= Dominant white =

Dominant white is a group of genetically related coat color conditions in the horse , best known for producing an all @-@ white coat , but also for producing some forms of white spotting and white markings . Dominant white horses are born with unpigmented pink skin and white hair with dark eyes , although the amount of white hair or spotting can vary depending on which genetic mutation is involved . Dominant white is a rare condition , and under normal conditions , at least one parent must be dominant white to produce dominant white offspring . However , most of the currently @-@ known alleles of dominant white can be linked to a documented spontaneous mutation in a single ancestor .

Dominant white can occur in any breed , and has been studied in many different breeds . Two color breeds , the American White Horse and Camarillo White Horse are characterized by their dominant white coats .

There are many different forms of dominant white ; in genetics , as of 2013 they are labeled W1 through W20 . All known dominant white coat colors are associated with the KIT gene . As the name suggests , these known white coats are inherited dominantly , meaning that a horse only needs one copy of a W allele to have the white or white spotted coat .

Dominant white is genetically distinct from Sabino and both genetically and visually distinct from gray and cremello . Dominant white is not the same as lethal white syndrome , nor are dominant white horses " albinos " . Albinism has never been documented in horses . Some forms of dominant white are thought to result in nonviable embryos when a zygote has two W alleles (is homozygous) . However , this has not been verified for all dominant white genetic variations .

= = Identification = =

Dominant white horses are born with pink skin and a white coat , which they retain throughout their lives . Although the term " dominant white " is typically associated with a pure white coat , such horses may be all @-@ white , near @-@ white , partially white , or exhibit an irregular spotting pattern similar to that of sabino horses . The amount of white hair depends on which mutation of W is involved . Non @-@ white areas of skin and hair are most commonly seen along the dorsal midline of the horse , known as the topline , and are especially common in the mane and on the ears . They may also have interspersed specks or spots of non @-@ white skin and hair . In addition , the hooves are most often white , but may have striping if there is pigmented skin on the coronary band just above the hoof . In some cases , foals born with residual non @-@ white hair may lose some or all of this pigment with age , without the help of the gray factor . Dominant white spotting does not affect eye color , and most dominant white horses have brown eyes . The pink skin is devoid of pigment cells (melanocytes) , and appears pink from the underlying network of capillaries . White hair is rooted in unpigmented pink skin . There are many other genetic factors that produce white , near @-@ white , and off @-@ white coat colors in horses , some of which are visually very similar to dominant white .

= = Prevalence = =

Dominant white is one of several potential genetic causes for horses with near @-@ white or completely white coats ; it may occur through spontaneous mutation , and thus may be found unexpectedly in any breed , even those that discourage excessive white markings . To date , dominant white has been identified in multiple families of Thoroughbreds , American Quarter Horses , Frederiksborg horses , Icelandic horses , Shetland ponies , Franches Montagnes horses , South German Draft horses , and in one family of the Arabian horse . The American White Horse , which is descended primarily from one dominant white stallion crossed on non @-@ white mares , is known for its dominant white coat , as is the Camarillo White Horse .

= = Inheritance = =

The W locus was mapped to the KIT gene in 2007 . The terms " Kit oncogene " and " dominant spotting " gene , symbolized by KIT and W respectively , can be used interchangeably . Current research has now shown that there are multiple forms , or alleles , of the W gene . All horses possess the KIT gene , as it is necessary for survival even at the earliest stages of development . The presence or absence of dominant white is based on the presence of certain altered forms of KIT . Each unique form is called an allele , and for every trait , all animals inherit one allele from each parent . The original or " normal " form of KIT , which is expected in horses without dominant white spotting , is called the " wild type " allele . Thus , a dominant white horse has one KIT allele with a mutation associated with dominant white spotting , and one wild type KIT allele .

= = = History of dominant white research = = =

Dominant white horses were first described in scientific literature in 1912 . Horse breeder William P. Newell described his family of white and near @-@ white horses to researcher A. P. Sturtevant of Columbia University :

" The colour of skin is white or so @-@ called pink , usually with a few small dark specks in skin . Some have a great many dark spots in skin . These latter usually have a few dark stripes in hoofs ; otherwise the hoofs are almost invariably white . Those that do not have dark specks in skin usually have glass or watch eyes , otherwise dark eyes ... I have one colt coming one year old that is pure white , not a coloured speck on him , not a coloured hair on him , and with glass [blue] eyes . "

Sturtevant and his contemporaries agreed that this colt 's blue eyes were inherited separately from his white coat . In 1912 , Sturtevant assigned the " white " trait to the White or W locus . At the time there was no means of assigning W to a position on the chromosome , or to a gene .

