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Contributions from historic popular sires increased recessive disease-causing alleles for two heritable eye conditions in dogs

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Introduction

Pedigree dogs have experienced substantial loss of genetic variation due to breed formation, closed registries, and breeding practices such as line breeding or using popular sires. This has unmasked many recessive disease-causing alleles, each with varying frequencies across countries and breeds (Donner *et al.*, 2023). In the UK, pedigree dog populations are maintained by numerous small-scale breeders, each contributing only a small portion to the gene pool. While breeding decisions have changed, the use of popular sires remains a concern for many breeds (Ilska *et al.*, 2025). Consequently, effectively communicating how breeding practices influence the frequency of disease-causing alleles is a primary goal for the Royal Kennel Club (RKC). However, the RKC lacks sufficient examples in dogs and instead relies on case studies from dairy cattle (Lewis and Windig, 2017). Retrospective analysis of Mendelian sampling trends across defined breeding "paths" can provide insights into selection decisions and sources of genetic variation (Garcia-Cortez *et al.*, 2008). We applied this approach in dogs to identify the genetic processes driving changes in allele frequencies for two monogenic recessive disease variants across five RKC-registered breeds.

Materials & Methods

Data and data handling. The RKC provided complete electronic pedigree data up to 1st January 2025 with available genetic test results recorded as "Clear" (reference homozygote), "Carrier" (heterozygote), or "Affected" (mutant homozygote) for primary lens luxation (PLL) or progressive retinal atrophy rod-cone degeneration 4 (PRA-rcd4), introduced in 2010 and 2012, respectively. PLL results were reported in Lancashire Heeler (6,500 dogs over 52 years with 9.3% tested), Sealyham Terrier (8,111 dogs over 57 years with 5.0% tested), and Miniature Bull Terrier (10,946 dogs over 80 years with 6.4% tested). PRA-rcd4 results were reported in Gordon Setter (21,231 dogs over 111 years with 4.9% tested) and Irish Setter (73,824 dogs over 85 years with 2.6% tested). Naïve estimates of disease-causing allele frequencies ranged from 0.20 to 0.28. Therefore, PLL and PRA-rcd4 are diseases of concern in these vulnerable breeds. All data cleaning was conducted in R (R Core Team, 2024). Individuals with a single parent were assigned a dummy to remove half-founders, and generation numbers were estimated forward in time.

Estimation of individual allele probabilities. The genotype probabilities were estimated for every dog in the pedigree using available genetic test results, pedigree information, and a modified version of the Python software AlphaPeel to allow genetic grouping of founders through unknown parent groups (UPGs) (Whalen *et al.*, 2019). Dogs in the base population (founders) were grouped by year of birth and country of origin, then neighbouring UPGs were combined to achieve a minimum "pseudorecord" of 100 in each (Legarra & Aguilar,

2025). After, the estimated (unphased) genotype probabilities were translated to allele probabilities following: 0.5×P(AB)+P(BB), where A represents the reference allele, and B represents the disease-causing (mutant) allele.

Partitioning of estimated allele frequencies. The R package AlphaPart was used to decompose the disease-causing allele frequencies by accumulating the Mendelian sampling terms into contributing paths (Obšteter *et al.*, 2021). The Mendelian sampling term represents the genetic variation in offspring arising from the random segregation and recombination of chromosomes during meiosis. In this study, it is the deviation of an individual's allele probability from the mean of their parents'. The UPGs were included through the Quass-Pollak transformation (Quass & Pollak, 1981), with each UPG having its own record, partitioning path, and allele frequency equal to the mean of the associated founders' allele frequencies. Thus, in addition to the within-pedigree paths defined, the results show each (or the combined) UPG(s) contribution to the overall estimated trend in allele frequency; however, these contributions are not discussed due to space constraints. Three different within-pedigree partitions were conducted: (1) male and female, (2) female, non-sire males, and each individual sire, (3) before genetic testing, not genetically tested, and genetically tested.

Results

Figures 1-3 show the three different partitions. In each, the black line represents the estimated allele frequency trends, which are equal to the sum of the defined paths (including UPGs).

Partitioning by sex. In the Sealyham Terrier, males initially contributed up to 0.098 more to the PLL-causing allele frequencies than females per generation; however, after the introduction of genetic testing, this pattern reversed, indicating breeders now select more intensely in males (Fig.1A). In the four other breeds, the male path increased, and female path decreased the disease-causing allele frequencies, both before and after genetic testing became available, as shown for the PRA-rcd4 in Irish Setters (Fig.1B).

