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RESEARCH ARTICLE

Genomic regions associated with the sex-linked inhibitor of dermal melanin in Silkie chicken

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Abstract A unique characteristic of the Silkie chicken is its fibromelanosis phenotype. The dermal layer of its skin, its connective tissue and shank dermis are hyperpigmented. This dermal hyperpigmentation phenotype is controlled by the sex-linked inhibitor of dermal melanin gene (*ID*) and the dominant fibromelanosis allele. This study attempted to confirm the genomic region associated with *ID*. By genotyping, *ID* was found to be closely linked to the region between GGA_rs16127903 and GGA_rs14685542 (8406919 bp) on chromosome Z, which contains ten functional genes. The expression of these genes was characterized in the embryo and 4 days after hatching and it was concluded that *MTAP*, encoding methylthioadenosine-phosphorylase, would be the most likely candidate gene. Finally, target DNA capture and sequence analysis was performed, but no specific SNP(s) was found in the targeted region of the Silkie genome. Further work is necessary to identify the causal *ID* mutation located on chromosome Z.

Keywords sex-linked inhibitor of dermal melanin (*Id*), Silkie, chromosome Z

1 Introduction

The genetics of skin coloration has been studied in many species. For example, in relation to premature grayhair and susceptibility to melanoma in horses [1], the multiple genomic regions implicated in the stripes and spots patterning the coats of domestic cats [2], and the sex-linked yellow color in the Syrian hamster [3]. In chickens, the genetics of plumage [4] and skin [5] has been investigated.

The Silkie chicken (*Gallus gallus*) is the most studied Chinese breed because it has some interesting anatomical characteristics, such as the crest, walnut comb, blue earlobes, beard, silkie-feathering trait, feathered legs and polydactyly [6,7]. In particular, the pigmentation of the dermal layer of its skin and shank, and its muscles and connective tissue [8] is a most noteworthy trait, and this breed has served as a model to identify genes that regulate melanocyte migration.

The melanocyte is the main type of dermal cell containing melanin. Melanoblasts are precursors of melanocytes, and during early embryogenesis, they originate from the neural crest [9]. In avian embryos, neural crest cells migrate from the trunk in two waves [10], one via the ventral pathway and the other via the dorsolateral pathway [11]. The melanoblasts of Silkie chickens can also reach the ventral regions of the embryo [12]. This generalized mesodermal pigmentation is a consequence of environmental factors that promote the abnormal migration of melanoblasts and their proliferation and differentiation [13], which in turn may be controlled by the inhibitor of dermal melanin (*ID*) and fibromelanosis (*FM*) loci [14].

In Silkie chicken, the hyperpigmentation phenotype is closely related to the sex-linked incompletely dominant inhibitor of dermal melanin (Id/id^+) and the autosomal dominant fibromelanosis (Fm/fm^+) loci [14,15]. *Id* has an epistatic effect on *Fm,* and pigmentation of the shank in the dermis occurs in the presence of id^+ and *Fm* with id^+ causing hyperpigmentation. Linkage analyses showed that *Id* is located near the end of the long arm of chromosome Z (chrZ) [16–20]. Dorshorst et al. [21] performed a genome-wide single nucleotide polymorphism (SNP)-trait association analysis to identify the genomic regions in which *ID* and *FM* are located. They identified SNPs that are associated with *ID* between 67.1 and 72.3 Mb on chrZ, but this region contains many genes.

Starting in 2009, we have worked to establish crossed chicken breeds to use for the identification of genes that are genetically related to *ID.* Herein we report that *ID* is associated with a chrZ region that contains ten functional genes, including *MTAP*, which encodes methylthioadenosine.

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2 Materials and methods

2.1 Ethics statement

All animal work was conducted according to the Guidelines for the Care and Use of Experimental Animals by the Ministry of Science and Technology of the People's Republic of China (Approval number: 2006-398). Blood samples were collected from the brachial veins of the chickens using a standard venipuncture procedure approved by the Animal Welfare Committee of the China Agricultural University (Permit Number: XK622).

