Genetic Factors Underlying Gluten-Sensitive Enteropathy

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Genetic epidemiology clearly has shown that there is a genetic predisposition to gluten-sensitive enteropathy (GSE), or celiac disease. The strong genetic component, as determined by the lambda sib (λ_s), has been calculated to lie in the range of 7.5 to 30, based on a 5% to 10% recurrence risk for siblings. Ninety-five percent of northern European patients with GSE carry a particular HLA-DQ $\alpha\beta$ heterodimer. Studies support the concept that the *HLA-DQ* gene acts as a dominant gene, and they also found that, in addition to HLA-DQ, a second locus within the major histocompatibility complex (MHC) is involved in the predisposition to GSE in the Dutch population. Genome scans conducted so far suggest that MHC and non-MHC loci collectively contribute to disease susceptibility. Since one, and probably even two, gene(s) from the MHC region itself determine at least 40% to 50% of the genetic predisposition to GSE, it is expected that the other loci each contribute only a little to the total genetic variation. The exact role of these additional genes (*ie*, whether they are involved in the initiation or the progression of the disease) remains to be determined.

Introduction

Gluten-sensitive enteropathy (GSE), or celiac disease, is a chronic disorder of the small intestine caused by a combination of genetic and environmental factors (*ie,* it is a multifactorial disorder). Gluten-sensitive enteropathy is the most common food intolerance in humans; prevalence is estimated to be as high as one in 150 to one in 300 in the Netherlands [1•,2••], which is comparable to other western European and North American populations [3•,4•,5,6]. Although GSE has been recognized for more than 2000 years [7], the observation that wheat is a major precipitating factor in GSE was made only 51 years ago by the Dutch pediatrician Dicke [8]. The disease-eliciting factor in wheat is the gluten molecule or, more specifically, its alcohol-soluble fraction, gliadin [9]. Withdrawal of gluten from the diet leads, in most cases, to a complete recovery from the disease symptoms. The strong role of gluten in the etiology of GSE makes it one of the major environmental risk factors for this disease. We now know that barley, rye, and presumably oats, contain proteins analogous to gluten and that GSE patients should also refrain from eating these grains [9].

Is has been known for some time that genetic factors play an important role in susceptibility to GSE [10,11]. The main evidence for this involvement comes from twin and family studies. One widely used measure of familial aggregation is the sibling recurrence risk ratio, which is defined as the ratio of disease manifestation in the siblings of GSE patients compared with GSE prevalence in the general population. This ratio is referred to as "lambda sib" (λ_s). Based on a 5% to 10% recurrence risk for siblings [12,13] and a population frequency of one in 150 to one in 300, the current estimates of λ_s for GSE range from 7.5 to 30, comparable with those of other multifactorial disorders. For example, the λ_s for primary biliary cirrhosis is around 10 [14], Behcet's disease is between 11.4 and 52.5 (in Turkey) [15], and ankylosing spondylitis is around 63 [16]. However, the discrepancy between the estimate for λ_s and that reported previously [11,17] is probably due to an underestimation of the true prevalence of GSE in the past. (Previous population frequencies ranged from 1 in 1000 to 1 in 2000 [18,19].) Nevertheless, if an equal number of "silent" GSE cases are present in both the general population and GSE families, the recurrence risk for siblings of GSE patients may also be higher than currently estimated. Hence, this may lead to slightly higher values for λ_s. Recent studies among siblings with GSE [20] showed that a high percentage of siblings (18%) who all were on a gluten-containing diet had an atrophic intestinal mucosa, and GSE was subsequently diagnosed. Because the authors could not submit all the siblings to intestinal biopsy, this figure may underestimate the real prevalence of the disease in family members.

Additional evidence for genetic factors in GSE comes from studies of twins. The concordance of GSE seen in monozygotic twins is approximately 70%, compared with approximately 20% in dizygotic twins [10]. In contrast, HLA-identical siblings show concordance rates of 30% to

50% [10]. Although these figures lead to large heritability estimates for GSE of 80 to 134 [21–23], it is clear that environmental factors also are involved.

