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Diving into the Unknown: A Genetic Investigation of Type-2 Diabetes-associated INSR Variants of Uncertain Significance

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Poster Title: Into the unknown: Diving into the unknown: A genetic investigation of type-2 diabetes-associated *INSR* variants of uncertain significance

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Abstract:

Type 2 diabetes is a complex metabolic disorder with interactions between genetic and environmental factors, making it more complicated to understand the clinical implications of identified genetic variants and disease pathology. Many of the diabetes-associated variants are currently classified as VUS and occur within the genes involved in insulin signaling and regulation, so we turned our focus on the human *INSR* gene. *INSR* encodes the insulin receptor protein that plays a major role in insulin signaling. Furthermore, *C. elegans* provides a simple model system to examine the functional consequences of these diabetes-associated VUS. We examined *INSR* diabetes-associated VUS through the orthologous *C. elegans* gene *daf-2*. Preliminary genetic and evolutionary conservation analyses suggest functional impact for some of these VUS with the potential to impact protein structure and function. Further bioinformatic analysis of pathogenicity predictions supported the conservation we observed across species. I chose the most interesting VUS c.1628C>T (p.Thr543Met) to move forward with based on its genetic loci, level of evolutionary conservation, and predicted pathogenicity. These provided support for further *in vivo* studies. Next, we designed and tested primers to amplify the VUS region within *daf-2*. We are currently working to optimize this polymerase chain reaction-based genotyping assay to assess CRISPR-Cas9-engineered *C. elegans* models containing the VUS. Our goal is to assess the functional impact of the VUS on the *daf-2* gene *in vivo* through phenotyping the mutant *C. elegans* VUS model. Studies such as this help us to begin to understand the functional impact of identified genetic variants in diabetes patients, paving the way for personalized medicine.