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Echinococcus granulosus genotypes in Iran: a systematic review

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Abstract

Cystic echinococcosis (CE) caused by *Echinococcus granulosus sensu lato (s.l.)* is a significant zoonosis, especially in developing countries of the Middle East, with many studies focusing on CE genotypes in Iran. We performed a systematic review to determine the exact status of *E. granulosus* genotypes in the country. We explored English (Pubmed, Scopus, ISI Web of Science and Science Direct) and Persian (Magiran, Iran Medex and Scientific Information Database) databases along with Google Scholar. Our review included 73 studies published prior to the end of 2015. In total, 2952 animal (intermediate and definitive) hosts were examined, and the prevalent genotypes comprised G1 (92.75%) and G6 (4.53%) in sheep, cattle, camels, goats and buffaloes; G3 (2.43%) in five herbivore hosts and dogs; G7 (0.2%) in sheep and goats; and G2 (0.06%) in dogs. G1 was mostly dominant in West Azerbaijan, whereas G3 and G6 were identified most frequently in the provinces of Isfahan and Fars, respectively. Regarding human CE infection, 340 cases were reported from Iran, with the identified genotypes G1 (n = 320), G6 (n = 13) and G3 (n = 7). Most CE-infected humans originated from Isfahan province (168 cases), whereas the lowest number of infected persons was noted in Kerman province (two cases). The information obtained from this systematic review is central to better understanding the biological and epidemiological characteristics of *E. granulosus s.l.* genotypes in Iran, leading to more comprehensive control strategies.

Introduction

Despite global community efforts to minimize parasitic helminthiases in humans and animals in recent decades, numerous cases of such devastating diseases are still reported worldwide (Carmena & Cardona, 2014; Bartsch *et al.*, 2016; Cucher *et al.*, 2016; Khademvatan *et al.*, 2016; Saki *et al.*, 2017; Weatherhead *et al.*, 2017). *Echinococcus granulosus sensu lato* (*s.l.*), a cestode helminth belonging to the Taeniidae family, is the causative agent of a prevalent zoonotic disease, cystic echinococcosis (CE) (Rojas *et al.*, 2014). This tapeworm uses canids and herbivores/omnivores as definitive and intermediate hosts, respectively, and human infection occurs accidentally by ingestion of the eggs (Rokni, 2009). The disease in humans entails the development of a fluid-filled hydatid cyst, which localizes in the liver and lungs and, to a lesser extent, in the abdominal cavity, muscle, heart, bone and nervous system (Craig *et al.*, 2007). The disease causes impotency, disability and decreased work productivity in endemic territories, including Australia, New Zealand, China, Russia, South America, North Africa and the Middle East (Battelli, 2009; Shariatzadeh *et al.*, 2015). As a consequence of CE, 1–3.6 million disability-adjusted life years (DALYs) are missed globally; most of these cases occur in low-income countries (Budke *et al.*, 2006; Torgerson *et al.*, 2015). Given the numerous traditional animal husbandries and access of dogs to waste materials of abattoirs there, Iran has been considered a hyperendemic region (Dalimi *et al.*, 2002; Pour *et al.*, 2011; Khademvatan *et al.*, 2013). More recently, the weighted prevalence of hydatidosis in human and animal intermediate hosts in Iran reached 4.2% (95% confidence interval (CI) = 3.0–5.5%) and 15.6% (95% CI = 14.2–17.1%), respectively. The pooled prevalence of *E. granulosus* infection in definitive hosts totalled 23.6% (95% CI = 17.6–30.1%) (Khalkhali *et al.*, 2017). Human infection in Iran was mostly concentrated in the south, whereas the lowest prevalence rate was observed in central parts of the country (Khalkhali *et al.*, 2017). The annual monetary burden of CE in the country was estimated to be *c.* USD 232.3 million (Mobedi & Dalimi, 1994; Harandi *et al.*, 2012a).