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It has been suggested that λ_s values of 10 or larger are possible only in the case of 1) recessive inheritance of a single disease gene, 2) dominant inheritance of relatively rare (<5%) disease-susceptibility alleles, or 3) epistatic or multiplicative action of alleles from two or more different disease loci [24•]. Until recently, only one genetic factor had been identified for GSE, namely, *HLA-DQ* encoded by the major histocompatibility complex (MHC) genes *DQA1* and *DQB* on chromosome 6 [9]. Virtually all GSE patients carry a combination of *HLA-DQA1*0501* and *HLA-DQB1*02* alleles, in either the *cis* or the *trans* configuration, which together form the *HLA-DQ2* heterodimer. In northern European populations, *HLA-DQ2* is predominant in the *cis* configuration. Most of the HLA-DQ2-negative GSE patients carry the *HLA-DQA1*0301* and *HLA-DQB1*0302* alleles, which combine to form the HLA-DQ8 heterodimer. There is considerable evidence that HLA-DQ2 and HLA-DQ8 play a direct role in GSE [10]. It was shown that these molecules are able to bind certain gluten-derived peptides in vitro, resulting in activation of gluten-specific T cells. Moreover, HLA-DQ2– and HLA-DQ8–restricted T cells were isolated from small intestinal biopsies of GSE patients [25,26]. However, since only a small percentage of HLA-DQ2/8 carriers develop GSE, the relative risk associated with HLA-DQ is estimated to be 4 to 5 [27•]. The genotype relative risk γ associated with HLA-DQ2/8 is more than 100, a value much higher than the relative recurrence risk ratio. The high γ value is due to the fact that the risk of GSE is almost negligible in those without the susceptibility genotype. Still, no more than 40% of the genetics of GSE can be explained by *HLA-DQ*, suggesting that a small number of non-HLA-linked genes and/or other genes from the MHC region confer the stronger genetic risk.

An investigation using family data proposed that the involvement of two distinct and unlinked genes (an HLA- and a non-HLA-linked locus) is necessary for the etiology of GSE [28]. Prerequisites for developing GSE are homozygosity at the non-HLA-linked locus (*ie*, recessive inheritance) and participation of an independently inherited gene from the MHC system, acting in a dominant fashion. However, the problem with this original model was that the predicted population prevalence of about 1 in 320 did not agree with the observed frequency (which was much lower at that time) [28]. Although several studies agreed on recessivity at the non-HLA-linked locus, they differed with respect to dominance or recessivity at the HLA-linked locus [29].

A study on HLA in 39 families from western Ireland showed a significant excess of concordant sib pairs with two HLA haplotypes in common and an excess of discordant pairs with no haplotype in common. These results supported the hypothesis that dominance at the HLA-linked locus confers susceptibility to GSE [30].

Interestingly, almost all GSE patients carry the *HLA-DQ2* gene on the extended DR3-DQ2 haplotype [31,32], which extends to at least the HLA-DP locus [33,34] toward the centromere and to the HLA-A locus toward the telomere region of the short arm of chromosome 6 [35,36]. The MHC region is known to display extensive linkage disequilibrium due to a decreased recombination frequency. However, there also may be a selective pressure to maintain this long haplotype in GSE patients because additional alleles—present on this haplotype—confer susceptibility to the disease. The entire MHC region recently was sequenced and was shown to contain many genes that play a role in the immune response [37••] and that might be considered as candidate genes or modifiers of the HLA-DQ2 effect in GSE patients. Some of these genes have been studied quite extensively, *eg*, the *TNFA* gene coding for tumor necrosis factor-α (TNF-α) [28,38•,39,40]. However, the strong linkage disequilibrium displayed by this region can lead to spurious results. Specific alleles at various loci in this region show an increased frequency in GSE patients, not because those alleles enhance or complement the HLA-DQ2 risk, but simply because they are in linkage disequilibrium with HLA-DQ2 (and thus over-represented in GSE patients).

The Search for Additional Gluten-Sensitive Enteropathy Genes

Several difficulties arise in the mapping of additional genes predisposing to GSE. One is incomplete penetrance of the individual disease genes. Another is the fact that a combination of multiple genetic and environmental factors may influence the disease risk, with each factor making a modest contribution. Among the environmental factors (other than the dose of gluten [41]), a bacterial or viral infection that induces a T_H1-like immune response has been implicated as a trigger in GSE. However, GSE usually develops at a specific point in time, often early in life, when the intestinal immune system is confronted with gluten for the first time. Unless microbial infections always coincide with the introduction of gluten in the diet, is it difficult to understand why these events occur at that particular point in time. Nevertheless, it is interesting that the *HLA-DR53 (DRB4*0101)* allele has been found to be associated with susceptibility to GSE. Twenty synthetic peptides constituting most of the α-gliadin sequence were tested for their binding to various purified DR molecules. Recently, it was shown that HLA-DR53 molecules could bind selectively and with high affinity to α-gliadin–derived peptides [42•]. HLA-DR53 recognizes a *Mycobacterium leprae* protein antigen, suggesting an important role for this molecule in protection against intracellular infections, such as leprosy [43] and blinding trachoma [44]: an interaction between infec-

