Editorial

Do Genes Determine Our Health? 
Implications for Designing Lifestyle Interventions and Drug Trials

Jennifer Wessel, PhD, MPH; David Marrero, PhD

Belalcazar et al\textsuperscript{1} exploited a genetic variant (L446P)\textsuperscript{2} in the glucokinase regulatory (\textit{GCKR}) gene, known to have inverse cardiometabolic effects, to investigate whether the effect of the 446L allele can be attenuated by an intensive lifestyle intervention (ILI) in the Look Action for Health in Diabetes (AHEAD) trial.\textsuperscript{3} Participants of Look AHEAD exhibited high adherence to the ILI, which demonstrated the success of an intensive lifestyle by significant weight loss,\textsuperscript{4} improved diabetes mellitus control,\textsuperscript{5} and reduced C-reactive protein (CRP) and triglyceride levels\textsuperscript{6} compared with usual care participants. The authors evaluated the interaction of the common variant in \textit{GCKR} to treatment assignment and triglyceride or CRP levels in participants with type 2 diabetes mellitus (T2DM) and unfavorable metabolic profiles. In 3214 participants with triglyceride and 1411 with CRP levels, the \textit{GCKR} 446L allele showed no benefit of participating in the ILI intervention on lowering triglyceride or CRP levels at the 1-year follow-up (49% randomized to ILI and 51% to usual care).

The 2 studies are similar by several epidemiological measures, for example, sample size, sex, and ethnicity; however, 1 primary difference in the design of the 2 trials is diabetes mellitus status. The Diabetes Prevention Program enrolled participants with impaired glucose tolerance while Look AHEAD participants were only eligible if they had T2DM at baseline. This could partially explain the difference in results reported by Belalcazar et al\textsuperscript{1} and Pollin et al.\textsuperscript{7} The increased glucokinase activity from 446L cannot be compensated in a diabetic state of decreased insulin secretion, and elevated glucose and triglyceride; whereas in a normoglycemic state increased glucokinase activity can still be modulated by weight loss through improved diet and exercise. Furthermore, studies assessing genetic risk scores containing \textit{GCKR} P446L and interactions (or subgroup analyses) associated with T2DM risk have reported stronger effects in younger (<50 years)\textsuperscript{16,17} and leaner (<25 or 25 to <30 versus ≥30 kg/m\textsuperscript{2})\textsuperscript{18} individuals. The average age (59.0 years) and body mass index (36.2 versus 34.0 kg/m\textsuperscript{2}) of participants at baseline were higher in Look AHEAD compared with the Diabetes Prevention Program, respectively.

The work by Belalcazar et al\textsuperscript{1} is intriguing and further contributes to the all-important understanding of gene–lifestyle interactions. Taking advantage of existing intervention and observational studies, their genotyped participants serves as a virtual clinical trial to efficiently gather evidence for the
potential adverse affects during drug development or modifying lifestyle to blunt the effects of our genes. Furthermore, these results can be used to inform the design of future trials. More work will need to be done to confirm the gene–lifestyle interaction on cardiometabolic outcomes in other studies and to further elucidate the in vivo effects of GCKR Pro446Leu polymorphism.

Disclosures
None.

References
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Jennifer Wessel and David Marrero

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