Using Genomic Biology to Study Pet Aging

Kelly S. Swanson, PhD
University of Illinois at Urbana-Champaign
Department of Animal Sciences
Division of Nutritional Sciences
Department of Veterinary Clinical Medicine
Urbana, IL
ksswanso@illinois.edu

Abstract

Due to improved disease management, nutrition and husbandry practices, companion animals are living longer, with seniors making up 30 to 40% of the pet population. As in humans, pet aging is accompanied by a variety of chronic disease states. Advances in genomic biology provide opportunities to increase our understanding of the aging process, identify mechanisms by which age-related illnesses occur, and design targeted prophylactics and/or therapeutics. This presentation will provide background information on the field of genomic biology, discuss recent pet genomics studies, and project what the future may hold as it pertains to veterinary medicine and pet nutrition.

Glossary of Abbreviations
HGP: Human Genome Project
mRNA: Messenger RNA
PCR: Polymerase Chain Reaction

Aging Pets

Due to improved disease management, nutrition and husbandry practices, companion animals are living longer, with seniors making up 30 to 40% of the pet population.[1] Aging is characterized by progressive organ degeneration, decline in stress response, homeostatic imbalances, and reduced immune surveillance. These physiological changes not only increase the risk of chronic disease development, it also is common to detect abnormalities in senior pets when examined physically or through standard laboratory testing (e.g., urinalysis, serum biochemistry), even when they are apparently in good health.[2] Wellness and health-care programs for senior and geriatric pets are common in veterinary hospitals. A key component of a senior care program is preventive health, including early disease detection and treatment.[3]

Aging is a multifactorial process affected by many genetic and environmental factors. Many theories have been proposed, but a few biological processes, including oxidative stress, epigenetic alterations, telomere shortening, and DNA damage, have been consistently shown to be involved and continue to be studied in humans and animal models. In addition to understanding the complicated processes involved, a key challenge in humans and pets is detecting these and other detrimental changes in a noninvasive manner so that intervention can begin early in the disease process. Genomic tools provide scientists with the opportunity to increase understanding of the aging process, identify mechanisms by which age-related illnesses occur, and design targeted prophylactics and/or therapeutics.

Genomic Biology

Nowadays, the field of genomics encompasses many things, including the ability to sequence DNA for genetic testing and measure messenger RNA (mRNA), or protein expression, and metabolite profiles (Table 1). An amazing amount of data may now be generated with automated, high-throughput sequencers and analyzed by high-powered computers, leaving human brain power as the bottleneck in the analytical system. With all the powerful tools that scientists have at their disposal, one may forget how far the field has come over the past few decades.

In the 1970s and 1980s, key developments in the genomics field included the discovery of restriction enzymes for DNA splicing, the introduction of polymerase chain reaction (PCR) and the first automated sequencers. At that time, the term "genomics" referred to the generation and analysis of information about genes and genomes.[4] Progress was certainly being made, but the term "high-throughput" was not in anybody's vocabulary. In the 1990s, the term "functional genomics" was coined and was quickly followed by many

Table 1. Common Genomic Terms

Genome	The totality of all DNA in an organism
Genomics	Study of genomes, including genome mapping and sequencing
Functional Genomics	Study of gene function
Nutritional Genomics	Study of nutrient-gene interactions
Proteomics	Study of all proteins found in a particular cell, tissue or organism
Metabolomics	Study of all metabolites found in a particular cell, tissue or organism

of the other 'omic terms used today. The 1990s also were an exciting time in the field because it is when the Human Genome Project (HGP) was launched (1990) and nearly completed. The HGP took over a decade to complete and included a sequencing battle referred to as the genome war between private industry and federally funded scientists.[5] The tools and concepts in the field have continued to evolve at a rapid pace, greatly increasing the speed and reducing the cost by which projects may be accomplished. As an example of how much things have changed, consider that while the HGP required over a decade of time, hundreds of scientists and nearly $3 billion to complete in the 1990s, the same can now be accomplished in a couple of days by a well-trained genomic biologist for less than $5,000 (*https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/*).

