Morphological and molecular analyses of *Taenia* and *Mesocestoides* species from red foxes (*Vulpes vulpes*) in northwestern China

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Short report

Keywords: Cestoda, tapeworms, Cyclophyllidea, Taeniidae, cox1

Posted Date: September 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-885658/v1>

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Version of Record: A version of this preprint was published at International Journal for Parasitology: Parasites and Wildlife on November 1st, 2021. See the published version at

Abstract

Background

The red fox (*Vulpes vulpes*) is a geographically widespread predator species, occurring across the northern Hemisphere. It has high veterinary-medical significance, in part owing to its definitive host role in the life cycle of several tapeworm species, including zoonotic ones. However, there have been only few reports on cyclophyllid tapeworm (Cestoda: Cyclophyllidae) infection in red foxes from China.

Methods

In this study, 263 tapeworms were collected from eight road-killed red foxes in Xinjiang Uygur Autonomous Region (XUAR, northwestern China). The tapeworms were analyzed based on morphological characters and mitochondrial cytochrome *c* oxidase subunit 1 (*cox1*) gene sequences.

Results

83 *Taenia* and 180 *Mesocestoides* tapeworms were identified according to the presence or absence of rostellum, and the number, the length and the shape of the large rostellar hooks. The morphological and molecular analyses revealed that i) 180 *Mesocestoides* tapeworms, here named as *Mesocestoides* sp. *Vulpes vulpes*, showed 99.21% (378/381 bp) identity to *Mesocestoides* sp. reported from red fox in Mongolia; and ii) 83 *Taenia* tapeworms belonged to three species. The first *Taenia* species (n = 16, named as *Taenia* sp. *Vulpes vulpes*), based on the length of large rostellar hooks (337–342 µm) and its *cox1* sequence, was identified as a potentially novel species, which is phylogenetically close to *Taenia laticollis*. The second species (n = 54, named as *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus*), was morphologically similar to *Taenia endothoracicus* according to the number (n = 52), the length (319–332 µm) and the shape of the large rostellar hooks. This species, infecting three red foxes, shared 100% *cox1* sequence identity with *Taenia* sp. *Rhombomys opimus* genotype C found previously in great gerbils (*Rhombomys opimus*) in the same region. The third species (n = 13, named as *Taenia polyacantha*-like), had shorter large rostellar hooks (178–180 µm) and showed 96.27% (361/375 bp) sequence identity to *Taenia polyacantha* reported from red fox in Italy. In addition, co-infections with two *Taenia* species and with *Taenia* and *Mesocestoides* species were also demonstrated.

Conclusions

The “great gerbil-red fox” life cycle of *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus*, belonging to the mitochondrial lineage of *T. endothoracicus*, is confirmed. The *T. polyacantha*-like species and *Mesocestoides* sp. *Vulpes vulpes* were found for the first time in red fox in China. *Taenia* sp. *Vulpes vulpes* is a potentially novel species, which is close to *Taenia laticollis* based on its phylogenetic

properties. The life cycle of *Taenia* sp. *Vulpes vulpes* and *Mesocestoides* sp. *Vulpes vulpes* should be further explored.

Background

The red fox (*Vulpes vulpes* Linnaeus, 1758), that is the largest species of true foxes (Carnivora: Canidae: *Vulpes*), is widespread in North-America, Asia, Europe and North Africa [1]. Its habitats overlap with activity areas of humans and domestic animals, leading to risks of infectious diseases (e.g. rabies and echinococcosis) relevant to public and veterinary health [2, 3].

