Using patterns in regions of homozygosity to evaluate the use of dogs as preclinical models in human drug development

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Introduction

- Animals are used as preclinical models for human diseases in drug development. Dogs, especially, are used in preclinical research to support the clinical safety evaluations during drug development, however, comparison of regions of homozygosity (ROH) patterns and phenotypes between dog and human are not well known.

- A ROH is defined as a continuous stretch of DNA sequence without heterozygosity in the diploid state (min ROH = established usually between 500kb and 1.5 Mb)[1,2].

- We calculated ROH patterns across distinct human cohorts: the Amish, IGSR 1000 genomes, Wellderly, Vanda 1K genomes.

- We then calculated ROH across different dog breeds (EMBARK project) with emphasis on the beagle, dog that is the preferred breed in drug development[1].

Objective: To determine the degree of inbreeding in dogs compared to human populations.

Application: To investigate the genetic validity of dogs as preclinical models for human drug development.
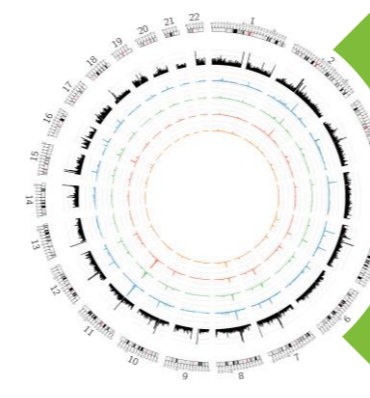
Methods
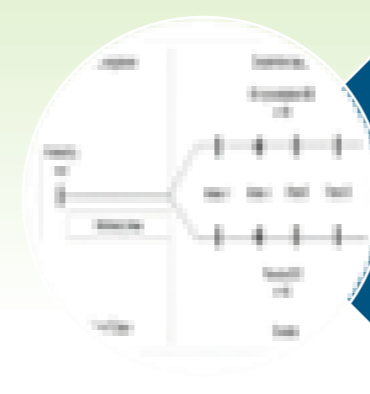
- Calculation of ROH in human cohorts including the Amish, IGSR 1000 genomes, Wellderly, and Vanda 1k genomes. We detected ROH using PLINK. ROH scores reflect the probability of a stretch of SNPs being homozygous due to LOH and they are determined via the homozygosity frequency for each SNP in the genome.
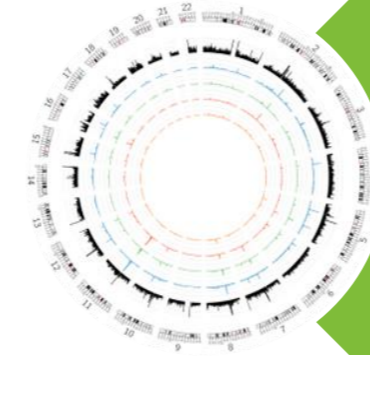
- We detected ROH using PLINK on the EMBARK dog data

- We next calculated the extent of the genome covered by ROH (F_{ROH})
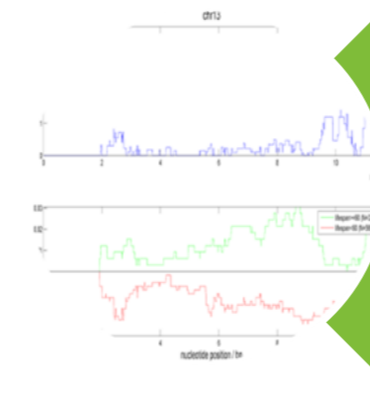
- ROH were defined as runs of at least 50 consecutive homozygous SNPs spanning at least 1500 kb, with less than a 1000 kb gap between adjacent ROH and a density of SNP coverage within the ROH of no more than 50 kb/SNP, with one heterozygote and 5 no calls allowed per window
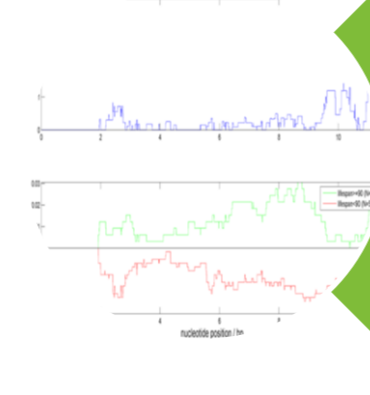
- Detection of ROH, depletion with confidence scores, LD in ROH, region analysis and comparison across species

