Asian Journal of Agriculture and Biology
https://doi.org/10.35495/ajab.2025.285

Original Article

Level of TFEC gene expression in piebald variants of ball python (*Python regius*)

Thanet Sophonnithiprasert[1], Ratchanok Kumsiri[2], Panan Kanchanaphum[1*]
[1]Biochemistry Unit, Faculty of Science, Rangsit University, Pathumthani, Thailand
[2]Pathobiology Unit, Faculty of Science, Rangsit University, Pathumthani, Thailand

**Corresponding author's email:* panan.k@rsu.ac.th
Received: 25 October 2025 / Revised: 14 January 2026 / Accepted: 19 January 2026 / Published Online: 30 January 2026

Abstract

The ball python, or *Python regius*, is a popular exotic pet known for its beautiful colors and patterns, particularly in the piebald morph. Piebald ball pythons have skin with white patches on a pattern with a brown and black background. The piebald trait results from a recessive mutation in the TFEC gene. There are three variations of piebald: low white, medium white, and high white. This study uses quantitative PCR (qPCR) to determine the levels of TFEC gene expression across these three piebald variants. In the four low white piebald samples analyzed, the reduction of TFEC gene expression ranged from 1.31 to 4.42-fold, compared to the wild type, displaying the lowest reduction fold of TFEC gene expression. This phenomenon shows the pattern on almost all the skin of the ball python. While in medium white, the reduction in TFEC gene expression ranges from 5.14 to 7.99-fold, indicating the equal distribution of patterned and white patches on the skin of the ball python. The last one, the greatest reduction in TFEC gene expression, is the high white piebald ball python. The average reduction of TFEC gene expression is between 17.28 to 48.92-fold, reflecting the almost white area in the skin. Our study is the first report of differential expression of the TFEC gene in the variant type of the piebald ball python.

Keywords: Piebald, Ball python, Python regius, Gene expression, TFEC gene, qPCR

How to cite this article:
Sophonnithiprasert T, Kumsiri R and Kanchanaphum P. Level of TFEC gene expression in piebald variants of ball python (*Python regius*). Asian J. Agric. Biol. 2026: e2025285. DOI: https://doi.org/10.35495/ajab.2025.285

Introduction

The ball python (*Python regius*) is a popular and famous exotic pet because of its varied and beautiful patterns and colors. Variations in these traits, known as "morphs," result from the combination of different chemical pigments that are regulated by specific genes (Brown et al., 2022). For example, albino morphs exhibit reduced melanin pigment, cinnamon morphs display increased melanin, and morphs such as clown, confusion, and spider show more complex pigment alterations. The piebald morph is particularly notable for its high market value and distinctive appearance, identified by a white area with the pattern of brown and black on a background skin (Fig. 1). A recessive mutation causes this trait (Ullate-Agote and Tzika, 2021), controlled by the TFEC gene (Garcia-Elfring et al., 2023; Tzika, 2024). The TFEC gene translates a transcription factor belonging to the MITF (Microphthalmia-associated transcription factor) family, which also includes mitf, tfe3, and tfeb (Garcia-Elfring et al., 2023). Members of this family contain basic helix-loop-helix and leucine zipper domains and play an important role in lysosomal signaling, metabolism, and pigmentation (Olsson et al., 2013). Piebald ball pythons carry a defect in the TFEC gene (Garcia-Elfring et al., 2023; Tzika, 2024). Because the piebald trait is recessive, only individuals homozygous for the mutant TFEC allele express the phenotype (Kumsiri et al., 2025). Kumsiri and her colleagues (2025) use PCR and qPCR to discriminate between wild type and heterozygous piebald in ball python. Garcia-Elfring et al. (2023) identified a candidate causal mutation in a reptilian transcription factor gene. They validated this locus in a squamate model using CRISPR/Cas9 gene editing and confirmed its effect on chromatophore development through transmission electron microscopy. These results provide evidence that a mutation in the TFEC gene determines the piebald phenotype in reptiles, like the reduced pigmentation observed in the piebald ball python. One of the few studies on snake pigmentation identified a mutation in the MITF family in leucistic Texas rat snakes. This mutation results in an all-white phenotype by causing the loss of melanophores and xanthophores, but not iridophores (Ullate-Agote and Tzika, 2021). Kuiper et al. (2004) demonstrated that a premature stop codon in the fifth exon of the TFEC gene in piebald ball pythons is expected to produce a protein lacking the basic helix-loop-helix and leucine zipper functional domains, which may disrupt target gene regulation. Tzika (2024) identified a TFEC gene mutation linked to the piebald phenotype in brown anole lizard and the ball python. Much evidence identified that the TFEC gene is linked to piebaldism in ball pythons.

