



# An overview of the genetic diversity of *Echinococcus granulosus sensu lato* in Turkey

## Türkiye'deki *Echinococcus granulosus sensu lato*'nun Genetik Çeşitliliğine Genel Bir Bakış

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### Abstract

*Echinococcus granulosus* is a parasite that causes great economic damage and poses a serious threat to health. Morphological differences and intermediate host preference are used to distinguish the species of *Echinococcus*. Ten genotypes and lion strains of *Echinococcus granulosus* have been identified in molecular studies to date. The elucidation of different genotypes of *Echinococcus* species detected in humans contributes to the understanding of the disease process. In genetic diversity analysis, species were classified as *Echinococcus granulosus sensu stricto*, *Echinococcus equinus*, *Echinococcus ortleppi*, *Echinococcus canadensis* and *Echinococcus felidis* genotypes. *Echinococcus granulosus sensu stricto* is the most common cause of human cystic echinococcosis worldwide and in Turkey. In this review, the distribution and epidemiology of *Echinococcus granulosus* genotypes detected in humans and animals in Turkey are discussed.

**Keywords:** *Echinococcus granulosus*, genetic diversity, genotypes, human, animals, cystic echinococcosis

### Öz

*Echinococcus granulosus* büyük ekonomik zarar oluşturan ve sağlık açısından önemli tehdit oluşturan bir parazittir. Morfolojik farklılıkları ve ara konak tercihi *Echinococcus* türlerini ayırt etmede kullanılmaktadır. Günümüze kadar yapılan moleküler çalışmalarda *Echinococcus granulosus*'un on genotipi ve aslan suşu tespit edilmiştir. İnsanlarda tespit edilen *Echinococcus* türlerinin farklı genotiplerin aydınlatılması oluşturduğu hastalık sürecinin anlaşılabilmesine katkı sağlamaktadır. Genetik çeşitlilik analizinde *Echinococcus granulosus sensu stricto*, *Echinococcus equinus*, *Echinococcus ortleppi*, *Echinococcus canadensis* ve *Echinococcus felidis* genotipi şeklinde türler sınıflandırılmıştır. *Echinococcus granulosus sensu stricto* insan kistik ekinokokkozunda dünya ve Türkiye çapında en çok görülen etkidir. Bu derlemede de, Türkiye'de insan ve hayvanlarda tespit edilen *Echinococcus granulosus* genotiplerinin dağılımı ve epidemiyolojisi tartışılmıştır.

**Anahtar Kelimeler:** *Echinococcus granulosus*, genetik çeşitlilik, genotipler, insan, hayvanlar, kistik ekinokokkoz



## INTRODUCTION

Echinococcosis is one of the 17 neglected tropical diseases prioritized to be achieved prevention, control, elimination, and eradication by the World Health Organization (WHO) by 2030.<sup>[1]</sup> Cystic echinococcosis (CE) is a zoonotic infection caused by the metacestode form of *E. granulosus* sensu lato, which causes health problems worldwide. In addition, this parasite causes significant economic loss, and it is ranked second on the global food-borne parasite list by the Food and Agriculture Organization (FAO).<sup>[2]</sup> CE is mostly endemic in rural areas where animal breeding is active, being in close contact with dogs such as Australia, Asia, South America and Mediterranean countries, including Turkey. The life cycle of the parasite maintains between carnivores such as canids and herbivores such as sheep, cattle and goats. Humans are considered accidental hosts due to not contributing to the perpetuity of the cycle.<sup>[1,3,4]</sup>

*E. granulosus* was firstly regarded as the only causative agent of CE though it was clear that there were different subspecies with variety in adult morphology, host specificity, and pathogenicity. In the early 1980s, there was consensus on four main species belonging to the *Echinococcus* genus as *E. granulosus*, *E. multilocularis*, *E. oligarthra*, and *E. vogeli*.<sup>[5]</sup> However, it was apparent that *E. granulosus* consisted of a significant number of variants in terms of morphology, host specificity, biochemical parameters, developmental biology, and geographic distribution. Therefore, these intra-specific differences were identified as strains. Correspondingly, the eleven strains were determined namely sheep, buffalo, Tasmanian sheep, pig, variant pig, camel, horse, cattle, American cervid, lion and Fennoscandian cervid strain.<sup>[2]</sup> Direct microscopy, serology and molecular methods can be used in the microbiological diagnosis of *E. granulosus*.<sup>[4]</sup> Since the early 1990s, molecular studies on mitochondrial DNA sequences have identified 10 different genotypes in the *E. granulosus* complex. As a result of the increased sequence data, genotype 'G nomenclature' (G1 to G7) was gradually substituted for the strain names. Accordingly, genotypes were determined as G1 (sheep strain), G2 (Tasmanian sheep strain), G3 (buffalo strain), G4 (horse strain), G5 (cattle strain), G6 (camel strain), G7 (pig strain), G8 (American cervid strain), G9 (variant pig strain) and G10 (Fennoscandian cervid strain). "G nomenclature" could not be applied the lion strain due to lack of biological sample.<sup>[5-10]</sup> Today, some evidence exists which supports that G2 is a sub-group of G1 (using *cox1* sequences) or G3 (using *nad1* sequences),<sup>[7,9]</sup> and G1-G3 genotype is considered as a single species as *E. granulosus* sensu stricto. In addition, the G9 genotype is now accepted as a microvariant of G7. Current taxonomic acceptance is that *E. granulosus* s.l. is a species complex which split into 5 species as *Echinococcus granulosus* sensu stricto (genotypes G1–G3), *Echinococcus equinus* (G4), *Echinococcus ortleppi* (G5), *Echinococcus canadensis* (G6/G7, G8, G10) and *Echinococcus felidis*.<sup>[2,11-13]</sup> G2 and G9 are no longer recognized as distinct genotypes; they are accepted as micro variants of G1-G3 and G7 genotypes, respectively (14).

Ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used for radiological diagnosis. The radiological appearance lesions caused by *E. granulosus* can vary from pure cystic lesions to solid-looking masses.<sup>[15]</sup> Ultrasonography (USG) is the most advantageous scanning method for noninvasive imaging of cystic lesions. USG is the most sensitive modality for detecting membranes, septa and hydatid sand. CT is an important diagnostic method in determining the number, size and anatomical location of cysts, in the evaluation of calcified hydatid cysts and in the evaluation of extrahepatic spread. MRI is superior to other methods in evaluating the cyst wall defect and the relationship of the lesion with the biliary tract.<sup>[16]</sup>

In the light of this information, we aimed to provide in this review some insights into the genetic variability of *E. granulosus* isolates retrieved from intermediate hosts including humans from Turkey.

### Human-based Studies

Many different target gene regions (partial mitochondrial cytochrome c oxidase subunit (*cox1*), NADH dehydrogenase 1 (*nad1*), internal transcriber spaces 1 (ITS1), elongation factor 1 alpha (*ef1a*), etc.) and methods such as sequencing after PCR, RFLP-PCR was used to determine the genetic diversity of *E. granulosus* s.l.<sup>[17]</sup>

There is a lot of research based on the genotyping of *E. granulosus* isolates from the human host in Turkey. In the study published by Bowles and McManus in 1993, *E. granulosus* isolates retrieved from the human hosts from various countries were examined with the rRNA ITS1 region targeted PCR-RFLP method. Two of these isolates were sent from Turkey and both were defined as sheep strains.<sup>[18]</sup> In the study conducted in the western region of Turkey, twenty-two samples collected from 12 sheep and 10 humans were examined for several mitochondrial genes (*CO1*, *atp6*, *nad1*, *rnrS*). Two species as *E. granulosus* s.s. and *E. canadensis* were identified in this study. For the first time, the G7 genotype (pig strain) was found in isolates of both sheep and humans.<sup>[19]</sup> In the study aimed to determine the genotypes of *E. granulosus* in formalin-fixed and paraffin-embedded tissues, tissue samples from 70 patients with histologically confirmed echinococcosis, PCR of 12S rRNA gene and mt-CO1 gene were performed. As a result, 29 of 70 samples (41.6%) were found to be positive on at least one PCR assay. In detail, 26 of 29 samples were identified as G1-G3 genotype and two of 29 were identified as G6 genotype.<sup>[20]</sup> In a study from the Thrace region, a total of 58 *E. granulosus* isolates derived from different hosts including 42 humans, 13 cattle, and three sheep were analyzed. In consequence, the majority of isolates (47 of 58) were classified as G1 genotype (sheep strain) and one of the human-derived isolates was identified as G7 (pig strain) genotype.<sup>[21]</sup> In a study conducted on the evaluation of 10 pediatric CE patients, all isolates were identified as *E. granulosus* (s.s.) (G1-G3 genotypes).<sup>[22]</sup>

