Abstract: Celiac disease (gluten-sensitive enteropathy) is a chronic inflammatory disease of the small intestine caused by an autoimmune response to ingestion of dietary gluten peptides. The only known treatment is to remove all gluten from the diet. Multiple studies have shown a strong association with human leukocyte antigen (HLA) as well as associations with 39 non-HLA risk loci. More than 90% of celiac disease cases express the HLA-DQ2 heterodimer and 5% express HLA-DQ8. The alleles that encode for HLA-DQ2 are HLA-DQA1*05 and HLA-DQB1*02 and HLA-DQ8 is encoded for by HLA-DQA1*03 and HLA-DQB1*0302. We have carried out a fine-scale association analysis of the 7.6 Mb extended major histocompatibility region (xMHC) on chromosome 6p using a set of 1,898 single nucleotide polymorphisms (SNPs) genotyped in 1,695 celiac disease cases and 520 controls from the U.S. The purpose of the analysis was to search for evidence of novel genetic determinants of celiac disease within the xMHC that are independent of the known high-risk HLA-DQ genotypes. Association analysis of all 1,898 SNPs was followed by SNP selection based on linkage disequilibrium and the rank-order of p-values in order to generate a minimal set of SNPs that appear to have independent effects on celiac disease risk. We present the genetic and statistical evidence for novel celiac disease susceptibility loci within the xMHC. Furthermore, the study highlights the analytical challenges and pitfalls of fine-scale association mapping within the xMHC, where known strong disease risk genotypes, complex linkage disequilibrium patterns and extensive genetic variation predominate.