tious agents and the recognition of gliadin-derived peptides could be imagined. Alternatively, the HLA-DQ molecule itself may play a role in microbial protection by serving as a receptor for certain viruses [24•,25,26,45]. Taken together, these observations lead us to consider genetic factors underlying the inflammatory response as key players in the pathogenesis of GSE.

There currently are two approaches to investigating the genetics of multifactorial diseases. The first is the study of genetic polymorphisms in candidate genes. These can be either functional candidates (*ie,* genes known to play a role in the pathophysiology of the disease, *eg,* genes involved in the inflammatory response) or positional candidates (*ie,* genes located in a region known to be linked to the disease). In the absence of a functional candidate gene, the second approach is a systematic screening of the entire human genome. Both association and genome-wide screens can be performed by linkage analysis in families or by association analysis using a case-control design.

Candidate gene analyses

Genes involved in the regulation of the inflammatory response may be considered as functional candidates for GSE. Cytokines, for example, have been implicated as functional candidates for GSE for two reasons: 1) stable variations in the production rates of cytokines are known to exist between individuals [46–48] and 2) significant increases in cytokine production in response to infections or other proinflammatory stimuli are reproducible within both high and low producers [49]. The cytotoxic T-lymphocyte–associated gene (*CTLA4*), located on chromosome 2q33 in humans, also has been studied for its role in GSE. *CTLA4* encodes a cell surface molecule, which provides a negative signal for T-cell activation. However, the various association studies carried out so far show conflicting results. An association study among white, French patients and controls showed the presence of the A-allele of the exon 1 CTLA4 single-nucleotide polymorphism (A/G) at position 49 on 82.2% of chromosomes in GSE patients, compared with 65.8% in controls [50•]. However, this could not be confirmed in Italian and Tunisian populations [51•]. More recently, the effect of the gene region on chromosome 2q33 containing the *CD28* and *CTLA4* genes was investigated in a genetically homogeneous population consisting of 107 Swedish and Norwegian families with GSE. A significant association with preferential transmission of the A-allele of the exon 1 +49 polymorphism by using the transmission disequilibrium test (TDT) with GSE was observed. These data strongly indicate that the CTLA4 region is a susceptibility region in GSE [52•]. These results could not be replicated in the Dutch population [53•]. The tissue transglutaminase (*tTG*) gene also was proposed as an attractive candidate gene for GSE. It is currently believed that tTG deaminates glutamine residues into negatively charged glutamic acid in gluten peptides, thereby enhancing the binding affinity to HLA-DQ2/8 and increasing the T-cell response. The coding region of the *tTG* gene was sequenced in eight English patients, but no differences between patients and controls were found [54•]. Linkage and association analysis of the *tTG* gene in 147 Dutch GSE families also excluded this gene as a causative factor for GSE [55•]. Other functional candidate genes currently being studied by various groups include those coding for IL-12 and INF–γ.

Various loci from the MHC region also have been considered as functional candidates for GSE since the majority of the genes present on the extended GSE haplotype are expected to play a role in the immune response. However, the results obtained so far are difficult to interpret because of the extensive linkage disequilibrium displayed by this region. This makes it particularly difficult to distinguish a real association (with a true functional polymorphism) from an indirect association due to linkage disequilibrium between a certain marker allele (*ie,* a "hitchhiker") and a functional polymorphism nearby. There have been studies to circumvent this, for example, by studying transmission of alleles from *HLA-DQ2* homozygote parents. Polvi *et al.* [56] reasoned that if the *DPB1*0101* allele does not play a role in GSE, parents homozygous for *DQ2* (but heterozygous for *DPB1*) would show random transmission of the DQ2 haplotypes to their affected children. However, they observed in six informative families that the transmitted DQ2 haplotype always contained the *DPB1*0101* allele, suggesting that *DPB1*—or a very closely linked gene—is an independent risk factor for GSE. Using a similar approach, the so-called homozygous parent TDT, Lie *et al.* [57] found allele 3 of locus D6S2223 on the DR3 haplotypes to be associated with a reduced susceptibility to type 1 diabetes mellitus. A similar finding also was made for GSE [58]; allele 3 of D6S2223 on the DR3 haplotypes also was found to be a protective allele for GSE. These two studies suggest that a gene in the vicinity of D6S2223 is involved in the pathogenesis of both of these immune-mediated diseases [57,58].

