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Systematic Review

Cystic echinococcosis in South America: systematic review of species and genotypes of *Echinococcus granulosus sensu lato* in humans and natural domestic hosts

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Abstract

OBJECTIVE To systematically review publications on *Echinococcus granulosus sensu lato* species/genotypes reported in domestic intermediate and definitive hosts in South America and in human cases worldwide, taking into account those articles where DNA sequencing was performed; and to analyse the density of each type of livestock that can act as intermediate host, and features of medical importance such as cyst organ location.

METHODS Literature search in numerous databases. We included only articles where samples were genotyped by sequencing since to date it is the most accurate method to unambiguously identify all *E. granulosus* s. l. genotypes. Also, we report new *E. granulosus* s. l. samples from Argentina and Uruguay analysed by sequencing of cox1 gene.

RESULTS In South America, five countries have cystic echinococcosis cases for which sequencing data are available: Argentina, Brazil, Chile, Peru and Uruguay, adding up 1534 cases. *E. granulosus* s. s. (G1) accounts for most of the global burden of human and livestock cases. Also, *E. canadensis* (G6) plays a significant role in human cystic echinococcosis. Likewise, worldwide analysis of human cases showed that 72.9% are caused by *E. granulosus* s. s. (G1) and 12.2% and 9.6% by *E. canadensis* G6 and G7, respectively.

CONCLUSIONS *E. granulosus* s. s. (G1) accounts for most of the global burden followed by *E. canadensis* (G6 and G7) in South America and worldwide. This information should be taken into account to suit local cystic echinococcosis control and prevention programmes according to each molecular epidemiological situation.

keywords *Echinococcus granulosus sensu lato*, genotypes, cystic echinococcosis, South America, neglected disease

Introduction

The larval stage of the cestode parasite *Echinococcus granulosus sensu lato* (s. l.) causes cystic echinococcosis or cystic hydatid disease, a chronic parasitic zoonosis that affects humans as well as domestic and wild mammals. Associated with poverty and poor hygiene practices, particularly in livestock-raising communities [1], this affliction is essentially preventable and considered a neglected disease by WHO. It has been estimated that 1–3.6 million DALYs are lost worldwide because of human cystic echinococcosis [2] and that up to $2 billion are lost annually in the livestock industry [3]. This zoonosis is distributed worldwide and is endemic or

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hyperendemic in South America, especially in Argentina, southern Brazil, Uruguay, Chile and mountainous regions of Peru and Bolivia.

Echinococcus granulosus s. l. requires two mammalian hosts to complete its life cycle: a definitive host (usually dogs or other canids) and an intermediate host (wild or livestock mammals). Humans act as accidental hosts. The strobilar adult stage develops as a flatworm in the gut of the definitive host and produces eggs with oncospheres by sexual reproduction. The infective eggs are released with the host faeces into the environment, where they are ingested by the intermediate host. Upon ingestion, the oncospheres are released, migrate through the intestinal wall and spread through the bloodstream to various organs, most commonly the liver and lung. Each oncosphere has the potential to develop into a metacestode (hydatid cyst). Within the hydatid cyst, protoscoleces, the next larval stage, are produced by asexual multiplication giving rise to fertile cysts. Protoscoleces are able to develop into adult parasites after hydatid cyst ingestion by the definitive host. Also, if content leakage from a fertile hydatid cyst occurs within the intermediate host, protoscoleces have the ability to develop into new hydatid cysts (secondary cystic echinococcosis).

Species and genotypes of *Echinococcus granulosus sensu lato*

Echinococcus granulosus s. l. is composed of numerous variants initially identified by J.D. Smyth and Z. Davies (1974) [4] who called them 'physiological strains'. This term was due to the observation of radical differences in the *in vitro* development of protoscoleces isolated from sheep and horse cysts [4, 5]. Since then, more strains were identified and several works have shown that the strains differ in many features such as protein profile [6], carbohydrate and lipid repertoires [7], hooks morphology [8–10], metabolic requirements (reviewed in [7]), fertile cyst development in natural infections (reviewed in 11), cyst development in experimental infections [12], intermediate host specificity, pre-patent period [13, 14], antigenicity [15] and infectivity and pathogenicity in humans [11, 16].

Later on, molecular biology techniques allowed the identification of DNA polymorphisms in mitochondrial genes of *E. granulosus* s. l. Those polymorphisms were detected by DNA sequencing [17, 18] and PCR-RFLP [19] and correlated with the strains described until then. This allowed to assign a genotype to each strain. Since then, several molecular tools have been applied to determine *Echinococcus* spp. genetic variability, such as Southern blot [20], PCR-SSCP [21], RAPD [22], multiplex PCR [23], LAMP [24] and HRM [25] among others. To date, ten genotypes (G1-G10) and the 'lion strain', only found in wild hosts, have been described [26].

In the last years, mitochondrial phylogenetic analysis allowed to classify most of the genotypes as new species [11, 27]. The new classification infers that *Echinococcus granulosus sensu stricto* (s. s.) groups the G1, G2 and G3 genotypes. Particularly, the G1 genotype is the most frequently found worldwide, produces fertile hydatid cysts mainly in sheep and is frequently isolated from humans. Recently, *E. granulosus* s. s. (G1) has been identified in cats; however, the epidemiological importance of the cat as intermediate host could be considered marginal due to the few cases reported since the first case was described [28, 29].

Echinococcus equinus (G4 genotype) has remarkable morphological and developmental differences with the G1 genotype and has only been found in horses and other equines, and no human cases have been reported [11]. *Echinococcus ortleppi* (G5 genotype) produces fertile cysts mainly in cattle and has been described in few human cases [30]. *Echinococcus canadensis* includes the G6, G7, G8 and G10 genotypes since phylogenetic analysis grouped them as a monophyletic group [27]. Camels and goats are the main intermediate hosts for the G6 genotype, pigs for the G7 genotype and cervids for the G8 and G10 genotypes. All these genotypes have been isolated from humans. Finally, the G9 genotype human cases described by Scott *et al.* (1997) [31] are now considered to have belonged to the G7 genotype [32]. In summary, the *E. granulosus* s. l. complex groups: *E. granulosus s. s.* (G1/G2/G3), *E. equinus* (G4), *E. ortleppi* (G5), *E. canadensis* (G6/G7/G8/G10) and *E. felidis* ('lion strain').

In this work, we provide new data and perform a comprehensive review of the circulating *E. granulosus* s. l. genotypes in domestic animals and human cases in South America identified by DNA sequencing. The information obtained on human echinococcosis was further integrated with data reported worldwide to compare the South American situation with the global scene.

Methods

Literature search

The literature search was conducted mainly using PubMed database (Figure S1) using three terms: echinococcus, echinococcosis or hydatid disease, in the period 1992–2014. Records obtained were further filtered by combining related keywords using Boolean operators. The keywords used were genotype, strain, species, sequence, molecular marker and gene in Title/Abstract. After removing duplicated reports, full articles in English or Spanish were retrieved by an in-house bash script. We further con-

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sidered those articles that reported *E. granulosus* s. l. genotype identification by DNA sequencing and analysed samples from domestic definitive and natural intermediate hosts from South American countries together with reports from human cases worldwide (inclusion criteria). We excluded cystic echinococcosis reports with ambiguous genotype description, such as cryptic sequence analysis. Finally, complementary searches were performed in four databases: Science Direct, Journal of Citation Reports, Scopus and Google Scholar and relevant articles were included in the final review if they met the inclusion criteria. Moreover, samples reported in more than one article were taken into consideration once. The combination of the different criteria aimed to retrieve as many relevant publications as possible but at the same time tried to narrow the amount of results only to those articles which employed an accurate method to identify *E. granulosus* s. l. genotypes. The aim of the present review is to highlight only results from sequenced samples since to date it is the most accurate method to unambiguously identify all *E. granulosus* s. l genotypes. We would like to mention that it is possible that relevant papers, which did not contain in their titles or abstracts the keywords used in our search, may have been overlooked.

