Stumpy Limb—An Embryonic Lethal Mutation in Japanese Quail (*Coturnix coturnix japonica*)

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An embryonic lethal mutant was found in Japanese quail and named “stumpy limb (SL)”. All SL embryos died at pre-hatching stages, showing brachycephaly, a thickened neck, short upper and lower beaks, and short and thick extremities, while their body length was similar to that of the normal embryos. Observations on the skeleton revealed a globular skull, unusual curvature of the *Processus palatinus maxillaris* of the upper beak, and shortening and thickening of the appendicular bones. Some embryos showed a bending of the humerus, femur and/or tibiotarsus. Abnormality was more conspicuous in the leg bones than in the wing bones. No conspicuous differences were observed in the vertebrae between the SL and normal embryos. A genetic analysis suggested that the mutation is controlled by an autosomal recessive gene, for which the gene symbol *sl* was proposed. — KEY WORDS : embryonic lethality, Japanese quail, limb abnormality, mutant, skeletal abnormality

In May, 1985, an abnormal embryo showing brachycephaly, a thick neck, short beaks, and short and thick limbs was found in Japan-Taiwan-mixture (JTM) strain of Japanese quail. Breeding of the JTM strain began in 1982 with F₁ hybrids of commercial quail from Japan and Taiwan. The abnormal embryo was first discovered at the 11th generation and thereafter the same abnormality was sporadically observed. The abnormal embryos were regarded as mutants and named “stumpy limb (SL)”. The SL mutants never hatched out of the egg shell, therefore the mutation was suspected to be accompanied by complete embryonic lethality.

In the domestic fowl, several mutants showing similar characteristics as the SL mutant have been reported, e.g., micromelia [2], chondrodystrophy [16], nanomelia [17], and so on. In the Japanese quail also, similar mutants have been discovered, i.e., micromelia

[13] and chondrodystrophy [8]. However, they were all discovered in the United States of America. The SL is the first micromelia-like mutant that was discovered in Japan.

The present paper describes morphological characteristics of the SL mutant of Japanese quail and its mode of inheritance.

Materials and Methods

Intra-JTM-strain matings were set up at the age of 40–60 days in each generation. The matings that produced SL mutant embryos were selected for production of eggs for the experiment. General care of quail is described elsewhere [20]. Eggs were incubated at about 37.5°C and candling was performed at 10 days of incubation. Dead embryos were examined and their stages of death were roughly estimated by their size and external appearance. At 19 days of incubation, observation was

performed for external appearances of both newly hatched chicks and embryos failing to hatch.

Observation of skeletons was performed with embryos at 15 days of incubation. After examination of external appearances and removal of the yolk, normal and mutant embryos were weighed and transferred to skeletal observation. The skeleton was observed under a dissecting microscope after stained with alizarin red S. The staining was performed by the same method as reported in the previous paper [21]. Measurement was performed with the stained bones for the size of the humerus, radius, ulna, carpometacarpus, femur, tibiotarsus, and tarsometatarsus. The results were analyzed by Duncan's New Multiple Range Test based on a one-way analysis of variance.

The pedigree of the JTM strain was analyzed to investigate the mode of inheritance of the SL character. In addition, segregation ratio of the mutant and normal embryos was investigated among offspring derived from the matings that had produced at least one mutant.

Results

Mutant characters : Externally, stumpy limb (SL) embryos were characterized by brachycephaly, short beaks, thick neck, and short and thick extremities (Fig. 1). The legs were markedly short and thick. This was the most pronounced abnormality of the SL embryo. The wings were similarly short and thick, but to a lesser extent. In spite of these abnormalities, body length (from the head top to tail) of the SL embryos was the same as that of the normal embryo (Fig. 1).

All of 26 SL embryos observed at the 19th day of incubation (hatching day) could not hatch out of the egg shell. However, the majority of them had drawn the yolk into the abdominal cavity. Twenty of the 26 SL embryos were already dead, whereas 6 embryos were alive and had opened a small hole in the egg shell. In contrast, all of 7 SL embryos observed at 15 days of incubation were alive.

Table 1 shows body weight of normal and SL embryos at 15 days of incubation. The SL female was the heaviest and the SL male was the lightest. The sex difference in mean body weight was significant ($P < 0.05$). While,

Table 1. Body weight of SL mutants and their normal siblings at 15 days of incubation (g, mean $\pm$ SD)

SL mutant		Normal	
Female	Male	Female	Male
5.6 $\pm$ 0.2 (3)	5.1 $\pm$ 0.1 (4)	5.3 $\pm$ 0.3 (7)	5.4 $\pm$ 0.3 (10)

The numeral in parentheses means the number of samples examined. The difference between the SL female and SL male is statistically significant ($P < 0.05$, Duncan's New Multiple Range Test). The differences in all other combinations are not significant.

normal embryos showed intermediate body weight. No significant difference was seen between normal embryos and SL females or between normal embryos and SL males.

