Post-Flood mutation of the *KIT* gene and the rise of white coloration patterns

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Identifying mutations and patterns of their appearance and impact is important in furthering the biblical creation model. Genes affecting coloration are relatively easy to identify and several have been well studied. Here, variation in a gene affecting the development and movement of pigment cells, *KIT*, is examined. This complex gene codes for a complex protein important in a number of pathways. Many mutations have been identified in each of the species studied. Interesting examples of epigenetic modification and reversions have been documented in mice. This gene has shown up in surprising places in cats and dogs. Some mutations result in pleiotropy, although this is variable depending on genetic background, type of mutation, and location of the mutation. Mutations also result in interesting variety including white animals and white spotting phenotypes.

Previously, creationist studies have pointed out the importance of evaluating genetic data to determine the types of mutations which have likely occurred throughout history. This will contribute to a deeper understanding of the role mutations play and better inform apologetic arguments as it further builds the creation model. Biblically we don't have enough information to know the genetic variability that existed at creation. We are not told how many animals were created in each kind. Also, although there were only two humans, Eve may have carried alleles in her egg cells that differed from those in her body. However, we do have an idea of the genetic variability that could be expected after the genetic bottleneck at the Flood. Unclean animals, such as pigs, horses, and mice, survived the Flood as single breeding pairs. Thus, up to four alleles for any particular locus could have been present. For humans, a maximum of 10 alleles could have made it through unless Noah's sons carried mutations.

Genes affecting coat color are relatively easy to discover and study since they obviously affect the appearance of the animal. So far, well over three hundred genes have been identified as affecting coat color in mammals.[1] Some of these, such as the *MC1R*[2] and *ASIP*[3] genes, have been fairly well studied and useful information has been obtained by examining mutation patterns at these loci. Mutations in these genes affect proteins involved in the signaling pathway for pigment production and explain a large amount of the color variation in mammals. Other genes affecting coloration are involved in pigment production or development (i.e. regulating the development and migration of pigment cells during embryogenesis).

The *KIT* locus

One locus important in embryogenesis, *KIT*, has been associated with white coat patterns in several mammalian species and piebaldism in humans. The white areas are depigmented due to the absence of melanocytes, the cell type which produces pigment.

KIT has also gone by several other names including *c-kit*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, stem cell factor receptor, mast cell growth factor receptor, and *CD117*.[4] It encodes a receptor tyrosine kinase involved in the development and homeostasis of several cell lines including melanocytic (pigment), hematologic (blood), mast, and germ cells.[5] This explains why heritable loss-of-function mutations sometimes have pleiotropic effects, not only resulting in white color patterns, but also anemia and/or infertility. Some of the stronger mutations cause a dominant white phenotype which is lethal in the homozygous condition. Activating (gain-of-function) mutations, which are generally somatic and not heritable, have been associated with progression in certain cancers.[6]

The *KIT* gene is rather complex consisting of 21 exons in a 70 kb region. Most of the exons are relatively short (<300 bp). The exception is the final exon which not only codes the terminal portion of the receptor, but also includes a 2,147 bp non-coding sequence that follows. This complex organization of the gene reflects the complex nature of the protein receptor it produces.

Extracellularly the receptor is made up of five immunoglobulin-like domains. Each is coded by one or two exons with the boundaries of the exons defining the boundaries of these domains. The receptor makes a single pass through the cell membrane and contains an intracellular kinase catalytic region divided by a hydrophilic insert. Most of the 10 exons coding the intracellular portion correspond to specific structural elements, such as α-helices or β-sheets.[7] Both mice and men express two isoforms of this membrane-bound receptor[8] from alternative splicing; these isoforms differ somewhat in their signaling characteristics.[9]

Expression of *KIT* and its ligand, sometimes referred to as stem cell factor, occur in waves during development and have intricate homeostatic patterns in the adult. Ligand binding induces activation of tyrosine kinase through dimerization of receptors.[6] This subsequently influences a variety of pathways downstream. The pattern of downstream activation is dependant on numerous other cellular factors.

Table 1. Summary of *KIT* mutations in pigs associated with white or partial white phenotypes.

