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Cystic echinococcosis: Future perspectives of molecular epidemiology

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ABSTRACT

Human cystic echinococcosis (CE) has been considered to be caused predominantly by *Echinococcus granulosus* sensu stricto (the dog-sheep strain). Molecular approaches on CE, however, have revealed that human cases are also commonly caused by another species, *Echinococcus canadensis*. All indices for classification and standardization of CE pathology including available images, epidemiology, diagnostics and treatment are currently based largely on a mixture of infections which include at least *E. granulosus* s.s. and *E. canadensis*. Involvement of other species of *Echinococcus* in CE including *E. ortleppi* or otherwise cryptic diversity demonstrated recently in Africa requires further elucidation. Molecular identification of the causative species in CE cases is essential for better understanding of pathogenesis and disease. This article stresses the importance of molecular species identification of human CE as a foundation for re-evaluation of evidence-based epidemiology.

1. Historical background

Cystic echinococcosis (CE) has generally been known as an endemic disease, mainly occurring in pastoral areas worldwide. The most important pathogen to humans is believed to be *Echinococcus granulosus* sensu stricto (s.s.), a synanthropic cestode which uses domestic dogs as definitive hosts and mainly sheep as intermediate hosts (Eckert and Deplazes, 2004; Eckert et al., 2001). Humans become infected accidentally via ingestion of eggs derived from feces of infected dogs, and human CE mainly manifests itself in the form of chronic hepatic disease (Brunetti et al., 2010). There are, however, different causative agents of CE which historically had been linked, often in the absence of unequivocal diagnosis, to distinct clinical characteristics. Epidemiological and pathological observations of CE suggested the presence of intraspecific variants (i.e. biological strains showing differing host specificity in metacestode development, see e.g., Thompson and Lymbery, 1988) within *E. granulosus* sensu lato (s.l.) (e.g., Rausch, 2003), and the cryptic complex was divided into numerous genotypes (G1-G10, with the doubtful existence of G9) based on mitochondrial DNA (mtDNA) sequences (Bowles et al., 1992a; McManus and Thompson, 2003; Nakao et al., 2007, 2013a). Recent taxonomic revisions have suggested that *E. granulosus* s.l. consists of five species: *E. granulosus* s.s. (G1, G2 and G3), *Echinococcus equinus* (G4), *Echinococcus ortleppi* (G5), *Echinococcus canadensis* (G6, G7, G8 and G10) and *Echinococcus felidis* (Table 1 and Fig. 1) (Hüttner et al., 2008; Nakao et al., 2007; Thompson and McManus, 2002).

Among this assemblage of species, *E. canadensis* has a broad spectrum of intermediate hosts from livestock to wildlife, which is responsible for the synanthropic and sylvatic life cycles of the associated genotypes (Alvarez Rojas et al., 2014; Nakao et al., 2013a,b; Romig et al., 2015). Domestic dog and livestock (camel and pig) are involved in the synanthropic cycle (G6 and G7, respectively), whereas wolf, dog and cervids (particularly moose and reindeer) in sylvatic or semi-sylvatic cycles (G6, G8 and G10) (Fig. 2) (Konyaev et al., 2013).

Although G6 and G7 are recognized from different areas and intermediate host animals (Lymbery et al., 2015), molecular evaluation does not indicate substantial differences, and phenotypic variation may reflect both natural and artificial factors. For example, the occurrence, respectively of G6 and G7, in areas where camels are reared naturally differs from those where pigs are reared. In sympatry, however, both species of potential hosts might be infected with G6 and G7; experimental infection would be useful to explore the potential for segregation and the degree to which G6 and G7 may be distinct. In contrast, recent detailed molecular studies may refute unequivocal differentiation of G6 and G7, and would

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Table 1
Pathogenic organisms causing cystic echinococcosis in humans and animals.

