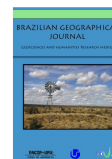




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### ARTICLES/ARTIGOS/ARTÍCULOS/ARTICLES

## A new spontaneous model of fibrodysplasia ossificans progressiva

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### ABSTRACT

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Fibrodysplasia ossificans progressiva (FOP) is a genetic disorder characterized by relentlessly progressive and seemingly uncontrollable progressive ossification of tendons, ligaments, fascia, and striated muscle with heterotopic bone formation resulting in immobilization and wheel chair confinement by age 30. Progress in its management has been compromised by lack of a natural animal model. Defleshed mammal skeletons were examined for evidence of heterotopic bone formation. The Southeast Asian mouse deer of the genus *Tragulus* was found to have an osseous sheath covering the lower back and upper thigh region consistent with the clinical definition of FOP. This heterotopic bone deposition is present in all adults males, including both wild obtained and zoo bred animals. We report the first known example of spontaneous, naturally occurring fibrodysplasia ossificans progressiva (FOP) in a non-human mammal.

*Tragulus* may offer the opportunity to examine many of the disease's most significant attributes experimentally.

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**PALAVRAS CHAVE:**

Ossificação heterotópica  
*Tragulus*  
Modelo animal  
Fibrodissiplasia ossificante

**RESUMO** – UM NOVO MODELO ESPONTÂNEO DE FIBRODISPLASIA OSSIFICANTE PROGRESSIVA. Fibrodissiplasia ossificante progressiva (FOP) é uma doença genética caracterizada por uma acentuada, progressiva e aparentemente incontrolável ossificação dos tendões, ligamentos, faciais e músculos estriados da formação de osso heterotópico resultando na imobilização em cadeira de rodas por 30 anos. Estudos mais avançados relacionados a sua gestão foi sempre comprometida pela falta de um modelo animal natural. Esqueletos de mamíferos “Defleshed” foram examinados para demonstrar a evidência de formação de osso heterotópico. O cervo-rato do sudeste asiático do gênero *Tragulus* foi diagnosticado por possuir uma bainha óssea cobrindo a parte inferior das costas e na região da coxa consistente com a definição clínica da FOP. Esta deposição óssea heterotópica está presente em todos os machos adultos, incluindo os obtidos selvagens e zoológico de animais desta linhagem. Nós relatamos o primeiro exemplo conhecido de natural de fibrodissiplasia ossificante progressiva (FOP) em um mamífero não-humano. *Tragulus* pode oferecer a oportunidade de examinar muitos dos atributos mais importantes da doença experimentalmente.

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## 1. Introduction

We report the first known example of spontaneous, naturally occurring fibrodysplasia ossificans progressiva (FOP) in a non-human mammal. The Southeast Asian mouse deer of the genus *Tragulus* (Artiodactyla: Tragulidae) have an osseous sheath covering the lower back and upper thigh region consistent with the clinical definition of FOP. This heterotopic bone deposition is sex related apparently with a genetic basis—it only occurs in males and is lacking in females; it is present in all adult males, including both wild obtained and zoo bred animals. *Tragulus* may offer the opportunity to examine many of the disease's most significant attributes experimentally.

The preparation of contemporary mammalian skeletal collections is focused on traditional structures and often does not include osteological features closely associated with the skin. The result can be exquisite preparations, but sometimes at the expense of unique osseous structures. A series of

remarkable preparations at the University of Kansas Natural History Museum highlights the osseous sheath covering the lower back and upper thigh region of the genus *Tragulus*, the Southeast Asian mouse deer (NOWAK, 1991). The sabertoothed mouse deer or chevrotains of the genus *Tragulus* (Artiodactyla: Tragulidae) are among the smallest artiodactyls. Some aspects of their ecology and distribution are fairly well understood as a few species are locally abundant; however, as nocturnal and solitary animals, most aspects of their biology are poorly known. Two species, *Tragulus javanicus* and *T. napu*, generally are recognized in the literature; however, recent systematic reviews (GRUBB, 2005; MEIJAARD; GROVES, 2004) recognized six species—*T. javanicus* from Indonesia; *T. kanchil* from China south to Malaysia; *T. napu* from Indochina, Cambodia, and Indonesia; *T. nigricans* from the Philippines; *T. vericolor* from Vietnam; and *T. williamsoni* from northern Thailand.

## **2. Materials and Methods**

*Tragulus* skeletons were macroscopically examined in the collections of the American Museum of Natural History (AMNH), Carnegie Museum (CM); Michigan State University (MSU); National Museum of Natural History (NMNH), Yale Peabody Museum (YPM), and Harvard University (MCZ).