Extensive intraspecies genetic diversity of CE has been recorded over a long period of time, and this condition may influence characteristics such as morphology, epidemiology, host specificity, infectivity and drug resistance (Carmena & Cardona, 2014). Four molecular

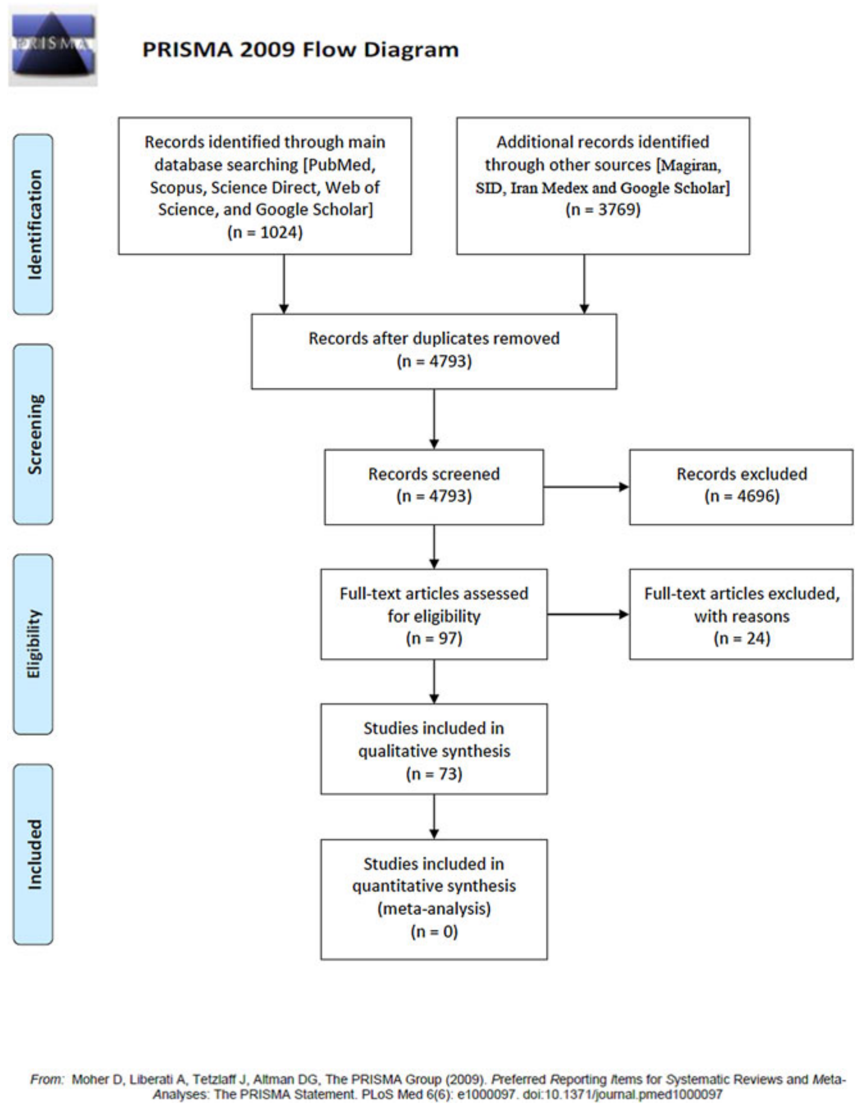

Fig. 1. PRISMA 2009 flow diagram.

