Chromosomal 'breakpoints' linked to canine cancer

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North Carolina State University researchers have uncovered evidence that evolutionary "breakpoints" on canine chromosomes are also associated with canine cancer. Mapping these "fragile" regions in dogs may also have implications for the discovery and treatment of human cancers.

When new species evolve, they leave genetic evidence behind in the form of "breakpoint regions." These regions are sites on the genome where chromosomes broke during speciation (when new species of dogs developed). Dr. Matthew Breen, professor of genomics at NC State, and graduate student Shannon Becker looked at the breakpoint regions that occurred when the canid (dog) species differentiated during evolution. They compared the genomes of several wild canine species with those of the domestic dog. By overlaying the genomes, they found shared breakpoints among 11 different canid species – the so-called evolutionary breakpoints.

"The interesting thing about the breakpoint areas in the canid chromosome is that they are the same regions that we have shown to be associated with chromosome breaks in spontaneously occurring cancers," Breen says. "It is possible that the re-arrangement of chromosomes that occurred when these species diverged from one another created unstable regions on the chromosome, and that is why these regions are associated with cancer."

The researchers' results appear in *Chromosome Research*.

"As species evolve, genetic information encoded on chromosomes can be restructured – resulting in closely related species having differently organized genomes," says Becker. "In some cases, species acquire extra chromosomes, called B chromosomes. We looked at these extra B chromosomes in three canid species and found that they harbor several cancer-associated genes. Our work adds to the growing evidence that there is an association between cancer-associated genomic instability and genomic rearrangement during speciation."

"The presence of clusters of cancer- associated genes on canid B chromosomes suggests that while previously though to be inert, these chromosomes may have played a role in sequestering excess copies of such genes that were generated during speciation," adds Breen. "We now need to determine whether these stored genes are active or inert – that information could give us new tools in cancer detection and treatment."

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Abstract:
The emergence of genome-integrated molecular cytogenetic resources allows for comprehensive comparative analysis of gross karyotype architecture across related species. The identification of evolutionarily conserved chromosome segment (ECCS) boundaries provides deeper insight into the process of chromosome evolution associated with speciation. We evaluated the genome-wide distribution and relative orientation of ECCSs in three wild canid species with diverse karyotypes (red fox,Chinese raccoon dog, and gray fox). Chromosomespecific panels of dog genome-integrated bacterial artificial chromosome (BAC) clones spaced at ~10-Mb intervals were used in fluorescence in situ hybridization analysis to construct integrated physical genome maps of these three species. Conserved evolutionary breakpoint regions (EBRs) shared between their karyotypes were refined across these and eight

additional wild canid species using targeted BAC panels spaced at ~1-Mb intervals. Our findings suggest that the EBRs associated with speciation in the Canidae are compatible with recent phylogenetic groupings and provide evidence that these breakpoints are also recurrently associated with spontaneous canine cancers. We identified several regions of domestic dog sequence that share homology with canid B chromosomes, including additional cancer-associated genes, suggesting that these supernumerary elements may represent more than inert passengers within the cell. We propose that the complex karyotype rearrangements associated with speciation of the Canidae reflect unstable chromosome regions described by the fragile breakage model.

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