Species[a]	Distribution	Definitive hosts	Intermediate hosts	Human infections	Strains used previously (genotypes)
Echinococcus granulosus sensu stricto	Worldwide	Dog	Sheep, goat, buffalo, various ungulates, macropodids	Commonest	Sheep strain (G1, G2 and G3)
Echinococcus canadensis[b]					
E. canadensis G6/G7	Worldwide (regional)	Dog, wolf	Camel, pig, cattle goat, reindeer, sheep	Common	Camel and pig strains (G6 and G7)
E. canadensis G8	Holarctic zone	Wolf	Moose, wapiti, muskox	Uncommon	Cervid strain (G8)
E. canadensis G10	Holarctic zone	Wolf, dog	Reindeer, wapiti, moose	Uncommon	Cervid strain (G10)
Echinococcus ortleppi	Worldwide (sporadic)	Dog	Cattle	Less common	Cattle strain (G5)
Echinococcus equinus	Worldwide (sporadic)	Dog, lion[c]	Equines	Unknown	Horse strain (G4)
Echinococcus felidis	Africa (regional)	Lion, spotted hyena	Warthog	Unknown	Lion strain

[a] All of the species listed had been treated as a single species, *E. granulosus*.
[b] The species were divided into three intraspecific groups according to genotypes.
[c] Wassermann et al. (2014).

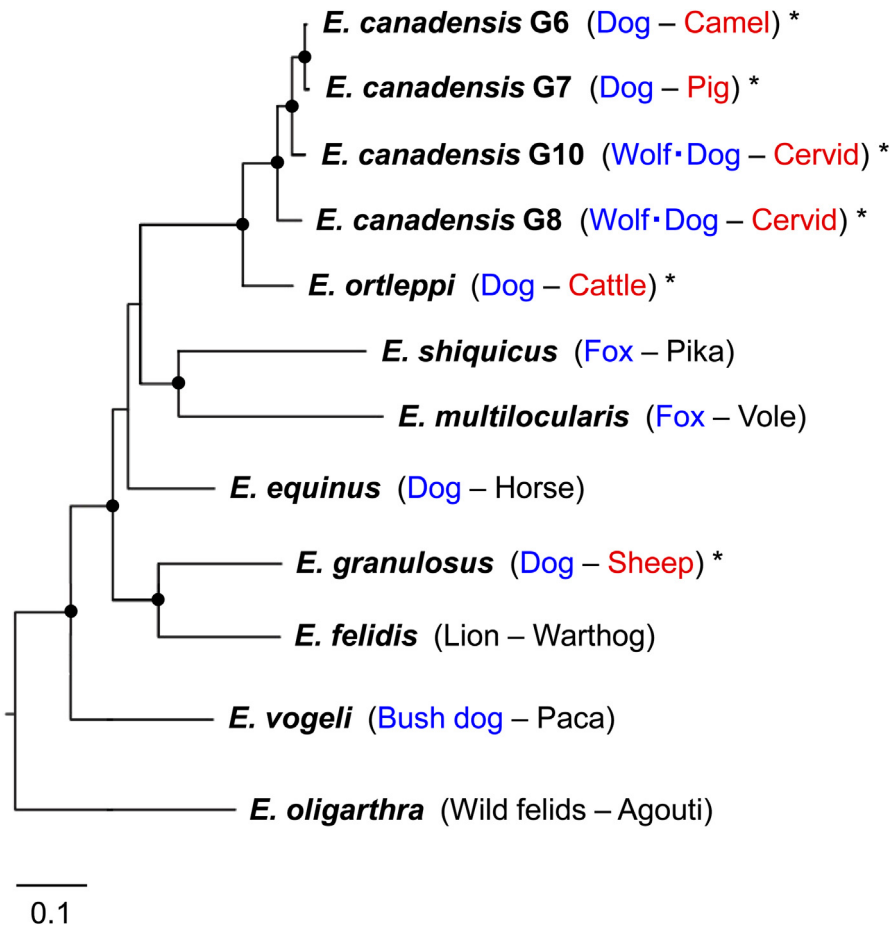

Fig. 1. A phylogeny of *Echinococcus* species (Nakao et al., 2013b). The maximum likelihood tree was generated using DNA sequences of all protein-coding genes from mitochondrial genomes (10098 nucleotide sites). An outgroup taxon (*Versteria mustelae*) was omitted from the tree. Closed circles indicate reliable nodes showing more than 90% bootstrap values. Scale bar represents the estimated number of substitutions per site. Definitive and intermediate hosts are shown in parentheses. Hosts in blue and red mean the family Canidae and the order Artiodactyla, respectively. Asterisks indicate species causing human cystic echinococcosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

refer both to *E. canadensis* along with G8 and G10. Our nomenclatural decision regarding genotypes, applied herein (use of G6/7 rather than G6 and G7), is consistent with recent independent discussions about the phylogenetic and taxonomic structure within *Echinococcus* (Alvarez Rojas et al., 2014; Nakao et al., 2007, 2013b; Romig et al., 2015; Saarma et al., 2009). Thus far, the specific status of *E. canadensis* is still controversial, whether it is attributed to one or multiple species remains to be unequivocally resolved (Lymbery et al., 2015; Nakao et al., 2013b, 2015).

