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Celiac attack

By Tim Fulmer, Staff Writer

The only current treatment for celiac disease, a disorder of the small intestine that results from a hypersensitivity to ingested gluten, is lifelong adherence to a gluten-free diet. However, it is difficult to follow such a diet, and any slipups can result in damage to the small intestine. A paper published in *Nature Genetics* identifies genetic variation in eight different regions of the genome that could contribute to celiac disease pathophysiology.[1] The finding potentially opens up multiple avenues for developing compounds that target the genetic or biochemical events underlying the disease.

The majority of celiac patients have variations in the *HLA-DQ* gene, which codes for major histocompatibility complex class II DQ, a cell-surface receptor on antigen-presenting cells. The variants *HLA-DQ2* or *HLA-DQ8* are expressed in >85% of celiac disease patients. However, most individuals in the general population who express these variants never develop celiac disease, indicating that non-HLA genes must also contribute to the disorder.[2]

A 2007 genome-wide association study by David van Heel and colleagues took steps toward finding some of the other genes and showed significant risk for celiac disease was associated with variation in chromosomal regions that included the two interleukin genes *IL2* and *IL21* ($p=2\times10^{-7}$).[3]

The new study, also by van Heel and colleagues, included 2,421 celiac patients and 4,828 controls of western European descent. The patients had severe forms of the disease and presented with atrophy of the intestinal villi and antibodies against tissue transglutaminase, an enzyme that plays a role in enhancing the immunogenicity of gluten-derived peptides and also the predominant disease autoantigen.

Data from the association study replicated last year's findings and identified seven additional regions associated with significant risk for the disease ($p<5\times10^{-7}$ for all).

Moreover, six of the newly identified regions harbor genes potentially involved in either T helper cell response (*IL2*, *IL21*, *IL12A*, *IL18RAP*), inflammation (*SH2B3*, *CCR3*, *RGS-1*) or cytoskeletal function (*TAGAP*, *LPP*).

The authors estimated that the seven newly identified regions, taken together with the *IL2* and *IL21* region, contribute 3–4% to the heritability of celiac disease. "Adding this value to the known 35–40% contribution of the *HLA-DQ2* and *HLA-DQ8* regions means that nearly 50% of disease heritability has been explained," said van Heel, corresponding author. He is professor of gastrointestinal genetics at **Barts and the London School of Medicine and Dentistry**.

Chaitan Khosla, professor and chair of the Department of Chemical Engineering at **Stanford University** and an expert in celiac disease, said the *Nature Genetics* study "will likely open new doors to many hypothesis-driven studies aimed at understanding celiac disease pathogenesis."

On the other hand, Khosla told *SciBX*, "the therapeutic implications of the paper are less clear." Follow-up studies, including experiments that establish cause and effect relationships, will be required, he said.

Åsa Torinsson Naluai, a researcher in the Institute of Biomedicine and the Genomics and Bioinformatics Core Facilities at **University of Göteborg**, added that confirming the data using family-based association tests could "eliminate possible differences between cases and controls that are due to factors other than disease." Naluai and colleagues are actively involved in identifying susceptibility genes in celiac disease.[4]

van Heel agreed. "Although the data indicate a strong correlation between these regions and celiac disease, studies in still larger groups of patients are necessary to identify the precise causal variants from each of the regions and determine how these variants impact biochemical processes that contribute to celiac disease pathogenesis," he told *SciBX*.

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>
> ***—Satish Keshav, John Radcliffe Hospital***

Only a handful of companies are working in the field.

Francisco Leon, executive director of clinical development and medical affairs at **Alba Therapeutics Corp.**, said a functional clustering of genes identified in the *Nature Genetics* paper and in previous publications broadly corresponds to two aspects of celiac disease—host immune response and cytoskeletal function involved in the intestinal epithelial barrier.

The most advanced celiac compounds are aimed at preventing transport of gluten across the mucosal epithelium or preventing build-up of excess gluten in the gut lumen.

Alba's larazotide acetate (AT-1001) is a synthetic peptide that inhibits epithelial barrier dysfunction. Although the compound's receptor has yet to be identified, clinical research showed that larazotide produced dose-dependent reductions in small bowel intestinal permeability in celiac patients.[5]

Larazotide acetate is in a placebo-controlled, dose-ranging Phase IIb trial, and Alba plans to begin a second Phase IIb trial early this year. Last December, Alba granted **Shire plc** exclusive rights to commercialize larazotide acetate outside the U.S. and Japan.

Alvine Pharmaceuticals Inc. is aiming to eliminate gluten from the lumen of the upper small intestine before the peptide can cross the epithelium and trigger an immune response. The company's ALV003,

a combination of glutamine-specific cysteine protease and a proline-specific prolyl endopeptidase engineered to digest gluten, is in Phase I testing. Alvine declined to comment on the *Nature Genetics* paper.

Alba's Leon said a third approach for treating celiac disease, blocking immune response, "has long been presumed but not exploited in clinical trials" because of the inadequate risk and benefit ratio associated with using aggressive immunosuppressive therapies.

However, according to Satish Keshav, consultant gastroenterologist at the **John Radcliffe Hospital**, "it is striking that the great majority of regions linked to risk for celiac disease in the *Nature Genetics* paper are involved in the immune aspects of the disorder rather than the intestinal epithelium." This might suggest that targeting key players in the immune response will result in better clinical outcomes than intervening at the level of the intestinal cells, Keshav said.

This could be encouraging for **ChemoCentryx Inc.**, which began a placebo-controlled Phase II trial of Traficet-EN to treat celiac disease last October. The antagonist of CC chemokine receptor 9 targets T cells that selectively migrate to the digestive tract, where they cause inflammation that can lead to multiple gastrointestinal disorders.

Nexpep Pty. Ltd. is also targeting the immune system. However, rather than preventing gluten from triggering an immune response, the company is introducing gluten into the body to induce tolerance to the peptide.

Based on evidence that peptide-based vaccines can recover immunological tolerance through induction of immunoregulatory T cells (Tregs),[6,7] the company designed a gluten-based vaccine to treat and potentially prevent celiac disease.

Robert Anderson, Nexpep's CSO, CMO and laboratory head at the **Walter and Eliza Hall Institute**, told *SciBX,* "The strategy relies on the fact that immunoregulatory T cells respond to antigen at lower concentrations than effector T cells. Consequently, the optimal dose of vaccine antigen will induce Tregs to suppress downstream activation of gluten-reactive T cells rather than trigger an autoimmune response."

This year, Nexpep will begin a placebo-controlled, dose-escalation Phase Ib trial in 32 celiac patients. The vaccine contains a combination of peptides derived from gluten proteins found in wheat, rye and barley.

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COMPANIES AND INSTITUTIONS MENTIONED

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