MediRabbit.com

Heterochromia of the iris in rabbits belonging to the Dutch breed.

Kimberly Butler, Beth DeGeorge, Gabriela Dunn, Julie VanGyzen, Michel Gruaz, Arie van Praag and Esther van Praag

Pigmentation of the iris can present anomalies in Dutch rabbits. It may be sectorial heterochromia within one iris, complete heterochromia of the iris between one eye and the other, or ocular albinism with a blue iris in both eyes.

Dutch rabbits, also known as Hollander or Brabander, belong to a very old breed and have been represented on antique etchings of the 16th century already. Its name refers to the Dutch province of Holland in the Netherlands. Indeed, it seems

Figure 1: Family of Dutch rabbits with the characteristic bicolor black and white markings and sharp and even edges between the colored and white areas. Photo: Arie Van Praag

Figure 2 : Young Harlequin or Tri-color Dutch rabbit with three different colors of fur. Photo: Arie Van Praag

Figure 3: Young male New-Zealand rabbit with an entirely white fur and pinkish eyes. Photo: Arie Van Praag

that it originates from this region even though rabbits showing a coat with Dutch markings were found more generally in the Netherlands, in Northern Belgium and in England. Even so, it was in England that the Dutch rabbit was selected for its beautiful coat and its distinctive markings in order to obtain animals presenting fully symmetric colored markings. The edges between colored and white areas should be as even and sharp as possible (Figures 1, 2).

The colored parts on the body include the ears, neck, sides of the head (cheeks and eyes) and the rear end, according to a straight line running behind the shoulders to the underneath of the rabbit's belly (Figures 1, 2). Their size is smaller too.

Hair color in rabbits

Hair growth is accompanied by the expression of the dark brown eumelanin and the yellow phaeomelanin pigments. The presence, absence, or variations in the combination of these pigments is determined genetically. The distribution of pigment density in the hair shaft will affect the intensity of the color. In long haired breeds, e.g., the Angora rabbit, the pigment granules are spread along a greater distance, causing the color to appear diluted, whereas in breeds with short hair such as the Rex rabbit, the granules are closer to each other and the color becomes more intense. The absence of any pigments causes albinism. Albino rabbits typically have a pale skin, white fur, and pink eyes.

Several hair coloration patterns are found in rabbits:

- Agouti. It is a multi-band arrangement of colors along the hair. Along the coloring of wild rabbits there are several variations such as brown-grey (Figures 10, 11), or gray as in Chinchilla rabbits.
- Self-color. Each hair has one single color. The main pigment is eumelanin.
- Multicolor. Areas of hairs with an eumelanin dominance alternate with areas of hair with phaeomelanin dominance or unpigmented hair.
- Albino. Albino rabbits have a very lightly colored skin, a white fur and pinkish eyes due to the transparency of the blood vessels.

In most rabbit breeds, genes controlling the color of the fur have undergone extensive manipulation by breeders in order to produce breed-specific colors or to achieve:

- Markings, areas with more or less large areas of white depigmented hair that form plaques or spots. It can be differentiated in large areas on the body as observed on the Dutch rabbit, or spotted as seen in the spotted rabbit or the Hotot rabbit.
- Patterning, genes expressing the eumelanin pigment are sensitive to temperature and the pigment is only synthetized under specific temperature conditions, as seen on the Himalayan or Russian rabbits, or the Sable dwarf.
- Shading, it includes a pointed coat and a partial discoloration over the body, except limbs, as observed in the Sable Netherland or Siamese Dwarf.
- Silver, these rabbits are born all black. A more or less important depigmentation of the hair tips leads to the silver effect, as seen on the Argenté de Champagne.

Genetics of the Dutch coat

Genetics of fur color is complex in rabbits. Part of the genes deals with the color of the hair shaft and the distribution of pigments along the shaft, or their absence. Other genes control the distribution of the colored areas or albino/white on the body. Finally a gene pool regulates the intensity of certain colors.

Ten loci determine the appearance of the fur: A, B, C, D, E, En, Du, Si, V, and W. Each one may have several dominant or recessive genes.