New *Echinococcus granulosus sensu lato* samples identified by DNA sequencing

Total protoscolex DNA was prepared from fresh, frozen in liquid nitrogen or 70% ethanol preserved isolates of *E. granulosus* s. l. by conventional techniques. In the case of samples with PCR inhibitors present (i.e. cyst layers), the DNeasy Blood & Tissue Kit (QIAGEN) was used [21]. Analysis of the mitochondrial cox1 gene was performed by PCR followed by sequencing as described [12]. The sequence obtained was aligned with published sequences for all species/genotypes from *Echinococcus* reported. A total of 131 samples were obtained from Argentina and Uruguay and were added to the reviewed data. Detailed information of genotype, host, geographical origin, number and reference from all the *E. granulosus* s. l. samples identified in South America until 2014 are shown in Table S1.

Results

Echinococcus granulosus s. l. genotypes isolated from natural intermediate and definitive hosts from South America

In South America, five countries have cystic echinococcosis cases identified in natural intermediate and definitive hosts for which sequencing data are available: Argentina, Brazil, Chile, Peru and Uruguay (Figure 1). A total of six genotypes have been found in the region: G1, G2, G3, G5, G6 and G7. The types of livestock affected are sheep, cattle, pig, goat and alpaca (Figure 1).The majority of the cases are caused by *E. granulosus* s. s. (genotypes G1/G2/G3). The G1 genotype shows the widest distribution and is the most frequently found in the species of livestock analysed as well as in the domestic definitive host (836/1379). The second most frequent genotype is G5 (348/1379) mainly isolated from Brazilian cattle (Table 1). Detailed information of genotype, host, geographical origin, number and reference from all the *E. granulosus* s. l. samples identified by DNA sequencing in South America until 2014 is described in Table S1. The genotypes circulating in Brazilian livestock are G1 (58.5%), G5 (41.0%) and G7 (0.5%) being cattle the principal hosts described (810/815). In Peru, the genotype G1 (89.6%) was found in alpacas, sheep, cattle, goats and pigs; G6 (3.1%) in goats; and G7 (7.3%) in pigs. The range of host species involved in maintaining the life cycle in Peru is the widest in the region since five species of livestock were found to have hydatid cysts (Figure 1, Table S1). With respect to the situation in Argentina, the genotype of 118 *E. granulosus* s. l. isolates from livestock and dogs from different provinces was determined and integrated with data from existing reports tallying up 373 samples (Table S1). A total of six genotypes are circulating in livestock in Argentina (Figure 1): G1 (49.3%) in sheep, cattle, goat and pig; G2 (1.7%) in sheep and cattle; G3 (0.3%) in sheep; G5 (2.6%) in cattle; G6 (8.4%) in goats and cattle; and G7 (37.7%) in pigs (Table S1). At least two different genotypes were isolated from each species of intermediate host, being the G1 genotype present in all of them (Figure 2a). Cattle and sheep are the main reservoirs of the G1 genotype. However, goats and pigs are the main reservoirs of the G6 and G7 genotypes, respectively (Figure 2a). Regarding the molecular epidemiological scenario in definitive hosts, a total of four genotypes (G1, G5, G6 and G7) were found in dogs (Figure 2a). These data show that at least the most widely distributed and frequent genotypes are developing the complete life cycle in Argentina. It is worth mentioning that in one case, a co-infection of the G1 and G6 genotypes was found [21]. Finally, there is still not enough information from Uruguay and Chile to draw conclusions (Table S1).

Taking into consideration all the available data from Argentina, a deeper analysis was performed. As shown in Figure 2a, 36.1% (30/83) of the human cases in Argentina are caused by the G6 genotype. Most of the reported G6 cases in livestock were isolated in Neuquen province.

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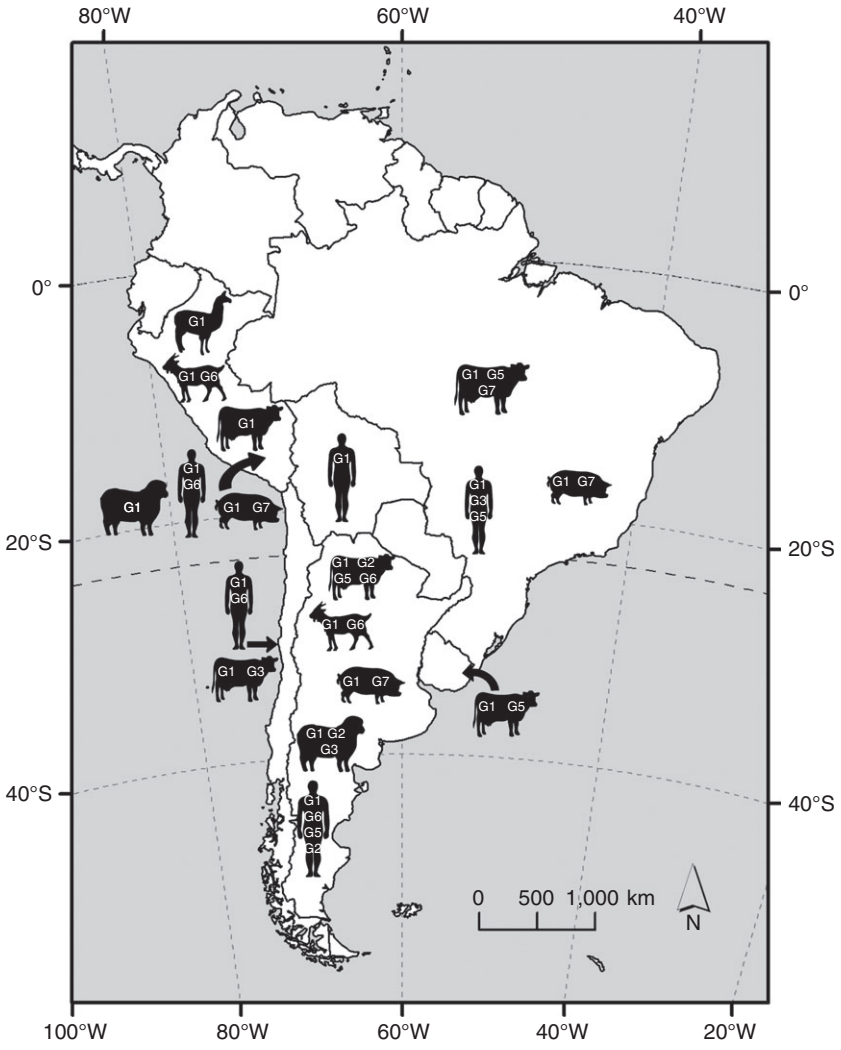

Figure 1 Schematic representation of the geographical and intermediate host distribution of *Echinococcus granulosus sensu lato* genotypes isolated in South America and identified by DNA sequencing. The position of the hosts figures is not indicative of the state/province/department location within a country.

Interestingly, concurrent geographical location of human and animal cases were found in this province, being goats the most frequent host harbouring the G6 genotype (Figure 2 and Table S1). It is imperative to analyse a larger number of samples from other provinces focusing on the main intermediate hosts described for this genotype, i. e. goats and camelids. Livestock density distribution in Argentina reveals the priority areas to analyse in the future: the provinces of Mendoza, Formosa, Chaco, Santiago del Estero, Salta, San Luis, La Rioja, Jujuy and Santa Cruz, where goat and/or camelid production are concentrated (Figure 2b) and for which the molecular epidemiological situation in livestock is scarce or unknown. It would also be useful to analyse whether South American camelids, such as alpacas, llamas and guanacos, play a role in maintaining the natural life cycle of *E. granulosus* s. l. in Argentina. The G6 genotype displays features that are important for cystic echinococcosis diagnosis and control such as sequence variability in the diagnostic antigen B [33, 34] and the vaccine EG95 antigen [35]. Also, differences in anti-EG95 antibody response to infection between the G1 and G6 genotypes have been described [15]. *Echinococcus equinus* (G4 genotype) has not been identified in South America yet, since the cystic echinococcosis cases found in horses lack genotype determination [36]. Also, there are still no reports of *E. canadensis* (G8 and G10 genotypes) in the region.