2.2 Animals

As a consequence of the epistatic interaction between *ID* and *FM*, a mapping population of chickens was developed to allow for individual segregation of *ID* and a clear classification of the shank dermal color phenotypes. Five male Youxima chickens (fm^+/fm^+, id^+/id^+) were mated with 12 female Sanhuang chickens (fm^+/fm^+, Id/w). Two F_1 generation males (fm^+/fm^+, Id/id^+) were chosen. Each was mated with six F_1 generation non-half-sib family female chickens (fm^+/fm^+, id^+/w) (Fig. 1), which allowed for segregation of *Id* in the fm^+ background in 342 F_2 individuals (both male and female). The trait phenotype of shank color was recorded at 4 and 12 weeks (Fig. 2).

F_0 (Youxi Partridge) ♂ fm fm/$Z^{id}Z^{id}$ × ♀ fm fm/Z^{Id} W (Sanhuang)

F_1 ♂ fm fm/$Z^{Id}Z^{id}$ × ♀ fm fm/Z^{id} W

F_2 fm fm/$Z^{Id}Z^{id}$: fm fm/$Z^{id}Z^{id}$: fm fm/Z^{id} W : fm fm/Z^{Id} W
=1 : 1 : 1 : 1

Fig. 1 Founding breeds for the mapping populations

White *Id* | Yellow *Id* | Cyan id^+ | Green id^+

Fig. 2 Shank color of crosses (F_2 generation) at 12 weeks

DNA samples from adults of other breeds were obtained from the Poultry Institute of Jiangsu Province, Chinese Academy of Agricultural Sciences, including the *ID* breeds, Jinhu Silkie and Kuaida Silkie, and the normally pigmented breeds, Anak, White Recessive, Qingyuan ma, Gushi, Wahui, and Cobb Broiler. DNA samples from Silkie and White Leghorn embryos were obtained from the chicken farm at the China Agricultural University.

2.3 Genotyping

Fifty-seven SNPs (Appendix A, Table S1, WUGSC2.1/galGAL3) between 67.1 and 72.3 Mb on chrZ [21] were used for genotyping the F_1 and F_2 generations of the crossed population. Each genomic DNA sample was diluted to 30 ng·μL^{-1} in double-distilled water and detected by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. To construct multilocus linkage maps for *ID*, CRI-MAP (Version 2.4) (http://www.animalgenome.org/tools/share/crimap/) was used.

2.4 RNA isolation and real-time quantitative PCR

Tissue from Silkie and White Leghorn chickens was obtained at embryonic times of 1.5, 3, 5, 8 and 13 days, and at 4 days after hatching. The embryonic time period represents the gradual change in pigmentation (data not shown). Beginning at embryonic day 5, tissue was collected from the head, heart and hind legs. At least three biological replicates of each breed were collected per time point. Tissue was homogenized with a TissueLyser LT (QIAGEN, Dusseldorf, Germany) in 1 mL TRIzol reagent (Tiangen, Beijing, China), and RNA was isolated according to the manufacturer's protocol. The real-time quantitative PCR (qPCR) primer sequences are shown in Appendix B-Table S2. Total RNA (1 μg) from each sample and M-MLV reverse transcriptase (Promega, Beijing, China) were used to synthesize first-strand cDNA. qPCR was performed using Roche SYBR Green–based real-time qPCR kit reagents, a Roche LightCycler480 instrument, 30 ng cDNA, and 3 pmol of each primer in a total volume of 15 μL. Thermal cycling parameters used [4] were the default settings, and the PCR products were subjected to melting curve analysis. The Basic Relative Quantification module of LightCycler480 software was used to analyze the data with the associated CT algorithm. Expression for each sample was normalized to glyceraldehyde 3-phosphate dehydrogenase expression. The results for the hyperpigmented and normally pigmented chickens were tested for significance using the unpaired *t*-test. Error bars in Fig. 3 represent the 95% confidence interval.