The coat of the Dutch rabbit is determined by the gene "Du" = Dutch. A homozygous Du/Du rabbit has a uniform coloration of its fur, without white hairs or a white nail. Heterozygous Du/du rabbits have a colored fur on most parts of their body, with one or few white markings, e.g., a few white hairs at the extremity of a limb, a nail, or tip of the nose. Only homozygous du/du rabbits will get the typical coat of Dutch rabbits with white markings/areas of white fur. The colored fur is gradually "invaded" by fully depigmented hairs on more or less extensive areas of the body. These white

Figure 4: Young male Dutch rabbits showing the classical white and black markings. Breeders have introduces other color variations such as chocolate. Photos: Arie Van Praag

markings appear on the head, neck, upper trunk, upper limbs, and evolve independently from each other.

The expression of the "Du" gene does, however, not explain the variation in the degree of white marking on the body of Dutch rabbits, neither the appearance of newborn with Dutch marking in breeds whose ancestors are Dutch rabbits. This is, for instance, observed in litters of the Hotot rabbit, a "black rabbit with a huge white marking covering the whole body" except around the eyes (Figure 5 A, B). There is usually one or more newborn with an incomplete marking of the coat. Sometimes one descendant presents an almost perfect "Dutch coat" (Figure 5 B).

Nowadays, it is suggested that the Dutch rabbit as well as breeds selected from the former carry the dominant "Hol" gene and many modifying polygenes or "modifiers" that influence the white marking and, consequently, the color of the eyes. The effect of one single polygene has little effect. It is the sum of polygenes that will greatly influence the degree of white marking on the body of the animal and eye color.

A

B

Figure 5: A: Young Hotot rabbits of a same nest, presenting varying degrees of white marking of their coat. B: Hotot rabbit referred to as a wrong Dutch as he presents the typical marking of the Dutch breed. Photos : Michel Gruaz

Consequently, it is interesting to note how genetics leads to numerous differences in coat and eye color. The expression of some polygenes leads to the presence of a few white hairs in the fur. All intermediaries are possible, with sporadic cases of rabbits with blue eyes. The ultimate stage of white marking is a rabbit with white fur and blue eyes.

Dutch with blue eyes

The iris is a component of the uveal tissue of the eye, which acts as a diaphragm of the eye. Its anterior part also determines the color to eyes.

The color of the iris, such as we perceive it, depends on three factors:

- Density of cells producing the melanin pigment, the melanocytes.
- Density of melanin pigments in the anterior layer and posterior epithelium of the iris.
- Density and structure of the collagen fibers in the anterior layer and the stroma of the iris.

