

Introduction to Canine Genomics: *What genetics tells us about dogs?*

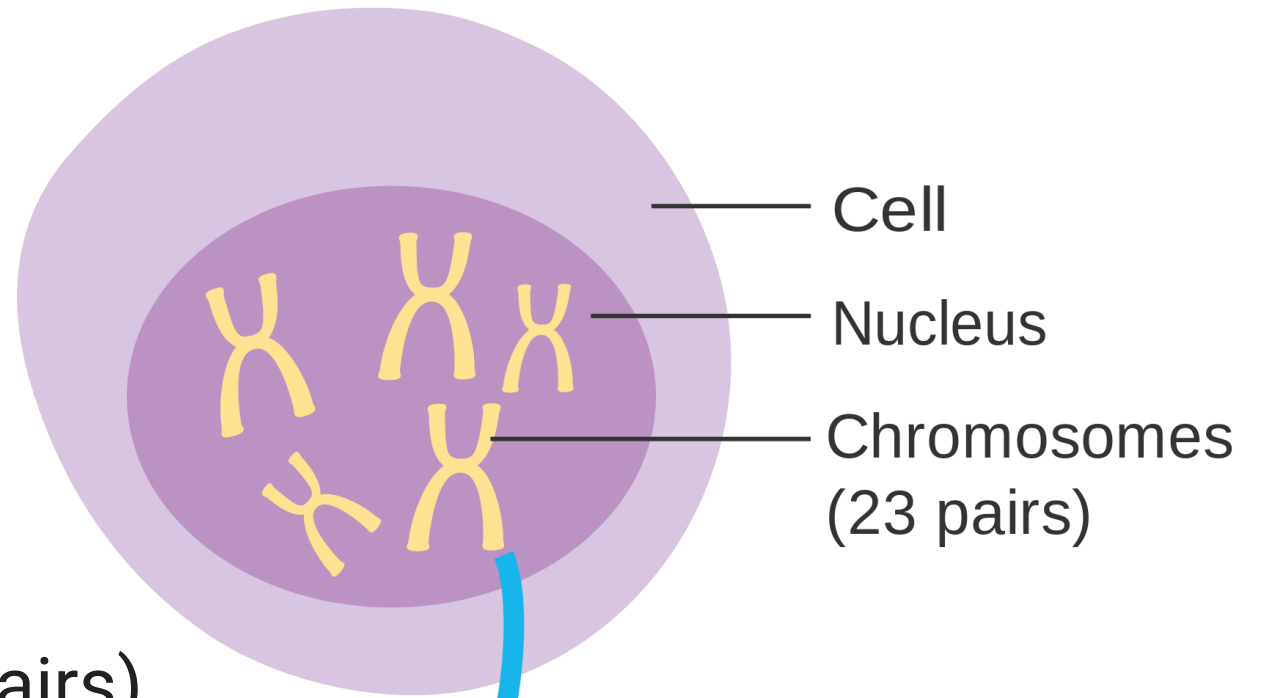
Kristopher Irizarry, PhD

Associate Professor, Bioinformatics & Genomics

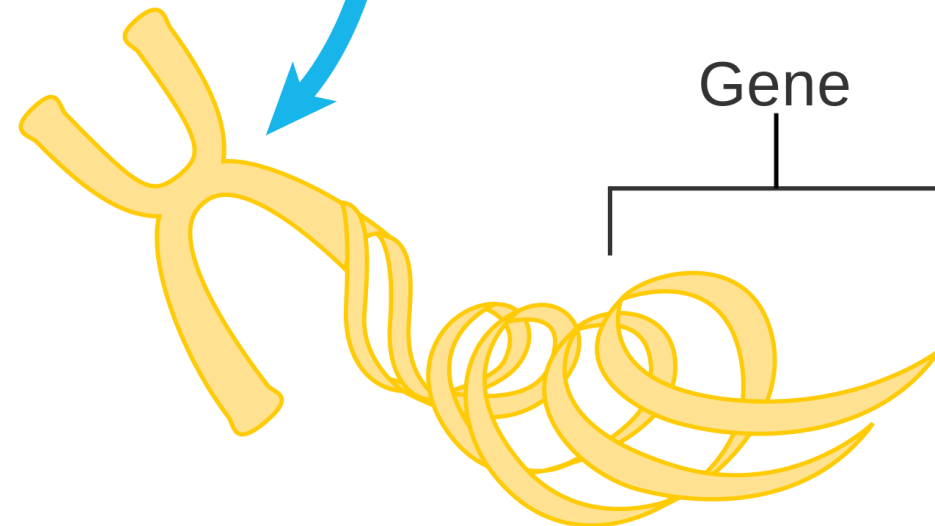
College of Veterinary Medicine

Western University of Health Sciences

Pomona, California

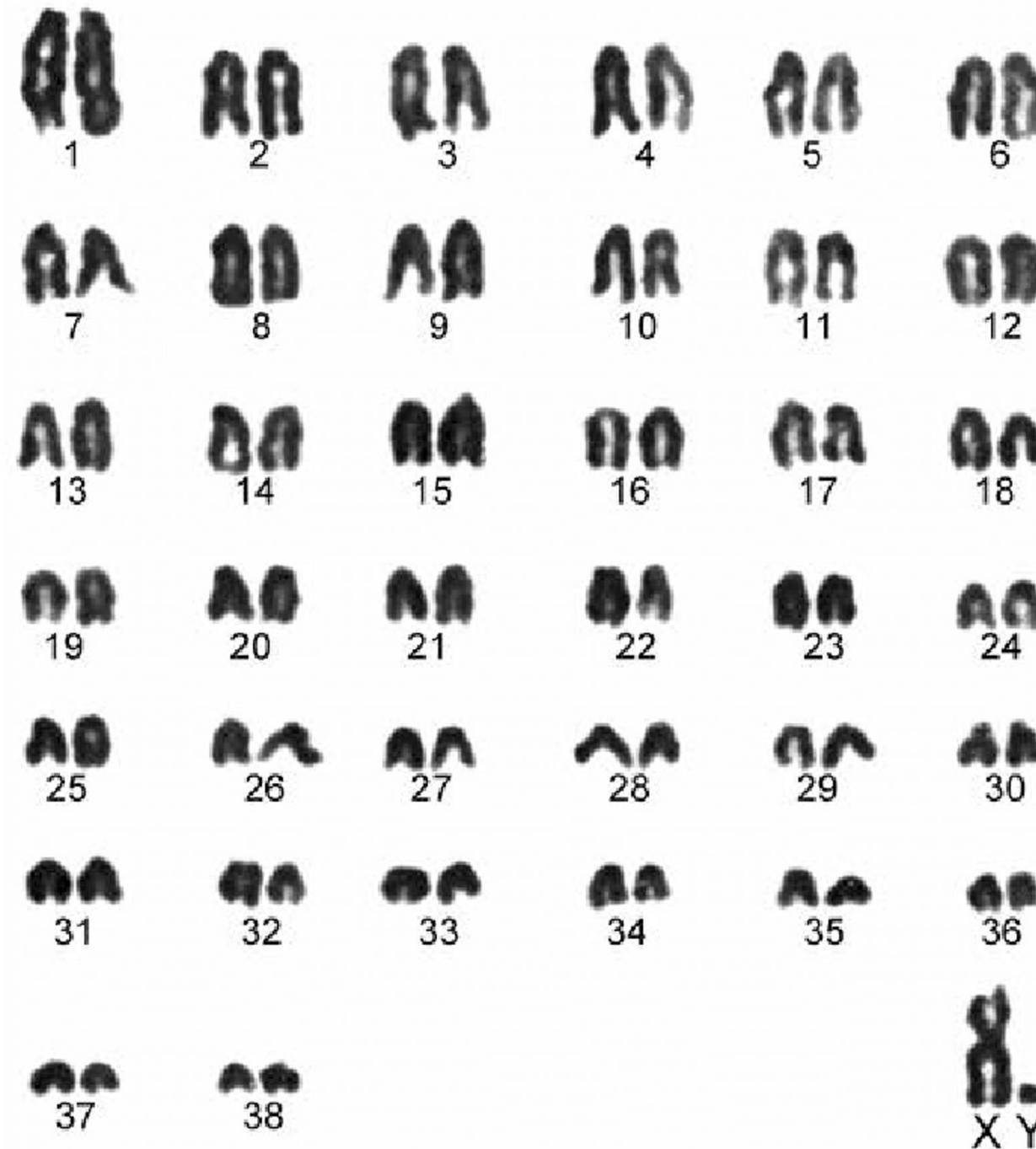


human → 46 chromosomes (23 pairs)
cat → 38 chromosomes (19 pairs)
dog → 78 chromosomes (39 pairs)



Canine Karyotype

Picture taken of the canine chromosomes using microscope



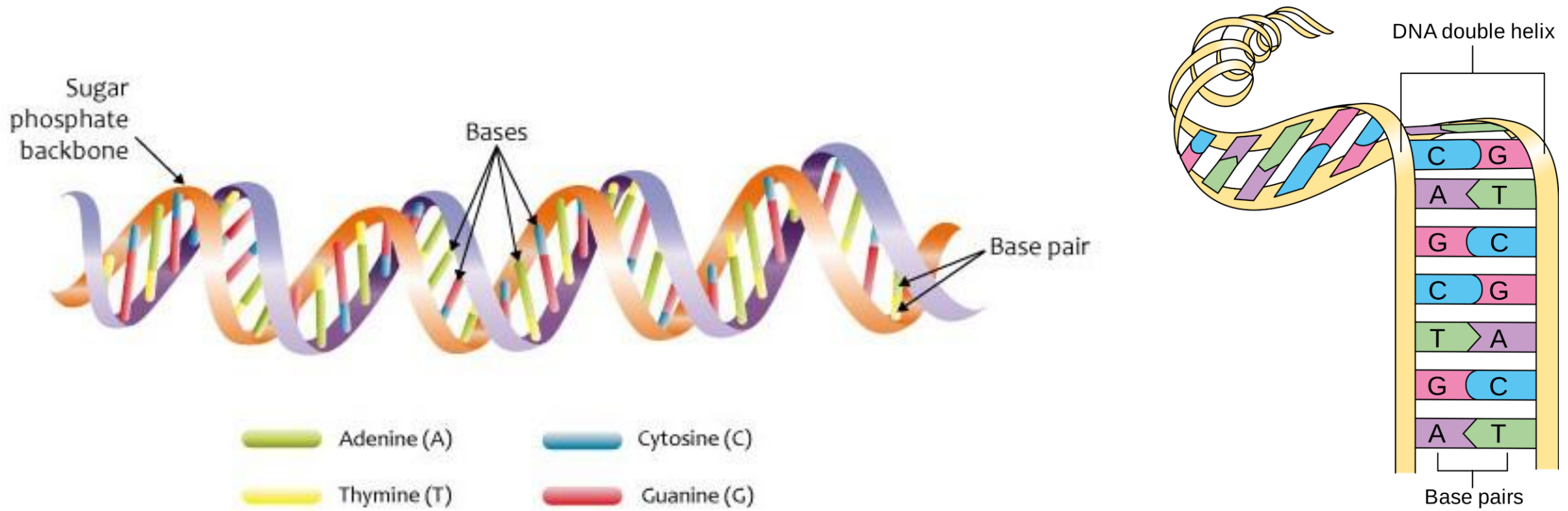
DOMESTIC DOG

78 chromosomes

39 pairs

2.5 billion base pairs in the canine genome (rungs of the ladder)

**** The genome is present in just about every cell of body****



https://upload.wikimedia.org/wikipedia/commons/f/ff/DNA_double_helix_%2813081113544%29.jpg

https://upload.wikimedia.org/wikipedia/commons/thumb/2/27/Diagram_showing_a_double_helix_of_a_chromosome_CRUK_065.svg/2000px-Diagram_showing_a_double_helix_of_a_chromosome_CRUK_065.svg.png



3,116,480 characters encoded in bible

Calculator Scientific

2500000000 ÷
3,116,480

DEG F-E

MC MR M+ M- MS M*

Trigonometry f Function

2 nd	π	e	CE	⌫
x ²	1/x	x	exp	mod
∛x	()	n!	÷
x ^y	7	8	9	×
10 ^x	4	5	6	-
log	1	2	3	+
ln	+/-	0	.	=

2.5 billion
characters in
more than 802
bibles

= 802.18

Calculator Scientific

248956422 ÷
3,116,480

DEG F-E

MC MR M+ M- MS M*

Trigonometry f Function

2 nd	π	e	CE	⌫
x ²	1/x	x	exp	mod
∛x	()	n!	÷
x ^y	7	8	9	×
10 ^x	4	5	6	-
log	1	2	3	+
ln	+/-	0	.	=



