



Dachshunds, DNA & DNA Testing

Cathryn Mellersh, Animal Health Trust, November, 2009





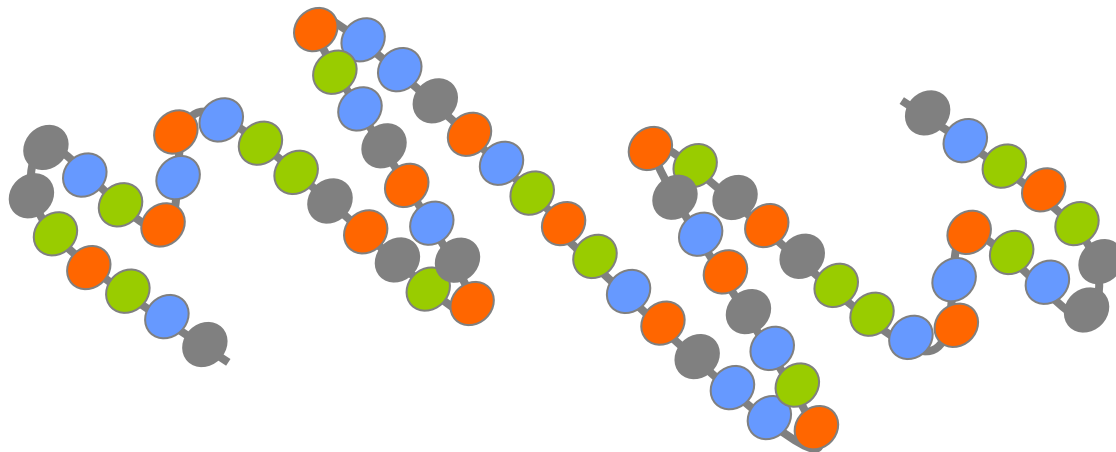
Talk Layout

- DNA – what it is, what it does, and how mutations in DNA cause inherited disease.
- How a mutation progresses through a pedigree.
- How a mutation is tracked down
- Cord1 DNA test
- Genotype-Phenotype discrepancies & possible causes
- EBVs



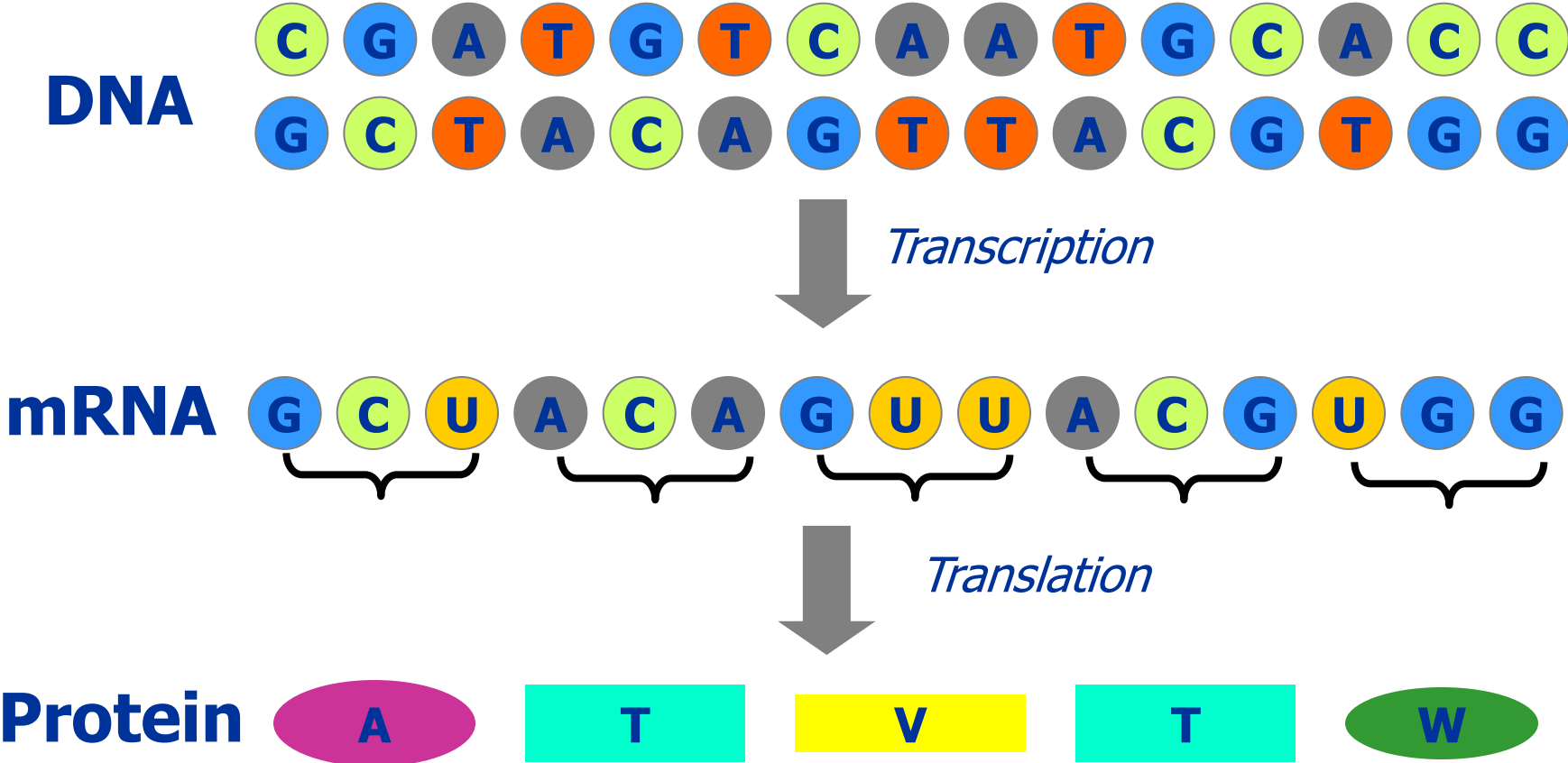
DNA

- DNA is a very long molecule & is found in virtually every cell of the body.