The density of pigmented cells and

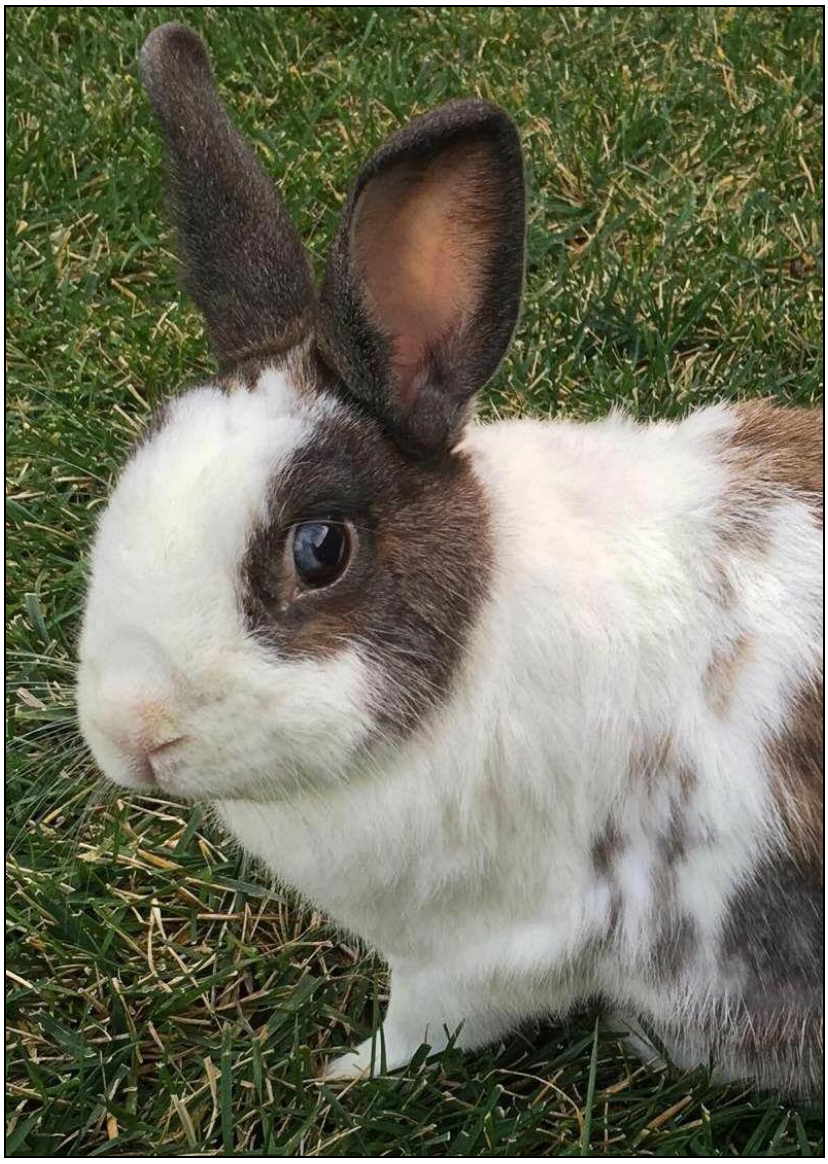

Figure 6: Dutch rabbit with a different pigmentation within the same iris. Photos: Kimberly Butler

melanin pigment varies greatly in brown or blue irises, less dense in the latter. The distribution of pigment cells within the iris is also different. In a blue iris, the melanin pigment is mainly found in the posterior epithelium, a bit in the stroma while the anterior layers have none and are translucent.

The blue or brown color of the iris is also determined by the refractive index of light in the iris, compared to the surrounding environment. In the case of blue eyes, light is little absorbed. Light waves are reflected to the outside environment or scatter throughout the structures of the eye. The structure of the anterior layer of the iris and the absence of melanin pigment favor the passage of short blue waves, which allows:

- Transmission of light waves deeper into the eye, to the pigmented cells of the posterior epithelium.
- Diffusion through reflection of an intense blue light.

The microscopic size of the different structures of the iris causes, in addition, a greater diffusion of short-wave light (blue) than long-wave light (red). The iris color is thus perceived as blue.

When pigmented cells are present in the anterior layer and posterior epithelium of the iris, part of the light is absorbed. The ratio of the reflected and scattered light results in the

gray, light brown or dark brown colors of the iris.

In the case of an iris with sectoral color variations, differences in blue and brown colors are caused by variations in the size of the different structures of the iris and/or changes in the density of pigmentation between the blue and brown parts of the iris.

In albino rabbits, the absence of melanin pigments in the anterior layer and posterior iris epithelium allows a full penetration of light without it being absorbed. Therefore the color of the iris of the eye is pink to purplish. These rabbits are usually photophobic.

In conclusion, rabbits with a colored coat have brown or gray eyes while those with a very white fur or albino have light blue or pinkish eye irises. Dutch rabbits can, however, sometimes, be born with blue irises in both eyes, a difference of color within the same iris or a difference of color of the iris of one eye compared to the other (Figures 6, 7, 8, 9, and 10). This phenomenon is also observed in rabbit breeds that have been selected from very marked (very white) Dutch rabbits like the Polish or Vienna White rabbits, both born with blue eyes (Figures 13, 14).

