Hypopigmentation as the Cause for the Neurological Disorder "Spider Wobble" in *Python regius*

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ENGL 2767: Comp II Science & Tech

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April 22, 2020

Abstract

The spider morph of the Ball Python (*Python regius*) is associated with the neurological disorder known as “spider wobble”, where affected individuals show clinical signs of balance and coordination abnormalities. However, the genetic cause of the spider wobble has never been experimentally determined. The purpose of this essay is to show that the spider morph of the ball python is likely pleiotropically linked to the wobble disorder. This is suggested in that other organisms with genetic mutations that reduce pigmentation often show signs of developmental and neurological abnormalities, including deafness, hereditary megacolon, reduced vision, and poor coordination. These mutations are often inherited in an incomplete dominant manner and, when homozygous, lead to severe or even lethal developmental abnormalities. Hypopigmentation is generally a single-gene trait, often associated with mutations that affect the migration of melanocytes during development, pleiotropically causing both the reduced melanin and the developmental disorder, and for this reason the two phenotypes cannot be separately selected for in a breeding program.

Keywords: neurological, pleiotropy, melanocyte, hypopigmentation, morph

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Ball pythons (*Python regius*) have become quite popular in the pet trade over the last thirty years and are now found in over 300 distinct genetic mutations ("The Big Morphlist", n.d.). The Spider morph is a coloration/pattern of the ball python that is associated with the neurological condition known as "Spider wobble" (Rose & Williams, 2014). The neurological condition appears to be inherited along with the Spider gene, suggesting a genetic relationship between the two, although the genetic and physiological causes are yet to be experimentally determined**.** Neurological conditions associated with hypopigmentation can be seen in a variety of other organisms (Reissmann & Ludwig, 2013), suggesting an association between the reduced pigmentation and the neurological disorder seen in the Spider morph. Spider ball pythons also appear to be homozygous lethal for the Spider gene, suggesting an incomplete dominant mode of inheritance (Huck, 2017). Support for the wobble and color phenotypes being produced by the same gene can be seen in that all ball pythons that carry the Spider allele appear to have the wobble phenotype to some degree, while full siblings of such individuals without the Spider allele do not show the wobble phenotype (Rose & Williams, 2014). For years there has been controversy among python breeders and keepers over whether or not the spider morph is ethical to breed, due to its association with the Spider wobble. A large part of this debate hinges on if it is possible to select for a less severe wobble, or if the wobble can even be completely eliminated from the Spider phenotype through careful breeding. The purpose of this essay is to show that the neurological condition known as "Spider wobble", seen in the Spider morph of *Python regius*, is likely caused by the same mutated gene that leads to the hypopigmentation, which

would mean that the Spider phenotype is pleiotropically linked to the neurological condition and, thus, cannot be separated from it through selective breeding.

History of the Spider Ball Python

Ball pythons have become popular pets around the world due to their laid-back temperaments and many color varieties. Since the 1990s, over 300 distinct genetic mutations have been found or produced that affect the color, pattern, or scales of ball pythons ("The Big Morphlist", n.d.). These varieties are known as morphs, and they are caused by mutations that alter the typical "wild type" ball python phenotype - the phenotype being the visible characteristics and traits. The first snake known to carry the Spider gene was imported from the wild in the 1990s ("The Spider Morph and the Wobble", n.d.) and was bred a few years later, producing more snakes carrying the Spider gene. The original snake showed what is now known as the "Spider wobble", as did his offspring that carried the Spider allele. The Spider phenotype is caused by a single gene, that, as of the time of this writing, is still described by many as being inherited in a dominant manner ("The Big Morphlist", n.d.), meaning only a single allele is necessary for the phenotype to be visually apparent. This mutation produces snakes with decreased pigmentation, which causes a web-like pattern along their back, leading to the name "Spider" (Barczyk, 2019). It has become one of the most popular ball python morphs to breed and has been crossed with multiple other mutations to produce a variety of color and pattern combinations. Spider ball pythons show neurological symptoms including head tremors, incoordination, corkscrewing of the head and neck, torticollis (head tilting), and inhibited righting reflexes (Rose & Williams, 2014) to varying degrees of severity. When keepers started noticing how severe the wobble was in certain snakes, to the point of impacting their feeding habits and locomotion, it became a possible ethical issue to continue breeding them. In 2017, the

