Lymphoma in Irish Wolfhounds

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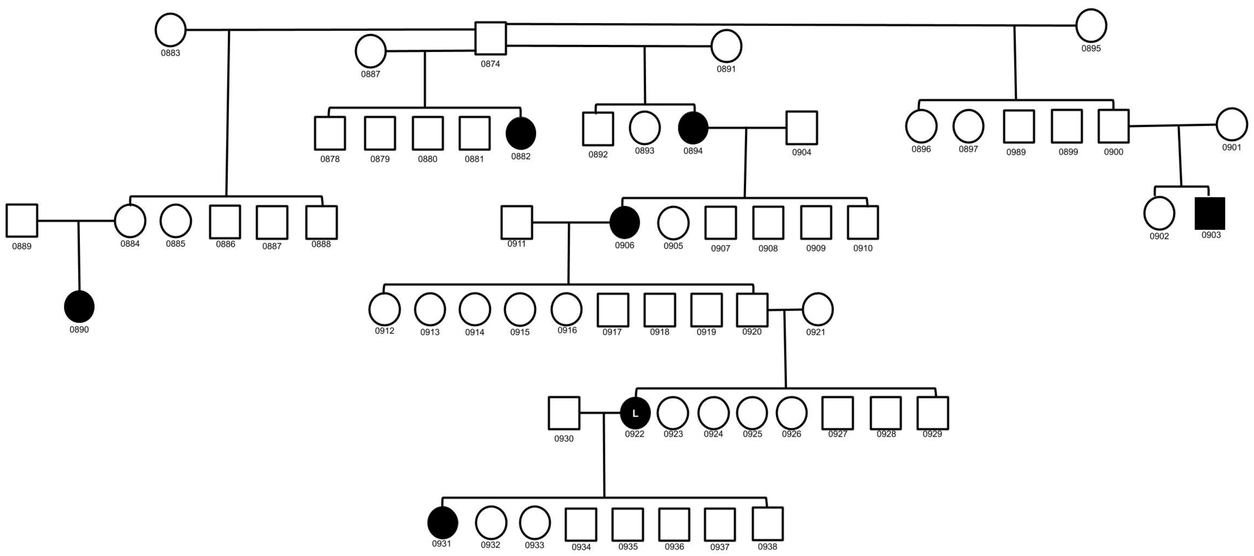
Introduction

Cancer in pedigree dogs is a significant problem, with tumor related deaths constituting 27% of all pedigree dog deaths according to a UK study of 15,881 canine deaths [1]. Among those purebred dogs, Irish Wolfhounds are among the most at-risk dogs, having the second highest mortality from cancer after Bernese Mountain Dogs [2]. This breed-related predisposition to developing cancer indicates a genetic component of cancer risk in dogs [3]. Specifically, lymphoma has been found to have significantly different frequencies in different breeds of dogs, demonstrating that there are genetic factors that put certain dogs at increased risk for lymphoma [4]. This genetic component of cancer in dogs has been explored by McAloney et al. in respect to the TERT gene, which codes for the enzyme Telomerase Reverse Transcriptase (TERT), which is involved in the maintenance of telomeres, sequences of DNA at the end of chromosomes, which protect coding DNA from damage and have been linked to cancer risk in humans. However, the results of this study suggest that polymorphisms with the TERT gene do not completely govern cancer risk in dogs, and the genetic risk for the development of cancer in dogs is more complex, involving several genes [5]. This complexity is what warrants a Genome Wide Association Study (GWAS) for lymphoma in Irish Wolfhounds. The results in this poster highlight some of the preliminary diagnostic and genetic insights that will ultimately provide the foundation for a GWAS that will help to identify the multiple genes that constitute genetic components of lymphoma risk in Irish Wolfhounds. Furthermore, the identification of the single nucleotide polymorphisms (SNPs) found by the GWAS can be used to create a genetic test to screen potential sires and dams for the risk their puppies may have in developing lymphoma at some point in their life. Extensive screening and its application for the identification of ideal breeding pairs has the potential to greatly minimize the prevalence of lymphoma in the Irish Wolfhound population in future generations. Furthermore, the study of cancer genomics in dogs is not only valuable to the field of veterinary medicine, but also to human medicine. Davis et al. describes how the similarities of canine and human cancers and their clinical presentations make dogs an exceptional model organism. The study of canine cancer genomics could prove to be an incredibly powerful tool for the advancement of both veterinary and human oncology [6]. In the era of personalized medicine for both humans and dogs alike, the understanding of the genetic components of cancer risk is more valuable than ever.

