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Molecular Parallelisms and Divergences Between Human and Canine Cancers

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Background: Tumorigenesis has been widely accepted as an evolutionary process. Evolutionary biology and cross-species cancer genomics can help us to study genome-wide changes at the somatic level involved in tumor development and progression. We performed whole-genome sequencing analysis by using GATAK pipeline and Mutect2 for twenty-four dog mammary cancers and identified 47715 somatic mutations comprising 210 exonic mutations. Comparison between human and dog reveals similarities and differences in the mutation profiles across both species, in terms of the mutated driver genes and mutation number, which are likely to influence tumor behavior and response to treatments. Human breast cancer had a higher median mutation burden comparable to canine mammary cancer, in exonic regions (2.67 and 0.187 average no. of mutations per tumor per megabase (Mb), respectively). We also observed the mutational signature contributions in canine mammary cancer. Signatures 4 and 2 in dog mammary cancer were analogous to human ageing-related mutagenesis (COSMIC signatures 1 and 5). Signature 4 prevalence, correlates with age of cancer diagnosis in a clock-like manner which supports the hypothesis of mutation accumulation theory in both species. On the basis of the fact that the proportion of the enriched mutation types which much less in signature 4 in dog compared with signature 1 in human implicating a potential divergence in ageing-related evolution during tumorigenesis..

Results: Genome-wide Ka/Ks ratio for human equals to 1.19, a hallmark of neutrality, and in the dog, Ka/Ks is 0.61, seems negative selection. As, most of the tumors in human have been evolving neutrally, which does not mean the absence of selection. It only reflects that the effect of positive selection in accelerating evolution is exactly canceled out by the effect of negative selection. Negative selection in canine mammary cancer indicates, maybe coding point mutations are lost through negative selection or there are other unknown reasons. These findings may suggest, the same organs in different mammals impose different selective pressures on the same set of genes in cancer. To address the mutation accumulation and antagonistic pleiotropy theory, we investigated Ka/Ks value 237 aging-related genes from human and dog.

Conclusion : An evolutionary trade-off suggests that the same gene can be favorable for fitness, but can confer risk of traits later in life after reproduction in human, but in dogs, it seems different. Aging-related genes do not show selection in canine mammary cancer. It demonstrates new aspects of cancer genomics.

Keyword: Somatic mutations, Tumorigenesis, Cancer genomics

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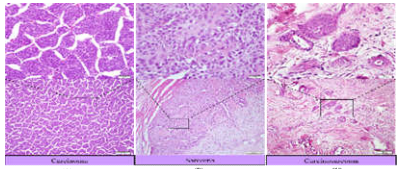

Figure 1

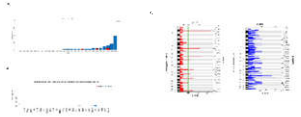

Figure 2

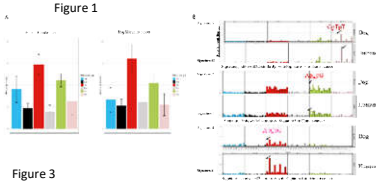

Figure 3

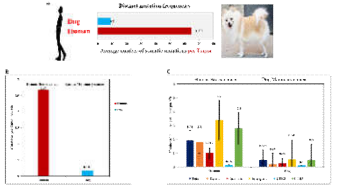

Figure 4

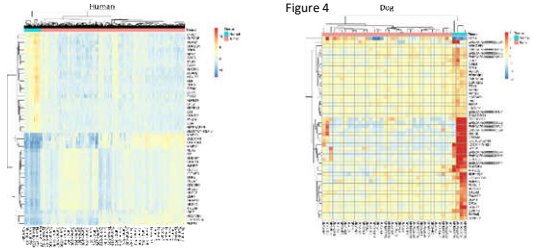

Figure 5