Allele	Phenotype	Breed	Mutation(s)	Inheritance
i	wild type	European wild boar	NA	—
I^{Be}	white belt	Hampshire	unknown	dominant
I^{P}	patch	Pietrain	gene duplication	semidominant
I^{1}	white	Large White	I^{P} allele with splice mutation in one copy	dominant
I^{2}	white	Large White	I^{1} allele with an additional duplication of the normal gene	dominant
I^{3}	white	Large White	I^{1} allele with an additional duplication of the copy with a splice mutation	dominant
RC1	white	Chinese White Rongchang	V84M, R173K, V893A	recessive
RC2	white	Chinese White Rongchang	V84M, V893A	recessive

Thus, the receptor does not behave as a simple on/off switch, but instead as an "inducible and malleable scaffold upon which multiple cellular regulatory mechanisms can be modulated."[10]

Variability in the *KIT* locus

Variability in the *KIT* locus will be examined with the following questions in mind. Is there evidence for mutation in this gene? If so, what type(s) of mutations occur and what effect do they have on phenotype? Are the mutations most likely pre- or post-Flood? Are there any particularly unusual patterns that exist in regard to these mutations (e.g. in type, timing and/or location)?

Pigs (*Sus scrofa*)

KIT resides on the short arm of chromosome 8 in the pig (SSC 8p12). At least eight different alleles have been identified (table 1).[11] The wild type (*i*) was identified in the European wild boar and most colored domestic European breeds. The belted phenotype (I^{Be}) of the Hampshire was mapped to this locus and is believed to be the result of a regulatory mutation. This dominant allele, which produces a white belt around the shoulders and front legs, is carried in the homozygous state with no apparent ill effects.

The patch allele (I^{P}), a semidominant mutation resulting from a gene duplication, produces a phenotype of white and colored patches that are separated by sharp borders. There are three related dominant white alleles (I^{1}, I^{2} and I^{3}). The first was discovered to have the same gene duplication as the patch allele with one copy containing a splice mutation. The splice mutation is the result of a G to A substitution in the first nucleotide of intron 17 which leads to skipping exon 17.[12] The second and third alleles contain an additional duplication of the copy without and with the splice mutation, respectively.[13] Despite the fact that dominant white alleles in other species can be lethal in the homozygote, these very popular white pigs are generally homozygous and show no ill effects.

Two additional alleles have been identified in the Chinese White Rongchang. These lacked the gene duplication and differed from the sequence in European pigs by up to 10 nucleotide substitutions. Three amino acids are affected (V84M, R173K, and V893A) from exons 2, 3, and 19 respectively. The first was considered worthy of further investigation in potentially being associated with the recessive white phenotype in these Chinese pigs.[14]

Since pigs are unclean, a maximum of four *KIT* alleles would have been carried by the pair on the Ark. The number of alleles in domestic pigs is at least twice this, indicating that new alleles have arisen post-Flood by mutation at this locus. Researchers identify mutations as a change in nucleotide sequence relative to the wild type, which in this case is the European wild boar. In reality, the wild boar itself may carry mutations, but there are other details that can sometimes help to identify alleles carrying mutations. Alleles responsible for impaired migration of melanocytes, resulting in white coloration, can logically be inferred to carry mutations. This would include the mutations found in European domestic pig breeds, but not necessarily all polymorphisms in the Chinese White Rongchang. Most likely all of the mutations affecting coloration are post-Flood since these alleles don't appear to be widely distributed in pigs. If the alleles were older and existed at the time of the population bottleneck, a much wider distribution would be predicted.

There is an obvious bias toward gene duplications in European pigs. Four alleles contain gene duplications, suggesting at least three separate duplication events affecting the germ-line, thus making them heritable. It was suggested that the initial duplication acts as a dynamic mutation, increasing the chance of a subsequent event. Increased sequence homology resulting from the duplication is believed to increase the probability of additional rounds of gene conversion, unequal crossing-over, and subsequent rearrangement.[15]

Horses (*Equus caballus*)

KIT resides on the long arm of chromosome 3 in the horse (ECA 3q).[16] There are over 15 alleles; 14 of which are associated with some degree of depigmentation (white or white spotted phenotype).[17] Roan horses are characterized

by white hairs interspersed with pigmented hairs throughout much of the body. This dominant phenotype is assumed to be lethal in the homozygote. It has been mapped to the *KIT* locus, although the causative mutation has yet to be indentified. Interestingly, some mRNA transcripts from a roan Belgian horse contained a 79 bp L1 element between exons 1 and 2. This resulted in a frame-shift and a non-functional protein. However, this L1 insertion was found in both roan and non-roan horses, although it was more common in the former.[18]