Piebald ball pythons exhibit three phenotypic variations, including low white, medium white, and high white piebald types, as illustrated in Fig. 1. In low white piebald individuals (Fig. 1A), patterned skin predominates, with limited white areas. Medium white piebalds (Fig. 1B) display an approximately equal distribution of patterned and white skin. The last one, high white piebalds (Fig. 1C) are characterized by predominantly white skin with minimal patterned regions. These phenotypic differences suggest variation in TFEC gene expression among the three piebald types. Not only does the expression of the TFEC gene in piebald cause the variant phenotype, but also various gene expressions can lead to differences in phenotype. For example, the variation in the expression of the TYR (tyrosinase) gene among different animals, such as Himalayan llamas, results in varying fur colors. The phenotype of these llamas is associated with specific mutations that affect the temperature-regulated activity of the TYR gene. This leads to certain regions of the body being white in color, while the warmer parts remain lacking in pigment (Anello et al., 2019). Currently, there are no studies on gene expression levels in piebald ball pythons. Therefore, this study utilizes quantitative polymerase chain reaction (qPCR) to assess TFEC gene expression levels in the piebald variants of ball pythons.

https://doi.org/10.35495/ajab.2025.285

Figure-1. The variant types of morph piebald in ball pythons. A is a low white variant. B is a medium white variant, and C is a high white variant.

Material and Methods

Sampling and RNA extraction

The shed skins from ball python samples were collected from commercial breeders in Thailand, including Reptile Collector by docjavet and Morph Hunter, as shown in Figure 2. All samples were stored at -20°C to prevent infestation by insect larvae. This study used three wild types, four low white piebalds, four medium white piebalds, and four high white piebalds. A 1.5 cm x 1.5 cm section was excised from each shed sample, immersed in the lysis buffer (1M Tris-HCl, pH 7.5, and 10% SDS), and homogenized using a stirring rod. The supernatant of the solution was used for RNA extraction. RNA extraction was conducted using GENEzol™ Reagent (Geneaid, New Taipei City, Taiwan). After mixing with GENEzol™ Reagent, chloroform was added, and the mixture was shaken well. The solution was spun at 10,000g for 10 minutes. The top layer was moved to a new tube, and the same amount of isopropanol was added. This mixture was centrifuged again at 10,000g for 10 minutes, and the supernatant was removed. The RNA pellet was washed with cold 70% ethanol and centrifuged at 10,000g for 3 minutes. The pellet was air dried and resuspended in 25 µL of DEPC water, and stored at -80°C until needed.

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Figure-2. Some of the skin samples used in this study.

cDNA synthesis

After RNA extraction, the concentration of RNA was measured using Nano (Thermo Scientific, Massachusetts, USA). Then the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, Massachusetts, USA) was employed for the synthesis of the first-strand cDNA. Subsequently, the second strand of cDNA synthesis was performed with oligo dT primer and 2 µg of each RNA sample. Subsequently, 1x Taq DNA polymerase, buffer, and a mixture of deoxynucleotide triphosphates (dATP, dTTP, dCTP, and dGTP). The cDNA was stored at -20°C until further use.

qPCR reaction and gene expression analysis

All primers used in this study for the qPCR reaction were designed according to the methodology described by Kumsiri et al. (2025), as shown in Table 1. The qPCR mixture included Luna Universal qPCR Master Mix (New England BioLabs, Massachusetts, USA), 0.8 µM of each primer (TFEC-F and TFEC-R) as described by Kumsiri et al. (2025), and cDNA extract as the template, with a final volume of 10 µL. The PCR protocol started with denaturation at 95°C for 3 minutes, then 35 cycles of denaturation at 90°C for 30 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 30 seconds. We measured the TFEC gene expression in cDNA samples from three groups of the piebald. The Glyceraldehyde-3-phosphate dehydrogenase gene (GAPDH) served as the reference gene. Each sample was tested in triplicate during the qPCR reaction. The GAPDH gene was used as a reference gene (Sun et al., 2012).