THIS SLIDE CONTAINS 200 BIBLES



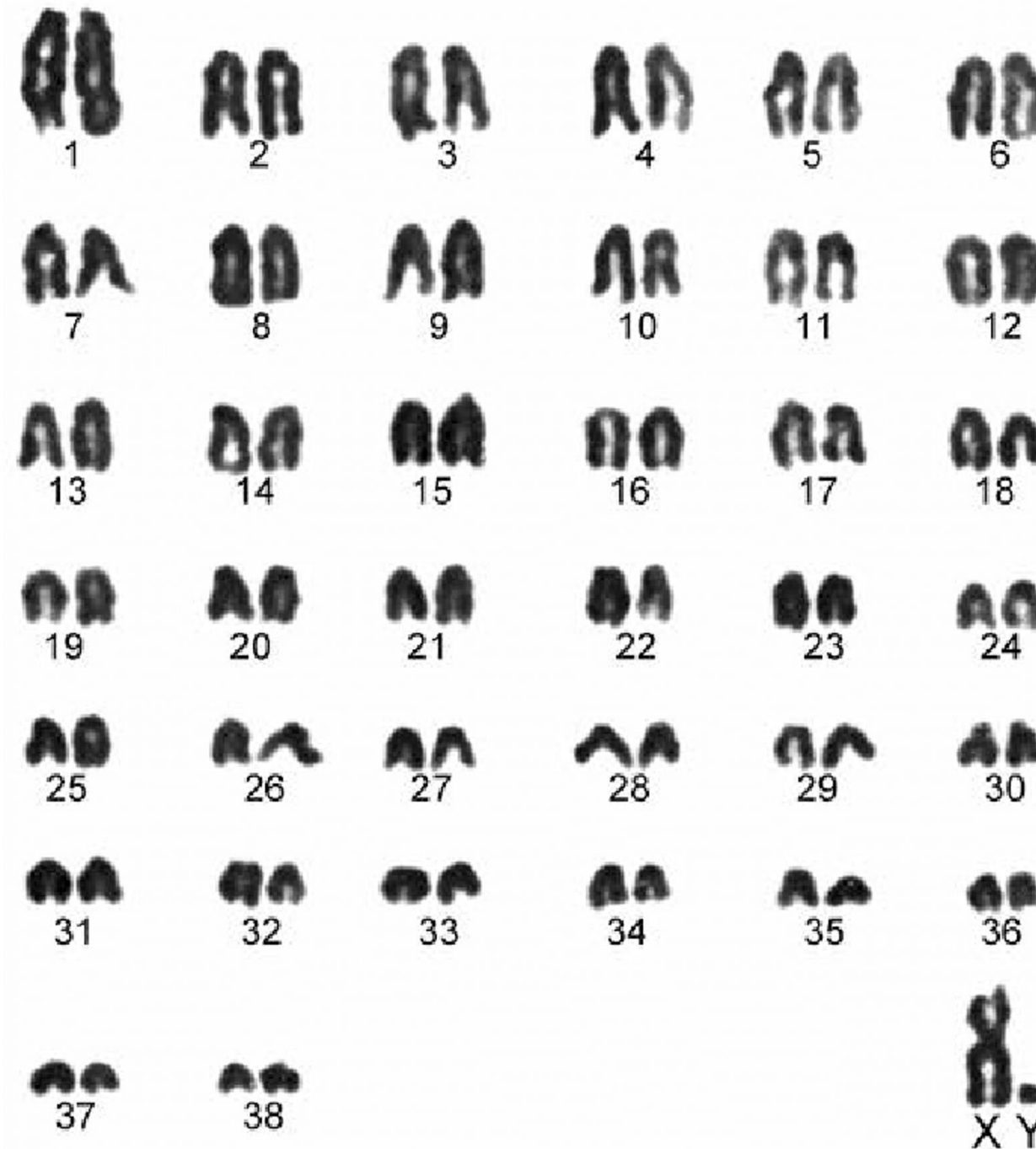
2.5 billion characters in 802.18 bibles

Showing 802 bibles requires more than 400 copies of this slide!

Canine Karyotype

Picture taken of the canine chromosomes using microscope

2.5 billion letters in canine genome



DOMESTIC DOG

78 chromosomes

39 pairs

Chromosome	Length (mm)	Base pairs	Variations	Protein-coding genes
1	85	248,956,422	12,151,146	2058
2	83	242,193,529	12,945,965	1309
3	67	198,295,559	10,638,715	1078
4	65	190,214,555	10,165,685	752
5	62	181,538,259	9,519,995	876
6	58	170,805,979	9,130,476	1048
7	54	159,345,973	8,613,298	989
8	50	145,138,636	8,221,520	677
9	48	138,394,717	6,590,811	786
10	46	133,797,422	7,223,944	733
11	46	135,086,622	7,535,370	1298
12	45	133,275,309	7,228,129	1034

Chromosome	Length (mm)	Base pairs	Variations	Protein-coding genes
13	39	114,364,328	5,082,574	327
14	36	107,043,718	4,865,950	830
15	35	101,991,189	4,515,076	613
16	31	90,338,345	5,101,702	873
17	28	83,257,441	4,614,972	1197
18	27	80,373,285	4,035,966	270
19	20	58,617,616	3,858,269	1472
20	21	64,444,167	3,439,621	544
21	16	46,709,983	2,049,697	234
22	17	50,818,468	2,135,311	488
X	53	156,040,895	5,753,881	842
Y	20	57,227,415	211,643	71
mtDNA	0.0054	16,569	929	13

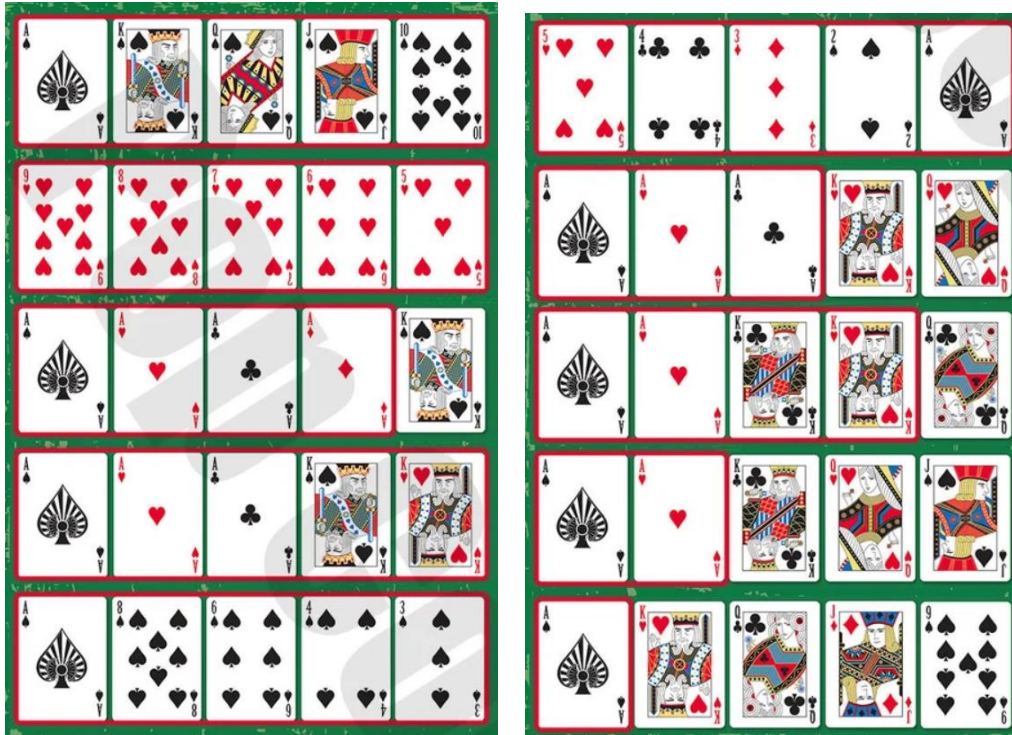
79.88 Bibles



2058 + 1309 + 1078 + 752 + 876 + 1048 + 989 + 677 + 786 + 733 + 1298 + 1034 + 327 + 830 + 613 + 873 + 1197 + 270 + 1472 + 544 + 234 + 488 + 842 + 71 + 13 = 20,412 protein coding genes Human Genome

25,000 genes encoded in the genome...

- With 52 cards in deck, there are 2,598,960 possible 5-card hands



Combinations nCr Calculator

$$C(n, r) = \binom{n}{r} = \frac{n!}{(r!(n-r)!)} = ?$$

n choose r

n (objects) =

r (sample) =

Clear

Calculate

Answer:

= 2.59896 E+6

Solution:

$$C(n, r) = ?$$

$$C(n, r) = C(52, 5)$$

$$= \frac{52!}{(5!(52-5)!)}$$

$$= \frac{52!}{5! \times 47!}$$

$$= 2.59896E + 6$$

$$= 2598960$$

CHARACTER COUNTER

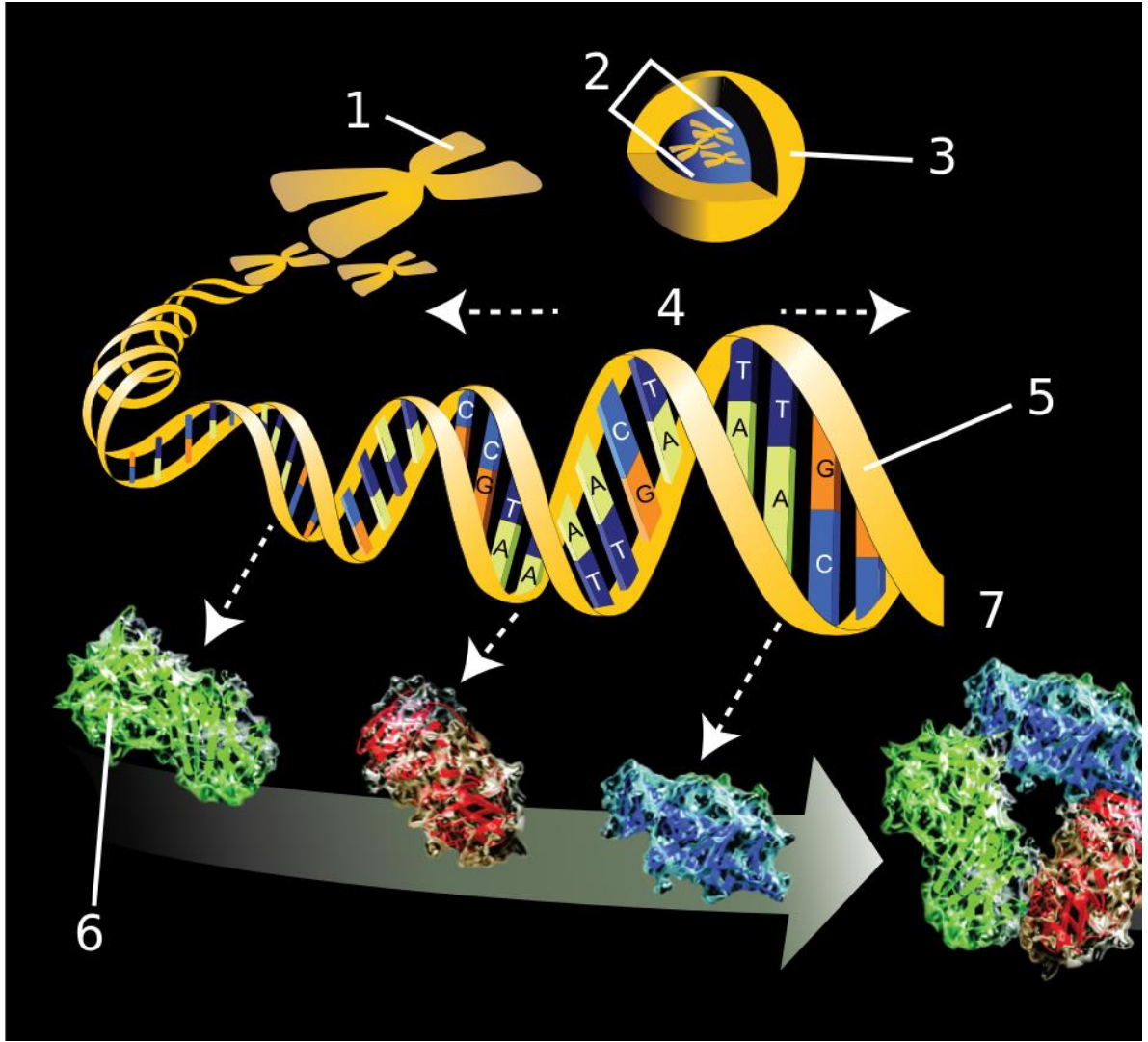
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Letter Density
7252 (25%)