2.5 DNA capture and sequencing data analysis

DNA samples from 18 Silkie, 21 Jinhu Silkie, 20 Gushi,

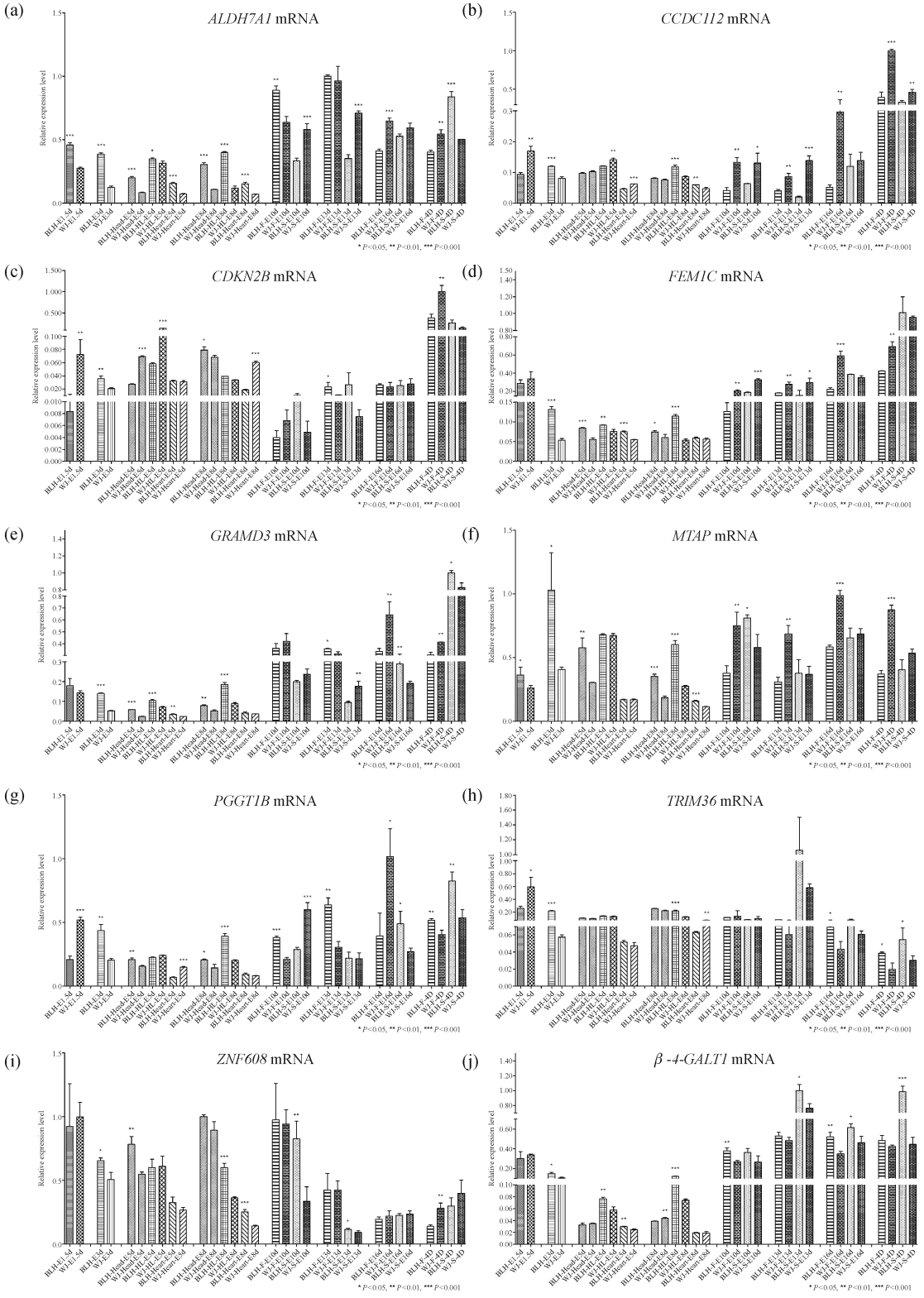

Fig. 3 The results of Q-PCR analysis of the expression of ten target functional genes. (a) *ALDH7A1* mRNA;(b) *CCDC112* mRNA; (c) *CDKN2B* mRNA; (d) *FEM1C* mRNA; (e) *GRAMD3* mRNA; (f) *MTAP* mRNA; (g) *PGGT1B* mRNA; (h) *TRIM36* mRNA; (i) *ZNF608* mRNA; (j) *β-4-GALT1* mRNA. BLH: White Leghorn. WJ: Silkie. * means $P < 0.05$. ** means $P < 0.01$. *** means $P < 0.001$. These P values are compared between BLH and WJ in each time and tissue. E: embryo. 4D: the 4th day after born. HL: hind-leg. F: shank skin. S: skin.

