Media News

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A Set of Firsts: Roche NimbleGen CGH Microarrays Enable the First Maps of Genome-Wide DNA Copy Number Variation (CNV) in Dogs

The unique evolutionary history of dogs (*Canis lupus familiaris*), domesticated over 14,000 years ago, includes artificial selection, population bottlenecks, and inbreeding, which has resulted in over 400 genetically distinct breeds. These characteristics provide a unique model organism with a broad phenotypic assortment of shapes, sizes, and temperaments to address fundamental questions in population genetics, evolution, and variations in their genetic architecture.

DNA structural variation is now recognized as a significant source of genetic diversity, however its complete biological impact remains unclear. In two recent studies, Roche NimbleGen Comparative Genomic Hybridization (CGH) microarrays were used to perform systematic and genome-wide analysis of DNA copy number variation (CNV) across dog breeds (1,2). Results from these landmark studies revealed that the extent of CNVs in the dog genome and their association with known and candidate disease genes is similar to mice and humans.

In the first study, Chen et al. analyzed seven pedigreed (or "purebred") dog breeds using a standard NimbleGen Dog CGH Whole-Genome Tiling Array consisting of 385,000 long oligonucleotide probes with a median probe spacing of 4675 bp. This analysis identified many CNVs in linkage disequilibrium with flanking sequence. Cluster analysis showed that CNV regions in dog breeds tend to group according to breed classes and may be associated with breed-specific traits.

In the second study, Nicholas et al. designed a custom NimbleGen CGH array targeting all predicted segmental duplication regions, which are now recognized as "hotspots" for genome copy number variation in humans and other model organisms. Analysis of the public canine genome reference sequence revealed an estimated 4.21% of the genome is comprised of segmental duplications, which overlap 841 genes and are enriched for certain biological functions and transcription factors. Analysis of a panel of 17 genetically and phenotypically diverse dog breeds and a gray wolf, identified extensive copy number variation (3583 CNVs mapping to 678 unique regions) that span 429 genes involved in a wide range of biological processes including gene regulation, sensory

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perception, and immune responses. In total, CNVs were shown to comprise 24 Mb of polymorphic sequence and 20% of the predicted segmental duplications exhibit CNVs.

To date, research on genetic variation in dogs has been largely limited to either single nucleotide polymorphism (SNP) or microsatellite studies. However, the landmark studies described above indicate that DNA copy number variation is a significant source of genetic and phenotypic variation in dogs. The availability of high-resolution maps of CNVs across dog breeds will allow researchers to evaluate the biological significance of breed-specific CNVs and associated candidate disease genes. According to the researchers, results from these studies illustrate how canine CNV discovery can impact the rapidly growing use of dog models, uncover and answer basic genetic mechanisms, and address diseases in both dogs and humans. Dogs share over 350 inherited diseases that are similar to those of humans. Therefore, continued studies of dog genome variation and its impact of disease will hopefully lead to translational research and improved health care for humans as well as "man's best friend".

Roche NimbleGen is a leading innovator, manufacturer, and supplier of a proprietary suite of DNA microarrays, consumables, instruments and services. Roche NimbleGen produces high-density arrays of long oligonucleotide probes that provide greater information content and higher data quality necessary for studying the full diversity of genomic and epigenomic variation. The enhanced performance is made possible by Roche NimbleGen's proprietary Maskless Array Synthesis (MAS) technology, which uses digital light processing and rapid, high-yield photochemistry to synthesize long oligonucleotide, high-density DNA microarrays with extreme flexibility. For more information about Roche NimbleGen, please visit the company's website at www.nimblegen.com

(1) Wei-Kang Chen, Joshua D. Swartz, Laura J. Rush, et al., *Genome Res.* published online November 17, 2008; doi: 10.1101/gr.083741.108
(2) Thomas J. Nicholas, Ze Cheng, Mario Ventura, et al., *Genome Res.* published online January 7, 2009; doi:10.1101/gr.084715.108

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health and quality of life. Roche is the world leader in in-vitro diagnostics and drugs for cancer and transplantation, and is a market leader in virology. It is also active in other major therapeutic areas such as autoimmune diseases, inflammatory and metabolic disorders and diseases of the central nervous system. In 2008 sales by the Pharmaceuticals Division totalled 36.0 billion Swiss francs, and the Diagnostics Division posted sales of 9.7 billion francs. Roche has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai, and invested nearly 9 billion Swiss francs in R&D in 2008. Worldwide, the Group employs about 80,000 people. Additional information is available on the Internet at www.roche.com.

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