Table-1. List of primers for qPCR.

Primer name	Sequence (5'-3)
TFEC-F	CAGTGCAACTCAAAGGGAACA
TFEC-R	GCAGACCCATGAAATCAATGGA
GAPDH-F	GAGCCCGCAGCCTCCCGCTT
GAPDH-R	CCCGCGGCCATCACGCCACAG

Results

Gene expression analysis

PCR products corresponding to the GAPDH and TFEC genes were detected in all samples. Analysis of melting curves confirmed the presence of a single PCR product. The non-template control (NTC) did not yield any PCR product.

TFEC gene expression levels were compared between the piebald and the wild type specimens. Table 2 presents the reduction in TFEC expression over time for both groups. In low white piebald individuals, the mean of TFEC expression was 1.31 to 4.42-fold lower than in wildtype. Medium white piebald individuals exhibited a reduction of 5.14 to 7.99-fold, while high white piebald individuals showed a decrease of 17.28 to 48.92-fold compared to wildtype. Figure 3 presented the reduction in TFEC gene expression over time. The letter "a" on LW bars, "b" on MW bars, and "c" on HW bars indicate no significant differences within each group, while significant differences are observed between groups.

Table-2. The comparison of the reduction time of the TFEC gene expression between piebald and wildtype. LW is the low white piebald. MW is the medium white piebald. HW is the high white piebald. The number 1 to 4 is the number of ball pythons.

Piebald variant	Reduction in TFEC gene expression 1 (fold)	Reduction in TFEC gene expression 2 (fold)	Reduction in TFEC gene expression 3 (fold)	Mean (fold)
LW1	5.87	4.68	2.71	4.42
LW2	1.49	1.21	1.23	1.31
LW3	3.17	1.61	2.26	2.35
LW4	1.92	4.83	1.36	2.70
MW1	6.66	7.09	6.67	6.81
MW2	4.05	4.78	6.58	5.14
MW3	9.33	3.92	10.74	7.99
MW4	8.46	6.20	8.99	7.89
HW1	91.71	23.88	20.23	45.27
HW2	26.83	9.89	15.12	17.28
HW3	62.34	22.57	27.47	37.46
HW4	78.79	40.86	27.10	48.92