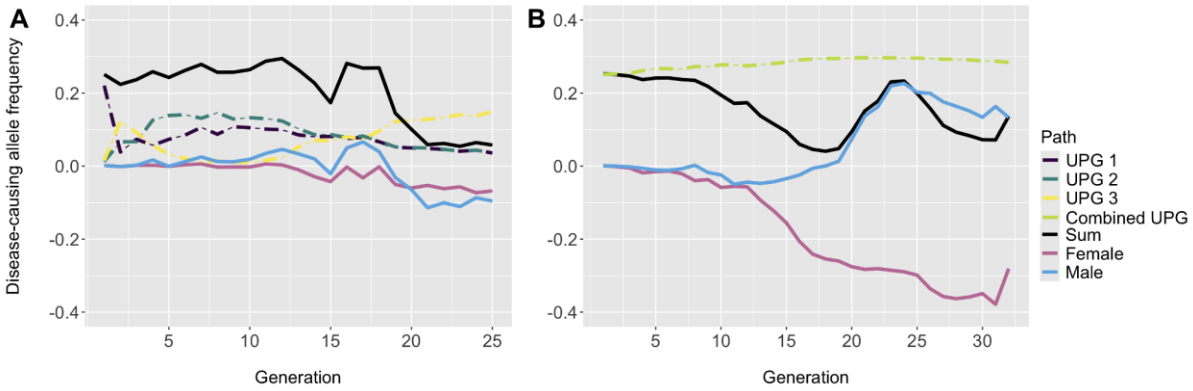

Figure 1: Estimated contributions of males (blue) and females (pink) by Mendelian sampling of disease-causing allele frequencies for A) PLL in the Sealyham Terrier and B) PRA-rcd4 in the Irish Setter.

Partitioning by individual sire. In the Irish setter, two show champion sires, Sire #1 (forest green) and Sire #2 (gold), contributed highly to the dissemination of the PRA-rcd4-causing allele (Fig.2A). Sire #1 was the first in a lineage of popular sires, with over 700 offspring. Sire #2 had fewer than 60 offspring; however, he was the paternal and maternal second great-

grandfather of Sire #1 (Fig.2B). Highly contributing popular sires were also identified in the Gordon Setter and Lancashire Heeler (not shown).

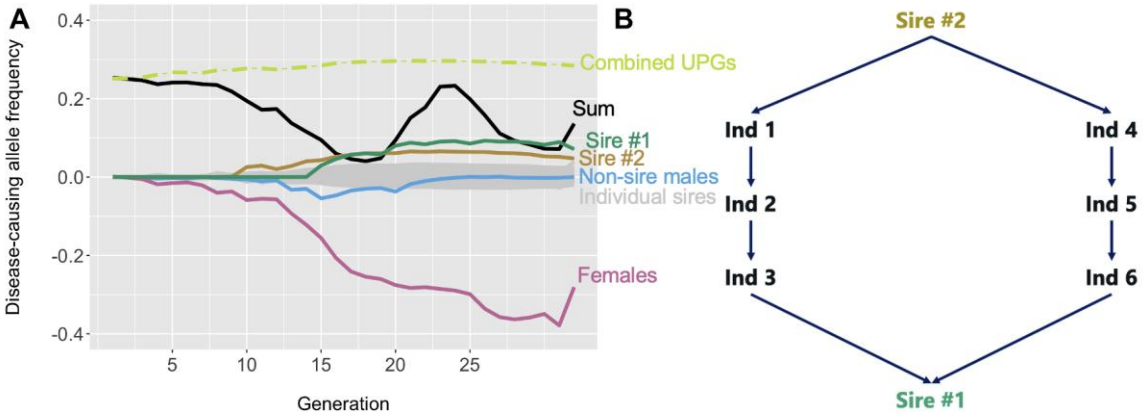

Figure 2: A) Estimated decomposition of allele frequency trend of each sire (grey, forest green, and gold), all non-sire males (blue), and all females (pink) for PRA-rcd4 in Irish Setters. B) Simplified pedigree for the top two sires identified.

Partitioning by genetic test. Across all five pedigrees, the contribution from genetically tested dogs to the disease-causing allele initially increased due to sampling bias, whereby "affected" dogs were used to identify the causative allele (dark green, Fig.3). Shortly after, the contribution from genetically tested dogs declined in line with the decreasing allele frequency following the introduction of genetic testing.

