Shared Genetic Risk Factors for Type 1 Diabetes and Celiac Disease

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Some families seem to be afflicted with more than their fair share of chronic illness — and sometimes more than one. Why does a particular disease develop in some members of a given family, whereas other members fall victim to apparently unrelated conditions? A simple model is that exposure to environmental risk factors in a genetically susceptible host leads to disease. A particular combination of genetic and environmental risk factors (together with chance and bad luck) leads to one disease, and another combination of factors leads to a different disease. Because members of the same family have exposure to many of the same genes and environmental factors, they are more likely to have a related set of diseases, assuming that the diseases share common risk factors. Although this model is appealing, few bona fide examples of such shared risk factors have been documented to date.

In this issue of the *Journal,* Smyth and colleagues provide an answer to the question of why some families seem to have an undue susceptibility to two autoimmune diseases: type 1 diabetes mellitus and celiac disease.[1] The study identified up to 15 genetic risk variants (or alleles) that contribute to both diseases and simultaneously demonstrated that 13 alleles were specific to one disease or the other. These observations support an emerging model of shared genetic risk factors for many common diseases, which may, in turn, identify previously unexpected biologic pathways that link diseases together.

In type 1 diabetes, which generally presents in childhood, the endocrine pancreas is attacked and destroyed by the body's immune system. Celiac disease is also autoimmune in nature, but it is the small intestinal mucosa that is attacked, leading to a chronic enteropathy caused by intolerance to gluten.

For years, epidemiologic data have suggested that the two autoimmune diseases share a common cause.[2] For example, the prevalence of celiac disease in children and adults with type 1 diabetes is higher than that in the general population by a factor of 5 to 10.[3] However, it has been difficult to identify shared risk factors, whether genetic or environmental, to explain the observed increase in risk.

When Smyth et al. initiated their study, unequivocal associations had already been drawn between 8 alleles and a risk of celiac disease and between 15 alleles and a risk of type 1 diabetes outside of the major histocompatibility complex (MHC) region.[4-6] However, only one allele had been shown to have a definitive association with both diseases (*SH2B3* on chromosome 12q24). In their study, Smyth et al. asked two simple questions: Do alleles that are associated with a risk of celiac disease also confer a risk of type 1 diabetes, and do alleles that are associated with a risk of type 1 diabetes also confer a risk of celiac disease?

The answer was a resounding yes. Of the eight previously validated celiac disease alleles, at least four also contributed to a risk of type 1 diabetes ($P<1.00\times10^{-4}$), with one other allele demonstrating a highly suggestive association ($P=0.002$). Of the 15 previously validated alleles conferring an increased risk of type 1 diabetes, at least 2 contributed to a risk of celiac disease ($P<1.00\times10^{-4}$), with 5 showing highly suggestive associations (ranging from $P=1.00\times10^{-4}$ to $P=0.05$). If subsequent studies confirm the highly suggestive associations, then about half the genetic risk alleles that have been identified to date are shared between the two diseases. It is worth noting that two of the six shared alleles actually had opposite effects in the two diseases: the minor alleles of *IL18RAP* on chromosome 2q12 and *TAGAP* on chromosome 6q25 conferred protection against type 1 diabetes but susceptibility to celiac disease. One can begin to imagine how combinations of these alleles lead to celiac disease and other combinations lead to type 1 diabetes, with multiple possible combinations for both diseases.

Another finding of the study was the identification of a new risk allele for both type 1 diabetes and celiac disease: a 32-bp insertion–deletion variant in the *CCR5* gene. This allele prevents the expression of the receptor on the surface of lymphocytes and other cells. Moreover, persons who

are homozygous for the mutant allele are highly resistant to infection with the human immunodeficiency virus (HIV).[7,8] That is, the mutant *CCR5* allele is protective against the development of both type 1 diabetes and celiac disease (two alleles are more protective than one allele) and also against HIV infection (but only when two copies of the mutant allele are inherited).

As this last observation highlights, the findings of Smyth et al. have implications beyond shared genetic causes of type 1 diabetes and celiac disease. Epidemiologic studies have suggested shared causes for other autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), an observation that is supported by genetic data (e.g., the *STAT4* gene[9]). But epidemiologic data have also linked diseases that might not be considered similar at first glance. For example, type 2 diabetes is associated with a reduced risk of prostate cancer.[10] Human genetics provides support for such epidemiologic observations, since an allele of *HNF1B* is associated with a risk of type 2 diabetes yet protection against prostate cancer.[11]

Finally, what are the clinical implications of this research? The most important implication is likely to be the ability to define biologic pathways, many of which are unexpected, that cause disease. Over many years, such insight may lead to the development of novel therapies to treat, prevent, or even cure disease. In theory, a more immediate clinical application would be to screen for the presence of risk alleles in asymptomatic patients with one disease (e.g., celiac disease) to predict whether another disease (e.g., type 1 diabetes) is likely to develop. However, such screening is controversial,[12] and the modest effect sizes of the alleles that were identified by Smyth et al. (an increase in risk of 10 to 20% per copy of the allele) are unlikely to add substantially to screening measures.

So there are indeed alleles that segregate in families and influence the risk of more than one disease. As we are beginning to understand, some combinations of alleles (together with environmental factors and chance) lead to celiac disease, and others lead to type 1 diabetes. There are going to be many combinations of these risk factors, and future research that is aimed at understanding these combinations and the underlying biologic pathways should lead to new insights into disease.

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1. Smyth DJ, Plagnol V, Walker NM, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 2008;359:2767-77.
2. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med 2002;346:180-8.
3. Saukkonen T, Savilahti E, Reijonen H, Ilonen J, Tuomilehto-Wolf E, Akerblom HK. Coeliac disease: frequent occurrence after clinical onset of insulin-dependent diabetes mellitus. Diabet Med 1996;13:464-70.
4. Hunt KA, Zhernakova A, Turner G, et al. Newly identified genetic risk variants for celiac disease related to the immune response. Nat Genet 2008;40:395-402.
5. van Heel DA, Franke L, Hunt KA, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet 2007;39:827-9.
6. Todd JA, Walker NM, Cooper JD, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 2007;39:857-64.
7. Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996;86:367-77.
8. Samson M, Libert F, Doranz BJ, et al. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 1996;382:722-5.
9. Remmers EF, Plenge RM, Lee AT, et al. *STAT4* and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med 2007;357:977-86.
10. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:2056-62.
11. Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007;39:977-83.
12. Freemark M, Levitsky LL. Screening for celiac disease in children with type 1 diabetes: two views of the controversy. Diabetes Care 2003;26:1932-9.