Utilizing Genetic Tests and Health Screenings in Planned Breedings

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Havanese National
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Introduction

- Eddie Dziuk
  - OFA Chief Operating Officer, 2001 - …
  - ‘85 BS Economics – Mt St Mary’s
  - ‘09 MBA – UMKC
  - Currently enrolled in U of MO Masters program for Data Science and Analytics
  - Involved in Purebred dogs since ’76
  - Breeder/Exhibitor/Judge
  - AKC Delegate
  - Disclosure: NOT a DVM

Utilizing Genetic Tests & Health Screening in Planned Breedings

- Daunting task to cover thoroughly in an hour
  - Variety of Topics
    - Ethics & Responsibilities
    - Genetics
      - Population Genetics
    - Application
  - Variety of Knowledge and Experience Base

Ethical/Responsible Dog Breeding

- Who is a dog breeder?
  - Someone that produces a litter of puppies
    - Purebred or Mixed
    - Purposeful/Planned or Accidental

Ethical/Responsible Dog Breeding

- Who Breeds? What Motivates Them? How Educated Are They?
  - Accidental
  - Casual ("Backyard")
    - No Health Testing
    - Selection often based on convenience
    - Few, if any, criteria for puppy placement
    - Motivation varies but might be financial or emotional
  - Commercial / High Volume
    - Business – has implications on health testing, selection, puppy placement, etc.
  - Purposeful Hobby Breeders
    - Ideally motivated by passion for the breed, thoughtful selection, and a desire to achieve quality
    - Does not inherently equate to "Responsible Breeders"

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- ***As a dog breeder, whether you realize it or not – to some degree you are also geneticists – "Every time you conduct a breeding, you are conducting a genetics experiment" Dr. Danika Bannasch, NPCCHC 2013***

Ethical/Responsible Dog Breeding

- No breeder intentionally wants to produce puppies that will suffer from genetic disease
- But, it's the actions taken up front to limit genetic disease that helps differentiate "Responsible Breeders" from the others
- "Responsible Breeder" Breeding Goals
  - Maintain and enhance the quality of the breed
    - In accordance with the Standard
    - Soundness, Temperament, Type, Function
  - Manage/Limit Genetic Disease

Ethical/Responsible Dog Breeding

Assuming we all agree that HEALTH is a major component of responsible dog breeding…

What is the only way to positively select for genetically healthy offspring?

Through the selection of genetically healthy parents!

Managing Genetic Disease – Genetic Testing

- Phenotypic Tests – Tests to identify clinically affected and normal individuals
- Genotypic Tests – Direct DNA tests for liability genes
- Pedigree Analysis – make assumptions regarding underlying genetic status, and identify carrier risk based on knowledge of disease status within the pedigree
- Estimated Breeding Values (EBVs)
- ***All genetic disease cannot be prevented. However, we have the knowledge and the tools to improve the genetic health of our puppies!***

Phenotypic Tests

- **Phenotypic Tests – Tests to identify clinically affected and normal individuals**
  - **Hip Dysplasia**
  - **Elbow Dysplasia**
  - **Congenital & Adult Onset Cardiac Disease**
  - **Congenital Deafness**
  - **Ocular Disease**
  - **Autoimmune Thyroiditis**
  - **Patellar Luxation**

Phenotypic Tests & Pedigree Analysis

- Depth AND Breadth
- Selecting FOR Healthy Genes
- Selecting AGAINST Deleterious Genes

Phenotypic Tests & Pedigree Analysis

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1st Generation	2nd Generation (Parents, Aunts, Uncles)	3rd Generation (Gr-parents, Gr-Aunts, Gr-Uncles)
		Paternal Grandsire "Fair" Sibs (6): Good Good
	Sire "Good" Sibs (8): Fair Fair Good Good	
		Paternal Granddam "Good" Sibs (8): Good {dysplastic}
Stud Dog A "Fair" Sibs (7): Fair Fair Good Good Good Excellent		
		Maternal Grandsire "Good" Sibs (?)
	Dam "Good" Sibs (10): Fair Fair Fair Good Excellent {dysplastic}	
		Maternal Granddam "Good" Sibs (9): Good

Phenotypic Tests & Pedigree Analysis

- Depth AND Breadth
- Selecting FOR Healthy Genes
- Selecting AGAINST Deleterious Genes

Stud Dog B "Good"
Sibs (9):
Fair
Fair
Good
{dysplastic}
{dysplastic}
{dysplastic}
{dysplastic}

Sire "Good"
Sibs (7):
Fair
Good
Good
Good
{dysplastic}

Dam "Good"
Sibs (6):
Fair
Fair
{dysplastic}
{dysplastic}

Paternal Grandsire "Fair"
Sibs (7):
Fair
Fair
Good
Good

Paternal Granddam "Good"
Sibs (?)

