**Project Title:** Lifespan and healthspan:metabolic and endocrine phenotypes that are predictive of longevity in DO mice

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**Abstract:** Physical changes can be observed and documented in aging humans, but the underlying biological processes linked to their decline are still unclear. New research indicates that an interrupted GH/IGF1 axis may play a part in longer lifespans in invertebrates, but contradictory evidence has shown that lower levels of GH and IGF1 in older humans may contribute to disease in their musculoskeletal systems. However, human dwarfs with low insulin, low glucose, and insulin sensitive GH-deficiency have lived increased lifespans. These contrasting observations need to be studied to unravel the mechanisms of human aging. My research aims to uncover any phenotypes connected to GH, IGF1, and insulin that are linked to longevity as well as any QTLs that may affect these clinical phenotypes. This research will use data from Diversity Outbred mice, which are more representative of human genetic and phenotypic variation than are standard inbred mice.

**Background and Significance:** Although physical changes can be observed in aging human populations, many of the biological and genetic phenomena that govern the aging process are still unknown. New research indicates that two biological mechanisms involving the IGF1/GH axis and the insulin/IGF1 signaling (IIS) pathway may affect longevity and quality of life.

GH (growth hormone) regulates growth, development, and carbohydrate and lipid metabolism (Perrini et al., 2010) while IGF1 (insulin-like growth factor 1) is regulated by GH secretions and coordinates growth, differentiation, and metabolism (van Heemst, 2010). GH secretions are linked to IGF1 levels and the progressive decline of GH levels seen in elderly individuals has been associated with lower than normal levels of IGF1 in more than 30% of their population (Perrini et al., 2010). This deficiency is correlated with age-related muscle wasting and bone mass loss, which may reduce quality of life and lifespan (Perrini et al., 2010). In contrast, invertebrate and mouse models have shown that extended longevity is actually correlated with impaired GH/IGF1 signaling.

In roundworm and fruit fly models, the mechanisms underlying the insulin and GH/IGF1 signaling pathways differ from the more complex mammalian networks. However, mice, round worms, and fruit flies all exhibit longer lifespans when GH/IGF1/insulin levels are low or their pathways are impaired (van Heemst, 2010). Conflicting evidence in mutant mice suggest that both impaired and correctly functioning insulin signaling are connected to longevity (van Heemst, 2010), but the extension of this knowledge to humans is controversial considering that defective insulin signaling has been associated with insulin resistance and diabetes. However, data from GH deficient and GH resistant human dwarfs have suggested that low glucose, low insulin, and conserved insulin sensitivity may be key biological features of human longevity (van Heemst, 2010). The goal of my research is to try to determine whether there are any features of the IIS and GH/IGF1 pathways in Diversity Outbred mice that may contribute to longevity and perhaps lead to an extended healthspan (quality of life).

DO mice are bred from Collaborative Cross mice, but they are heterozygous at nearly every gene because of their outbred breeding strategy (Svenson, 2012). These mice make it possible to analyze complex traits such as aging because each mouse is an individual coming from a pool of nearly limitless alleles and phenotypes.

**Experimental Approach:**

**Specific Aim One:** To test the hypothesis that phenotypes linked to the GH/IGF1/insulin signaling pathways are correlated to longevity in the Diversity Outbred mouse model. Data from the DO mice of varying sexes and generations will be analyzed in RStudio using statistical tests to flush out any phenotypes linked to lifespan.

**Specific Aim Two:** To test the hypothesis that QTLs are linked to phenotypes correlated with lifespan and that QTLs are linked to lifespan in the Diversity Outbred mice. Data from DO mice will be analyzed using RStudio and the R/qtl2 package to identify QTLs.

**Specific Aim Three:** To test the hypothesis that phenotypes linked to the GH/IGF1/insulin signaling pathways change over time in the Diversity Outbred mice. Data from the DO mice will be analyzed using mathematical and statistical tests in RStudio.

**References:**

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