Genetic basis of blue eyes in the rabbit (*Oryctolagus cuniculus*)

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Abstract. Blue eye colour in domestic rabbits (*Oryctolagus cuniculus*) represents a genetically complex pigmentation phenotype that has traditionally been attributed to the Vienna locus (*V*), particularly the recessive *vv* genotype responsible for the classical blue-eyed white (BEW) phenotype. However, increasing evidence from rabbit molecular genetics indicates that ocular pigmentation is not exclusively determined by Vienna, but is also influenced by other pigmentation loci and regulatory mechanisms, including tyrosinase (*TYR*, C locus) expression dynamics and modifier genes such as *MLPH*. In particular, tissue-specific regulation of *TYR* demonstrates that eye and coat pigmentation can be partially uncoupled, producing phenotypes that cannot be explained by a single Mendelian locus. This mini-review synthesizes current literature on rabbit coat and eye colour genetics, with emphasis on Vienna-associated epistasis, TYR-mediated pigmentation pathways, and the broader polygenic architecture underlying pigmentation traits. It further discusses rare phenotypic combinations, including blue-eyed individuals outside classical BEW genetic backgrounds, and highlights the current limitations in identifying non-Vienna molecular determinants of blue eye colour in rabbits. The review integrates both fundamental genetic mechanisms and applied perspectives relevant to show rabbit breeding and selection.
Key Words: blue eyes, breeding, coat colour, epistasis, melanophilin, *Oryctolagus cuniculus*, pigmentation genetics, rabbit, TYR, Vienna gene.

Introduction. Blue eyes in domestic rabbits are classically associated with the Vienna (v) gene, but several pigment genes and regulatory mechanisms can also influence eye and coat pigmentation (Castle 1922, 1924, 1930; Sawin 1955). The available rabbit-specific literature focuses on Vienna, tyrosinase (TYR, C locus), and melanophilin (MLPH, dilute locus), with broader context from vertebrate pigmentation genetics (Aigner et al 2000; Bud et al 2011; Dorożyńska & Maj 2021).

The aim of this mini-review is to critically synthesize and contextualize current knowledge on the genetic basis of blue eye pigmentation in domestic rabbits, with a primary focus on the Vienna locus while also evaluating the contribution of tyrosinase regulation and other pigmentation-associated genes. A secondary objective is to highlight gaps in the current molecular understanding of non-Vienna blue eye phenotypes and to relate genetic mechanisms to their practical implications in selective breeding and show rabbit populations.

Vienna gene and classical blue-eyed white (BEW). The Vienna locus (V) carries a recessive allele v that produces blue-eyed white (BEW) rabbits when homozygous (vv). In white Rex rabbits, allelism tests (crosses, backcrosses, full-sib matings) showed that a recessive mutation at the Vienna locus is responsible for blue eyes; genotype vv is recessive epistatic to major coat-colour loci A, B, C, D, E, so any genotype at these loci appears as white coat with blue eyes when vv is present (Pang & Xu 2013). Combining vv with the Rex recessive allele rr yields blue-eyed white Rex rabbits (Pang & Xu 2013). The Vienna gene underlies several BEW exhibition breeds such as Vienna White, BEW Rex, BEW Netherland Dwarf and BEW Hermelin/Polish Dwarf (Proorocu et al 2019).

Tyrosinase (C locus) and eye-only pigmentation. The TYR (C locus) controls albinism series alleles that affect both coat and eye colour (Aigner et al 2000). Sequencing of TYR in multiple breeds (including White Vienna) identified several missense mutations linked to

albino, Himalayan, and chinchilla phenotypes and additional neutral variants (Botha et al 2011; Petrescu-Mag et al 2012; Botha et al 2013; Covrig et al 2013; Petrescu-Mag et al 2014; Utzeri et al 2021). A detailed strain study showed that in Vienna White rabbits with pigmented eyes but unpigmented coat, tyrosinase transcripts are present in the eye pigment layers but absent from skin, demonstrating tissue-specific TYR expression: normal eye pigmentation with white coat due to lack of TYR transcription in hair follicles rather than coding mutations (Aigner et al 2000). This indicates that blue or non-brown eye states in rabbits can arise from differential expression of pigment genes, not only from Vienna (Table 1).

