Congenital hypothyroidism (CH) is a hormone disorder attributed with the reduced size, abnormally located or absence resulting in a partial to nonfunctional thyroid gland. [1] One in every three thousand newborns are diagnosed with congenital hypothyroidism, and without early newborn screenings and hormone replacement therapy untreated babies develop permanent intellectual disabilities and slow overall body growth. [3] Paired Box 8 (PAX8) mutations have been associated with congenital hypothyroidism [2]. PAX8 codes for a transcription factor which regulates the development of the thyroid gland during embryogenesis. [4]. PAX8 knockouts result in the complete absence of the entire thyroid gland, however no intermediate mutations within the PAX8 gene have yet to be characterized nor have phenotypic associations.

**Primary Objective**: To investigate thyroid gland phenotypes (absence, reduced, mislocation and wild type) and identify specific linked nonsynonymous mutations associated with each phenotype within the coding regions of PAX8.

**Long-term Objective**: By creating site-specific phenotype associations this knowledge will contribute to the improved hereditary predictions from the parent with PAX8 mutations to more consistently and accurately diagnose newborns with HC at the genomic level.

**Aim 1**: Use Next Generation sequencing to identify and quantify nonsynonymous mutations in the PAX8 coding regions in mice with various thyroid gland phenotypes associated with CH.

**Hypothesis**: Mice with synonymous thyroid gland phenotypes carry identical mutation patterns corresponding each trait (reduced size, mislocation, absence).

**Rationale:** Individuals with CH display consistent symptoms despite the variety of thyroid gland malformations caused by PAX8 mutations. By mapping mutations motifs per phenotype (reduced, mislocation, absent) a greater understanding can be gained of the genomic background of CH. By linking consistent genotype data to thyroid gland phenotypes ultimately can lead to high successes in accurate diagnosis and novel personalized treatment options.

**Aim 2:**

**Hypothesis:**

**Rationale:**

**Aim 3:**

**Hypothesis:**

**Rationale:**

**Conclusion:**

Reference:

[1]Ramos, H. E., et al. "Extreme phenotypic variability of thyroid dysgenesis in six new cases of congenital hypothyroidism due to PAX8 gene loss-of-function mutations." *European Journal of Endocrinology* 171.4 (2014): 499-507.

[2]Magliano, M. Pasca Di, R. Di Lauro, and M. Zannini. "Pax8 has a key role in thyroid cell differentiation." *Proceedings of the National Academy of Sciences* 97.24 (2000): 13144-3149.

[3]Park, S. M. "Genetics of congenital hypothyroidism." *Journal of Medical Genetics* 42.5 (2005): 379-89.

[4]Tell Gianluca, et al. "Structural defects of a Pax8 mutant that give rise to congenital hypothyroidism." *Biochemical Journal* 341.1 (1999): 89.