

## Genetics of Type 2 Diabetes

Type 2 diabetes (T2D) is a disease in which insulin is abnormally secreted or does not act correctly, leading to elevated blood glucose.<sup>1</sup> Over time, elevated glucose levels can lead to multiple organ damage. Diabetes is the leading cause of chronic renal failure, adult blindness, and limb amputation, and is a major risk factor for heart disease, stroke, and birth defects.<sup>2</sup> T2D accounts for more than 90% of diabetes in the US and worldwide.<sup>2</sup> As of 2005, it was estimated that 7% of the US population had diabetes, including those who had not yet been diagnosed.<sup>1</sup> The prevalence has increased in children and adolescents, likely due in part to an increase in obesity.<sup>1</sup>

T2D is believed to be a multi-factorial disease, i.e., it is influenced by both genetic and environmental factors. People with a family history of the disease are at higher risk of developing it themselves since they share genetic background and likely share similar environments. It has been estimated that 30%-70% of T2D risk can be attributed to genetics, with multiple genes involved and different combinations of genes playing roles in different subsets of individuals.<sup>2</sup> It is not yet known how many genes are involved or how much control each exerts over the development of the disease, but recent research has identified a number of promising candidates.<sup>2</sup>

The gene showing the strongest association so far with T2D is *TCF7L2*. Variations in *TCF7L2* are associated with impaired insulin secretion and increased hepatic glucose production,<sup>1</sup> which may partially explain the development of T2D in people carrying *TCF7L2* variations. People who carry one copy of a variant *TCF7L2* have an approximately 1.5 times increased risk of T2D, while people who carry two copies of a variant have an approximately 2.4 times increase risk.<sup>1</sup> About 7% of the US population carries two copies of the variant.<sup>1</sup> *TCF7L2* is a transcription factor involved in cell proliferation and in adipogenesis, myogenesis, and pancreatic islet development.<sup>2</sup> It activates the genes encoding intestinal proglucagon and glucagon-like peptides-1 and -2.<sup>2</sup> Its effect on the expression of these genes likely explains its association with T2D.<sup>2</sup>

Genome-wide association studies have uncovered a number of other promising candidate genes. Among them are *SLC30A8*, a zinc transporter that makes zinc available for cocrystallization with and subsequent secretion of insulin; and *PPAR $\gamma$* , a receptor that controls the expression of several genes and affects insulin sensitivity.<sup>2,3</sup> Variations in each of the candidate genes alone increase the risk for T2D modestly.<sup>3,4</sup> However, there is a stepwise increase in T2D risk as the number of variations carried by a single person increases. People who carry more than 12 variants are at greatest risk.<sup>3</sup>

Some companies offer genetic testing for variations in the *TCF7L2* gene, which in theory could help to predict who will be affected by T2D. But without knowing the genotype of the several other genes associated with T2D, that information will yield relatively little information. The strongest predictors continue to be positive family history, increased BMI, increased blood pressure, and increased serum levels of triglycerides, apolipoprotein A-1, and liver enzymes.<sup>3</sup> Attention to such factors, combined with new research data identifying genetic risk factors, will help in reducing the prevalence of T2D.

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