Echinococcus granulosus s. l. genotypes identified in human cases from South America

In South America, 155 human cystic echinococcosis cases with sequencing information have been reported. The main *E. granulosus* s. l. genotypes infecting humans are

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Table 1 South American species and genotypes of *Echinococcus granulosus sensu lato* identified in domestic natural hosts (intermediate and definitive) and humans in South America by molecular markers sequencing

		South American cases				
Species	Genotype (strain)	Intermediate natural host[a]	Definitive host[b]	Number of cases[a+b]	Human cases[c] (%)	References[a+b+c]
E. granulosus sensu stricto (s.s.)	G1 (sheep)	**Sheep**, camelids, cattle, goats, pigs, cats	Dog	836	112 (72.3)	This work, [20, 21, 28, 37, 38, 40–47]
	G2 (Tasmanian sheep)	**Sheep**, cattle	–	6	6 (3.9)	[20, 21, 38]
	G3 (buffalo)	**Sheep**	Dog	3	1 (0.6)	[42, 44]
E. ortleppi	G5 (cattle)	**Cattle**	Dog	348	3 (1.9)	This work, 21, 38, 40, 45, 48, 52.
E. canadensis	G6 (camel)	**Goats**, cattle	Dog	38	33 (21.3)	This work, [10, 20, 21, 41, 42, 49–51]
	G7 (pig)	**Pigs**, cattle	Dog	148	–	This work, [20, 21, 40–42, 46]
		Total		1379	155	

The main intermediate host of each genotype in South America is highlighted in bold.

G1 (72.3%) and G6 (21.3%) (Table 1). This information is of particular interest since these genotypes belong to two different species, *E. granulosus* s. s. and *E. canadensis*, respectively, according to the new classification of the complex. Human cases caused by the genotypes G2, G3 and G5 (Figure 1) have also been reported, but with lower frequencies (<4%) (Table 1). Particularly, in Chile and Peru, G1 and G6 are present in humans being G1 responsible for 96% (24/25) and 95% (38/40) of the cases, respectively. It is interesting to note that despite the high number of human cases identified in Peru, none was caused by the G7 genotype, even though this genotype has been isolated from pigs in this country. In spite of the fact that there are few human cystic echinococcosis cases with genotype information from Brazil ($N = 6$), three genotypes were found (G1, G3 and G5). The only human cystic echinococcosis case from Bolivia belonged to the G1 genotype (Figure 1 and Table S1).

The most complete molecular epidemiological picture for human cystic echinococcosis corresponds to Argentina ($N = 83$). The genotypes identified in patients were G1 (54.2%), G2 (7.2%), G5 (2.4%) and G6 (36.1%) (Figure 2a, Table S1). In agreement with the situation in Peru, the data reviewed in this work strongly support the idea that in Argentina pigs are the only reservoir of the G7 genotype (Figure 2a) and that this genotype seems not to be a substantial human health problem. For an accurate determination of human infection risk with the G7 genotype in Argentina, we integrated the information on genotypes from human echinococcosis cases with density (animals/ha) of swine livestock all over the country. The main producers of pigs are the provinces of Cordoba and Santa Fe, followed by a lower production in Buenos Aires, Chaco, Entre Rios, Misiones, Formosa and San Luis (Figure 2b). Unfortunately, there is little or no genotype information on human cases reported from these provinces (Table S1). As shown in Figure 2b, there is an intensive bovine livestock activity in Argentina. Cattle were found to harbour the genotypes G1, G2, G5 and G6, which are all infective to humans (Figure 2a). This highlights the fact that cattle play a crucial role in maintaining the life cycle of almost all circulating genotypes in Argentina and also in human transmission, especially taking into account the high reported median fertility rate of cattle cysts in this country (42%) [21, 37, 38].

Human cystic echinococcosis worldwide

A total of 877 human cystic echinococcosis isolates have been sequenced and reported worldwide (Figure 3a and Table S2). *Echinococcus granulosus* s. s. is the aetiological agent of most human cases worldwide (Figure 3a) being

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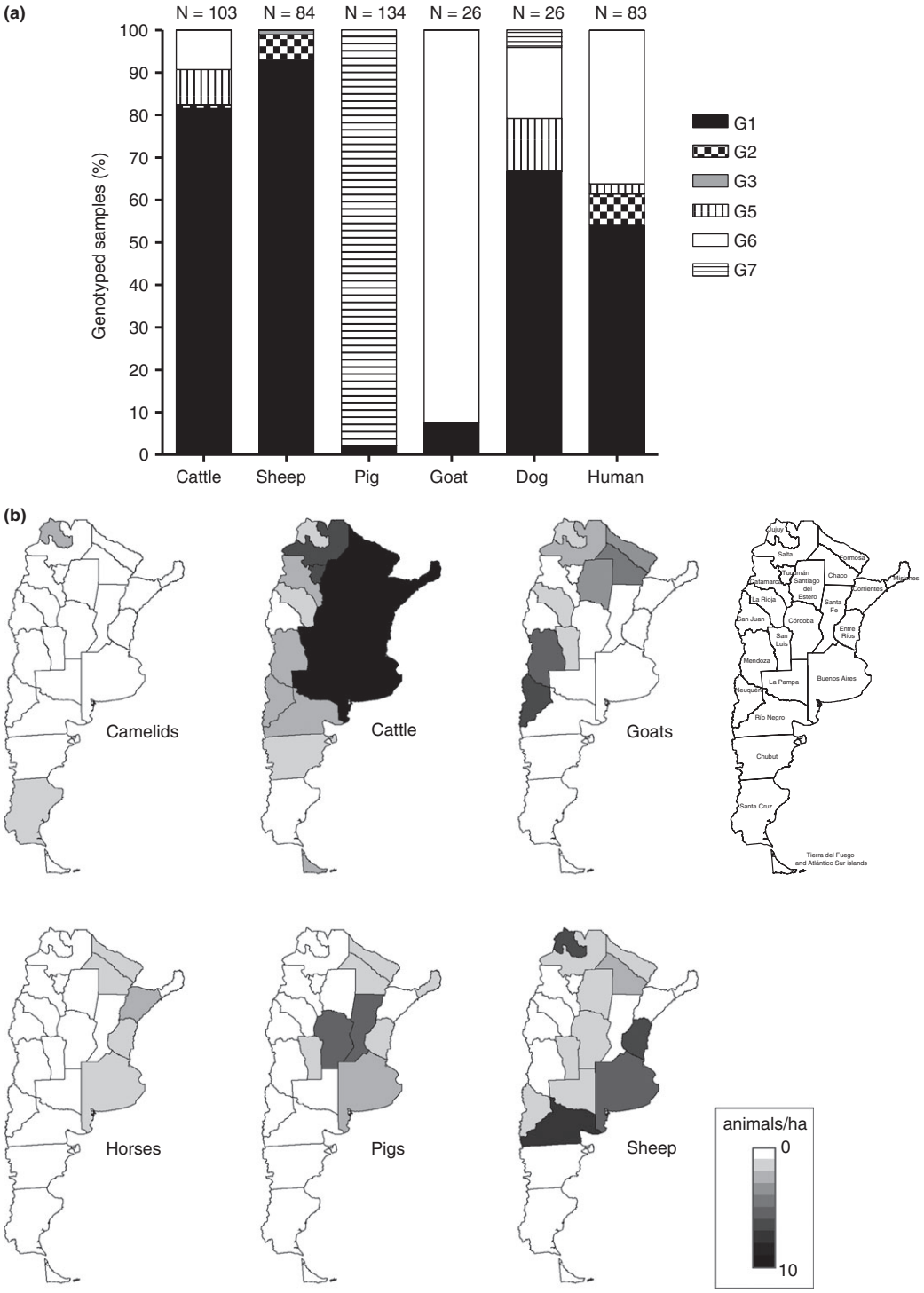

Figure 2 Molecular epidemiological situation of cystic echinococcosis in Argentina. (a) *Echinococcus granulosus sensu lato* genotypes harboured in definitive and intermediate hosts. Samples with genotype identification by DNA sequencing are shown. (b) Livestock density (animals/ha) in Argentina. Data source: Ministerio de Agricultura, Ganadería y Pesca de la Nación, Secretaría de Agricultura, Ganadería y Pesca and Secretaría de Ambiente y Desarrollo Sustentable-INTA.

