SMART Approach

Closing the genetic gap in Celiac disease

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Overview

Celiac disease (CeD) is an immune-mediated enteropathy triggered by gluten in genetically susceptible individuals. It requires genetic variants in the HLA-DQA1/DQB1 locus (e.g. DQ2.5, DQ8), exposure to gluten, and additional factors like viruses to trigger the inflammatory process. Diagnosis combines symptoms (diarrhea, malabsorption, extraintestinal, like dermatitis herpetiformis), elevated tTG IgA, and biopsy showing villous atrophy/ intraepithelial lymphocytosis. Management: lifelong gluten-free diet, vitamin deficiency monitoring, which can be quite burdensome.

Genetic testing offers current and future insights. First, genetic testing of the HLA region can *exclude* CeD (>99% NPV if HLA-DQ2/8 negative), support diagnosis in equivocal cases or identify relatives of a CeD patient at risk for CeD. Second, over 40 non-HLA genetic loci have been identified that may predict severity and guide use of immunomodulators, but gaps in our understanding and application to clinical medicine of this genomic information remain.

This article highlights the author's approach to CeD in clinical practice including use of genetic testing in some cases

Introduction.

Celiac disease (CeD) is a relatively common immune-mediated gastrointestinal disorder whose prevalence varies between 0.7% and 1% depending on diagnostic methodology (e.g., serology vs biopsy) and dietary exposure to gluten (1,2). The genetics of CeD appear, at first sight, straightforward but are, in fact, much more complex.

Genetics of Celica Disease

HLA antigens.

The simple part relates to the strong association between CeD and certain human leukocyte antigen (HLA) haplotypes with almost all definitively diagnosed celiac patients being either HLA DQ2 or DQ8 positive (1-3). Furthermore, the HLA-DQ2.5 haplotype, comprised of the alleles HLA-DQA1*05 and HLA-DQB1*02, is the most common haplotype in CeD and is present in 90–95 % of all cases.

Homozygosity for HLA-DQ2.5 confers the highest risk of developing CeD, which is up to 30%, versus a 3% risk in heterozygous carriers. These genes encode alpha and beta chains which results in HLA-DQ heterodimers functioning as an antigen presenting receptor on the surface of antigen presenting cells. In this way, HLA-DQ2 and -DQ8 heterodimers present deamidated gluten peptides to CeD4+ T lymphocytes which initiates the immune response that ultimately leads to the characteristic inflammatory infiltrate and mucosal injury (3). However, the frequency of HLA-DQ2.5 in the general population is around 35%, a prevalence that is much higher than that of CeD and leads to two conclusions: first, HLA DQ2 testing is not useful in the diagnosis of celiac disease (1) and, second, other factors, whether genetic or environmental, must be necessary for disease expression.

The frequency, in CeD, of DQ8 positivity is lower at 10-20% and this haplotype is present in 11-12% of the general population, again limiting its diagnostic value. Taken together, between 30 and 40% of celiac patients will be positive for either HLA DQ2 or 8 or both. So, while the high prevalence of these haplotypes renders them unhelpful in diagnosis, their presence in almost all confirmed cases of CeD means that their absence virtually excludes the diagnosis (4). Haplotyping can also be used to exclude risk for the future development of CeD (4). Interestingly some other immune mediated diseases linked to CeD, such as type I diabetes and thyroiditis, may share these haplotypes (5). Other haplotypes such as HLA DQ7 have been associated with CeD but their overall prevalence is so low (<1%) that routine testing is not recommended (6).

Abbreviations used in this paper: CeD, Celiac disease; CVID, common variable immunodeficiency; GWAS, genome-wide association studies; HLA, human leukocyte antigen; miRNAs, microRNAs.

Key Words: Celiac, genetic, genetic testing, HLA-DQ2, HLA-DQ2.5, HLA-DQ8, gluten, gluten-free diet, duodenum, maldigestion, diarrhea, missing genetics, endoscopic biopsy.

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Relatives of patients with celiac disease.