21 White Leghorn, 20 Cobb Broiler, 20 Beijing fatty, 20 Wahui, and 22 White Recessive chickens were pooled as breed-specific samples. An Agilent SureSelect DNA Capture array was designed according to the manufacturer's protocol to capture the targeted genomic region on chrZ from 80659505 bp to 82097083 bp as shown in the resequence reference assembly for chrZ [22], and libraries for the targeted genome were collected using the Agilent SureSelect Target Enrichment system. IlluminaHiSeq 2000 (Illumina, San Diego, CA, USA) mate-pair sequencing was performed with these libraries by BerryGenomics Company (Beijing, China). The reads were mapped onto the chicken genome resequence reference assembly.

3 Results and discussion

3.1 The genomic region associated with *ID*

Dorshorst and colleagues mapped the *ID* locus to the 67.1–72.3 Mb regions of chrZ [21]. Youxima and Sanhuang chickens were crossed to segregate the *Id* allele in 342 F_2 individuals. The 67.1–72.3 Mb region of chrZ was refined by using 57 markers in the F_1 and F_2 generations (markers are according to WUGSC 2.1/galGAL3 (the May 2006 assembly)). By CRI-MAP (2.4) analysis, the multilocus linkage maps was constructed about *ID* and it found that *ID* is closely linked with GGA_rs16127903 and GGA_rs14685542. Then we isolated the 1346191 bp region of chrZ that is completely associated with *ID* according to genotyping. Bellott and colleagues [22] resequenced chrZ of chicken in 2010, and the length of chrZ was increased to 83952565 bp. Therefore, the GGA_rs16127903 to GGA_rs14685542 sequence was used for a BLASTN analysis. In that region, ten functional genes and four "Z amplicons" gene families were found: *ADCY10Z*, *C2Orf3Z*, *MRPL19Z*, *RICSZ*. Only ten functional genes were examined because these four families contain hundreds of copies of their genes and constitute approximately one-third of the protein-encoding genes on chrZ.

3.2 Functional gene expression

The ten functional genes examined were *ALDH7A1* (aldehyde dehydrogenase 7A1), *CCDC112* (coiled-coil domain containing 112), *CDKN2B* (cyclin-dependent kinase inhibitor 2B), *FEM1C* (fem-1 homolog c), *GRAMD3* (GRAM domain-containing 3), *MTAP* (methylthioadenosinephosphorylase), *PGGT1B* (protein geranylgeranyltransferase type I, beta subunit), *TRIM36* (tripartite motif-containing 36), *ZNF608* (zinc finger protein 608), and *β-4-GALT1* (beta-1,4-galactosyltransferase, polypeptide 1). These genes were all expressed between incubation on day 1.5 through to 4 days after hatching, with no significant different in the expression levels of *β-4-GALT1*, *TRIM36* and *ZNF608* during that time. Before embryonic day 10, the expression of *CDKN2B* and *GRAMD3* was significantly greater in Silkie embryos than in White Leghorn embryos. Conversely, during the same time period, the expression of *MTAP, ALDH7A1* and *FEM1C* was significantly greater in White Leghorn embryos than in Silkie embryos. After embryonic day 10, the expression of *CCDC112* in the shank of Silkie embryos was significantly greater than in the White Leghorn embryos, but expression of *MTAP, ALDH7A1* and *FEM1C* was significantly greater in Silkie embryos than in White Leghorn embryos, which represents a reversal of the expression levels found before day 10 (Fig. 3). ALDH7A1 is reported to cause pyridoxine-dependent seizures [23]. GRAMD3 appears in human retinal pigment epithelium [24]. PGGT1B is necessary in skin keratinocytes [25]. TRIM36 may interact with the kinetochore protein CENP-H and delay cell cycle progression [26]. ZNF608 is sequentially related to Drosophila brakeless (Brakeless, also known as Scribbler or Master of thickveins, it is a nuclear protein of unknown function.) [27]. β-4-GALT1 has been suggested to promote stable lamellipodia formation [28], but in our experiment, the results of expression of *β-4-GALT1* differed from previous findings, because there was no significant different between Silkie and White Leghorn embryos. Thus it is suggested that β-4-GALT1 controls stable lamellipodia formation, which would be inconsistent with melanoblast migration in hyperpigmented Silkie chickens [29,30]. Although FEM1 family proteins are conservative in many species, such as humans, mice and zebrafish [31], *FEM1C*, is necessary for sex determination only [32], and therefore *FEM1C* was not considered to be a candidate for *ID*. *CDKN2B* and *MTAP* are involved in melanin formation or melanoma proliferation [33,34]. *MTAP* is a housekeeping gene in normal cells, but its expression decreases in melanomacells, thereby promoting melanoma cell proliferation. It is speculated that *MTAP* might be ID because MTAP activity is related to melanoma proliferation and the expression of *MTAP* was significantly greater in White Leghorn embryos than in Silkie embryos.