Coding DNA



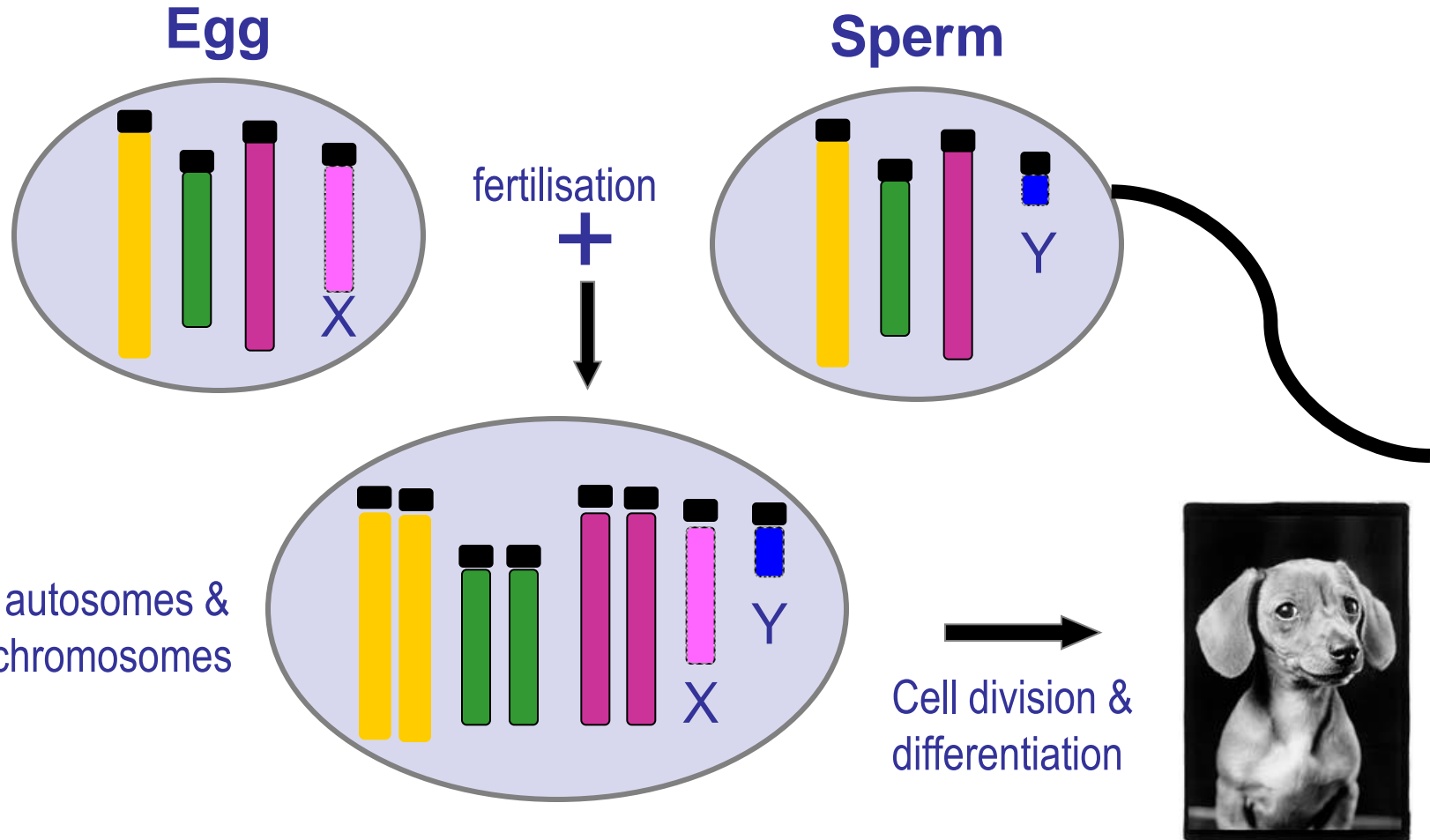


DNA

- DNA is a code/blueprint for every physical characteristic of a dog that is not determined by the environment.
- The code is determined by the order of nucleotides along the DNA.
- ALL 2,500,000,000 nucleotides are copied every time a cell divides.
- Mistakes that arise are called **MUTATIONS**.
- Most mutations that arise are repaired whereas a tiny minority persist.
- Most mutations have no effect, whereas some can be advantageous.
- Some mutations have a deleterious effect & cause inherited disease.



