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International meeting

Canine genomics and veterinary: from domestication to pathologies

Department of Veterinary Medicine, University of Milan

June 18th 2018, Milan - Via Mangiagalli 25, Room C03, 08:30-13:30

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International meeting

Canine genomics and veterinary: from domestication to pathologies

Department of Veterinary Medicine, University of Milan

June 18th 2018, Milan - Via Mangiagalli 25, Room C03, 08:30-13:30

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Programme of the Congress

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Genetics of Morphology, Behavior, and Breed Origins in the Domestic Dog.

E. A. Ostrander[1],*, J. Plassais[1], D. Dreger[1,2], J. Kim[1], B. W. Davis[1,3], A. Hogan[1], H. G. Parker[1]

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Abstract

Each of the nearly 400 dog breeds in existence today has a unique history and genetic profile. To date, however, studies of modern breed formation and relationships have relied on common breeds, a single collection site, and/or small numbers of genetic markers, thus limiting the traceable variation which would allow the accurate assessment of ancestry patterns that link modern breeds one to another. In addition, previous studies of breed relationships have focused only on the similarities between breeds, not on the processes by which they were developed. In this study we have assembled the largest and most diverse dataset of dog breeds analyzed to date representing 161 breeds originating from six continents reflecting the extensive phenotypic variation and heritage that coalesce in modern breeds. Our whole genome sequencing catalogue also spans hundreds of breeds, with over 150 breed represented. We combined genetic distance measures, introgression analyses, and genome-wide haplotype sharing to establish 23 clades, revealing geographic patterns of breed development and independent origins of common physical and behavioral traits. We have used this data, as well as whole genome sequence data, to conduct studies of morphologic variation and behavior. Our work identifies new genes associated with traits of interest under selection in various dog breeds. In addition, our studies identify classes of genes, also under selection, that were important in the creation of breeds of varying occupation. Canine genomics is thus maturing to a point where the domestic dog genetic system can be utilized to learn about the history, health, and future of this fascinating species.

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Clinical and epidemiological features of congenital heart diseases in dog: what has changed from 1997 to 2017. A single referral center experience.

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Abstract

The presented data were collected at Clinica Gran Sasso a single veterinarian referral center of cardiovascular diseases in small animals (CGSvrc) from 1997 to 2017. 1531 dogs, belonged to 93 pure breed and mongrel affected by single congenital heart defect were included. From 1997 to 2007 the most common were pulmonic stenosis (PS:33,2%), patent ductus arteriosus (PDA:25,2%) and sub aortic stenosis (SAS:22,8%). The prevalent pure breeds were Boxer (SAS:45,2%, PS:17%), and German Shepard (PDA:17%). In 2000 on base of these epidemiological observations, and thanks to the support of the Boxer club d'Italia and FSA, a screening program has begun at CGS. The aim was the identification of Boxer affected by PS and SAS, in order to improve the selection of the breeders. The diagnostic procedure based on clinical and echocardiographic examinations were standardized, and the proposed guidelines were used in several referral Italian veterinary clinics. The prevalence of the screened diseases decreased in the whole Boxer population, SAS from 11,5% to 1,5% and PS from 5% to 0,5%. French Bulldog (FB) represent one of the most fashionable breeds in Italy. In the last 10 years the puppies' registrations to Italian Kennel Club (ENCI) augmented from 548 to 2348, and at the CGSvrc the prevalence of FB affected by PS increased from 7,4% to 41,2%. FB belongs to the same clade of Boxer, shows a high predisposition to PS, and severe patterns are common (PS type hour-glass, partial pulmonary atresia and double chamber right ventricle). The successful obtained with the screening program in Boxer suggested us to propose an analogous approach on PS in FB. The traditional diagnostic procedures (clinical and echocardiographic examinations) will be supplemented by the new genomic technologies that represent precious tools in the evaluation of the breeders

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The genetic hallmarks of dog breed development reveal shared patterns of historical human-dog interactions.

D. L. Dreger[1,3], A. Talenti[2], H. G. Parker[3], E. A. Ostrander[3],*,
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Abstract

Each Approximately 15,000 years ago, the wild grey wolf gave rise to the first domestic dogs. Multiple domestication events likely took place throughout modern day Eurasia, though the precise times and locations are a hotly debated topic among researchers. Distinct populations of dogs, varying in physical appearance and behavior, developed to reflect the needs or desires of the human cultures in which they were formed. Rich in history, Italy is home to at least 24 unique dog breeds. Genetic analysis of these breeds, in relation to global dog breeds, has highlighted key technological advancements and movements of the region's people. We have analyzed DNA from 1,609 dogs, representing 182 breeds, and 16 wild canids, on a panel of 142,840 markers genome-wide. Twenty-four of these breeds are native to Italy, with 3 represented by both Italian and American populations. Through analysis of phylogeny and identity-by-descent haplotype sharing, patterns of breed formation have emerged that parallel the developmental progression of humans. Selection for common physical and behavioral phenotypes in hunting sighthounds, without evidence of recent shared genetic history, reveals shared human needs and biologically ideal forms. Identification of breed relationships to the isolated Fonni's Dog of Sardinia exposes geographic regions of development and tracks shared migration with human cultures. Finally, molecular evidence of historic agricultural practices is observed in the shared genetics of livestock guardian breeds.

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Susceptibility of Breed Dogs to Cancer.