The SL embryos showed striking skeletal abnormalities (Fig. 2). The skull was more globular than the normal. The *Processus palatinus maxillaris* of the upper beak was curved downward and showed "parrot beak"-like appearance. However, shortening of the lower beak was not pronounced. The long bones in the wing and leg were shorter and thicker than normal. Some embryos showed a bending or curvature in the humerus, femur and/or tibiotarsus. The phalanges of the leg were also reduced and thickened, on the contrary those of the wing seemed to be quasi-normal.

Measurement was performed for length and mid-shaft width of long bones to reveal the degree of the shortening and thickening. Results are summarized in Table 2. Obvious differences were recognized between the SL mutants and their normal siblings excluding three exceptions, *i.e.*, no significant differences were seen in width of the radius and two kinds of carpometacarpi between the SL male and normal male sibling. Sex differences were generally observed in the SL mutant, while the normal sibling showed no significant sex differences. In the SL mutant, significant differences were seen in length and width of several bones between left and right sides, *i.e.*, in regard to the humerus length and tibiotarsus width in the male and radius width in the female. In contrast, normal siblings showed no significant differences in laterality for all bones examined. Table 3 shows ratios of the SL mutant to the normal for each appendicular bone. Reduction in length was more conspicuous

Table 2. Length and width of the appendicular bones in SL and normal embryos at 15 days of incubation (mm, mean±SD)

Bones	SL mutant						Normal					
	Female (3) ¹⁾			Male (4)			Female (7)			Male (10)		
	Left	Right		Left	Right		Left	Right		Left	Right	
Wing												
Humerus	L ²⁾ 4.62±0.03 ^b	4.63±0.06 ^b		3.95±0.35 ^d	4.36±0.23 ^c		5.23±0.17 ^a	5.24±0.17 ^a		5.16±0.20 ^a	5.15±0.16 ^a	
	W 0.77±0.03 ^a	0.77±0.06 ^a		0.75±0.11 ^{ab}	0.71±0.03 ^b		0.61±0.02 ^c	0.61±0.02 ^c		0.61±0.02 ^c	0.62±0.03 ^c	
Radius	L 3.40±0.15 ^b	3.40±0.17 ^b		3.20±0.12 ^c	3.19±0.15 ^c		4.14±0.11 ^a	4.12±0.10 ^a		4.08±0.16 ^a	4.06±0.16 ^a	
	W 0.38±0.03 ^a	0.35±0.05 ^b		0.34±0.05 ^{bc}	0.33±0.03 ^{bd}		0.30±0.00 ^d	0.30±0.00 ^d		0.31±0.02 ^{cd}	0.31±0.03 ^{cd}	
Ulna	L 3.97±0.08 ^b	3.98±0.03 ^b		3.70±0.11 ^c	3.65±0.07 ^c		4.44±0.15 ^a	4.43±0.14 ^a		4.37±0.14 ^a	4.37±0.14 ^a	
	W 0.57±0.03 ^a	0.53±0.06 ^{ab}		0.54±0.03 ^{ab}	0.51±0.03 ^b		0.46±0.02 ^c	0.46±0.02 ^c		0.46±0.04 ^c	0.45±0.03 ^c	
Carpometacarpus ³⁾	L 2.85±0.05 ^b	2.85±0.05 ^b		2.66±0.09 ^c	2.66±0.11 ^c		3.36±0.10 ^a	3.33±0.14 ^a		3.23±0.12 ^a	3.24±0.13 ^a	
	W 0.50±0.01 ^a	0.48±0.03 ^{ab}		0.44±0.05 ^{cd}	0.46±0.05 ^{bc}		0.41±0.02 ^d	0.41±0.02 ^d		0.41±0.03 ^d	0.41±0.03 ^d	
Carpometacarpus ⁴⁾	L 2.37±0.19 ^b	2.38±0.20 ^b		2.19±0.09 ^c	2.20±0.04 ^c		2.89±0.11 ^a	2.86±0.11 ^a		2.81±0.10 ^a	2.80±0.10 ^a	
	W 0.28±0.03 ^a	0.28±0.03 ^a		0.26±0.03 ^{ab}	0.26±0.05 ^{ab}		0.23±0.03 ^{bc}	0.24±0.02 ^{bc}		0.24±0.03 ^{bc}	0.22±0.03 ^c	
Leg												
Femur	L 6.78±0.29 ^b	6.72±0.19 ^b		5.93±0.38 ^c	6.33±0.35 ^{bc}		8.83±0.35 ^a	8.82±0.32 ^a		8.80±0.46 ^a	8.78±0.44 ^a	
	W 1.03±0.06 ^a	1.03±0.06 ^a		1.05±0.05 ^a	1.01±0.03 ^a		0.84±0.05 ^b	0.85±0.04 ^b		0.84±0.06 ^b	0.83±0.05 ^b	
Tibiotarsus	L 7.58±0.68 ^b	7.42±0.78 ^b		6.67±0.61 ^c	6.65±0.70 ^c		11.23±0.41 ^a	11.21±0.36 ^a		11.23±0.65 ^a	11.23±0.64 ^a	
	W 1.07±0.12 ^b	1.07±0.12 ^b		1.00±0.01 ^b	1.29±0.24 ^a		0.83±0.04 ^c	0.84±0.05 ^c		0.81±0.05 ^c	0.82±0.06 ^c	
Tarso-metatarsus	L 5.23±0.32 ^{bc}	5.38±0.23 ^b		4.92±0.56 ^{bc}	4.86±0.38 ^c		8.00±0.32 ^a	7.99±0.32 ^a		7.96±0.45 ^a	7.97±0.45 ^a	
	W 1.65±0.13 ^a	1.58±0.08 ^{ab}		1.50±0.10 ^b	1.53±0.09 ^b		1.24±0.07 ^c	1.20±0.08 ^c		1.19±0.06 ^c	1.19±0.09 ^c	

