Contribution of Rare Variants in Identifying New Therapeutic Targets

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Diabetes ranks among the leading causes of mortality and disability worldwide, with a significant economic burden that affects healthcare systems globally. In this presentation, I will focus on type 2 diabetes (T2D), which accounts for approximately 90-95% of all diabetes cases. T2D is characterized by a progressive decline in insulin secretion often coupled with insulin resistance and metabolic syndrome. While lifestyle factors such as obesity and physical inactivity are well-known contributors, research over the past 25 years has demonstrated that T2D also develops on a genetically predisposed background, as indicated by substantial heritability estimates from family and twin studies (exceeding 40%).

Traditionally, T2D genetics has been viewed through a lens of either monogenic or polygenic causes. However, recent studies have highlighted a more nuanced continuum that includes monogenic, oligogenic, and polygenic factors, each playing a complementary role in T2D pathophysiology. Advances in rare variant research specific to oligogenic T2D are not only enhancing our understanding of disease mechanisms but are also opening avenues for precision medicine that could significantly improve T2D management. To identify these rare oligogenic variants, researchers have employed two main strategies: (i) targeted sequencing of specific candidate genes combined with functional genetic analysis and (ii) comprehensive whole-exome or whole-genome sequencing to uncover low-frequency variants associated with increased T2D risk.

In my presentation, I will explore several key genes implicated in oligogenic T2D, illustrating how these findings deepen our understanding of T2D mechanisms and reveal new potential targets for drug development.