Tapeworms (cestodes) have a domestic or sylvatic life cycle based on predator-prey interactions between a carnivore (definitive host) and a herbivore (intermediate host) [4]. Previously, the red fox was reported to harbor at least 22 species of cyclophyllidean cestodes, including *Taenia taeniaeformis*, *Taenia pisiformis*, *Taenia polyacantha*, *Taenia hydatigena*, *Taenia multiceps*, *Taenia pisiformis*, *Taenia serialis*, *Taenia crassiceps*, *Taenia ovis*, *Taenia polyacantha*, *Taenia* spp., *Echinococcus multilocularis*, *Echinococcus perfoliatus*, *Echinococcus granulosus*, *Echinococcus shiquicus*, *Mesocestoides lineatus*, *Mesocestoides corti*, *Mesocestoides* spp., *Dipylidium caninum*, *Diplopylidium noelleri*, *Alaria alata*, and *Hymenolepis* spp. [5–25].

Previously, *Echinococcus granulosus*, *E. multilocularis*, and *E. shiquicus* were found in Tibetan fox (*Vulpes ferrilata*) and red fox in China [25]. The aim of the present study was to identify tapeworms from road-killed red foxes in Xinjiang Uygur Autonomous Region (XUAR), northwestern China.

Methods

Sample collection

In this study, eight red foxes were used. These animals were road-killed in the Gurbantunggut Desert, the northern region of XUAR in the period 2015-2019. During necropsy, all tapeworms were removed from the small intestine (Table S1, Fig. S1), subsequently washed in physiological saline prior to morphological identification and DNA extraction.

Morphological identification

The staining procedure was performed as reported [26]. In brief, the scolex of representative tapeworms were stained with acetate carmine and observed with an Olympus DP70 digital camera (Olympus, Tokyo, Japan).

DNA extraction and molecular analysis

After detailed morphological examination, 40 tapeworm specimens were selected for molecular analysis (as shown in Table S1). DNA was extracted from a small part of the immature strobila using the TIANamp Genomic DNA Kit (TIANGEN, Beijing, China). A conventional PCR was performed to amplify an

approx. 450-bp-long part of the mitochondrial cytochrome *c* oxidase subunit I gene (*cox1*) as reported previously [27]. Sequences from this study were compared to those in GenBank with the BLASTn program (<https://blast.ncbi.nlm.nih.gov>). New sequences were deposited in GenBank (*cox1*: MZ475884, MZ512998-MZ513000). A phylogenetic tree was constructed using the Neighbor-Joining method in MEGA 7.0 software.

Results

Morphological identification

Six foxes (#1, #3, #5, #6, #7 and #8) were found infected with 263 tapeworms. According to the presence or absence of rostellum, 83 were identified as *Taenia* spp., while 180 belonged to the genus *Mesocestoides*. According to the number, the length and measurement data (total length, total width, posterior length, anterior length and guard length) of large rostellar hooks, 83 *Taenia* tapeworms were assigned to three species. The first species (n=16, removed from red fox #1) and the second species (n=54, from red foxes #3, #5, #7 and #8) were similar to *Taenia endothoracicus*, *Taenia krepkogorski* and *Taenia macrocystis* in the number and length of large rostellar hooks (Table S2, Table S3). The third species (n=13, from red foxes #5, #6 and #8) belonged to *Taenia polyacantha* according to the number and length of large rostellar hooks.

Molecular identification

Based on the *cox1* gene, BLASTN analysis indicated that i) all 180 *Mesocestoides* tapeworms from red foxes #1 (n=80) and #3 (n=100) were most closely related to *Mesocestoides* sp. (accession number: AB792718) from red fox in Mongolia, showing 99.21% (378/381 bp) sequence identity to it. Provisionally, this species was named as *Mesocestoides* sp. *Vulpes vulpes* (MZ475884); ii) the first *Taenia* species was most closely related to *Taenia* sp. *Rhombomys opimus* (accession numbers: MW321849 and MW321850) detected in great gerbils in our previous work [28], but sharing only 88.03% (309/351 bp) sequence identity with it. Provisionally, this species was named as *Taenia* sp. *Vulpes vulpes* (MZ512998), and it belonged to Clade B of the *cox1* phylogenetic tree (Fig. 1); iii) the second *Taenia* species was 100% identical in its *cox1* sequence to *Taenia* sp. *Rhombomys opimus* genotype C (accession numbers: MW321849 and MW321850) detected in great gerbils (*Rhombomys opimus*), originating from the same region as the relevant three road-killed red foxes (#5, #7 and #8) in this study. Provisionally, this species was named as *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus* (MZ512999), and belonged to Clade A of the *cox1* phylogenetic tree (Fig. 1); and iv) the third *Taenia* species was most closely related to *Taenia polyacantha* (accession number: MT806362) from red fox in Italy, sharing 96.27% (361/375 bp) *cox1* sequence identity. Provisionally, this species was named as "*Taenia polyacantha*-like" (MZ513000), and it belonged to Clade C of the *cox1* phylogenetic tree (Fig. 1).

