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BIOLOGY

Spontaneous pre-axial polydactyly in Swiss mice

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ABSTRACT: *Spontaneous polydactyly has been described in several species, but only one report about it in Swiss mice. The aim of the current study was to report the spontaneous occurrence of pre-axial polydactyly in Swiss mice. Clinical examination showed one extra toe laterally to the first digit, in the plantar region, alopecia in the back, altered face growth anatomy and changed perineal region anatomy. Pre-axial polydactyly in the tibial side, fused metatarsals and Y-shaped free phalanges were evidenced in the radiographic images. Pre-axial polydactyly observed in the plantar region differed from that in reports on albino Swiss mice with post-axial polydactyly (Po/Po^{+}) phenotype featured by one extra toe in the ulnar side of one, or both, front limbs, which is the dominant feature. The observed findings highlight the importance of both clinical examinations and close attention by professionals involved in rodents' breeding on physical changes resulting from different causes, including the genetic ones, since they reveal mutations and, sometimes, new biomodels.*
Key words: *heterogeneous, genetic anomaly, laboratory animals.*

Polidactilia pré-axial espontânea em camundongos Swiss

RESUMO: *A polidactilia espontânea foi descrita em várias espécies, mas há apenas um relato em camundongos Swiss. O objetivo do presente estudo foi relatar uma ocorrência de polidactilia pré-axial em camundongos Swiss. O exame clínico revelou um dedo extra lateralmente ao primeiro dedo na região plantar, alopecia dorsal, anatomias facial e da região perineal alteradas. Nas imagens radiográficas foram evidenciados polidactilia pré-axial no lado tibial, metatarsos fundidos e falanges livres em forma de Y. A polidactilia pré-axial observada diferiu do relato existente de polidactilia pós-axial (Po/Po^{+}) caracterizado por um dedo extra no lado ulnar de um ou ambos os membros anteriores e de característica dominante. Os achados observados destacam a importância dos exames clínicos e da atenção cuidadosa dos profissionais envolvidos na criação de roedores sobre as alterações físicas decorrentes de diferentes causas, inclusive as genéticas, em revelar mutações e, às vezes, novos biomodelos.*
Palavras-chave: *heterogêneo, anomalia genética, animais de laboratório.*

INTRODUCTION

Swiss (SW) mice result from breeding performed by Dr. Lynch and Dr. Webster in 1932 and are distributed worldwide (CHIA et al., 2005). Genetic anomalies can be spontaneous in SW mice during embryogenesis and polydactyly is among these anomalies, it happens due to flaws in the polarizing activity regulatory sequence zone. Such sequencing is observed in chromosome 5 in mice and it account for ectoderm moderation during limb development (AL-QATTAN et al, 2018). Polydactyly induces the formation of extra fingers or toes that can be bony, positioned in pre-axial (radial or tibial), central (axial) and postaxial (ulnar or fibular) position; moreover it can occur in combination to other congenital syndromes (HAYES, et al 1998; HUI & JOINER, 1993; AHMED et al, 2017; UMAIR et al, 2018).

Spontaneous polydactyly has been described in several mutant mice and there is only one report on spontaneous postaxial polydactyly (Po/Po$^{+)}$ in the ulnar side of Swiss mice's forelimbs (NAKAMURA et al, 1962). The aim of the current study was to report the spontaneous occurrence of pre-axial polydactyly in Swiss mice crossbreed colony conducted in the Núcleo de Animais de Laboratório (NAL) of Universidade Federal Fluminense (UFF). The study followed all Brazilian legal requirements (BRASIL, 2008).

Two couples from the Swiss mice colony (3rd and 4th birth) generated offspring with spontaneous anatomical anomalies in 2018. In total

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20% (3/15) offspring of one of the couples was affected, 13.3% (2/15) of the other couple's offspring. The total of affected mice from both couples showed 02 male mice affected and 03 female ones. Environmental enrichment in micro isolators kept in ventilated racks made sure about mice's well-being. Room was kept under 12h light/dark photoperiod, at 21 ºC. Diet was based on balanced feed for rodents and sterile water.

