How Extension And Agouti Really Work!

The horse originally evolved to be bay and dun in colour. Prezwalski's horse is typical of what the ancestors of the modern horse looked like (colour wise at least) before nature in the form of mutations at cellular level, and humans by selective breeding, created and multiplied a whole range of new colours.

The genes responsible for controlling black and red pigment production are agouti and extension. The primitive or wild type version of both genes is denoted by A and E respectively. And this is how they work....

Believe it or not but skin cells in the horse produce red pigment by default – true story! Black pigment production is only switched on when special protein molecules located in the outer membranes of the melanocytes (melanocytes are the skin cells that produce pigment in the skin and coat) receive a signal from a hormone called alpha-melanocyte-stimulating hormone (a-MSH). These protein molecules are called melanocortin 1 receptor protein (MC1R) molecules and the instructions for making this protein is controlled by the Extension gene.

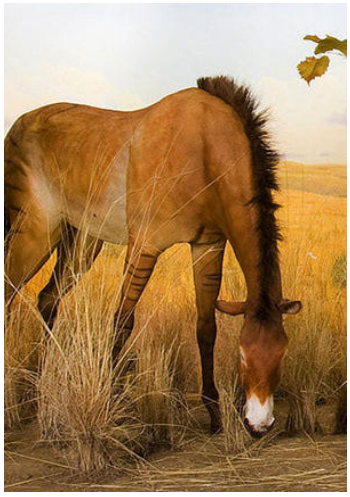
The MC1R protein molecules have special receptors on them and these receptors are designed specifically to bind to the a-MSH hormone (like a lock - protein molecules, and key - hormone). When this binding action happens it activates the protein molecules, setting off a series of chemical reactions inside the cell to which they're attached that switches it from producing red pigment to producing black pigment. If the MC1R protein molecules are not activated by the hormone they continue to produce red pigment by default.

There are several ways in which MC1R protein molecules are stopped from being activated by the hormone. The receptors on the molecules can be blocked by another type of protein or peptide (like putting a cover over the keyhole in the lock that prevents the key from being inserted into the lock). Or the protein molecules themselves can be 'deformed' or faulty as the result of a mutation in the gene that produces them (the Extension gene). So the key no longer fits into the keyhole, not because the key is faulty but because the keyhole is either damaged or not quite the right keyhole for that key.

In a nutshell, chestnut horses have 'deformed' or 'faulty' MC1R protein molecules that are unable to bind with the a-MSH hormone. The fault is caused by a missense mutation in both copies of their extension gene; a missense mutation occurs when one amino acid in the DNA chain is replaced by another amino acid (kinda like typing hAt instead of hOt - just that one letter switch completely changes the meaning of the word). In this instance, the 'typo' in the DNA chain causes a loss of function in the resulting protein molecules produced by the gene. These protein molecules can't bind with the a-MSH hormone so in an individual with 2 copies of this faulty gene, none of their skin cells get switched over to producing black pigment. Behold the totally red horse lol!

As mentioned, the other way in which MC1R protein molecules can be stopped from working is when they're blocked or prevented from binding with the hormone by the actions of another protein or peptide. And this is precisely what the peptide produced by the primitive or wild type version of the Agouti gene does.

The primary function of the Agouti gene is to produce a paracrine signalling peptide that disables the MC1R protein molecules by attaching itself to them. This blocks or nullifies the actions of the a-MSH hormone, preventing it from contacting or binding correctly with the protein molecules. Therefore, the molecules to which the peptides have attached themselves remain dormant and do not send off the required signals to instruct 'their' cells to switch to producing black pigment. They continue to produce red pigment instead. In horses, this disabling does not occur over the entire horse but is restricted to the body only. It's almost certainly a primitive form of camouflage; the agouti gene in most mammals has a similar lightening or banding affect that helps them blend in with their natural environment. Remember the horse was also originally dun, and bay + dun creates a flat beige colour that blends nicely into open grasslands. Bright shiny bays like we know today did not exist until shortly before, or more likely after, domestication.



The above is the action of a primitive, or wild type, version of the Agouti gene. Difficult though it may be to get one's head around it, the fact is that bay preceded black. It is the black or aa horse that carries a mutation in its Agouti genes, not the bay AA horse with its primitive or wild type Agouti genes!!

The mutation in question is a frame shift mutation caused by a deletion in the DNA sequence in the second exon of the Agouti gene. Frame shift mutations cause the gene to produce abnormal proteins with incorrect amino acid sequences. In the Agouti gene, this mutation has caused a loss of function in that the altered version of the gene is unable to produce a functioning paracrine signalling peptide. And without a correctly functioning paracrine signalling peptide the primitive function of disabling the MC1R protein molecules in certain areas of the body to allow the skin cells to continue to produce red pigment can't happen!

An individual that carries at least one copy of a normally functioning Agouti gene can still produce enough functioning peptide to cancel out the effects of the defective gene. But.... an individual with 2 copies of the defective Agouti gene completely lacks the ability to produce any functioning peptide at all. Therefore, it also completely lacks the ability to disable any of its MC1R protein molecules anywhere on its body. So its a-MSH hormone can happily activate all its MC1R protein molecules, regardless of location, and switch on black pigment production over its entire body!