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Project: Genetics of Inherited Neuroendocrine Reproductive Disorders

Over the last 3 decades, hormonal metabolic cues (such as leptin) have been implicated in the regulation of energy status of the organism, by influencing food intake and energy expenditure as well as pubertal onset and reproductive capacity. The precise molecular neuroendocrine circuits that mediate this coordination are incompletely understood, and the full spectrum of implicated hormones is unknown.

Several Fibroblast Growth Factors (FGFs) have been associated with reproductive disorders (*e.g.* CHH) such as Fibroblast growth factor 21 (FGF21), an hormone that signals through FGF receptor 1 (FGFR1) and its obligate co-receptor βKlotho, encoded by the *KLB* gene. As well, mutations in FGF8 and FGF17 have also proved detrimental for endocrine function along development of obesity traits.

The major aim of the project will focused on identifying novel genes and pathways implicated in both reproduction and metabolism. We hypothesize that patients with severe GnRH deficiency harbor mutations within FGF genes and associated-pathways. As well, tissue-specific differential gene expression over developmental stages will highlight candidate genes related to both reproduction and metabolism.

This project includes a cohort of 400 CHH probands previously diagnosed and will entail detailed assessments for the spectrum of CHH associated phenotypes including metabolic assessment. When available, affected and unaffected family members will be phenotyped and included in the study. The current proposal will utilize WGS data from existing and newly identified patients. Candidate gene identification will be based on several in-house developed tools and analysis pipelines, as well as available software (*e.g.* GeneMania / Interactome Based Association Scoring (IBAS)) which incorporate predictive models of gene expression, protein-protein interaction, and protein function helping in the expansion of known networks to include novel candidates. Rare sequencing variant (RSV) from candidate genes identified within our exome data will then be used to generate gene-collapsed associations using BURDEN test. Functional studies will be highly dependent on the specific genes identified. Briefly, it will include *in vitro* signaling, expression studies, and *in vivo* models similar to those previously conducted in our laboratory with FGFR1, FGF8, or KLB genes.

This project will apply interdisciplinary strategies combining genetics, bioinformatics and molecular/cellular biology in both humans and mice. This line of research could identify novel biomarkers and drug targets for the commonly observed co-occurrence of reproductive and metabolic disorders in conditions such as hypogonadism, infertility, polycystic ovarian syndrome, obesity and type 2 diabetes.