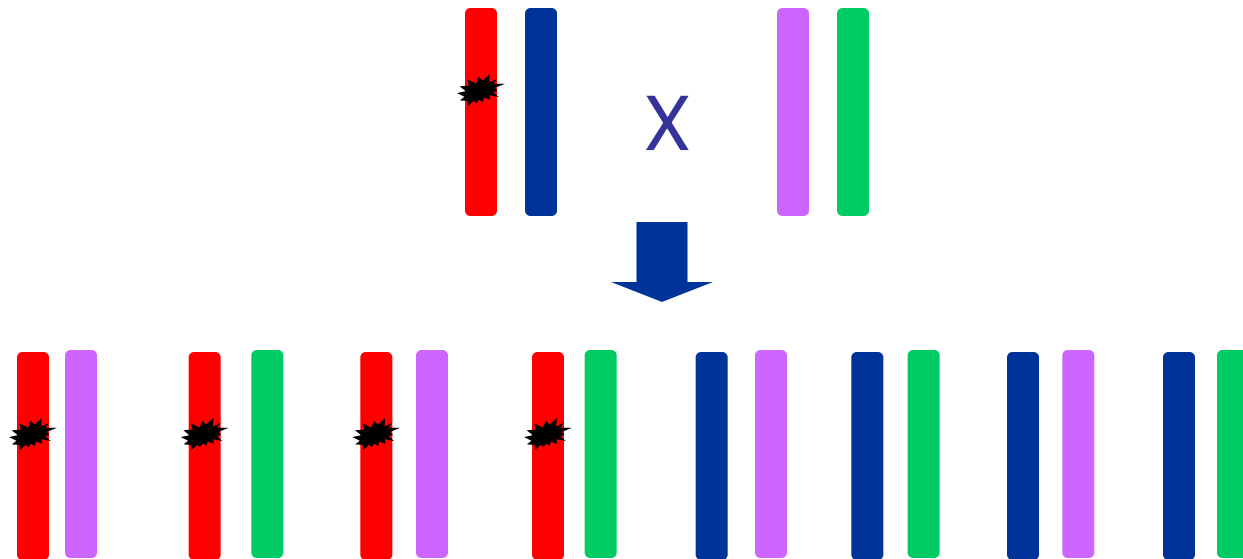
Chromosomes



DNA is carried on chromosomes

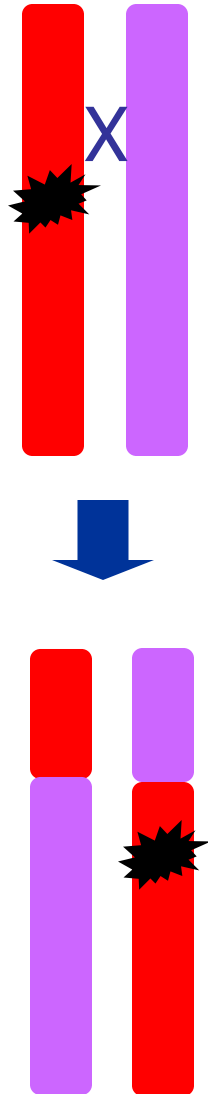


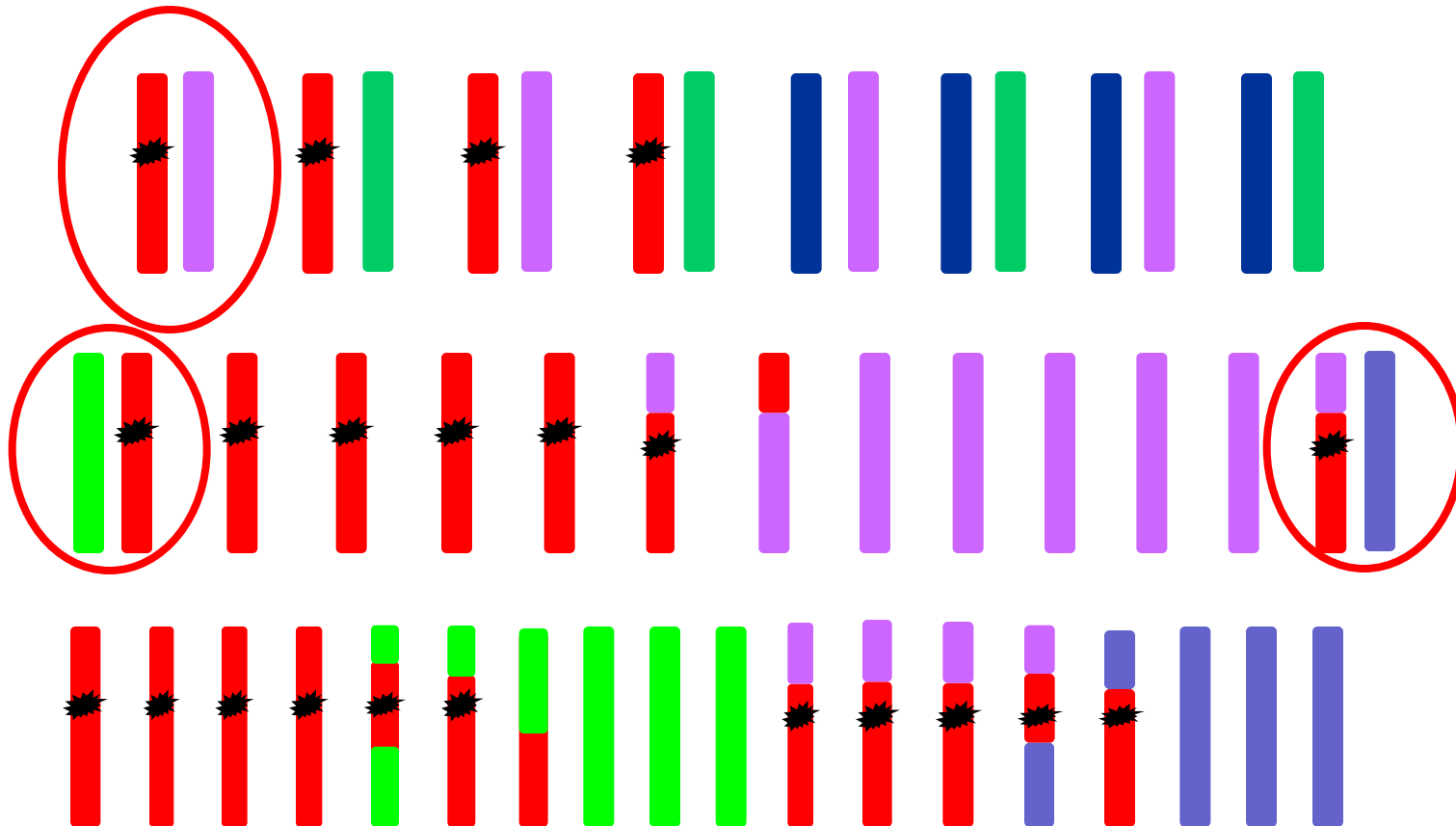
Spontaneous Mutation