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Abstract

There are nearly 400 breeds of dogs worldwide. Selection for specific morphologic and behavioral traits has led to populations of individuals with strong genetic and physical homogeneity. The strong genetic selection of traits by humans has led to an excess of disease in domestic breeds, with some breeds showing a particularly high incidence of a small set, or even only one, disorder. These disorders are of interest to human geneticists, as nearly all mimic some human disease. Our studies have focused on genetic susceptibility to cancer. Analysis of case and control populations of dogs with histiocytic sarcoma, squamous cell carcinoma as well as invasive bladder cancer have revealed genetic information about both susceptibility and progression to cancer in small sets of breeds. These data highlight new roles for previously identified tumor suppressor genes of relevance to human cancer studies. The work has been facilitated by the availability of whole genome sequence data from large numbers of dogs, which serves as a filter to distinguish between variants that are likely to be disease-associated versus those that are not. Studies of both tumor and germline DNA provide information regarding the initiation of cancer, and how it metastasizes. We find commonalities of mutation type and gene family among disparate types of cancer, likely reflecting the very recent history of dog breeds.

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Canine model for studies on pathogenesis of cancer: the experience of canine lymphoma.

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Abstract

Canine lymphoma is the most frequent hematopoietic disease and is considered an excellent tumor model since it shares many features with the human counterpart in terms of morphological and phenotypical classification, incidence, risk factors and diagnostic-therapeutic approaches. Dogs tend to develop mainly aggressive lymphomas and diffuse large B cell lymphoma (DLBCL) is by far the most frequent subtype. Thus, other subtypes, such as peripheral T cell lymphoma and T zone lymphoma that are rare in humans, are quite frequent in dogs. Studies on predisposition have recently shown that different breeds tend to develop specific lymphoma subtypes. A recent study of the European Canine Lymphoma Network demonstrated that breed-associated risk for developing lymphoma differs between Europe and US. This is particularly true for Golden retrievers that have a high predisposition to develop lymphoma, opening interesting perspectives aimed to investigate possible genetic predisposition. New recent molecular approaches have shown that DLBCL represents a heterogeneous tumor that cannot be unraveled by morphology and immunophenotype. In our lab, we have finalized the first large-scale study on canine DLBCL using next-generation sequencing. We integrated data from transcriptome by RNA-seq, genome-wide methylation sequencing and copy number variations by array comparative genomic hybridization. Furthermore, we validated our results both identifying protein markers that predict overall and event free survival and testing target therapies in vitro and in vivo model. DLBCLs segregated in two transcriptomic subgroups also characterized by distinct methylation profiles and associated with survival. The dogs with inferior survival showed a higher expression of transcripts involved in T-cells and macrophages regulation. Results presented here are innovative and open new perspectives both in the treatment of this lymphoma in dog and in terms of comparative medicine.

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Prostate cancer in the dog: a potential animal model for aggressive prostate cancer in man.

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Abstract

Among mammals, the only species showing spontaneous prostatic carcinoma is the dog. Canine prostatic carcinomas are rarer than in men but frequently showing undifferentiated morphology resembling the most aggressive human counterpart. Genetically engineered mice and cell culture have been employed in the study on human prostate cancer, however in these mice tumors are frequently different from the human ones. In addition, murine induced prostate cancers rarely develop bone metastases as in men and dog. Cell cultures, they are surely useful, however, they totally lack the tissue microenvironment that can play a role in cancer progression. For these reasons, animal models remain important and studies already highlighted relevant immunohistochemical similarities between human and canine prostate carcinomas. An intriguing field of research in prostate cancer is the expression of both androgen and estrogen receptors. Paralleling with the human counterpart, a decreasing in both androgen and estrogen receptors beta has been observed in canine aggressive prostate carcinomas. Moreover, in men frequently prostate carcinomas become refractory to castration therapies and tumor growths even if anti-androgen drugs are administered. Canine prostate carcinoma is not sensible to anti-androgen therapies, so that they could be an interesting potential model for the study of castration refractory human prostate cancers. Concerning estrogen receptors beta, when they bind estradiol they show an antiproliferative effect and a decreasing of these receptors promote cancer growth. Recently, studies individuated substances that could restore the estrogen receptor number, but they still need experiments and the dog could be a potential animal model. In addition, preneoplastic lesions such as prostatic intra-epithelial neoplasia and proliferative inflammatory atrophy, typically observed in men, have been recently recognized in canine prostate, indicating the dog as possible animal model for the study of human prostatic cancer initiation and progression.

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Beyond pedigree and towards applied genomics.

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Abstract

In the past two centuries, breeding practices led to more than 400 modern dog breeds showing high genetic drift, small population size without admixing events, increased between-breeds differentiation and inbreeding depression. Inbreeding depression and reduced population sizes are major drawbacks of human-driven selection in the dog species. Therefore, increasing the breed genetic basis is extremely important for their welfare and biodiversity. The availability of efficient and affordable genomic techniques such as dense SNPs arrays, together with the effort of the scientific community, allowed the production of massive genomic data of purebred dogs (Parker et al., 2017; Talenti et al., 2018). However, the 75% of the 1 billion living dogs are free-ranging and breeding (Pilot et al., 2015), with largely unknown ancestry. Genomic tools could be useful in this, in improving welfare and possibly enlarging the genetic basis of small dog populations. In this study, we evaluate a combined approach to assign the ancestors of different admixed and purebred dogs, sampled by saliva swab following European rules and genotyped by the 230K SNP chip. We compared three admixed individuals with 183 breeds and populations, including wild canids and wolves from Talenti et al., 2018. A combination of ranked supervised admixture and haplotype sharing (Beagle 4; Browning & Browning, 2013), allowed us to guess the most likely populations of three different admixed dogs. Results diverged in the three cases. We confirmed the supposed ancestry of one dog, partially confirmed the second dog and defined the third dog as a true mongrel, with 5 different breeds found as top ancestry scores comparable in size and morphology. These results suggest usefulness of genomic metrics in define the make-up even for admixed dogs. The genomic era in this species reached the maturity and this information deserves to be included for a better management of single dog and breeds facing for example health and longevity challenges.

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