Maternal Grandsire "Good"
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{dysplastic}
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Maternal Granddam "Good"
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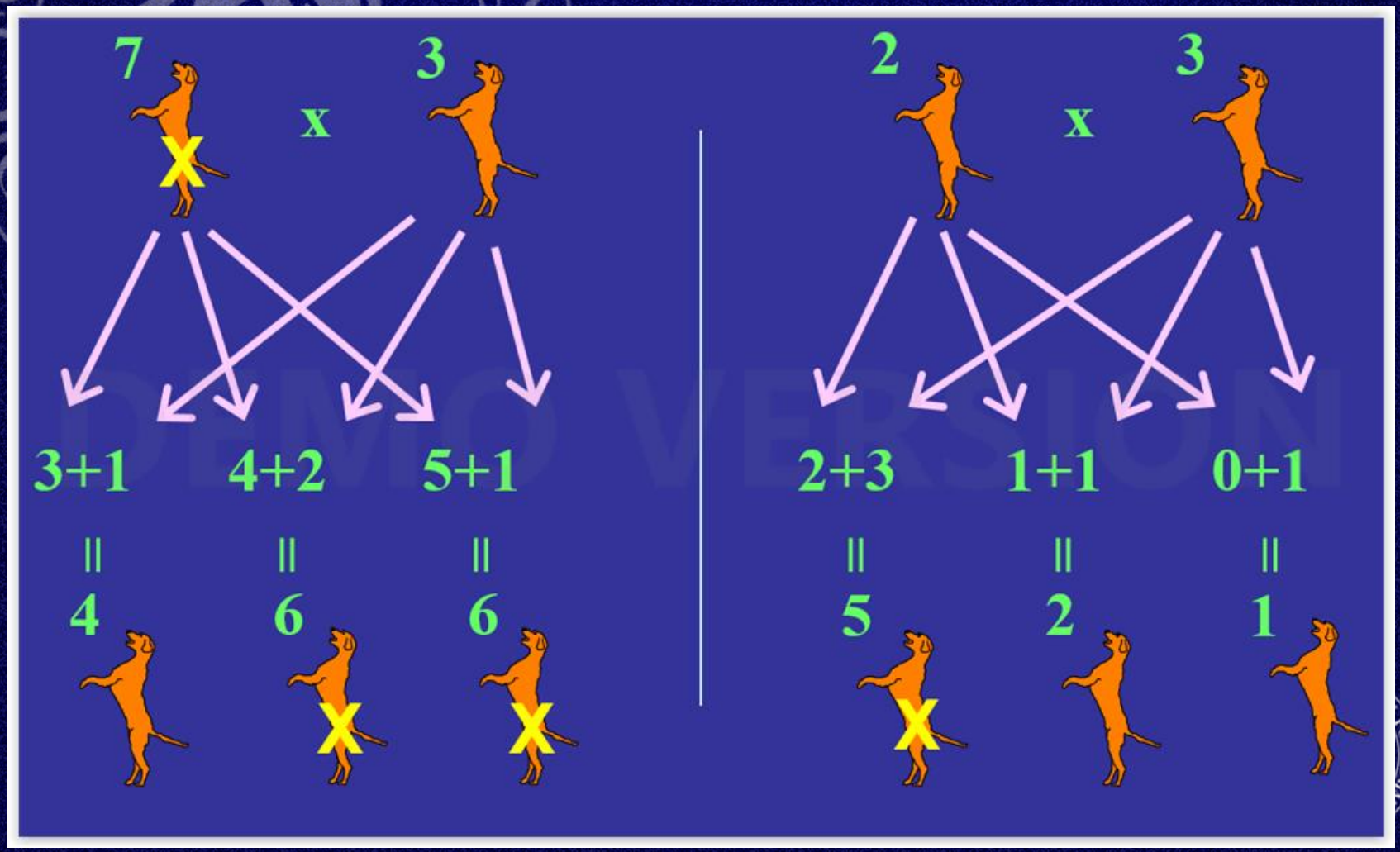
Fair
Good
Excellent

Phenotypic Tests & Pedigree Analysis

- Polygenic Disease: Threshold Traits



Phenotypic Tests – example Hips

- Progeny results of matings between parents with known hip scores (N=490,966)

- Excellent = 1
- Good = 2
- Fair = 3
- Borderline = 4
- Mild = 5
- Moderate = 6
- Severe = 7
- Examples
  - Excellent Sire x Excellent Dam: 1+1 = 2
  - Excellent Sire x Fair Dam: 1+3 = 4
  - Fair Sire x Fair Dam: 3+3 = 6
  - Mild Sire x Fair Dam: 5+3 = 8

Keller G, Dziuk E, Bell J. How the Orthopedic Foundation for Animals (OFA) is tackling inherited disorders in the USA: Using hip and elbow dysplasia as examples. *The Veterinary Journal* 186 (2011) 197-202.