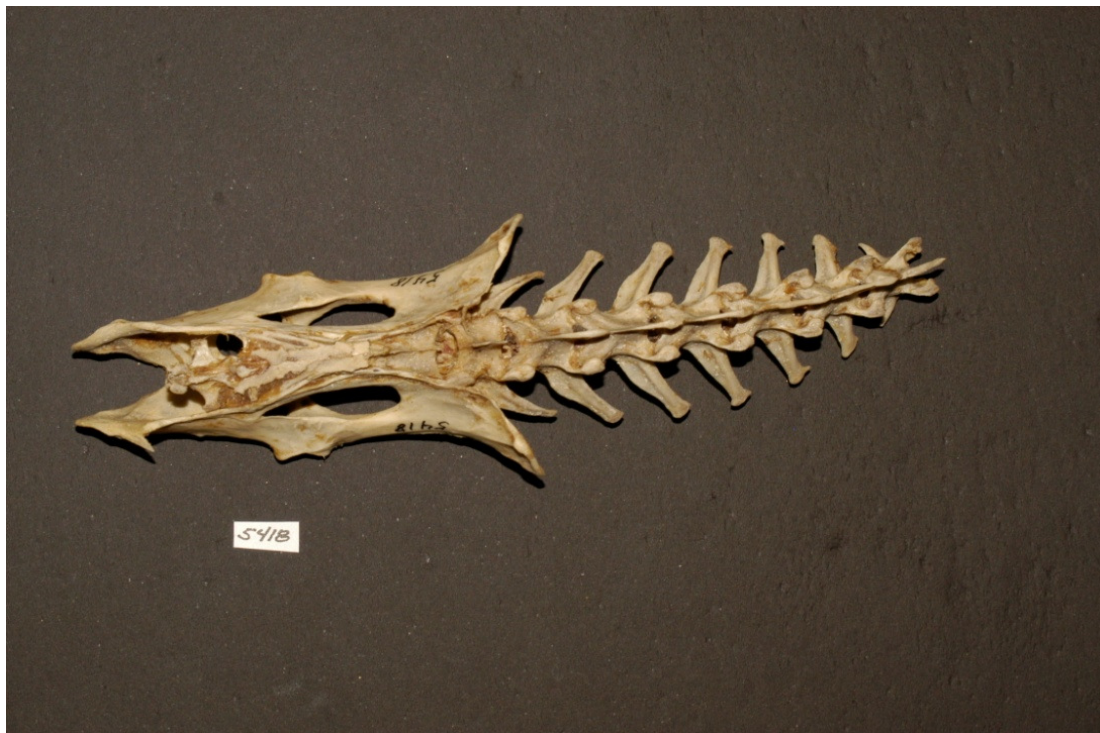
## **3. Results**

Remarkable heterotopic bone formation produced an osseous sheath extending from the pelvis to the lumbar spine and down over the thighs (Figure 1).



**Figure 1.** Dorsal and ventral view of the pelvic and abdominal region of an adult male *Tragulus napu* (KU 163960). Dermal ossifications extend from caudal-most ischiopubis to iliac crest and cephalidly from sacrum in a paraspinal distribution.

This phenomena was limited to males, but was initially overlooked, because of the tissue preparation (Figure 2). The Southeast Asian mouse deer of the genus *Tragulus* was found to have an osseous sheath covering the lower back and upper thigh region consistent with the clinical definition of FOP. This heterotrophic bone deposition is present in all adults males, including both wild obtained and zoo bred animals.



**Figure 2.** Dorsal view of 19th century preparation of an adult male *Tragulus nigricans* (KU 165574). Note residual heterotypic bone attached to sacrum. When the preparation technique was to remove all material extraneous to the skeleton as has been traditionally done, one may see no, or only minimal evidence of the bone we herein call FOP. This is exemplified in a dorsal view of wild caught specimen that was prepared in the early 1900s.

#### 4. Discussion

A remarkable skeletal sexual dimorphism is present in apparently all species of the genus *Tragulus*-an osseous sheath covering the lower back and upper thigh region in males, but lacking in females (Figures 1, 2). It is believed to function as a pelvic shield in males, which are aggressive, solitary, and engage in combat with large, saber-like canines. Perhaps because of the lack of specimens, and especially the lack of material prepared specifically to elucidate this ossified sheath, little work has been done on the ossifications. The pelvic region and sheath was originally noted (LYDEKKER, 1922) and figured (LEKAGUL; MCNEELY, 1977), albeit few details are visible. It was described as “Unique to tragulids is an ossified plate, derived from an aponeurosis (a membranous sheet of tendon) to which the sacral vertebrae attach” (VAUGHAN *et al.* 2000).

The osseous sheath is interesting as a unique anatomical feature for artiodactyls, as well as all mammals, but it may also have important medical

ramifications as a potential model for the devastating human disease, fibrodysplasia ossificans progressiva (FOP). FOP, first described by Guy Paten (1692), is a genetic disorder characterized by progressive ossification of tendons, ligaments, fascia, and striated muscle (KAPLAN, *et al.* 1994, 1996; MAHBOUBI, *et al.*, 2001, ROCKE, *et al.*, 1994). As opposed to simple calcification or deposition of calcium in crystalline form, these structures are actually composed of bone. The relentlessly progressive and seemingly uncontrollable nature of FOP results in immobilization and wheel chair confinement by age 30 in humans (COHEN, *et al.*, 1993, ROCKE, *et al.*, 1994).