Analysis of COX1 amino acid sequences showed that i) *Mesocestoides* sp. *Vulpes vulpes* has 100% (127/127 aa) identity to *Mesocestoides* sp. (accession number: AB792718) from red fox in Mongolia; ii)

Taenia sp. *Vulpes vulpes* shares 93.16% (109/117 aa) identity with *Taenia* sp. *Rhombomys opimus* (MW321849) (Fig. S2A); and iii) "*T. polyacantha*-like" (from Clade C in Fig. 1) has 100.00% (125/125 aa) identity to *Taenia polyacantha* (MT806362) (Fig. S2B).

Discussion

The previously known geographical range of *Taenia endothoracicus*, with red fox as its definitive host, included Iran and North Africa. Polycephalic larvae occur in the thoracic cavity of rodents from the genera *Meriones*, *Gerbillus* and *Rhombomys*. In our previous work, *Taenia* sp. *Rhombomys opimus* genotypes A, B and C were demonstrated from the thoracic cavity of great gerbils in Gurbantungut Desert with 5.3% (10/188) prevalence [28]. A lot of protoscolices were observed in large white and web-shaped cysts, which caused shrinking and stiffness in the lung parenchyma [28]. Interestingly, here adults of *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus* were found in four red foxes, and the corresponding *cox1* sequence had 100% identity to that of *Taenia* sp. *Rhombomys opimus* genotype C in great gerbils. Furthermore, the sampling sites of the three red foxes (#5, #7 and #8) and of the two great gerbils (#27 and #31) infected with *Taenia* sp. *Rhombomys opimus* genotype C are situated in the same area (44°67'-44°70' N, 86°34'-86°39' E) [28]. Previously, Lin et al reported that great gerbils are important in the diet composition of red foxes in Gurbantungut Desert, and accounted for 16.48% of prey items based on 273 fecal samples of red foxes [29]. These findings suggest that the life cycle of *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus* involves the great gerbil and the red fox (Fig. S3). In addition, the shape of large rostellar hooks was compared among *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus*, *Taenia endothoracicus*, *Taenia krepkogorski* and *Taenia macrocystis* (as shown in S pptx). The results indicated that the shape of large rostellar hooks is similar between *T. endothoracicus* and *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus*. Interestingly, the shape of cysts showed significant difference between *T. endothoracicus* reported from Iran and *Taenia* sp. *Rhombomys opimus* in this work (Fig. S4) [28, 30, 31], suggesting that *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus* belongs to a genetic lineage separate from *T. endothoracicus*. However, unfortunately, the *cox1* sequence of the latter species is not available in GenBank to confirm this.

According to the length of the large rostellar hooks and definitive host (*Vulpes*), *Taenia* sp. *Vulpes vulpes* is similar to *Taenia endothoracicus*, *Taenia krepkogorski* and *Taenia macrocystis*. However, when the shape of the large rostellar hooks was compared among them, *Taenia* sp. *Vulpes vulpes* showed obvious differences from these three tapeworm species (as shown in S pptx). Due to the lack of *cox1* data of *T. endothoracicus*, *T. krepkogorski* and *T. macrocystis*, the taxonomy of *Taenia* sp. *Vulpes vulpes* should be further investigated in the future.

