

Distribution Map of *Echinococcus granulosus* Sensu Lato Genotypes in Human Cases in Turkey: A Systematic Meta-Analysis

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ABSTRACT

Objective: To date, many studies have been performed on genotyping of *E. granulosus* s.l. in Turkey. However, a systematically analysis of the data human *E. granulosus* s.l. genotypes in Turkey is lacking. In this context, the aim of this study is to provide summary information about the distribution of *E. granulosus* s.l. genotypes which have been detected with molecular methods in human isolates in Turkey.

Materials and Methods: Both English and Turkish studies in four international and national databases up to September 2022 were searched with keywords related “Echinococcus” to access the eligible articles for our study. The selected articles were transferred StatsDirect software for performing meta-analysis.

Results: Out of 3497 articles from literature search, 24 records were eligible for inclusion in this meta-analysis. All data were obtained from 34 cities in all regions of Turkey. Total of 815 human cases whose genotypes were sequenced and identified. With the present study, identified species of *E. granulosus* s.l. in Turkey were determined as follows, from most common to the least: *E. granulosus* sensu stricto (G1-G3): 97.8%, *E. equinus* (G4): 0.12%, *E. canadensis* (G6-G10): 2.0%. In addition, according to proportion of the genotypes, while G1(48%; 95%CI: 40-49%) and G1-G3 complex genotype (47%; 95%CI:41-48%) were detected in all regions of the country, G3 (2.8%; 95%CI:1-3%) was detected in Southeast and Eastern Anatolia, G4 (0.12%; 95%CI:0.1-1%) only in Central Anatolia, G6 (0.25%; 95%CI:0.2-1%) only in Eastern Anatolia, G7 (0.25% ; 95%CI: 0.2-1%) in Aegean and Marmara regions, and G6/G7 (1.5% ; 95%CI: 0.7-2%) in Aegean, Central Anatolia and Eastern Anatolia.

Conclusion: With this meta-analysis study, it has been revealed that the most predominant *E. granulosus* genotypes of humans cystic echinococcosis in Turkey were G1 and G1-G3 complex. The present study will be a guide for genotyping studies have not been performed in the other regions of the country. The more in-depth meta-analysis studies are needed to better understand the molecular characterization of *E. granulosus* s.l. in other hosts such as dogs, sheep and cattle in Turkey.

Keywords: *Echinococcus granulosus*, meta-analysis, Turkey, genotype

INTRODUCTION

Echinococcus granulosus is a worldwide distributed tapeworm and it causes a parasitic disease called as Cystic Echinococcosis (CE). This zoonotic disease transmitted to intermediate hosts (like livestock animals and human) from dogs or other wild canid definitive hosts (1). As well as CE causes economic losses due to loss of meat and milk yield in animals, it is an important disease in terms of public health considerable morbidity and mortality in humans (2).

E. granulosus, adult tapeworms are found in intestines of canids, while they shed the eggs in their stool onto grass and meadow which are eaten by the livestock or various ungulated animals where the larvae grow into a fluid filled hydatid cyst. Canids acquire infection by eating cyst infected liver, lungs or other organs of intermediate animals. Humans are also intermediate hosts however they are dead-end (aberrant hosts) in this life cycle. They are infected by ingestion of contaminated food or water with parasite eggs (3).

CE is known to find in all continents except Antarctica. Especially the highest prevalence rates are in North Africa, Middle East, Central Asia, Eastern Russia, West China and South America regions. Turkey is also considered one of the highly endemic countries for CE in both humans and animals (4–6). In the HERACLES project, which was carried out with the partnership of 9 scientists from 5 countries between 2013 and 2018, it was estimated that there were 106 237 (95% CI 33 829–330 751) human CE cases in rural areas in Turkey at the stage of prevalence studies by using abdominal ultrasound screening (7,8).

E. granulosus, previously considered to be as a single species, is now recognised as an assemblage of cryptic species that have differences in morphology, development and host specificity including infectivity and pathogenicity. In recent studies, lots of molecular researches have been made to understand the taxonomy of *Echinococcus*, and the species composition within the genus has now almost been cleared (9). Thanks to the modern DNA-based methods, it was confirmed that *E. granulosus sensu lato* (s.l.) has genetic variability between G1-G10. Then, with further revisions genotype G1-G3 were named as *E. granulosus sensu stricto* (s.s.), G4 as *E. equinus*, G5 as *E. ortleppi*, G6-G10 genotypic cluster as *E. canadensis* and the "lion strain" as *E. felidis* (10).