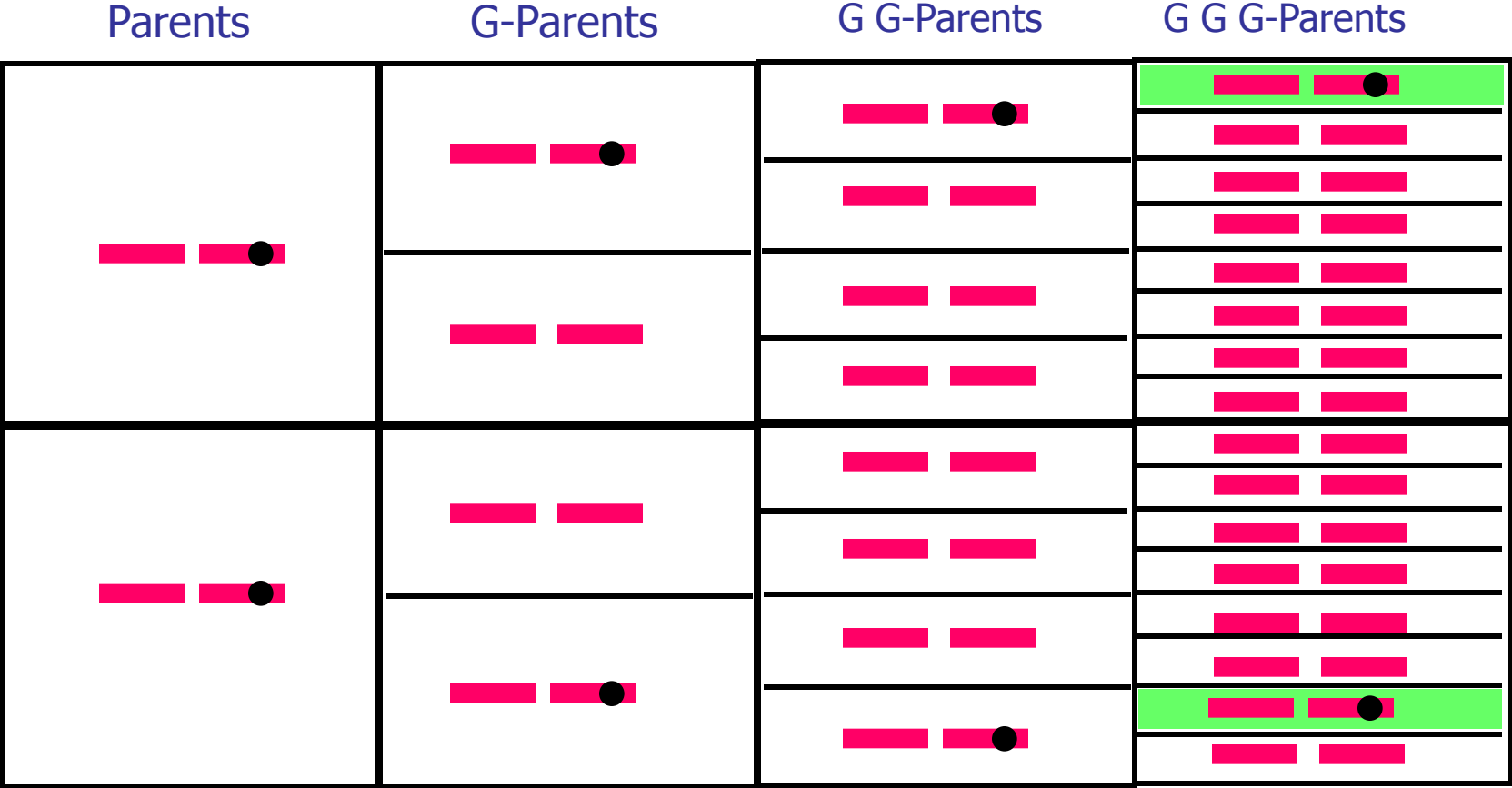
Recombination





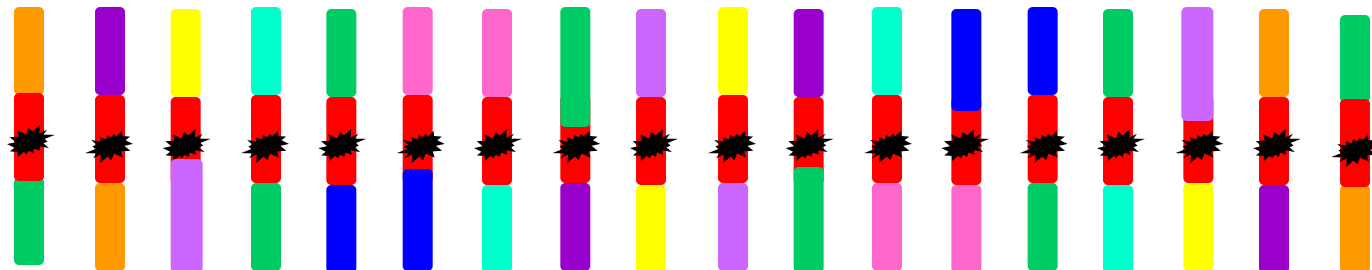
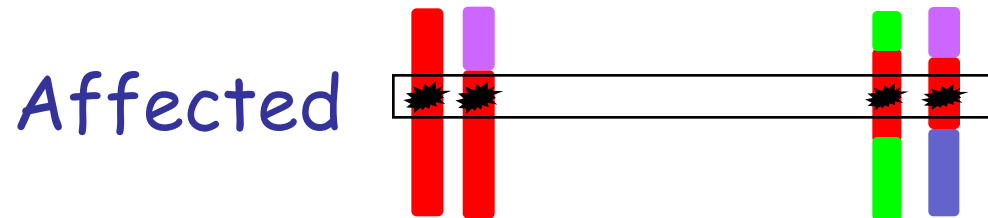
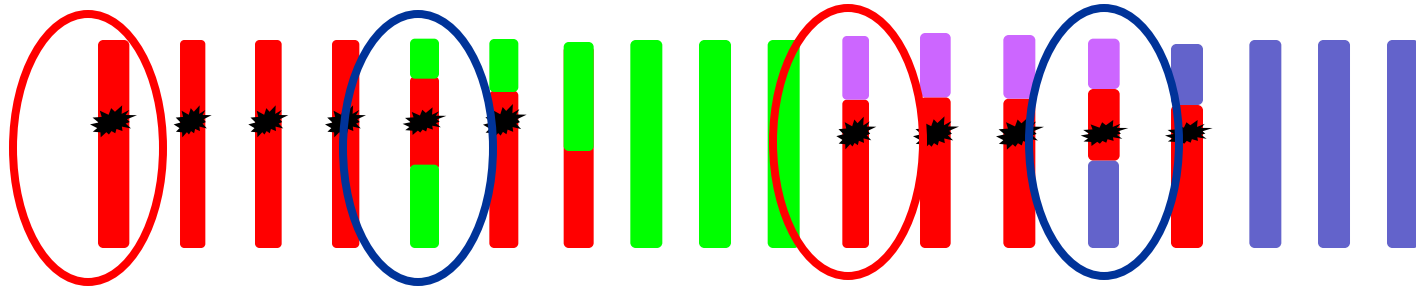


