**Application number/Title:** 40415 - Burden of variants in obesity-related genes

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**Keywords provided by the Applicant PI to describe the research project:**
MC4R, genetics/genotyping, obesity, rare disease, setmelanotide

**Application Lay Summary:**

The hypothalamic melanocortin 4 receptor (MC4R) pathway plays a critical role in controlling energy expenditure. Alterations in genes within this pathway, including in POMC, LEPR, and PCSK1, have been shown to lead to hyperphagia and severe forms of monogenic obesity. In addition, other genes positioned within this pathway are predicted to contribute to MC4R pathway-mediated obesity. We seek to evaluate UK Biobank data to determine: 1) the association between potentially deleterious variants in the MC4R pathway and obesity, 2) the prevalence of these variants in the UK Biobank population, and 3) the "genetic burden" of carrying multiple variants in different genes within this pathway.

To achieve these aims, we will first identify literature-derived, experimentally tested, and computationally predicted deleterious variants in obesity genes of interest. Next, we will use UK Biobank data to determine the association between these variants and obesity. We will also construct models to determine whether having multiple variants both within and across candidate genes increases the probability of having obesity. Finally, we will estimate the overall prevalence of both individual variants and high-impact genetic burden combinations in the UK Biobank population. We expect this project will take approximately 3 years to complete.

We anticipate that the findings from this study will be relevant to public health in several ways. First, results from these analyses will determine the burden of severe forms of genetic obesity in the UK Biobank population. Second, combinations of deleterious variants may identify new subclasses of obesity for which precision medicine treatments targeting these variants may ultimately be

developed.  Finally, these results may improve the treatment of serious and life-threatening forms of obesity by identifying the subset of individuals for whom novel therapeutics that target the MC4R pathway may be particularly beneficial.