This family of white horses produced Old King in 1908 , a dark @-@ eyed white stallion that was purchased by Caleb R. and Hudson B. Thompson . Old King was bred to Morgan mares to produce a breed of horse known today as the American White Horse . A grandson of Old King , Snow King , was at the center of the first major study of the dominant white coat color in horses , conducted in 1969 by Dr. William L. Pulos of Alfred University and Dr. Frederick B. Hutt of Cornell . They concluded , based on test matings and progeny phenotype ratios , that the white coat was dominantly inherited and embryonic lethal in the homozygous state . Other factors , such as variations in expressivity and the influence of multiple genes , may have influenced the progeny ratios that Pulos and Hutt observed . The white coat of the American White Horse has not yet been mapped .

A 1924 study by C. Wriedt identified a heritable white coat color in the Frederiksborg horse . Wriedt described a range of what he considered to be homozygote phenotypes : all @-@ white , white with pigmented flecks , or weißgraue , which transliterates to " white @-@ gray . " The German term for gray horse is schimmel , not weißgraue . Heterozygotes , according to Wriedt , ranged from roaned or diluted to more or less solid white horses . Reviewers , such as Miguel Odriozola , reinterpreted Wriedt 's data in successive years , while Pulos and Hutt felt that his work had been " erroneous " because Wriedt never concluded that white was lethal when homozygous .

Other researchers prior to modern DNA analysis developed remarkably prescient theories . The gene itself was first proposed and named W in 1948 . In a 1969 work on horse coat colors , A los colores del caballo , Miguel Odriozola suggested that various forms of dominantly inherited white spotting might be arranged sequentially along one chromosome , thus allowing for the varied expression of dominant white . He also proposed that other , distant genes might also influence the amount of white present .

Between the time of Pulos and Hutt 's study in 1969 and the beginning of molecular @-@ level research into dominant white in the 21st century , a pattern known as " Sabino " became regarded by some as a more likely cause of white phenotypes . Sabino is a type of white spotting , and the one allele now mapped , the dominantly inherited Sabino @-@ 1 (SB @-@ 1) , is genetically related , though distinct . When homozygous , SB @-@ 1 can produce nearly all @-@ white horses that resemble dominant white . Other genes responsible for all possible patterns labeled " Sabino "

have not yet been identified , though some forms of the splashed white gene may be responsible for certain patterns .

In 2007 , researchers from Switzerland and the United States published a paper identifying the genetic cause of dominant white spotting in horses from the Franches Montagnes horse , Camarillo White Horse , Arabian horse and Thoroughbred breeds . Each of these dominant white conditions had occurred separately and spontaneously in the past 75 years , and each represents a different allele (variation or form) of the same gene . These same researchers identified a further seven unique causes of dominant white in 2009 : three in distinct families of Thoroughbreds , one Icelandic horse , one Holsteiner , a large family of American Quarter Horses and a family of South German Draft horses .

= = = Allelic series = = =

The KIT gene contains over 2000 base pairs , and a change in any of those base pairs results in a mutant allele . Over forty such alleles have been identified by sequencing the KIT genes of various horses . The resultant phenotype of most of these alleles is not yet known , but 20 have been linked to dominant white . To date , DNA tests can identify if a horse carries the various identified W alleles , some commercially available .

W1 is found in Franches Montagnes horses descended from a white mare named Cigale born in 1957 . Cigale 's parents ' coats were not extensively marked . A single nucleotide polymorphism (SNP) , a type of mutation in which a single nucleotide is accidentally exchanged for another , is thought to have occurred with Cigale . This mutation (c.2151C > G) is thought to severely affect the function of KIT . It is a nonsense mutation located on Exon15 of KIT Some horses with the W1 mutation are born pure white , but many have residual pigment along the topline , which they may then lose over time . Based on studies of KIT mutations in mice , the severity of this mutation suggests that it may be nonviable in the homozygous state . However , horses with the W1 mutation have been found to have normal blood parameters and do not suffer from anemia .