https://doi.org/10.35495/ajab.2025.285

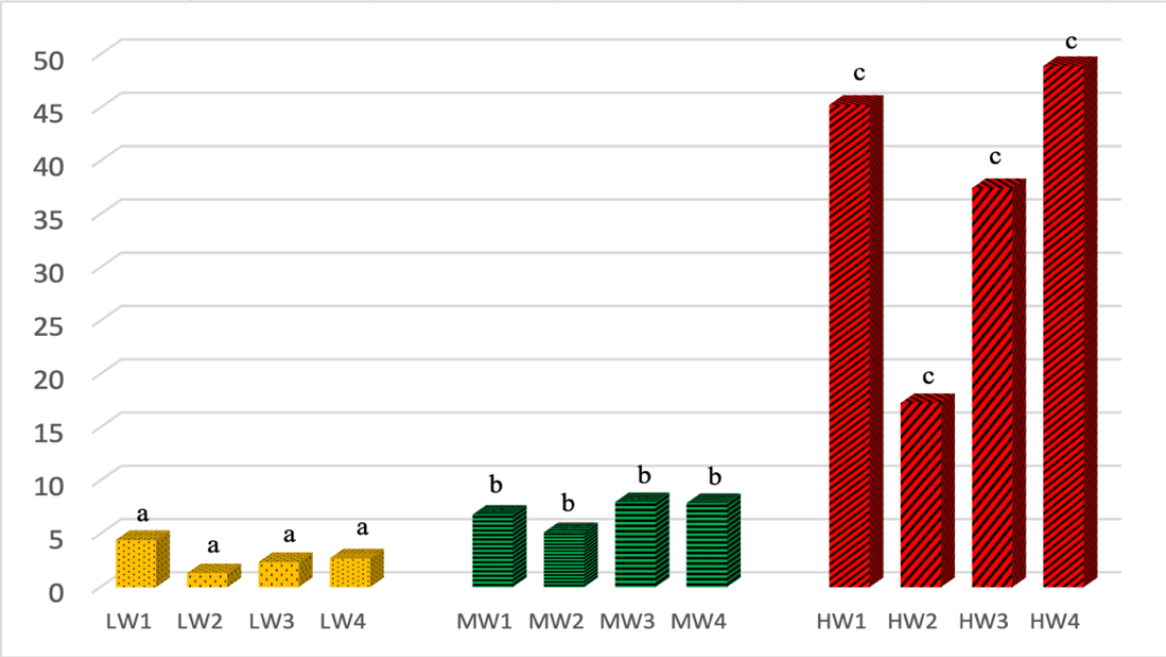

Figure-3. The comparison of TFEC gene expression among low white piebald (LW), medium white piebald (MW), and high white piebald (HW) groups to the wild type.

Discussion

The TFEC gene, which is the major cause of piebaldism in the ball python (Garcia-Elfring et al., 2023; Tzika, 2024 and Kumsiri et al., 2025), translates a transcription factor belonging to the MIT (microphthalmia-associated transcription factor) family, which also includes MITF, TFE3, and TFEB. The MIT family was found to be involved in many genetic diseases that relate to abnormal pigmentation, such as Waardenburg syndrome type II (Tassabehji et al., 1994). This disease is identified by sensorineural hearing loss and pigmentary abnormalities in the hair, skin, and eyes, such as lighter patches of hair, light-colored skin, and different-colored eyes (heterochromia iridis) (Steingrimsson et al., 1994). Not only the abnormality of pigmentation, but also Mannan et al. (2025) reported the microphthalmia-associated transcription factor (MiTF) family-altered renal cell carcinoma (MiTF RCC), causing the rearrangement of the renal cell carcinoma and TFEB-altered renal cell carcinoma. As well as in humans, knocking out the TFEC gene leads to abnormal hair pigmentation in mice (Groza et al., 2023). However, mice with a partially truncated TFEC gene, like the piebald ball python, show normal pigmentation (Steingrimsson et al., 2002). In zebrafish, Lister and colleagues (Lister et al., 1999) found that the MITFA mutations are characterized by a loss of melanophores (melanin-producing cells) and an increase in iridophores (cells that produce coloration by reflecting light on guanine nanocrystals). Moreover, the differentiation of iridophores resulted from TFEC mutations (Petratou et al., 2021). Additionally, reduced expression of the MITF gene in the Texas rat snake results in the loss of both melanophores and xanthophores (Ullate-Agote and Tzika, 2021). There is a report that describes how TFE3 and TFEB play an important role in lysosomal acidification and autophagy (Martina and Puertollano, 2017). Additionally, MITF, TFE3, and TFEB have been involved in cancer development (Levy et al., 2006).

Table 2 shows that TFEC gene expression in all piebald phenotypes was lower than in the wild type. Specifically, TFEC gene expression in low white piebald, medium white piebald, and high white piebald individuals was averagely reduced by 2.69, 6.96, and 37.23-fold, respectively, compared to the wild type. In the group of four low white piebald samples, the reduction ranged from 1.31 to 4.42-fold, displaying the lowest reduction fold of TFEC gene expression, resulting in the predominant skin of the ball python being patterned and a low white area. In medium white piebald ball pythons, the reduction in TFEC gene

expression ranges from 5.14 to 7.99 fold, indicating the equal distribution of patterned and white patches on the skin of the ball python. On the other hand, high white piebald ball pythons express an average reduction in TFEC gene expression of 17.28 to 48.92-fold, showing the highest reduction fold of TFEC gene expression, demonstrating the predominance of white area in the skin. This is the first report to exhibit the linkage between TFEC gene expression levels and the phenotypic variation seen in the piebald ball python.