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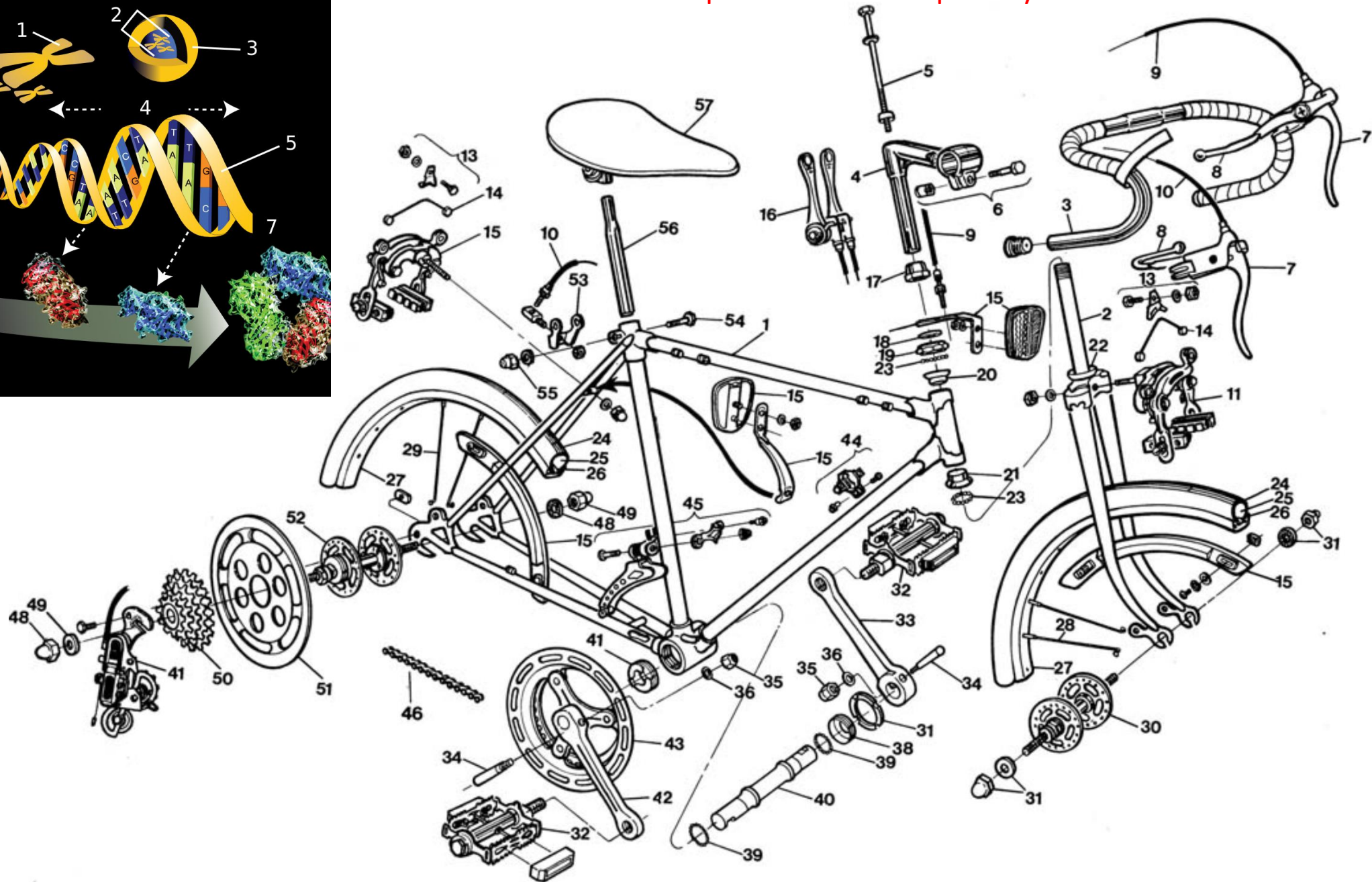
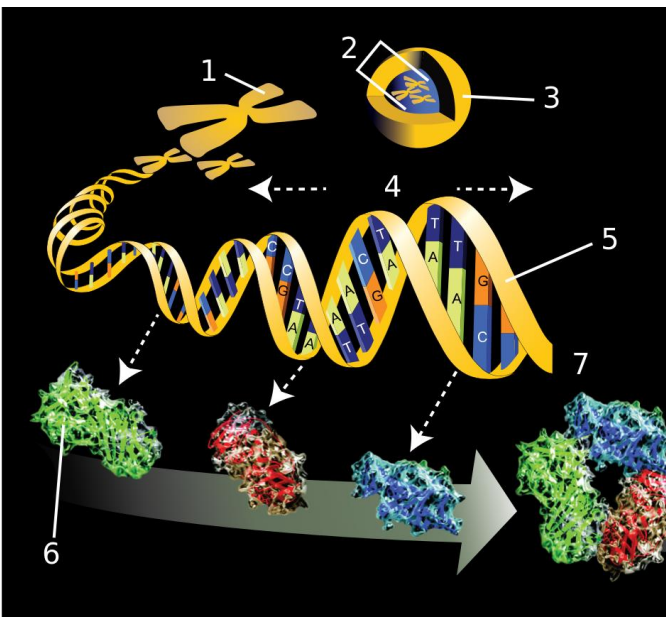
29,009 – 7252 = **21,757 digit number** (remember a google is a 1 with 100 zeros after it)

GENES ENCODE “PARTS” USED BY CELLS IN THE BODY – these parts make up molecular machines the body uses to survive



- 1. Chromosome
- 2. Nucleus of Cell – Contains Genome
- 3. Cell
- 4. DNA comprising chromosome
- 5. DNA Base Pairing
- 6. Protein encoded by gene in chromosome
- 7. Multi-Protein Complex in cell (encoded by 3 genes)

Think of all the individual parts that make up a bicycle ...

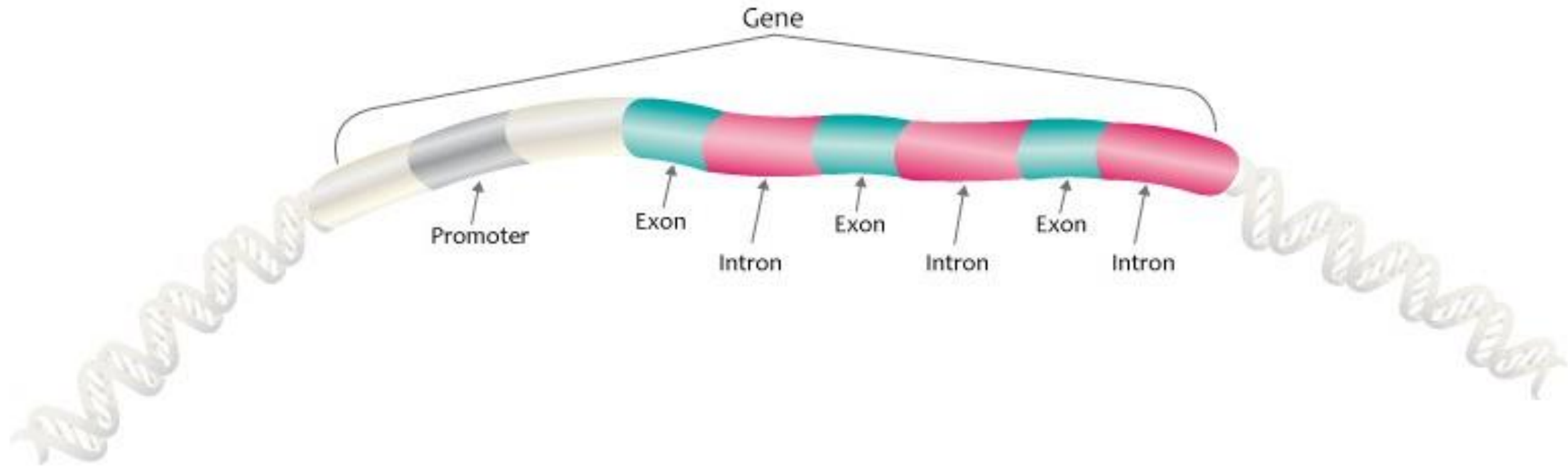


EXON = important part

INTRON = not important

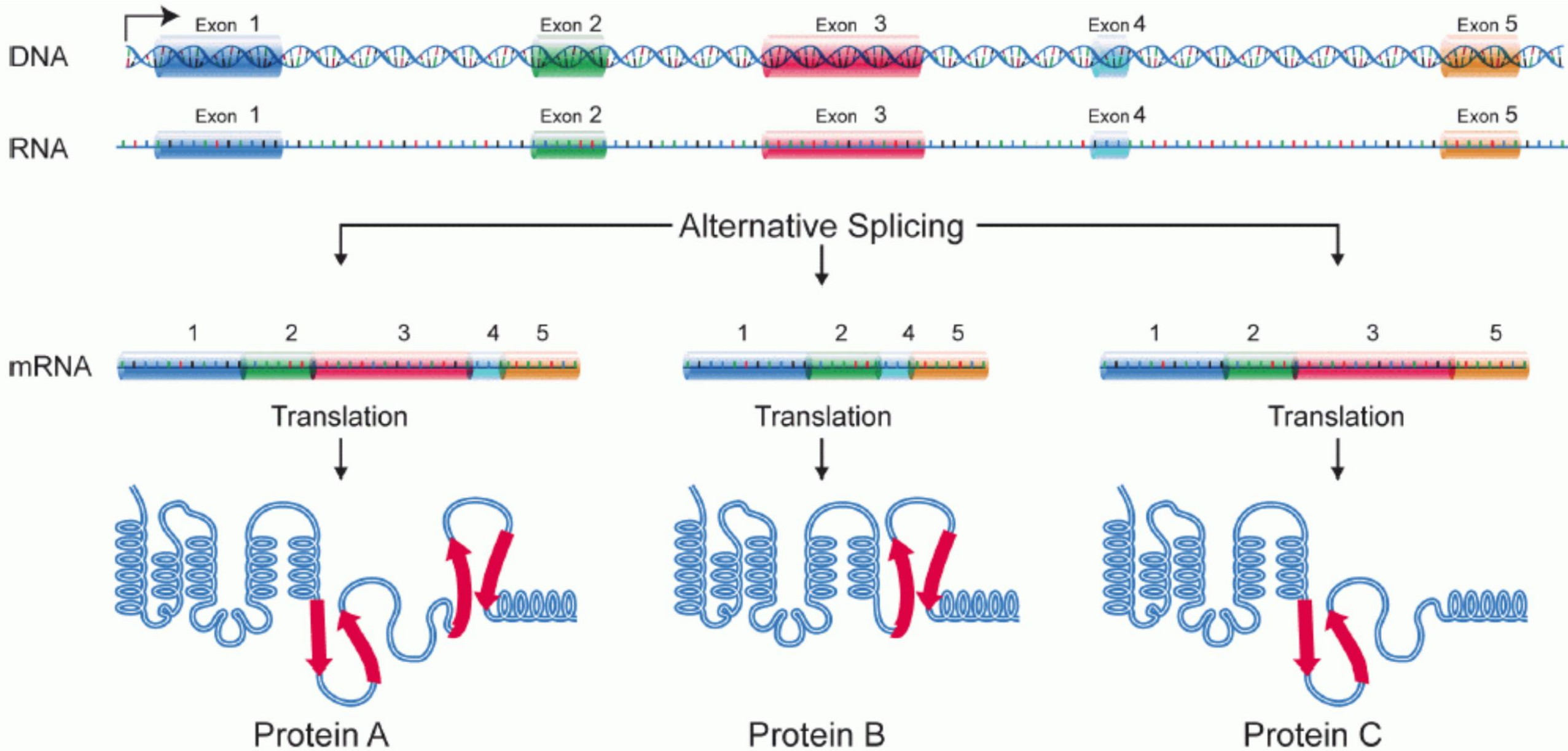


<https://www.google.com/search?q=model+car+carefully+separate++pieces>



[https://upload.wikimedia.org/wikipedia/commons/f/f7/Gene_structure %2813080962024%29.jpg](https://upload.wikimedia.org/wikipedia/commons/f/f7/Gene_structure_%2813080962024%29.jpg)

COMPLEXITY OF GENETICS: Even a single gene can be used to make “alternative” biological machines (called proteins)



Dog domestication occurred over 30,000 years and resulted in changes to the dog brain that are shared among all domestic dog breeds.



In 2015 Lee et al. reported the sequencing and phylogenetic analysis of the mitochondrial control region derived from a 360,000 to 400,000 year old *Canis cf. variabilis* mandible obtained from a region in Siberia from which multiple ancient and contemporary canid samples have been identified.

Lee EJ, Merriwether DA, Kasparov AK, Nikolskiy PA, Sotnikova MV, Pavlova EY, Pitulko VV. Ancient DNA analysis of the oldest canid species from the Siberian Arctic and genetic contribution to the domestic dog. PLoS One. 2015 May 27;10(5):e0125759.



Ovodov et al. (2011) describe the discovery of 33,000 year old dog remains within the Altai Mountains of Siberia including a complete skull and mandible that were excavated from the site in 1975.

33,000 year old dog skull and mandible represent early stage of canine domestication.

A) aerial view, B) profile, C) palate, D) left mandible, E) left lower tooth row (scale on ruler in cm). Sub-triangular hole in the skull is the place of initial sampling for 14C dating in 2007.

Ovodov ND, Crockford SJ, Kuzmin YV, Higham TF, Hodgins GW, van der Plicht J. A 33,000-year-old incipient dog from the Altai Mountains of Siberia: evidence of the earliest domestication disrupted by the Last Glacial Maximum. PLoS One. 2011;6(7):e22821.

Artificial Selection in Dogs

(let's start with morphological phenotypes)

Dogs have tremendous anatomical variation . . .