W2 is found in Thoroughbred horses descended from KY Colonel , a stallion born in 1946 . While KY Colonel was described as a chestnut with extensive white markings , he is known for siring a family of pure white horses through his white daughter , White Beauty , born in 1963 . The W2 allele is also linked to a single nucleotide polymorphism (c.1960G > A) , but it is a missense mutation located on Exon17 .

W3 is found in Arabian horses descended from R Khasper , a near @-@ white stallion born in 1996 . Neither of his parents were white , and the causative mutation (c.706A > T) is thought to have originated with this horse . It is a nonsense mutation on Exon4 . Horses with the W3 allele often retain interspersed flecks or regions of pigmented skin and hair , which may fade with time . Some members of this family possess blue eyes , but these are thought to be inherited separately from the white coat . Based on similar studies in mice , researchers have named W3 as potentially homozygous nonviable .

W4 is found in Camarillo White Horses , a breed characterized by a white coat , beginning with a spontaneous white stallion born in 1912 named Sultan . Like W1 and W3 , horses with this type of dominant white may be pure white or near @-@ white , with pigmented areas along the topline that fade with time . This mutation is also an SNP (c.1805C > T) , a missense mutation on Exon12 .

W5 is found in Thoroughbreds descending from Puchilingui , a 1984 stallion with sabino @-@ like white spotting and roaning . Horses with the W5 allele exhibit a huge range in white phenotype : a few have been pure white or near @-@ white , while others have sabino @-@ like spotting limited to high , irregular stockings and blazes that covered the face . Twenty @-@ two members of this family were studied , and the 12 with some degree of dominant white spotting were found to have a deletion in exon 15 (p.T732QfsX9) , in the form of a frameshift mutation . A later study found that the members of this family with the greatest depigmentation were compound heterozygotes who also carried the W20 allele .

W6 is found in one near @-@ white Thoroughbred born to non @-@ white parents in 2004 . The potential range of expressivity , therefore , is not yet known . The mutation (c.856G > A) is thought

to have occurred spontaneously in this horse . It is a messense mutation on Exon5 .

W7 is found in another near @-@ white Thoroughbred born in 2005 to a dam that had nine other offspring , all non @-@ white . She did not possess the W7 allele , which results from a splice site mutation (c.338 @-@ 1G > C) , located on Intron2 of KIT .

W8 is found in one Icelandic horse with sabino @-@ like white spotting , mottling , and roaning . Both parents and four maternal half @-@ siblings , all non @-@ white , were found without the W8 allele . The W8 allele is also a splice site mutation (c.2222 @-@ 1G > A) , located on Intron15 .

W9 is found in one all @-@ white Holsteiner horse with a single nucleotide polymorphism (c.1789G > A) . No relatives were studied , but both parents are non @-@ white . It is a missense mutation on Exon12 .

W10 was found in a study of 27 horses in a family of American Quarter Horses , 10 of which are white or spotted and 17 that were solid and non @-@ white . The 10 family members with W10 had a deletion in exon 7 (c.1126 _ 1129delGAAC) . Like W5 , a wide range of phenotypes were observed . The most modestly marked had large amounts of white on the face and legs and some medium @-@ sized belly spots , while another was nearly all @-@ white . It is a frameshift mutation on Exon7 . The founder of this line was GQ Santana , foaled in 2000 .

W11 is found in a family of South German Draft horses descending from a single white stallion , in which the causative mutation is thought to have originated . The mutation responsible for the W11 phenotype is a splice site mutation of intron 20 (c.2684 + 1G > A) .

W12 is found in Thoroughbreds , and is a deletion mutation found on Exon3 .

W13 is found in Quarter Horses , and is a splice site mutation on Intron17 .

W14 is a deletion mutation on Exon17 , found in Thoroughbreds .

W15 is found in Arabians , and is a missense mutation on Exon10 .

W16 is found in the Oldenburger and is a missense mutation on Exon18 .

W17 is found in a Japanese Draft horse and is a missense mutation on Exon14 .

W18 is a splice site mutation on Intron8 (c.1346 + 1G > A) found in a bay Swiss Warmblood with extensive speckling . Both parnts were solid @-@ colored and had no extended head or leg markings .