approaches – single-gene analysis using mitochondrial DNA, microsatellite markers for polymorphic DNA loci, full-genome exploration, and comparison of discrepancies among mitochondrial and nuclear DNA for species hybridization – have been used to categorize *Echinococcus* species into several genotypes (Ito & Budke, 2017). Most of our understanding in this area originates from the investigation of Bowles and colleagues into *cox1* and *nad1* mitochondrial genes (Bowles *et al.*, 1992). Accordingly, ten deduced strains of CE have been characterized and encompassed in a number of clades, including *E. granulosus sensu stricto* (*s.s.*) (G1–3), *E. equinus* (G4), *E. ortleppi* (G5) and *E. canadensis* (G6–10), and *E. felidis* (the lion strain) (Amer *et al.*, 2015). G1 and G2 are sheep strains, whereas G3 and G5 are buffalo and cattle strains, respectively. G4 is found in horses, G6 in camels, G7 in pigs and G8–10 in cervids (Rojas *et al.*, 2014). G1 genotype is the most commonly reported in human CE cases globally. Additionally, studies have reported that the subsequent strains are infective to humans (Grosso *et al.*, 2012). Host–parasite immunological interplay and cross transmission templates can justify the emergence of *Echinococcus* strains and their related genetic diversity (Bowles *et al.*, 1992; Thompson, 2013; Thompson & Jenkins, 2014). Detecting these genetic variations in *E. granulosus s.l.* populations is significant for better understanding of various life cycles of CE in endemic regions of Iran and shedding light on more efficient prevention strategies, as well as diagnosis and treatment of CE (Shariatzadeh *et al.*, 2015).

Thus far, numerous papers have investigated CE genotypes in animal hosts and human cases in Iran. However, there is a lack of collective and processed data for systematic review. Accordingly, we performed a qualitative evaluation to clarify the status of CE genotypes in the country.

Methods

Search strategy

To unravel the genetic distribution of hydatid genotypes in Iran, a systematic review was designed on the basis of literature in English and Persian available online. Four English (PubMed, Scopus, Science Direct and ISI Web of Science) and three Persian (Scientific Information Database, Iran Medex and Magiran) databases were explored for published papers from inception to 31 December 2015, as was Google Scholar as a common, multilingual engine for both English and Persian terms. The

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Table 1. Genotypes of *Echinococcus granulosus* identified in domestic natural hosts (intermediate and definitive) and humans in Iran.

Genotype	Intermediate natural host (a)	Definitive host (b)	No. of cases (a + b)	Human cases	Total (n)	References (a + b + c)
G1	Sheep, cattle, camels, goats, buffaloes		2738	320	3058	Harandi *et al.*, 2002; Rahimi *et al.*, 2007; Yousofi Darani *et al.*, 2007; Karimi & Dianatpour, 2008; Sharbatkhori *et al.*, 2009; Kia *et al.*, 2010; Gholami *et al.*, 2011; Pour *et al.*, 2011; Parsa *et al.*, 2011, 2012; Rostami Nejad *et al.*, 2011; Shahnazi *et al.*, 2011; Sharifiyazdi *et al.*, 2011; Yakhchali & Mardani, 2011, 2013; Hajialilo *et al.*, 2012; Harandi *et al.*, 2012b; Hosseini *et al.*, 2012; Hosseinzadeh *et al.*, 2012; Nejad *et al.*, 2012; Rajabloo *et al.*, 2012; Sadri *et al.*, 2012; Dousti *et al.*, 2013; Hanifian *et al.*, 2013; Haniloo *et al.*, 2013; Khademvatan *et al.*, 2013; Moazeni *et al.*, 2013; Mobedi *et al.*, 2013; Sadjjadi *et al.*, 2013; Youssefi *et al.*, 2013; Eslami *et al.*, 2014; Nikmanesh *et al.*, 2014; Pestechian *et al.*, 2014; Sharafi *et al.*, 2014; Vahedi *et al.*, 2014; Fadakar *et al.*, 2015; Farhadi *et al.*, 2015; Rostami *et al.*, 2015; Spotin *et al.*, 2015; Oskouei *et al.*, 2016; Maldonado *et al.*, 2017
G2		Dogs	2		2	Parsa *et al.*, 2012; Sharafi *et al.*, 2014
G3	Sheep, cattle, camels, goats, buffaloes	Dogs	72	7	79	Sharbatkhori *et al.*, 2009; Pour *et al.*, 2011; Sharbatkhori *et al.*, 2011; Sharifiyazdi *et al.*, 2011; Hajialilo *et al.*, 2012; Harandi *et al.*, 2012b; Parsa *et al.*, 2012; Dousti *et al.*, 2013; Hanifian *et al.*, 2013; Pezeshki *et al.*, 2013; Yakhchali & Mardani, 2013; Nikmanesh *et al.*, 2014; Pestechian *et al.*, 2014; Sharafi *et al.*, 2014; Babazadeh *et al.*, 2015; Farhadi *et al.*, 2015; Rostami *et al.*, 2015; Shariatzadeh *et al.*, 2015; Oskouei *et al.*, 2016
G6	Sheep, cattle, camels, goats, buffaloes		134	13	147	Harandi *et al.*, 2002; Karimi & Dianatpour, 2008; Sharbatkhori *et al.*, 2010; Rostami Nejad *et al.*, 2011; Shahnazi *et al.*, 2011; Sharifiyazdi *et al.*, 2011; Hajialilo *et al.*, 2012; Harandi *et al.*, 2012b; Hosseinzadeh *et al.*, 2012; Nejad *et al.*, 2012; Rajabloo *et al.*, 2012; Sadjjadi *et al.*, 2013; Eslami *et al.*, 2014; Nikmanesh *et al.*, 2014; Pestechian *et al.*, 2014; Sharafi *et al.*, 2014; Rostami *et al.*, 2015; Shariatzadeh *et al.*, 2015; Spotin *et al.*, 2015
G7	Sheep, goats		6		6	Hosseinzadeh *et al.*, 2012; Fadakar *et al.*, 2015
Total			2952	340	3292	

