Comment on: Marquez et al. Low-Frequency Variants in *HMGA1* Are Not Associated With Type 2 Diabetes Risk. Diabetes 2012;61:524–530

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We read with interest the article in *Diabetes* by Marquez et al. (1) that followed a recent abstract from this group (2) in which it reported that *HMGA1* gene variants were associated with type 2 diabetes (T2D). It is surprising, therefore, that the same authors now conclude the opposite (1). We have described four functional *HMGA1* variants that were associated with T2D in ~10% of 3,278 Italian patients (3) and confirmed this finding in two other populations—U.S. and French (3).

We have no explanation as to why the Marquez group does not agree with itself. There are several explanations, however, for the discrepancies between our studies and the results of Marquez et al. (1).

1. Marquez et al. (1) genotyped French individuals without intensive screening and/or interviews of control subjects. Because a large percentage of the nondiabetic population has the genetic potential to develop T2D, it is difficult to exclude the prediabetic subjects with insulin resistance from the control subjects without extensive screening. In our study (3), we included two Italian control groups. The first encompassed 2,544 interviewed control subjects; no individuals or family members had a history of T2D or related conditions (hypertension, hyperlipidemia, or premature cardiovascular disease). The prevalence of the c.136–14_136–13insC variant (the one now evaluated by Marquez et al.) was 7.23% in patients; only 0.43% in control subjects. The second control group included 784 unrelated, healthy, "non-interviewed" individuals; the prevalence of the variant was 3.32%. This second group proved that interviews are needed to screen out prediabetics in T2D gene studies. Thus, the discordant results of Marquez et al. (1) may have been due in part to their use of unscreened control subjects.

2. In our work (3), genomic DNA was either directly sequenced or analyzed for specific *HMGA1* mutations using TaqMan allelic discrimination (and the TaqMan technique confirmed by direct sequencing). Genotyping by Marquez et al. (1) was by high-resolution melting (HRM) only. HRM is less specific (4). Thus the discordant results reported by Marquez et al. (1) may have also been due to less accurate genotyping.

3. We found that decreased HMGA1 protein expression correlated with *HMGA1* variants in the same individuals that underwent genetic analysis. Marquez et al. (1) did not examine HMGA1 protein expression in their French patients. Rather, for inexplicable reasons, they measured mRNA abundance in a Scandinavian population with different origins and genetic background (1).

Despite these methodological flaws, Marquez et al. (1) found that the association of variant c.136–14_136–13insC with T2D was close to significance ($P = 0.06$). The reported odds ratio of 1.49 is relatively high compared with other genes associated with T2D. We believe that *HMGA1* is an important gene in the development of T2D. The studies of Marquez et al. (1) are important only because they highlight the pitfalls that can occur when investigating genes for T2D.

ADDENDUM

While the article was under revision, a related study was published by Liu et al. (5).

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