

Transmission of Enigmatic *Mundinia* Parasites

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Abstract

Mundinia, the recently established *Leishmania* subgenus, includes five species, three of which are pathogenic to humans. Although *Mundinia* represents the oldest branch of the genus *Leishmania*, most species have escaped the attention of scientists and have only been discovered in the last 20 years. Their transmission ecology is enigmatic, with unknown identity of reservoir hosts and insect vectors. This mini-review summarizes the history of *Mundinia* discovery and the current knowledge about the reservoirs and vectors with emphasis on the role of biting midges (Diptera: Ceratopogonidae) in their transmission.

Keywords: *Mundinia*; *L. macropodum*; *L. enriettii*; *L. orientalis*; *L. martiniquensis*; *Culicoides sonorensis*

Introduction

Leishmania (Kinetoplastida: Trypanosomatidae) are digenetic parasites circulating between mammal or reptile vertebrate hosts and insect vectors. They are currently divided into four subgenera. The most important and abundant human parasites belong to subgenera *Viannia* and *Leishmania*, the third subgenus *Sauroleishmania* includes reptile parasites [1]. The fourth subgenus *Mundinia* was established in 2016 by Espinosa, et al. for five species previously known as the *L. enriettii* complex. It is the most ancient group, diverging at the base of a phylogenetic tree of the *Leishmania* genus [1].

Literature Review

Mundinia is an exceptional and enigmatic subgenus in several aspects:

Worldwide geographical distribution

The five species are distributed on all continents except Antarctica (Figure 1): *L. enriettii* occurs in Brazil, *L. sp.* strain GH5, not yet formally described, in Africa (Ghana), *L. orientalis* in southeast Asia and *L. macropodum* in Australia, representing the only *Leishmania* species known from that continent. The fifth species, *L. martiniquensis*, has been reported from areas as distant as the island of Martinique, Florida, central Europe and southeast Asia. This wide distribution of the subgenus has been attributed to its ancient origin and is explained by the formation of individual species from a common ancestor after the breakup of Gondwana [2]. However, in the case of *L. martiniquensis*, the recent introduction and anthropogenic spread must be considered, as the infection is only known from humans and domestic animals.

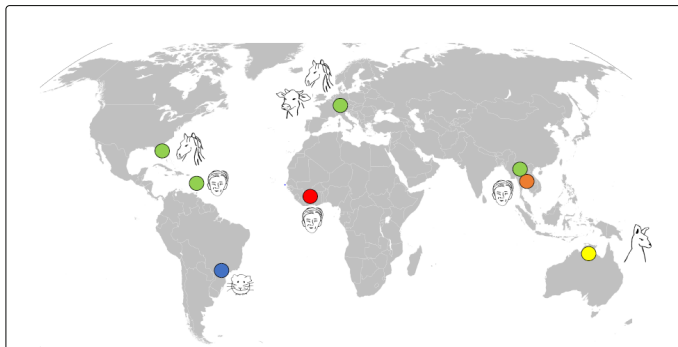


Figure 1: Geographical distribution of five *L. (Mundinia)* species and schematic representation of hosts from which they were isolated. **Note:** (●) *L. (Mundinia) enriettii* (●) *L. (Mundinia) martiniquensis* (●) *L. (Mundinia) sp.* from Ghana (●) *L. (Mundinia) orientalis* (●) *L. (Mundinia) macropodum*

The hidden way of life

Despite their ancient origins, three species (*L. macropodum*, *L. orientalis* and the unnamed African species) have escaped scientific knowledge and have only been discovered in the last 20 years. The remaining two species have been known for a long time, but were reported very sporadically. This is particularly true for the Brazilian *L. enriettii*. It was first isolated in 1948 from domestic guinea pigs, then detected 20 years later in 1967 and after another long gap again in 1994, each time in domestic guinea pigs [3,4]. However, as a species non-pathogenic to humans, *L. enriettii* has become a popular model organism for experimental studies. *Leishmania martiniquensis* was first described in 1995 in an HIV-infected man in Martinique and was initially misidentified as a monoxenous “lower” trypanosomatid. Two years later, the same parasite was also reported in Martinique in an immunocompetent patient [5,6]. In 2014, Pothirat, et al. showed that autochthonous infections in cattle or horses sporadically reported from Florida, Switzerland and Germany and occasionally causing human infections in south-east Asia, belong to the same *Mundinia* species [7-11]. In the same year the name *L. martiniquensis* was established [12]. In Thailand, *L. martiniquensis* is not the only species of the subgenus *Mundinia*, the other being *L. orientalis*, formally described in 2018 [13]. In older literature, all Thai isolates were confused and referred to as “*L. siamensis*”. This name was first used by Sukmee, et al. for the sequence of their isolate submitted in GenBank and then introduced into the scientific literature by Müller, et al. [9,14]. As the name “*L. siamensis*” has never been formally described, it is not a valid name and should no longer be used.