International Herpetological Society (IHS) banned the display or sale of any Spider ball pythons at their events in the UK (International Herpetological Society, 2017). This further fueled the controversy, which not only involved ethics, but debates over the genetics behind the wobble, including talk of whether or not the neurological condition is truly caused by the Spider allele its self. If not caused by the same gene, the Spider phenotype could potentially be selected for apart from the wobble.

Other Species with Hypopigmentation

Many other animal species have neurological and developmental disorders associated with pigmentation mutations. Mutations associated with the mechanisms behind the development, migration, and function of melanocytes, cells that produce melanin, have been shown to cause both the altered phenotype and the abnormal, even lethal, development abnormalities seen in hypopigmented organisms (Reissmann & Ludwig, 2013). Melanocytes, which are important for outward pigmentation and proper function of the ears and eyes, come from precursor cells that begin in the neural crest. These precursor cells differentiate not only into melanocytes but also into cells found in the nervous system (Irizarry & Bryden, 2016; Bismuth & Arnheiter, 2009). Mutations that decrease the pigmentation of animals can have pleiotropic effects, in that they may decrease or prevent the migration of melanocytes or their precursors (Dessinioti et al., 2009). Pleiotropy is when one gene can have multiple, seemingly unrelated, effects on the phenotype. Blue-eyed white cats, white Boxer dogs, American paint horses, and certain white patterned ferrets, among other species (Strain, 2015), are all phenotypes with an increased risk for deafness. Some hypopigmentation phenotypes are associated with more severe clinical signs than deafness, such as megacolon, eye disorders, and neurological conditions, and may even be lethal. Such mutations are seen in merle dogs (Fuller, 2016), Lethal

White Overo horses (Santschi et al., 1998), brown-eyed pastel mink (Shackelford & Cole, 1947), black-eyed white Campbell hamsters (Jepson, 2016), English spotted rabbits (Fontanesi et al., 2014), and white spotted mice (Baxter et al., 2004), among others. Dominant Silver in Zebra Finches ("Dominant Silver Zebra Finch", n.d.) is an example of a reported lethal gene in birds that is associated with hypopigmentation. Lastly, in reptiles, the Enigma leopard gecko (Bargen, 2013) and Jaguar carpet python ("Carpet Python Morphs", n.d.) are phenotypes characterized by reduced or altered pigmentation that show similar symptoms to Spider ball pythons, including incoordination, head tremors, and other neurological signs. Even humans can suffer from disorders associated with hypopigmentation mutations, including hereditary deafness due to Tietz syndrome and Waardenberg syndrome (Baxter & Pavan, 2012) and bleeding disorders due to Chediak-Higashi syndrome (Toro et al., 2018).

Homozygous Lethal

Many of the hypopigmentation mutations that cause severe clinical signs are a form of "dominant white", in which a heterozygous individual - one with only a single copy of the mutated allele - has reduced pigmentation, while a homozygous dominant individual - one with two copies of the allele - is almost completely white and often suffers from deformities, sometimes lethal ones. These genes are known as incomplete dominant, as the heterozygous and homozygous forms are phenotypically distinct. Dominant white arctic foxes (Filistowicz et al., 1997), white spotted gerbils (Cope, 2011), white spotted Chinese hamsters (Henwood et al., 1987), and white/mosaic chinchillas (Kern, n.d.) are examples of incomplete dominant lethal mutations associated with hypopigmentation. Spider ball pythons are often reported as dominant, meaning a heterozygous Spider would be phenotypically the same as a homozygous Spider; they would look the same. However, when breeding two Spider ball pythons together, no proven