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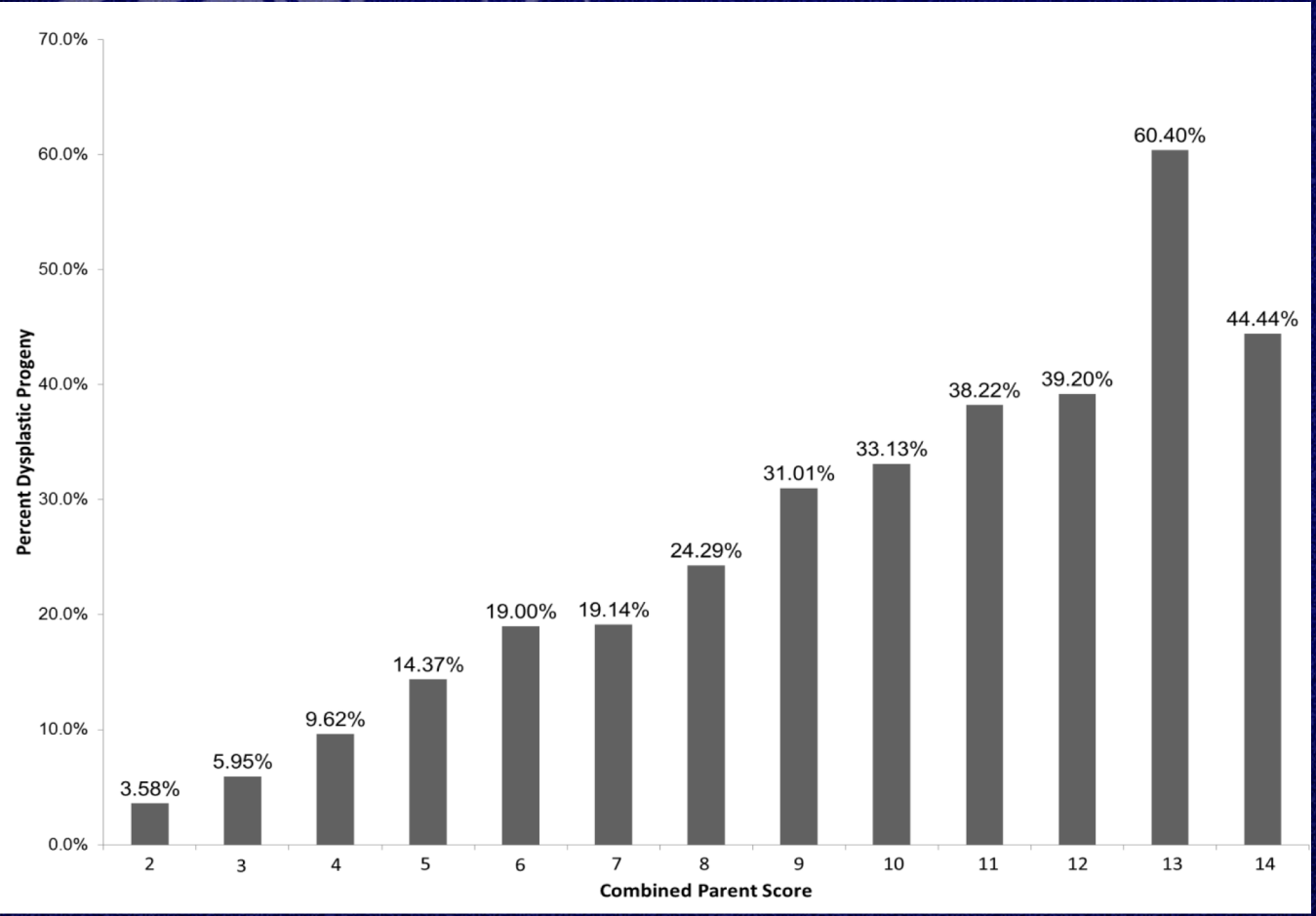

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Phenotypic Tests – example Elbows

- Progeny results of matings between parents with known elbow scores (N=67,599)

