Dottorato di ricerca in Scienze Veterinarie [XXXII] CICLO - Anno di corso: [2°/3°]

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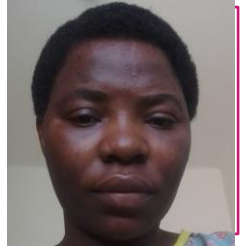

Precision medicine approach in oncology and genetics in dogs

1) Introduction: High recurrent mutations *BRAF* p.V595E urothelial occur in and prostatic carcinoma in dogs.[1] *BRAF* oncogene is a major driver of mutation in cancer thus it represent a key therapeutic target in many cases. complex interplay between VEGF and BRAF mutations and the correlation between angiogenesis and the evolution of *BRAFV600E* kinase inhibitor–acquired resistance is still poorly understood

Objective: aims to investigate the entanglement between angiogenic markers and other morphological and molecular features in urine samples

Materials and Methods: Sample retrieval, *V595E BRAF* analysis, VEGF measurement, Zymography and MMP2, Histology and Cytology.

Results:

Fig.1

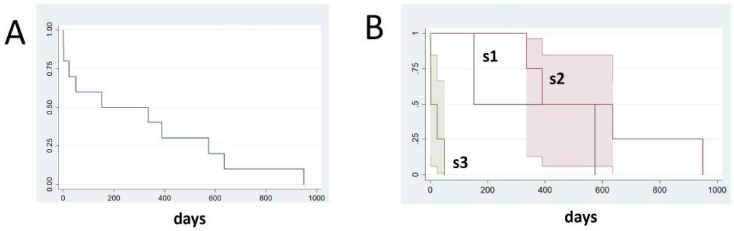

Fig. 2

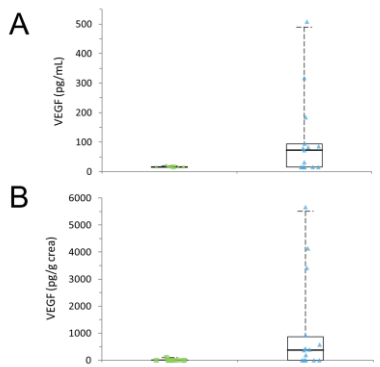

Fig. 3

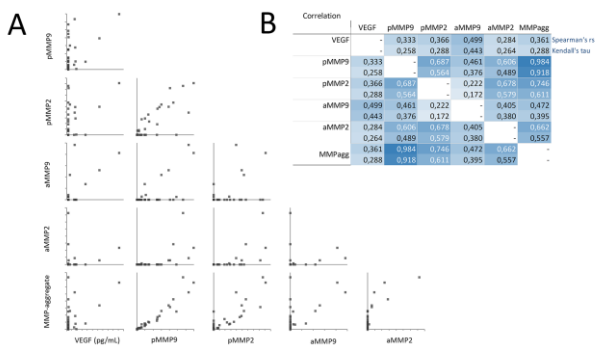

Fig. 4

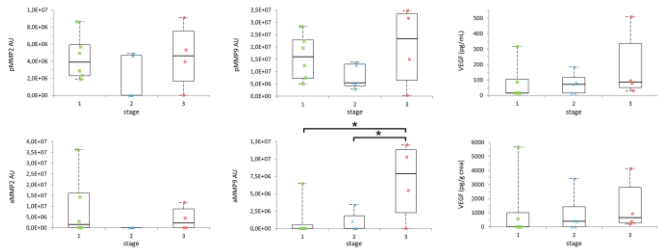

Fig 1: survival time between affected (A) and healthy (B) dogs
Fig 2: VEGF concentration in affected(A) and healthy(B) dogs
Fig 3:correlation analysis-angiogenic factor, VEGF and MMP
Fig 4: correlation analysis- angiogenic maker and cancer stage (1, 2, 3)

Conclusions: Combined approach of two or more BRAF and MEK1/2 inhibitors, including an antiangiogenic approach would be a more targeted innovative rationale of inhibiting the RAS-MAPK pathway. In summary, precision medicine will aid diagnostic accuracy and decrease therapy failures, with continuous research and next-generation sequencing technological advancement. References: Mochizuki H, Kennedy K, Shapiro SG, Breen M. BRAF mutations in canine cancers. *PLoS One*. 2015; **10**:e0129534.

2) Genetic study on a *SGCD* missense variant:

	AA	AG	GG
Muscular dystrophy-affected dog			1
Other Lagotto Romagnolo dogs from Italy [a]	293		
Other Lagotto Romagnolo dogs [a]	448		
Sequenced Lagotto Romagnolo genomes [b]	29		
Sequenced dog genomes from various breeds (DBVDC cohort) [b]	931		

Association of the missense variant in *SGCD* with the muscular dystrophy phenotype in Lagotto Romagnolo dog. N:B [a] phenotypes are unknown. [b] DBVDC cohort.

A Lagotto Romagnolo dog was detected to have a missense variant of *SGCD* gene and the mutant allele was confirmed using the Sanger sequencing in a Lagotto Romagnolo dog. The single available DNA samples from the affected dog carried the mutant allele in homozygous state (Table). A population control of 741 Lagotto Romagnolo dogs in which 198 of them were genotyped using the TaqMan™ SNP Genotyping Assay. However, the mutant *SGCD* allele was detected only in the affected dog, whereas it was absent in all controls.

Conclusions: The study represents an example of precision medicine approach by using whole genome sequencing and Sequence variant filtering of an affected patient. Rapid MGB TaqMan genotyping allowed to rapidly screen a large cohort of Lagotto dogs to assess the rarity of the mutated allele. References: Vainzof M, Souza LS, Gurgel-Giannetti J, Zatz M. Sarcoglycanopathies: an update. Neuromuscul Disord. 2021 Oct;31(10):1021-1027. doi: 10.1016/j.nmd.2021.07.014.