Results

Runs of Homozygosity by cohort
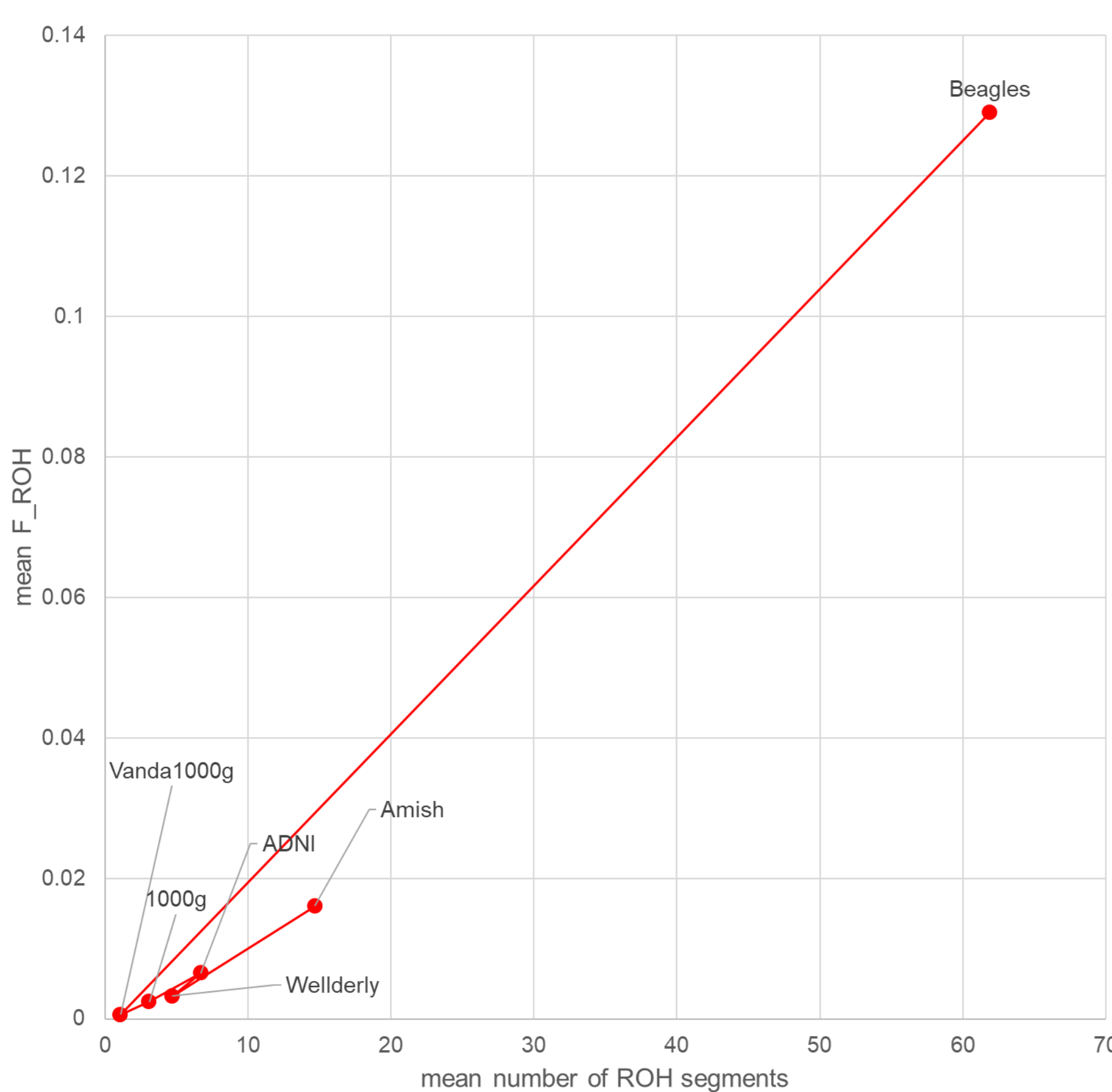
ROH Patterns Across Human Cohorts

