HOW A MUTATION IN THE MOUSE AGOUTI GENE THAT CHANGES THE COAT COLOR OF THIS BROWN MOUSE TO YELLOW HELPS TO EXPLAIN THE MECHANISM OF ACTION OF THE RENAL DYSPLASIA MUTANT ALLELES: how a mutation in a single gene can lead to a highly variable phenotype that is inherited as dominant with incomplete penetrance.

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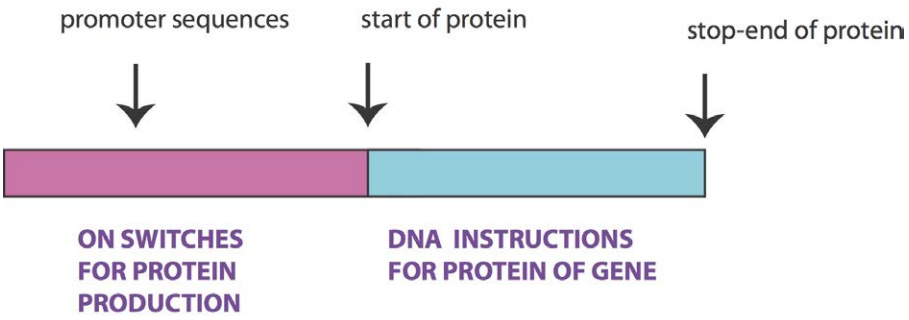
PART 1

The mouse Agouti gene (A) is expressed in hair follicles and codes for a protein that determines whether black/brown pigment or yellow pigment is deposited in the hair shaft. In normal (wild type) mice the agouti protein determines that black/brown pigment is deposited in the hair shaft leading to a grey-brown color. Mutations in the agouti gene that produce excess amounts of the agouti protein results in yellow mice.

Here is a **simplistic** diagram of the mouse agouti gene.