In horses and cattle, *L. martiniquensis* causes skin lesion while in humans, a wide spectrum of manifestations ranging from cutaneous and diffuse cutaneous to visceral forms has been reported [5,6,8-10,14,15]. Similarly, *L. orientalis* is also responsible for both diffuse cutaneous and visceral leishmaniasis [16]. The African *Mundinia* species was hidden among human cutaneous leishmaniasis cases in the Volta region of Ghana caused by *L. major*. However, in 2009 the parasite was identified as a new *Leishmania* species, in 2015 the strain was isolated and according to phylogenetic analysis placed into the subgenus *Mundinia* [17,18]. Australia was traditionally considered a continent where *Leishmania* species were not

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endemic until 2004, when a case of autochthonous cutaneous leishmaniasis was described in red kangaroos (*Macropus rufus*) in Australia's Northern Territory [19].

Unknown reservoirs

No reservoir wild hosts have been identified for any species of the subgenus *Mundinia*. *Leishmania enriettii* has only been found in domestic guinea pigs, but experimental infections of wild guinea pigs (and several other species of wild mammals) have failed [3]. In the case of *L. macropodum*, all Australian causes of CL have been diagnosed in captive animals - red kangaroos (*Macropus rufus*), the northern wallaroo (*M. robustus woodwardi*), the black wallaroo (*M. bernardus*) and the agile wallaby (*M. agilis agilis*) [19,20]. All records have been restricted to the rural Darwin area in the Northern Territory with a humid tropical climate, where only agile wallabies are native, but further epidemiological studies are needed to determine their possible role as reservoirs of *L. macropodum* [20]. The autochthonous cases of *L. martiniquensis* in horses and cattle in central Europe and Florida are truly enigmatic, the animal reservoirs are completely unknown and have yet to be identified, and the same is true for human-infecting species in Thailand and Ghana. In Thailand, *Leishmania* DNA has been found in *Rattus rattus*, making this rodent species suspected of serving as a reservoir, but the capacity of black rats to harbour the parasite long-term and their infectiousness to sand flies has not yet been proven [21]. Experimental studies on the genera *Arvicanthis* and *Mastomys* have been done but did not demonstrate a reservoir role of these rodents for the Ghanaian *Mundinia* species [22]. *Mundinia* have probably evolved a well-balanced relationship with their reservoir hosts over a long evolutionary history and cause only asymptomatic unapparent infections, which are thus difficult to detect.

Unique vectors

Although species identity for vectors of any *Mundinia* species is not confirmed yet, the findings so far are fascinating. For many years, there was a widely accepted paradigm that *Leishmania* species pathogenic to humans are transmitted exclusively by phlebotomine sand flies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World [23,24]. But most *Leishmania* of the subgenus *Mundinia* have never been found in sand flies, with exception of PCR detection of *Mundinia* DNA in Thai *Sergentomyia* (*Neophlebotomus*) *gemmea* and *S. iyengari* [25,26]. However, molecular findings cannot be considered as a proof of the vector identification. Without microscopy, it is not possible to distinguish late mature infections from early ones which are non-specific and may be lost with defecation in refractory vectors [27]. The paradigm of exclusive transmission of *Leishmania* by sand flies has been seriously challenged by discoveries related to the subgenus *Mundinia* published in the last decade.

In areas of Australian *L. macropodum* distribution, the extensive field survey revealed DNA of the parasites in 6% females of three species of biting midges of the genus *Forcipomyia* (Diptera: Ceratopogonidae) while no *Leishmania*-positive specimens were detected among nearly 2000 sand fly females collected. Importantly, heavy late stage infections and presence of metacyclic forms in biting midges were confirmed also microscopically [28]. Consequent laboratory experiments have revealed susceptibility of North American *C. sonorensis* to infection with *L. enriettii*, *L. macropodum* and *L. orientalis* [29,30].

Altogether, these studies had showed that biting midges satisfy most of Killick-Kendrick's criteria of vector competence [31]. However, the most important criterion was still missing, namely the demonstrations of transmission by the vector bite. This has changed with the recent publication of Becvar, et al [32]. These authors compared the development of all 5 *Mundinia* species in biting midges and sand flies

and demonstrated experimental transmissions of three *Mundinia* species, *L. martiniquensis*, *L. orientalis* and *L. sp.* from Ghana by biting midges *C. sonorensis* to BALB/c mice. The parallel experiments with the same parasite lines and epidemiologically relevant sand fly species resulted in limited infections and no transmission to mice. This study therefore provides the strong evidence that biting midges may play a role in the transmission of *Mundinia* parasites.

Discussion and Conclusion

Further field-based studies are necessary to identify particular vector species in areas of pathogen transmission. Besides Australian *Forcipomyia* species, another good candidate emerged in 2021, when *L. martiniquensis* DNA was detected in wild caught *C. mahasarakhamense* near the home of a leishmaniasis patient in Lamphun province, northern Thailand [33].

Finally, the reduced repertoire of enzymes modifying LPG side chains, a molecule important for *Leishmania* and *Viannia* development in the sand fly, is also indicative of non-standard *Mundinia* vectors [34]. The identification of vectors and reservoir hosts of *Mundinia* parasites is a significant challenge and is also of importance in the context of the unique geographical distribution of *L. martiniquensis*, which is the only species of the *Leishmania* genus occurring in Central Europe.

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