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A New Spontaneous Model of Fibrodysplasia Ossificans Progressiva

Bruce D. Rothschild, M.D., Larry D. Martin M.S., Ph.D., and Robert M. Timm, M.S., Ph.D.

Abstract: 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 heterotrophic 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 adults 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.

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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<sup>1</sup>. 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<sup>2,3</sup> 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.

A remarkable skeletal sexual dimorphism is present in apparently all species of the genus—an osseous sheath covering the lower back and upper thigh region in males, but lacking in females (Figs. 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 described<sup>4</sup> and figured<sup>5</sup>, 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<sup>6</sup>.”

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 in 1692, is a genetic disorder characterized by progressive ossification of tendons, ligaments, fascia, and striated muscle<sup>7,8,9,10</sup>. 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<sup>10,11</sup>.

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<sup>9</sup> and prophylactic efforts have had only limited effect<sup>12,13</sup>. Its rarity in humans precludes any 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<sup>14</sup>.

*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<sup>14</sup>. Kaplan et al. (<sup>14</sup>, p. 229) noted that “no known living animals have been available for further study.” However a recent paper<sup>15</sup> 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<sup>16,17</sup>. 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.<sup>18</sup> 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 cm in diameter<sup>19</sup>. Norris et al.<sup>20</sup> 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.<sup>21</sup> 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<sup>18,22</sup>. 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. Seibod and Davis<sup>22</sup> 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<sup>23</sup> citation of Lorge's<sup>23</sup> diagnosis of progressive ossifying myositis (multiple spicules) in a horse cannot be further assessed at this time. Lorge<sup>24</sup> described ossification of atrophied muscle that is more characteristic of myositis ossificans than of FOP<sup>25</sup>. Thus, we have 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<sup>19</sup> 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"<sup>15,16</sup>.

Neither the cat model or *Tragul* fully mirrors human FOP, in part because the latter is often associated with congenital malformations of distal limbs<sup>15,18</sup>. *Tragul* 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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## References

1. Nowak, RM. *Walker's Mammals of the World*, 5<sup>th</sup> ed. Baltimore: Johns Hopkins University Press, 1991.
2. Meijaard, E, Groves, CP. A taxonomic revision of the *Tragul* mouse-deer (Artiodactyla). *Zool J Linnean Soc* 2004;**140**:63–102.

- 3 Grubb, P. Order Artiodactyla. Pp. 637–722 in Wilson, DE, Reeder, DM. eds. *Mammal species of the world: A taxonomic and geographic reference*, 3rd ed. Washington: Smithsonian Institution Press, 2005.
- 4 Lydekker, RL. *The Royal Natural History*. London: Frederick Warne and Co., 1922.
- 5 Lekagul, B, McNeely, JA. *Mammals of Thailand*. Bangkok: Kurusapha Ladprao Press, 1977.
- 6 Vaughan, TA, Ryan, JM, Czaplewski, NJ. *Mammalogy*. Fort Worth: Saunders College Publishing, 2000.
- 7 Kaplan, FS, Strear, CM, Zasloff, JA. Radiographic and scintigraphic features of modeling and remodeling in the heterotopic skeleton of patients who have fibrodysplasia ossification progressiva. *Clin Orthop Rel Res* 1994;**304**:238–247.
- 8 Kaplan, FS, Shore, EM, Zasloff, MA. Fibrodysplasia ossification progressiva: Searching for a skeleton key. *Calcif Tissue Intl* 1996;**59**:75–78.
- 9 Mahboubi, S, Glaser, DL, Shore, EM, Kaplan, FS. Fibrodysplasia ossification progressiva. *Pediatr Radiol* 2001;**31**:307–314.
- 10 Rocke, DM, Zasloff, M, Peeper, J. Age-and-joint specific risk of initial heterotopic ossification in patients who have fibrodysplasia ossification progressiva. *Clin Orthop Rel Res* 1994;**301**:243–248.
- 11 Cohen, RB, Hahn, GV, Tabas, JA. The natural history of heterotopic ossification in patients who have fibrodysplasia ossification progressiva. A study of forty-four patients. *J Bone Jt Surg* 1993;**75A**:215–219.
- 12 Brantus, JF, Meunier, PJ. Effects of intravenous etidronate in acute episodes of fibrodysplasia ossification progressiva. An open study. *Clin Orthop Rel Res* 1998;**346**:117–120.
- 13 Zasloff, MA, Rocke, DM, Crofford, LJ. Treatment of patients who have fibrodysplasia ossification progressiva with isotretinoin. *Clin Orthop Rel Res* 1998;**346**:121–129.
- 14 Kaplan, FS, Shore, EM, Pignolo, RJ, Glaser, DL. Animal models of fibrodysplasia ossification progressive. *Clin Rev Bone Min Metab* 2005;**3(3–4)**:229–234.
- 15 Kan, L, Hu, M., Gomes, WA, Kessler, JA. Transgenic mice overexpressing BMP4 develop a fibrodysplasia ossification progressiva (FOP)-like phenotype. *Am J Pathol* 2004;**165**:1107–1115.
- 16 Kaplan, FS. Fibrodysplasia ossification progressiva: An historical perspective. *Clin Rev Bone Min Metab* 2005;**3(3–4)**:179–181.

- 17 Tung, C-H, Lai, N-S. Clinical image: Fibrodysplasia ossificans progressive seen on three-dimensional computed tomography. *Arthritis Rheum* 2008;**58**:250.
- 18 Valentine, BA, et al. Fibrodysplasia ossificans progressivea in the cat. A case report. *J Vet Intern Med* 1992;**6**:335–340.
- 19 Warren, HB, Carpenter, JL. Fibrodysplasia ossificans in three cats. *Vet Pathol* 1984;**21**:495–499.
- 20 Norris, AM, Pallett, L, Wilcock, B. Generalized myositis ossificans in a cat. *J Am Animal Hosp Assoc* 1980;**16**:659–663.
- 21 Waldron, D, Pettigrew, V, Turk, M, Turk, J, Gibson, R. Progressive ossifying myositis in a cat. *J Am Vet Med Assoc* 1985;**187**:64–65.
- 22 Siebold, HR, Davis, CL. Generalized myositis ossificans (familial) in pigs. *Pathol Vet* 1967;**4**:79–88.
- 23 Rosenstirn, J. A contribution to the study of myositis ossificans progressive. *Ann Surg* 1918;**68**:485–520, 591–637.
- 24 Lorge, V. Ossification du périmysium interne et atrophie consécutive des fibres musculaires. *Ann Méd Vét* 1871;**20**:239–244.
- 25 Resnick, D. *Diagnosis of bone and joint disorders*. Philadelphia: W. B. Saunders, 2002.

**Figure 1.** Dorsal and ventral view of the pelvic and abdominal region of an adult male *Tragulus napu* (KU 163,960). Dermal ossifications extend from caudal-most ischiopubis to iliac crest and cephalidly from sacrum in a paraspinal distribution.

**Figure 2.** Dorsal view of 19th century preparation of an adult male *Tragulus nigricans* (KU 165,574). Note residual heterotypic 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.





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