The gene regions of mitochondrial genes and nuclear ribosomal DNA are generally used to identify genotypes/species *Echinococcus* spp. Various molecular methods are important techniques involving sequencing of partial mitochondrial cytochrome c oxidase subunit 1 (cox1), and NADH dehydrogenase 1 (nad1) genes, analysis of nuclear ribosomal DNA regions (ITS1, ITS2) by polymerase chain

reaction-restriction fragment length polymorphism (PCR-RFLP) and random amplification of polymorphic DNA (RAPD-PCR). The genetic characterization determined by these developed molecular methods has been significant in understanding the transmission pattern of the parasite between intermediate and definitive hosts (11,12).

E. granulosus s.s (genotypes G1-G3) is globally most common causative species of human CE. However, less frequently other genotypes can also cause human CE. Although, three genotypes (G1-G3) were defined in *E. granulosus* s.s, G2 has recently been stated that it is no longer considered a valid genotype, and a microvariant of G3 (13,14). *Echinococcus equinus* (genotype 4) was considered to be non-infectious to human and found in only animals for long time, however two recently reported studies have shown that this species is also zoonotic (15,16). *E. canadensis* cluster is splitted in two clades which are genotypes G6/7 (camel strain and pig strain, respectively) and genotypes G8/G10 (cervid strains). *E. canadensis* (G6/G7) is second most common cause of human CE (11.07%). Also, a few genotype G8/G10 human CE infections were reported so far. The last species *E. felidis* was detected in lions and a warthog from Uganda and no human infection was reported until now (10,17,18).

To date, numerous studies have been performed on genotyping of *E. granulosus* s.l in Turkey. However, it is important to analyse systematically the data about human *E. granulosus* s.l. genotypes in Turkey. Thus, in this study we aimed to provide summary information about the distribution of *E. granulosus* s.l. genotypes which have been detected with molecular methods in human isolates in Turkey until September 2022.

MATERIALS AND METHODS

Search strategy

English and Turkish studies published in various databases which are "Google Scholar", "PubMed" and "ULAKBIM" (Turkish Academic Network and Information Center), YOK thesis (Turkish Council of Higher Education Thesis Center) databases until September 2022 were investigated to access the eligible articles for our study. For this purpose, as alone or a combine "*Echinococcus granulosus*", "*Echinococcus granulosus* s.l." "Genotype", "Cyst hydatid", "Cystic echinococcosis" and "Turkey" keywords were used. For studies which were not indexed by above databases, references of identified studies were also examined.

Inclusion and Exclusion Criteria

The following criteria were taken into consideration to include in our study: (1) online accessible full-text articles, (2) studies conducted in Turkey, (3) the studies based

on molecular methods that identify the genotypes of *E.granulosus* s.l.

In this study, this type of articles were excluded: Duplicate manuscripts, letters to the editor, review articles, animal studies (in mixed studies of animal and human samples, only human samples were considered), non-molecular studies, molecular studies which were no identified genotype type or ambiguous description of *E.granulosus* s.l genotypes and articles with insufficient information.

Data extraction

This study was carried out following the guidelines of the PRISMA statement (19). According to inclusion and exclusion criteria, eligible studies were exported to an Excel sheet. The following data was extracted from each included studies: year of the publication, number of samples, number of identified genotypes, region or city of study.

Statistical Analysis

After entered the data of eligible articles in Excel, they were transferred StatsDirect software (<https://www.statsdirect.com/>) for performing meta-analysis (20). According to random effect-models; odds ratio, 95% confidence intervals (CIs) were estimated for each study containing G1, G1-G3, G6/G7, G7, G4, G3 and G6 genotypes. Then, the I² indicator value and the Q test were used to investigate heterogeneity between results. Also, the presence of publication bias was assessed with the Eger test.

RESULTS

According to search in various databases which are included "Google Scholar", "PubMed", "ULAKBIM" and YOK thesis, total 3497 articles were found. Out of 3497 articles from these literature sources, 24 records were eligible for inclusion in this meta-analysis and the study evaluation and selection procedure were shown in flow diagram (Figure 1).