Tania polyacantha, infecting red foxes, was previously reported from Finland, Norway, Denmark, Wales, Germany, France, Switzerland, Austria, Poland, Bulgaria, Italy, Yugoslavia and Japan [32, 33]. In this study, 13 adult tapeworms of "*Taenia polyacantha*-like" were found for the first time in three red foxes (#5, #6 and #8) in China. At the same time, differences between these isolates are obvious in the shape of the large rostellar hooks and sequences of the *cox1* gene (96.27%, 361/375 bp).

Previously, *M. lineatus*, *M. corti* and *Mesocestoides* spp. were found in red foxes in Portugal, Romania, Denmark, Italy and Mongolia [6, 7, 13, 17]. Hitherto only *M. lineatus* was reported from this genus in China [34]. In our study, however, *Mesocestoides* sp. *Vulpes vulpes* (accession number: MZ475884) was found in two red foxes. This species candidate is phylogenetically most closely related to *Mesocestoides* sp. (accession number: AB792718) collected from red fox (*Vulpes vulpes*) in Mongolia, with which it shared 99.21% (378/381 bp) *cox1* sequence homology. These two clustered as a sister group to *M. corti* and *Mesocestoides canislagopodis* (Fig. 1). Since the latter species has a broad range of canid and felid definitive hosts [35], it should be examined in the future if further predator species may harbor adult *Mesocestoides* sp. *Vulpes vulpes* in northwestern China. In addition, the taxonomic relationships and the geographical distribution of *Mesocestoides* sp. *Vulpes vulpes* should also be explored.

It is a principle phenomenon that coinfection with multiple tapeworm species may occur in the same red fox individual. In a previous report from the Netherlands, up to eight cestode species were found together in the same red fox [11]. Here *Taenia* sp. *Vulpes vulpes* coinfecting with *Mesocestoides* sp. *Vulpes vulpes*, "*T. polyacantha*-like" coinfecting with *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus* the same red fox in China. The broad range of food items of red foxes in the Gurbantunggut Desert might account for this coinfection phenomenon.

Conclusion

The life cycle of *Taenia* sp. *Vulpes vulpes* & *Rhombomys opimus*, belonging to the mitochondrial lineage of *T. endothoracicus*, involves the great gerbil and the red fox. "*Taenia polyacantha*-like" and *Mesocestoides* sp. *Vulpes vulpes* were found for the first time in red fox in China. *Taenia* sp. *Vulpes vulpes*, a potentially novel species, is phylogenetically closely related to *T. laticollis* based on the *cox1* gene.

Abbreviations

cox1: cytochrome *c* oxidase subunit I; XUAR: Xinjiang Uygur Autonomous Region.

Declarations

Acknowledgements

The authors thank the contributions by the staff at the School of Medicine and School of Animal Science and Technology, Shihezi University.

Authors' contributions

GL, YW conceived and designed the study, and wrote the manuscript. GL, NJ, YZ, SZ, XC, WH, XG and YW performed the experiments, analyzed the data. SH contributed to study design and edited the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (81960379 and 31960709), International Scientific and Technological Cooperation in Bingtuan (2020BC008) and Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2020-PT330-003).

Availability of data and materials

The sequences obtained and analysed during the present study are deposited in the GenBank database, under the accession numbers (tapeworms *cox1* gene: MZ475884, MZ512998, MZ512999 and MZ513000).

Ethical approval and consent to participate

This study was approved by the Animal Ethics Committee of Shihezi University (Approval No. A2015-063-01 and A2018-143-01).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Ablimiti AQ. Classification and distribution of mammals in Xinjiang[M]. Beijing: Science Press; 2013.
2. Centers for Disease Control and Prevention (CDC). Human rabies—Texas and New Jersey, 1997. MMWR Morb Mortal Wkly Rep. 1998;47:1–5.
3. Wang Z, Wang X, Liu X. Echinococcosis in China, a review of the epidemiology of *Echinococcus* spp. Ecohealth. 2008;5:115–26.
4. Thompson RCA. Parasite zoonoses and wildlife: one health, spillover and human activity. Int J Parasitol. 2013;43:1079–88.