¹⁾ No. samples examined ²⁾ L and W indicate length and width, respectively ³⁾ Larger one of the two carpometacarpus
⁴⁾ Smaller one of the two carpometacarpus Means with different superscripts are significantly different ($P<0.05$, Duncan's New Multiple Range Test).

Table 3. Ratio of the SL mutant to the normal for length and width of the wing and leg bones taken from 15-day embryos

Bones		Female		Male	
		Left	Right	Left	Right
Wing					
Humerus	Length	0.88	0.88	0.77	0.85
	Width	1.26	1.26	1.23	1.15
Radius	Length	0.82	0.83	0.78	0.79
	Width	1.27	1.17	1.10 ¹⁾	1.06 ¹⁾
Ulna	Length	0.89	0.90	0.85	0.84
	Width	1.24	1.15	1.17	1.13
Carpometa-carpus	Length	0.85	0.86	0.82	0.82
	Width	1.22	1.17	1.07 ¹⁾	1.12
Carpometa-carpus	Length	0.82	0.83	0.78	0.79
	Width	1.22	1.17	1.08 ¹⁾	1.18
Leg					
Femur	Length	0.77	0.76	0.67	0.72
	Width	1.23	1.21	1.25	1.22
Tibiotarsus	Length	0.67	0.66	0.59	0.59
	Width	1.29	1.27	1.23	1.57
Tarsometa-tarsus	Length	0.65	0.67	0.62	0.61
	Width	1.33	1.32	1.26	1.29

¹⁾ The difference between the SL and normal embryos is not statistically significant (see Table 2).

in the leg bones than in the wing bones, *i.e.*, the ratio was 77-90% in the wing bones, while it was 59-77% in the leg bones. On the contrary, the increase in width in the SL skeleton was similar between the wing and leg bones. The ratio was 112-127% for the wing bones and 121-133% for the leg bones. The right tibiotarsus of the SL male showed exceptionally high value of 157%.

Mode of inheritance: It was impossible to perform mating experiments with SL mutants, because all mutants died before hatching. Therefore, the incidence of mutant embryos was investigated at 15-19 days of incubation, as mortality of embryos before 15 days of incubation was negligible. The segregation ratio of normal and mutant embryos was 96 and 33 in the progeny from 7 pairs of externally normal-looking parents that produced both normal and mutant embryos. This ratio was in good accordance with 3:1 ($\chi^2=0.02$, $0.80 < P < 0.90$). Sex ratio was normal in both normal and mutant embryos. Accordingly, it can be concluded that the stumpy limb mutant character is controlled by an autosomal re-

cessive gene. Here, it is proposed to give the gene symbol *sl* to the mutant gene.