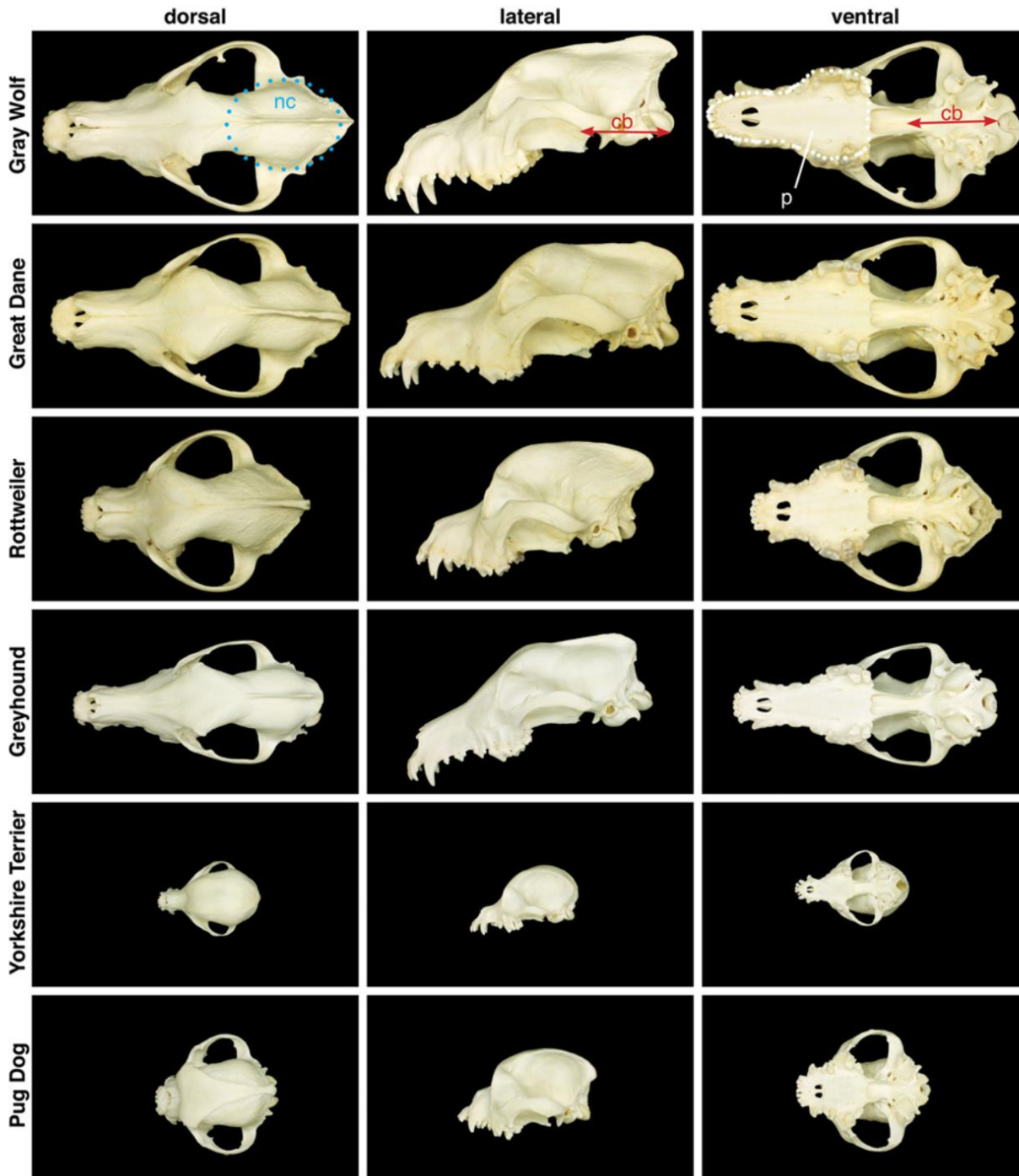
Figure 1. The Diversity of Dog Breeds. Breeds vary according to many traits, including size, leg length, pelage (coat), color, and skull shape. Shown are **borzoi** (Panel A), **basset hound** (Panel B), **Chihuahua** (Panel C), **giant schnauzer** (Panel D), **bichon frise** (Panel E), **collie** (Panel F), **French bulldog** (Panel G), **dachshund** (Panel H), **German shorthaired pointer** (Panel I), **papillon** (Panel J), and **Neapolitan mastiff** (Panel K). (Images courtesy of Mary Bloom, American Kennel Club.)

The Genetics of Canine Skull Shape Variation

Jeffrey J. Schoenebeck and Elaine A. Ostrander¹

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Genetics, Vol. 193, 317–325 February 2013



ABSTRACT A dog's craniofacial diversity is the result of continual human intervention in natural selection, a process that began tens of thousands of years ago. To date, we know little of the genetic underpinnings and developmental mechanisms that make dog skulls so morphologically plastic. In this *Perspectives*, we discuss the origins of dog skull shapes in terms of history and biology and highlight recent advances in understanding the genetics of canine skull shapes. Of particular interest are those molecular genetic changes that are associated with the development of distinct breeds.

Figure 1 A montage of canine craniofacial shape demonstrates the incredible morphologic diversity of *Canis familiaris*. Dorsal, lateral, and ventral perspectives of various breeds of dogs. Lateral views are articulated so that the skull base (red line, wolf) is approximately parallel between breeds. Prominent differences across breeds include palate shape (p, indicated by white dots), neurocranium shape (nc, enclosed by blue dots), cranial base length (cb, red line). Also note the angle of the palate relative to the cranial base.

SOMETIME during the Paleolithic, a remarkable transformation occurred. Small numbers of gray wolves adopted a new pack master—humans. Through the process of domestication, the modern dog emerged. Today most dogs share little resemblance to their lupine ancestors. As a result of artificial selection, dogs radiated to fill niches in our lives, becoming our herders, guardians, hunters, rescuers, and companions (Wilcox and Walkowicz 1995). The range of sizes

A Simple Genetic Architecture Underlies Morphological Variation in Dogs

August 2010 | Volume 8 | Issue 8 | e1000451

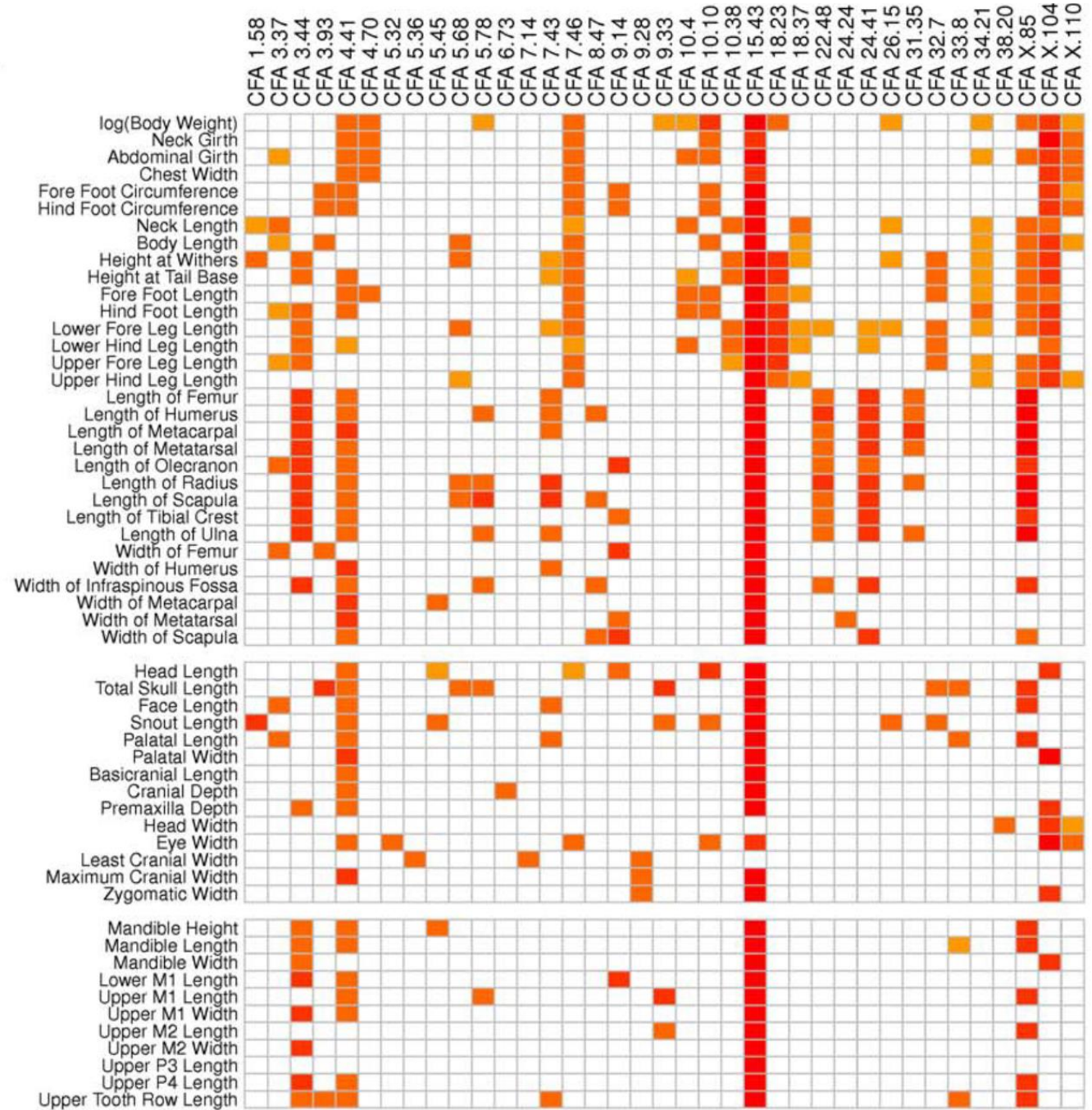
Adam R. Boyko^{1,2,9}, Pascale Quignon^{3,9}, Lin Li^{2,9}, Jeffrey J. Schoenebeck³, Jeremiah D. Degenhardt², Kirk E. Lohmueller², Keyan Zhao^{1,2}, Abra Brisbin², Heidi G. Parker³, Bridgett M. vonHoldt⁴, Michele Cargill⁵, Adam Auton², Andy Reynolds², Abdel G. Elkhahloun³, Marta Castelhana⁶, Dana S. Mosher³, Nathan B. Sutter^{2,6}, Gary S. Johnson⁷, John Novembre⁴, Melissa J. Hubisz², Adam Siepel², Robert K. Wayne⁴, Carlos D. Bustamante^{1,2,¶*}, Elaine A. Ostrander^{3,¶*}

Abstract

Domestic dogs exhibit tremendous phenotypic diversity, including a greater variation in body size than any other terrestrial mammal. Here, we generate a high density map of canine genetic variation by genotyping 915 dogs from 80 domestic dog breeds, 83 wild canids, and 10 outbred African shelter dogs across 60,968 single-nucleotide polymorphisms (SNPs). Coupling this genomic resource with external measurements from breed standards and individuals as well as skeletal measurements from museum specimens, we identify 51 regions of the dog genome associated with phenotypic variation among breeds in 57 traits. The complex traits include average breed body size and external body dimensions and cranial, dental, and long bone shape and size with and without allometric scaling. In contrast to the results from association mapping of quantitative traits in humans and domesticated plants, we find that across dog breeds, a small number of quantitative trait loci (≤ 3) explain the majority of phenotypic variation for most of the traits we studied. In addition, many genomic regions show signatures of recent selection, with most of the highly differentiated regions being associated with breed-defining traits such as body size, coat characteristics, and ear floppiness. Our results demonstrate the efficacy of mapping multiple traits in the domestic dog using a database of genotyped individuals and highlight the important role human-directed selection has played in altering the genetic architecture of key traits in this important species.

Figure 4. Summary of associations across genomic regions for multiple traits.

A



CFA 1 = *Canis familiaris* Chromosome 1

Author Summary

Dogs offer a unique system for the study of genes controlling morphology. DNA from 915 dogs from 80 domestic breeds, as well as a set of feral dogs, was tested at over 60,000 points of variation and the dataset analyzed using novel methods to find loci regulating body size, head shape, leg length, ear position, and a host of other traits. Because each dog breed has undergone strong selection by breeders to have a particular appearance, there is a strong footprint of selection in regions of the genome that are important for controlling traits that define each breed. These analyses identified new regions of the genome, or loci, that are important in controlling body size and shape. Our results, which feature the largest number of domestic dogs studied at such a high level of genetic detail, demonstrate the power of the dog as a model for finding genes that control the body plan of mammals. Further, we show that the remarkable diversity of form in the dog, in contrast to some other species studied to date, appears to have a simple genetic basis dominated by genes of major effect.



Trends in Genetics

A Mutation in the Myostatin Gene Increases Muscle Mass and Enhances Racing Performance in Heterozygote Dogs

Dana S. Mosher¹, Pascale Quignon¹, Carlos D. Bustamante², Nathan B. Sutter¹, Cathryn S. Mellersh³, Heidi G. Parker¹, Elaine A. Ostrander^{1*}

1 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States of America, **2** Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, New York, United States of America, **3** Animal Health Trust, Center for Preventive Medicine, Newmarket, United Kingdom

Double muscling is a trait previously described in several mammalian species including cattle and sheep and is caused by mutations in the myostatin (*MSTN*) gene (previously referred to as *GDF8*). Here we describe a new mutation in *MSTN* found in the whippet dog breed that results in a double-muscled phenotype known as the “bully” whippet. Individuals with this phenotype carry two copies of a two-base-pair deletion in the third exon of *MSTN* leading to a premature stop codon at amino acid 313. Individuals carrying only one copy of the mutation are, on average, more muscular than wild-type individuals ($p = 7.43 \times 10^{-6}$; Kruskal-Wallis Test) and are significantly faster than individuals carrying the wild-type genotype in competitive racing events (Kendall’s nonparametric measure, $\tau = 0.3619$; $p \approx 0.00028$). These results highlight the utility of performance-enhancing polymorphisms, marking the first time a mutation in *MSTN* has been quantitatively linked to increased athletic performance.