Table 1

Rabbit pigment genes relevant to blue or white phenotypes

Gene / Locus	*Main effect in rabbits*	*Relevance to eye/coat colour context*	*Citations*
Vienna (V/v)	Recessive vv → BEW (blue eyes, white coat), epistatic to A, B, C, D, E	Canonical blue-eyed white phenotype across several breeds	(Pang & Xu 2013; Proorocu et al 2019)
TYR (C locus)	Albino/Himalayan/chinchilla series; eye-only vs coat+eye expression differences	Explains albino and partial pigmentation; Vienna White strain shows eye-only TYR expression	(Aigner et al 2000; Utzeri et al 2021)
MLPH (dilute locus)	Frameshift mutation → dilute "blue/grey" coat in many breeds (e.g., Blue Vienna)	Alters coat shade (blue/grey) but does not by itself define Vienna-type blue eyes	(Fontanesi et al 2014; Fontanesi 2021)

Broader pigmentation architecture and implications. Rabbit genetic resources show that many classical coat-colour loci (MC1R, ASIP, TYR, MLPH, TYRP1, KIT, etc.) underlie diverse pigmentation phenotypes, with several breeds carrying combinations of these variants (Fontanesi 2021). The TYR locus in rabbits mirrors human and mouse albinism genetics, with multiple alleles modulating both coat and eye pigmentation (Aigner et al 2000; Utzeri et al 2021). More generally, vertebrate pigmentation evolution often involves both coding and cis-regulatory mutations, especially in upstream developmental and signaling genes (Elkin et al 2023). This supports the idea that, in rabbits, additional loci and regulatory changes beyond the Vienna gene can contribute to blue or depigmented eyes, although specific non-Vienna blue-eye mutations in rabbits are not yet molecularly characterized in the available literature.

Blue eye phenotype in show rabbit breeding. The fascination with blue-eyed domestic rabbits within the context of exhibition breeding extends far beyond mere aesthetic preference, evolving into a refined and disciplined pursuit that combines genetics, husbandry, and an appreciation for phenotypic harmony. Blue ocular expression, whether associated with the Vienna gene or arising from alternative phenotypic mechanisms, represents a delicate trait that requires both technical understanding and a practiced eye to preserve and enhance across generations. For dedicated breeders, this feature is not an isolated goal, but rather an integral component of a broader commitment to producing animals that meet rigorous show standards while maintaining overall vitality and structural soundness.

Effective care is foundational to this endeavor. Show rabbits must be raised in environments that optimize both physical health and coat condition, as these factors directly influence the clarity and visual impact of eye color. Nutritional balance, stress minimization, and meticulous hygiene contribute to the development of animals that not only exhibit the desired ocular traits but also present themselves with the composure and condition expected in competitive settings. Regular observation is essential, allowing

breeders to monitor subtle changes and ensure that any deviations from expected development are addressed promptly.

Selection practices demand a high degree of precision and long-term planning. Breeders must evaluate not only the presence of blue ocular traits but also their consistency, expression, and compatibility with other defining characteristics. The inheritance patterns associated with these ocular phenotypes can be complex, particularly when multiple genetic influences are involved, requiring careful pairing strategies and detailed record-keeping. Decisions are often made with future generations in mind, balancing the desire to intensify specific traits with the necessity of maintaining genetic diversity and avoiding unintended consequences.

Amelioration, in this context, becomes a continuous and iterative process. It is guided by both formal standards and the breeder's individual vision, shaped through experience and engagement with the wider exhibition community. Over time, this process refines not only the animals themselves but also the breeder's expertise, fostering a deeper understanding of how subtle genetic interactions manifest in observable traits. Ultimately, the pursuit of blue-eyed show rabbits exemplifies the intersection of science and passion, where careful stewardship and aesthetic sensibility converge to produce animals of remarkable beauty and distinction (Figure 1).

Figure 1. Filoftea-Elena Bica with her own BEW show rabbit.

