IOWA STATE UNIVERSITY
Department of Agriculture and Life Sciences

University Honors Capstone Project
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Abnormal Presentation of Feline Congenital Hypothyroidism

Introduction:

The aim of this study was to identify the causative allelic change that resulted in the atypical form of congenital hypothyroidism noted within a feline research breeding colony used to study glaucoma. Retrospective analysis of archival records as well as whole genome sequencing (WGS) of specific members of the breeding colony were performed. A pedigree was constructed to determine the inheritance pattern of the disease.

Background:

Simple congenital hypothyroidism occurs as a result of the triiodothyronine (T3)/thyroxine (T4) production pathway being disrupted within the endocrine system, specifically within the thyroid endocrine signaling pathway, thyroid transport, peripheral thyroid metabolism, or the thyroid gland itself, causing lowered quantities of these products in the body. Congenital hypothyroidism means it is present from birth. The sometimes transitory and incomplete block in thyroid production seen in our novel and atypical form of hypothyroidism manifests as affected kittens, which may achieve some thyroid production and function, such that as adults they are spared the full developmental consequences of severe congenital hypothyroidism, despite their thyroid hormone associated levels not being fully normalized.

The transitory nature of this condition manifested with kittens who were detrimentally affected in their development both in terms of their gait and mentation, yet as the cats grew to be adults their T3 and T4 levels were somewhat but not completely normalized. This clinical picture is in sharp contrast to that seen for the simple and complete congenital forms of the disease (Greco, Deborah S., 2006).

References:

- Scriver, Charles R., Beauget, Arthur L., Sly, William S., Valle, David. *The Metabolic and Molecular Bases of Inherited Disease Volume II.* New York, McGraw-Hill Inc, 1960.
- Scriver, Charles R., Beauget, Arthur L., Sly, William S., Valle, David. *The Metabolic and Molecular Bases of Inherited Disease Volume III.* New York, McGraw-Hill Inc, 1960.
- Greco, Deborah S. "Diagnoses of Congenital and Adult-Onset Hypothyroidism in Cats". *Clinical Techniques in Small Animal Practice,* v. 21, pg 40-44, 2006.

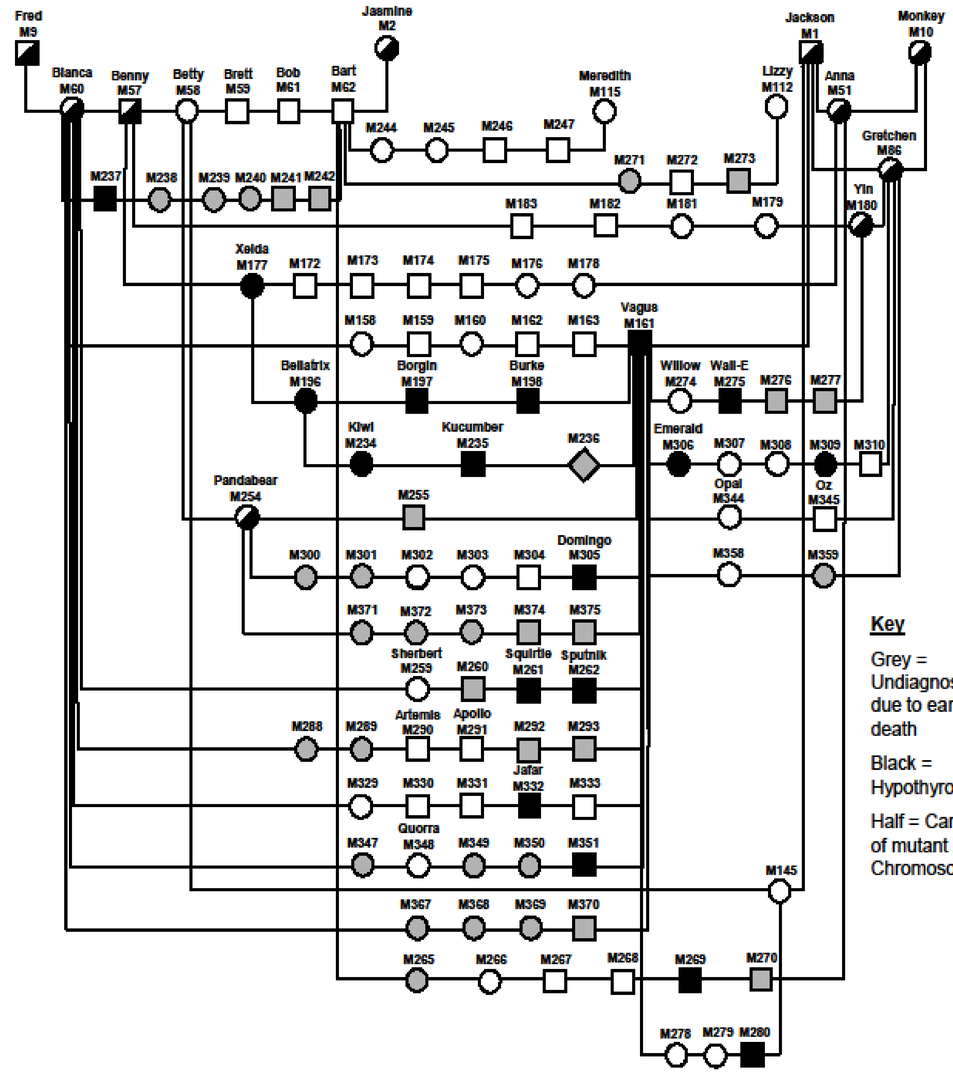

Figure 1: Hypothyroid Colony Pedigree Suggestive of Partial X-linked Inheritance of Mutant X-Chromosome

Methods:

In order to develop a complete pedigree and assess the mode of inheritance of the hypothyroidism seen within the colony, analysis of archival health records had to be performed. Each paper record had to be thoroughly studied to extract the data necessary for the study. This data was then compiled into an excel document to appropriately compare each of the cats' characteristics and determine the traits of disease. From there, a pedigree was constructed and various inheritance patterns were tested to see if any matched up.

Results:

It has been determined that the inheritance is polygenic. The disease is likely not informed by a single gene as is evidenced by the inheritance denoted in the pedigree. Instead, the disease is inherited via multiple genes working in conjunction with each other. This study pointed to the disease inheritance being partially X-linked. In looking at the X-linked component, it is imperative that one factors in X-chromosome inactivation.

The pedigree is suggestive specifically of X-linked recessive inheritance of a "mutant" X-chromosome carrying the disease. In this way, the "mutant" form of the X-chromosome is permissive to the condition. The abnormal ratio of affected to non-affected cats in a litter as described by X-linked inheritance can be attributed to X-chromosome inactivation and/or genetic interaction between genes on the X-chromosome. This inactivation and gene relationship play key roles in the status of each animal.

Future Plan of Action:

The results of the study have been sent to Dr. Leslie Lyons, an associate professor at the University of Missouri, to be studied further. Dr. Leslie Lyons is a renowned geneticist who studies a number of species but has focused on cats to develop biomedical models. The hope is that she can help pinpoint the allelic mutation causing this form of hypothyroidism in the breeding colony. The discovered inheritance pattern will help to decrease the number of possible causative agents.