W19 was found in three part @-@ Arabians with bald face markings , white leg markings extending above the knees and hocks , and irregular belly spots . All three horses tested negative for sabino @-@ 1 , frame overo and splashed white . W19 is a missense mutation on Exon 8 (c.1322A.G ; p.Tur41Cys) . This gene is predicted to be " probably damaging " and one of the three horses has solid @-@ colored offspring that do not carry the allele .

W20 is a missense mutation on Exon14 (c.2045G > A ; p.Arg682His) originally discovered in 2007 but not recognized for having a subtle role in increasing white markings and white pigmentation . It appears in many breeds , but its effects were first recognized in the W5 family of Thoroughbreds and was determined to be the causative factor in the most extensively @-@ depigmented (" white ") horses .

These alleles do not account for all dominantly inherited white spotting in horses . More KIT alleles are expected to be found with roles in white spotting . Most W alleles each occur within a specific breed or family and arise as spontaneous mutations . The KIT gene itself seems prone to mutation , and so new alleles of W could occur in virtually any breed .

= = = Molecular genetics = = =

The KIT gene encodes a protein called steel factor receptor , which is critical to the differentiation of stem cells into blood cells , sperm cells , and pigment cells . A process called alternative splicing , which uses the information encoded in the KIT gene to make slightly different proteins (isoforms) for use in different circumstances , may impact whether a mutation on KIT affects blood cells , sperm cells , or pigment cells . Steel factor receptor interacts chemically with steel factor or stem cell factor to relay chemical messages . These messages are used during embryonic development to signal the migration of early melanocytes (pigment cells) from the neural crest tissue to their eventual destinations in the dermal layer . The neural crest is a transient tissue in the embryo that

lies along the dorsal line . Melanocytes migrate along the dorsal line to a number of specific sites : near the eye , near the ear , and the top of the head ; six sites along each side of the body , and a few along the tail . At these sites , the cells undergo a few rounds of replication and differentiation , and then migrate down and around the body from the dorsal aspect towards the ventral aspect and the limb buds .

The timing of this migration is critical ; all white markings , from a small star to a pure white coat , are caused by the failed migration of melanocytes .

A certain degree of the eventual amount of white , and its " design " , is completely random . The development of an organism from single @-@ celled to fully formed is a process with many , many steps . Even beginning with identical genomes , as in clones and identical twins , the process is unlikely to occur the same way twice . A process with this element of randomness is called a stochastic process , and cell differentiation is , in part , a stochastic process . The stochastic element of development is partly responsible for the eventual appearance of white on a horse , potentially accounting for nearly a quarter of the phenotype . The research team that studied dominant white cited " subtle variations in the amount of residual KIT protein " as a potential cause for the variability in phenotype of horses with the same kind of dominant white .

= = = Lethality = = =

Early embryonal lethality , also known as early embryonic death or a non @-@ viable embryo , may occur when the embryo possesses two dominant white alleles , or have the homozygous genotype . The reason for this is that many mutations for W are caused by nonsense mutations , frameshift mutations or DNA deletions , which , if homozygous , would make it impossible to produce a functional KIT protein . However , it is possible that homozygous embryos from alleles of missense and splice site mutations might be viable because they have less effect on gene function . A 2013 study also unearthed horses that were compound W5 / W20 heterozygotes , almost completely white , essentially with greater depigmentation than could be accounted for by either allele alone .

The embryonic lethality hypothesis was originally supported by Pulos and Hutt 's 1969 study of Mendelian progeny ratios . Conclusions about Mendelian traits that are controlled by a single gene can be drawn from test breedings with large sample sizes . However , traits that are controlled by allelic series or multiple loci are not Mendelian characters , and are not subject to Mendelian ratios .

Pulos and Hutt knew that if the allele that created a white coat was recessive , then white horses would have to be homozygous for the condition and therefore breeding white horses together would always result in a white foal . However , this did not occur in their study and they concluded that white was not recessive . Conversely , if a white coat was a simple autosomal dominant , ww horses would be non @-@ white , while both Ww and WW horses would be white , and the latter would always produce white offspring . But Pulos and Hutt did not observe any white horses that always produced white offspring , suggesting that homozygous dominant (WW) white horses did not exist . As a result , Pulos and Hutt concluded that white was semidominant and lethal in the homozygous state : ww horses were non @-@ white , Ww were white , and WW died .

