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Clinical Casebook

Ringo, a Golden Retriever Muscular Dystrophy (GRMD) dog with absent dystrophin but normal strength

C.E. Ambrósio [a], M.C. Valadares [b], E. Zucconi [b], R. Cabral [a], P.L. Pearson [b], T.P. Gaiad [a], M. Canovas [b], M. Vainzof [b], M.A. Miglino [a,b], M. Zatz [b,*]

[a] *School of Veterinary Medicine and Animal Science, Department of Surgery, Anatomy Sector, University of São Paulo, São Paulo, Brazil*
[b] *Human Genome Research Center, Biosciences Institute, IB-USP, University of São Paulo, R. do Matão, 106, São Paulo, SP-CEP 05508-090, Brazil*

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The closest model to human Duchenne Muscular Dystrophy (DMD) is the Golden Retriever Muscular Dystrophy (GRMD) dog, which carries a point mutation in the splice acceptor site in intron 6 of the orthologe X-linked dystrophin gene, leading to the absence of protein in the muscles. These dogs present clinical signs within the first weeks of life involving the limbs as well as masticatory muscles. Diaphragmatic and intercostal muscles impairment leads to progressive respiratory failure. Death occurs from bronchopneumonia and cardiac arrest, usually before 2 years of age.

Here, we report the case of Ringo, an exceptional GRMD dog showing an unusually mild course. Currently, at age 4 years and 10 months he is able to run, jump and open doors while standing on his rear paws. He was also able to breed naturally, which apparently has never been reported before.

Ringo is descendant of Beth, a GRMD female carrier donated by Dr. Joe Kornegay (University of North Carolina, USA), and all affected descendants carry the same original mutation. The diagnosis in all dogs was established right after birth through DNA genotyping and elevated serum creatine kinase (CK). At birth, Ringo's serum CK level was increased 10-fold as compared to his three normal sibs. One affected brother had a comparable serum CK while the other had a 20-fold increase. At 15 days serum CK in the affected dogs was 4- to 5-fold higher than in normal siblings. Pedigree analysis (Fig. 1) revealed that Ringo had two affected brothers from the same litter. One of them died at 2 weeks of age. The other one is still alive but with a much more severe phenotype, comparable to the usual clinical phenotype. Ringo was able to copulate naturally with four carrier females, which resulted in a total of 38 descendants: 12 affected males, 7 affected females, 11 carriers and 8 normal dogs. As the result of the first mating, with Xenna, 9 puppies were born: 1 affected female, 3 normal males and 5 carrier females. As the result of the second mating, with the female Hope, 12 puppies were born: 7 affected males, 1 affected female, 3 carrier females and one normal male. Four males showed a severe course and died of acute respiratory failure in the first days of life. However, interestingly, one male, Suflair, is also showing a mild course. He was born in April 2006 and at age 2 years and 1 month is able to run and jump, presents a normal posture tone and no contractures. The third mating was in 2007 with Lady, a carrier female from the kennel that was found to be accidentally pregnant. There were two possible fathers: Ringo and Suflair. Paternity testing (with microsatellite markers) confirmed that Ringo was the culpable father, which generated 7 additional offspring(s): 2 affected females, 2 affected males, 2 normal males and 1 carrier female. The fourth mating, with Kira, generated 10 puppies born in September of 2007: 4 affected males, 2 affected females, 2 carrier females and 2 normal males. However, 4 normal dogs died of a viral infection.

Ringo's performance has apparently never been observed in GRMD dogs. Although their phenotype may be highly variable, even among dogs from the same litter, most of the GRMD dogs are severely affected and die before 24 months of age. In the Brazilian colony, we observed that 24% died within the first 2 weeks, 17% died before 6 months, 24% before 12 months, 11% before 18 months and 24% after 24 months of age.

* Corresponding author. Tel.: +55 11 30917581.
E-mail address: mayazatz@usp.br (M. Zatz).

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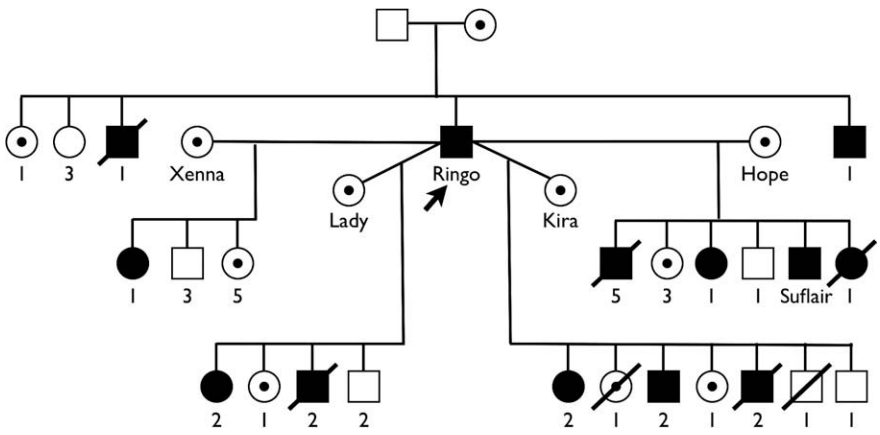

Fig. 1. Ringo's Pedigree. The numbers below each symbol represent how many animals in each category: ■ affected male, ● affected female, ⊙ carrier female, ○ non-carrier female and □ normal male.

Interestingly, histopathological and immunohistochemistry analysis from Ringo's biceps biopsy showed typical features of a dystrophic process with variability in fiber size, splitting, degeneration and connective tissue as well as complete dystrophin deficiency, comparable to severely affected GRMD dogs (with both rod- and C-terminal anti-dystrophin antibodies). Sarcoglycans were partially deficient, and utrophin was overexpressed, in a pattern similar to the observed in severely affected dogs.

How much dystrophin is required in order to mitigate the clinical phenotype has always been an open question. Ringo's phenotype, which is not explained by higher amounts of dystrophin or up-regulation of utrophin, shows that GRMD dogs may have a mild course despite the complete absence of dystrophin, which opens a new avenue of investigations. On the other hand this observation reinforces the importance of taking into account clinical variability in the assessment of results of therapeutic trials that are currently underway. What is protecting Ringo and Suflair from the mitigating effect of the dystrophin mutation? The observed father to son transmission rules out X-linked inheritance and therefore this unusual phenotype could be due to modifier genes, to multifactorial inheritance or to other epigenetic factors. Complete absence of dystrophin expression associated with a mild clinical course has been recently reported in humans (Neuromuscul Disord 2006;16:865–6). "*Treasure your exceptions*", says Victor Dubowitz. Maybe Ringo and his descendants could enhance our comprehension on unknown mechanisms that might protect skeletal muscle to degenerate despite the absence of dystrophin.