Title: Celiac Disease *GeneReview* – Other Loci
Authors: Taylor AK, Lebwohl B, Snyder CA, Green PHR
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Other Gene Loci Associated with Celiac Disease

In addition to the *HLA-DQA1* and *HLA-DQB1* gene variants that predispose to celiac disease, there is large additional genetic influence on the development of the disorder. Identical twins have a concordance of 70% for celiac disease, which is much higher than that between HLA-identical sibs (30%) [Greco et al 2002].

Genome-wide association studies (GWAS) and follow up research have so far identified 41 non-HLA loci with an association to celiac disease [Garner et al 2014]. However, the 41 loci combined contribute to only approximately 5% of the disease risk. Much of the genetic risk remains unexplained. Interestingly, many of the risk loci being identified with respect to celiac are risk loci shared with other common, chronic, immune-mediated diseases [Dubois et al 2010].

Of the genes known to be associated with celiac disease, many are involved in the immune system or in intestinal permeability.

Genes involved in the immune system

- ***MICA* and *MICB*.** MHC class I chain-related genes (MIC) express non-conventional HLA class I molecules involved in the hypersensitive innate immune response in individuals with celiac disease (see Molecular Genetic Pathogenesis). MICA and MICB are stress molecules that are induced on the surface of enterocytes as a response to stress and inflammation. They are overexpressed in celiac disease in response to IL-15, a cytokine induced by exposure to gliadin (described in Guandalini et al [2014]).

  MICA binds to and upregulates NK (natural killer) receptors on intestinal epithelial cells (IELs) and leads to direct killing of enterocytes. Certain genetic variations in *MICA* and *MICB* contribute to the increased risk of celiac disease. In one study, specific allelic variants including *MICA*-A5.1 and *MICB*-CA24 conferred a fourfold increase in risk for celiac disease [Bolognesi et al 2003].

- **Interleukins IL-2 and IL-21.** IL-2, a cytokine involved in T-cell activation and proliferation, is secreted by antigen-stimulated T cells. IL-21, a T-cell-derived cytokine, enhances B, T, and NK (natural killer) cell proliferation and interferon-γ production. Both IL-2 and IL-21 are involved in mechanisms of other intestinal inflammatory diseases. A recent genome-wide association study identified sequence variants of *IL2* and *IL21* as risk factors for celiac disease [van Heel et al 2007].

- **CTLA4.** Cytotoxic T lymphocyte antigen-4 (CTLA-4) is expressed on the surface of helper T cells and inhibits T cell activation. The CTLA-4 CT60 A/G polymorphism is associated with celiac disease susceptibility [Song et al 2013].

Genes involved in intestinal permeability

- **Myosin IXB *(MY09B).*** *MYO9B* encodes a myosin molecule involved in actin remodeling of the cytoskeleton and tight junction assembly. A common sequence variant leads to enhanced epithelial permeability. In one report, individuals in the Dutch population homozygous for this variant had a 2.3 times greater risk for celiac disease than those without the variant [Monsuur et al 2005]. Wolters et al [2007] found an association of a single nucleotide variant of *MY09B* (rs7259292) with refractory celiac disease type II (RCDII) and enteropathy-associated T-cell lymphoma (EATL), complications of celiac disease with poor prognoses.

- **PARD3 and MAGI2.** These are tight junction genes and have been shown to have a weak association with celiac disease (reviewed in Romanos et al [2008]).

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