All data were obtained from 34 provinces in all regions of Turkey. Total of 815 human cases whose genotypes were sequenced and identified. As shown on the map, genotyped human CE cases have been reported from all 7 regions in Turkey. In addition, while G1 and G1-G3 genotypes were detected in all regions of the country, G3 was detected in Southeast and Eastern Anatolia, G4 only in Central Anatolia, G6 only in Eastern Anatolia, G7 in Aegean and Marmara regions, and G6/G7 in Aegean, Central Anatolia and Eastern Anatolia (Figure 2).

As it was shown in forest plot diagrams in Figure 3, in the general population of identified genotypes of *E.granulosus* s.l cases in Turkey, Genotype G1 was found the most common genotype with its proportion 48% (95% CI: 40-49%) followed by G1-G3 with very close proportion 47% (95% CI: 41-48%). Since there was only one G4 genotype reported in Turkey, the lowest rate was Genotype G4 (0.12%; 95% CI from 0.1 to1%). According to the Egger probability values calculated to detect publication bias, only genotypes G1 and G3 showed significant differences ($p<0,05$) (Table 1).

Table 1. Proportion, publication bias and heterogeneity of genotypes of human echinococcosis in Turkey

	Genotype	Proportion % (95% CI)	Cochran Q Value	df	I ₂ (%)	p-value	Egger Bias or Bias	p-value
<i>E.granulosus</i> s.s	G1*	48% (40-49%)	1376	23	98.3 %	<0.0001	11.93	0.03
	G1-G3*	47% (41-48%)	1453	23	98.4%	<0.0001	-17.47	0.72
	G3*	2.8% (1-3%)	64	23	64.2%	<0.0001	0.92	0.0039
<i>E. equinus</i>	G4	0.12% (0.1-1%)	5.7	23	0%	<0.9999	0.05	0.29
<i>E. canadensis</i>	G6€	0.25% (0.2-1%)	8.4	23	0%	<0.9975	0.09	0.27
	G6/G7€	1.5% (0.7-2%)	29	23	22%	<0.015	0.35	0.13
		0.25% (0.2-1%)	8.4	23	0%	<0.0001	0.11	0.13

*G1 and G3 genotypes belong to *E. granulosus* s.s (G1-G3). In this case, total proportion is 97.8 %.
 €G6, G6/G7 and G7 genotypes belong to *E. canadensis*. In this case, total proportion is 2.0 %.

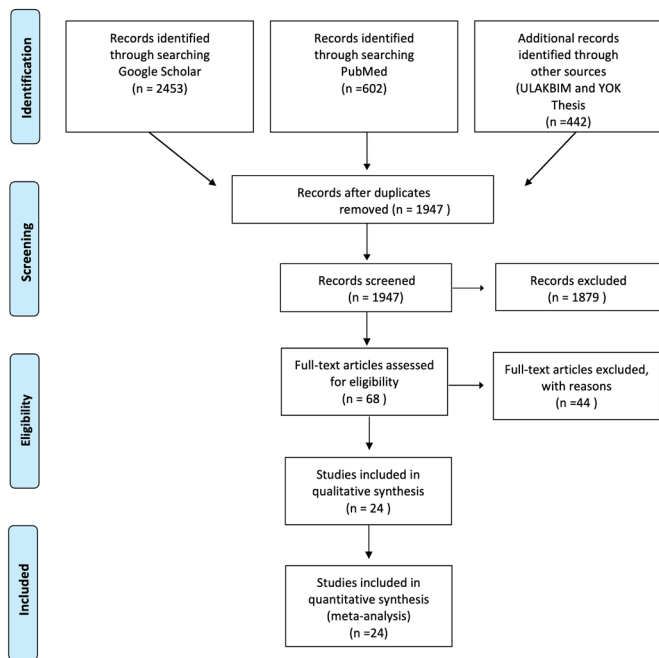


Figure 1. Flow diagram of the study and meta-analysis process

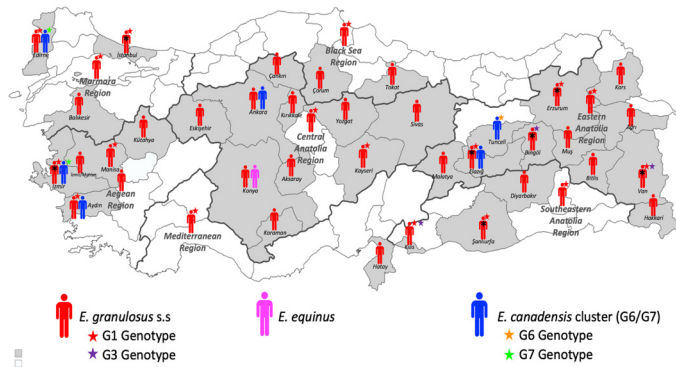


Figure 2. Distribution map of identified of genotypes of human CE cases in Turkey. (The asterisks on red human icons (*) indicate that *E. granulosus* s.s also exits in that province)