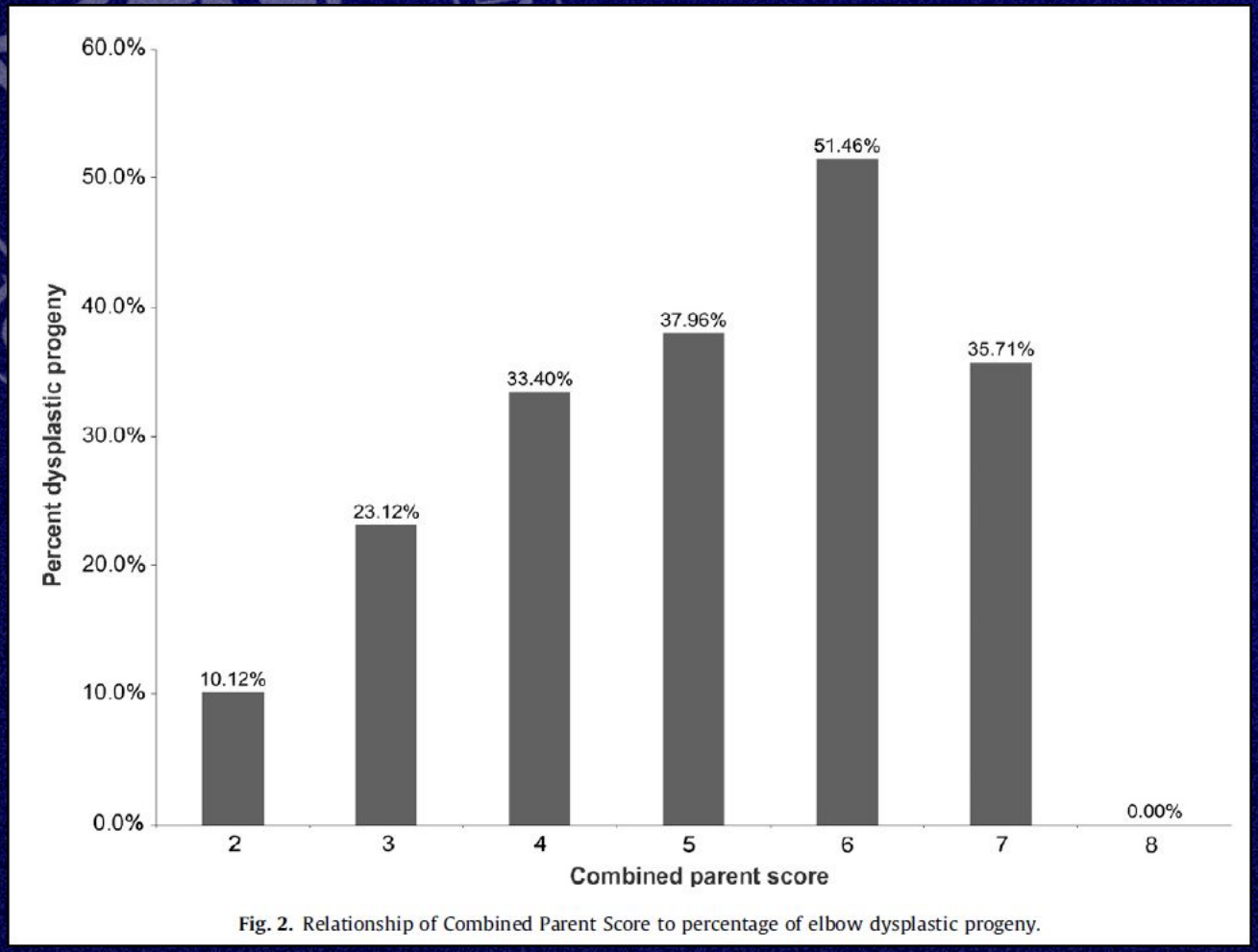

Fig. 2. Relationship of Combined Parent Score to percentage of elbow dysplastic progeny.