The Tobiano color pattern typically consists of large white patches on the body and limbs which often extend across the dorsal midline. It is common among American Paint Horses and is found in other diverse breeds as well. Although no differences exist in the coding region of *KIT*, similarity was noted between this phenotype and several spotting patterns in mice that involved chromosomal rearrangements near this gene. Subsequently, a large paracentric chromosomal inversion was identified about 100 kb downstream from *KIT* which is suspected to disrupt regulatory sequences for the gene resulting in this dominant white spotting pattern. This allele was identified in Tobiano individuals from 12 different breeds, indicating an ancient origin. Homozygous individuals are phenotypically indistinguishable from heterozygotes; both are fully viable.[19]

The Sabino white spotting pattern involves white patches on the face and legs which may extend up to the belly. Sometimes the belly and midsection have a more diffuse scattering of white hairs similar to the roan phenotype. One allele causing this phenotype was discovered with a T to A substitution in intron 16. This resulted in many transcripts missing exon 17. Homozygotes had more pronounced expression of the defective transcript and a white phenotype, but were fully viable. Also, heterozygotes that carried a second allele for a different spotting pattern, such as Tobiano, were white as well.[20]

There are eleven additional alleles that have been identified in horses with white or partial white phenotypes, all of which arose within the last 100 years. Three of these involve splice mutations in an intron, two involve a deletion in an exon resulting in a frameshift and premature stop codon, four involve non-synonymous substitutions which change the amino acid (missense mutation), and two involve non-synonymous substitutions which replace the amino acid with a stop codon (nonsense mutation). Some of these are associated with a dominant white phenotype which is believed to be lethal in the homozygous state. While none of the mutations were found in the homozygous state, not all resulted in a dominant white phenotype. Furthermore, in four cases only one white horse, presumably the founder animal, was tested. It remains to be seen which of these alleles may allow for viable homozygotes.[17]

Considerably more than four *KIT* alleles are present in horses, indicating an increase in alleles due to post-Flood mutation. Of the 14 alleles associated with depigmentation, and thus most likely the result of mutation, the origin of 11 were documented in the last 100 years. The other three appear to be older as they have a wider distribution in domestic horses. Still, it is likely that they are post-Flood since they do not appear to be present extensively in the equine baramin (which includes donkeys and zebras).

Mice (*Mus musculus*)

In laboratory mice *Kit*[21] is on chromosome 5 (MMU 5). There are 97 alleles, 66 of which arose via spontaneous mutation.[22] These alleles, only some of which have had the underlying mutation identified, show a variety of phenotypes and pleiotropic effects. Only a few will be discussed here.

The dominant white spotting allele (*W*) in heterozygous mice results in fully viable and fertile adults with a white belly spot, white feet and tail tip. It was noted that in the early post-natal period these mice have unusual blood values. This allele in the homozygous condition is usually lethal due to severe macrocytic anemia. Few homozygotes are born alive, and those normally die within a day or two. The very few that survive to adulthood are black-eyed, white, severely anemic, and sterile. The difference in viability of homozygotes has been attributed to the different genetic backgrounds in which it occurs.[23] The allele is attributed to a G to A substitution at a splice donor site in intron 10 which results in exon skipping in the transmembrane region.[24,7]

A viable dominant white spotting allele exists (W^v) where a white belly spot, white feet and tail tip are also seen along with significant dilution of the remaining coat pigment. Heterozygous mice are usually viable and fertile, but slightly anemic. In the homozygote the lifespan is near normal; they are black-eyed, white, less anemic than dominant white (*W*/*W*) mice, and may be semi-fertile.[23] This allele carries a single missense (T660M) mutation.[25] A number of other alleles were found that result in a similar phenotype to *W* (W^a, W^j, W^x) or W^v (W^b, W^e).[23]

Initially it appeared that mutations in mice had a similar effect on all three tissue types: melanocytic, hematologic and germ. However, mutations appeared that soon showed this was not always the case. For example, the fertile white mutation (W^j) appears to be the result of a missense (R816W) mutation in this gene. It is associated with anemia and pigment defects, but mice are fertile even in the homozygote (if it survives; there is an increased postnatal fatality rate).[26] In contrast, an induced mutation (Y719F), which alters the binding site for the p85 subunit of PI 3-kinase, has a negative effect on spermatogenesis and oogenesis, yet no observable pigment or hematopoietic defects.[27]