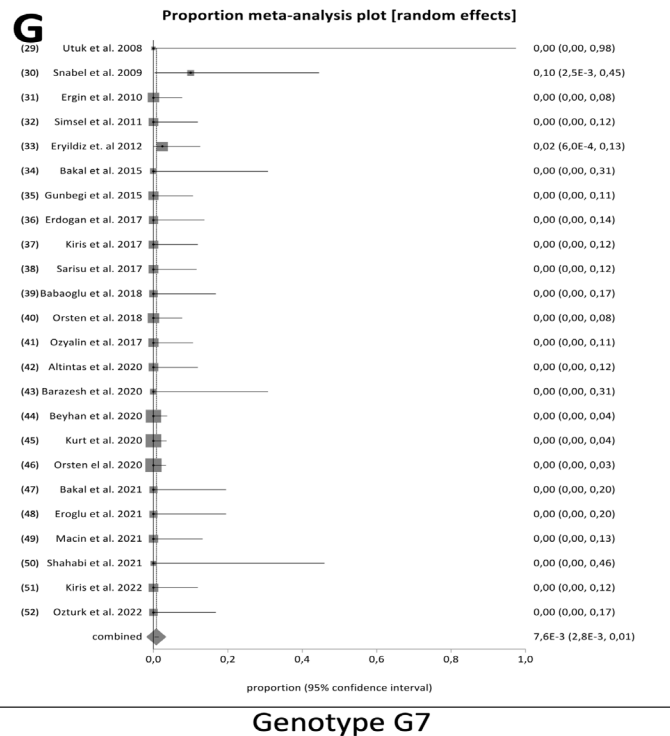
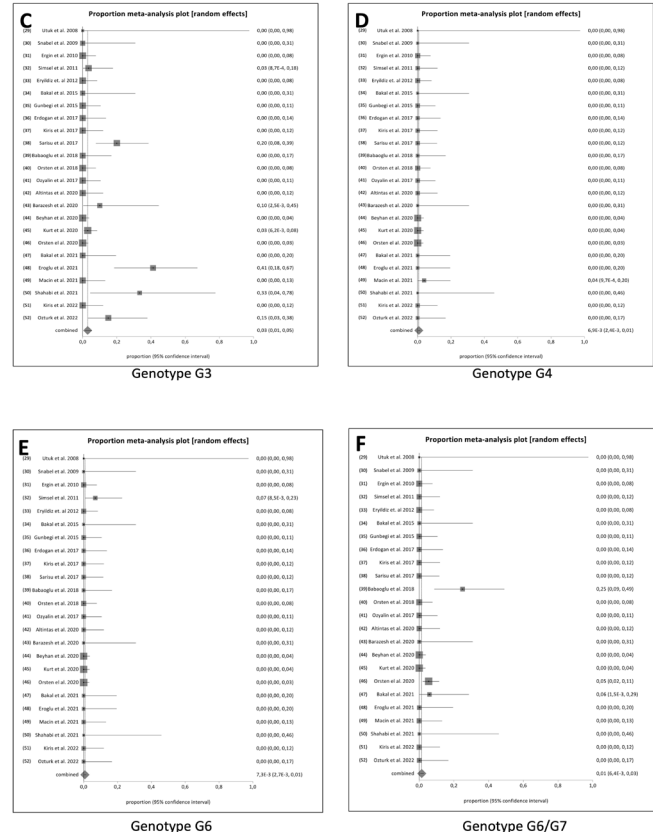
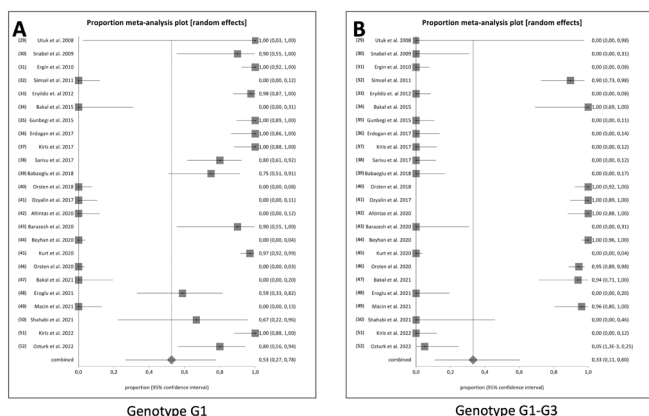