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Managing Polygenic Disease

- Examples: cardiac anomalies, hip & elbow dysplasia, patellar luxation
- Identify phenotypic traits tied to the underlying genes
- Phenotypic breadth of pedigree provides information on the possible range of genes carried
- Treat disorders as threshold traits
- Breed normal dogs from (mostly) normal litters to select for normalcy

Genotypic Tests

- Genotypic Tests – DNA tests for liability genes
  - Direct Mutant Gene Tests
    - vWD (von Willebrands), PRA (Progressive Retinal Atrophy)
    - Havanese:
      - Factor VIII Deficiency (VetGen)
      - Neonatal Ataxia (U of Missouri)
  - Known mutations in the bases (CGAT) in the nucleotides that make up DNA
    - Can be Insertions, Deletions, Base Pair Changes

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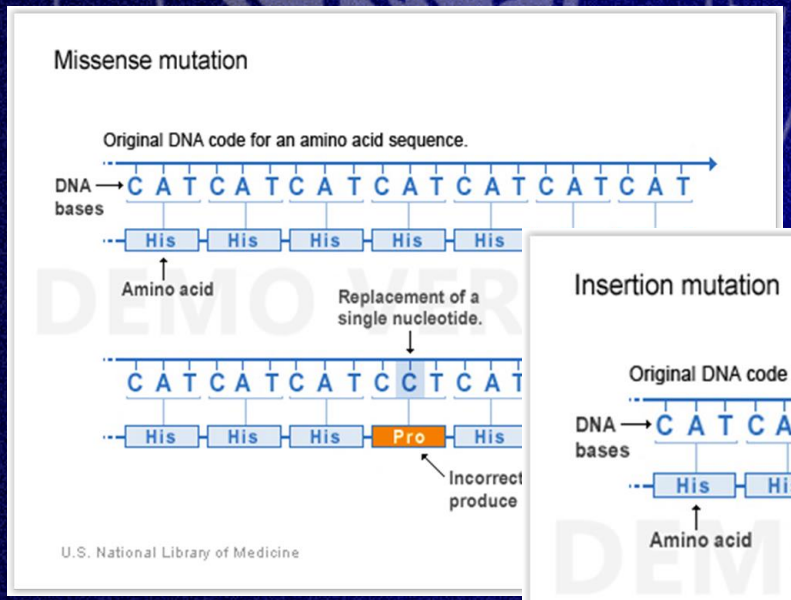
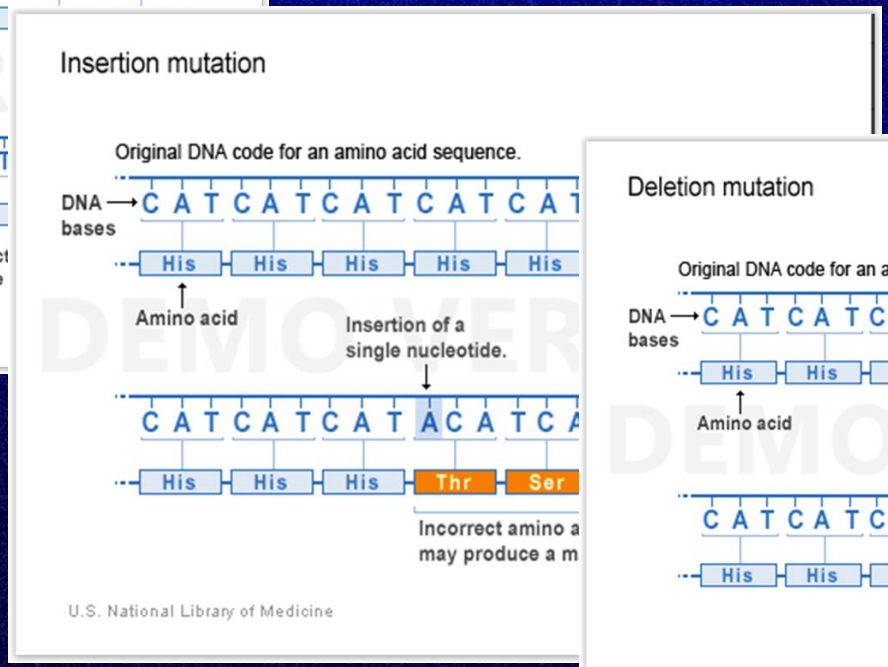
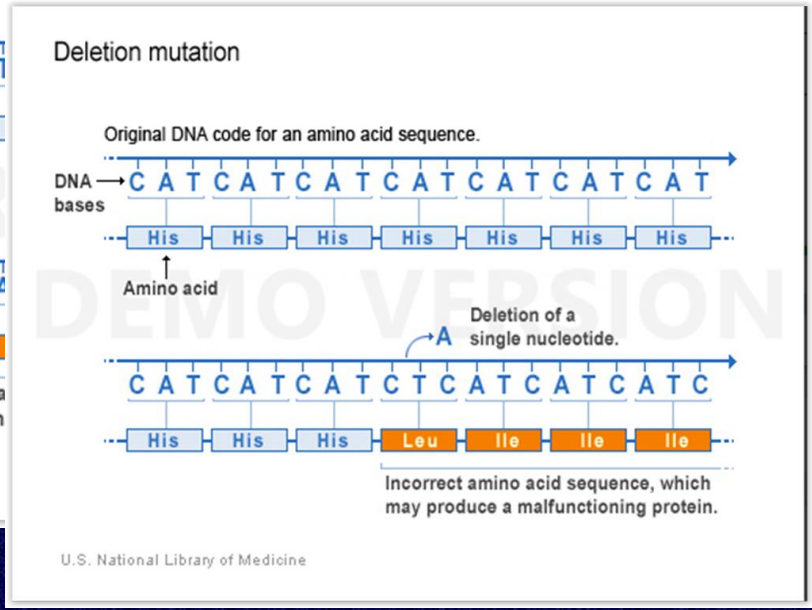