Human genome arranged circularly end-to-end: from inside to outside, the rings display ROH across different human cohorts starting from the innermost: 1000g, ADNI, Wellderly and Amish (blue). The outermost ring represent conservation score averaged per region of the human genome.
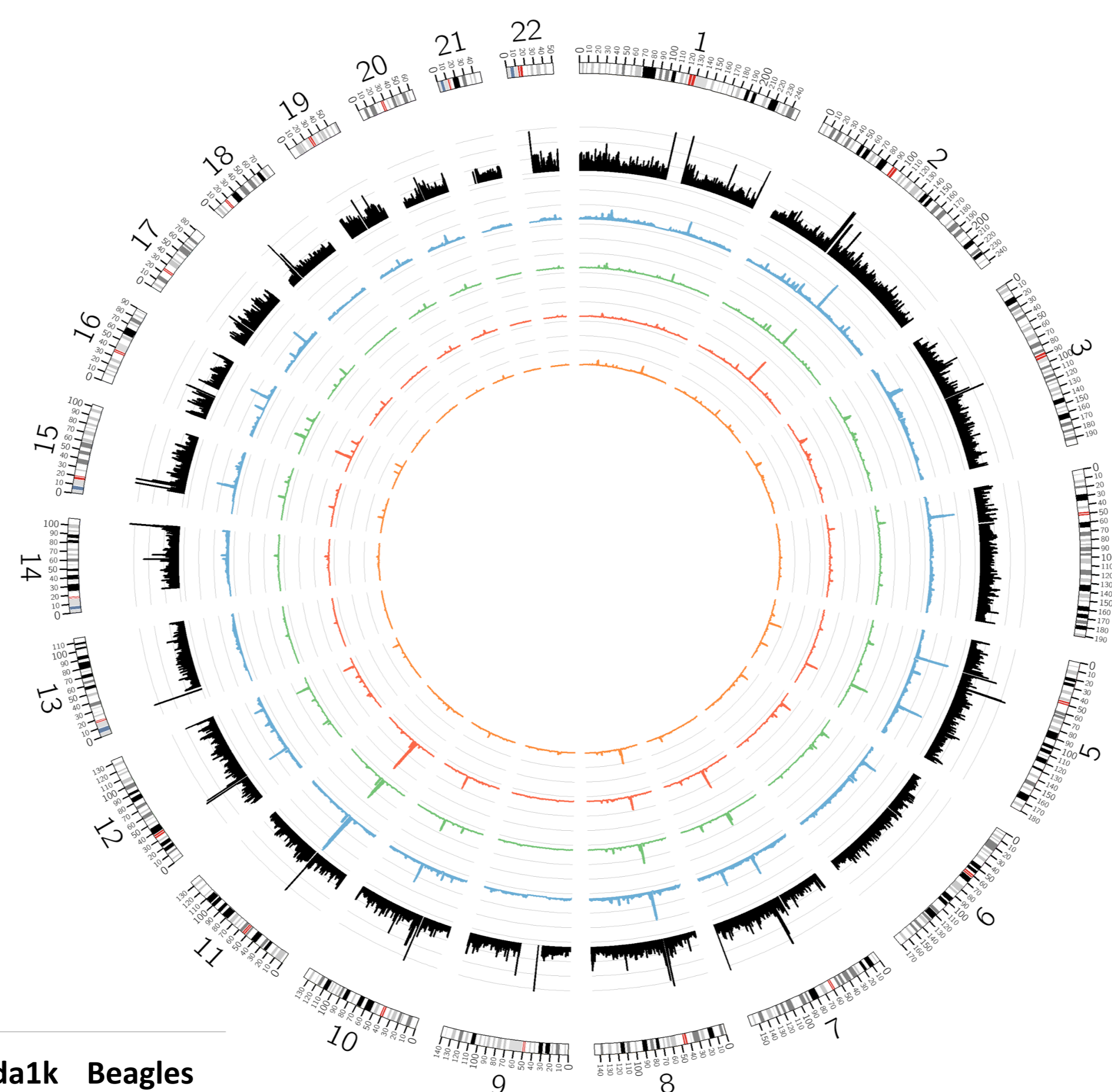
ROH: length and number
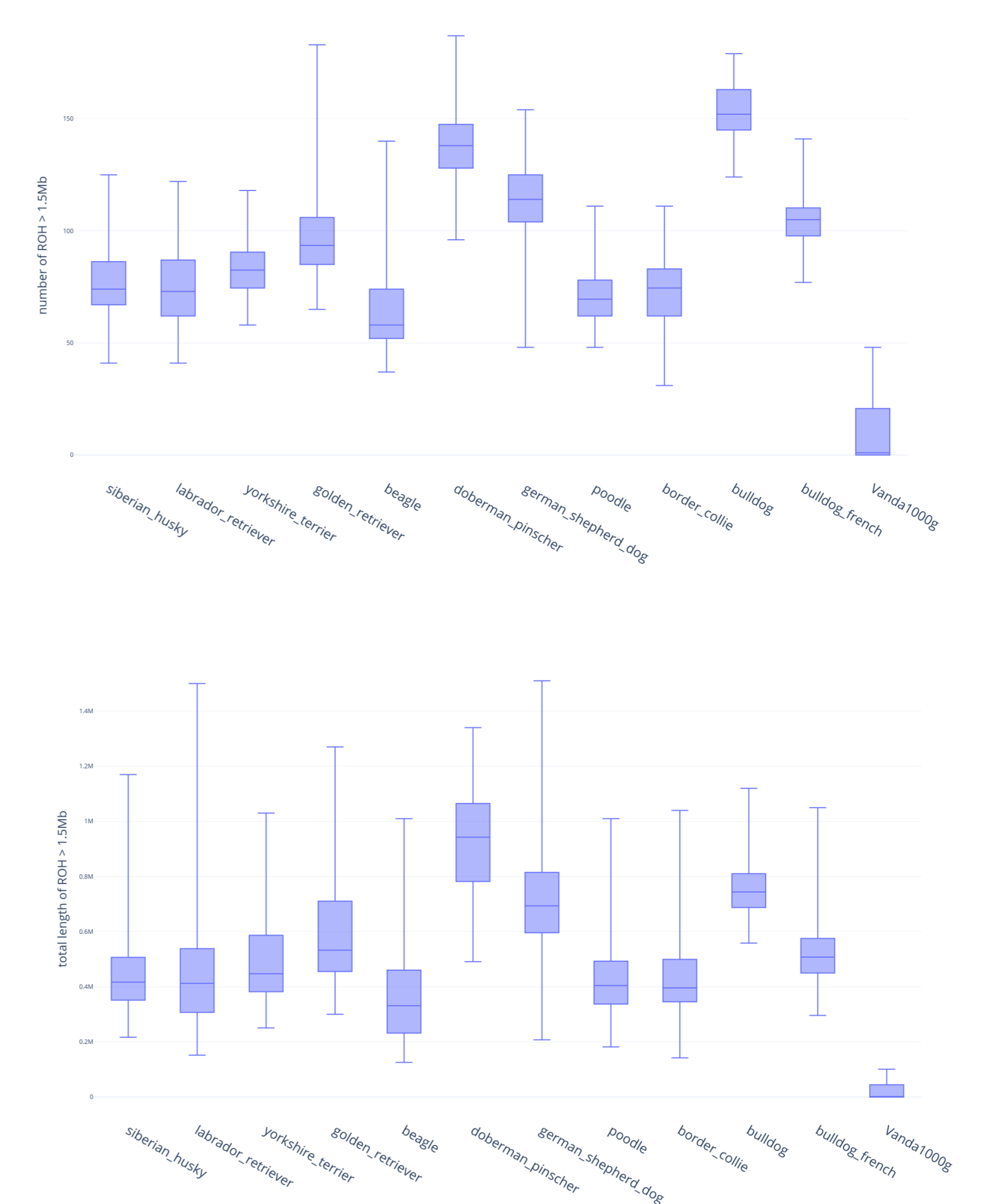
	Amish	Wellderly	ADNI	1000g	Vanda1k	Beagles
total ROH (n)	13165	2404	5534	1977	1012	4896
mean ROH per individual	14.74	4.7	6.72	3.14	1.03	61.97
mean length (kb)	6343	2203	3067	2445	1863	5203
median length (kb)	3577	1858	1856	2309	1746	3137
mean F_ROH	0.016057	0.003233	0.006532	0.002402	0.000604	0.128986
median F_ROH	0.013029	0.002821	0.004122	0.001553	0.000469	0.094472