current review was conducted using the following Medical Subject Headings (MeSH) terms: '*Echinococcus granulosus*', '*Echinococcus*', 'Echinococcosis', 'Hydatid', 'Hydatic', 'Iran', 'Prevalence', 'Epidemiology' and 'Genotype', alone or combined together with 'OR' or/and 'AND' operators.

Study selection and data extraction

Eligibility of studies and inclusion criteria were checked carefully by two independent reviewers (S. Khademvatan and S. Aryamand). Contradiction among studies was obviated by discussion and consensus (Foroutan-Rad *et al.*, 2016a, b; Majidiani *et al.*, 2016; Foroutan *et al.*, 2017a, b, c; Khademvatan *et al.*, 2017; Khalkhali *et al.*, 2017; Maleki *et al.*, 2017). The inclusion criteria were as follows: (1) peer-reviewed original research papers; (2) cross-sectional studies based on various polymerase chain reaction techniques and investigating the genotypes of *E. granulosus* in Iran; (3) published in English or Persian; (4) published online from inception to 31 December 2015; (5) full-text articles were available. Papers that failed to meet these criteria were excluded. The required data were collected accurately using a data extraction form, on the basis of the first author, province, geographical region (north, south, east, west, centre), infected organ, genotypes (G1, G2, G3, G4, G5, G6, G7, G8, G9, G10), intermediate and definitive hosts, human cases, type of diagnostic method and the DNA/RNA fragment used in detection. The review was conducted in accordance with PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (Moher *et al.*, 2010). ArcGIS (http://www.esri.com) was used for mapping the geographical distribution of various genotypes of *E. granulosus* in Iran.

Results

In total, 73 of 4793 studies met the inclusion criteria and were included in the systematic review (fig. 1). Literature search results and study properties (species, genotypes, animal intermediate host, definitive host, number of animal and human cases) are presented in table 1. Table 2 and supplementary fig. S1 show the geographical diversification of genotypes detected in different provinces in Iran. The number of each genotype in each of the various hosts is shown in table 3.

Intermediate and definitive animal hosts

In total, 2952 animal (intermediate and definitive) hosts were examined for cystic echinococcosis. Five *E. granulosus s.l.* genotypes exist in Iran (G1, G2, G3, G6, G7), and five livestock species (sheep, goats, cattle, buffaloes, camels) were affected by CE (table 1). With the exception of G7, which is localized in Khorasan province, eastern Iran, other genotypes were detected mostly in central and western parts of the country

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Table 2. Numbers of *E. granulosus s.l.* genotypes identified in various regions of Iran.