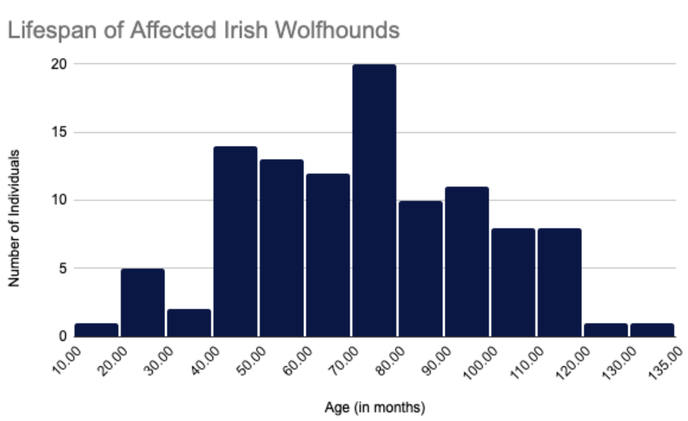
Methods

All results were obtained through data collected from the Irish Wolfhound Database (IWDB), which is a "private initiative among Irish Wolfhound breed enthusiasts around the world." The database contains the pedigree information on 165,650 Irish Wolfhounds as of August 2020. It is worth noting, however, that information regarding lifespan and cause of death are provided at the breeders' and owners' discretion, which is a potential source of bias in the data. However, the large sample size should compensate for this potential source of error in respect to the validity of the findings. Blood samples for DNA extraction have been collected from 45 affected dogs and 100 controls previously and stored in -80°C until COVID research restrictions will be lifted.

Preliminary Results



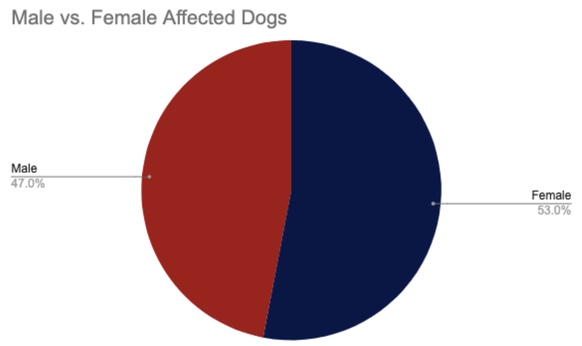
This is small sample of a much larger pedigree that contains 1032 total dogs, 53 of which are affected. The pedigree shows an inheritance pattern that closely resembles a complex mode of inheritance, which is supported by the current scientific literature which has found that cancer risk in pedigree dogs is governed by many genes.

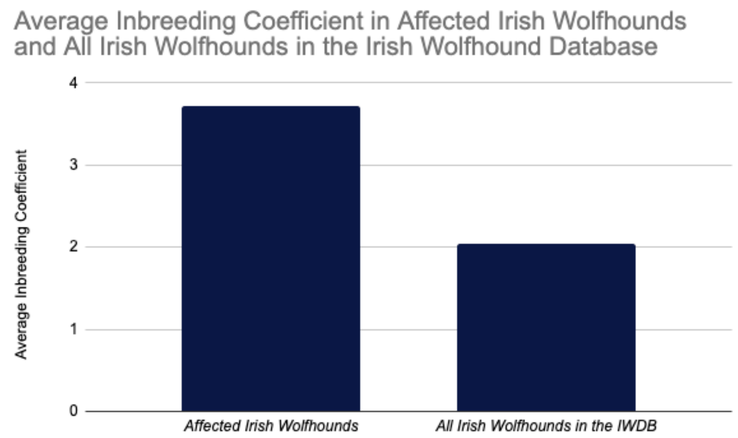


The lifespan of the 106 dogs sampled ranges from 10 months to 132 months with an average life expectancy of 72.75 months (or 6.06 years). This finding supports the claim made by Grüntzig et al. that lymphoma risk peaks at 6 years of age. The histogram of these data shows a unimodal, nearly normal distribution. This is contrary to what one would expect as lymphoma is often categorized into early onset and late onset, which would have a bimodal distribution.

Preliminary Results (continued)

Although there are more affected females than males in the 266 affected dogs sampled, the findings are insignificant with a chi-square value of 0.36 and p=1, the greater number of affected females can be attributed to random chance. This indicates that the genetic risk for lymphoma is not sex-linked.





The affected Irish Wolfhounds have a significantly higher average inbreeding coefficient with a 95% confidence level (p=0.047). This is evidence to the strong genetic component in lymphoma risk in Irish Wolfhounds.

Type of Lymphoma in Irish Wolfhounds: Lymphoma is cancer of lymphocytes that have become malignant. Lymphocytes are derived from the hematopoietic system, largely the bone marrow. However, once produced and differentiated into T and B cells, lymphocytes can be found in many sites of the body (lymph nodes, spleen, liver, blood, bone marrow). Thus, these malignant lymphocytes, i.e. lymphoma, can be found in one or multiple sites. In our Wolfhounds, immune phenotyping was not available at the time many of these dogs were diagnosed. Thus, it is not clear if these were T or B cell lymphomas. However, the majority of them were diagnosed with straightforward multicentric lymphoma, meaning that multiple sites of the body were affected, leading to weight loss, lethargy, general decline and ultimately death.

Discussion

This is the beginning of a study that will ultimately better classify and quantify the clinical signs of lymphoma in Irish Wolfhounds. This would allow for veterinarians to better identify lymphoma presentation in Irish Wolfhounds specifically, which could make possible early intervention which could add years to the affected dog's life. Furthermore, this is the foundation for Genome Wide Association Study (GWAS) which will allow us to identify the genes responsible for putting Irish Wolfhounds at risk for developing lymphoma at some point in their life. Finding the mutations responsible for lymphoma will allow Irish Wolfhound breeders to test potential breeding pairs to minimize the likelihood that their puppies will be affected. Ultimately, the combination of genetic testing and the use of the results of said genetic testing in dog breeding will reduce the frequency of lymphoma in Irish Wolfhounds. This is a testament how scientists, veterinarians, and dog breeders can come together to foster a healthier population of dogs.

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