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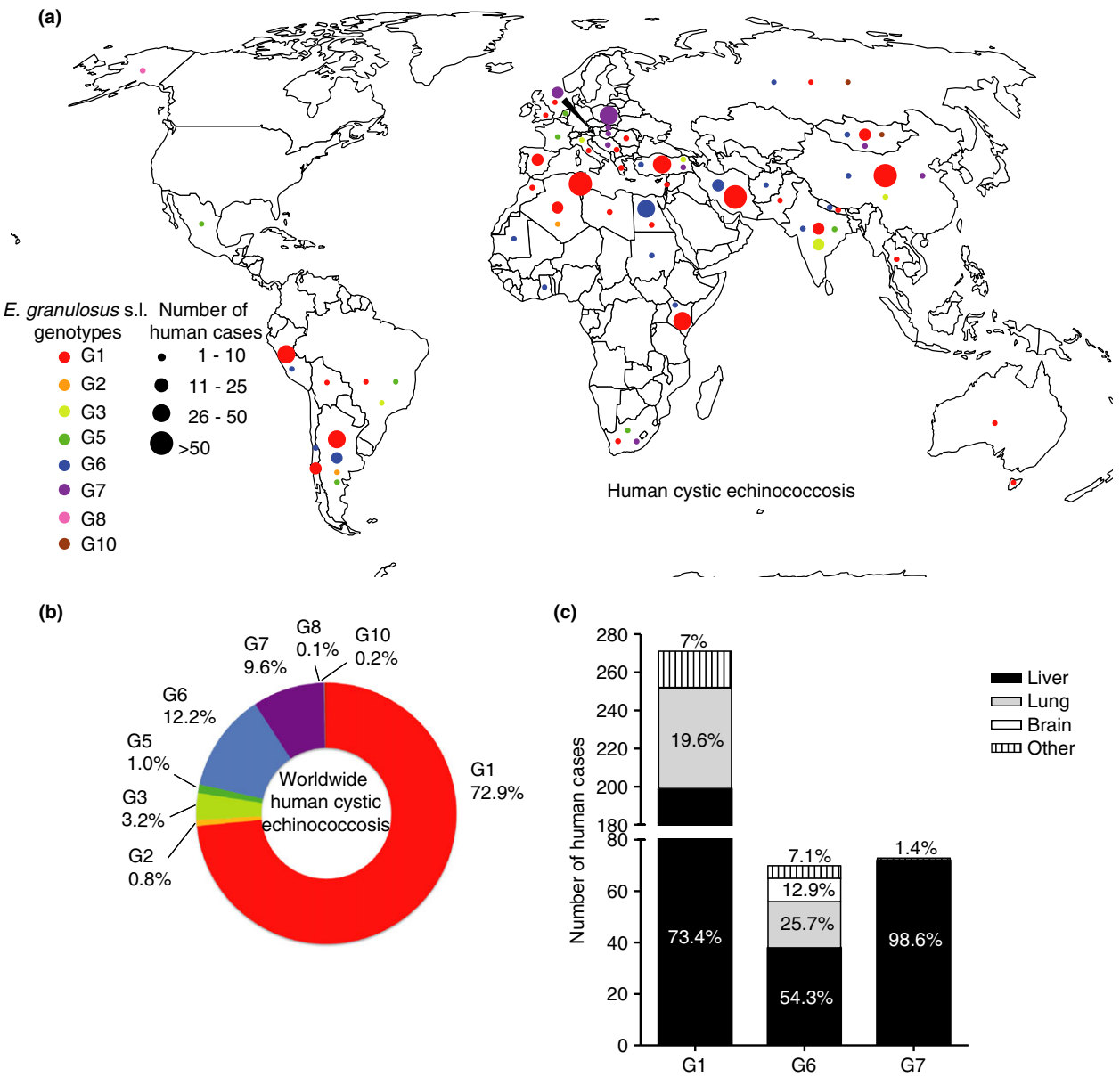

Figure 3 Human cystic echinococcosis cases in the world with genotype identification by DNA sequencing. (a) Worldwide distribution of *Echinococcus granulosus sensu lato* genotypes isolated from humans. (b) Percentage of human cases caused by each *E. granulosus* s. l. genotype (c) Human hydatid cysts organ location of *E. granulosus* s. s. (G1 genotype) and *E. canadensis* (G6 and G7 genotypes). The category 'Other' includes organ location with fewer than three cases reported. The position of the dots shows the geographical country distribution independently of the state/province/department location.

G1 the most frequently identified genotype (72.9%) (Figure 3a and B), as observed in South America. Therefore, this genotype has the greatest epidemiological relevance due to its wide distribution. Moreover, the G6 and G7 genotypes historically considered poorly infective to humans account for 12.2% and 9.6% of human cases worldwide, respectively (Figure 3b). The geographical distribution of human cystic echinococcosis caused by these two genotypes clearly differs (Figure 3a). The G6 genotype is present in human cases from America, Asia and Africa, while the G7 genotype cases have been detected in several European countries. The remaining

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genotypes were rarely found in patients (<3.3%). No G4 human cases have been reported to date (Figure 3b and Table S2), reinforcing the hypothesis that this genotype is unable to establish infection in humans [11, 32]. Our results are in accordance with those recently reported by [32], who also surveyed human echinococcosis cases worldwide. In spite of the fact that these authors included in their analysis all the cases reported independently of the methodology used for genotype determination, the relative abundance of each *E. granulosus* s. l. species/genotype to the global burden of human cystic echinococcosis is similar.

The corresponding cyst anatomical location was reported in 48.9% of the reviewed human cystic echinococcosis cases (Table S2). Due to the fact that the G1, G6 and G7 genotypes are the most relevant from a sanitary aspect, we focused on their organ tropism regardless sex, age or ethnic background of the hosts. As can be observed in Figure 3c, liver is the most affected organ by the three genotypes. Interestingly, the G7 genotype seems to infect almost exclusively the liver (98.6%), while the G1 genotype also develops in lungs in a high proportion of the cases (19.6%). G6 genotype was found in liver (54.3%), lung (25.7%), brain (12.9%) and other organs (7.1%) although it has been described to have a brain location preference [39].

Conclusions

Echinococcus granulosus s. l. is composed of: *E. granulosus* s. s. (G1/G2/G3 genotypes), *E. equinus* (G4 genotype), *E. ortleppi* (G5 genotype), *E. canadensis* (G6/G7/G8/G10 genotypes) and *E. felidis* ('lion strain'). The different species/genotypes display distinctive features of biological and epidemiological significance, which emphasises the need of studies concerning molecular characterisation and distribution in endemic areas. In this work, we provided new data and reviewed all those articles with sequencing identification of species/genotypes reported in natural intermediate and definitive hosts in South America as well as in human cases worldwide.