Large numbers of homozygous DQ2 parents are hard to obtain, but a recent family-based study on type 1 diabetes showed that statistical approaches also can be developed to distinguish a true risk locus from a hitchhiker [59••]. A similar approach followed by van Belzen *et al.* [60•] for GSE implicated allele 10 of the *MICB* gene as a potential susceptibility allele. In combination with HLA-DQ2, both loci contribute equally to disease risk. The relative risk for GSE for carriers of the HLA-DQ2–MICB10 haplotype is almost 7. The *MICB10* allele very rarely is found on normal chromosomes (3%) and has a relative risk of 5.1, which is even higher than the relative risk of the *HLA-DQ2* allele. Another gene from the MHC region that has been studied quite intensively is the *TNFA* gene, but, unfortunately, the results are ambiguous [28,38•,39,40,61•].

A complete list of candidate genes studied for GSE is summarized in Table 1.

Table 1. Candidate gene studies in gluten-sensitive enteropathy

Study	Gene	Chromosome	Year	Association	Patients (*P*)/families (*F*)
Clot *et al.* [42•]	*HLA-DRB4 (DR53)*	6p21	1999	Yes	Italian and Tunisian *P*
Garrote *et al.* [62]			2000	No	9 HLA-DQ2 neg Spanish *P*
McManus *et al.* [40]	*TNF*	6p21	1996	Yes	52 *P*
McManus *et al.* [39]				No	25DQ2 neg *P*
Polvi *et al.* [38•]			1998	No	Finnish *F*
de la Concha *et al.* [61•]			2000	Yes	71 CD Spanish *F*
Djilali-Saiah *et al.* [50•]	*CTLA4*	2q33	1998	Yes	101 French *P*
Clot *et al.* [51•]			1999	No	Italian and Tunisian *F*
Holopainen *et al.* [63]	*CD28/CTLA4*		1999	Yes	69–100 Finnish *F*
Wijmenga *et al.* [53•]	*CTLA4*		2000	No	Dutch *F*
Grillo *et al.* [64]	*ELN17 3 (WS*)*	7q11.23	2000	No	74 Italian *F*
Aldersley *et al.* [54•]	*tTG*†	20q12	2000	No	8 *P*
van Belzen *et al.* [55•]			2000	No	Dutch *F*
van Belzen *et al.* [60•]	*MICB*	6p21	2000	Yes	Dutch *F*

*Williams syndrome—a genetic disorder due to a deletion in the 7q11.23 region that includes the elastin (ELN) gene.
†Tissue transglutaminase.
neg—negative.

Systematic genome-wide scans

In contrast to the candidate gene analysis, genome-wide scans are not based on prior knowledge regarding the disease process but allow the evaluation of large numbers of known and unknown genes. Linkage analysis reveals whether marker alleles of a series of anonymous DNA markers spanning all 22 autosomes segregate with a disease within a family. Linkage analysis is a powerful approach to localizing human disease genes, and it has been used successfully for a large number of monogenic diseases. The more classic approach of studying transmission of marker and disease alleles in large multigenerational families often is not feasible for more complex genetic disorders like GSE. The affected sib pair approach is a well-known alternative for mapping genes underlying complex diseases. In short, polymorphic markers are used to identify chromosomal regions in which affected pairs of siblings with GSE show more allele sharing than expected by chance. In the absence of a linked disease, gene siblings normally share 50% of their alleles. If a marker is located close to a disease susceptibility gene, siblings are expected to show more than 50% allele sharing for that particular marker. The advantage of the sib-pair design is that the inheritance pattern and the disease gene frequency and penetrance do not need to be specified (since these are usually unknown). A disadvantage of this design is the necessity of studying large numbers of sib pairs in order to obtain significant evidence for the observed excess of allele sharing. To date, a number of genome-wide scans have been conducted for GSE, most of which used affected sib pairs. However, the results of these studies (summarized in Table 2) are far from conclusive [65•–67•,68••,69•].