Region	Province	G1	G6	G3	G2	G7
North-east	Khorasan	74	–	–	–	–
North	Gilan	2	–	–	–	–
	Golestan	95	10	–	–	–
	Mazandaran	140	–	–	–	–
North-west	West Azerbaijan	818	–	2	–	–
	East Azerbaijan	91	1	2	–	–
	Ardabil	59	–	6	–	–
	Zanjan	168	–	4	–	–
Centre	Isfahan	603	50	47	–	–
	Tehran	99	1	3	–	–
	Semnan	45	15	–	–	–
West	Lorestan	163	–	3	2	–
South-west	Khuzestan	421	1	1	–	6
	Kohgiluye and Boyer-Ahmad	93	–	–	–	–
	Chaharmahal va Bakhtiari	30	–	–	–	–
South	Fars	97	57	–	–	–
South-east	Kerman	60	12	11	–	–
East	–	–	–	–	–	–
Total		3058	147	79	2	6

(supplementary fig. S1). Molecular studies revealed that *E. granulosus s.s.* clade (G1–3) was involved in most cases of infection, among which the G1 genotype was the most diverse and prevalent, with 2738 of 3058 (92%) cases in animal hosts, and dominant in 17 provinces, particularly in West Azerbaijan (table 2). The geographical distribution and involvement of various intermediate hosts demonstrates why G1 is the most abundant in the country. Results also revealed that the dog–sheep cycle of CE is widespread in most parts of Iran, indicating that G1 is viable for transmission. Most G3 and G6 cases were reported from Isfahan and Fars provinces, respectively (table 2). Animal host involvements of each recognized genotype in Iran are as follows: G1 (92.75%) and G6 (4.53%) in sheep, cattle, camels, goats and buffaloes; G3 (2.43%) in five herbivore hosts and dogs; G2 (0.06%) in dogs; and G7 (0.2%) in sheep and goats (table 3). In one study, genotype co-infection with G1, G3 and G6 was discerned. With respect to G2 and G7 genotypes, more sequencing data from various animal hosts (intermediate and definitive), particularly from provinces with fewer studies, are required to reach a rational consensus on the host range and geographical distribution of these genotypes. The findings suggest that special attention be paid to water buffaloes in subsequent works, as they may play a role in lifecycle maintenance of G1, G3 and G6 strains in Iran. Some characteristics of the G6 genotype are significant for CE diagnosis and control strategies (Kamenetzky *et al.*, 2005; Chow *et al.*, 2008; Muzulin *et al.*, 2008). No sequencing information exists for the G4 genotype in Iran, necessitating molecular studies in horses. No molecular evidence from G8–10 genotypes has been reported from the country.

In general, in the case of neighbouring countries there was a low diversity in the animal hosts examined and subsequently in CE genotypes isolated, with most studies focused on *E. granulosus s.s.* (Utuk *et al.*, 2008; Latif *et al.*, 2010; Simsek *et al.*, 2011; Eryıldız & Şakru, 2012; Hama *et al.*, 2012; Hama & Shareef, 2016; Hasan *et al.*, 2016; Gökpınar *et al.*, 2017; Hassan *et al.*, 2017). With some exceptions (Al-Qaoud *et al.*, 2003; Trachsel

Table 3. Numbers of *E. granulosus s.l.* genotypes identified in animal and human hosts in Iran.

	Sheep	Cattle	Goats	Camels	Buffaloes	Dogs	Humans	Total
G1	1362	525	613	173	52	13	320	3058
G2	–	–	–	–	–	2	–	2
G3	1	36	10	20	1	4	7	79
G6	2	54	9	63	–	6	13	147
G7	–	–	–	–	–	6	–	6
Total	1365	615	632	256	53	31	340	3292

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et al., 2007; Ziadinov *et al.*, 2008), the strains identified in definitive hosts in Iran are partly identical to detected genotypes in adjacent countries.