Pulos and Hutt reported that neonatal death rates in white foals were similar to those in non @-@ white foals , and concluded that homozygous white fetuses died during gestation . No aborted fetuses were found , suggesting that death occurred early on in embryonic or fetal development and that the fetus was " resorbed . "

Prior to Pulos and Hutt 's work , researchers were split on the mode of inheritance of white and whether it was deleterious (harmful) . Recent research has discovered several possible genetic pathways to a white coat , so disparities in these historical findings may reflect the action of different genes . It is also possible that the varied origins of Pulos and Hutt 's white horses might be responsible for the lack of homozygotes . Therefore , it remains to be proven whether all equine dominant white mutations cause embryonic lethality in the homozygous state .

The white (W) locus was first recognized in mice in 1908 . The mutation of the same name produces a belly spot and interspersed white hairs on the dorsal aspect of the coat in the heterozygote (W / +) and black @-@ eyed white in the homozygote (W / W) . While

heterozygotes are healthy , homozygous W mice have severe macrocytic anemia and die within days . A mutation which affects multiple systems is " pleiotropic . " Following the mapping of the KIT gene to the W locus in 1988 , researchers began identifying other mutations as part of an allelic series of W. There are over 90 known W alleles , each representing a unique mutation on the KIT gene , which primarily produce white spotting from tiny head spots to fully white coats , macrocytic anemia from mild to lethal , and sterility . Some alleles , such as sash produce white spotting alone , while others affect the health of the animal even in the heterozygous state . Alleles encoding small amounts of white are no more likely to be linked with anemia and sterility than those encoding conspicuous white . Presently , no anecdotal or research evidence has suggested that equine KIT mutations affect health or fertility . A recent study showed that blood parameters in horses with the W1 mutation were normal .

= = " White " horses that are not dominant white = =

White horses are potent symbols in many cultures . An array of horse coat colors may be identified as " white , " often inaccurately , and many are genetically distinct from " dominant white . "
" Albino " horses have never been documented , despite references to so @-@ called " albino " horses . Dominant white is caused by the absence of pigment cells (melanocytes) , whereas albino animals have a normal distribution of melanocytes . Also , a diagnosis of albinism in humans is based on visual impairment , which has not been described in horses with dominant white nor similar coat colors . In other mammals , the diagnosis of albinism is based on the impairment of tyrosinase production through defects in the Color (C) gene . No mutations of the tyrosinase or C gene are known in horses .

= = = Non @-@ white colors = = =

Cremello or Blue @-@ eyed cream horses have rosy pink skin , pale blue eyes and cream @-@ colored coats , indicating that pigment cells and pigment are present in the skin , eyes , and coat , but at lower levels . Dominant white horses do not have pigment cells , and thus no pigment , in the skin or coat . In addition , dominant white horses seldom have blue eyes . Other genetic factors , or combinations of genetic factors , such as the pearl gene or champagne gene , can also produce cremello @-@ like coats . These coat colors may be distinguishable from dominant white by their unusually colored eyes .
Gray horses are born any color and progressively replace their colored coat with gray and white hairs . Most gray horses have dark skin , unless they happen to also carry genes for pink or unpigmented skin . Unlike dominant white horses , grays are not born white , nor is their skin color affected by their coat color change .
Leopard complex horses , such as the Appaloosa and Knabstrupper breeds , are genetically quite distinct from all other white spotting patterns . The fewspot leopard pattern , however , can resemble white . Two factors influence the eventual appearance of a leopard complex coat : whether one copy or two copies of the Leopard alleles are present , and the degree of dense leopard @-@ associated white patterning that is present at birth . If a foal is homozygous for the LP allele and has extensive dense white patterning , they will appear nearly white at birth , and may continue to lighten with age . In other parts of the world , these horses are called " white born . " " White born " foals are less common among Appaloosa horses , which tend to have blankets and varnish roans , than Knabstruppers or Norikers , which tend to be full leopards .
Tovero , Medicine hat or War bonnet are terms sometimes applied to Pinto horses with residual non @-@ white areas only around the head , especially the ears and poll , while most the remaining of the coat is white . While dominant white horses may have areas of residual pigment only around the ears and poll , the term " medicine hat " usually refers to horses with more commonly known white spotting genes , most often tobiano , combined with frame overo , sabino or splashed white .