A genome scan performed on GSE sib pairs from western Ireland found that the most significant non-MHC locus was on chromosome 6p, about 30 cM telomeric from HLA. This locus had a multipoint maximum lod score of 4.66 (compared with 4.44 for HLA-DQ) and appeared to have a recessive mode of inheritance [65•]. The regions found in the Irish study—on chromosomes 6p23 (distinct from HLA), 6p12, 3q27, 5q33.3, 7q31.3, 11p11, 15q26, 19p13.3, 19q13.1, 19q13.4, and 22cen—were not replicated by linkage analysis in 28 UK families with GSE. The UK study showed excess sharing of marker alleles on chromosome 6p, but did not find support for a predisposing locus telomeric to HLA. Moreover, the only other confirmed linkage in the UK study was on chromosome 15q26, in a region corresponding to the localization of an insulin-dependent diabetes mellitus (IDDM) susceptibility locus (IDDM3). This UK study provided indirect support for IDDM3 as a candidate locus conferring susceptibility to GSE in some families [66•]. Another study in the United Kingdom examined the same loci using a pedigree-based linkage approach. In a cohort of 21 families with 60 affected individuals and 125 unaffected family members, no evidence was found to support the earlier findings [67•]. A genome-wide scan undertaken in Italy [68••] was performed on 110 affected sib pairs and their parents, using 281 polymorphic DNA markers. Systematic linkage analysis was first performed on 39 pairs in which both sibs had a symptomatic form of GSE. Replication of the regions of interest was then carried out on 71 additional pairs in which one sib had a symptomatic form and the other a silent form of GSE. In addition to the HLA locus, this study suggested the presence of a risk factor on the distal part of the long arm of chromosome 5 that was involved in both forms of GSE (symptomatic and silent). Furthermore, it was suggested that a risk locus on the distal part of the long arm of chromosome 11 possibly differentiates the two forms [66•]. More recently, a genome-wide search using 352 microsatellite markers in 60 Finnish families with GSE

Table 2. Human genome screening and linkage studies in families with several affected siblings with gluten-sensitive enteropathy*

Study	Chromosome region	Maximum lod score	Markers	Families, *n*	Year
Zhong *et al.* [65•]	6p23	4.66	328 ms	15 Irish	1996
	7q31.1	2.99			
	11p11	3.92			
	15q26	2.12			
	22 cen	2.69			
Houlston *et al.* [66•]	No conf 3, 5, 7, 11, 19, 22	—	23 ms†	28 UK	1997
	15q26 (IDDM3)	1.99		20 UK	
Brett *et al.* [67•]	No conf 7q31.3,11p11,15q26, 22 cen	—	11 ms (4 loci)	21 UK	1998
Greco *et al.* [68••]	6p21	3.5	254 généthon	103 Italian	1998
	5qter	1.8			
	11qter	1.8			
Liu *et al.* [69•]	6p	22	352 ms	60 Finnish	2000
	4	2.6			
	5qter	1.4			
	7	1.5			
	15	1–2			

*Linkage tested in accordance with the maximum-likelihood score. Suggested linkage lod score 2.2; significant linkage lod score 3.6 [70].
†Markers chosen were either identical to or mapped very close to the original markers used by Zhong *et al.* [65•].
conf—confirmation; ms—microsatellites.

found evidence of strong linkage at the HLA locus and lod scores ranging from 1 to 2.6 for markers on chromosomes 4, 5, 7, and 15 [69•]. The results of the genome-wide linkage studies performed so far support the polygenic nature of the disease: a large number of different gene loci seem to be involved. Since most genome scans were performed in different populations, population-specific genes may complicate the picture even further. However, it should be realized also that most of these genome scans were performed in a relatively small number of families or affected sib pairs; the power of the individual studies might have been insufficient to reveal all the different genes involved in the etiology of GSE [70]. In addition, there might have been differences in diagnostic criteria, which may have led to the mapping of diagnostic "subtypes."