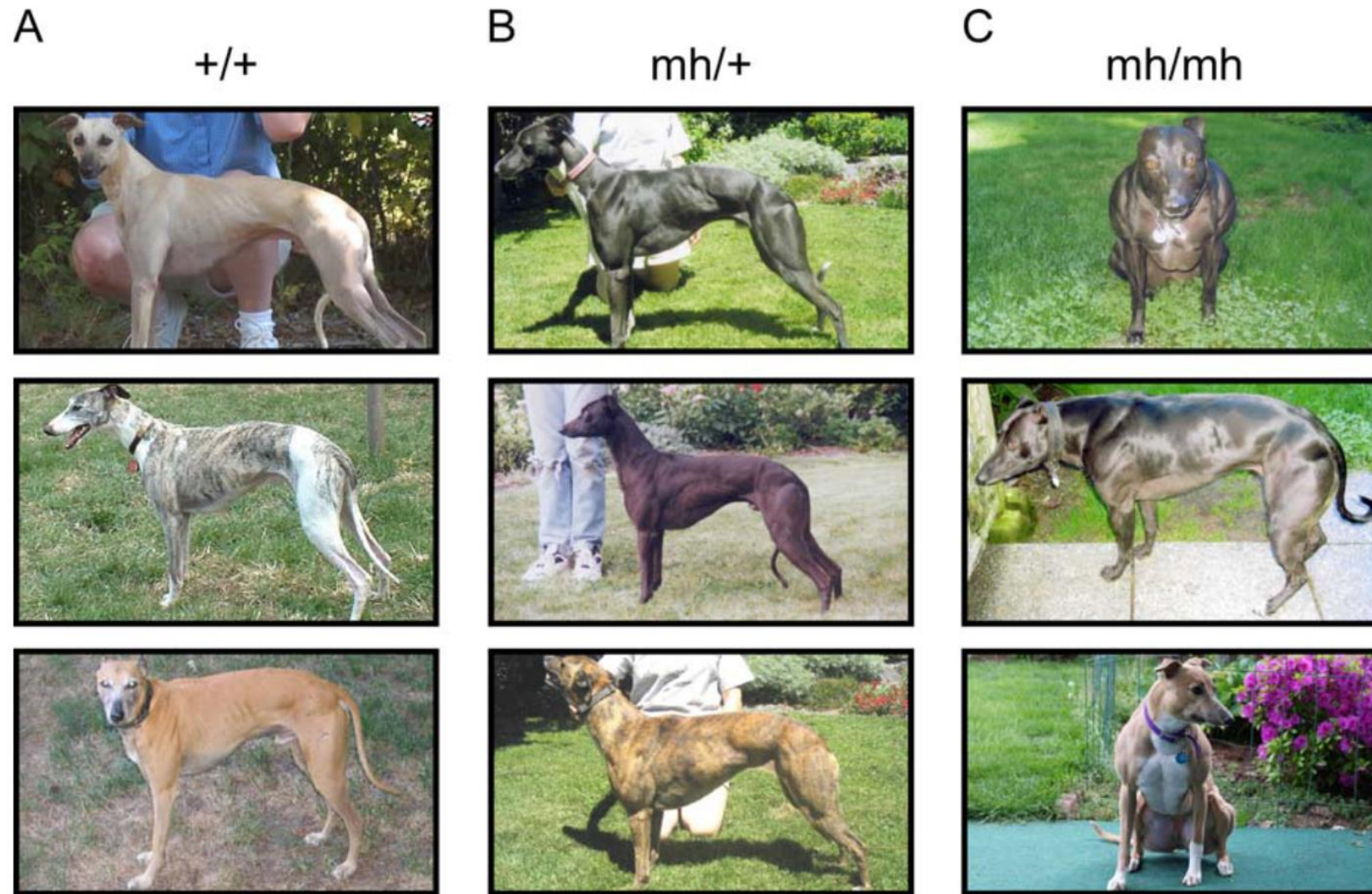


Figure 1. Comparison of Whippets with Each of the Three Potential Genotypes

(A) Dogs have two copies of the wild-type allele (+/+).

(B) Dogs are heterozygous with one wild-type allele and one mutant *cys* → stop allele (*mh/+*).

(C) Dogs are homozygous for the mutant allele with two copies of the *cys* → stop mutation (*mh/mh*).

All photos represent unique individuals except for the top and middle panels in the righthand column.

doi:10.1371/journal.pgen.0030079.g001

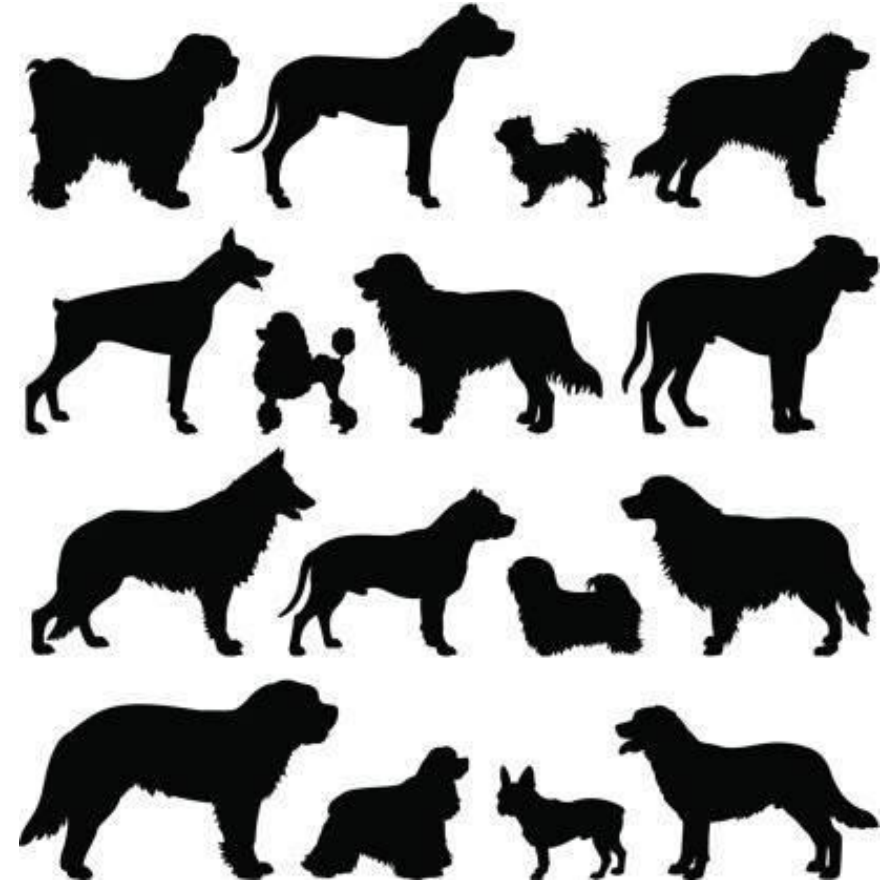
The genetic programs associated with anatomical traits are not encoding behavior

- Many breeds share the same anatomical traits

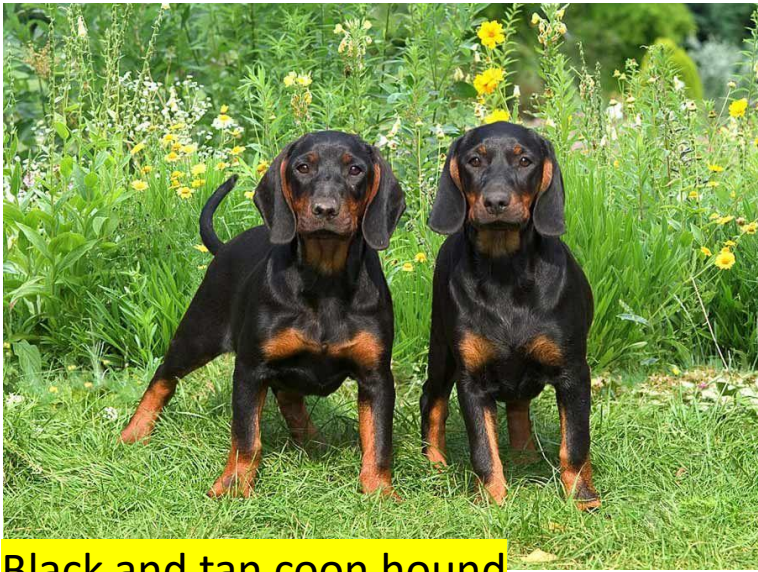
- Coat color
- Body size
- Head shape
- Ear morphology (erect/hanging and shape)
- Extent of musculature
- Length of fur
- Shape of tail
- Length of tail

Presence / absence of a specific anatomical trait doesn't indicate breed

Presence / absence of a specific anatomical trait doesn't indicate BEHAVIOR

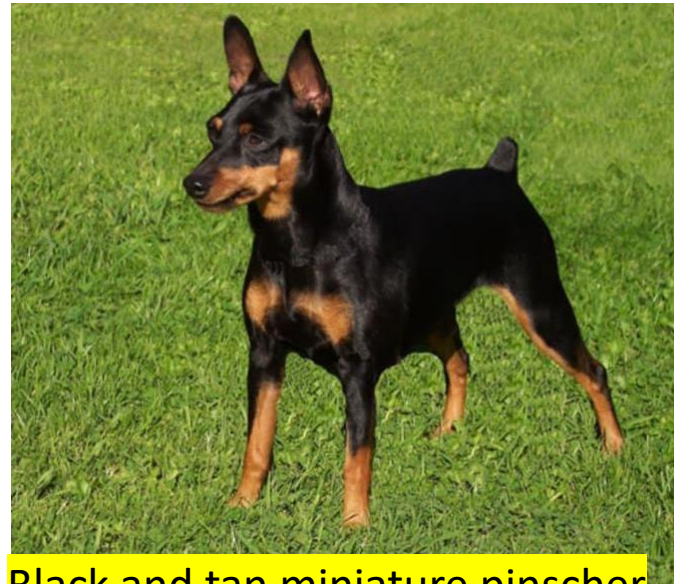


<https://www.pinterest.com/pin/234679830555769934/>



Black and tan coon hound

<https://www.pinterest.com/pin/356347389273205119/>



Black and tan miniature pinscher



Rottweiler



Doberman Pinscher

https://i2.wp.com/live.staticflickr.com/5127/5305610099_b6a91ee327_b.jpg

[https://img.pixers.pics/pho_wat\(s3:700/FO/57/51/96/46/700_FO57519646_92d8a8b10d078ada120312f042b97932.jpg,700,647.cms:2018/10/5bd1b6b8d04b8_220x50-watermark.png,over,480,597.jpg\)/stickers-doberman-pinscher.jpg.jpg](https://img.pixers.pics/pho_wat(s3:700/FO/57/51/96/46/700_FO57519646_92d8a8b10d078ada120312f042b97932.jpg,700,647.cms:2018/10/5bd1b6b8d04b8_220x50-watermark.png,over,480,597.jpg)/stickers-doberman-pinscher.jpg.jpg)

COMPARISON OF ADOPTION AGENCY BREED IDENTIFICATION AND DNA BREED IDENTIFICATION OF DOGS

This study was undertaken to compare breed identification by canine adoption agencies with identification by DNA analysis of 20 dogs of unknown parentage

BACKGROUND

Breed Specific Regulations:

- Government legislation, housing associations, landlords, and insurance companies may either prohibit ownership or impose constraints on ownership of specific breeds or mixed breeds
- Restrictions may ban ownership, require owners to move or relinquish their dogs, require dogs to be muzzled or confined in a specific manner, and may even result in confiscation and/or euthanasia
- Restrictions are typically worded as “any purebred X (name of breed) or dog that has any characteristics of breed X”
- Identity of the dog might be assigned by a variety of people
- If people are unsure what breed a dog is, they are often forced to guess and asked to name “the breed the dog looks most like”

Shelter Dogs:

- The majority are mixed breeds of unknown parentage
- It is common practice for staff to assign breed based on appearance
- Breed identity elicits behavioral expectations and affects ease of adoption

MATERIALS AND METHODS

Subjects:

- 40 dogs met the entrance criteria of having been adopted, being available on specific dates for photographs and blood samples, and having fully erupted canine teeth
- These dogs were placed in 4 weight categories and 5 were randomly selected from each category:
 - < 20 pounds, 21-40 pounds, 41-60 pounds, and > 60 pounds
- 20 dogs entered the study:
 - 12 Spayed Females; 1 Intact Female; 7 Castrated Males
 - 5.5 months to 12 years old
- The dogs had been acquired between 2.5 months and 11.5 years prior to the study
- The dogs had been adopted from 17 different locations (shelters, rescue groups, foster housing, animal control and similar agencies)

DNA Analysis:

- MARS VETERINARY™, Lincoln, Nebraska, performed the DNA analyses and reported to have “an average accuracy of 84% in first-generation crossbred dogs of known parentage”
- All of the breeds identified by the adoption agencies were in the MARS database
- Breeds must comprise at least 12.5% of the dog’s make-up to be reported

DOG BREED IDENTIFICATION

V Voith, C Chadik, E Ingram, K Irizarry, K Mitsouras, J Marilo
Western University of Health Sciences Pomona, California

RESULTS

See Poster Photographs and Legends. The grid behind the dogs depicts 1 foot squares.