The current understanding of the geographic distribution of *E. granulosus* s.l. genotypes together with the different clinical features presented by patients suggests that CE may be caused by

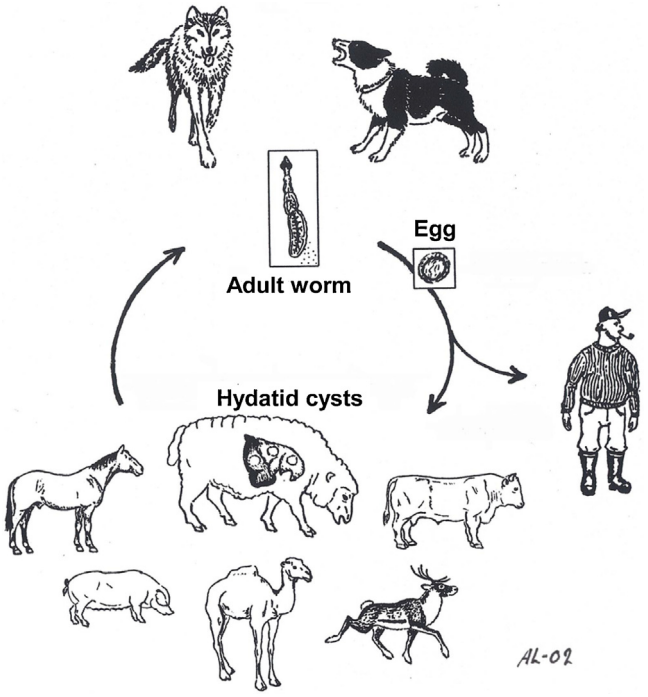

Fig. 2. The life cycle of *Echinococcus granulosus* sensu lato based on Eurasian data (Alvarez Rojas et al., 2014).

different species of *Echinococcus*. According to a recent summary of 1661 genotyped cases published worldwide, the majority (88%) is caused by *E. granulosus* s.s. (Alvarez Rojas et al., 2014). Molecular identification of human CE cases is strongly recommended for better understanding of epidemiology, pathology and the course of infections, particularly in areas of sympatry, where multiple etiological agents of CE overlap.

2. Pathology and epidemiology of CE highlight the need for a differential molecular diagnostic

Experts of the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) have differentiated CE into 6 pathological stages based on ultrasound imaging: CL, CE1, CE2, CE3 (including 3a and 3b), CE4 and CE5 (Brunetti et al., 2010). The WHO-IWGE stages may represent a continuum for disease progression, or could denote identifiable outcomes or endpoints for CE in humans and have been defined as follows: CL is small with no evident pathognomonic signs; CE1-CE2 and CE3b are active; CE3a is transitional; and CE4 and CE5 are inactive or otherwise benign. Thus, a critical question for resolution is whether or not there are characteristic or typical associations linking CE pathology and clinical outcomes with specific species or genotypes (Rossi et al., 2016).

Recent studies based on molecular identification have shown that CE caused by *E. canadensis* G6/7 is not rare but rather commonly observed in humans and synanthropic ungulates including camels and pigs throughout the world (Fig. 2). In some endemic areas (for example, Poland, Mongolia) the majority of confirmed human CE cases are not due to *E. granulosus* s.s. but have been attributed to *E. canadensis* G6/7 (Dybicz et al., 2013, 2015; Ito et al., 2014), although the proportion of the latter is minor (12%) according to worldwide records (Alvarez Rojas et al., 2014). Coinfections may also occur: Recently, a human case infected with both *E. granulosus* s.s. and *E. canadensis* was reported from Tunisia (Oudni-M'rad et al., 2016). There are only a few reported human cases due to *E. ortleppi* (e.g., Bowles et al., 1992b; de la Rue et al., 2011; Guarnera et al., 2004; Mogoye et al., 2013) and its importance is not yet clear. There are many countries where *E. ortleppi* has been reported from animals (Cardona and Carmena, 2013; Carmera and Cardona, 2014; Romig et al., 2015), but relatively few localities where this species has been confirmed to be in sympatry with *E. granulosus* s.s. or *E. canadensis* (G6/7) (Fig. 3). Discovery of additional cases might be anticipated when molecular identification becomes common, but currently the importance of this species in CE appears to be negligible as compared with *E. canadensis* (Amer et al., 2015; Alvarez Rojas et al., 2014; Bowles et al., 1992b; de la Rue et al., 2011; Grenouillet et al., 2014; Guarnera et al., 2004; Romig et al., 2015; Tigre et al., 2016).