5. Abuladze KI. "Principles of Cestodology, edited by K. I. Skryabin. Vol. IV. Taeniata-cestodes of animals and man and the diseases caused by them." (1964).
6. Eira C, Vingada J, Torres J, Miquel J. The Helminth Community of the Red Fox, *Vulpes Vulpes*, In Dunas de Mira (Portugal) and its effect on host condition. *Wildlife Biology in Practice*. 2006;2:26–6.
7. Barabási SS, Fok E, Gubányi A, Mészáros F, Cozma V. Helminth fauna of the small intestine in the European red fox, *Vulpes vulpes* with notes on the morphological identification of *Echinococcus multilocularis*. *Sci Parasitol*. 2010;11:141–51.
8. Hofer S, Gloor S, Muller U, Mathis A, Hegglin D, Deplazes P. High prevalence of *Echinococcus multilocularis* in urban red foxes (*Vulpes vulpes*) and voles (*Arvicola terrestris*) in the city of Zürich, Switzerland. *Parasitology*. 2000;120:135–42.
9. Laurimaa L, Moks E, Soe E, Valdmann H, Saarma U. *Echinococcus multilocularis* and other zoonotic parasites in red foxes in Estonia. *Parasitology*. 2016;143:1450–8.
10. Dybing NA, Fleming PA, Adams PJ. Environmental conditions predict helminth prevalence in red foxes in Western Australia. *Int J Parasitol Parasites Wildl*. 2013;2:165–72.
11. Franssen F, Nijse R, Mulder J, Cremers H, Dam C, Takumi K, et al. Increase in number of helminth species from Dutch red foxes over a 35-year period. *Parasit Vectors*. 2014;7:166.
12. Karamon J, Dąbrowska J, Kochanowski M, Samorek-Pieróg M, Sroka J, Różycki M, et al. Prevalence of intestinal helminths of red foxes (*Vulpes vulpes*) in central Europe (Poland): a significant zoonotic threat. *Parasit Vectors*. 2018;11:436.
13. Saeed I, Maddox-Hyttel C, Monrad J, Kapel CM. Helminths of red foxes (*Vulpes vulpes*) in Denmark. *Vet Parasitol*. 2006;139:168–79.
14. Borgsteede FHM. Helminth parasites of wild foxes (*Vulpes vulpes* L.) in The Netherlands. *Z Parasitenkd*. 1984;70:281–5.
15. Morishima Y, Tsukada H, Nonaka N, Oku Y, Kamiya M. Coproantigen survey for *Echinococcus multilocularis* prevalence of red foxes in Hokkaido, Japan. *Parasitol Int*. 1999;48:121–34.
16. Petersen HH, Al-Sabi MNS, Enemark HL, Kapel CMO, Jørgensen JA, Chriél M. *Echinococcus multilocularis* in Denmark 2012–2015: high local prevalence in red foxes. *Parasitol Res*. 2018;117:2577–84.
17. Fontana M. C, et al. Helminth parasites of the red fox *Vulpes vulpes* (L. 1758) and the wolf *Canis lupus italicus* Altobello, 1921 in Emilia-Romagna, Italy. *Ital J Zool*. 2016;83:503–13.
18. Brochier B, De Blander H, Hanosset R, Berkvens D, Losson B, Saegerman C. *Echinococcus multilocularis* and *Toxocara canis* in urban red foxes (*Vulpes vulpes*) in Brussels, Belgium. *Prev Vet Med*. 2007;80:65–73.
19. Hanosset R, Saegerman C, Adant S, Massart L, Losson B. *Echinococcus multilocularis* in Belgium: prevalence in red foxes (*Vulpes vulpes*) and in different species of potential intermediate hosts. *Vet Parasitol*. 2008;151:212–7.