Examinations were conducted in mice offspring's at the age of seventh days and all their body parameters were regular, except for one extra toe laterally to the first digit, in the plantar region in both sexes. Mice offspring postnatal development evidenced alopecia (Figure 1A) or hypotrichosis on the back, altered face growth anatomy, small eyes and half-closed eyelids (Figure 1B). The juvenile phase showed increased angle opening between forelimbs, and this feature has changed their way of walking, mainly in males, since their perineal and scrotum regions (Figure 1C) were larger than the normal. Mating was performed for one year, when mice reached sexual maturity age. However, only 01 couple generated 04 offspring, in a single delivery, with phenotype 100% equals to that of the parents.

In comparison x-ray imaging of normal SW (Figure 1D), pre-axial polydactyly in the tibial

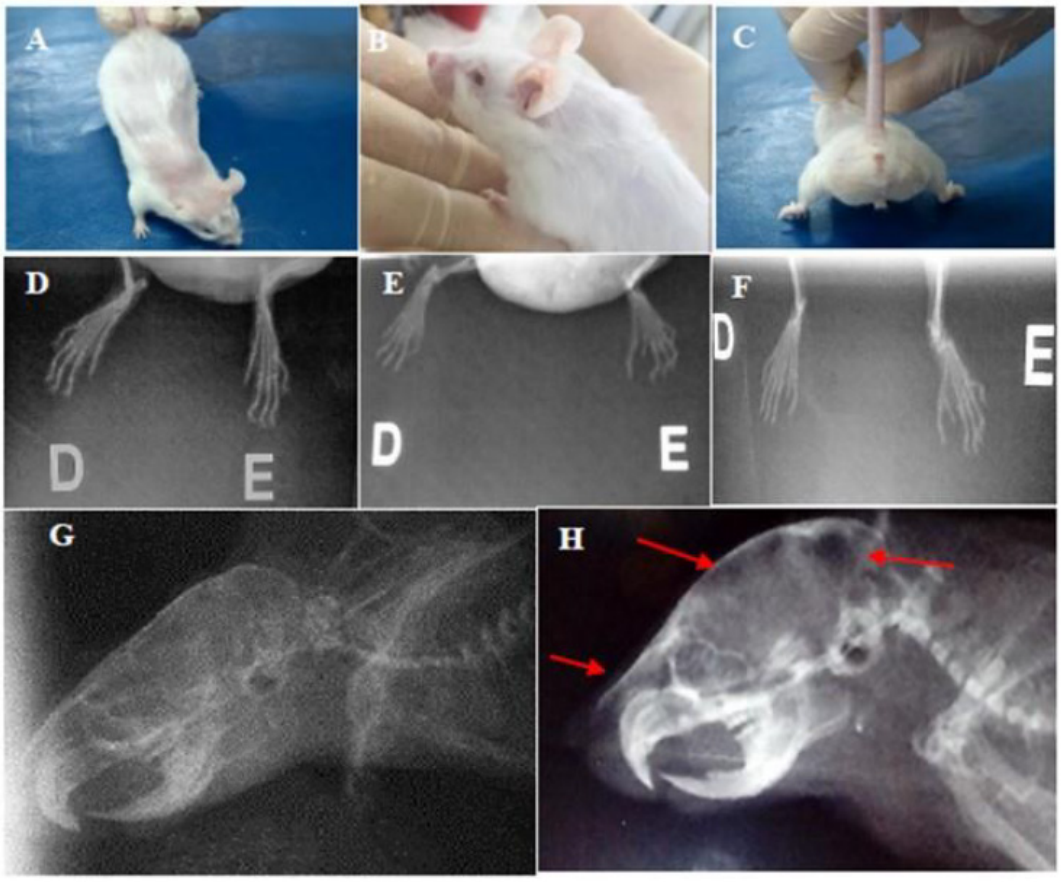

Figure 1 – Swiss (SW) mice affected by spontaneous pre-axial polydactyly. Alopecia on the back (A). Hypotrichosis, altered face growth anatomy, small eyes and half-closed eyelids (B). Increased angle opening between forelimbs with altered scrotum regions (C). X-ray imaging, dorsoventral projection toes in the plantar region in normal SW (D). Pre-axial polydactyly in the tibial side on the left foot of male SW with one extralong digit laterally to the first digit connected to the cuneiform bone and Y-shaped free phalanges in the right foot (E). X-ray imaging, female SW right and left foot with extra elongated toe laterally to the first toe and inserted in the metatarsal bone with metatarsal bone thicker in the left foot (F). X-ray imaging skull lateral projection of normal SW mouse (G). Affected SW showed rostrum shortening (arrow) and two radiolucent areas under parietal and interparietal bones (arrows) (H).

