

The 2013 Genetics Society of America Medal Elaine A. Ostrander



THE Genetics Society of America is proud to announce Elaine A. Ostrander as recipient of the 2013 Genetics Society of America Medal. Elaine is presently the Chief of the Cancer Genetics Branch at the National Genome Research Institute (National Institutes of Health). Her numerous outstanding contributions to Genetics over her career add to the legacy of this prestigious award. In particular, her parallel research pursuits during the last 15 years on the genetic basis of phenotypic variation between dog breeds and on genome-wide associations in human cancers attest to the breadth, creativity, and significance of her work.

Elaine's beginnings as a scientist were in molecular biology, studying how higher-order DNA structure influenced gene expression while as a graduate student at Oregon Health Sciences University (Ostrander *et al.* 1988). She continued along these lines as a postdoctoral fellow under James Wang at Harvard (Ostrander *et al.* 1990), whom Elaine credits as being instrumental in her career development (Ostrander 2012b). During a brief stint at University of California, Berkeley, with Jasper Rine, and continuing in her own laboratory at the Fred Hutchinson Cancer Center in Seattle, Elaine began using her molecular skills to develop DNA markers for genetic mapping (Ostrander *et al.* 1992), focusing very early on the dog (Ostrander *et al.* 1993, 1995). At the same time, she was funneling her passion for genetics toward investigations of human cancer, first in screening women and men for BRCA1 mutations that were associated with breast and prostate cancer, respectively (Langston *et al.* 1996a,b; Malone *et al.* 1998), and later in whole-genome scans for risk loci (Gibbs *et al.* 2000).

Building Canine Genetics

Elaine is passionate about dogs, and she essentially founded modern canine genetics. Some scientists have long recognized the many alluring facets of the dog as a species and as a genetic model, and Elaine has played a major role in raising awareness with numerous reviews and books (Sutter and Ostrander 2004; Parker and Ostrander 2005; Spady and Ostrander 2008; Parker *et al.* 2010). Intriguing questions include how genes underlie

behaviors and instincts of various breeds (*e.g.*, aggressive vs. docile, herding or hunting expertise, etc.), the huge diversity in morphometric traits among breeds (*e.g.*, size, shape), domestication history, and breed-associated diseases. With collaborators, she built the first genetic maps of the canine genome with microsatellite markers (Mellersh *et al.* 1997; Werner *et al.* 1999), followed by a high-resolution physical map (using radiation hybrid mapping) (Guyon *et al.* 2003).

The efforts dedicated to building genetic and physical maps of the canine genome began to yield fruits: the mapping of phenotypic loci for eye disease in collies (Lowe *et al.* 2003), neoplasias in German shepherds (Lingaas *et al.* 2003), and finally a spectacular article that identified a major locus that determines breed size as insulin-like growth factor 1 (Sutter *et al.* 2007). This article used a gene-mapping paradigm that clearly reveals the power of dog genetics to map simple and complex traits. Principally, the strategy exploits two aspects of domesticated dog breeds: (1) Most were created recently and trace their roots to very few founders, and (2) humans selected for specific features in making the breeds. Therefore, the alleles underlying notable distinctions between breeds, as well as linked polymorphisms, pre-existed their divergence. Meanwhile, the generations that have passed since divergence of breeds essentially represent a powerful genetic experiment. By exploiting quasi-fixed recombinant haplotype blocks present in different breeds, coupled with the low level of segregating alleles within a given breed, Ostrander and collaborators showed that phenotypic traits can be mapped with gene-level resolution.

Doggedly Defining the Genetic Basis of Diversity

The remarkable history of dog breeding has provided Elaine and her collaborators with a rich genomic resource for correlating genes with morphological as well as behavioral traits. Sometimes the findings have been unexpected, such as the discovery that an additional *fibroblast growth factor 4* (*fgf4*) gene introduced through retrotransposition is likely responsible for the short legs of many breeds including dachshunds and basset hounds (Parker *et al.* 2009). The fact that all of the variation in dog coats (the length, texture,

curliness, and patterns of hair) can be attributed to the combinatorial action of a mere three genes was another elegant demonstration of the power of applying genetic analyses to the traits most desired in purebreds. After learning of this work, one gazes at their cock-a-poo's charming facial furnishings or their labrador's short, dense coat with a new appreciation.

Elaine's projects also have strong evolutionary implications, notably in the anatomical changes that accompanied the domestication of dogs from their wolf ancestors. An example is the dramatic differences in craniofacial morphology that is a defining feature of dog breeds, from the flattened face of the bulldog to the elongated snout of the Afghan hound. Comparative genome-wide association studies (GWAS) pointed to the *bone morphogenetic 3* locus as a key contributor in the selective breeding that has led to such diversity in skull shape (Schoenebeck *et al.* 2012; Schoenebeck and Ostrander 2013). Overall, Elaine and colleagues have determined that most morphological variation in domestic dogs can be traced to 51 genomic regions (Boyko *et al.* 2010).

Another problem Elaine has championed that is ripe for further exploration is the genetic basis for contrasting behaviors in seemingly similar animals. Alaskan sled dogs bred for their athletic performance can be distinguished by their proficiency as sprinters or as long-distance runners, with accompanying, distinct genetic profiles. Genomic analyses have identified single-nucleotide polymorphisms strongly associated with such behavioral differences, as in the *myosin heavy chain 9* gene, that might promote greater heat tolerance in sprint dogs (Huson *et al.* 2012). The ramifications of such work for understanding the attributes of elite athletes that contribute to their superior skills have been well appreciated by Elaine and her colleagues (Ostrander *et al.* 2009).

Challenging Cancer Genetics

Half of Elaine's laboratory has focused on the genetics of human cancer, particularly prostate cancer, which involves large international collaborations to conduct and validate GWAS results (Kote-Jarai *et al.* 2011; Jin *et al.* 2012; Lu *et al.* 2012). While the biomedical relevance of this work is extremely high (~17% of American men will get prostate cancer), the genetics are proving to be somewhat more difficult than trait mapping in dogs. However, recent studies have successfully identified candidate loci associated with susceptibility to prostate cancer in high-risk families and certain populations (Jin *et al.* 2012; Stott-Miller *et al.* 2012; Taioli *et al.* 2012; Xu *et al.* 2013).

Intriguingly, what may seem like disparate research directions are intimately linked for an astute geneticist. Elaine has also used her powerful genome-wide strategies to uncover polymorphisms involved in a variety of canine cancers. Because a poorly understood sarcoma that is rare in humans is quite common in Bernese mountain dogs, her group was able to find a haplotype common to the vast majority of affected animals, thereby pinpointing defective regulation of

genes that had been implicated in human cancer (Shearin *et al.* 2012). Elaine has articulated persuasively how the high resemblance of some canine and human diseases, the knowledge gained from veterinary medicine, and the ability to identify the genes underlying breed-associated diseases make dogs such a compelling model for human medical genetics (Ostrander 2012a).

The lessons that can be learned from Elaine's career thus far are that devotion to developing a new model for genetic analyses, the insight to capitalize on untraditional resources, and cross-disciplinary thinking lead to a greater understanding of human biology and health. Elaine's pioneering studies have demonstrated that man's best friend is indeed a good friend to great science.

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