Adopting agencies identifications

- All dogs had been identified as mixed breeds at time of adoption
- 16 dogs had been described as a specific breed mix
- 4 dogs were only identified by a “type” (2 “shepherd” mixes and 2 “terrier” mixes)
- 1 dog had been identified by both a specific breed (Chow Chow) and a “type” (terrier)

DNA and Adoption Agency Comparison

- Only 25% (4/16) of the dogs identified by agencies as specified breed mixes were also identified as the same predominant breeds by DNA (3 were only 12.5% of the dogs’ composition)
- No German Shepherd Dog ancestry was reported by DNA in the 2 dogs identified only as “shepherd mixes” by adoption agencies
- In the 3 dogs described as terrier mixes, a terrier breed was only identified by DNA in one dog
- In 15 of the 16 dogs, DNA analyses identified breeds as predominant that were not proposed by the adoption agencies

DISCUSSION

- Looking at the photographs, it is apparent that many mixed breed dogs do not closely, if at all, resemble the predominant breeds identified by DNA
- Mixed breed dogs may not look like their parents or grandparents
- These results do not allow a conclusion that shelter personnel cannot identify purebred dogs
- Breed identities at adoption agencies can be assigned by owners relinquishing their dogs, by anyone working or volunteering at a facility, or be based on what a puppy’s mother looks like

CONCLUSIONS

- There is little correlation between dog adoption agencies’ identification of probable breed composition with the identification of breeds by DNA analysis
- Further evaluation of the reliability and validity of visual dog breed identification is warranted
- Justification of current public and private policies pertaining to breed specific regulations should be reviewed

REFERENCES

- Voith VL, Ingram E, Mitsouras K, Irizarry K. (2009). Comparison of Adoption Agency Breed Identification and DNA Breed Identification of Dogs. Journal of Applied Animal Welfare Science, 12, 253-262.



Adopted as: “Terrier”/Chow Chow mix at 7.5 months old
DNA: 23%each: American Staffordshire Terrier, Saint Bernard
12.5%: Shar-Pei



Adopted as: Cocker Spaniel mix at 5 years old
DNA: 23%each: Fottweiler, American Eskimo Dog, Golden Retriever, Nova Scotia Duck-Billing Retriever



Adopted as: Border Collie mix at 7 weeks old
DNA: 23%each: English Springer Spaniel, German Wirehaired Pointer



Adopted as: “Shepherd” mix at 11 weeks old
DNA: 23%: Lhasa Apso
12.5%each: Bisdon Prize, Australian Cattle Dog, Italian Greyhound, Pakinese, Shih Tzu



Adopted as: German Shepherd/Labrador mix at 1 year old
DNA: 12.5%each: German Shepherd, Australian Shepherd, Siberian Husky, Chow Chow, Dalmatian



Adopted as: Labrador mix at 2 years old
DNA: 12.5%each: Chow Chow, Dachshund, Nova Scotia Duck-Billing Retriever



Adopted as: Corgi mix at 3 months old
DNA: 12.5%each: Pomeranian, Tibetan Terrier, Shih Tzu, Black Russian Terrier, American Water Spaniel



Adopted as: German Short-haired Pointer mix at 5 months old
DNA: 23%each: French Bulldog, Chow Chow, 12.5%each: Great Dane, Gordon Setter, Dalmatian, Chamber Spaniel



Adopted as: “Terrier” mix at 3 months old
DNA: 23%: Dalmatian
12.5%each: Boxer, Chow Chow, Newfoundland



Adopted as: Silky Terrier mix at 3.5 years old
DNA: 23%each: Pekinese, Australian Shepherd



Adopted as: Chow Chow mix at 6 weeks old
DNA: 23%each: German Shepherd Dog, American Staffordshire Terrier
12.5%each: Chow Chow, Bull Terrier



Adopted as: “Shepherd” mix at 1 year old
DNA: 12.5%each: Boxer, Dalmatian, Dachshund, Glen of Inval Terrier, Australian Shepherd Dog



Adopted as: Australian Shepherd Dog mix at 4 months old
DNA: 12.5%: Akita, Maltese



Adopted as: Australian Shepherd Dog mix at 3 months old
DNA: 23%each: Runder Schnauzer, German Shepherd Dog
12.5%: English Setter



Adopted as: Labrador mix at 5 years old
DNA: 12.5%each: R. Bernard, Gordon Setter, Chow Chow, Golden Retriever



Adopted as: Australian Shepherd Dog/Labrador mix at 3 months old
DNA: 12.5%each: Australian Shepherd Dog, Boxer, Golden Retriever



Adopted as: King Charles’ Spaniel mix at 1 year old
DNA: 12.5%each: Cavalier King Charles’ Spaniel, Chihuahua, Shih Tzu



Adopted as: Miniature Pinscher/Poodle mix at 3 months old
DNA: 50%: Miniature Pinscher, 12.5%: Sch.ound



Adopted as: “Terrier” mix at 6 months old
DNA: 23%: Border Collie, 12.5%each: Cocker Spaniel, Bassett Hound



Adopted as: Tibetan Terrier mix at 5 years old
DNA: 23%: Shih Tzu, 12.5%each: Pekinese, Cocker Spaniel, Miniature Schnauzer



Adopting agencies identifications

- All dogs had been identified as mixed breeds at time of adoption
- 16 dogs had been described as a specific breed mix
- 4 dogs were only identified by a “type” (2 “shepherd” mixes and 2 “terrier” mixes)
- 1 dog had been identified by both a specific breed (Chow Chow) and a “type” (terrier)

DNA and Adoption Agency Comparison

- Only 25% (4/16) of the dogs identified by agencies as specified breed mixes were also identified as the same predominant breeds by DNA (3 were only 12.5% of the dogs’ composition)
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Because visual identification of breed is INACCURATE

- breeds assigned to mixed-breed dogs for hundreds have been wrong
- Before genetic breed tests, high confidence in visual breed assignment
- Nobody knew that visual identification was wrong
- Even when many hundreds of people agree on the visual breed assignment, it does not agree with DNA mixed-breed ancestry analysis



Many mixed breed dogs have no common anatomical traits with their ancestral breed make up.

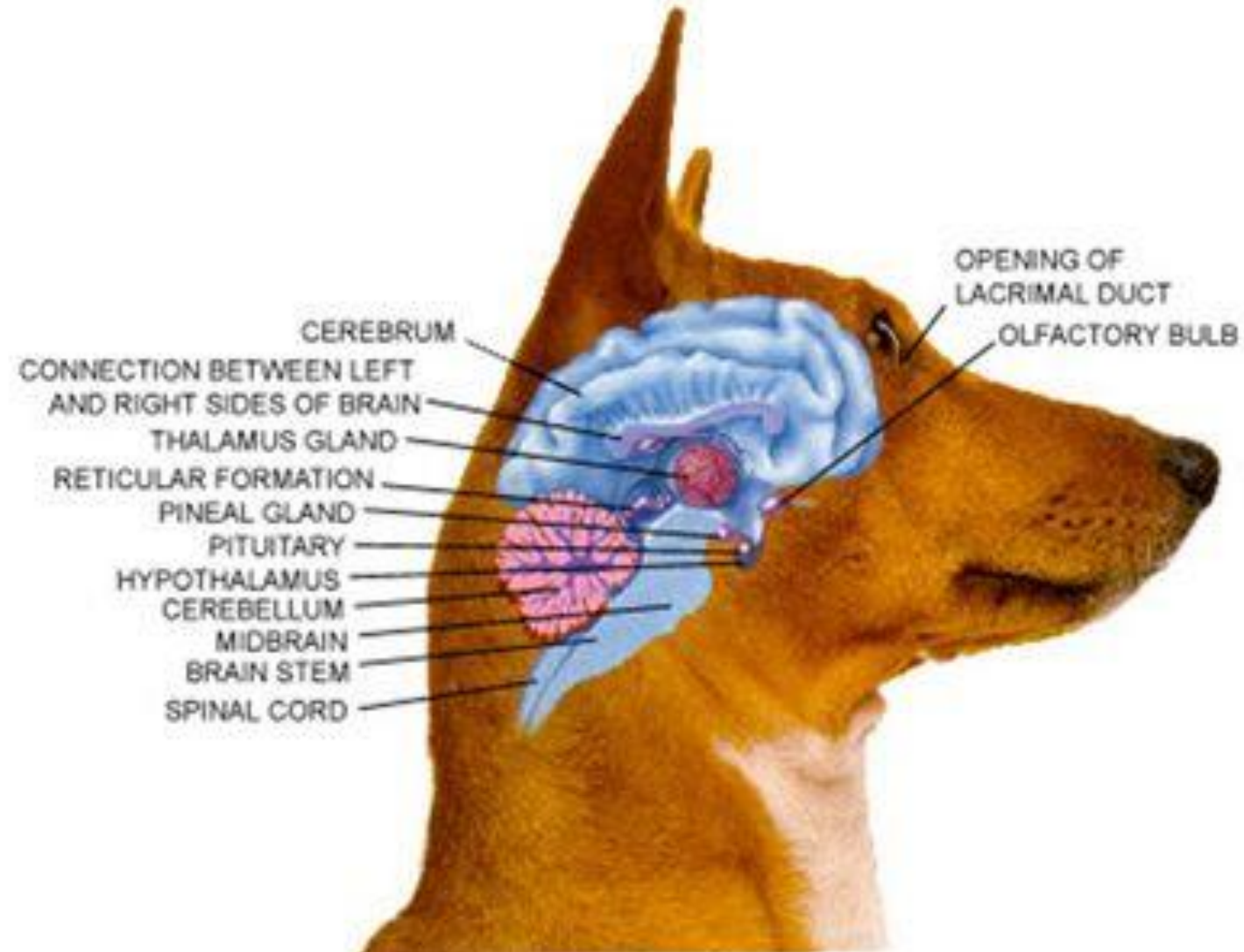
This means that many mixed-breed dogs with breed ancestry from breeds labelled as “dangerous” do not look anything these breeds.

Subsequently, these dogs are not counted as those breeds AND those breeds never get credit for the good behavior of these dogs

Subsequently, the contribution from these dogs is never included in data about the breed, so this is another way in which collected data is inaccurate, and biased against certain breeds.

Artificial Selection in Dogs

(And now, *let's consider brain related phenotypes*)



How did dog brains change during domestication?

Saetre et al. (2004) investigated the mRNA expression levels of 7762 genes in **dogs, wolves and coyotes** in three regions of the brain: **the hypothalamus**, **the amygdala**, and the **frontal lobe**.

RNA was obtained from post-mortem brains and hybridized to human microarrays

In the first set of gene expression experiments 156 genes were identified as having region specific expression in all three species. In a second set of experiments, **114 genes exhibiting expression differences between species within each brain region were identified.**

Gene Ontology (GO) analysis revealed enriched terms included **neurogenesis, cell-cell signaling, and neurotransmission**

Saetre P, Lindberg J, Leonard JA, Olsson K, Pettersson U, Ellegren H, Bergström TF, Vilà C, Jazin E. From wild wolf to domestic dog: gene expression changes in the brain. Brain Res Mol Brain Res. 2004 Jul 26;126(2):198-206.)

Dopamine in the medial amygdala network mediates human bonding

Shir Atzil^a, Alexandra Touroutoglou^a, Tali Rudy^{a,b}, Stephanie Salcedo^a, Ruth Feldman^{c,d}, Jacob M. Hooker^a, Bradford C. Dickerson^{a,e}, Ciprian Catana^{a,1}, and Lisa Feldman Barrett^{a,b,1,2}

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Edited by Linda M. Bartoshuk, University of Florida, Gainesville, FL, and approved January 6, 2017 (received for review July 26, 2016)

Research in humans and nonhuman animals indicates that social affiliation, and particularly maternal bonding, depends on reward circuitry. Although numerous mechanistic studies in rodents demonstrated that maternal bonding depends on striatal dopamine transmission, the neurochemistry supporting maternal behavior in humans has not been described so far. In this study, we tested the role of central dopamine in human bonding. We applied a combined functional MRI-PET scanner to simultaneously probe mothers' dopamine responses to their infants and the connectivity between the nucleus accumbens (NAcc), the amygdala, and the medial prefrontal cortex (mPFC), which form an intrinsic network (referred to as the "medial amygdala network") that supports social functioning. We also measured the mothers' behavioral synchrony with their infants and plasma oxytocin. The results of this study suggest that synchronous maternal behavior is associated with increased dopamine responses to the mother's infant and stronger intrinsic connectivity within the medial amygdala network. Moreover, stronger network connectivity is associated with increased dopamine responses within the network and decreased plasma oxytocin. Together, these data indicate that dopamine is involved in human bonding. Compared with other mammals, humans have an unusually complex social life. The complexity of human bonding cannot be fully captured in non-human animal models, particularly in pathological bonding, such as that in autistic spectrum disorder or postpartum depression. Thus, investigations of the neurochemistry of social bonding in humans, for which this study provides initial evidence, are warranted.