Geneticists concluded that there was a sudden mutation of the recessive gene with complete penetrance "v", which is responsible for the

Figure 7: Rabbits belonging to other breeds may also have a sectorial heterochromia of the iris. Here a lop rabbit with a very white fur and a possible spotted origin. Photos : Julie VanGyzen

Figure 8: Another Dutch rabbit avec small depigmented areas in the irises of both eyes. Photos: Maria-Gabriella Atzori

Figure 9: Lateral view of a Dutch rabbit with heterochromia between the iris of one eye and the other : brown and normal on his right side and blue on his left side. Photos : Beth DeGeorge

Figure 10: Rabbits with a different pattern of fur coloration may also be affected by sectorial heterochromia of the iris. It includes rabbits with the agouti pattern, similar to that of wild rabbits, but also rabbits belonging to the Chinchilla breed. Photos : Gabriela Dunn

white fur/blue eyes in homozygous v/v animals. This model of mutation does, however, not consider that:

- Dutch rabbits may have one or both blue eyes (Figures 9, 12).

- Breeds that descend from the Dutch rabbit are the result of a slow and precise selection from the Dutch rabbit.

In extreme cases, the following types were obtained:

- Rabbit with a fully white coat and preservation of the pigmentation of the iris, as observed in Hotot rabbits (Figure 5).
- Rabbits with an entirely white and depigmentation of the iris, or "white with blue eyes" like the Vienna White rabbit or the Polish dwarf rabbit (Figures 13, 14).

There is, thus, a correlation between the degree of white marking of the coat and the appearance of blue eyes in rabbit belonging to the Dutch breed. Various hypotheses have been proposed. The most likely one remains that suggested by Searle in 1968: the existence of a recessive "du" gene is accompanied by a certain number of polygenes modifying the marking that are expressed under certain conditions only.

Heterochromia of the iris

Heterochromia is defined as variations of color within areas of a same iris (sectorial heterochromia or *heterochromia iridum*) (Figures 6, 7, 8, 10, 11) or a difference of color of the iris of one eye, compared to the other eye (*heterochromia iridis*) (Figure 9).

In the Dutch rabbit, the observed types of iris heterochromia have no clinical importance and do not seem to be associated to other ocular anomalies. These include a

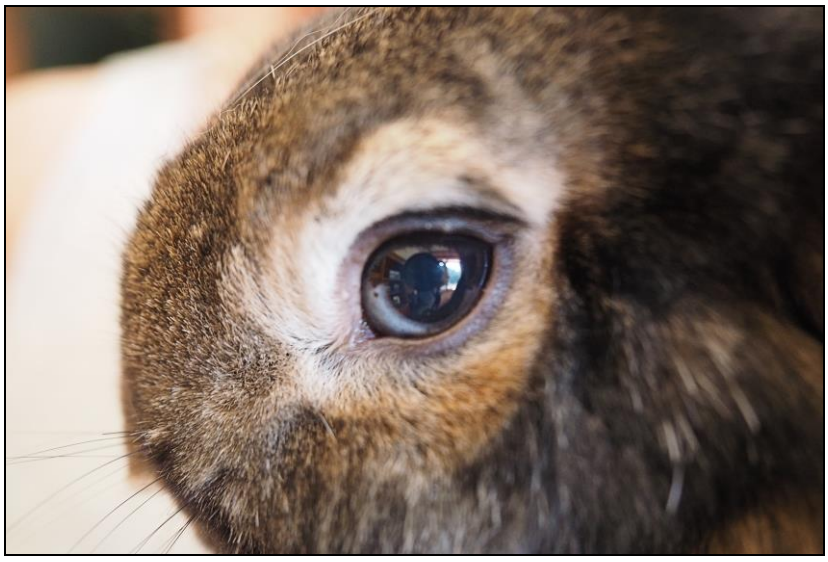

Figure 11 : Heterochromia of the iris in both eyes in a lop rabbit with agouti fur. Photos : Nancy Ainsworth

hypoplasia of the iris, a colobome of the iris, or a displacement of the central position of the pupil (corectopia). The latter has been observed in a Vienna White rabbit (Figure 13).