Figure 3. Forest plot of random effect meta-analysis presenting human cystic echinococcosis cases of *E. granulosus* Genotypes G1 (A) G1-G3 (B), G3 (C), G4 (D), G6 (E), G6/G7 (F) and G7 (G), in Turkey from 24 publications. The square (■) indicates the proportion of each study and lines (—) are 95% confidence intervals. The combined estimate from the random effects is shown as (⊖)

DISCUSSION

Cystic echinococcosis is one of neglected zoonotic diseases infecting humans and animals. Causative agent of this serious disease is genotypes and species belonging *E. granulosus* s.l. complex. Different genotypes from G1 to G10 have been identified by the studies carried out to date, and it has been stated that some of these genotypes differ at the species level. With the emergence of molecular techniques, identification of *E. granulosus* s.l. genotypes has been carried out in recent years (17,21). Identification of genotypes/species of this parasite play significant role for development of genotype specific treatment and vaccines, control of disease, discovering interaction of definitive and intermediate hosts (22). In addition, there are some studies in which meta-analysis of identified genotypes of *E. granulosus* s.l., and these studies are significant in terms of giving summary information about the current situation in the region. Borhani et al. summarized the available information on the geographic distribution, molecular epidemiology, and transmission dynamics of *Echinococcus granulosus* sensu lato and *Echinococcus multilocularis* in humans and animals in Iran, Turkey, and Pakistan (23). In this present study, the distribution of genotyped human CE cases on the map is shown. Similar to our study, in a meta-analysis study that included only 559 human samples in Iran, it was reported that G1, G2, G3 and G6 genotypes were found in Iran. However, as there was only one human CE case of Genotype G2, only this study was not analyzed (24). In another studies 1534 samples and 340 samples belong to humans and animals were analyzed in South America and Iran, respectively (25,26). Genotype G1 was reported as the most common genotype in these studies. Furthermore, a review by Macin et al. was published in which was discussed the distribution and epidemiology of *E. granulosus* s.l. genotype detected in human and animals in Turkey (27). In our present study, the distribution of *E. granulosus* s.l. genotypes detected in humans was shown on the map according to region and provinces, the genotype proportion of the total determined genotypes was detected and meta-analyses of them was carried out.

The G1 genotype is responsible for the majority of human CE cases in worldwide. Also, G1 genotype were detected in all regions of Turkey. However, G4 genotype was reported in only one human case in Konya province and with this present study it was detected the least common genotype (0.12%; 95%CI:0.1-1%). This species was considered not to be zoonotic for long time. However, human infections were reported in only Uzbekistan and Turkey (15,16).

Echinococcus granulosus s.s (G1-G3) was found second common genotype (47%) in Turkey and it was also detected in all regions such as G1 genotype. This G1-G3 complex genotype includes G1, G2 and G3 genotypes and it is called as *E.granulosus* s.s. This genotype was

also detected in all countries and regions like Middle east, Europe, South America and Asia and one of the most common genotypes (19,21). The genotype G3 was found in 5 provinces in Turkey including Bingol, Van, İzmir, Erzurum, Kilis. Similarity the present study, the human cases of this genotype were reported in Italy, Romania, India, Tunisia, and Brazil (10).

CONCLUSION

As a result of this study, it has been revealed that the most predominant *E.granulosus* genotypes of humans CE in Turkey were reported G1 and G1-G3 complex genotypes. We believe that the map showing the genotype distribution of human cases in Turkey in this study will shed light on future studies. Since genotypes G1 and G1-3 have been shown to be the most common genotypes affecting the Turkish population, disease control interventions targeting intermediate hosts (such as sheep, buffalo, cattle) and definitive host (dogs) may be most beneficial. These findings and showing the distribution of genotypes on the map improve the understanding of the molecular diversity of *E granulosus* s.l. Nonetheless, the more in-depth meta-analysis studies are required for better understanding molecular characterization in various hosts such as dog, sheep and cattle in Turkey. In addition, this present study will be a guide for where genotyping studies have not been performed in the other regions of the country.

Competing interests: The authors declare that they have no competing interest.

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