Several alleles have been identified where the mutations involve major rearrangements in the 5' regulatory region of this gene. W^{57} carries an 80 kb deletion in the 5' region; homozygotes have an irregular white band on the trunk, a white head spot, very mild anemia, and normal fertility. The white banded (W^{bd})[28] and sash (W^{sh})[29] alleles arose separately by spontaneous mutation involving a large 5' inversion affecting the orientation of numerous upstream genes. Heterozygotes carry a white band or sash on the trunk;

homozygotes exhibit black eyes, white fur with possible residual ear and snout pigment, with normal fertility and red blood cell parameters. All three alleles are associated with mast cell deficiency from a lack of *KIT* expression. Interestingly, the W^{sh} allele is associated with increased *Kit* expression in dermatomal cells during embryonic development which is believed to cause the pigmentation defects.[30] This is in contrast to W^{57} where *KIT* expression is down regulated in early trunk melanoblasts.[28] Several tissue specific control elements have been identified in this upstream region.[30]

A cryptic promoter has been identified in exon 16 which is active in post-meiotic germ cells in the testes of mice. This cell specific promoter is only active during a short temporal window during spermatogenesis and results in a third gene product: a truncated protein which lacks the extracellular, transmembrane and first tyrosine kinase domains. [31] This truncated protein is suspected to play a role in fertilization since it has been observed to trigger parthenogenetic completion of meiosis II and pronuclear formation when microinjected into mouse eggs.[32]

Reverse mutations are considered to be rare in mammals, but 12 mutations affecting pigmentation in mice show unusual phenotypic instabilities. One of these, the viable yellow at the *Agouti* locus, has been examined in previous creationist literature.[3] Seven of these mutations are at the *KIT* locus (W^{a}, W^{J2}, W^{37}, W^{42}, W^{ei}, $W^{v} = W^{55}$, W^{rio}). Mice heterozygous for the W^{rio} mutation are mostly white with some scattered pigmented hairs. In a French study, 3.6% of the heterozygotes exhibited strongly pigmented spots on a typical mutant background nearly devoid of pigment cells. Melanocyte cell lines were established from six independent reversion spots. Three of these appear to have undergone somatic reversion via mitotic recombination. One showed an increase in *KIT* expression and response to *KIT* ligand despite retaining a $W^{rio}/+$ genotype. The remaining two failed to respond to Kit ligand. While the underlying mechanism for phenotypic reversion was not demonstrated in the last three cell lines, the authors suggest that enhanced *KIT* expression, compensatory mutation, and/or another receptor tyrosine kinase in a similar pathway could compensate for *KIT* mutations on some genetic backgrounds.[33]

There is evidence that epigenetic inheritance can occur at this locus. Unlike the epigenetic inheritance described at the *Agouti* locus,[3] this does not appear to be associated with DNA methylation. It occurs in offspring of mice heterozygous for a targeted gene mation (KIT^{tm1Alf}), which contains a *lacZ* insertion in the first exon. The homozygous wild type offspring retain, to a variable extent, the mutant phenotype of white feet and tail tip from a marked decrease in mature mRNA. Additionally, continued expression of full length *KIT* mRNA and increased expression of the truncated *KIT* mRNA during the post meiotic phase of sperm formation were observed in mice heterozygous for the mutant gene and in paramutated mice. These gene products were detected in mature sperm as well. Suspecting that the presence of this RNA might induce the mutant phenotype, researchers microinjected total RNA from heterozygotes into fertilized eggs which induced the mutant phenotype about half the time.[34]

Humans

In humans *KIT* resides on chromosome 4 (4q12). Loss-of-function mutations at this locus are associated with a condition known as piebaldism, a dominant disorder characterized by patches of white skin on the forehead, abdomen, and/or limbs. Thus far, nearly 50 different alleles have been identified in people exhibiting piebaldism including: 28 missense mutations, 5 splice mutations, 9 small deletions, 4 large deletions, and two small insertions.[35] The extent of depigmentation tends to correlate with the region where the mutation occurs. Generally, mutations affecting the extracellular region of *KIT* are milder while those affecting the intracellular region are more severe.[36] The explanation for this is that mutations in the intracellular region generally prevent the receptor from transmitting the signal while retaining the extracellular site used to bind its ligand and induce dimerization.[37] In other words, these mutant receptors can tie up normal receptors because they can still form dimers with them; this results in a dominant negative effect. Mutations affecting the extracellular region appear to prevent the mutant receptor from forming dimers and only haploinsufficency results. Unlike similar mutations in the mouse, anemia and fertility problems are not associated with piebaldism in humans.[38]