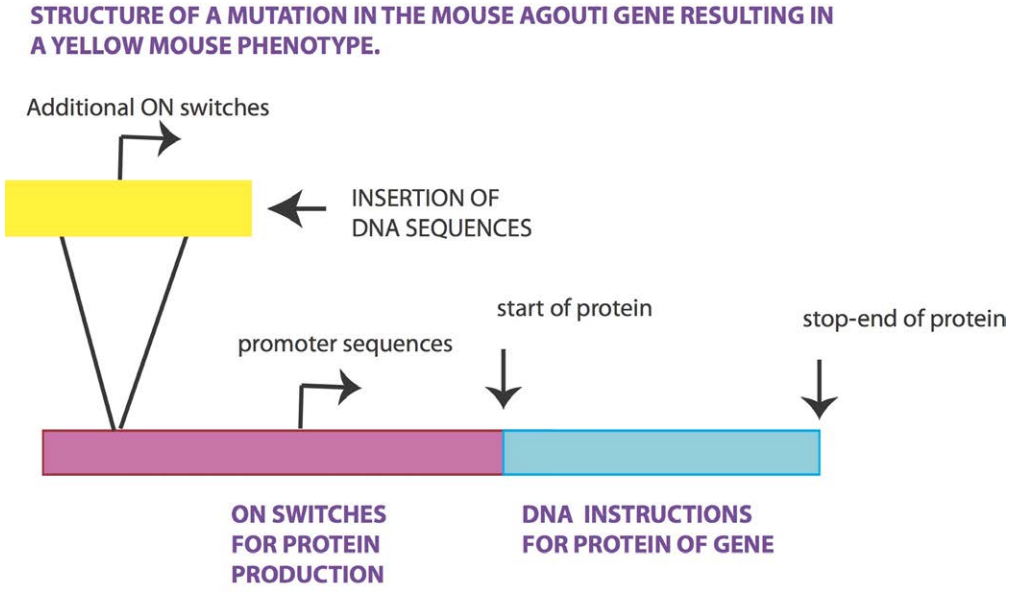
STRUCTURE OF THE WILD TYPE AGOUTI GENE



PHENOTYPE

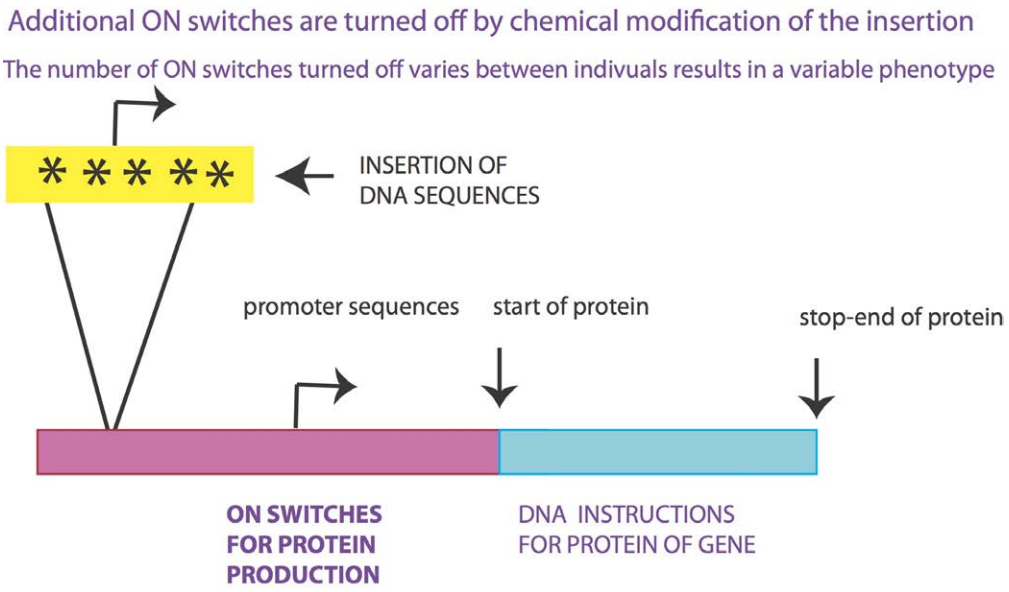
PART 2 - Description of an Agouti mutation that turns this brown mouse to yellow - The Agouti Viable Yellow Mutant strain of mice (A^{vy}).

The yellow coat color of this mouse is due to an insertion of DNA sequences into the region of the gene that controls the amount of Agouti protein that is produced. This inserted DNA contains additional ON switches for the Agouti gene. The excess amounts of the Agouti protein result in yellow pigment in the hair shaft.



PART 3 Chemical modification of the additional ON switches causes a variable phenotype ranging from completely yellow, to mottled to wild type.

Mice containing the additional DNA sequences are susceptible to chemical modifications (methylation) during embryogenesis. This alteration turns off some or all of the additional on switches. The number of ON switches that are turned off depends on the extent of the chemical modification of this DNA and has been shown to be influenced by the environment (for example the diet of the mother). Since the number of ON switches that are turn off varies amongst individuals, the amount of yellow is variable in these individuals. This results in mice with a coat color that can range from yellow (no chemical modification) to wild type (grey-brown) and everything in between (mottled) as shown in the mice below.



PART 4

Similarities between of the mechanism of action of the Agouti Viable Yellow Mutant and mutations in the canine COX-2 gene that cause renal dysplasia.

GENE	Disruption of DNA that controls amount of protein produced (**promoter** region of the gene).	Chemical modification (methylation) of promoter - applies to mutant genes only	Variable chemical modification of promoter- applies to mutant genes only	Chemical modification during embryogenesis applies to mutant genes only	Variable phenotype	Enviornmetal influences during embryogenesis	Mode of inheritance	Lower amounts of protein produced- applies to mutant genes only
AGOUTI (A^{vy})	✔	✔	✔	✔	✔	✔	Dominant with incomplete penetrance	✔
COX-2 RD alleles	✔	✔	✔	✔*	✔	Highly probable*	Dominant with incomplete penetrance	Highly probable*

Unlike the Agouti viable yellow mouse mutant that is clearly visible kidney defects typical of this inherited form of RD can only be seen with a renal wedge biopsy. The incomplete penetrance of the Cox-2 mutant alleles leads to a highly variable range of kidney defects. Animals with a moderate to severe defect may have no symptoms until the renal function is diminished by 70-75%, and this can take years to develop. This is why RD is actually a late onset disease. Most dogs with one or two copies of a RD mutant allele are sub-clinical. For more information please see:

https://www.dogenes.com/RDfacts1.html

REFERENCES:

Whiteley, Mary H. "Allelic variation in the canine Cox-2 promoter causes hypermethylation of the canine Cox-2 promoter in clinical cases of renal dysplasia." Clinical epigenetics 6.1 (2014): 7.

*KEY FINDING FROM THIS PAPER:

1. Methylation of the canine Cox-2 promoter occurs only in clinical cases of RD.
2. The wild type promoter (normal gene) is never methylated even in heterozygotes (carriers).
3. Subjects that are biopsy negative and have an RD allele are not methylated. WT/WT animals are never methylated.
4. Methylation of the Cox-2 promoter must have occurred early in embryogenesis before germ-line differentiation occurred as methylated DNA is found in various adult tissues other than kidney.
5. The degree of methylation varies amongst individuals and therefore explains the variable phenotype and wide-ranging degree of kidney defects.
6. Methylation of the Cox-2 promoter is independent of genetic background (Breed).

REFERENCES FOR THE AUGOUTI VIABLE YELLOW STRAIN OF MICE.

Michaud, Edward J., et al. "Differential expression of a new dominant agouti allele (Aiapy) is correlated with methylation state and is influenced by parental lineage." Genes & development 8.12 (1994): 1463-1472.

Wolff, George L., et al. "Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice." The FASEB Journal 12.11 (1998): 949-957.

Morgan, Hugh D., et al. "Epigenetic inheritance at the agouti locus in the mouse." Nature genetics 23.3 (1999): 314-318.