In South America, the countries with a larger number of analysed samples display a greater genetic complexity, for example Argentina, Brazil and Peru. *Echinococcus granulosus* s. s. (G1 genotype) account for most of the global burden of human and livestock cases in South America. Also, *E. canadensis* (G6 genotype) plays a significant role in South American human cystic echinococcosis. Taking into account the molecular epidemiological situation, it is relevant to evaluate the pathogenicity, diagnosis performance and response to chemotherapy of the G6 genotype since antigenic differences between the EG95-related proteins from the G1 and G6 genotypes were observed [15]. Additionally, for an accurate determination of the public health relevance of *E. canadensis* (G7 genotype) in South America, a molecular epidemiological survey should be carried out in those regions where swine breeding is concentrated.

With respect to the worldwide situation of human cystic echinococcosis, *E. granulosus* s. s. (G1 genotype) accounts for most of the global burden followed by *E. canadensis* (G6 and G7 genotypes). No human cases of cystic echinococcosis caused by *E. equinus* (G4 genotype) have been detected yet. This could be due to the fact that this genotype is not infective for humans or that a higher number of samples from horse breeding regions should be tested.

The data reviewed in this work provide useful information that should be taken into account to suit local cystic echinococcosis control and prevention programmes according to each molecular epidemiological situation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart of articles selection process.

Table S1 Genotype, host, geographic origin, number and reference from all the Echinococcus granulosus *sensu* lato samples identified by sequencing of molecular markers in South America until 2014.

Table S2 Human cystic echinococcosis cases in the world with genotype determined by sequencing of molecular markers. Country, genotype (number of cases), molecular marker, organ and refence are shown.

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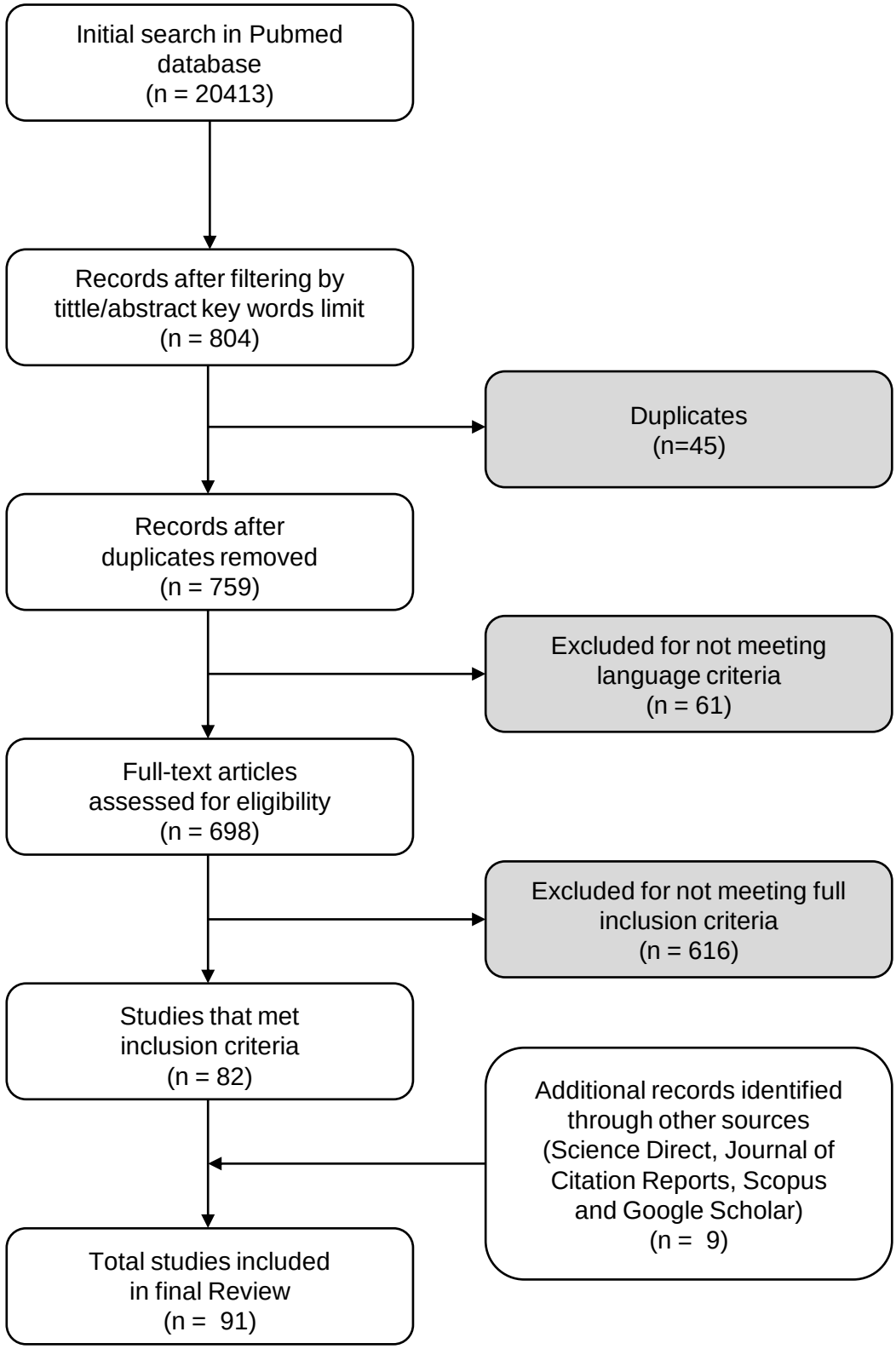

Figure S1. Flow chart of articles selection process

Table S1-Genotype, host, geographic origin, number and reference from all the *Echinococcus granulosus sensu lato* samples identified by sequencing of molecular markers in South America until 2014