Inheritance of Mutation Down a Pedigree





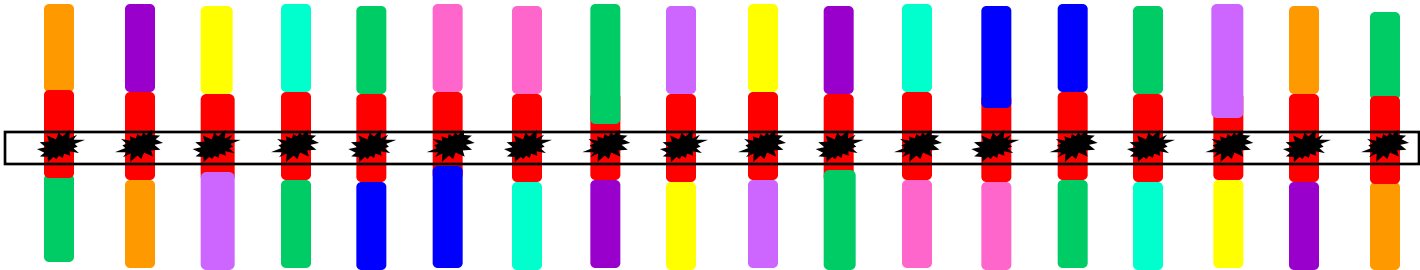
Shared Region of DNA



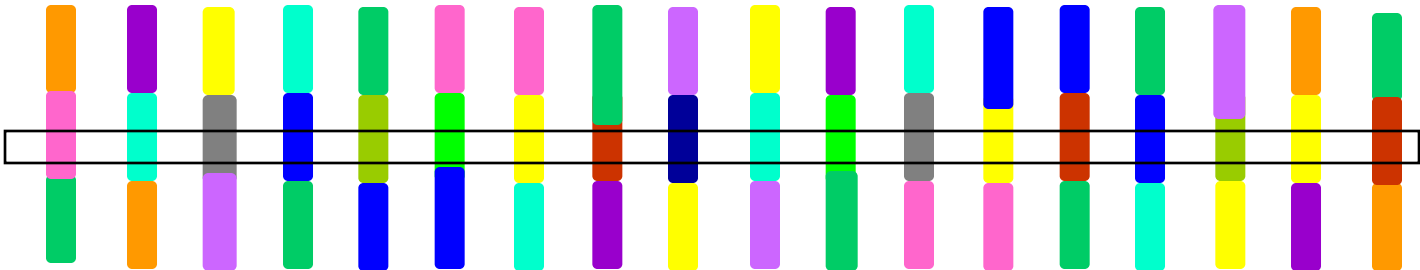


Mutation Identification

Affected



Unaffected



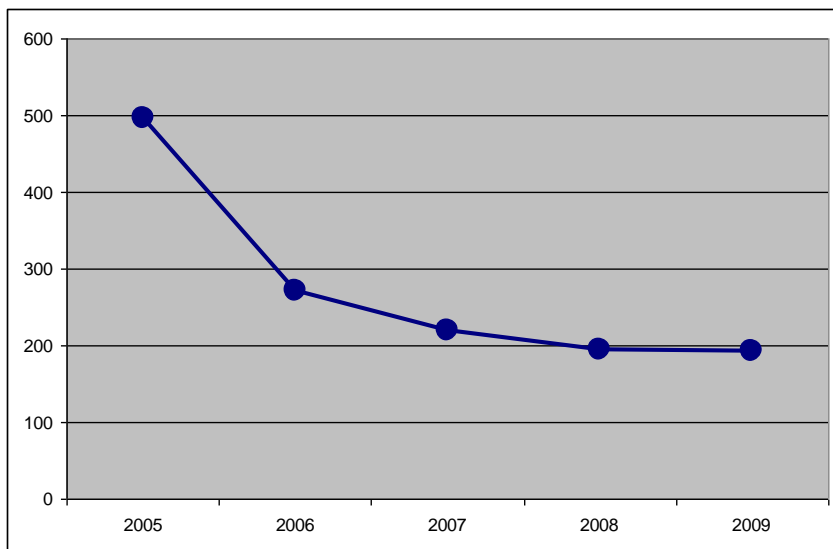


Cord1 Mutation

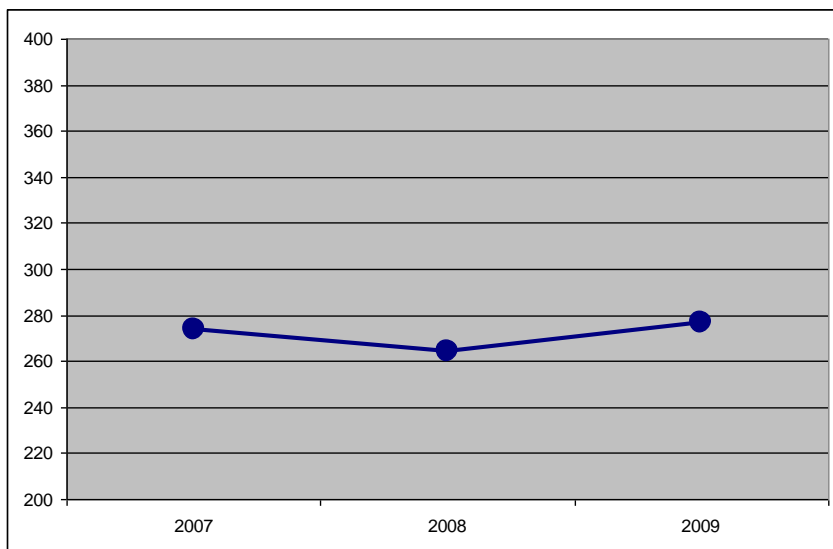
- 44 nucleotide insertion in *RPGRIP1* gene
- The insertion lies in a coding part of the gene
- The insertion changes the reading frame of the gene
- The change in reading frame generates a premature STOP codon in an early part of the gene.
- DNA test launched in 2005
- The DNA test assays whether the dog under investigation carries zero, one or two copies of the *RPGRIP1* mutation.
- It does not assay for any other mutation anywhere else in the DNA.