Heterotopic bone in FOP forms rigid synostoses with the normal skeleton. Heterotopic refers to occurrence in an unusual part of the body. It shares with normal bone the similar histologic appearance of mature cortical and trabecular organization.

There is no established treatment for FOP and prophylactic efforts have had only limited effect (BRANTUS; MEUNIER, 1998, ZASLOFF *et al.*, 1998). Its rarity in humans precludes scientific assessment of therapeutic efficacy or even natural history of the disease. A natural animal model would allow clarification of its pathophysiology, natural history, and allow meaningful assessment of therapeutic intervention (KAPLAN, *et al.*, 2005).

*Tragulus* provides a useful model for FOP, given its reproducibility and its apparent genetic basis. It only occurs in males and was present in all the adults suitable for observation, including both wild obtained and zoo bred animals. This contrasts with a more sporadic occurrence in cats and pigs of a condition that resembles aspects of FOP (KAPLAN, *et al.*, 2005). Kaplan *et al.* (2005, p. 229) noted that “no known living animals have been available for further study.” However, a recent paper (KAN *et al.*, 2004) may provide a mouse model that along with *Tragulus* could establish the experimental basis for a controlled study of the cause(s) and treatment of FOP.

The ossifications observed in *Tragulus* mirror that seen in human FOP, especially that illustrated by the skeleton of Harry Eastlack and as illustrated in a recent cat scan (KAPLAN, 2005; TUNG; LAI, 2008). Mr. Eastlack donated his skeleton, which now resides in the Mütter Museum of The College of Physicians of Philadelphia, and provides the classic standard for recognition of FOP. The pathology described in previous spontaneous animal

models appears to be somewhat different. In cats, muscle masses and calcification in or around muscles has been described, but documentation of full heterotopic ossification seems lacking in most reports. Valentine, *et al.*, (1992) reported firm enlargement of caudal thigh and gastrocnemius muscles, with 'defined areas' of mineralization. Individual muscle fibers (not muscles) were surrounded by abnormal calcium deposits; however, there was no heterotopic bone formation. In contrast, they describe proliferative tissue with many hard, gritty or bony foci 0.1–4.0 cm in diameter (WARREN; CARPENTER, 1984). Norris *et al.* (1980) reported widespread fibrosis and ossification of skeletal muscles, primarily as spicules. However, ossification adjacent to the femur was noted, producing the appearance of a second "femur", complete with a fatty marrow cavity. Most of the observed pathology in this cat was due to calcification, not ossification. 'Mineralized' connective tissue was present as spicules in abdominal musculature and as plaques in the small intestine. Waldron *et al.* (1985) did note flat plates or cylindrical bone masses in the sporadic feline case they reported.

Similar osteological reactions have not been reported in other animals. The spontaneous occurrence of lesions in a boar (and 34 of the 115 pigs it sired) is described as parosteal fibrosis and osseous metaplasia with joint fusion, but not as heterotopic bone (SIEBOLD; DAVIS, 1967; VALENTINE *et al.*, 1992). Multiple firm enlargements on necropsy were found to be large, irregular masses of cancellous (with pseudomarrow of fatty or fibrous tissue) extracortical bone, often continuous with adjacent skeletal bone. Seibold and Davis (1967) reported showing a section at a 1944 Armed Forces Institute of Pathology conference (AFIP accession 104031) for which the consensus diagnosis was progressive myositis ossificans. Minority diagnoses included osteoma (excluded because of lesional atrophic fibrosed muscle tissue), osteosarcoma (excluded because microscopic appearances were 'generally benign'), osteitis fibrosia (excluded because underlying bones 'were not sufficiently affected'), and multiple hereditary cartilaginous exostoses (excluded because of lack of cartilaginous cap).

Rosenstirn's (1918) citation of Lorge's (1871) diagnosis of progressive ossifying myositis (multiple spicules) in a horse cannot be further assessed at this time. Lorge (1871) described ossification of atrophied muscle that is more



characteristic of myositis ossificans than of FOP (RESNICK, 2002). Thus, there are few earlier examples of this disease and most have serious problems in the details of their expression as models of FOP.

Terminology is a challenge. The term myositis ossificans has been used inappropriately (WARREN; CARPENTER, 1984) because FOP ‘does not involve muscle, is multicentric, often symmetrical, and unrelated to trauma’. Myositis ossificans ... is a peripheral zone of orderly maturation from fibrous to osseous tissue. Definitions however, are open to question. Whether these spontaneous models represent a different stage of FOP or entirely different diseases remains unclear. The mouse embryonic stem cell chimeric c-Fos model does have heterotopic ossification, but “lack the anatomic specificity seen in the human disease” (KAN, *et al.*, 2004, KAPLAN, 2005).

Neither the cat model or *Tragulus* fully mirrors human FOP, in part because the latter is often associated with congenital malformations of distal limbs (KAN, *et al.*, 2004, VALENTINE, *et al.* 1992). *Tragulus* however, offers an opportunity to examine experimentally many of the disease’s most significant attributes in a mammal that can be bred in captivity, the ossifications occur spontaneously, and are sex related.

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