20. Rataj AV, Bidovec A, Ele D, Vengut G. *Echinococcus multilocularis* in the red fox (*Vulpes vulpes*) in Slovenia. Eur J Wildlife Res. 2010;56:819–22.
21. Romig T, Thoma D, Weible AK. *Echinococcus multilocularis* - A zoonosis of anthropogenic environments? J Helminthol. 2006;80:207–12.
22. Mrcvs IWBBM. *Echinococcus multilocularis*: a political zoonosis. Companion Animal. 2013;18:368–71.
23. Dibble ED, Font WF, Wittrock DD. Helminths of the red fox, *Vulpes vulpes* L. in west central Wisconsin. J Parasitol. 1983;69:1170–2.
24. Loos-Frank B. Shedding of gravid proglottids and destrobilation in experimental infections of foxes with *Mesocestoides leptothylacus* Loos-Frank, 1980 (Cestoda). J Helminthol. 1987;61:213–8.
25. Jiang W, Liu N, Zhang G, Renqing P, Xie F, Li T, et al. Specific detection of *Echinococcus* spp. from the Tibetan fox (*Vulpes ferrilata*) and the red fox (*V. vulpes*) using copro-DNA PCR analysis. Parasitol Res. 2012;111:1531–9.
26. Li XJ, Yang YM. Identification of *Taenia* cestodes in Xianggelila, Yunnan by molecular and morphological methods. J Pathogen Biol. 2009;4:196–7.
27. Hrčková G, Miterpáková M, O'Connor A, Šnáběl V, Olson PD. Molecular and morphological circumscription of *Mesocestoides* tapeworms from red foxes (*Vulpes vulpes*) in central Europe. Parasitology. 2011;138:638–47.
28. Ji N, Chen X, Liu G, Zhao S, Tan W, Liu G, et al. *Theileria*, *Hepatozoon* and *Taenia* infection in great gerbils (*Rhombomys opimus*) in northwestern China. Int J Parasitol Parasites Wildl. 2021;15:79–86.
29. Lin X, Wu K, Shi L. Food habitats of the red fox (*Vulpes vulpes*) in the Junggar Basin Desert. Acta Theriologica Sinica. 2010;30:346–50.
30. Mowlavi GR, Kia EB, Mobedi I. Natural infection of the gerbil *Meriones libicus* with the metacestode of *Taenia endotheracicus* in Arak, central Iran. J Helminthol. 2004;78:275–6.
31. Kamranrashani B, Kia E, Mobedi I, Mohebbali M, Zarei Z, Mowlavi G, et al. Helminth Parasites of *Rhombomys opimus* from Golestan Province, Northeast Iran. Iran J Parasitol. 2013;8:78–84.
32. Loos-Frank B, Zeyhle E. The intestinal helminths of the red fox and some other carnivores in southwest Germany. Z Parasitenkd. 1982;67:99–113.
33. Ihama Y, Sato H, Makino Y, Kamiya H. Two *Taenia* species found in Japan, with new distribution record of *Taenia polyacantha* Leuckart, 1856 (Cestoda: Taeniidae). Parasitol Int. 2000;48:303–6.
34. Zhou XN. list of parasitic germplasm resources in China (cestode)[M]. Shanghai China: Shanghai Science and Technology Press; 2015.
35. Skirnisson K, Jouet D, Ferte H, Nielsen ÓK. Occurrence of *Mesocestoides canislagopodis* (Rudolphi, 1810) (Krabbe, 1865) in mammals and birds in Iceland and its molecular discrimination within the *Mesocestoides* species complex. Parasitol Res. 2016;115:2597–607.

Figures

Figure 1

Phylogenetic relationships of *Taenia* and *Mesocystoides* species from red foxes based on *cox1* sequences.

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