Numbers of dogs tested



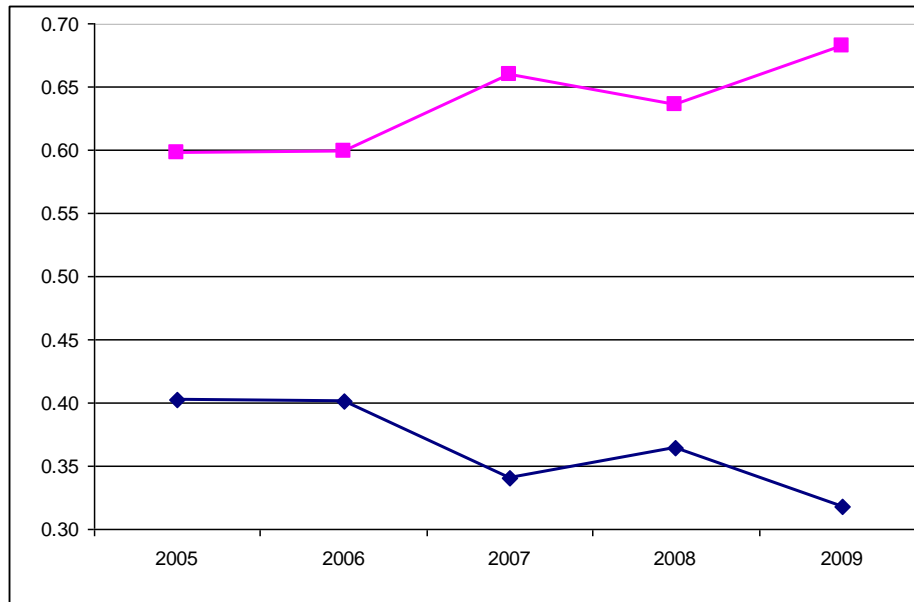
MLHDs Tested 2005 - 2009



MSHDs Tested 2007 - 2009



MLHDs



Normal allele frequency

Mutation frequency



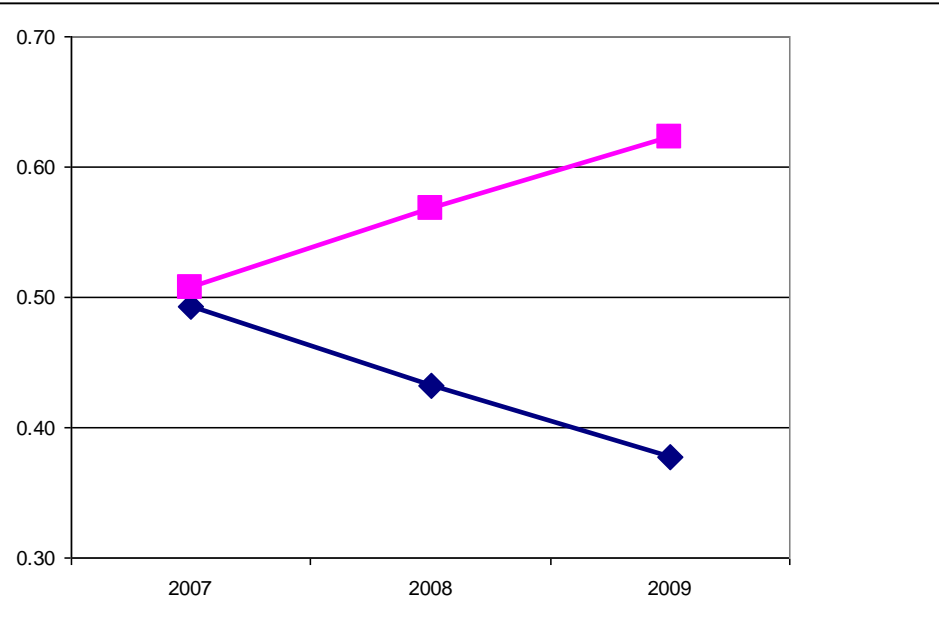
Carriers

Clears

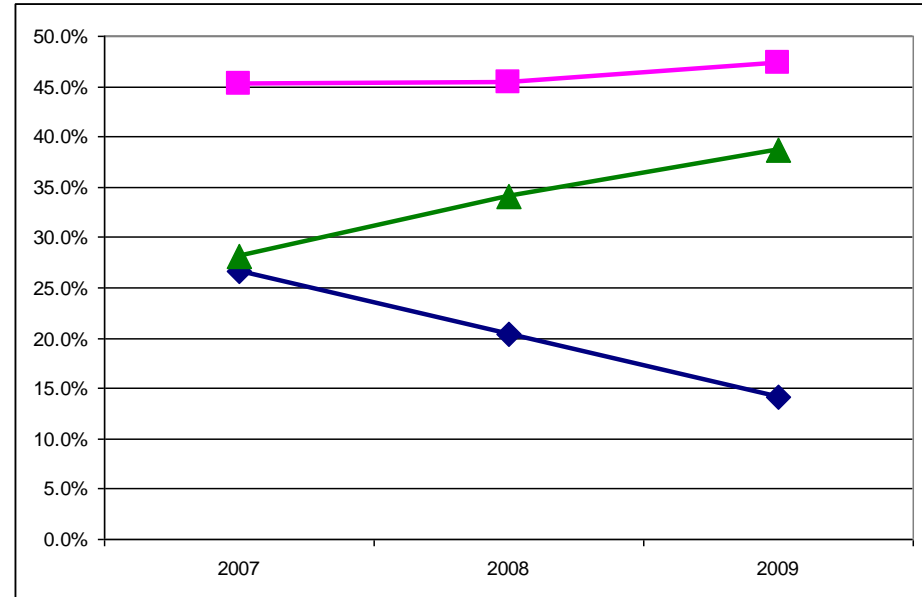
Affecteds



MSHDs



Normal allele frequency
Mutation frequency



Carriers
Clears
Affecteds



Variation

- Not all dogs that are homozygous for *RPGRIP1* mutation develop PRA at the same age.
- Some dogs that are homozygous for *RPGRIP1* mutation don't develop clinical signs until middle – late age.