A higher incidence of neurological issues such as epileptic crisis/seizures has been observed in white rabbits with blue eyes that were selected from the Dutch rabbit (Figures 13, 14). Causes are idiopathic, but visual or auditory stimuli may become triggering factors. Those attacks last a few minutes and present different phases.

Iris heterochromia is also observed in other rabbit breeds, in particular Chinchilla or Hotot rabbits. These rabbits often have a white nail or few white hairs. This anomaly can also be observed in lop rabbits with a very white fur (Figure 7).

In cats and few dog breeds, there is an association between blue eyes and congenital deafness. This association could not be established in Dutch rabbits and rabbits with white fur and blue eyes.

Histology of blue eyes

Histological analyses of blue eye show that there is a depigmentation of the mesodermal sheet of the iris, while the anterior sheets that developed from the ectoderm are pigmented. In a 6 months old rabbit with Dutch markings and heterochrome eyes, the blue eye showed hypochromia on the front part of the back of the eye (*fundus*). It is accompanied by a reduced pigmentation in the retinal epithelium and the choroid, in comparison with the normal pigmented brown eye. A

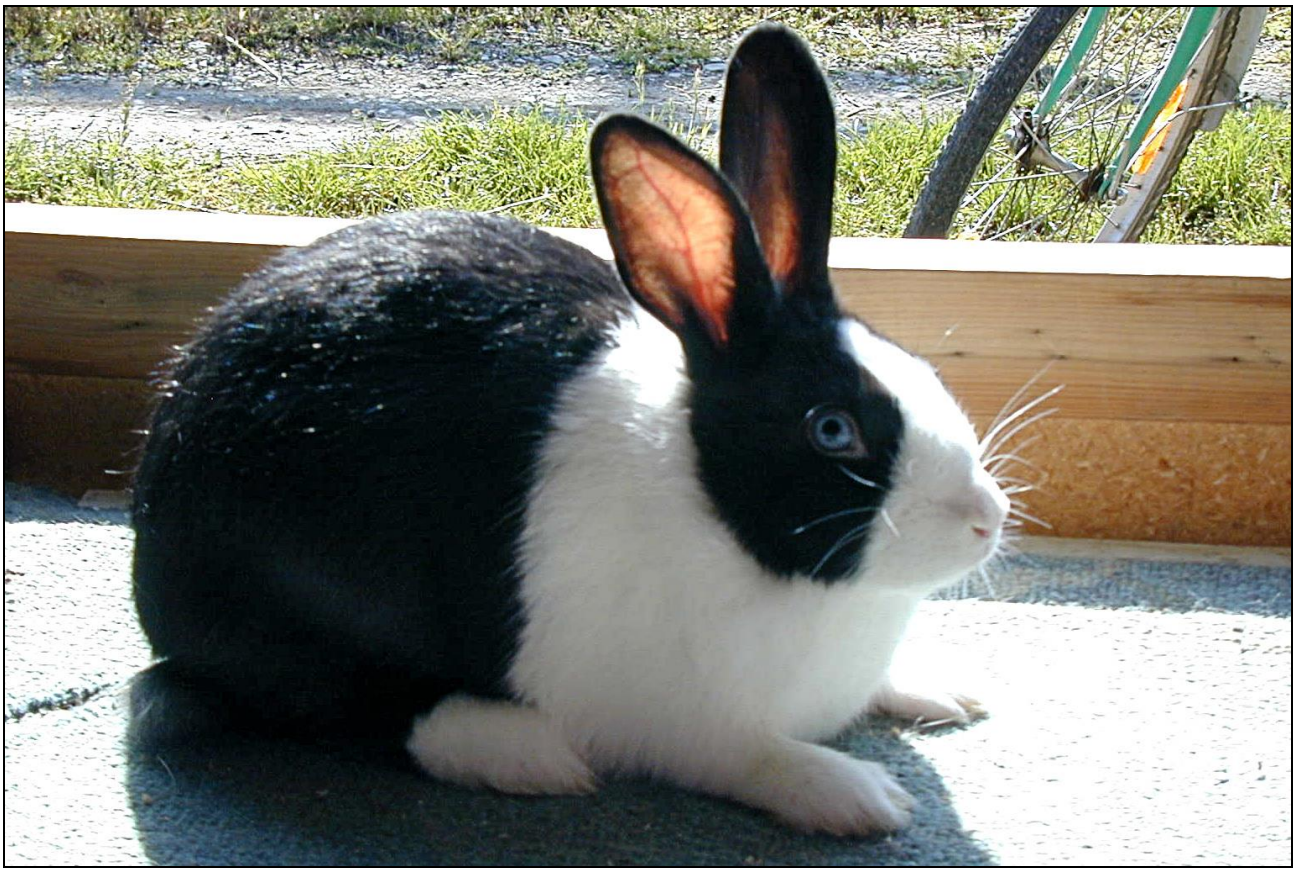

Figure 12: Young Dutch rabbit with a reduced pigmentation of both eyes, with blue brilliant irises. Photo: Michel Gruaz