Genotypic Tests

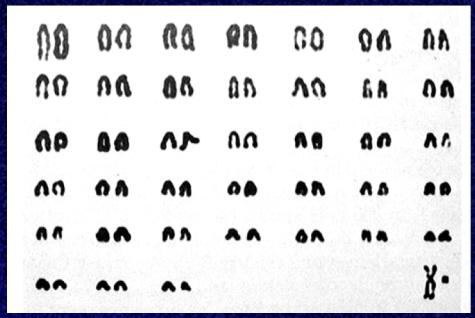
- 2001: handful commercially available DNA tests…vWD, PRA, SNB, CY

Genotypic Tests

- 2018 (146 OFA registerable DNA Tests)

Adult Onset Neuropathy	DVDOB (DINGS)	Lafora Epilepsy	Primary Lens Luxation
Adult Paroxysmal Dyskinesia	Early Retinal Degeneration	Lagotto Storage Disease	Primary Open Angle Glaucoma
Agouti	Ectodermal Dysplasia	Leonberger Polyneuropathy (LPN1)	Progressive Retinal Atrophy
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	Episodic Falling	Leonberger Polyneuropathy 2 (LPN2)	Progressive Retinal Atrophy (CNGA)
Benign Familial Juvenile Epilepsy	Exercise Induced Collapse	Leukoencephalomyelopathy (LEMP)	Progressive Retinal Atrophy (cord 1 PRA)
Buff	Factor VII Deficiency	Lupoid Dermatosis	Progressive Retinal Atrophy (crd4)
Canine Leukocyte Adhesion Deficiency (CLAD)	Factor VIII Deficiency	Macrothrombocytopenia	Progressive Retinal Atrophy (Dominant)
Canine Multifocal Retinopathy	Factor XI Deficiency	Mucopolysaccharidosis IIIA (MPS IIIA)	Progressive Retinal Atrophy (GR1 PRA)
Canine Multiple System Degeneration (CMSD)	Familial Enamel Hypoplasia (FEH)	Mucopolysaccharidosis IIIB (MPS IIIB)	Progressive Retinal Atrophy (GR2 PRA)
Centronuclear Myopathy	Familial Nephropathy	Mucopolysaccharidosis VI (MPS VI)	Progressive Retinal Atrophy (IG-PRA1)
Cerebellar Ataxia	Fanconi Syndrome	Mucopolysaccharidosis VII (MPS VII)	Progressive Retinal Atrophy (PRA3)
Cerebellar Ataxia (NCL-A)	Fucosidosis	Multi Drug Resistance (MDR1)	Progressive Retinal Atrophy (prcd PRA)
Cerebellar Degeneration	Gangliosidosis (GM1)	Muscular Dystrophy	Progressive Retinal Atrophy (rcd1)
Cleft Lip/Palate and Syndactyly	Gangliosidosis (GM2)	Musladin-Lueke Syndrome	Progressive Retinal Atrophy (rcd2)
Cleft Palate (CP1)	Glanzmann's Thrombasthenia	Mycobacterium Avian Complex	Progressive Retinal Atrophy (rcd3)
Cobalamin Malabsorption	Globoid Cell Leukodystrophy	Myotonia Congenita	Progressive Retinal Atrophy (rcd4)
Collie Eye Anomaly	Glycogen Storage Disease Type IIIa (GSD IIIa)	Narcolepsy	Progressive Retinal Atrophy (Type A)
Cone Degeneration	Hemophilia A	Necrotizing Meningoencephalitis (NME)	Progressive Retinal Atrophy (X-Linked)
Cone Rod Degeneration (crd3)	Hemophilia B	Neonatal Ataxia	Progressive Retinal Atrophy 1
Cone Rod Dystrophy 2 (crd2)	Hereditary Cataract (HSF4-1)	Neonatal Cerebellar Cortical Degeneration (NCCD)	Pyruvate Dehydrogenase Phosphatase (PDP1)
Congenital hypothyroidism with Goiter	Hereditary Cataract (HSF4-2)	Neonatal Encephalopathy	Pyruvate Kinase Deficiency
Congenital Macrothrombocytopenia	Hereditary Footpad Hyperkeratosis	Neonatal Encephalopathy w/Seizures	Retinal Dysplasia/OSD
Copper Toxicosis	Hereditary Nasal Parakeratosis (HNPK)	Neuroaxonal Dystrophy (NAD)	Severe Combined Immunodeficiency
Craniomandibular Osteopathy	Hereditary Necrotizing Myelopathy (ENM)	Neuronal Ceroid Lipofuscinosis (NCL)	Spinal Dysraphism
Cyclic Neutropenia (Gray Collie Syndrome)	Hereditary Nephritis	Neuronal Degeneration	Spinocerebellar Ataxia
Cystinuria Type 1A	Histiocytic Sarcoma	Osteochondrodysplasia	Spongiform leukoencephalomyelopathy (SLEM)
Cystinuria Type 2A	Hyperuricosuria	P2Y12 Receptor Platelet Disorder	Startle Disease
Cystinuria Type 3	Hypomyelination	Perianal Fistula	Stationary Night Blindness
D Locus - dilute pigment	Ichthyosis	Persistent Muellerian Duct Syndrome	Thrombopathia
Degenerative Encephalopathy	Imerslund-Grasbeck Syndrome	Phosphofructokinase Deficiency	Trapped Neutrophil Syndrome
Degenerative Myelopathy	Inherited Myopathy	Pituitary Dwarfism	Von Willebrands
Degenerative Myelopathy SOD1B	Juvenile Addison's Disease (JADD)	Polyneuropathy (LPN1)	Von Willebrands Type I
Dermatomyositis	Juvenile Dilated Cardiomyopathy (JDC)	Polyneuropathy (NDRG1)	Von Willebrands Type II
Dilated Cardiomyopathy (DCM)	Juvenile Laryngeal Paralysis & Polyneuropathy (JLPP)	Primary Ciliary Dyskinesia (PCD)	Von Willebrands Type III
Dilated Cardiomyopathy (DCM1 & DCM2)	Juvenile Myoclonic Epilepsy	Primary Hyperoxaluria	Xanthinuria Type 2a
Dominant Black	L2HGA	Primary Hyperparathyroidism (PHP)	Xanthinuria Type 2b
Dry Eye Curly Coat Syndrome	LAD3		

