Measures of Homozygosity and Relationship to Genetic Diversity in the Bearded Collie Breed. Lay Summary (J.M. Belanger)

In purebred dogs, limited genetic diversity, popular sire effects, and common ancestry can lead to elevated levels of inbreeding and homozygosity. Inbreeding and a high degree of homozygosity are associated with a reduction in health and overall fitness. Historically, breeding goals have focused on maintaining breed-defining characteristics and removing deleterious traits. These goals may increase the level of homozygosity, thus reducing heterozygosity. To maximize genetic diversity, that is heterozygosity, it has been suggested that breeding decisions should include measures of genetic diversity. In the past, breeders utilized pedigree relatedness to balance mate choice for desirable traits while avoiding excessive inbreeding. Now, commercial companies offer genetic tests for inbreeding based upon single nucleotide polymorphisms (SNPs) in array analyses. This leads to the question of what are the best measures of genetic diversity? In the publication, “Measures of Homozygosity and Relationship to Genetic Diversity in the Bearded Collie Breed”, coefficients of inbreeding (COI) were determined for a population of Bearded Collies using three types of data: pedigree, single nucleotide polymorphisms (SNP), and whole genome sequencing (WGS).

For COI based on pedigree information, there must be accurate and complete information from multiple generations. Pedigree COI based on an all-generation pedigree of 11,989 Bearded Collies was 29%, whereas using only 10- or 5- generation pedigree COIs were 24% and 5%, respectively, illustrating the need for deep, comprehensive pedigree data to generate accurate COI. Interestingly, Bearded Collies with a greater number of unique ancestors did not necessarily have the lowest COIs.

The introduction of SNP arrays and WGS technologies allows for the determination of a single individual’s COI. This COI is typically based upon stretches of homozygous DNA in what is referred to as runs of homozygosity (ROH), where the level of inbreeding is represented by the statistic *FROH*. When comparing the COI (29%) from the all-generation pedigree data, the COI was not significantly different from the *FROH* for the WGS (32%). In contrast, the SNP array *FROH* (35%) was significantly higher than the all-generation pedigree COI. The manner in which the SNP array is designed causes an overestimation of inbreeding.

The publication also asked the question of whether the diversity that is being measured reflects functionality. That is, some changes in DNA have no impact on the function of a gene and therefore, would selection on non-impactful variation be fruitful in making breeding decisions? In other words, while the SNP array data measures diversity, that diversity may not reflect overall gene function.

To assess the functional impact of variants, WGS data is much more reflective of the vast variability in an animal when compared to the SNP array data. The number of DNA variants that had a predicted impact on gene function was determined for WGS in 23 Bearded Collies. The impact of the variants was determined by a functional effect prediction program. The majority of the variants (99%) were predicted to have a neutral impact (no functional impact). Of the predicted high-impact variants (0.06%) in the Bearded Collie, 12.7% were homozygous for the allele predicted to be changed in an impactful manner. Of those, only 30 were found in ROH that would be reflective of inbreeding practices; importantly, all 30 were found within the shortest ROHs, indicating these were a consequence of ancestral breeding practices and not due to recent breeding strategies.

Overall, DNA measurements proved to be more accurate than pedigree-based measurements. However, simply cataloging homozygosity doesn’t account for genomic regions with breed-defining traits that are needed for a breed to pass those traits on to future generations. It may seem reasonable to suggest outbreeding with the goal of increasing genetic diversity and/or preventing the expression of deleterious genes. Yet the practical goal of pedigree dog breeding is to create and maintain homozygosity of positive breed-specific traits and health-related traits through targeted selection.

Therefore, incorporating measures of genetic diversity into breeding schemes requires accurate and informative tools. Genetic diversity within regions of the genome that are impactful while still accommodating breed-defining homozygosity is vital, and the currently available measures do not account for these nuances associated with homozygosity. Furthermore, DNA measures reflect only the genetic variability of an individual dog and not the population as a whole. The health of a dog breed depends upon the genetic health of the population, not just the individual dog. Clearly, more work to define accurate and functional DNA diversity is necessary before there is widespread implementation of some of the existing measures of diversity.

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