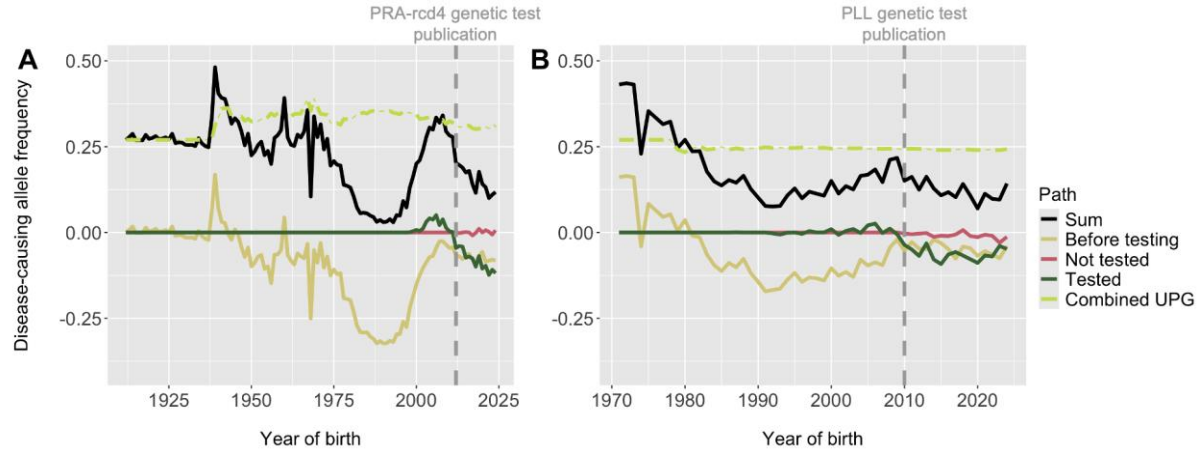

Figure 3: Estimated contributions of before testing (yellow), not genetically tested (red), and genetically tested (dark green) paths on disease-causing allele frequencies for A) PRA-rcd4 in the Gordon Setter and B) PLL in the Lancashire Heeler.

Discussion

Decomposition of estimated allele frequencies, by Mendelian sampling terms, into contributing paths identified key processes driving changes in temporal allele frequencies across two monogenic recessive inherited eye diseases in five RKC-registered breeds. In four of the pedigrees, male path increased, while female path decreased the frequency of the disease-causing allele (Fig.1B), possibly due to separate lineages for sires and dams or less variation in males from popular sires (Antonios *et al*., 2023). Highly contributing sires were identified in three breeds; nearly all were show champions, and most were known popular sires. The one highly contributing, non-popular sire was in the Irish Setter and illustrates the

long-term consequences of line breeding in pedigree dogs (Sire #2, Fig.2B). Previously, in simulations, both popular sires and line breeding have been shown to increase the risk of recessive allele dissemination relative to random mating (Leroy and Baumung, 2011). Finding two highly contributing sires in the Irish Setter was not surprising, as the Irish Setter has "extensive" historic popular sires, with 15 accounting for 79% of long-term contributions (Lewis and Windig, 2017). All highly contributing sires were born between 1960 and 1985, before pedigree digitisation in 1990 and over 25 years before genetic testing (~10 generations). For each sire, genotype probabilities were highly certain (genotype probability for "affected" greater than 0.99) due to high connectivity with genetically tested descendants. However, we may underestimate sires' contributions due to unrecorded offspring prior to digitisation. Still, our study highlights the popular sire effect as a main factor behind the previous rise in the frequency of the PRA-rcd4-causing allele in the Irish Setter and Gordon Setter, and the PLL-causing allele in the Lancashire Heeler.

Positively, genetically tested dogs led to a reduction in disease-causing allele frequencies in all years after genetic testing was introduced across all five breeds (Fig.3). A decline was seen in both the "genetically tested" and "before tested" paths after genetic test introduction, suggesting that breeders used genetic test results to switch to lineages with lower disease-causing allele frequencies. For example, by no longer using previous popular sire lines. This shows dog breeders have used genetic testing to successfully select against the disease-causing allele, concurring with Lewis and Mellersh (2019).

Conclusions

By partitioning disease-causing allele frequencies into breeding paths across the entire pedigree, we have identified instances of the popular sire effect in three of five dog breeds, with inbreeding in the Irish Setter that increased the disease-causing allele frequency in the population. While these historical dogs still contribute, our results show that the decline in disease-causing allele frequency is largely driven by genetic testing conducted by breeders. By providing familiar, species- and breed-specific examples to illustrate the consequences of breeding choices, these findings are essential for promoting good practices among current and future dog breeders.

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