= = = Lethal White = = =

Foals with Lethal white syndrome (LWS) have two copies of the Frame overo gene and are born with white or nearly white coats and pink skin . However , unlike dominant white horses , foals with LWS are born with an underdeveloped colon that is untreatable , and if not euthanized , invariably die of colic within a few days of birth . Horses that carry only one allele of the LWS gene are healthy and typically exhibit the " frame overo " spotting pattern . In cases of " solid " horses with frame overo ancestry , uncertain " overo " (non @-@ tobiano) phenotype , or horses with multiple patterns , the LWS allele can be detected by DNA test .

= = = Sabino = = =

Both dominant white and " Sabino @-@ White " horses are identified by all @-@ white or near @-@ white coats with underlying pink skin and dark eyes , often with residual pigment along the dorsal midline . However , there are genetic differences . The term " dominant white " is reserved for known W alleles . Dominant white horses are heterozygous for any one of 11 known alleles of the KIT gene (e.g. W8 / +) . Homozygosity for some of the 11 known alleles may not create a viable embryo . In contrast , Sabino @-@ White horses are homozygous for the Sabino 1 allele of the KIT gene (SB1 / SB1) .

Another type of sabino patterning , called simply " sabino , " " minimal sabino " if slight , or if particularly dramatic , " maximum sabino , " refers to horses that test negative for any of the Dominant White alleles , negative for Sabino 1 , and also negative for Tobiano and Frame overo . Initially , dominant white was separated from sabino on the grounds that the former had to be entirely white , while the latter could possess some pigment . However , the 2007 and 2009 studies of dominant white showed that many dominant white alleles produce a range of white phenotypes that include horses with pigmented spots in hair and skin . Each of the larger families of dominant white studied included pure @-@ white horses , horses described as having " sabino @-@ like " white markings , as well as white horses described as " maximal sabino . "

More recently , dominant white and sabino were distinguished from one another on the grounds that dominant white alleles produce nonviable embryos in the homozygous state , while Sabino 1 was viable when homozygous . However , not all KIT alleles currently identified as " dominant white " have been proven lethal .

The similarities between Dominant White , Sabino 1 , and other forms of sabino may reflect their common molecular origin : The W1 @-@ W11 series and SB1 have been mapped to KIT . The researchers who mapped Sabino 1 suggested that other sabino @-@ like patterns might also map to KIT . Similarly , major alleles for white leg and facial markings have also been mapped to or near to the KIT gene .

= = = Mosaicism = = =

Mosaicism in horses is thought to account for some spontaneous occurrences of white , near @-@ white , spotted , and roan horses . Mosaicism refers to mutations that occur after the single @-@ cell stage , and therefore affect only a portion of the adult cells . Mosaicism may be one possible cause for the rare occurrence of brindle coloring in horses . Mosaic @-@ white horses would be visually indistinguishable from dominant whites . Mosaicism could produce white or partially white foals if a stem cell in the developing foal underwent a mutation , or change to the DNA , that resulted in unpigmented skin and hair . The cells that descend from the affected stem cell will exhibit the mutation , while the rest of the cells are unaffected .

A mosaic mutation may or may not be inheritable , depending on the cell populations affected . Though this is not always the case , genetic mutations can occur spontaneously in one sex cell of a parent during gametogenesis . In these cases , called germline mutations , the mutation will be present in the single @-@ celled zygote conceived from the affected sperm or egg cell , and the condition can be inherited by the next generation .

= = Homologous conditions = =

In humans , a skin condition called piebaldism is caused by more than a dozen distinct mutations in the KIT gene . Piebaldism in humans is characterized by a white forelock , and pigmentless patches of skin on the forehead , brow , face , ventral trunk and extremities . Outside of pigmentation , piebaldism is an otherwise benign condition . In pigs , the " patch , " " belted , " and commercial " white " colors are caused by mutations on the KIT gene . The best @-@ known model for KIT gene function is the mouse , in which over 90 alleles have been described . The various alleles produce everything from white toes and blazes to black @-@ eyed white mice , panda @-@ white to sashed and belted . Many of these alleles are lethal in the homozygous state , lethal when combined , or sublethal due to anemia . Male mice with KIT mutations are often sterile . To date , no such pleiotropic effects have been described in horses with KIT mutations .