WHY?

Could there be other genes involved?

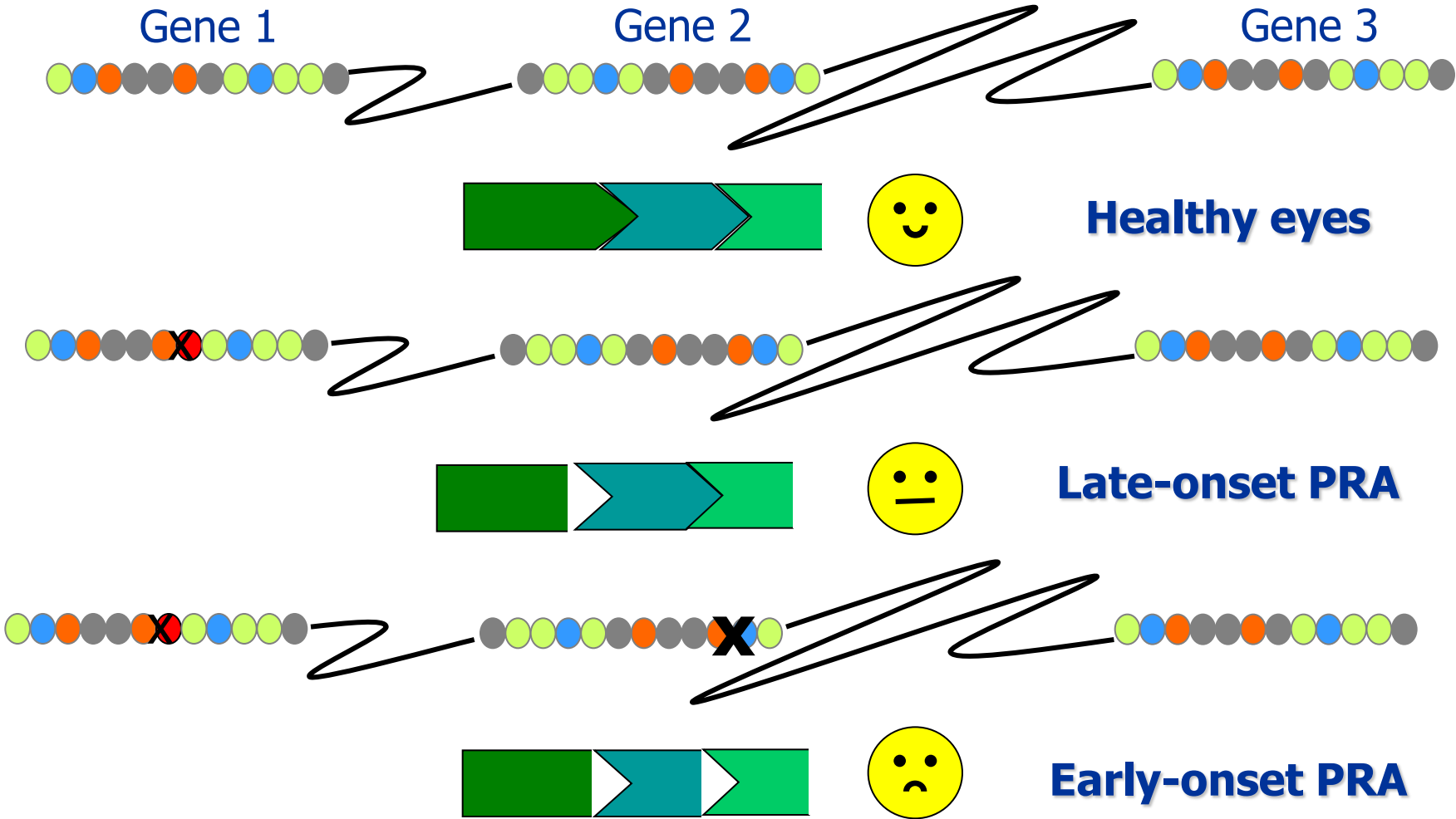


Further Research

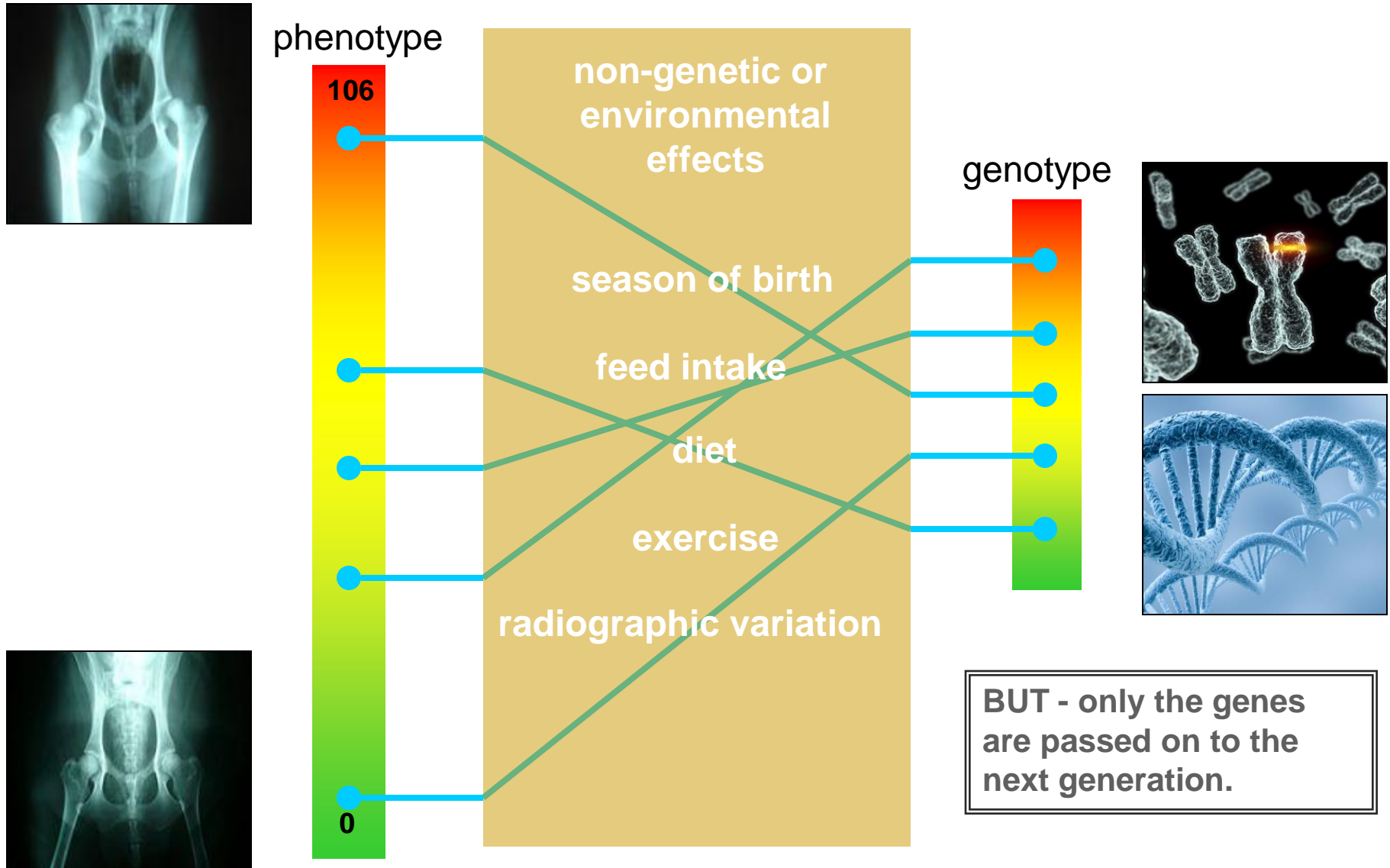
- Established a collaboration with David Sargan at University of Cambridge Vet School to investigate the causes for the observed variation.
 - Keiko Miyadera, PhD student – investigating the variation at a molecular level.
 - Claudia Busse, Ophthalmology resident – investigating the variation at a clinical level.



