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Genetics of hypoThyroidism in dog as a model organism

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The domestic dog is not only man's best friend and accompanying animal in our daily life, but also in the long-term challenge of unraveling the genetics behind complex diseases. Besides living in the same environment as we do, dogs may spontaneously develop several diseases that are analogous to those affecting humans. In addition to these peculiar features, dogs' unique genome structure and the respective availability of valuable genomic and molecular tools for its analysis overall facilitate the identification of disease-causing genes. We have studied a common endocrine disease affecting both humans and dogs– hypoThyroidism, which in the latter has in most cases an autoimmune etiology. Here we present a multi-breed analysis of genetic risk factors predisposing to hypoThyroidism in dogs belonging to three high-risk breeds - the Gordon setter, Hovawart and the Rhodesian ridgeback. Using an integrated genome-wide association and meta-analysis strategy, we identified the presence of a major hypoThyroidism risk locus shared by these breeds on chromosome 12 ($p=2.1x10-11$). Additional characterization of the candidate region revealed a shared ~167 kb risk haplotype being significantly enriched across the affected dogs ($p<0.001$). The identified haplotype harbors three genes that have not previously been associated with hypoThyroidism, thus representing interesting targets for the discovery of novel disease pathways and mechanisms. This study is of utmost importance for the improvement of hypoThyroid dogs' health and it may also help to enlarge our knowledge regarding the genetics of the human counterpart of this disease and searching for its missing heritability.

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Next generation sequencing of Thyroid neoplasms to determine mutational status

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The prognosis for patients with Thyroid carcinoma is generally dependent on age and tumour stage at time of diagnosis. Nonetheless, the biological aggressiveness of individual tumours cannot always be predicted from the initial clinical features, making it difficult consistently to identify patients who will die from their disease. Moreover, the occurrence of non-specific lymphocytic Thyroiditis of varying severity adjacent to Thyroid tumours is frequently observed. Risk factors for the development of Thyroid cancer include radiation exposure, somatic and germline genetic mutations. Common mutations that precede the development of Thyroid carcinoma target the mitogen-activated protein kinase (MAPK pathway) and include BRAF, RET/PTC and RAS. We employed a NGS sequencing approach for parallel interrogation of the presence of somatic mutations in samples from 82 patients. We hypothesised this approach might have utility as an adjunct diagnostic in tissue and FNA analyses and in understanding the molecular patho-biological processes in carcinogenic progression. Adopting a null hypothesis approach, we used the oncomine comprehensive assay and Ion PGM™ semi-conductor sequencing technology to analyze hundreds of the most referenced oncology biomarkers including hotspot mutations, CNVs, gene fusions and indels. The method involved multiplex PCR requiring 10 ng of input DNA. The most commonly detected mutations involved: DDR2, NRAS, PI3KCA, MET, ERBB2, FGFR3, MET, STK11, EGFR, BRAF and TP53. The number of somatic variants per sample was higher among FTC (mean=28.2, Median=9) than PTC (mean =9.9, median = 6). In addition, we detected the SQSTM1-NTRK1 fusion transcript in RNA from 2 PTC samples. The number of predictive biomarkers that are assessed in clinical practice is rapidly increasing with the availability of drugs that target specific molecular alterations. NGS has the advantage of providing information on known and novel molecular alterations and multiple genes can be sequenced simultaneously in the clinical laboratory setting. This study identified significant pathological mutations among PTC and FTC DNA and RNA samples that may have potential diagnostic and therapeutic implications.

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