Genotype	Host	Country	Province/Department/State	Number of samples	Molecular Marker Sequenced	Reference
G1	Alpaca	Peru	Puno	4	COX1, ND1	Sánchez et al., 2012
G1	Cattle	Argentina	Santa Fe	7	COX1	This work (2007-2014)
G1	Cattle	Argentina	Buenos Aires	1	COX1	This work (2007-2014)
G1	Cattle	Argentina	Buenos Aires	3	COX1	Kamenetzky et al., 2002*
G1	Cattle	Argentina	Corrientes	2	COX1	Kamenetzky et al., 2002*
G1	Cattle	Argentina	Córdoba	1	COX1	Kamenetzky et al., 2002*
G1	Cattle	Argentina	Tucumán	3	COX1	Kamenetzky et al., 2002*
G1	Cattle	Brasil	ND	2	COX1	Kamenetzky et al., 2002*
G1	Cattle	Chile	ND	1	COX1	Kamenetzky et al., 2002*
G1	Cattle	Peru	ND	1	COX1	Kamenetzky et al., 2002*
G1	Cattle	Uruguay	ND	1	COX1	Kamenetzky et al., 2002*
G1	Cattle	Argentina	ND	5	COX1	This work (2007-2014)
G1	Cattle	Uruguay	ND	4	COX1	This work (2007-2014)
G1	Cattle	Peru	Puno	7	COX1	Sánchez et al., 2010
G1	Cattle	Peru	Junín	11	COX1	Sánchez et al., 2010
G1	Cattle	Peru	Cusco	9	COX1	Sánchez et al., 2010
G1	Cattle	Peru	Arequipa	12	COX1	Sánchez et al., 2010
G1	Cattle	Peru	Huancavelica	5	COX1	Sánchez et al., 2010
G1	Cattle	Brasil	Rio Grande do Sul	358	COX1	Balbinotti et al., 2012
G1	Cattle	Peru	Cajamarca	7	COX1, EF1A	Moro et al., 2009
G1	Cattle	Peru	Ancash	1	COX1, EF1A	Moro et al., 2009
G1	Cattle	Peru	Ayacucho	4	COX1, EF1A	Moro et al., 2009
G1	Cattle	Peru	Lima	2	COX1, EF1A	Moro et al., 2009
G1	Cattle	Peru	Puno	2	COX1, EF1A	Moro et al., 2009
G1	Cattle	Argentina	Buenos Aires	41	COX, ND1	Andresiuk et al., 2013
G1	Cattle	Argentina	Buenos Aires	25	COX1, ND1	Andresiuk et al., 2009
G1	Cattle	Brasil	Rio Grande do Sul	115	COX1, MDH, EgAgB4	Badaraco et al., 2008*
G1	Dog	Argentina	Neuquén	10	COX1	Soriano et al., 2010*
G1	Dog	Brasil	Rio Grande do Sul	10	COX1, 12SrRNA	de la Rue et al., 2011
G1	Dog	Argentina	Chubut	1	COX1	Kamenetzky et al., 2002*
G1	Dog	Argentina	Rio Negro	3	COX1	Kamenetzky et al., 2002*
G1	Dog	Argentina	Jujuy	1	COX1	Kamenetzky et al., 2002*
G1	Dog	Argentina	Santa Fe	1	COX1	Kamenetzky et al., 2002*
G1	Dog	Argentina	Neuquén	2	COX1	Soriano et al., 2010*
G1	Goat	Argentina	Neuquén	2	COX1	Soriano et al., 2010*
G1	Goat	Peru	Lima	1	COX1, EF1A	Moro et al., 2009
G1	Cat	Uruguay	ND	1	COX1, 12SrRNA	Armua-Fernandez et al., 2014
G1	Human	Argentina	Catamarca	1	COX1	This work (2007-2014)
G1	Human	Peru	Pasco	4	COX1	Santiveñez et al., 2008
G1	Human	Peru	Junín	7	COX1	Santiveñez et al., 2008
G1	Human	Peru	Ayacucho	3	COX1	Santiveñez et al., 2008
G1	Human	Peru	Huancavelica	1	COX1	Santiveñez et al., 2008
G1	Human	Peru	Lima	4	COX1	Santiveñez et al., 2008
G1	Human	Peru	Puno	3	COX1	Sanchez et al., 2010
G1	Human	Peru	Junín	5	COX1	Sanchez et al., 2010
G1	Human	Peru	Cusco	1	COX1	Sanchez et al., 2010
G1	Human	Peru	Arequipa	1	COX1	Sanchez et al., 2010
G1	Human	Peru	Huancavelica	2	COX1	Sanchez et al., 2010
G1	Human	Peru	Ayacucho	2	COX1	Sanchez et al., 2010
G1	Human	Brasil	Rio Grande do Sul	4	COX1, 12SrRNA	de la Rue et al., 2011
G1	Human	Peru	Lima	1	COX1, EF1A	Moro et al., 2009
G1	Human	Peru	Junín	1	COX1, EF1A	Moro et al., 2009
G1	Human	Peru	Huancavelica	2	COX1, EF1A	Moro et al., 2009
G1	Human	Chile	ND	19	COX1	Manterola et al., 2008
G1	Human	Argentina	Santa Cruz	2	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Chubut	1	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Rio Negro	3	COX1, ND1	Rosenzvit et al., 1999*
G1	Human	Argentina	Rio Negro	8	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Neuquén	9	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Buenos Aires	2	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Entre Ríos	2	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Santiago del Estero	1	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Tucumán	5	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Catamarca	1	COX1	Kamenetzky et al., 2002*
G1	Human	Chile	ND	2	COX1	Kamenetzky et al., 2002*
G1	Human	Bolivia	ND	1	COX1	Kamenetzky et al., 2002*
G1	Human	Peru	ND	1	COX1	Kamenetzky et al., 2002*
G1	Human	Argentina	Neuquén	10	COX1	Guarnera et al., 2004*
G1	Human	Chile	ND	1	ND1	Schneider et al., 2008
G1	Human	Chile	Panguipulli	1	COX1, ND1	Espinoza et al., 2014
G1	Human	Chile	Santiago	1	COX1, ND1	Espinoza et al., 2014
G1	Sheep	Argentina	Rio Negro	2	COX1	This work (2007-2014)
G1	Cattle	Chile	Osorno	3	COX1, ND1	Espinoza et al., 2014
G1	Cattle	Chile	Nueva Imperial	2	COX1, ND1	Espinoza et al., 2014
G1	Cattle	Chile	Pitrufquén	1	COX1, ND1	Espinoza et al., 2014
G1	Sheep	Argentina	Chubut	4	COX1	This work (2007-2014)
G1	Sheep	Argentina	Chubut	7	COX1, ND1	Rosenzvit et al., 1999*
G1	Sheep	Argentina	Buenos Aires	1	COX1	This work (2007-2014)
G1	Sheep	Argentina	ND	2	COX1	This work (2007-2014)
G1	Sheep	Argentina	Rio Negro	3	COX1	Kamenetzky et al., 2002*
G1	Sheep	Argentina	Santa Fe	1	COX1	Kamenetzky et al., 2002*
G1	Sheep	Argentina	Tucumán	2	COX1	Kamenetzky et al., 2002*
G1	Sheep	Argentina	Neuquén	15	COX1	Soriano et al., 2010*
G1	Sheep	Peru	Puno	8	COX1	Sanchez et al., 2010