There is no significant difference in TFEC gene expression within each ball python of the same group, as shown in Figure 3. However, the results show an important difference between groups (low white, medium white, and high white). Particularly, in the low white piebald group, the reduction in TFEC gene expression does not exceed 5-fold. Whilst the reduction range of TFEC gene expression is from generally 5-fold to 10-fold in medium white piebald, and the reduction range over 17-fold is found in the high white piebald group.

Currently, there are a few studies that investigate the level of gene expression in reptiles. Handi and Inamdar (2023) reported that there is a 7-fold higher expression of the anti-mullerian hormone (AMH) gene compared to the transcript level in female embryos of the tropical lizard *Calotes versicolor* (Daud.) during the developing testis stage, emphasizing its conserved role in Mullerian duct regression and testis differentiation. Additionally, Modahl et al. (2024) informed that the different expression of genes that are involved in toxin production in elapid and viperid snakes. They found that the viperid milked venom gland (MVG) in *Crotalus viridis* showed 43-fold higher expression than in *Pseudonaja textilis.* Grossen et al. (2025) reported levels of gene expression in in central circadian clock system, including period (per), cryptochrome (cry), circadian locomotor output cycles kaput (clock), and basic helix-loop-helix ARNT-like protein 1 (bmal1), in the reptilian brain. Another interesting investigation that studied in the ball python, Kumsiri et al. (2025), used quantitative PCR (qPCR) to evaluate the level of TYR (tyrosinase) gene expression in various albino morphs, including classic albino, Candy, and Candino. The results revealed that TYR gene expression in the Candy and Candino morphs was reduced by 7.88-fold and 36.93-fold, respectively, compared to the wild type. No TYR gene expression was found in the classic albino of the ball python. That is the first report to demonstrate differences in TYR gene expression across various albino types in the ball python. Kumsiri et al. (2025) and our study are the pioneers that study the level of gene expression in the ball pythons, which is related to the variations in color and pattern. However, at this moment, the knowledge about the genes that regulate or link to the color and pattern in the ball python is not sufficient. For example, the scientists do not understand the gene that controls the dot pattern found in the coral glow or banana morph, the bright color in the pastel morph, and the complex pattern in the clown pattern, as shown in Figure 4.

Figure-4. Some morph of the ball python. A is coral glow morph, B is pastel morph, C is clown morph.

https://doi.org/10.35495/ajab.2025.285

An additional interesting topic in the level of gene expression in the ball pythons is the variation among the BEL morph (blue-eyed leucistic). The BEL individual with both parents is a Mojave morph, or called Super Mojave, shows pale black color on the head, as shown in Figure 5. While the BEL individual with parents is not both Mojave morph, such as the Butter morph, Phantom morph, and Russo morph, it displays an entirely white body with no pale black in the head. This variation indicates differences in melanin synthesis. This phenomenon is remarkable. In future work, we will determine the level of TYR gene expression in the BEL variant.

While PCR and qPCR are powerful molecular techniques for distinguishing between heterozygous of the albino and piebald morphs of the ball pythons to the wild type (Kokiattrakool et al., 2024; Kumsiri et al., 2025). These studies are the first reports to differentiate between the phenotype of the heterozygous of the recessive gene and wild type in the ball pythons using PCR and qPCR. However, PCR and qPCR have several drawbacks, such as requiring expensive and complex equipment and being time-consuming (Kanchanaphum, 2018). To diminish these limitations, loop-mediated isothermal amplification (LAMP) can be used. LAMP is one of the efficient molecular techniques for *in vitro* amplifying DNA, like PCR. There are many applications for the LAMP technique, such as Kanchanaphum (2018), who used LAMP to determine human DNA from a blood sample. To improve the efficiency and sensitivity of the LAMP, qLAMP or quantitative LAMP has been developed. There are many studies and applications of qLAMP. For instance, the aflatoxin-producing Aspergillus in peanut and dried shrimp samples were detected by qLAMP (Kumsiri and Kanchanaphum, 2020), and Kumsiri and colleagues (Kumsiri and Kanchanaphum, 2021) applied qLAMP to identify the SRY gene in human male DNA from blood strain samples. and qLAMP have an advantage over PCR and qPCR, so qLAMP may be improved and modified for differentiation between heterozygous of the recessive gene that linked to the morph of ball pythons, including albino, clown, or piebald and wild type.