Clinically benign features of CE caused by *E. canadensis* were observed in Alaska and neighboring Canada, where G8 and G10 are exclusively distributed (Finlay and Speert, 1992; Jenkins et al., 2011, 2013; Lamy et al., 1993; Nakao et al., 2013b; Pinch and Wilson, 1973; Rausch, 2003; Wilson et al., 1968). In northern Fennoscandia, CE cases among reindeer herding populations have a presumptive diagnosis as *E. canadensis* (Lavikainen, 2005; Lavikainen et al., 2003), primarily because synanthropic *E. granulosus* s.s. is not known to have expanded northward into the boreal forests (Rausch, 2003). These clinical reports suggested that CE due to *E. canadensis* is a relatively benign disease, characterized by pulmonary involvement of small hydatid cysts with a thinner cyst wall, and by spontaneous recovery due to cyst rupture (Finlay and Speert, 1992; Lamy et al., 1993; Lavikainen, 2005; Pinch and Wilson, 1973; Rausch, 2003; Wilson et al., 1968). In contrast, however, a severe disseminated peritoneal CE case caused by G8 has been diagnosed in Alaska (Castrodale et al., 2002), and some severe historical cases of CE have been reported in northern Fennoscandia (Lavikainen, 2005; Lavikainen et al., 2003). In Mongolia, most of the adult hepatic CE cases treated surgically were caused by *E. granulosus* s.s., whereas all hepatic CE cases in children were attributed to *E. canadensis* G6/7 and G10 (Ito et al., 2014). CE cases caused by *E. canadensis* in Mongolia might also be mild as in Alaska and Canada, and spontaneous healing during childhood could explain the low prevalence in adults. Alternatively, the lack of adult CE cases caused by *E. canadensis* might be due to severity of the disease and early death of children infected with this parasite (Ito et al., 2014). Follow-up studies of children in CE cases caused by *E. canadensis* from Mongolia would be highly informative and can provide the basis for evaluation of this difference in patient age. Mongolia may be one of a limited number of co-endemic countries where CE cases caused by the two species can be directly compared and differences in their pathology and organotropism can be identified (Brunetti et al., 2010; Eckert et al., 2001; Torgerson and Deplazes, 2009).

The clinical characteristics of *E. canadensis* G6/7 are difficult to distinguish from those of *E. granulosus* s.s., because both pathogenic species have sympatric distributions in co-endemic areas (Fig. 2). Several recent reports stress differences between *E. granulosus* s.s. and *E. canadensis*: organotropism of the latter to the brain (Sadjjadi et al., 2013), differences in Eg95-related proteins (Alvarez Rojas et al., 2013), minor variation in Antigen B8/5 gene sequence (Mamuti et al., 2007), minor difference in growth rate (Guarnera et al., 2004), and difference in antibody responses (Ito et al., 2014).

Consequently, data on CE, often attributed to *E. granulosus* s.s., probably originated from observations of a mixture of *E. granulosus* s.s. and *E. canadensis* infections. For example, approximately 70% of CE is located in the liver, 20% in lungs, with few infections in other organs (Eckert et al., 2001). These percentages may be affected by the presence of different causative agents (Sadjjadi et al., 2013). Accordingly, the pathology, epidemiology and chemotherapeutic efficacy in cases of CE should be re-evaluated, recognizing that etiology involves at least these two species and multiple genotypes. In addition, standardization for ultrasound imaging should be re-evaluated and linked to molecular identification of parasites by mitochondrial DNA (mtDNA) markers. Molecular identification of the species causing CE is essential evidence for any further discus-