While CeD is much more common among the first-degree relatives of known cases, its hereditability does not follow a simple dominant or recessive pattern, again indicating the likely contribution of other factors. Thus, approximately 10% of first-degree relatives and dizygotic twins will be affected (7) with concordance rate for monozygotic twins being only 49% in one study (8).

In summary, HLA haplotypes DQ2 and 8, though necessary for CeD to develop (8), do not by any means explain the emergence of the pathological phenotype or the hereditability of the disease. Are there other genetic factors? Evidence suggests that environmental factors are also relevant (8,9) but what are these?

Genetic modifiers of CeD.

To identify genetic variants that might explain this "genetic gap" A number of authors performed genome-wide association studies (GWAS) in CeD (10-12). In the most recent study among 52,342 adults screened for CeD, Alam and colleagues confirmed 41 previously associated loci (10,11) and identified 15 novel genetic variants. The mapped genes were most highly regulated in the small intestine, stomach and brain (12). Again, loci shared with other autoimmune disorders have been identified and genes involved in immune responses figured prominently (11,12). However, non-HLA region genetic factors seem to have a relatively low impact and certainly fall a long way short of closing the "genetic gap".

How I do it

Changing landscape of the CeD phenotype.

Over almost five decades in clinical medicine I have witnessed a dramatic shift in the clinical presentation of celiac disease – from the cachectic children with steatorrhea and nutritional deficiencies I saw as a medical student and resident to the adults I see today who present with, maybe, a little diarrhea or mild fatigue but are otherwise well and in whom CeD is sought because of sub-fertility, a low iron level, or other modest laboratory abnormalities, for example. The reasons for this dramatic shift in CeD presentation are not completely understood. We certainly cast our net a lot wider when searching for CeD nowadays and our task has been greatly simplified by the widespread availability of highly sensitive and specific antibody tests. We are also more aware of other causes of celiac-type enteropathy, including drug effects and disorders such as common variable immunodeficiency (CVID).

Do I biopsy everyone?

Yes! Two reasons, one historical and difficult to shake off and one more understandable.

First, I was brought up in GI with THE BIOPSY as the gold standard whether obtained via a Crosby capsule (in my early days) or through the endoscope; I find it difficult to shake this off, especially as one of my teachers was the late Michael N Marsh M.D. – of the Marsh classification.

Second, I like to have a baseline biopsy which becomes invaluable if the symptomatic response to a gluten-free diet is incomplete and you need an objective measure of response. My approach is to take 6 biopsies at various locations in the second and third part of the duodenum. While additional biopsies from the duodenal bulb have been advocated, my enthusiasm for this approach has been dimmed by frequent reports of non-specific "acid-peptic disease"-related duodenitis.

How I use genetic testing.

So, when do I have recourse to genetic testing? Here the answer is simple – never to make a diagnosis of celiac disease but occasionally to exclude the diagnosis when the data just do not add up. Relevant scenarios would include – negative serology but biopsy shows features consistent with CeD or positive serology but completely normal biopsy (remember, of course, that disease can be patchy). In situations such as these the diagnosis must be accurate – a diagnosis of CeD condemns the patient to a life-long and expensive gluten-free diet. A genetic test that demonstrates that the patient carries *neither* HLA-DQ2 or DQ-8 excludes CeD for all intents and purposes

Conclusions

Those who have labored for decades to define the pathophysiology of other chronic inflammatory are envious of celiac disease: a well-defined immune trigger, almost universal linkage with two HLA haplotypes and an excellent clinical response to removal of the offending dietary component. What's the problem? This lies in what I have referred to as the "genetic gap" as exemplified by the failure of the haplotypes to explain most of the risk for CeD and its heritability. GWAS studies have closed this gap but only a little and there is no doubt that host and environmental factors are also involved but their relative contributions remain to be defined. Could, as some have suggested (13), microRNAs (miRNAs) be involved given their reported roles in other autoimmune disorders?

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Contributions.

EMMQ, concepts, writing and approving the initial and final manuscript.

Conflicts of Interest.

The author declares that he has no competing interest.