3.3 Target DNA capture and sequencing

By target DNA capture and sequencing, many SNPs were found in the target region. Given that *ID* is inherited in an X-linked recessive fashion, Silkie, Jinhu Silkie and Gushi chickens will be id^+/id^+ homozygotes, and the White Leghorn, Cobb Broiler, Beijing fatty, Wahui and White Recessive reference breed will be *Id/Id* homozygotes. Based on the results of the sequence capture study, we identified 53 homozygous SNPs common to the Silkie, Jinhu Silkie and Gushi chickens not found for the reference breeds (Table 1).When consideration of the genotype was discounted, only three candidate SNPs remained:ChrZ_80762601(A/G), ChrZ_80813721(T/C) and ChrZ_81683233(A/T) (Table 2). However, these SNPs are

Table 1 Sequencing data based on genotype

Chromosome	Relative locus	Silkie–Jinhu and Silkie–Gushi shared homozygous SNPs		Genotypes of the reference breeds				
		Ref	Alt	Cobb Broiler	White Leghorn	Beijing fatty	Wahui	White Recessive
chrZ	2321	A	G	1/1	1/1	1/1	–	1/1
	5321	A	G	1/1	1/1	–	–	1/1
	40214	A	G	1/1	1/1	–	1/1	1/1
	72985	G	C	1/1	1/1	1/1	0/1	1/1
	83822	G	C	1/1	–	1/1	1/1	1/1
	84032	T	A	1/1	1/1	1/1	–	1/1
	88662	A	C	1/1	1/1	1/1	1/1	0/1
	118162	T	C	1/1	1/1	–	1/1	–
	191536	A	G	1/1	–	–	1/1	1/1
	192350	C	G	–	0/1	1/1	0/1	–
	221100	C	G	1/1	1/1	0/1	1/1	1/1
	221157	C	T	0/1	–	0/1	1/1	0/1
	221172	A	C	–	–	–	1/1	1/1
	244086	C	G	1/1	1/1	1/1	1/1	1/1
	254088	T	G	1/1	–	1/1	1/1	0/1
	254178	C	A	1/1	1/1	1/1	1/1	0/1
	280024	A	G	–	1/1	1/1	1/1	1/1
	283040	C	T	–	1/1	1/1	1/1	1/1
	341728	A	T	1/1	1/1	1/1	1/1	1/1
	354810	A	C	1/1	1/1	0/1	0/1	1/1
	354825	A	C	1/1	1/1	–	–	–
	409749	A	G	1/1	1/1	1/1	–	1/1
	460397	C	T	1/1	1/1	1/1	1/1	1/1
	460403	C	T	1/1	1/1	1/1	1/1	1/1
	460407	A	C	1/1	1/1	1/1	1/1	1/1
	463090	C	T	–	–	0/1	–	1/1
	468704	C	T	1/1	1/1	1/1	1/1	1/1
	538448	T	A	0/1	1/1	1/1	–	0/1
	538453	G	A	0/1	1/1	1/1	1/1	0/1
	549422	T	C	1/1	–	–	1/1	0/1
	666040	A	G	1/1	0/1	0/1	1/1	0/1
	729694	A	G	1/1	1/1	0/1	0/1	0/1
	729950	G	A	1/1	1/1	1/1	0/1	0/1
	733499	G	C	1/1	0/1	1/1	1/1	–
	740135	T	C	1/1	1/1	1/1	0/1	0/1
	743503	T	C	1/1	–	–	–	–
	761539	G	A	1/1	1/1	0/1	1/1	0/1
	782432	C	T	1/1	1/1	1/1	1/1	0/1
	865966	T	A	1/1	–	0/1	1/1	1/1
	954985	A	C	0/1	–	1/1	1/1	1/1
	955036	A	C	1/1	–	1/1	1/1	1/1
	955067	C	A	0/1	1/1	1/1	1/1	1/1