G1	Sheep	Peru	Junín	18	COX1	Sanchez et al., 2010
G1	Sheep	Peru	Arequipa	2	COX1	Sanchez et al., 2010
G1	Sheep	Peru	Huancavelica	1	COX1	Sanchez et al., 2010
G1	Sheep	Peru	Ayacucho	12	COX1	Sanchez et al., 2010
G1	Sheep	Argentina	Tierra del Fuego	8	COX1	Zanini et al., 2006
G1	Sheep	Peru	Ayacucho	2	COX1, EF1A	Moro et al., 2009
G1	Sheep	Peru	Lima	13	COX1, EF1A	Moro et al., 2009
G1	Sheep	Peru	Ica	17	COX1, EF1A	Moro et al., 2009
G1	Sheep	Argentina	Buenos Aires	33	COX, ND1	Andresiuk et al., 2013
G1	Pig	Peru	Ayacucho	4	COX1	Sanchez et al., 2012
G1	Pig	Peru	Lima	3	COX1, EF1A	Moro et al., 2009
G1	Pig	Argentina	Rio Negro	2	COX1	Kamenetzky et al., 2002*
G1	Pig	Argentina	Buenos Aires	1	COX1	Kamenetzky et al., 2002*
G1	Pig	Brasil	Rio Grande do Sul	2	COX1	Monteiro et al., 2014
G1	Pig	Peru	ND	1	COX1	Kamenetzky et al., 2002*
G2	Cattle	Argentina	Tucumán	1	COX1	Kamenetzky et al., 2002*
G2	Human	Argentina	Tucumán	5	COX1	Kamenetzky et al., 2002*
G2	Human	Argentina	Tucumán	1	COX, ND1	Rosenzvit et al., 1999*
G2	Sheep	Argentina	Tucumán	2	COX1	Kamenetzky et al., 2002*
G2	Sheep	Argentina	Tucumán	2	COX, ND1	Rosenzvit et al., 1999*
G2	Sheep	Argentina	Buenos Aires	1	COX, ND1	Andresiuk et al., 2013
G3	Dog	Brasil	Rio Grande do Sul	1	COX1, 12SrRNA	de la Rue et al., 2011
G3	Human	Brasil	Rio Grande do Sul	1	COX1, 12SrRNA	de la Rue et al., 2011
G3	Cattle	Chile	Pitrufquén	1	COX1, ND1	Espinoza et al., 2014
G3	Sheep	Argentina	Neuquén	1	COX1	Soriano et al., 2010*
G5	Cattle	Argentina	Buenos Aires	1	COX, ND1	Andresiuk et al., 2013
G5	Cattle	Brasil	Rio Grande do Sul	55	COX1, MDH, EgAgB4	Badaraco et al., 2008*
G5	Cattle	Brasil	Rio Grande do Sul	276	COX1	Balbinotti et al., 2012
G5	Cattle	Argentina	Santa Fe	5	COX1	This work (2007-2014)
G5	Cattle	Argentina	Buenos Aires	1	COX1	This work (2007-2014)
G5	Cattle	Uruguay	ND	2	COX1	This work (2007-2014)
G5	Cattle	Argentina	Santa Fe	2	COX1	Kamenetzky et al., 2002*
G5	Cattle	Brasil	ND	3	COX1	Kamenetzky et al., 2002*
G5	Dog	Argentina	Catamarca	1	COX1	Kamenetzky et al., 2002*
G5	Dog	Argentina	Catamarca	1	COX1	López et al., 2002*
G5	Dog	Argentina	Catamarca	1	COX1	This work (2007-2014)
G5	Human	Brasil	Rio Grande do Sul	1	COX1, 12SrRNA	de la Rue et al., 2011
G5	Human	Argentina	Misiones	1	COX1	Vizcaychipi et al.,. 2004
G5	Human	Argentina	Tucumán	1	COX1	Kamenetzky et al., 2002*
G6	Dog	Argentina	Rio Negro	1	COX1	Kamenetzky et al., 2002*
G6	Dog	Argentina	Catamarca	1	COX1	Kamenetzky et al., 2002*
G6	Dog	Argentina	Neuquén	2	COX1	Kamenetzky et al., 2002*
G6	Goat	Argentina	Neuquén	1	COX1	Kamenetzky et al., 2002*
G6	Goat	Argentina	Mendoza	2	COX1	Kamenetzky et al., 2002*
G6	Goat	Argentina	Neuquén	21	COX1	Soriano et al., 2010*
G6	Goat	Peru	Ica	2	COX1, EF1A	Moro et al., 2009
G6	Goat	Peru	Moquegua	3	COX1, EF1A	Moro et al., 2009
G6	Human	Argentina	Rio Negro	3	COX, ND1	Rosenzvit et al., 1999*
G6	Human	Argentina	Neuquén	12	COX1	Kamenetzky et al., 2002*
G6	Human	Argentina	Buenos Aires	1	COX, ND1	Rosenzvit et al., 1999*
G6	Human	Argentina	La Pampa	1	COX1	Kamenetzky et al., 2002*
G6	Human	Argentina	Catamarca	4	COX1	Kamenetzky et al., 2002*
G6	Human	Argentina	Catamarca	6	COX1	This work (2007-2014)
G6	Human	Peru	Huancavelica	1	COX1	Santivañez et al., 2008
G6	Human	Peru	Lima	1	COX1, EF1A	Moro et al., 2009
G6	Human	Argentina	Neuquén	3	COX1	Guarnera et al., 2004*
G6	Human	Chile	ND	1	COX1	Manterola et al., 2008
G6	Cattle	Argentina	Neuquén	5	COX1	Soriano et al., 2015*
G7	Cattle	Brasil	Rio Grande do Sul	1	COX1, MDH, EgAgB4	Badaraco et al., 2008*
G7	Dog	Argentina	Neuquén	1	COX1	Kamenetzky et al., 2002*
G7	Pig	Argentina	Buenos Aires	3	COX1	Kamenetzky et al., 2002*
G7	Pig	Argentina	Santa Fe	15	COX, ND1	Rosenzvit et al., 1999*
G7	Pig	Argentina	Santa Fe	6	COX1	Kamenetzky et al., 2002*
G7	Pig	Peru	Lima	8	COX1, EF1A	Moro et al., 2009
G7	Pig	Argentina	Neuquén	18	COX1	Soriano et al., 2010*
G7	Pig	Argentina	ND	87	COX1	This work (2007-2014)
G7	Pig	Argentina	Santa Fe	2	COX1	This work (2007-2014)
G7	Pig	Brasil	Rio Grande do Sul	3	COX1	Monteiro et al, 2014
G7	Pig	Peru	Ayacucho	4	COX1, ND1	Sanchez et al., 2012

*Samples reported in more than one article were taken into consideration once.

Table S2- Human cystic echinococcosis cases in the world with genotype determined by sequencing of molecular markers.

Country, genotype (number of cases), molecular marker, organ and refence are shown

Country/Genotype	G1	G2	G3	G4	G5	G6	G7	G8	G10	Molecular Marker Sequenced	Organ	Reference
Afghanistan						1				ND1	liver	Schneider et al., 2008*
Albania	1 (G1-G3)									ND1	ND	Schneider et al., 2008*
Algeria	7									COX1, ND1	lung	Bardonnet et al., 2003
Algeria	5									COX1, ND1	lung	Bart et al., 2004
Algeria	2	1								COX1, ND1	ND	Maillard et al., 2007
Algeria	5									COX1	ND	Badaraco et al., 2008
Argentina	3					4				COX1	ND	Rosenzvit et al., 1999
Argentina	2									COX1	ND	Kamenetzky et al., 2000
Argentina	20					5				COX1	ND	Kamenetzky et al., 2002
Argentina	13									COX1	liver	Guarnera et al., 2004
Argentina	3									COX1	lung	Guarnera et al., 2004
Argentina	1									COX1	liver and lung	Guarnera et al., 2004
Argentina	1									COX1	liver and peritoneum	Guarnera et al., 2004
Argentina	1									COX1	kidney and spleen	Guarnera et al., 2004
Argentina		3								COX1	liver	Guarnera et al., 2004
Argentina		2								COX1	lung	Guarnera et al., 2004
Argentina		1								COX1	liver and lung	Guarnera et al., 2004
Argentina					1					COX1	liver	Guarnera et al., 2004
Argentina						7				COX1	liver	Guarnera et al., 2004
Argentina						5				COX1	lung	Guarnera et al., 2004
Argentina						1				COX1	spleen	Guarnera et al., 2004
Argentina						1				COX1	liver and spleen	Guarnera et al., 2004
Argentina						1				COX1	liver, lung, spleen	Guarnera et al., 2004
Argentina					1					COX1	liver	Vizcaychipi et al., 2004
Australia	1									COX1	ND	Bowles et al., 1992a
Australia (Tasmania)	1									COX1	ND	Bowles et al., 1992a
Austria	1									ND1	liver	Schneider et al., 2008*
Austria							19			ND1	liver	Schneider et al., 2008*
Austria							4			ND1	liver	Schneider et al., 2010*
Austria	1									ND1	ND	Schneider et al., 2010*
Bolivia	1									COX1	ND	Kamenetzky et al., 2002
Brazil	4		1		1					COX1	ND	de la Rue et al., 2011

