eosinophilic cationic protein and neutrophil elastase [28]. Viscous mucus production [29] as well as small intestinal bacterial overgrowth [30] could also play an important role for augmenting permeability for antigen presentation. All mechanisms mentioned above can induce an inappropriate immunological response to dietary gluten, which may explain elevated celiac serology without manifestation of CD in 12 of our patients. In these cases HLA typing is a very useful tool to discriminate CD patients from mere positive serology. Further studies are needed to characterize risk factors in genetically predisposed CF patients, which are involved in the development of CD.

## CONCLUSION

The prevalence of HLA-DQ2/-DQ8 in CF patients does not differ from the general German population. However, the prevalence of CD in CF patients (1.1 %) is higher than in the general German population (0.9 %). The coexistence of CF and CD may have a great impact on morbidity, quality of life, and treatment outcome. Therefore, all CF patients should be screened with celiac serology early in the course of disease. Furthermore, CF patients - especially those with positive celiac serology - could be assessed for HLA-DQ2 and -DQ8 to identify those at risk for developing CD. CF patients at risk should be screened with celiac serology on a regular basis. In conclusion, CF might be a risk factor for CD despite a similar genetic predisposition compared to the general population.

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