Comment on: Barker et al. (2008) Two Single Nucleotide Polymorphisms Identify the Highest-Risk Diabetes HLA Genotype: *Diabetes* 57:3152–3155, 2008

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Barker et al. (1) recently proposed two single nucleotide polymorphisms (SNPs) to identify the highest HLA risk for type 1 diabetes. The SNP rs7454108, genotyped by TaqMan probes, tags the HLA haplotype DR4-DQA1*0301-DQB1*0302 (DR4-DQ8), whereas rs2040410, genotyped using PCR–restriction enzyme digestion, tags DR3-DQA1*0501-DQB1*0201 (DR3-DQ2.5). The initial role of HLA in type 1 diabetes was indicated by association with the HLA-DR3 and -DR4 antigens, but, more recently, the *HLA-DQA1* and *-DQB1* genes were shown to be more strongly associated with this disease (2,3). Individuals homozygous for DR3-DQ2.5 or DR4-DQ8 have an increased risk of developing type 1 diabetes. The highest-risk genotype is formed by DR3-DQ2.5 and DR4-DQ8 haplotypes, probably due to transcomplementation between HLA-DQA1 and HLA-DQB1 alleles on homologous chromosomes (4,5).

We have recently proposed a set of tagging SNPs for detecting HLA risk alleles in celiac disease that can also be used for detecting type 1 diabetes risk (6). Among the known HLA variants that confer risk of celiac disease are the HLA-DQ2.5 and -DQ8 haplotypes, which are the same risk factors as those attributed to type 1 diabetes. Two tagging SNPs were used to predict these heterodimers, and both can be typed using TaqMan technology. The first, tagging HLA-DQ8, is the same SNP as that used by Barker et al. For HLA-DQ2.5, SNP rs2187668 was used, and it is a perfect proxy of SNP rs2040410 ($D' = 1$ and $r^2 = 1$). The tagging SNP rs2187668 showed an overall sensitivity of 1.000, a specificity of 0.999, and a positive predictive value of 0.998 (6). Using both tagging SNPs rs7454108 and rs2187668, it will be possible to predict whether an individual is homozygous DQ2.5, homozygous DQ8, or heterozygous DQ2.5/DQ8.

The TaqMan technique used in both studies (1,6) is cost-effective and time saving when applied to large research cohorts, high-risk groups, and population screening studies. This method can also be useful in other disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and other HLA DR3-DQ2– or DR4-DQ8–associated diseases.

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