Genotypic Tests

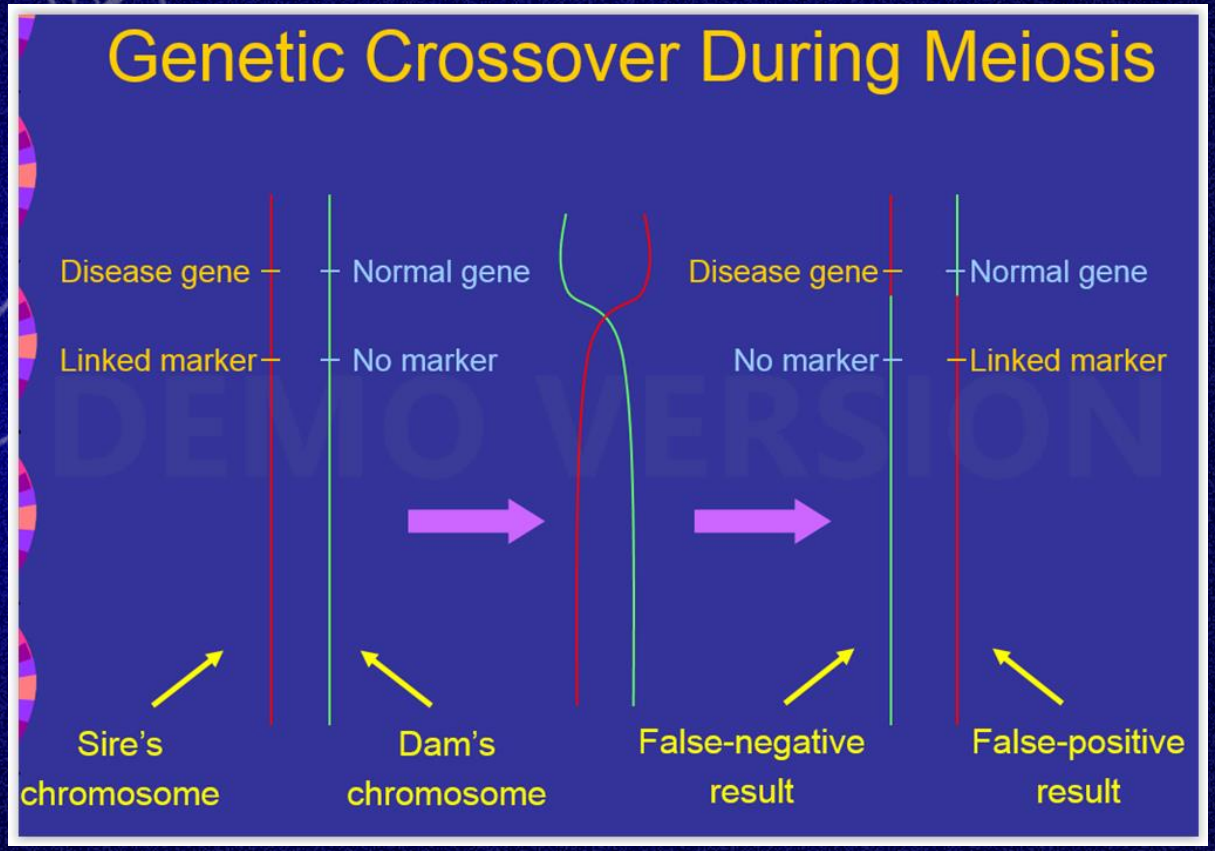


- 39 Chromosomes
- Mode of Inheritance: Single Autosomal Recessive

Parent 1 Status	Parent 2 Status		
	Normal/Clear	Carrier	Affected
Normal/Clear	All = Normal/Clear	1/2 = Normal/Clear 1/2 = Carrier	All = Carrier
Carrier	1/2 = Normal/Clear 1/2 = Carrier	1/4 = Normal/Clear 1/2 = Carrier 1/4 = Affected	1/2 = Carrier 1/2 = Affected
Affected	All = Carrier	1/2 = Carrier 1/2 = Affected	All = Affected

Genotypic Tests

- Genotypic Tests – DNA tests for liability genes
  - Linkage or Haplotype Tests
  - Test chromosomal region rather than the exact (unknown) mutation – as a result some margin of error possible



Genotypic Tests

- Other complicating variables
  - Incomplete Penetrance – Disease mutation present but the dog appears clinically normal
    - Modifying Genes
    - Environmental Influence
    - ???
  - Expressivity – Dogs with the same mutation manifest the trait or disease to different degrees (example Brindle)
  - Epistasis – One mutation masks the effects of another (example White Boxer)
  - Risk Susceptibility – Mutation confers risk, but may not be the only cause (DM)

Genotypic Tests

- Proliferation of Labs
  - No central certifying organization
    - Processes, Procedures, Use of Known Control Samples
    - IPFD – International Partnership for Dogs has begun to address this issue
- Breed Specificity
- Multiple mutations can cause the same disease expression
    - PRA in Golden Retrievers