Bulgaria	9 (G1-G3)					COX1	ND	Casulli et al., 2012
Chile	2					COX1	ND	Kamenetzky et al., 2002
Chile	19			1		COX1	ND	Manterola et al., 2008
Chile	1					ND1	liver	Schneider et al., 2008*
Chile	2					COX1	liver	Espinoza et al., 2014
China	1					COX1	ND	Bowles et al., 1992a
China	7					COX1, ND1	abdominal cavity	McManus et al., 1994
China	3					COX1, ND1	liver	Zhang et al., 1998b
China	1					ATP6	brain, lung and liver	Yang et al., 2006
China	13					ATP6	ND	Yang et al., 2005
China	45					COX1	ND	Bart et al., 2006a
China				2		COX1	liver	Bart et al., 2006a
China	91 (G1-G3)					COX1, EIF 1a	ND	Nakao et al., 2010
China	23 (G1-G3)					COX1	ND	Ma et al., 2012
China	36					COX1, ND1, ATP6	liver	Ma et al., 2008
China	1					COX1, ND1, ATP6	lung	Ma et al., 2008
China	31					COX1	liver	Li et al., 2008
China	1					COX1	abdominal cavity	Li et al., 2008
China	1					COX1	pelvic cavity	Li et al., 2008
China	4					ATP6	liver	Yang et al., 2009
China				1		COX1, EIF	ND	Nakao et al., 2010
China	28					COX1	ND	Zhong et al., 2014
China	6				4	COX1	liver	Zhang et al., 2014
China	20	2				ND1, ATP6	ND	Yan et al., 2013
Egypt	1					12SrRNA	liver	Aaty et al., 2012
Egypt				24		12SrRNA	liver	Aaty et al., 2012
Egypt				5		12SrRNA	lung	Aaty et al., 2012
Egypt				1		12SrRNA	multiple organs	Aaty et al., 2012
former Yugoslavia	10				3	ND1	liver	Schneider et al., 2008*
former Yugoslavia					1	ND1	liver and lung	Schneider et al., 2010*
former Yugoslavia					5	ND1	liver	Schneider et al., 2010*
France			2			COX1, ATP6	liver	Grenouillet et al., 2014
Ghana				1		ND1	liver	Schneider et al., 2008*
Greece	1					ND1	liver	Schneider et al., 2008*
Hungary					1	ND1	liver	Schneider et al., 2008*
India	13					COX1	ND	Sharma et al., 2013

India		17				COX1	ND	Sharma et al., 2013
India			1			COX1	liver	Sharma et al., 2013
India				1		COX1	brain	Sharma et al., 2013
Iran	2					COX1, ND1	liver	Zhang et al., 1998a
Iran	2					COX1, ND1	lung	Zhang et al., 1998a
Iran	1					COX1, ND1	ND	Sharbatkhori et al., 2009
Iran				1		ND1	spleen	Schneider et al., 2008*
Iran	25			6		COX1, ND1	ND	Shahnazi et al., 2011
Iran	8					ND1	liver	Sadjjadi et al., 2013
Iran				8		ND1	brain	Sadjjadi et al., 2013
Iran				1		COX1, ND1	ND	Harandi et al., 2012
Iran	6					COX1	ND	Yanagida et al., 2012
Iran	5					COX1, ND1	liver	Pezeshki et al., 2013
Iran	1					COX1, ND1	lung	Pezeshki et al., 2013
Iran	1					COX1, ND1	spleen	Pezeshki et al., 2013
Iran				1		COX1, ND1	ND	Hajialilo et al., 2012
Italy	1	7				COX1, ND1	ND	Busi et al., 2007
Italy	1					12SrRNA	Muscle	Vicidomini et al., 2007
Italy	1					ND1	liver	Schneider et al., 2008*
Kenya	49			10		COX1, ND1	ND	Casulli et al., 2010
Lebanon	1					ND1	liver	Schneider et al., 2008*
Libya	3					COX1	ND	Tashani et al., 2002
Libya	2					COX1, ND1	ND	Abushhewa et al., 2010
Mauritania				1		COX1, ND1	ND	Bardonnet et al., 2002
Mauritania				1		COX1, ND1	liver	Bardonnet et al., 2003
Mauritania				1		COX1, ND1	lung	Bart et al., 2004
Mauritania				2		COX1, ND1	ND	Maillard et al., 2007
Mexico			1			COX1	liver	Maravilla et al., 2004
Mongolia	12			29 (G6-G7)	1	COX1	liver	Ito et al., 2014
Mongolia	1			1	1	1 (G6-G10)	COX1, ND1	ND	Jabbar et al., 2011
Morocco	1					COX1, ND1	liver	Bardonnet et al., 2003
Nepal	1					COX1	liver	Ito et al., 1998
Nepal				2		COX1, ND1	lung	Zhang et al., 2000
Netherlands			1			COX1, ND1	spleen	Bowles et al., 1993
Pakistan	2					COX1	ND	Latif et al., 2010
Peru	1					COX1	ND	Kamenetzky et al., 2002

Peru	17		1			COX1	lung	Santivañez et al., 2008
Peru	2					COX1	liver	Santivañez et al., 2008
Peru	4		1			COX1	lung	Moro et al., 2009
Peru	14					COX1	ND	Sanchez et al., 2010
Poland				4		ND1, ITS1	ND	Kedra et al., 1999
Poland				6		COX1, ND1	liver	Scott et al., 1997
Poland				30		ND1	liver	Dybicz et al., 2013
Portugal	1 (G1-G3)					COX1	kidney	Beato et al., 2013
Romania	1					COX1	ND	Badaraco et al., 2008
Romania	1					ND1	liver	Schneider et al., 2008*
Romania	1					ND1	heart	Schneider et al., 2008*
Romania	1					ND1	heart and brain	Schneider et al., 2010*
Romania	2					COX1, ND1, BG1/3	liver	Bart et al., 2006b
Romania	1					COX1	ND	Mitrea et al., 2012
Romania	10 (G1-G3)					COX1, ND1	lung	Piccoli et al., 2013
Romania	49 (G1-G3)				1 (G6-G10)	COX1, ND1	liver	Piccoli et al., 2013
Russia					1	COX1	ND	Nakao et al., 2013
Russia	6		2			COX1	ND	Konyaev et al., 2012
Slovakia				2		ND1	ND	Turcekova et al., 2003
South Africa	5	1		2		ND1, 12SrRNA	ND	Mogoye et al., 2013
Spain	2					COX1, ND1	ND	Gonzalez et al., 2003
Spain	13					COX1, ND1	liver	Daniel Mwambete et al., 2004
Spain	8					COX1, ND1	lung	Daniel Mwambete et al., 2004
Spain	2					COX1, ND1	peritoneal cavity	Daniel Mwambete et al., 2004
Sudan			3			COX1, ND1	lung	Omer et al., 2010
Sudan			2			COX1, ND1	liver	Omer et al., 2010
Thailand	1					ND1	liver	Schneider et al., 2008*
Tunisia	22 (G1-G3)					COX1, EIF 1a	ND	Boufana et al., 2014
Tunisia	7					COX1	ND	M´rad et al., 2005
Tunisia	4					COX1	lung	M´rad et al., 2005
Tunisia	20					COX1	liver	Lahmar et al., 2009
Tunisia	39					COX1	ND	Boubaker et al., 2013
Turkey	1					COX1	ND	Utuk et al., 2008
Turkey	19					ND1	liver	Schneider et al., 2008*
Turkey	1					ND1	lung	Schneider et al., 2008*
Turkey	9			1		COX1, ND1	ND	Eryildiz et al., 2012

Turkey	9						1			COX1, ND1, ATP6	ND	Snabel et al., 2009
Turkey	2		1			2				COX1	ND	Simsek et al., 2011
United Kingdom	1									COX1	liver	Craig et al., 2012
United States (Alaska)								1		COX1, COX2, ATP6, ND1, ND3	liver	McManus et al., 2002
Total by genotype	**639**	**7**	**28**	**0**	**9**	**107**	**84**	**1**	**2**			
Total of samples	**877**											

ND: Not determined or single sequenced sample could not be associated to an specific organ localization

*Samples reported in more than one article were taken into consideration once.

Note1: The G9 genotype (Scott et al., 1997) was considered to be G7 genotype according to Pawlowski and Stefaniak, 2003.

Note 2: Only those samples that were unambiguously assigned as G1-G10 genotypes by molecular marker sequencing according to McManus 2013 were considered for the calculation of the relative importance of each genotype in human echinococcosis.