Discussion

The stumpy limb (SL) mutant of Japanese quail was characterized by shortening and thickening of the head and appendicular skeletons and embryonic lethality at prehatching stages. And this character was found to be controlled by an autosomal recessive gene. The length of the mutant limb bones is about 60-90% of the normal in the embryos at 15 days of incubation. There is no independent epiphyseal center of ossification in long bones of birds [11]. Ossification begins at the central cylinder of bone and extends toward the ends. The ends of the bones remain cartilaginous for a while and act as elongation fronts. Ossification of long bones begins around 9-10th day of incubation in the chick [11]. This stage corresponds to 7-8th day of incubation in the Japanese quail. Therefore, it is inferred that the action of the mutant gene is expressed between 7 and 15 days of incubation.

In the chondrodystrophic embryos of the domestic fowl [16] and the micromelic embryos of the duck [1], both of which show shortening of the extremities, the abnormality of the epiphyseal cartilage of leg bones has been observed, *i.e.*, irregularity in cell arrangement and cell formation. The SL mutant may exhibit a similar histological abnormality. In the epiphyses of the SL mutant bone also, ossification might be obstructed. In other words, osteoblasts and osteoclasts might be unable to play their own proper role, leading to the shortening of the bones. On the other hand, mid-shaft width of the mutant bone was broader than the normal. This indicates that perichondral ossification may be excessive. Regulatory system for the action of osteoblasts might be abnormal in the perichondral region of the SL long bones.

Body weight and bone size of 15-day SL embryos showed significant sex difference. It is uncertain whether the difference is due to a participation of sex hormones or a mere sampling error. Further investigation would be necessary for this problem.

Laterality difference was seen in humerus length of the SL male, radius width of the SL female and tibiotarsus width of the SL male.

The differences in the humerus and tibiotarsus are thought to be due to the bending or curvature occurring in these bones. The bending portion of these bones was especially thickened, giving rise to the increase in the mid-shaft width. The reason why laterality difference was seen in the radius is unknown, for this bone showed neither bending nor curvature.

A number of embryonic lethal mutations accompanied by gross anomalies are discovered in the poultry, *e.g.*, micromelia [13], crooked neck dwarf [19], and chondrodystrophy [8] in the Japanese quail; micromelia [2], chondrodystrophy [16], crooked neck dwarf [3], and nanomelia [17] in the domestic fowl; chondrodystrophy in the turkey [10]; and micromelia in the duck [1]. Among these mutants, the micromelia of the Japanese quail and chondrodystrophy of the domestic fowl and turkey are similar to the SL mutant. Others are thought to be different in view of morphological characteristics and mode of inheritance.

The micromelic embryo of Japanese quail reported by Hill *et al.* [13] is very similar in appearance to the SL mutant. It is also characterized by short and thick extremities and the thickened neck. However, some discrepancies are present between the two mutants. The micromelic embryo dies at 11-16 days of incubation and none is found alive at hatching time. In contrast, all SL embryos were alive before 16 days of incubation and some of them survived to hatching time. Moreover, the lower mandible of the micromelic embryo is markedly reduced and the upper beak is shortened and curved, giving rise to a so-called "parrot beak" appearance. The SL mutant also shows somewhat parrot-beak-like appearance, as both the upper and lower beaks are shortened and the former curves slightly downward, but the reduction of the lower beak is not so marked. These differences may suggest that the two mutants are not genetically identical. However, there remains a possibility that differences in background genes might be responsible for the discrepancies in the lethal stage and expressivity of the beak abnormality.

The chondrodystrophic embryos of the domestic fowl [16] exhibit shortened limbs, somewhat similar to the SL mutant quail. The majority of the mutant embryos are alive at hatching time and a few of them can hatch,

contrasting with the SL quail embryos, for the majority of the SL quail embryos were dead at the hatching time and none could hatch. Chondrodystrophic embryos of the turkey [10] are also similar to the SL quail in having shortened and thickened extremities. The following differences are recognized between the two mutants. Death of the turkey embryos begins at the mid stage of incubation, but that of SL quail embryos occurred definitively just before hatching. Pronounced shortening of the lower mandible is observed in the turkey embryos, while shortening of the mandible was generally mild in the SL quail. However, these differences may reflect species differences. It would be interesting to investigate whether these mutant characters are attributed to a common biochemical disorder.