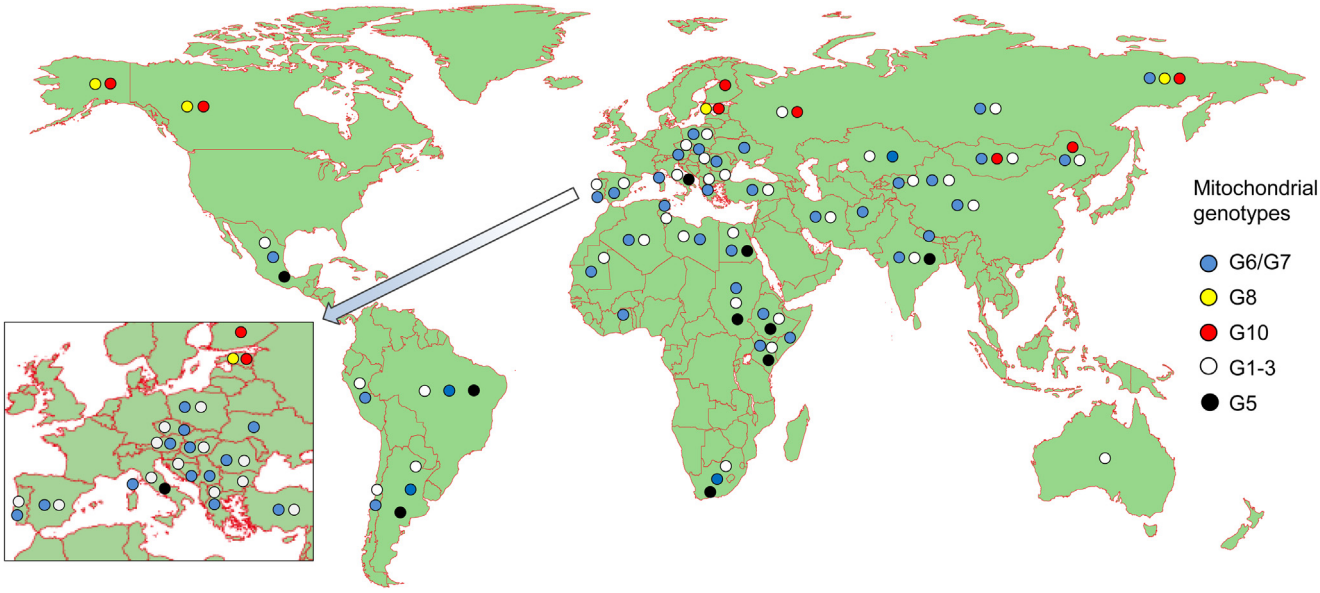

Fig. 3. Global distribution of the genotypes of *Echinococcus canadensis* and *Echinococcus granulosus* sensu stricto, based on molecular identification including areas of confirmed sympatry for *E. ortleppi* (Alam-Eldin et al., 2015; Alvarez Rojas et al., 2014; Cardona and Carmena, 2013; Carmera and Cardona, 2014; Casulli et al., 2010; Dybicz et al., 2013, 2015; Farhadi et al., 2015; Guarnera et al., 2004; Hailemariam et al., 2012; Hüttner et al., 2009; Ito et al., 2013, 2014; Jabbar et al., 2011; Jenkins et al., 2011, 2013; Kędra et al., 1999, 2000; Konyaev et al., 2013; Lavikainen, 2005; Lavikainen et al., 2003, 2006; Lymbery et al., 2015; Mbaya et al., 2014; Mogoye et al., 2013; Moks et al., 2006; Monteiro et al., 2014; Moro et al., 2009; Nakao et al., 2007, 2013b, 2015; Oksanen and Lavikainen, 2015; Omer et al., 2010; Oudni-M'rad et al., 2016; Rinaldi et al., 2014; Rodriguez-Prado et al., 2014; Romig et al., 2015; Saarma et al., 2009; Schneider et al., 2010; Schurer et al., 2013, 2014; Sharma et al., 2013a,b; Šnábel et al., 2009; Sweatman and Williams, 1963; Thompson and Jenkins, 2014; Umhang et al., 2014; Wang et al., 2015; Yang et al., 2015; Zhang et al., 2014). Closely related genotypes G6/7 of *E. canadensis* are shown with a single symbol. Records of *E. granulosus* s.s. (G1-3), which has a broad cosmopolitan distribution, are shown only when found in areas of sympatry with *E. canadensis* except Australia (Alvarez Rojas et al., 2016). Additional records of *E. ortleppi* (G5) are also shown on this map only where it has been recorded sympatrically with *E. granulosus* s.s. or *E. canadensis* (G6/7) (Amer et al., 2015; Bowles et al., 1992b; de la Rue et al., 2011; Guarnera et al., 2004; Mogoye et al., 2013; Tigre et al., 2016).