Genotypic Tests

- Proliferation of Labs

Animal Genetics	Genetic Technologies (Australia)	Michigan State University	University of Copenhagen
Animal Health Trust	Genomia	North Carolina State University	University of Kentucky
Antagene	Genoscoper	OFA/University of Missouri	University of Minnesota/Canine Genetics Lab
Auburn University	GenSol	Optigen	University of Missouri
Clemson	HealthGene	Orivet	University of Pennsylvania
Cornell University	Helica	Paw Print Genetics	University of Utrecht
DDC Veterinary	Jefferson Medical College	PennGEN	VetGen
Embark	Labgenvet	ProjectDOG	VetNostic
Eurovetgene	Laboklin	UC Davis - VGL	Washington State University
			Wisdom Health

Take Aways

- Breeders must consider many aspects in their selection criteria – conformation, temperament, working ability, health
- An individual is not an eye, a hip, or a heart. Each individual carries tens of thousands of genes, and each is a part of the breed's gene pool
- Breeding decisions based on a single testable gene or phenotypic test are often inappropriate, must factor:
  - appropriateness of the test
  - severity of the disease – quality of life
  - prevalence in the breed population
  - size of the overall gene pool
- ***Use Health Screening as a TOOL to apply selective pressure to produce healthier dogs!***

Havanese CHIC Requirements

- **Hip Dysplasia**
  - Either OFA or PennHIP
- **Eye Examination**
- **Patellar Luxation**
- **Congenital Deafness**
- **As of 8/7/18: 2,889 CHIC Havanese**