Gain-of-function mutations have also been identified in *KIT*. Many of these are somatic mutations associated with sporadic gastrointestinal stromal tumors (GISTs). Most of these mutations occur in exon 11 which codes the juxtamembrane domain of *KIT*. This intracellular region precedes the first tyrosine kinase domain and is believed to be important in dimerization. Less commonly, specific mutations in exons 9, 13 and 17 have been identified. These regions code for portions of the extracellular region, first tyrosine kinase (TK) domain, and second TK domain, respectively.

Germline gain-of-function *KIT* mutations have been identified in a dozen families and are associated with multiple GISTs. Mutation in the juxtamembrane domain is present in eight of these families. Among the remaining families mutations have been identified affecting the extracellular region, the first TK domain, and the second TK domain. Patients in some families also exhibit hyperpigmentation in certain regions of the body and/or mast cell tumors.[39]

A maximum of 10 alleles would be expected to make it through the Flood in humans, unless Noah's sons carried mutations. Considering both gain- and loss-of-function heritable mutations, more than 60 alleles have been identified to date. All are rare and would be post-Flood. While the data in mice tended to emphasize the importance of genetic background on the severity of the phenotype for any particular mutation, the human data highlights the importance of the location of the mutation in understanding its influence on phenotype.

Other interesting patterns

KIT has a propensity to show up in unusual places. For example, an acute transforming feline retrovirus, Hardy-Zuckerman 4 feline sarcoma virus, was identified with the oncogene *v-kit* in its genome. This virus induces multicentric fibrosacromas in the domestic cat. Compared to the cellular form (often called *c-kit*) there are some deletions at either end of the gene as well as a few point mutations.[40]

KIT has also been identified on the B chromosomes in the fox and raccoon dog. B chromosomes are supernumerary chromosomes, often rich in repetitive DNA, present in the karyotypes of some species. This was the first instance of a coding gene identified on a B chromosome. It is possible this gene could be transcribed as it includes a significant 5' region where transcription regulatory sequences would be expected to reside.[41]

Conclusion

KIT is an amazingly complex gene important in a number of critical pathways. Clearly there has been an increase in the alleles at this locus for the species examined here. The vast majority of these alleles are clearly the result of mutation given how they affect the function of the receptor. There is considerable diversity in the types of mutations found at this locus. Unlike the previously studied receptor involved in coloration, the MC1R, *KIT* mutations are more likely to have pleiotropic effects. Pleiotropy is affected by genetic background and the location and type of mutation.

Pleiotropy was best documented in mice. There may be several reasons for this. First, laboratory mice are often highly inbred. Possibly some lines carry other mutations impairing their ability to compensate for the loss of *KIT*. Rodents in general seem to have a propensity for rather rapid genetic change, and this may come at a cost of being less able to compensate for future mutations. Second, mice are relatively easy to study in detail and some of the documented pleiotropy could be from increased scrutiny of these laboratory animals. It was interesting that pleiotropy was virtually absent in pigs, where gene duplication involving *KIT* was identified in many alleles.

Interestingly, the number of human *KIT* alleles identified is comparable to the number documented for human *MC1R* alleles.[42] Many of these alleles are quite rare, but were identified because of color differences. While there are suspected advantages to some mutant *MC1R* alleles in certain environments, no similar situation has been proposed for *KIT* alleles in humans.[43] The lack of documented pleiotropy for most human *KIT* mutations suggests that other factors are able to compensate for the loss of *KIT*. It is also possible that mild pleitropy associated with loss-of-function *KIT* alleles may be identified with further scrutiny.

One final observation about *KIT* mutations is their association with interesting variety. White horses have been admired throughout history and are important in biblical prophecy. White sows are very popular because of their high productivity and good mothering ability. White coloration in animals and a white forelock in humans certainly add to the variety and beauty found in creation.

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