# The Impact of Adenylate Cyclase 3 Loss in SF1 Neurons on Obesity

Du, Sabrina (School: West High School)

Obesity is a detrimental disease that causes individuals to suffer higher risks for developing cardiovascular diseases, diabetes, and cancer. Recently, a population study found that a loss of the adenylate cyclase 3 (ADCY3) gene was responsible for several cases of monogenic severe obesity. Yet, the mechanisms behind this remain unclear. This study sought to determine both phenotypic and genotypic effects from a loss of ADCY3 in SF1 neurons (KO) on obesity. Female KO mice had significantly increased body weights while male KO weights were unaffected when compared to controls ($p<0.05$). After qPCR, several obesity-associated thermogenic genes had downregulated expression only in females (PGC1B, ADCY3: $p<0.05$), likely reflecting decreased non-shivering thermogenesis and heightened obesity. However, several immune-related genes were upregulated or downregulated in females (CCL2, ITGAX: $p<0.05$), providing an inconclusive result. Comparatively, male KO mice exhibited no differences for any genes. Thus, ADCY3 SF1 KO likely plays a role in the natural sexual dimorphism found in human obesity and increases obesity development in females by decreasing non-shivering thermogenesis. Although the immune response result requires further investigation, it suggests that cytokines may be regulated differently than monocytes and macrophages in brown adipocytes. Moreover, a loss of ADCY3 in the brain could likely regulate ADCY3 expression in BAT, as normalized protein expression assays revealed decreased ADCY3 protein expression in female KO BAT compared to control. Overall, these results demonstrate that ADCY3 could serve as a promising drug target in obesity treatment and advance understanding of the natural sexual dimorphism found in human obesity.