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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).

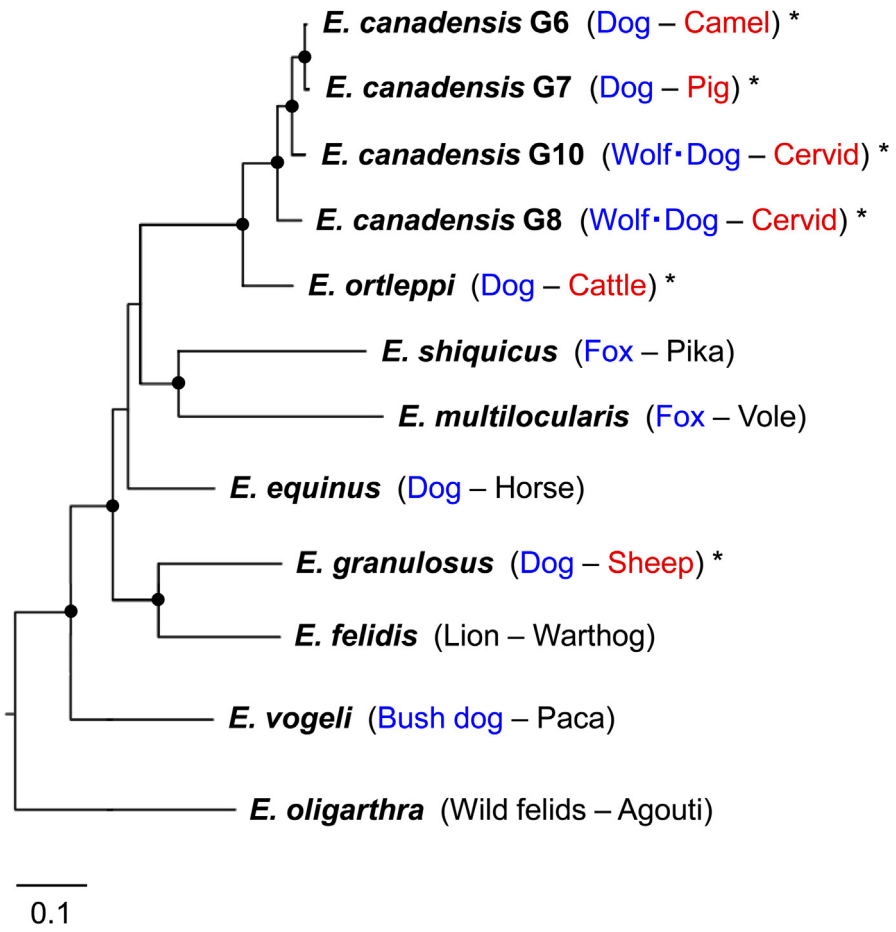

Fig. 1. A phylogeny of *Echinococcus* species (Nakao et al., 2013b). The maximum likelihood tree was generated using DNA sequences of all protein-coding genes from mitochondrial genomes (10098 nucleotide sites). An outgroup taxon (*Versteria mustelae*) was omitted from the tree. Closed circles indicate 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