Black coat and blue eyes: **a rare phenotypic expression**. The occurrence of blue eyes in domestic rabbits exhibiting a fully black coat represents a rare and genetically nuanced phenotypic combination. Under typical circumstances, a dense black coat is correlated with high levels of eumelanin, which also manifests in dark ocular pigmentation, resulting in brown or nearly black eyes. The presence of blue eyes within this context indicates a

dissociation between coat pigmentation and ocular pigmentation, driven by specific genetic mechanisms that selectively influence melanin deposition in the ocular tissues.

One of the most recognized contributors to this phenomenon is the Vienna gene, which can disrupt normal pigmentation patterns and produce blue ocular expression even in otherwise dark-coated individuals. However, the expression is often variable, ranging from fully blue eyes to partial or mosaic ocular coloration, reflecting incomplete penetrance and complex inheritance patterns. Beyond this, additional genetic interactions may contribute to similar outcomes, though these are less well characterized and may lack consistency across breeding lines.

From a breeding and exhibition standpoint, the juxtaposition of a deep black coat with blue eyes creates a striking visual contrast that is highly valued yet difficult to stabilize. Achieving this phenotype in a predictable and reproducible manner requires careful selection, rigorous record-keeping, and a thorough understanding of underlying genetic principles. As such, it remains a specialized objective within advanced breeding programs, illustrating both the challenges and the aesthetic rewards inherent in the refinement of show rabbit phenotypes (Figure 2).

Figure 2. Eight specimens of blue eyed rabbits; original photo by Filoftea-Elena Bica.

Conclusions. Current rabbit-specific data clearly establish the Vienna recessive allele *vv* as a major, epistatic determinant of blue-eyed white rabbits. This locus remains the most consistently documented genetic basis for the classical BEW phenotype, overriding the expression of major coat-colour loci and producing a uniform white coat associated with blue ocular pigmentation. At the same time, evidence from studies on tyrosinase (C locus) demonstrates that pigmentation is not governed solely by allelic variation, but also by differential gene expression. Tissue-specific TYR transcription, particularly the decoupling of expression between ocular tissues and hair follicles, provides a compelling explanation for phenotypes in which eye pigmentation is preserved or modified independently of coat colour. This highlights a broader principle in rabbit pigmentation genetics, namely that phenotypic outcomes may arise from both structural mutations and regulatory mechanisms.

Furthermore, the contribution of additional loci such as MLPH and other classical coat-colour genes underscores the polygenic background against which the Vienna gene operates. These loci do not directly determine blue ocular expression in the Vienna sense, but they modulate the overall pigmentation landscape, influencing how such traits are perceived and expressed. The integration of these genetic factors reinforces the view that coat and eye colour in rabbits represent a complex, multilayered system rather than a single-gene trait.

Importantly, the occurrence of blue eyes in non-BEW contexts, including rare combinations such as fully pigmented (e.g., black-coated) individuals with blue ocular expression, further supports the hypothesis that additional, yet insufficiently characterized genetic or epigenetic mechanisms are involved. While the Vienna gene can account for part of this variability, the incomplete penetrance and phenotypic diversity observed in breeding populations suggest that other loci or regulatory pathways remain to be elucidated. At present, these non-Vienna determinants of blue ocular pigmentation are not well defined at the molecular level in the available literature, representing a clear gap in current knowledge.

From an applied perspective, particularly in the context of show rabbit breeding, these findings carry practical implications. The deliberate selection for blue ocular traits, whether within BEW lines or in more complex phenotypic combinations, requires not only an understanding of Mendelian inheritance but also an appreciation of gene interactions, expression variability, and long-term genetic stability. Breeders must navigate the balance between aesthetic objectives and genetic robustness, recognizing that the pursuit of rare or visually striking traits may introduce additional variability or unpredictability.

In conclusion, while the Vienna locus remains the cornerstone of blue-eyed phenotypes in domestic rabbits, the broader genetic architecture of pigmentation - encompassing TYR expression dynamics, modifier loci, and potential undiscovered mechanisms - indicates that blue ocular expression is a more complex and multifactorial trait than traditionally assumed. Continued research integrating molecular genetics, controlled breeding experiments, and phenotypic analysis will be essential for fully elucidating the determinants of this trait and for supporting both scientific understanding and responsible breeding practices.

Conflict of interest. The authors declare that there is no conflict of interest.

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