may stratify because of other factors. For example, two samples of the same European American population could differ in age of the subjects at disease onset as a result of differing recruitment settings and strategies that differentially determine age at ascertainment (*e.g.*, pediatric versus adult clinic). To test the hypothesis that age at onset of disease might explain differential effects of *SUMO4* alleles on T1D risk, we carried out transmission disequilibrium testing separately in two sets of subjects with onset before or after 8 years of age. Again, the two populations had similar transmission ratios and were no different from each other (A:G = 146:135 versus 136:124; $\chi^2 = 0.007$; $P = 0.935$).

Age at onset is only one possible difference between the two European American groups in which opposing effects were reported. The two population samples could still differ by many other factors that depend on setting and context of recruitment, such as socioeconomic status, environment, nutrition and exposure to pathogens. If they are not due to some kind of technical or statistical artifact, the contradictory observations of Guo *et al.* and Bohren *et al.* might offer an opportunity to study the interactions of a complex disease locus with other loci or environmental or demographic factors of a magnitude sufficient to cause the effect of an allele to switch from predisposing to protective.

Finally, the possibility remains that these contradictory findings do not represent real associations and were the result of chance alone. As hundreds of laboratories are testing thousands of candidate variants, statistical adjustment for multiple hypothesis testing within each individual research group may not be sufficient protection against publication of spurious results. One solution to this problem may be the centralization of sample resources for each disease into a repository whose size will provide the required power to all researchers in the field, such as the Type 1 Diabetes Genetics Consortium, which aims to collect data from thousands of families with T1D for genetic studies.

**URLs.** Family Based Association Test software is available at http://www.biostat.harvard.edu/~fbat/fbat.htm. The Type 1 Diabetes Genetics Consortium is available online at http://www.t1dgc.org.

*Note: Supplementary information is available on the Nature Genetics website.*

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## To the editor:

In the August 2004 issue, Guo *et al.*[1] reported highly significant evidence for association between type 1 diabetes (T1D) and multiple polymorphisms in and near the gene *SUMO4*, encoding a new small ubiquitin-like modifier. The authors also showed that the 163A→G SNP (rs237025; resulting in the amino acid substitution M55V) influences immune responses by modulating NFκB activity. Both genetic and functional studies suggested that the 163G allele was associated with increased risk for T1D in a collection of European American families. But this conclusion was contradicted by the positive association with the 163A allele observed in the British data set studied by Guo *et al.*[1] and in a separate report[2] consisting primarily of a British data set. These inconsistent results raised the possibility that the reported association might be a false positive. Therefore, we tested this hypothesis in a Korean case-control cohort consisting of 386 individuals with T1D and 553 normal controls. The individuals with T1D were selected from the Korean Type 1 Diabetes Genetic Consortium[3,4] using the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[5]. All affected individuals were on insulin therapy upon hospital discharge. Their mean age was 13.4 years (range 0.3–23.0 years). The nondiabetic control subjects had no family history of diabetes and were selected from the same geographical area. Their mean age was 39.2 years (range 18.1–80.7 years). The GG and AG genotypes had a higher frequency in affected individuals (62.0%) than in controls (52.1%), with a relative risk of 1.5 ($P < 0.003$; **Supplementary Table 1** online). Our results, consistent with the report by Guo *et al.*[1], provide additional support for an association between the *SUMO4* 163A→G SNP and T1D. Given the association differences across populations, it will be important to investigate the *SUMO4*-T1D association in other populations to understand the mechanisms responsible for these population differences, including gene-gene and gene-environment interactions.

*Note: Supplementary information is available on the Nature Genetics website.*

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## In reply:

**We reported highly significant evidence for association between type 1 diabetes (T1D) and the gene *SUMO4* (ref. 1). Two studies presented in this issue (Smyth *et al.* and Qu *et al.*) do not support our initial observation, but a third study in the Korean population provides confirmatory evidence (Park *et al.*). Such discrepant associations have been reported for many complex diseases, including T1D. The discrepancies may be caused by genotyping errors, random variation due to small sample size, spurious association, genetic heterogeneity or population differences in gene-gene and gene-environment interactions.**

**We ruled out genotyping errors by regenotyping a subset of the samples.**