Nevertheless, the genome scans conducted so far suggest that both MHC and non-MHC loci collectively contribute to disease susceptibility. The regions identified thus suggest the involvement of several chromosomes. Since one, and probably even two, gene(s) from the MHC region itself determine at least 40% to 50% of the genetic predisposition to GSE, it is expected that the other loci each contribute only a little to the total genetic variation. The exact role of these additional genes and how they exert their effect (either in the initiation or progression of the disease) remains to be determined.

Recently, Becker *et al.* [71••] compared the map locations of all non-MHC candidate loci from 23 published genome scans of (auto)immune diseases by using suggestive, significant, and highly significant linkage estimations. The autoimmune diseases reported in their study included multiple sclerosis, Crohn's disease, familial psoriasis, and human type 1 diabetes mellitus. Although there were marked differences among the different studies with respect to experimental design, patient populations, sample size, markers used, and calculations of results, the authors drew some interesting conclusions. First, it appeared that in almost all autoimmune/inflammatory diseases, no single gene exerts a predominant effect. Second, all the loci fall into 18 defined clusters; these clusters contain a large number of genes of known and unknown function, suggesting a possible shared genetic basis among different autoimmune diseases. These results also suggest that the genes found at these clusters likely are involved in primary or secondary regulation of the immune system. Hence, additional, and more unique, genes may be responsible for determining the disease specificity.

Present and Future of Genetic Studies in Gluten-Sensitive Enteropathy

It was stated recently that GSE is strongly heritable, oligogenic, but genetically complex [72•]. Genome-wide scans performed so far suggest a great number of linked loci, thereby confirming the complex genetic etiology of GSE. With respect to the central role of the immune system in the regulation of inflammation, most association studies in GSE have focused on genes that participate in the regulation of the immune and inflammatory response, including the CTLA4 and cytokine genes. So far, none of these genes was shown to be a major determinant of the disease. If they appear to play a role, they are neither necessary nor sufficient for the development of the disease. In certain genetic

backgrounds, however, these genes may be of significance for the development of disease. Nevertheless, the combined approach of linkage studies and candidate gene analysis is expected to reveal part of the underlying processes in GSE.

Roberton and Vyse [73] recently revised the genetics of systemic lupus erythematosus (SLE). Loci linked with lupus were mapped in lupus-prone mouse strains and in recently published studies in human families with multiple members affected with SLE. It was shown that more than 20 non-MHC loci are linked with mouse SLE. Nine non-MHC loci were corroborated in human SLE. Some of the mouse loci are syntenic with human loci, raising the tantalizing possibility of common susceptibility genes in mice and man [73]. A similar approach is currently being performed in inflammatory bowel disease. It seems that mouse models for different autoimmune disorders show, in part, linkage to the same chromosomal regions, suggesting that genes from these regions are implicated in the T_H1/T_H2 balance [74]. A systematic approach to studying the genes that control chronic inflammation and play a role in the etiology of autoimmune diseases remains high priority in our attempts to understand the disease pathogenesis in GSE. Such an approach also may offer new insights toward understanding the heterogeneity of the diseases. Detailed insight into the different genetic factors underlying GSE eventually may lead to a better prediction of the disease prognosis of individual patients and also may open up the possibility of selecting patients for specific immunomodulation therapy.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Csizmadia CG, Mearin ML, von Blomberg BM, *et al.*: **An iceberg of childhood coeliac disease in the Netherlands [letter].** *Lancet* 1999, **353:**813–814.

Gluten-sensitive enteropathy is frequently unrecognized and screening studies have shown a prevalence of one in 300 to one in 100 in the general population. The prevalence of unrecognized GSE in young children in the Netherlands was found to be one in 198.

2.•• Rostami K, Kerckhaert J, Tiemessen R, *et al.*: **Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice.** *Am J Gastroenterol* 1999, **94(4):**888–894.

This study showed that the specificity and positive predictive value of endomysial antibody (EMA) for celiac disease was excellent. The sensitivity of EMA, however, differed between celiac disease subgroups; in patients with total villous atrophy, the sensitivity of EMA was 100% (17/17). However, in patients with partial villous atrophy, the sensitivity of EMA was disappointing, only 31% (9/29).

3.• Hovdenak N, Hovlid E, Aksnes L, *et al.*: **High prevalence of asymptomatic coeliac disease in Norway: a study of blood donors.** *Eur J Gastroenterol Hepatol* 1999, **11(2):**185–187.

The study indicates a prevalence of one in 340 among asymptomatic and presumably healthy people.

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