Atzil S, Touroutoglou A, Rudy T, Salcedo S, Feldman R, Hooker JM, Dickerson BC, Catana C, Barrett LF. Dopamine in the medial amygdala network mediates human bonding. Proc Natl Acad Sci U S A. 2017 Feb 28;114(9):2361-2366.

How did dog brains change during domestication?

Li et al. (2013) assessed population differentiation between Chinese native dogs, Gray wolves and German Shepherds using 48,455 SNPs.

GO biological process enrichment analysis revealed that 42 genes were associated with behavior.

The authors make the case that human artificial selection during the primary splitting of dogs from wolves was associated with rapid brain evolution. Furthermore, they connect the emergence of dog-specific behaviors during domestication with altered gene expression changes in their brains.

Li Y, Vonholdt BM, Reynolds A, Boyko AR, Wayne RK, Wu DD, Zhang YP. Artificial selection on brain-expressed genes during the domestication of dog. Mol Biol Evol. 2013 Aug;30(8):1867-76.

How did dog brains change during domestication?

A second study by Li et al. (2014) compared the published re-sequenced genomes of three wolves and ten dogs (5 ancient dogs, 5 contemporary dogs) to an additional three wolves and three Chinese native dog genomes that the group sequenced to identify regions of the genome exhibiting the most dramatic differences between dogs and wolves.

The genes **GRIK3, GABRA5, GRIK2, BCL2, and MECP2** were identified in the analysis as exhibiting **fixed alleles** between dogs and wolves.

GO enrichment identified significantly enriched biological processes: adenylate-cyclase inhibiting G-protein coupled receptor activity, glutamate receptor signaling pathway.

Glutamate is the brain's main excitatory neurotransmitter and regulates behaviors, emotions, cognitive abilities as well as learning and memory.

Li Y, Wang GD, Wang MS, Irwin DM, Wu DD, Zhang YP. Domestication of the dog from the wolf was promoted by enhanced excitatory synaptic plasticity: a hypothesis. Genome Biol Evol. 2014 Nov 5;6(11):3115-21.

The neuropeptide hormone, **oxytocin**, has a well-established role underlying social bonding in mammals where, through evolution, it has **mediated hierarchical social relationships as well as organization of social interactions**. In humans, **oxytocin coordinates parental responses after physical contact with offspring, interactions between sexual partners, interactions with friends, and empathetic interactions with strangers**.

Feldman R. The Neurobiology of Human Attachments. Trends Cogn Sci. 2017 Feb;21(2):80-99.

LETTERS

Oxytocin increases trust in humans

Michael Kosfeld^{1*}, Markus Heinrichs^{2*}, Paul J. Zak³, Urs Fischbacher¹ & Ernst Fehr^{1,4}

Trust pervades human societies^{1,2}. Trust is indispensable in friendship, love, families and organizations, and plays a key role in economic exchange and politics³. In the absence of trust among trading partners, market transactions break down. In the absence of trust in a country's institutions and leaders, political legitimacy breaks down. Much recent evidence indicates that trust contributes to economic, political and social success^{4,5}. Little is known, however, about the biological basis of trust among humans. Here we show that intranasal administration of oxytocin, a neuropeptide that plays a key role in social attachment and affiliation in non-human mammals⁶⁻⁸, causes a substantial increase in trust among humans, thereby greatly increasing the benefits from social interactions. We also show that the effect of oxytocin on trust is not due to a general increase in the readiness to bear risks. On the contrary, oxytocin specifically affects an individual's willingness to accept social risks arising through interpersonal interactions. These results concur with animal research suggesting an essential role for oxytocin as a biological basis of prosocial approach behaviour.

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. Nature. 2005 Jun 2;435(7042):673-6

Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin

Gül Dölen^{1†}, Ayehe Darvishzadeh¹, Kee Wui Huang¹ & Robert C. Malenka¹

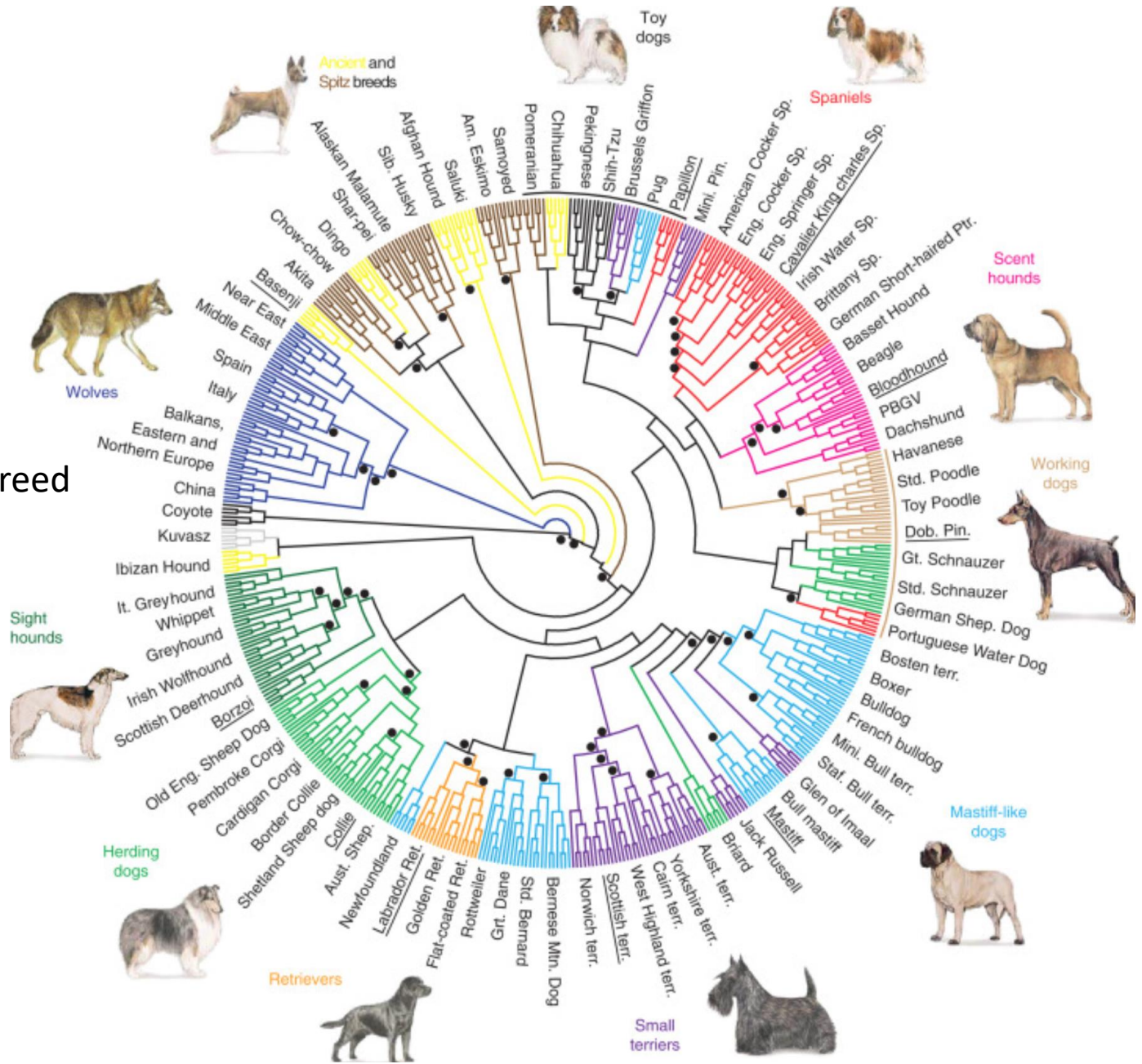
Social behaviours in species as diverse as honey bees and humans promote group survival but often come at some cost to the individual. Although reinforcement of adaptive social interactions is ostensibly required for the evolutionary persistence of these behaviours, the neural mechanisms by which social reward is encoded by the brain are largely unknown. Here we demonstrate that in mice oxytocin acts as a social reinforcement signal within the nucleus accumbens core, where it elicits a presynaptically expressed long-term depression of excitatory synaptic transmission in medium spiny neurons. Although the nucleus accumbens receives oxytocin-receptor-containing inputs from several brain regions, genetic deletion of these receptors specifically from dorsal raphe nucleus, which provides serotonergic (5-hydroxytryptamine; 5-HT) innervation to the nucleus accumbens, abolishes the reinforcing properties of social interaction. Furthermore, oxytocin-induced synaptic plasticity requires activation of nucleus accumbens 5-HT_{1B} receptors, the blockade of which prevents social reward. These results demonstrate that the rewarding properties of social interaction in mice require the coordinated activity of oxytocin and 5-HT in the nucleus accumbens, a mechanistic insight with implications for understanding the pathogenesis of social dysfunction in neuropsychiatric disorders such as autism.

Dölen G, Darvishzadeh A, Huang KW, Malenka RC. Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature. 2013 Sep 12;501(7466):179-84

What is a dog breed?

Closed breeding pool

Criteria for inclusion in breed is having parents of the breed



Look the same because small number of genes (~50 out 25,000) are the same



https://live.staticflickr.com/1/891557_a274434069_b.jpg

Look the same because have identical genomes (25,000 out 25,000 genes) are the same



<https://blogs.bcm.edu/wp-content/uploads/2018/03/Smaller-iStock-79331031-twins.jpg>

Because humans that look the same HAVE the same genome, most people assume that identical looking dogs of the same breed also have the same genome. THIS IS FALSE: members of same dog breed HAVE TREMENDOUS VARIATION in genes that do not encode anatomical traits. Consequently, the idea that the behavior is identical among breed members is wrong.

Combinations nCr Calculator

$$C(n, r) = \binom{n}{r} = \frac{n!}{(r!(n-r)!)} = ?$$

n choose r

n (objects) =

r (sample) =

Clear

Calculate

Answer:

= 79800

Solution:

$$C(n, r) = ?$$

$$C(n, r) = C(400, 2)$$

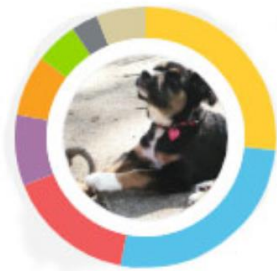
$$= \frac{400!}{(2!(400-2)!)}$$

$$= \frac{400!}{2! \times 398!}$$

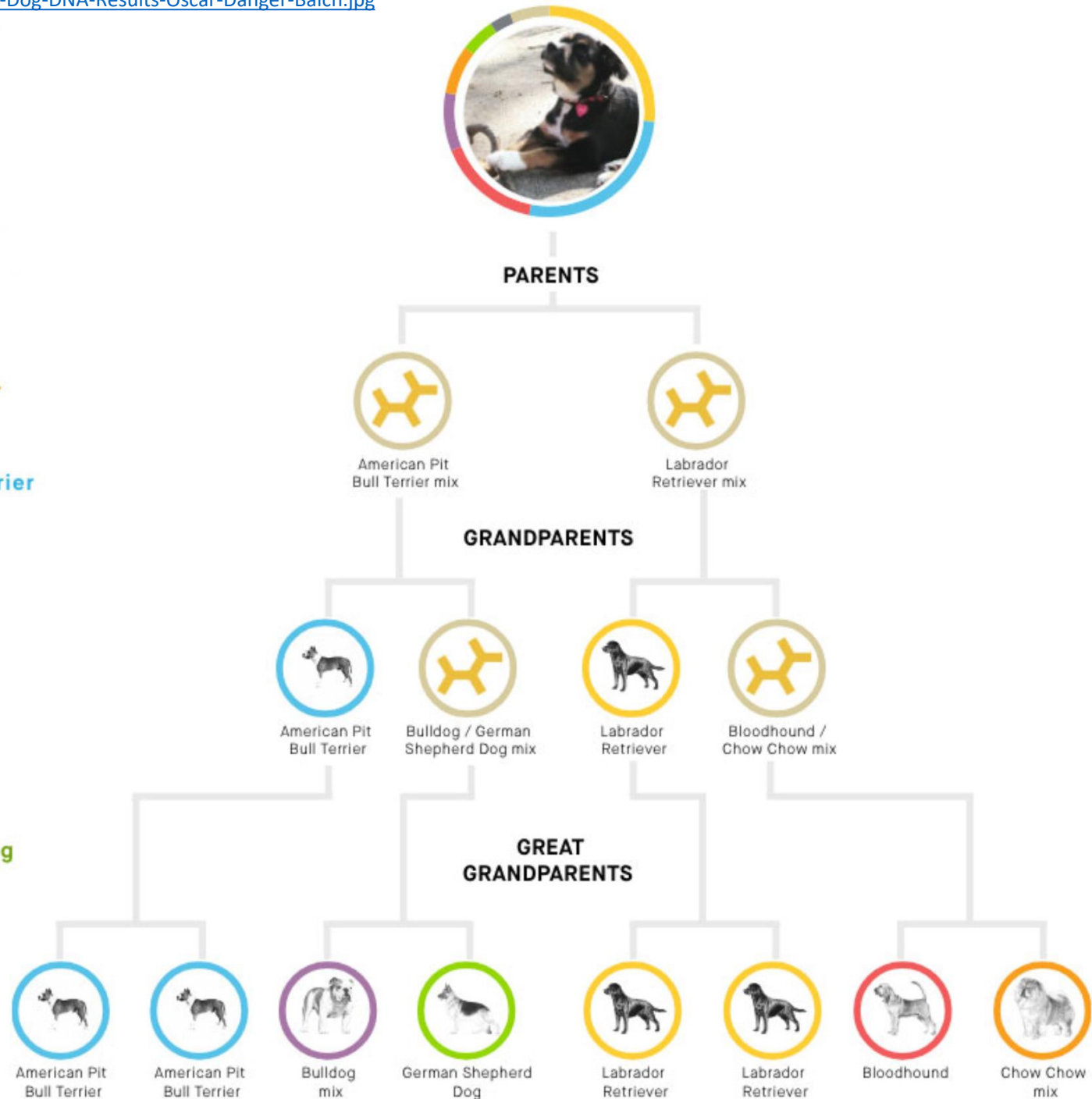
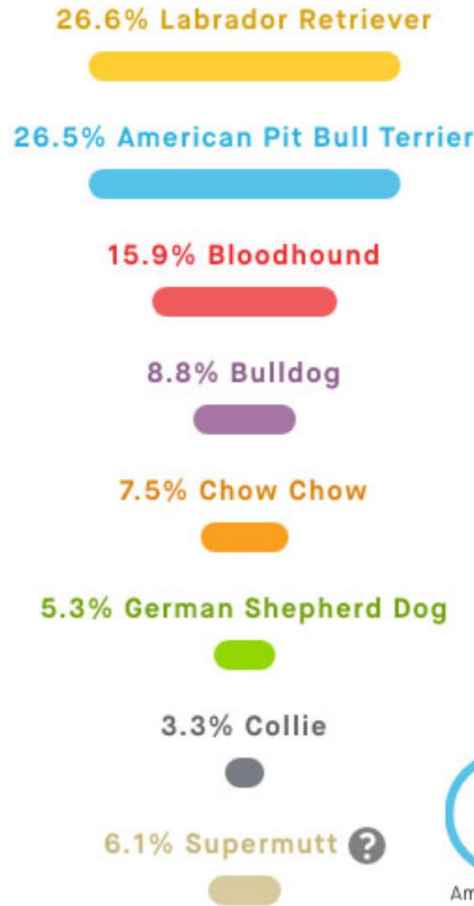
= 79800

