

Identification of genes that link obesity and stress/emotional behaviors using outbred rats.

Leah C Solberg Woods¹, Mackenzie Fitzpatrick¹, Alexandria M Szalanczy¹, Angela Beeson¹, Christina Dyson², Aron Geurts¹, Jeff L Weiner², Eva E Redei³

¹Department of Internal Medicine, Section on Molecular Medicine, Wake Forest University School of Medicine, Winston Salem, NC, USA,

²Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA

³Department of Psychiatry and Behavioral Science, Northwestern University, Chicago, IL, USA

Obesity and major depressive disorder (MDD) have been increasing in prevalence, especially since the COVID-19 pandemic. Obesity and MDD are bi-directionally associated, and both are influenced by genetics and the environment. The molecular mechanisms that link these two diseases, however, are not fully understood. My laboratory has used outbred HS rats to identify genes for adiposity traits, having identified *Krtcap3* and *Adcy3* as causal genes. We identified a coding mutation in *Adcy3*, a gene that catalyzes the synthesis of cAMP from ATP and is known to play a role in both obesity (via satiety signaling and peripheral metabolism) and MDD in humans and rodent models. The role of this coding mutation, however, is unknown. Very little is known about *Krtcap3*, a gene identified through mediation analysis. We used CRISPR-cas9 to create *Krtcap3* knock-out (KO) and *Adcy3* mutant (MUT) models to validate the role of each gene in obesity. We subsequently demonstrated that both genes play a role in stress and/or emotional behaviors, with differing effects based on sex. Specifically, *Krtcap3* KO females exhibit increased eating and adiposity under chronic stress conditions relative to non-stressed KO rats, in contrast to WT rats. *Krtcap3* KO female and male rats also have increased serum corticosterone in response to a psycho-social stress relative to WT rats. *Adcy3* MUT males show increased food drive as well as increased passive coping behavior in the forced swim test relative to WT rats, while *Adcy3* MUT females show no differences in food drive, but do show increased anxiety-like behaviors relative to WT females. Studies are ongoing to understand how these genes link obesity and emotional health behaviors. These studies show that two genes identified for obesity in HS rats also play a role in stress/emotional behaviors, thereby shedding light on genetic links between these two diseases.