



# A Comprehensive Review of p53 Mutations and Cancer Incidence in Companion Animals






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<p><b>Background and Motivation</b></p> <p>p53 is a major tumor suppressor known as the 'guardian of the genome'. It is an important and well-studied gene that codes for the tumor suppressor protein under the same name. p53 mutations often lead to loss of important regulatory functions and are involved in many cancer processes. Normally, when p53 detects DNA damage, it activates a sequence of downstream proteins that will either fix the affected cell, lead to cell senescence or undergo apoptosis. Somatic p53 mutations occur in almost every type of human cancer. This is one of the main reasons for the vast clinical interest in uncovering the many forms of cancerous p53 mutations.</p> <p style="text-align: center;">OPEN</p>	<p><b>Canine and feline Germline Mutations</b></p> <p>6 total germline mutations discovered in dogs and no germline mutations discovered in cats.</p>  <p><b>Figure 1.</b> All canine germline mutations uncovered from previous research. Equivalent canine and human mutations are in blue color.</p> <p>Li-Fraumeni syndrome is a devastating but quite rare disease which causes a person affected to develop many types of cancer over their lifetime, often beginning in childhood. In Marfe et al., 2012, an English Setter dog appeared to have a multi-cancer like syndrome, where multiple types of cancer were present in one patient. From a melanoma tumor sampled in this dog, a germline missense mutation, of arginine to glutamine was discovered in codon 236. The human equivalent mutation is located at codon 248 according to the Blast sequence. Codon 248 is in fact one of the most frequently mutated p53 hotspot mutation in people. Furthermore, this same mutation in people has been associated with Li-Fraumeni syndrome.</p> <p>Another interesting case was observed in a canine mammary tumor, where two different germline mutations were discovered. The mutations observed are one large deletion spanning exons 3-7 and a missense mutation that lead to substitution of the amino acid proline to leucine at codon 69. This was the only case of two different p53 germline mutations seen in one canine.</p> <p style="text-align: center;">OPEN</p>	<p><b>Canine and Feline Somatic Mutations</b></p> <p>250 canine somatic mutations were compiled overall, of those 175 different mutations, 47 feline somatic mutations compiled, 41 different mutations from one another.</p>  <p><b>Figure 2.</b> All canine somatic mutations. Equivalent canine and human mutations are in blue color.</p>  <p><b>Figure 3.</b> All feline somatic mutations. Equivalent feline and human mutations are in blue color.</p> <p style="text-align: center;">OPEN</p>	<p><b>Conclusions</b></p> <p>It appears that many p53 mutations in dogs and to a lesser degree in cats, have corresponding and pathologically important mutations in humans. Both veterinary and human cancer research can be influential to one another and contribute to cancer therapeutics. Practically, where differences are identified, therapeutics can be adjusted accordingly such as we have identified with differences in functional domain mutations.</p>
<p><b>Methods</b></p> <p>The mutations are obtained and sequenced directly from canine and feline tumors and tumor-made cell lines. We focus on mutations which are more likely to be pathogenic and tumorigenic and therefore did not include silent and intron mutations as some of these may be misclassified and are in fact polymorphisms in these domestic species. Using Basic Local Alignment Search Tool (BLAST), we align TP53 (tumor protein p53) isoform a found in homo sapiens with TP53 in canis lupus familiaris and felis catus (only one isoform present in both species). Using the aligned sequences, canine and feline alterations detected in the literature were compiled against their human counterparts.</p> <p>The information obtained here is assembled into cohesive figures for both dogs and cats, germline and somatic alterations. We then analyze the mutational data and note any associations of interest.</p>	<p><b>Acknowledgements</b></p> <p><b>Financial support</b> was provided by the Student's Training in Advanced Research (STAR) Program.</p> <p><b>Research Grant:</b> RO1 CA250338-01</p> <p><b>Student Support:</b> National Institutes of Health T32 GM010959</p> <p>Thank you to Dr. Xinbin Chen for mentoring me through the grant writing, research process and paper writeup. Thank you to my family and friends for their constant support.</p>		

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