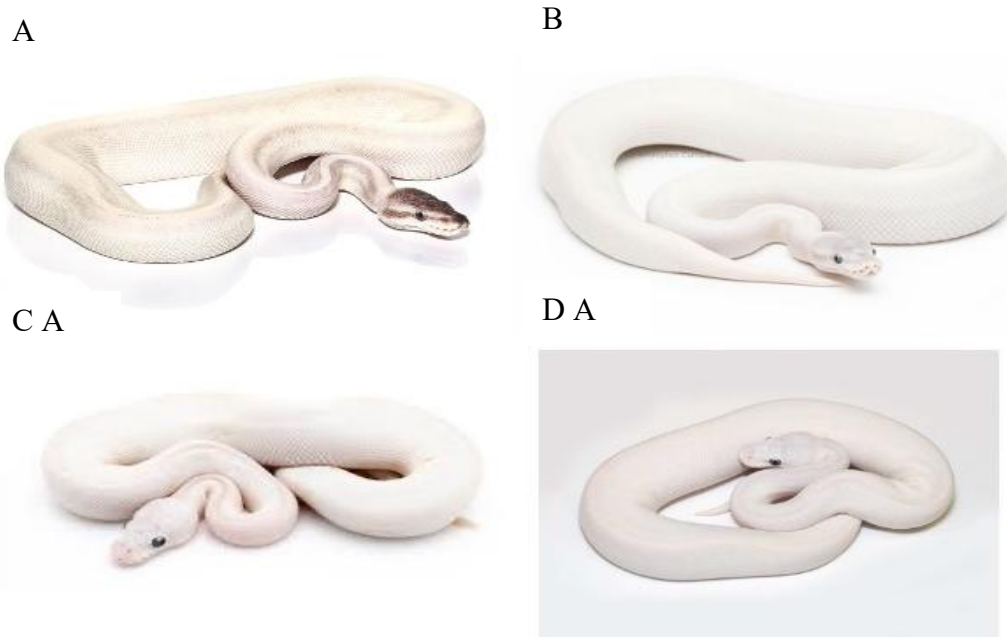

Figure-5. The variation of BEL. A is BEL (Mojave-Mojave), B is BEL (Butter-Butter), C is BEL (Butter-Mojave) and D is BEL (Phantom-Russo).

Conclusion

This study is the first report on the different expression of the TFEC gene in the variant type of the piebald ball python. In the low white piebald group, the reduction of TFEC gene expression does not exceed 5-fold. At the same time, the reduction in TFEC gene expression in the medium white is approximately 5- to 10-fold. The high white piebald group shows the highest reduction of the TFEC gene expression, exceeding 17-fold.

Acknowledgements

We would like to sincerely thank Mr. Stewart Miller for critically correcting English grammar.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: This work was supported by the Fundamental Fund, Thailand Science Research and Innovation (TSRI).

Ethical Approval Statement

The study received approval from the Ethics Review Board for Animal Research at Rangsit University prior to the commencement of the experiment (RSU-AEC 001-2022).

Contribution of Authors

Sophonnithiprasert T: Contributed to sample collection, conducted laboratory experiments, performed data analysis and wrote the initial draft of the manuscript

Kumsiri R: Participated in the laboratory experiments and data analysis.

Kanchanaphum P: Supervised the project, secured funding, conducted laboratory experiments, performed data analysis and interpretation and critically revised the manuscript for intellectual content.

All authors have read and approved the final draft of the manuscript for submission.

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