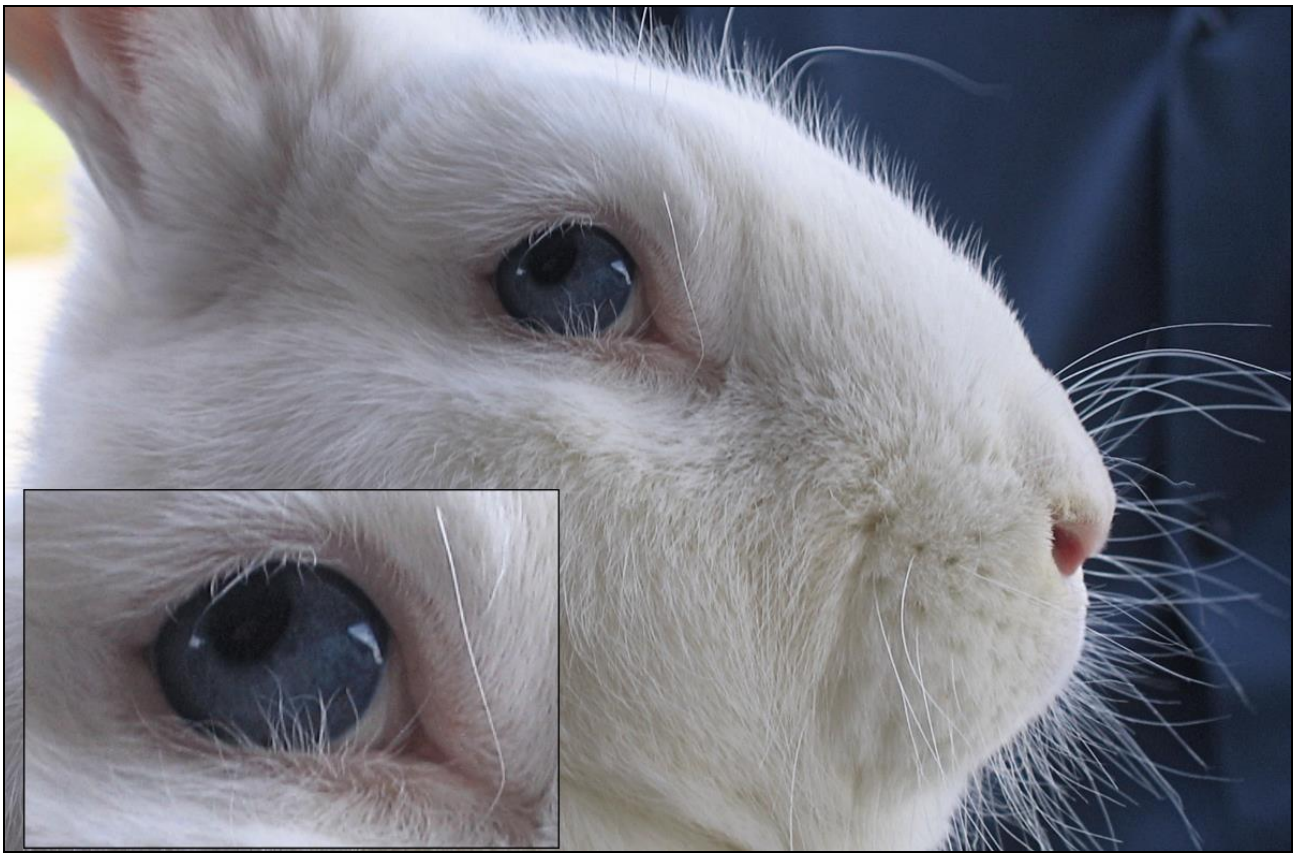

Figure 13: Displacement of the central position of the pupil (corectopia) in a Vienna white rabbit, a breed that has been selected from the Dutch rabbit. Photo: Michel Gruaz

decrease of the amount of pigmented cells was, however observed in the stroma of the iris in both eyes.

Acknowledgements

Many thanks to Tal Saarony (USA), to Janet Geren (USA) and to a person who wishes to

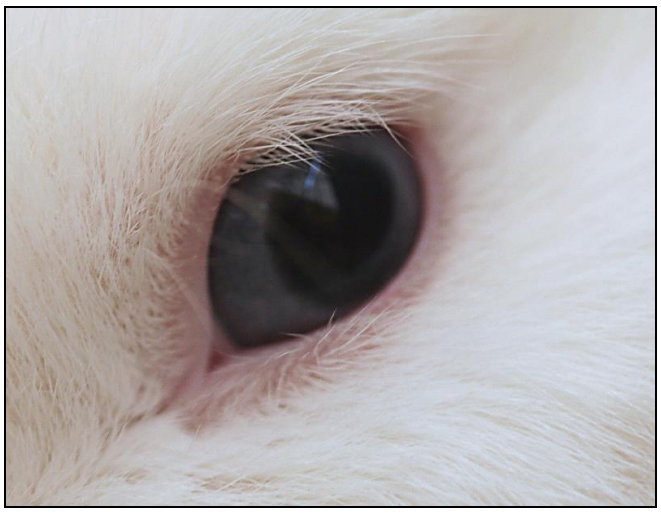

Figure 14: Rabbits with a white fur, light colored skin and blue eyes are sensitive to visual and auditory stimuli. They can lead to seizures. Here a dwarf rabbit. Photos: Arie van Praag

MediRabbit.com is funded solely by the generosity of donors.

Every donation, no matter what the size, is appreciated and will aid in the continuing research of medical care and health of rabbits.

Thank you

remain anonymous for his help to find rabbits with heterochrome eyes.

References

Arnold J. Les modèles de pigmentation chez le lapin. Dans : PARCOURS ANIMALIER, Escapades zootechniques, Cheminement cuniculicole. http://www.cuniculture.info/Docs/Documentation/Arnold/Chapitre-05.pdf

Boucher S. Nouvelle données sur les lapins blancs aux yeux bleus. http://d.roueyre.free.fr/Yeux_bleus.htm

Goin J. Ophtalmologie des NAC : Principales affections oculaires chez le lapin. Le Point Vétérinaire 2015;359:24-32. http://www.lepointveterinaire.fr/bdd/165/165_4591

Hinkle A. Color Genetics of the Dwarf Hotot. American Dwarf Hotot Specialty Club Guidebook. 2011; 112-16.

Miklos Botha M, Petrescu-Mag V, Hettig A. Genetic disorders in domestic rabbits (*Oryctolagus cuniculus*). International Journal of the Bioflux Society. Rabbit Genetics 2014; 4:7-47.

Reiswig R. Rabbit Eye Color Examples. http://www.vgr1.com/vision/color/

Rennie IG. Don't it make my blue eyes brown: heterochromia and other abnormalities of the iris. Eye (Lond). 2012;26(1):29-50.

Searle A.G., 1968; Comparative genetics of coat colour in mammals, Logos press Academic press, London, 308p.

Toyoguchi M. Cheng L, Freeman WR. Heterochromia in rabbit - Heterochromia in a Dutch pigmented rabbit. International Journal of Ophthalmology 2007; 7(4):932-933.