# Comment on: Chang et al. (2007) Association Study of the Genetic Polymorphisms of the Transcription Factor 7-like 2 (*TCF7L2*) Gene and Type 2 Diabetes in the Chinese Population: *Diabetes* 56:2631–2637

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We read with interest the article by Chang et al. (1), who were the first group to report a novel allelic association (rs290487) of the TCF7L2 gene with type 2 diabetes in the Han Chinese population (1). The link between the TCF7L2 gene and type 2 diabetes in Caucasians was first reported by deCODE genetics through the fine-mapping of a previously identified suggestive linkage region on chromosome 10q. Two highly significant single nucleotide polymorphisms (SNPs), rs12255372 T-allele and rs7903146 T-allele, were reported to be in strong linkage disequilibrium with the microsatellite DG10S478. Therefore, the deCODE genetics authors recommended that these two SNPs be genotyped in replication studies (2). Although genetic association studies are commonly plagued by a lack of reproducibility (3), the link between the TCF7L2 gene and type 2 diabetes was successfully replicated in more than 25 studies. This represents the most robust association found thus far in genetic association studies of complex diseases. The association was consistently observed across different populations of diverse genetic backgrounds including Asians, namely, Indians and Japanese (4), and now, by Chang et al., in the Han Chinese population.

The replication study by Chang et al. is commendable because instead of testing just the two strongly associated SNPs reported in the original study, they chose to thoroughly interrogate the candidate gene by genotyping thirteen tagging SNPs. These tagging SNPs captured >90% of the haplotypes for all of the SNPs with minor allele frequencies >20% across the TCF7L2 gene. The work by Chang et al. demonstrates proof of concept for the "gene-based approach" (5), in which all of the common genetic variants within the candidate gene are considered in replication studies. If their replication study had been confined to the two previously reported SNPs, they would have failed to detect the association between the TCF7L2 gene and type 2 diabetes because rs7903146 and rs12255372 T-alleles are rare and not associated with type 2 diabetes in the Han Chinese. This lack of association is probably due to inadequate statistical power to detect these two SNPs with relatively low allele frequencies (<5%). Their thorough interrogation of the entire candidate gene resulted in identifying a novel allelic association (rs290487 C-allele and type 2 diabetes). This allele seems to be particularly relevant in the Han Chinese population, as the minor allele frequency is ~40% and contributes greatly in population-attributable risk.

The gene-based approach, which captures all potential causal alleles, is advantageous when replication studies are conducted in populations different from those in the original study. Chang et al.'s study and others demonstrate that different genetic variants in the TCF7L2 gene are associated with risk of type 2 diabetes in different populations (6). To conclude, we argue that the gene-based approach should be encouraged in replication studies. As demonstrated by Chang et al., while it is imperative to validate the markers of interest in the deCODE genetics study, further studies will become more valuable when tagging SNPs are identified based on the linkage disequilibrium pattern in that particular population. The new identification of tagging SNPs is a necessary precursor to capturing other genetic polymorphisms in the population of interest.

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