In a molecular level, collagen plays an important role in osteogenesis [12]. Collagen is classified into about 12 types [5, 12]. The most abundant of these is type I collagen, which is the major structural protein of bone, skin, vessels, and other fibrous tissues. The molecule is a triple helix composed of three chains (two identical ones known as $\alpha 1(I)$ and a similar chain known as $\alpha 2(I)$, each of which is composed of about 1,100 amino acids). The biosynthesis of type I collagen is achieved through complicated pathways [12, 14]. The gene for $\alpha 1(I)$ is on chromosome 17 and that for $\alpha 2(I)$ is on chromosome 7 in humans [15]. Collagen is formed from procollagen through many processes of modification. It is known in humans that abnormality of type I collagen gives rise to a severe skeletal defect "osteogenesis imperfecta (OI)" [6], which is known at a molecular level to be ascribed to a partial deletion of coding sequence in $\alpha 1(I)$ and/or $\alpha 2(I)$ genes and subsequent short pro- $\alpha 1(I)$ and/or pro- $\alpha 2(I)$ chains [4, 7, 9, 12, 22]. OI is classifiable into 4 types (type I-IV) according to symptoms of patients [6]. Among them type II would be of special interest in relation to the present study, since it shows perinatal lethality and is generally characterized by defective long bones in the limbs and continuously beaded ribs. According to Sillence *et al.*, the OI type II is further classified into 3 groups, A, B, and C [18]. The patient with OI type II-B is characterized as follows: (1) The disease is thought to be an autosomal recessive trait. (2) The patient shows perinatal lethality.

(3) The patient has a small chin and markedly shortened arms, forearms, and legs. (4) The humeri, radii, ulna, femora, and tibiae are short and broad. (5) Angulation of the tibiae is seen. (6) The ribs show minimal or no beading. These abnormal characteristics are extremely similar to those of the SL mutant quail. Thus, there is a possibility that the primary cause of bone abnormality in the SL mutant quail might reside in abnormality of type I and/or other-type collagen genes. The SL mutant quail would be useful for research in osteology. Especially in view of the extreme similarity mentioned above, it might be a useful animal model for the OI type II human skeletal disease.

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ニホンウズラに見いだされた致死性突然変異 “stumpy limb”の特徴および遺伝分析

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ニホンウズラの“stumpy limb”ミュータントは孵化直前の完全致死性を示し、その特徴は次のようであった。(1) 短頭症を呈し、頸部が正常なものより肥厚していた。(2) 上嘴の上縁部の湾曲が正常個体よりも強度であるため、いわゆる“parrot beak”様の外観を呈したが極端なものではなく軽度のものであった。(3) 翼および脚が正常個体に比べ短く太かった。(4) 翼および脚の骨、すなわち、上腕骨、橈骨、尺骨、手根中手骨、大腿骨、脛骨、足根中足骨、および足指骨が正常なものに比

べ短く太かったが、この異常は翼よりも脚の骨においてより顕著であった。指骨の異常はほとんどみられなかった。遺伝分析の結果、本突然変異は常染色体性の単一劣性遺伝子によって支配されていることが判明し、この突然変異遺伝子に対し遺伝子記号 *sl* を提唱した。本ミュータントは骨形成研究のための実験動物として有用であり、また、その異常形態がヒトの疾患「骨形成不全症Ⅱ型」に極めて良く似ているので、この疾患の動物モデルとなり得る可能性がある。

Explanation of Figures

Fig. 1. Stumpy limb (left) and normal (right) embryos at 19 days of incubation. (Feathers of the wings and legs have been removed for observation.) The mutant embryo shows a stumpier head, thicker neck, broader wing, and shorter and thicker leg than the normal. The mutant beak is shorter than the normal and shows strange curvature.

Fig. 2. The skeletons of normal and SL embryos at 15 days of incubation. (a, femur, b, tibiotarsus, c, tarsometatarsus, d, toe bones, e, *Processus palatinus maxillaris*, f, humerus, g, radius, h, ulna, i, carpometacarpus, j, finger bones) A : The whole skeletons of nor-

mal (left) and SL (right) embryos. The femur, tibiotarsus, and tarsometatarsus of the SL embryo are shorter and thicker than those of the normal embryo. The toe bones are also shorter and thicker than the normal. B : SL (upper) and normal (lower) skulls. The SL skull is more globular and the *Processus palatinus maxillaris* of the upper beak is more strongly curved than the normal. C : Normal (left) and SL (right) appendicular skeletons. Shortening and thickening of the long bones are more noticeable in the leg than in the wing. A bending of the tibiotarsus is sometimes observed in SL embryos.

Fig. 1

A

B

Fig. 2

C