sions, particularly in areas where *E. granulosus* s.s. and *E. canadensis* have sympatric distributions.

3. Future perspectives of molecular epidemiology

Currently, the causative agent of echinococcosis in humans and animals can definitively be identified after surgery or necropsy, respectively, using molecular genotyping if available. Morphology of the rostellar hooks of the parasite can also be used for a species level differentiation, if the cyst is fertile (Harandi et al., 2002). Ultrasound or other imaging technologies can give direct evidence of CE only when the cyst has diagnostic features, even without serology. Imaging and serology, or often even histopathology, however, cannot provide definitive diagnosis of the causative species or intraspecific entity. When diagnosis of CE is clear from non-invasive imaging, there is no medical indication to conduct a biopsy simply for genotyping, especially considering the risk of secondary cyst formation associated with invasive diagnostic procedures (Kawakami et al., 2013; Kern et al., 1995). In human cases, almost all molecular evidence of causative species is obtained from resected CE lesions. Thus far, it means that there is no tool to differentiate the two species without surgery in many suspected cases of CE. Highly reliable and active epidemiological studies, as a basis toward the control of echinococcoses, are only possible if accurate identification at the species-level can be provided; current indirect methods for diagnosis do not provide this capacity.

In the future, molecular detection and identification of pathogen-specific DNA, RNA or any other biomarkers such as metabolites may become feasible using blood, saliva or urine samples, thus eliminating the need for needle biopsy for recovery of pathology specimens (Aoki et al., 2015; Bothale et al., 2015; Kawakami et al., 2013; Kern et al., 1995). Such protocols can be expected to contribute to an accurate epidemiological picture of infections. Basic molecular taxonomic data of *Echinococcus* species are increasingly applied in epidemiological studies (Alvarez Rojas et al., 2014, 2016; Casulli et al., 2012; Nakao et al., 2010, 2013a; Romig et al., 2015; Yanagida et al., 2012) and are a pre-requisite in projects which focus on control and prevention of echinococcoses. Such an approach for molecular differentiation of CE cases in developing countries is difficult without active collaborative projects with research groups having such advanced skills. However, the major areas with sympatric distribution of the two species are in Europe (Fig. 3), and in addition, there is a high risk of rapid increase in CE cases in big cities in the western European countries including Germany due to migration and globalization. It may also be anticipated that many additional CE cases have been or will be confirmed among refugees from the Middle East or immigrants from Eastern Europe. Therefore, the "Heracles" project for European Register of Cystic Echinococcosis (ERCE) (http://www.Heracles-FP7eu) may contribute to development and application of broad-based molecular protocols for diagnostics (Alvarez Rojas et al., 2014; Rossi et al., 2016; Tamarozzi et al., 2015).

Current phylogenetic and historical evidence suggests that *E. granulosus* s.s. initially emerged in the Middle East coincidental with domestication of sheep (Casulli et al., 2012; Moro et al., 2009; Nakao et al., 2010, 2013a; Yanagida et al., 2012). The ancestor of *E. granulosus* s.s. might have been distributed in northeastern parts of Africa, at least, when Africa and Arabian Peninsula were not separated by the Red Sea. Such a history would be consistent with the currently recognized sister-species relationship for *E. granulosus* s.s. and *E. felidis* which also indicates a deeper temporal association for species of *Echinococcus* in large carnivores and ungulates prior to domestication of caprines (e.g., Zarlenga et al., 2014). Further comparative studies of intra-species diversity of *E. granulosus* s.s. distributed in the Middle east and Africa are necessary for a better understanding of the origin and evolution of host relationships among these species and populations, since the African origin of *E. granulosus* s.s. is possible (Wassermann et al., 2016).