Even though the plug-and-play reagents, highly automated sequencers and powerful computers were not available in the 1980s and 1990s, scientists appreciated the widespread implications the field would have on medicine, agriculture and veterinary medicine.[4,6] Training as a postdoctoral researcher in functional genomics soon after the first draft version of the human genome had been published (2001), I quickly realized how powerful the genomic tools we had at the time were and imagined not only what that could mean for human medicine but also for companion animals once they were chosen for study. In regard to research, one must decide whether to focus on what is hardwired in the animal (DNA) or what may be manipulated once it is conceived (mRNA, protein, metabolites). Although genomic biology has shed a lot of light on the canine and feline genomes and what that may mean from a genetics perspective,[7] progress has been slow in regard to functional genomics and nutritional genomics, especially when it comes to aging research.

Genomics and Pet Aging

Our laboratory has published several publications on the mRNA expression profiles of young adult versus geriatric dogs, including skeletal muscle,[8] cerebral cortex,[9] adipose,[10] colonic mucosa,[11] and liver[12] tissues. Others have used genomic tools to measure mRNA expression of the prostate gland of immature, young adult dogs and geriatric dogs[13]; circulating neutrophil-related mRNA expression of growing puppies, young adult dogs and senior dogs[14]; and myocardial mRNA expression of young adult and geriatric cats.[15] The results and implications of these studies will be discussed.

Continued progress in this field is possible but will require financial resources from a variety of funding sources and teams of well-trained scientists who are passionate about companion animal health. As a newly appointed assistant professor, I was inspired by a poem written 20 years earlier by Donald Patterson, professor of medicine and medical genetics at the University of Pennsylvania and a pioneer in the field of veterinary genetics:[16]

"We'd like to explain what pathology means
In terms of what's wrong with the structure of genes
Know if a control or a structural locus
Constitutes the exact pathological focus

With the help of the enzymes that slice DNA
And cloning techniques, we now have a way
To study the actual sequence of bases
To know when those purines are not in their places"

As I prepared these proceedings, I stumbled onto a similarly written poem of my own from 2005. Being inspired and apparently having too much time on my hands and/or procrastinating on other tasks, I created a version of my own highlighting the major genomic projects and most powerful tools of the time and adding the importance that nutrition plays in chronic disease:

"It's the 21st century and we've witnessed remarkable feats
The first draft of the canine genome sequence is now complete
The 7X draft sequence is robust with very few gaps
And dogs, wolves, and a coyote are being used
to create a SNP map

The art of sequencing has been mastered;
solving genetic diseases will soon follow
But our knowledge of complex diseases
still remains quite hollow
Today's science includes nanotechniques,
microarrays, and SNP profiles
And bioinformatics techniques required
for interpreting the data we compile

For complex diseases, genetics and
environment definitely play a role
But the impact of diet on these conditions
may end up stealing the show
The search for mechanisms of disease will be
hard and long; it will not be noted for its brevity
But these endeavors will be worth it, eventually
leading to enhanced health and longevity"

While sharing this piece of work is somewhat embarrassing and is atypical for conference proceedings, I do so to make a point. Although impressive technological advancements were made from 1982 to 2005 and even more have been made since then, the goals and challenges pertaining to pet health and disease have remained the same. That is not to say that progress has not been made but speaks to the complicated nature of aging and chronic diseases and substantiates the need for more research. Given the availability of powerful molecular tools that enable high-throughput analysis of DNA, RNA, proteins, and metabolites, high-speed computers capable

of handling vast and complicated datasets, and a conceptual framework that now applies functional genomics to nutrition and health, we are living in and contributing to a historical time in science. Moving forward, genomic biology should be used effectively as an important component of research programs to understand the aging process and its relation to chronic disease states, which may contribute to early disease detection and development of prevention and treatment strategies.

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