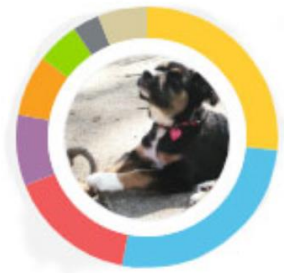


Assuming 400 breeds
~80,000 possible
Designer dogs composed
of 50/50 mix of two breeds



Mixed Breed





Mixed Breed



This dog is NOT a member of any of the breeds identified by genetic test

Breed is a human construct, and based on closed breeding pool

This dog is AN INDIVIDUAL

But even when DNA tests identify breed mixes, people subjectively assign traits to the component breeds, especially behavioral traits.

If the dog does something good . . . It must be the “lab in him”

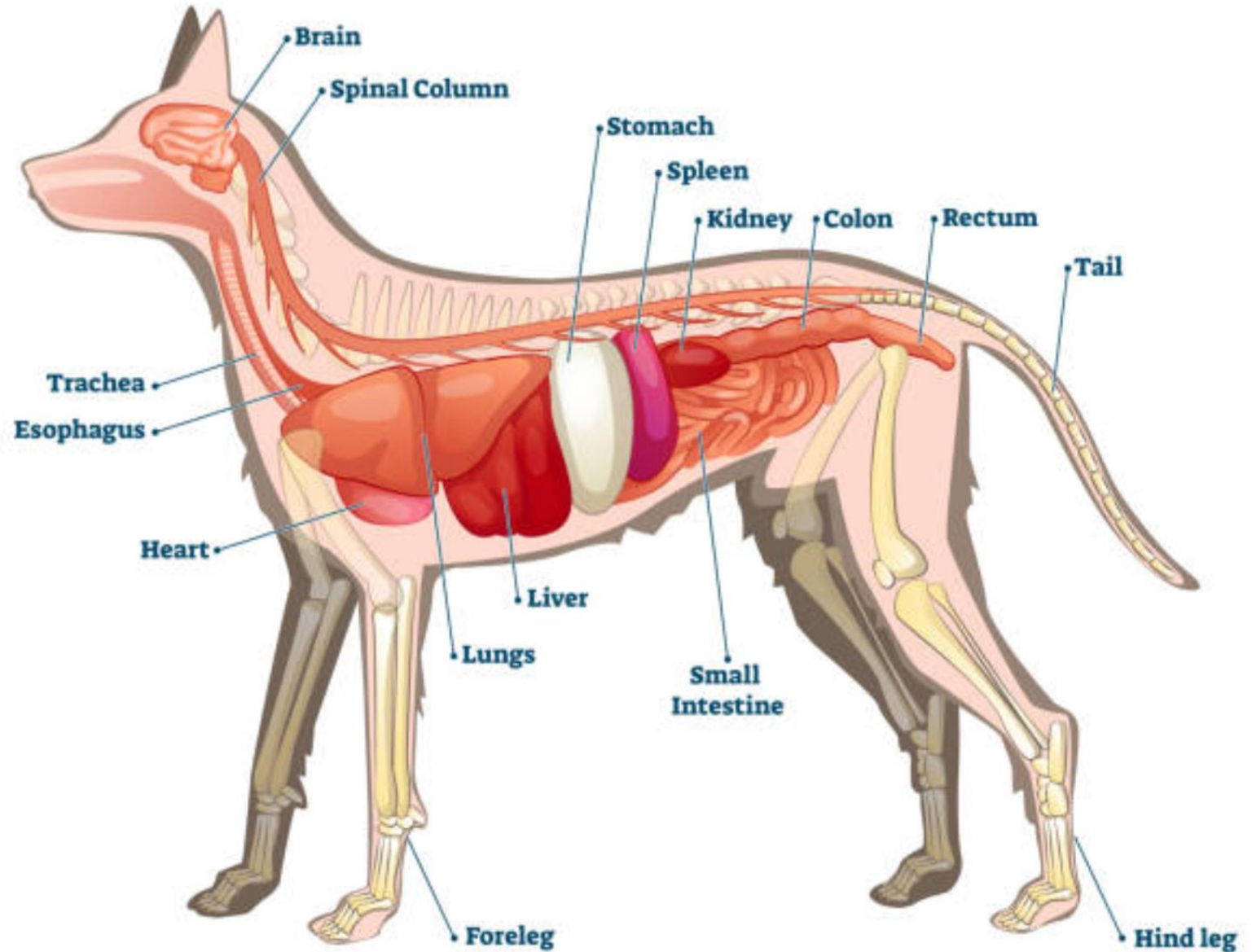
If the dog does something bad . . . It must be the “American Pit Bull Terrier in him”

if you repair a faucet in the bathroom, is that the “maternal grandpa” in you?

ANATOMY OF A DOG



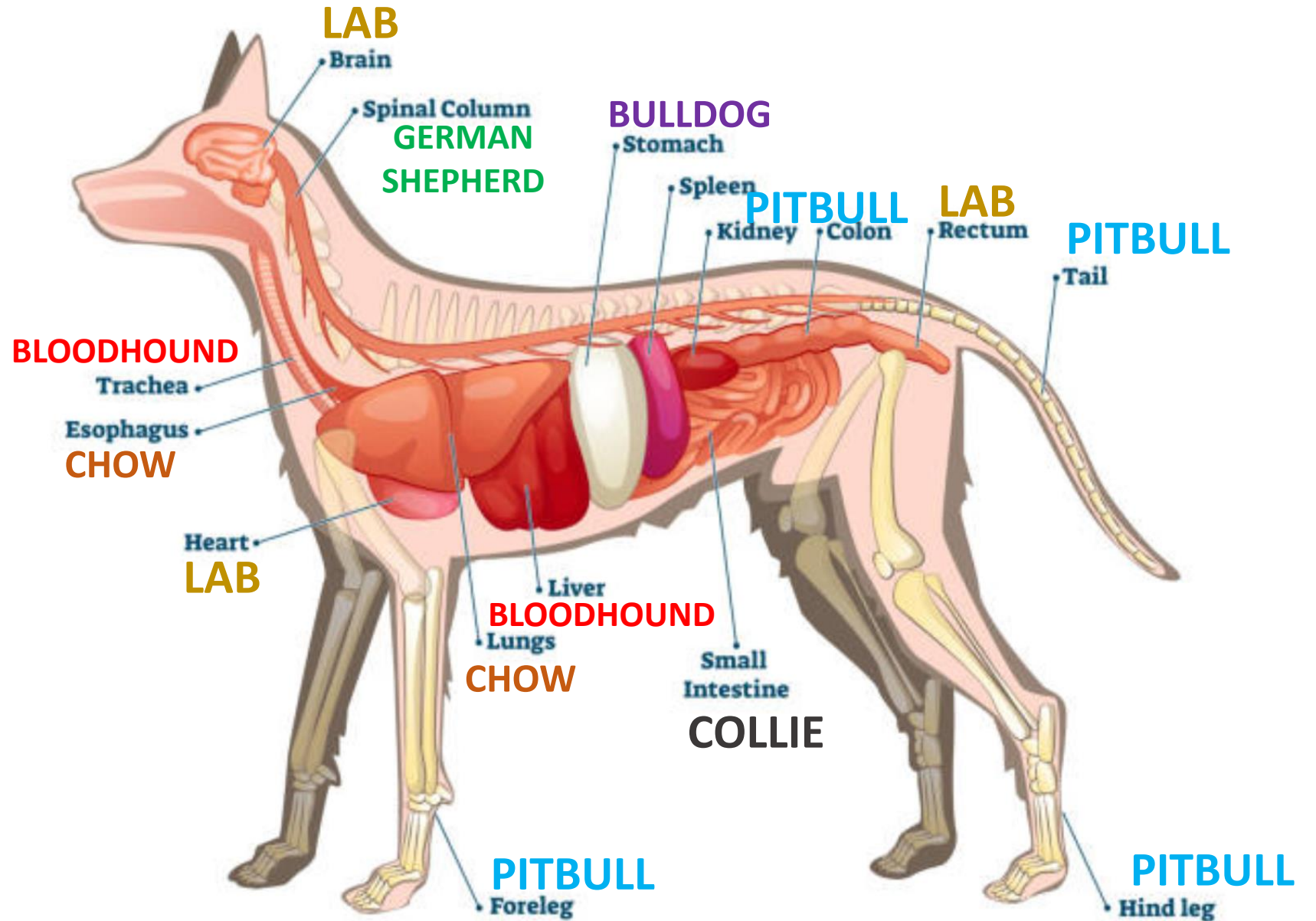
Mixed Breed

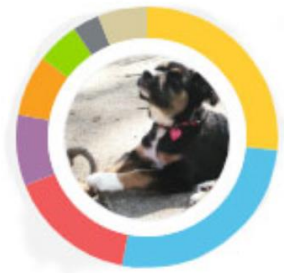


ANATOMY OF A DOG

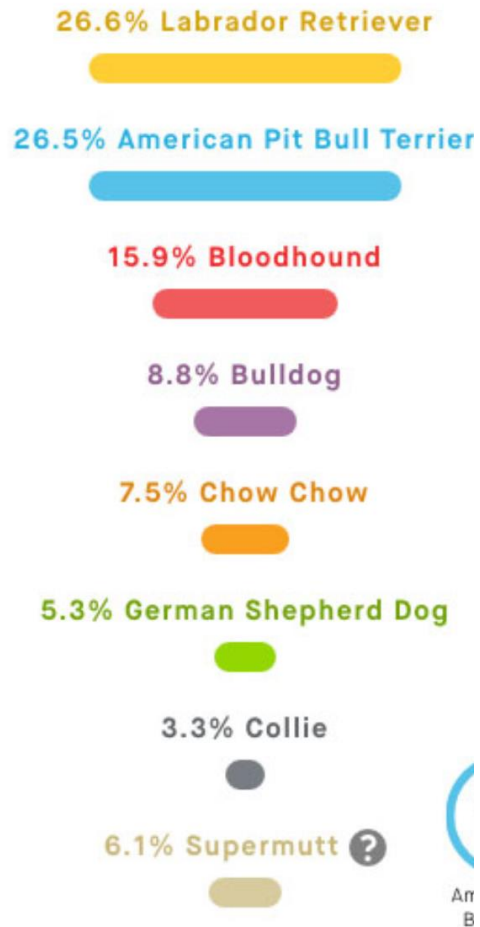


Mixed Breed





Mixed Breed



Trying to assign behavior to a component of the ancestral breeds is not based in science

In fact, it is a subjective circular argument that produces skewed data

If this dog bit someone, we could say it is an individual dog

Or, incorrectly, we can assign the bite to the breeds

American Pit Bull Terrier

Bulldog

Chow

German Shepherd

BUT THIS DOG IS **NONE* OF THESE BREEDS

... But then we omit a “count” for a bite by Bloodhound or Lab

BUT THIS DOG IS **NONE OF THESE BREEDS**

We should treat dogs as individuals rather than continue to produce subjectively assigned associations between behaviors and arbitrarily assigned breeds responsible for the behavior . . . Until we stop, our data will always be inaccurate.

QUESTIONS?