Human cases

In total, 340 cases of CE in humans have been reported, with sequencing data, from Iran. Major *E. granulosus* genotypes in infected individuals include G1 (n = 320) and G3 (n = 7) as *E. granulosus s.s.*, and G6 (n = 13) as *E. canadensis* (tables 1 and 3). Alongside the exclusive G1 genotype, which is dominant globally, G6 is the most prevalent clade in human infections in Iran, similar to recent data from South American countries (Cucher *et al.*, 2016). Based on the study of Sadjjadi *et al.* (2013) in Iran, *E. canadensis* is responsible for brain infections, suggesting an alternative predilection site to the liver. Consequently, nationwide research is required to clarify the exact epidemiological status and biological behaviour of this clade in Iran. Based on our results, the highest and lowest incidences of human CE infections were in Isfahan (168 cases) and Kerman (two cases) provinces, respectively. Considering the capability of cattle and camels to harbour multiple genotypes (table 1), these animals probably play a central role in preserving the CE life cycle and the risk of human transmission, particularly camels in central arid parts of Iran, where they are possibly involved in G6 environmental maintenance. The absence of G7 (pig strain) in human cases may be partially attributed to the lack of pig breeding in Islamic culture. Human cases in Afghanistan and Pakistan have been discerned as the G1 strain, whereas more diverse CE genotypes have been isolated from human subjects in Iraq and Turkey than in Iran (Rojas *et al.*, 2014).

Discussion

Cystic echinococcosis is an important neglected parasitic disease worldwide. In a review of the current situation of echinococcosis in Asia, Ito & Budke (2017) discussed various aspects of CE throughout the continent but provided no data for Iran. The current work and a previously published meta-analysis (Khalkhali *et al.*, 2017) appropriately report up-to-date information regarding the epidemiology of CE in Iran. Several strains of CE with specific epidemiological and biological emphases have been categorized in various clades, including the following: *E. granulosus s.s.* (G1–3), *E. equinus* (G4), *E. ortleppi* (G5) and *E. canadensis* (G6–10), and *E. felidis* (the lion strain). More studies using sophisticated molecular tools are a requisite to revealing more genotype diversity and their respective hosts in Iran. This paper reviewed works featuring sequencing discrimination of CE genotypes in natural hosts and human cases in Iran. Reportedly, G6 was the second most abundant genotype in all hosts, after G1. Regarding antigenic variations in EG95-related proteins of G1 and G6, studies should focus on the diagnosis, chemotherapy and pathogenicity of the G6 strain (Alvarez Rojas *et al.*, 2013). The lack of human cases of the G4 genotype may be attributable to the requirement of additional host samples and sequencing information and/or the non-infectious condition of the G4 genotype for human hosts. A wide range of animals were proven to be involved in the ecological maintenance of pastoral and sylvatic life cycles of CE. Our review was confined to published literature, and therefore our findings may not provide a full representation of CE genotypes throughout Iran. In conclusion, the data obtained from this systematic review could benefit local and nationwide CE control initiatives, such as effective CE vaccines for dogs and livestock, improved diagnostic methods for humans and definitive hosts, efficient treatment options and development of well-structured mathematical models for better evaluation of cost-effective interventions.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S0022149X18000275

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Conflict of interest. None.

Ethical standards. This study was approved by the Ethical Committee of Urmia University of Medical Sciences, Urmia, Iran (IR.UMSU.REC.1395.511).

Author contributions. S. Khademvatan and M. Foroutan conceived the study; S. Khademvatan and S. Aryamand designed the study protocol; M. Foroutan and S. Khademvatan searched the literatures; S. Aryamand extracted the data; H. Khalkhali analysed and interpreted the data; H. Majidiani wrote the manuscript; S. Khademvatan, H. Majidiani, M. Foroutan and K. Hazrati Tappeh critically revised the manuscript. All authors read and approved the final manuscript.

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