PhD Student, **Malene Revsbech Christiansen**, MSc (engineering).

Place of enrolment: University of Copenhagen, Faculty of Health and Medical Sciences

Principal supervisor: Associate Professor **Tuomas O. Kilpeläinen**, University of Copenhagen, Novo Nordisk Foundation Center for Basic Metabolic Research

Title of project: Genetic regulation of leptin levels during weight loss – implications for weight management and metabolic health

ABSTRACT

Background: Obesity is a global epidemic and a key driver for the increase in type 2 diabetes worldwide, causing a heavy burden on public health systems. Obesity is challenging to treat; while initial weight loss can be achieved with lifestyle modifications, long-term maintenance of lower body weight usually fails. The adipocyte-secreted hormone leptin has an important role in weight regulation. Leptin supplementation is an effective treatment against severe obesity caused by monogenic leptin deficiency, where exogenous leptin normalizes body weight. However, there is still a lack of understanding of how leptin impacts body weight and metabolic health in the general population. We have recently provided new insights into leptin physiology by identifying 10 common genetic variants associated with circulating leptin levels in a weight-stable state. However, it remains unclear what biological mechanisms regulate variability in leptin production during weight loss interventions, which may be particularly relevant for the success in avoiding weight regain after weight loss. Determining the genetic basis of leptin regulation in response to weight loss is important, as it will give insights into leptin physiology during weight loss, provide knowledge on biological factors that may drive weight regain, and may pinpoint targets for new therapies.
Aim: We aim to identify and characterize novel genetic regulators of leptin levels in response to weight loss and examine their implications for weight management, insulin resistance, and risk of type 2 diabetes.
Methods: We will first identify genetic variants regulating changes in leptin levels in response to weight loss using data from six weight loss interventions with leptin measured before and after the intervention. In follow-up analyses, we will examine the associations of the variants with weight regain after weight loss, and use data from five prospective Danish cohort studies to examine whether the variants are associated with five-year weight gain and changes in insulin resistance and related metabolic comorbidities in the general Danish population. We will also map the associations of the variants with risk of type 2 diabetes and other human complex phenotypes by applying phenome-wide association studies across summary results from published genome-wide association studies and the UK Biobank. Finally, we will pinpoint the causal genes in the leptin-associated gene regions using in vitro studies in human adipocytes, where we will assess the effects of gene knockdown on leptin gene expression, leptin production, and insulin- or dexamethasone-induced leptin secretion.
Expected outcome and perspective: We expect to identify multiple novel genetic regulators of changes in leptin levels in response to weight loss interventions and to provide an overview of their impact on weight management and metabolic health in obese patients and the general population. By identifying the causal genes that underlie leptin regulation during weight loss interventions, we may also pinpoint targets for new treatments against obesity and related comorbidities.