Table 2
Representative molecular methods to discriminate the members of *Echinococcus granulosus* sensu lato, based on nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Cytochrome *c* oxidase subunit 1 (*cox1*), NADH dehydrogenase 1 (*nad1*), Cytochrome *b* (*cob*) are major genes to be tested. Useful sample material for molecular identification: Hydatid sand or debris of germinal layers preserved in > 70% ethanol, or paraffin embedded histopathologic specimens.

Methods	Targets	Discrimination abilities		References
		Intraspecific level (*E. canadensis* genotypes)	Interspecific level	
DNA barcoding	mtDNA	able	able	Bowles et al. (1992a,b)
PCR-RFLP[a]	nDNA	able	able	Bowles and McManus (1993)
LAMP[b]	mtDNA	unable	able	Wassermann et al. (2014)
PCR-SSCP[c]	mtDNA	able	able	Sharbatkhori et al. (2009)
mPCR[d]	mtDNA	depends on the primer set	able	Boubaker et al. (2013)

[a] PCR-restriction fragment length polymorphism.
[b] Loop-mediated isothermal amplification.
[c] Single strand conformation polymorphism.
[d] Single-tube multiplex PCR.

Thus far, there are only three recognized genotypes of *E. granulosus* s.s. (G1–G3). However, Wassermann et al. (2016) found a large, 20 × 20 cm, mass in the leg muscles, with no additional lesions in the liver, of a 55 year old male living in southern Ethiopia, and confirmed it to be a new genotype independent from G1-3. Several apparently isolated and otherwise unusual cases of human CE from Africa have been associated with hydatids in the musculature, but not the liver, although none of these were definitively identified. These cases, which have only been sporadically reported, potentially may be attributed to a cryptic genotype of *E. granulosus* s.s. that had not been recognized previously (Macpherson et al., 1989; Magambo et al., 1998; Romig et al., 2011). Characterization of this genotype by Wassermann et al. (2016) demonstrates the power of molecular approaches and the continuing need to adequately document diversity within *Echinococcus*. It is apparent that hidden diversity remains to be discovered or revealed, and that new genotypes will not be recognized in the absence of uniform applications of molecular-based approaches to identification.

In parallel, we might anticipate that human infections due to *E. felidis*, the sister species of *E. granulosus* s.s. (Fig. 1), may eventually be confirmed among CE cases in Africa where populations of lion definitive hosts remain extant. The risk of exposure and infection not only for local residents, but also for conservation biologists, park rangers and eco-tourists must be considered. An important contribution would be the development of increasingly rapid and simple methodologies for identification and novel tools that can provide direct evidence of infections (Alvarez Rojas et al., 2014; Ito, 2013; Nakao et al., 2013a; Romig et al., 2015; Wassermann et al., 2016).

4. Concluding remarks

The majority of CE cases historically were attributed or presumed to be caused by *E. granulosus* s.s., mainly G1. However, recent molecular studies of CE cases have revealed that *E. canadensis* (G6/7) is not rare, but common (Fig. 3). Therefore, to clarify the epidemiology of CE cases, the causative species of *Echinococcus* should be identified with appropriate molecular tools. Clinical features of the cases confirmed should be analyzed at an international level in a comparative context to explore potential variability in presentation of disease that may reflect associations with particular population groups or geographic origins. Surveillance of host animals other than humans should be carried out in order to obtain robust evidence on the life cycles of *E. granulosus* s.s., *E. canadensis*, and other potentially zoonotic species with respect to areas of endemism and patterns of circulation.

A need remains to accurately identify the causative agents of CE as a basis for increasingly refined options for diagnostics and treatment and as the foundation to understand the nuances of local-scale patterns of transmission and circulation which influence the potential for disease. Table 2 shows the molecular tools for differentiation of *E. granulosus* s. l. previously overviewed by several groups (e.g., Dinkel et al., 2004; Nakao et al., 2013a; Wassermann et al., 2014). We suggest that attainment of such a global goal depends on our future capacity to develop collaborative networks to introduce molecular-based identification of all CE specimens, as they are discovered, recognized, collected and archived, especially in areas of sympatry for multiple species (e.g., Brooks et al., 2014). It will go far in providing a robust cornerstone for final resolution of taxonomy and species diversity.

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