Results Summary

- We calculated the extent of the genome covered by ROH (F_{ROH}) (human 3.2Gb, dog 2.5Gb).

- F_{ROH} differed significantly between the Amish and the 1000 genomes, and between the human and the beagle genomes. The mean F_{ROH} per 1Mb was ~16kb for Amish, ~0.6kb for Vanda 1k, and ~128kb for beagles.

- This result demonstrated the highest degree of inbreeding in beagles, far above that of the Amish, one of the most inbred human populations.

Conclusions

- **The fraction of the genome covered by ROH (F_{ROH}) was significantly different between human populations (Amish and 1000 genomes) and between humans and beagles.**

- **In the Amish population, one of the most inbred human populations, the F_{ROH} was 12x smaller in comparison to the beagle population.**

- **ROH patterns in beagles increase their susceptibility to inbreeding depression and may introduce deleterious or recessive traits into their genome.**

- **Due to the high degree of inbreeding observed in beagles, preclinical research should use caution in generalizing from dog to human, despite the physiological similarities between the species.**

References

1. Sams, A. J. & Boyko, A. R. Fine-Scale Resolution of Runs of Homozygosity Reveal Patterns of Inbreeding and Substantial Overlap with Recessive Disease Genotypes in Domestic Dogs. *G3 (Bethesda).* **9**, 117–123 (2019).

2. Ceballos, F. C., Joshi, P. K., Clark, D. W., Ramsay, M. & Wilson, J. F. Runs of homozygosity: windows into population history and trait architecture. *Nat. Rev. Genet.* **19**, 220–234 (2018).

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