side of the plantar region was evidenced in the dorsoventral projection on the left foot of male SW with one extra-long digit laterally to the first digit and connected to the cuneiform bone. The extra toe was positioned next to the first toe also presented partially fused metatarsals and Y-shaped free phalanges in the right foot (Figure 1E). The dorsoventral projection of female right foot showed extra elongated toe laterally to the first toe. The extra toe was inserted in the metatarsal bone of the first toe, in the left foot, which made the metatarsal bone look thicker (Figure 1F). In comparison to the skull of normal SW mouse (Figure 1G), skull lateral projection showed alteration in skull bones with emphasis on the frontal bone, which showed rostrum shortening and two radiolucent areas under parietal and interparietal bones, which suggests hydrocephalus (Figure 1H).

Polydactyly is an autosomal dominant inheritance affecting several species, mainly mammals. It is a common anomaly in hands and/or feet that presents several morphological phenotypes in combination or not with other malformations and diagnosis is often given through clinical examinations completed by radiographic imaging (HUI & JOINER, 1993; AHMED et al, 2017; UMAIR et al, 2018, AL-QATTAN, 2018). Polydactyly in mice can have dominant, semi-dominant or recessive inheritance depending on the affected gene - 458 genotypes can be involved in it (MGI, 2020). The pre-axial phenotype is the most common one among spontaneous mutations; it has semi-dominant or recessive inheritance (GRÜNEBERG, 1942; CARTER, 1951, SEARLE 1964; JOHNSON, 1967; CHAN et al, 1995; YADA et al, 2002).

Pre-axial polydactyly in the plantar region on the tibial side was the radiographically found anomaly type in the current study. The present observations have differed from reports on albino Swiss mice with post-axial polydactyly (Po/Po^{+}) phenotype, which is featured one extra toe in the ulnar side of one or both front members – it is a dominant feature (NAKAMURA et al, 1962). The current research reported changes in skull bones' formation resembling heterozygous "extra toes" in mice (Xt), as well as other spontaneous mutations described in mice, which express polydactyly genes and severe syndromes associated with craniofacial bone defects and brain abnormalities (GRÜNEBERG 1942; JOHNSON, 1967; HUI & JOINER, 1993; HAYERS et al 1998; AL-QATTAN, 2018). Research conducted with Doublefoot (Dbf) mutant mice - whose mutation is dominant and account for non-viable and heterozygous homozygotes, reduced viability and fertility - reported that head and limb dysmorphogenesis, including digit bifurcation, are generated by the same signaling molecules at embryonic development (HAYES et al, 1998). Syndromes involving morphological changes in urogenital organs and in the musculoskeletal system, such as torsion of the posterior limbs and tibia reduction or loss, are also often associated with polydactyly (GRÜNEBERG, 1942; CARTER 1951; SEARLE, 1964). The percentage of affected offspring, low fertility, anatomical changes in the perineal region, scrotal pouch and increased abduction angle among hind limb of the assessed Swiss mice, was compatible to that of luxate mice (lx) (CARTER, 1951; YADA et al, 2002).

Findings observed in Swiss mice, mainly pre-axial polydactyly associated with craniofacial bone malformations, anatomical changes and alopecia, highlight the importance of both clinical examinations and attention by professionals involved in rodents' breeding on physical changes resulting from different causes, including genetics ones, that can evidence mutations and, sometimes, new biomodels.

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BIOETHICS AND BIOSSECURITY COMMITTEE APPROVAL DECLARATION

We, authors of the paper entitled "Spontaneous pre-axial polydactyly in Swiss mice"declare, for due purposes, that the project that gave rise to data of such paper has not been submitted for evaluation of the Ethics Committee of the "Federal Fluminense" University. However, we are aware of content of the resolutions of the National Council for the Control of Animal Experimentation – CONCEA (http://www.mct.gov.br/index.php/content/view/310553.html) if it involves animals. Therefore, the authors assume full responsibility for the data presented therein and are available for possible questions, should they be required by competent bodies.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The founding sponsors had no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

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