Multiple Mutations

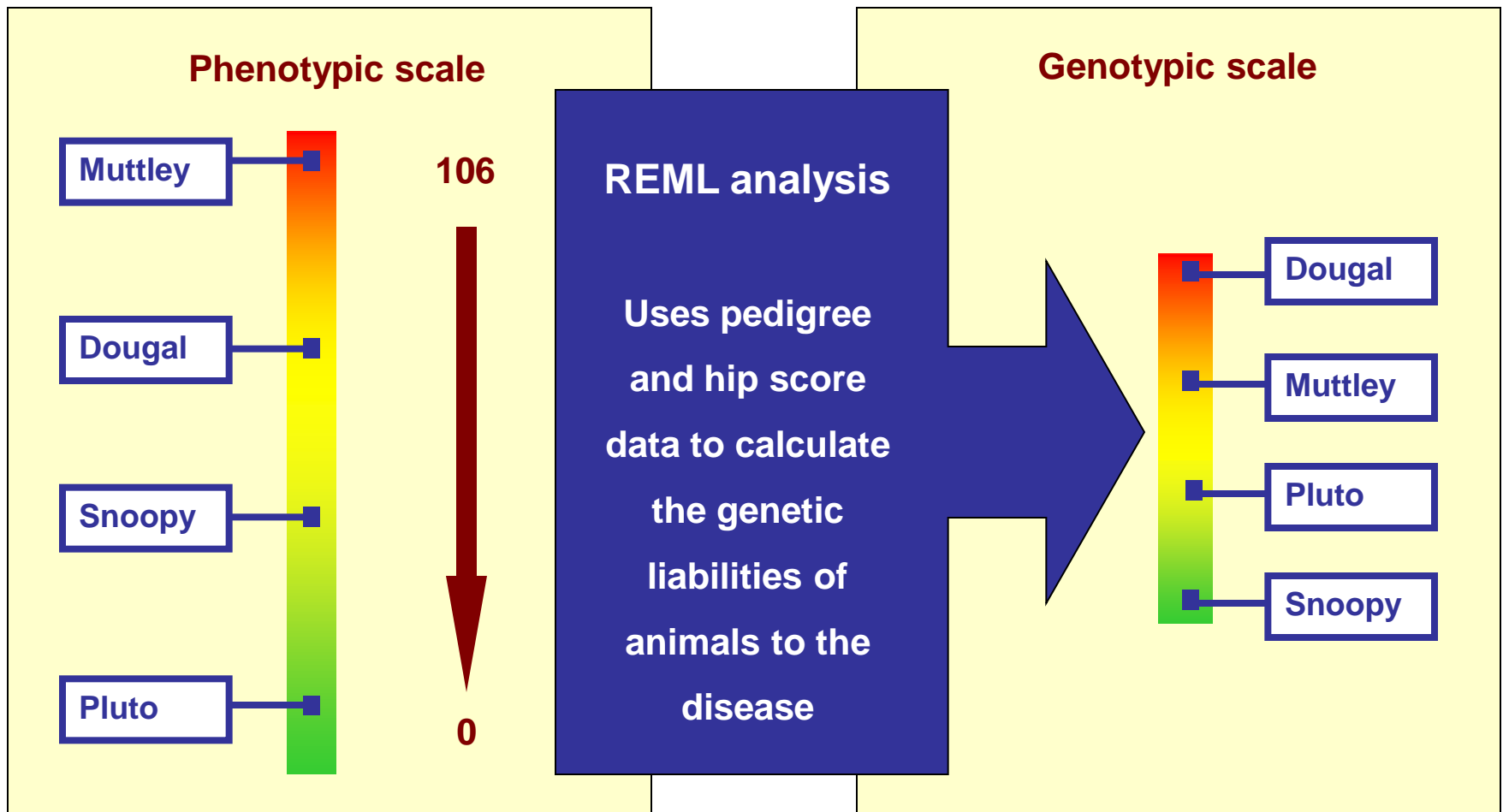


Why do we need Estimated Breeding Values?



What are Estimated Breeding Values?

EBVs are simply estimated genetic liabilities of individuals to disease...





EBVs