viable super Spiders (the term used for homozygous Spider ball pythons) have ever been produced and the offspring are believed to either die during embryonic development or soon after hatching (Huck, 2017). There is some evidence to suggest that super Spiders are a form of "lethal white", and that those who die right before or after hatching will show a white phenotype (Huck, 2017). There has been great debate by breeders over why no known super Spiders have been produced, but similar findings of lethal homozygous offspring in other ball python morphs with associated neurological disorders (Carter, n.d.) and the Jaguar carpet python (Carpet Python Morphs, n.d.) would seem to indicate that the Spider gene is also homozygous lethal. This incomplete dominance strongly suggests that there is only one gene involved with the wobble and Spider phenotypes, as both the changes in the color - from the Spider phenotype to the white phenotype - and the extent of the developmental abnormalities - from neurological symptoms to embryonic death - occur between the heterozygous and homozygous forms of the Spider ball python.

The Two Traits are Inseparable

This strong association between the Spider wobble and the Spider coloration/pattern is further supported in that it does not appear as though the two can be separated by selective breeding, indicating they are caused by the same gene mutation. Full siblings of Spider ball pythons that do not carry the Spider allele do not show signs of the wobble disorder (Rose & Williams, 2014), providing a clear distinction between carriers and non-carriers. Spider ball pythons are known for having varying severities in neurological symptoms among individuals, with some showing minimal clinical signs. However, despite attempts to only breed such snakes with a minimal wobble, the severity of the clinical signs of the parents cannot be used to predict the severity in their offspring. This variation appears random rather than heritable ("The Spider

Morph and the Wobble", n.d.), and is likely due to the random distribution of the melanocytes during development. Mutations that lead to random, varying amounts of pigmentation can lead to variations in clinical signs. This can be seen in double merle dogs, where some may not be blind or deaf, others just deaf, and still others are both blind and deaf (Clark et al, 2006). Just as no two merle dogs have the exact same patterning on their body, no two Spider ball pythons have the same pattern, and this, along with environmental factors, is likely the reason for the varying clinical signs seen in Spider ball pythons.

Not a Case of Linkage

Some breeders would argue that the Spider gene is not truly pleiotropic with the Spider wobble, but is simply linked. Linked genes are those that are very close on the same chromosome to one another, and, thus, are usually inherited together. However, this does not appear to be the case in Spider ball pythons, as crossing over, while rare, would still occur. Crossing over would separate the two genes, producing non-Spider offspring with the wobble and Spider offspring without the wobble. Another argument is that the wobble, due to its varying severity, must be caused by many genes interacting with one another and not just a single mutation. The combination of mutated genes is often believed to be due to inbreeding, where related snakes are bred to one another and recessive mutations build-up in the offspring. However, this complexity, again, would suggest that some non-Spider offspring would inherit the wobble as well. The Spider morph is not a recessive mutation, and for this reason is generally out-crossed (bred to unrelated individuals), so despite all Spiders descending from one individual ("The Spider Morph and the Wobble", n.d.), inbreeding is not an issue and abnormally high numbers of unrelated genetic disorders should not be found in most Spider ball pythons.

Conclusion

In conclusion, the evidence suggests that the mutation behind the Spider phenotype of the ball python is pleiotropic to the Spider wobble. The hypopigmentation seen in these snakes is directly associated with the Spider wobble, with the alterations in the migration/function of the melanocytes leading to abnormalities during embryonic developmental, resulting in offspring with the neurological disorder. Like many other hypopigmentation mutations seen in various species of animals, the low amount of melanin in the Spider ball python appears to be associated with physiological and neurological abnormalities. Homozygous Spider ball pythons are likely lethal due to an extreme lack of pigmentation, further evidence that melanin is directly associated with the development of the Spider wobble. If the Spider wobble truly is pleiotropic with the Spider coloration, then one trait cannot be selected for without the other, and future breeding programs will not succeed in breeding the wobble out of the Spider ball python.

There have been questions as to whether or not it is ethical to breed snakes with a neurological defect, one that can impair movement, breeding, and feeding behavior. Further research into the mutation behind the Spider color and the physiological and developmental causes of the Spider wobble itself are necessary before making any conclusions about the physical and psychological impacts this disorder may have on affected snakes.

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