(*Continued*)

Chromosome	Relative locus	Silkie–Jinhu and Silkie–Gushi shared homozygous SNPs		Genotypes of the reference breeds				
		Ref	Alt	Cobb Broiler	White Leghorn	Beijing fatty	Wahui	White Recessive
chrZ	967807	A	C	1/1	–	1/1	1/1	1/1
	996017	G	C	–	–	–	–	–
	1088274	T	C	–	1/1	0/1	1/1	0/1
	1094160	C	T	1/1	1/1	1/1	1/1	0/1
	1233167	T	C	1/1	1/1	1/1	–	–
	1255948	T	A	1/1	–	0/1	1/1	0/1
	1255959	C	T	1/1	–	1/1	0/1	0/1
	1255999	A	G	1/1	1/1	1/1	1/1	0/1
	1256029	A	T	1/1	1/1	–	–	0/1
	1363748	G	A	1/1	–	0/1	0/1	0/1
	1400989	C	G	–	1/1	–	1/1	–

Note: 1/1 denotes homozygous minor allele; 0/1 denotes heterozygous minor allele; – denotes homozygous reference allele.

heterozygote in the Silkie, Jinhu Silkie and Gushi chickens, which is inconsistent with the theoretically expected inheritance pattern. We also performed an InDel analysis but after comparison with the reference reed sequences, the initial 10 candidate InDels were not present (Table 3).

Table 2 Sequencing data without consideration of the genotype

	Relative locus [position]	Silkie–Jinhu and Silkie–Gushi shared SNPs		Genotype			Genotypes of the reference breeds				
		Ref	Alt	Jinhu	Gushi	Silkie	Cobb Broiler	White Leghorn	Beijing fatty	Wahui	White Recessive
chrZ	103096	A	G	0/1	0/1	0/1	–	–	–	–	–
	154216	T	C	1/1	0/1	0/1	–	–	–	–	–
	1023728	A	T	0/1	0/1	0/1	–	–	–	–	–

Note:1/1 denotes homozygous minor allele; 0/1 denotes heterozygous minor allele; – denotes homozygous reference allele.

Table 3 InDel sequences

	Relative locus [position]	Silkie–Jinhu and Silkie–Gushi shared Indels	
		Reference allele	Alternative allele
chrZ	42365	TTTTTGTTTTGTT	TTTTTGTT
	143621	ATT	ATTCTT
	234203	GTCTT	GTCTTCTT
	327975	GTCATTC	GTCATTCATTC
	537090	AT	ATGTGTGTGT
	745905	GAATTCATCCAAATTCATCCA	GAATTCATCCA
	783875	C	CAAGTT
	1181206	GGT	GGTGT
	1341702	TGAAGAAGAAGAAGAAGAAGAAGAAGAAG	TGAAGAAGAAGAAGAAGAAGAAGAAG
	1429331	GGT	GGTGT

4 Conclusions

Id has an epistatic effect on *Fm,* pigmentation of the shank dermis in chickens occurs with id^+ and *Fm* with id^+ causes hyperpigmentation in the Silkie chicken [7,8]. Given that id^+ is homozygous in Silkie chicken, we speculated that the gene corresponding to *ID* in our targeted region would be expressed at a higher level in Silkie than in White Leghorn chickens. *ID* should be expressed during early embryo development because melanocytes are present by day 3 of embryo development in Silkie chickens and can be observed by eye from day 8. Considering the functions of the proteins encoded by the ten genes in our targeted chrZ region and their expression levels during embryonic development, it seems possible that *MTAP* would be *ID*.

To attempt to identify the causative mutation we performed a target DNA capture and sequencing analysis based on genotype and without consideration of the genotype. We also performed an InDel analysis. However, given the theory behind target DNA capture and the complex structure of chrZ, the causal mutation could not be unambiguously identified. Further work is necessary to identify this mutation.

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Compliance with ethics guidelines Ming Tian, Rui Hao, Suyun Fang, Yanqiang Wang, Xiaorong Gu, Chungang Feng, Xiaoxiang Hu and Ning Li declare that they have no conflict of interest or financial conflicts to disclose.

All applicable institutional and national guidelines for the care and use of animals were followed.

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