**Project Title:**Determining the effects of genetic diversity on the ghrelin-insulin pathway

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**Summary/Abstract:**

Diabetes is a disease that inhibits the body’s ability to produce or respond to the hormone insulin, making it difficult to regulate blood sugar levels. The disease leads to a variety of health complications and is a leading cause of death in the United States[3]. Previous studies have identified the way in which ghrelin, a hormone associated with hunger, affects insulin production indirectly by causing delta cells to secrete somatostatin. Using data from a group of DO mice, this study will examine the effects of genetic variation on the roles of ghrelin and somatostatin in insulin suppression and regulation. This study will shed more light on the mechanisms that drive the diabetes, informing future research and treatment possibilities.

**Significance and Background:**

Diabetes is a metabolic disorder that inhibits the body’s ability to maintain a healthy blood glucose level. Typically, people affected by the disease either cannot produce or become resistant to insulin, the hormone that allows glucose to enter cells and give them energy. Diabetes is a serious health concern in the United States. In 2010 diabetes was the seventh leading cause of death in the nation, and with 1.4 million Americans diagnosed with diabetes every year, it needs to be addressed presently[3].

A recent study has elucidated the pathway through which ghrelin downregulates insulin secretion in beta cells in the islet tissue. Ghrelin actually signals delta cells, to secrete more somatostatin, which in turn decreases the production of insulin by beta cells.[2] This finding offers a straightforward explanation of the well-known insulinostatic actions of ghrelin[2].

Diversity Outbred (DO) mice are unique among laboratory mice in their broad genetic diversity[1]. It gives a powerful advantage in our ability to generalize conclusions to other genetically diverse populations and allows us to examine the effects of genetic variation on known biological pathways and mechanisms[1].

My study will investigate the effects of genetic diversity on the ghrelin-insulin pathway.

**Experimental Approach:**

This study will attempt to answer questions surrounding the newly clarified relationship between ghrelin and insulin. I should be able to confirm the results of DiGruccio et al.’s research by determining if it holds true for a group of DO mice and allow it to be further generalized to genetically diverse populations. Alternatively, the results of the study could indicate a difference in the pathway (or its importance in glucose regulation) among the different founder strains of the DO mouse population.

I will use the qtl2 package and the statistical programming language R to accomplish my aims.

**References:**

[1] Churchill, Gary A., Daniel M. Gatti, Steven C. Munger, Karen L. Svenson, 2012 The diversity outbred mouse population. Mamm Genome 23:713-718.

[2] DiGruccio, Michael R., Alex M. Mawla, Cynthia J. Donaldson, Glyn M. Noguchi, Joan Vaughan, Christopher Cowing-Zitron, Talitha van der Meulen, Mark O. Huising. 2016 Comprehensive alpha, beta, and delta cell transcriptomes reveal that ghrelin selectively activates delta cells and promotes somatostatin release from pancreatic islets. Molecular Metabolism 5:449-458.

[3] "Statistics About Diabetes." *American Diabetes Association*. N.p., n.d. Web. 07 June 2017.