Twenty hydatid cyst materials obtained from humans in Adana province were examined and it was reported that they were compatible with the G1 genotype.<sup>[23]</sup> A study from Aydın province, the majority of *E. granulosus* isolates (15/20) were defined as G1 genotype and rest of (5/20) were defined as G6/7 genotype.<sup>[24]</sup> In a research conducted by Orsten et al., the determination of genetic variation using partial mt-CO1 gene and population structure of *E. granulosus* s.s. were determined in a total of 46 human-derived isolates from various regions of Turkey. Accordingly, all the isolates were found to be *E. granulosus* s.s. (G1-G3 genotypes).<sup>[25]</sup> A study from Erzurum province, a total of five alveolar and 106 hydatid cysts as well as 23 formalin-fixed paraffin-embedded (FFPE) samples were analyzed. Accordingly, it was confirmed that *E. multilocularis* cases, searched genetic variations of the isolates, and for the first time determined genotypes of *E. granulosus* s.l. infecting humans in the province. All the *E. granulosus* isolates were identified as G1-G3 genotypes.<sup>[26]</sup> In a study that aimed to determine the genotypes of *E. granulosus* s.l. isolates derived from the human host and investigated their relationship with cyst characteristics using mt-CO1 gene PCR and sequencing. As a result, a total of 110 hydatid cyst isolates were confirmed as *E. granulosus* sensu lato. 104 of 110 isolates were identified as *E. granulosus* s.s. (G1-G3) and six isolates of 110 were identified as *E. canadensis* (G6/7).<sup>[27]</sup> In the study from Van province, 102 echinococcal cysts were collected from the operated patients and the genomic analysis was performed using ITS1 fragment by PCR-RFLP and mt-CO1 gene by PCR and after evaluate with sequencing. Consequently, all isolates was found to be accordance with G1-G3 genotypes.<sup>[28]</sup> In the study published by Macin et al. in 2021, 100 hydatid isolates retrieved from different hosts were examined by mt-CO1 targeted PCR and a total 83 of 100 isolates were found to be positive. As a result, 57 of cattle-derived and 25 of human derived isolates were identified as *E. granulosus* s.s. (G1-G3 genotypes). Surprisingly, one of the human-derived isolate was identified as *E. equinus* (G4 genotype). With this study, *E. equinus* of human host origin was reported for the first time in Turkey and second time reported in worldwide.<sup>[29]</sup> According to a multicentre study, a total of 60 pathologically confirmed human hydatid cysts and 90 specimens of livestock derived hydatid cysts from Iran and Turkey were analyzed using nad5 gene targeted PCR. Out of 21 samples from Turkey, 16 (76.2%) and five (23.8%) were classified as G1 and G3 genotypes, respectively. It was determined that none of the samples isolated from human host in Iran or sheep host in Turkey were G3 genotype.<sup>[30]</sup> A study from southeast region, a total of 159 tissue samples taken from suspected echinococcosis cases were examined by PCR based methods. As consequence, it was determined that eight of 25 (32%) echinococcal isolates were *E. multilocularis* and 17 of 25 isolates were *E. granulosus* s.s. (G1-G3 genotypes).<sup>[31]</sup>

### Animal-based Studies

In its life cycle, *E. granulosus* uses members of the Canidae family such as dogs and wolves as its final host, and many animals such as sheep, goats, cattle, and camels as intermediate hosts. In this context, it is aimed to determine the gene regions and genotypes in the isolates of these animals. According to Vural et al.(2008), a total of 112 hydatid cysts were examined in Kars from sheep (100 isolates) and cattle (12 isolates). In a total of 107 isolates, including nine from cattle and 98 from sheep, haplotypes corresponding to the G1 strain have been identified. It has been determined that five isolates belong to the G3 genotype of two sheep and three cattle.<sup>[32]</sup> According to Utuk et al. (2008) examined a total of 205 samples consisting of 179 sheep, 19 cattle and seven goat isolates from Diyarbakir, Elazığ, Erzurum, Sanliurfa, Van and Malatya, and all 17 mt-CO1 sequences examined were identified as corresponding to *E. granulosus* sensu stricto (G1).<sup>[33]</sup> According to Simsek et al.(2010) examined 1758 cattle in Erzurum and found hydatid cysts in 33.9% of cattle of the 220 bovine isolates, 147 showed the same band pattern as the 12S rRNA assay and the G1-G3 complex *E. granulosus* sensu stricto has been described as.<sup>[34]</sup> According to Simsek et al. (2011) examined a total of 54 samples in Elazığ and Erzurum, 31 of which were sheep liver, 23 of which were cattle (12 liver and 11 lung). They classified all 54 samples obtained from sheep and cattle as *E. granulosus* sensu stricto (G1-G3 complex).<sup>[35]</sup> In 2011, 166 buffalo viscera were examined in the Black Sea Region. It was determined that 10.24% of buffaloes were infected with cystic echinococcosis. Based on mt-CO1 sequencing analyzes, six cysts out of nine isolates were found to belong to the G1 genotype (domestic sheep strain), while three cysts showed variant genotypes of the *Echinococcus granulosus* complex G1-G2-G3.<sup>[36]</sup> In 2013, the horse liver sample was grouped with *E. granulosus* sensu stricto (G1-G3) according to the mt-12S rRNA-PCR result. The partial mt-CO1 sequence corresponded to G1. This is the first molecular characterization study of *E. granulosus* horse isolate in Turkey.<sup>[37]</sup> Oguz et al. (2018) conducted a study on the determination of the genotype of *E. granulosus* eggs found in the feces of dogs and the prevalence of this parasite by copro-PCR method in Van province and detected *E. granulosus* sensu stricto in four out of 10 (40%) infected samples.<sup>[38]</sup> In 2019, a fluid-filled cyst was taken from the liver of a donkey. PCR amplification of 12S rRNA and CO1 yielded bands of 254 and 446 base pairs, respectively, for all three cyst samples.<sup>[39]</sup> In a study by Barazesh et al. (2019), a total of 90 specimens infected with hydatid disease cysts were collected in the Iranian city of Bonab (30 sheep and 30 cattle, 60 specimens) and Van (15 sheep and cattle 30 specimens). Polymerase chain reaction (PCR) targeting partial CO1 and nad1 was performed. All samples sequenced from Iran corresponded to the G1 (100%) genotype. Fifteen (78.9%) samples from Turkey were defined as G1, only one sample (5.3%) as G3 genotype, and 3 isolates (15.8%) as G1/G3 genotype.<sup>[40]</sup> Mehmood et al. (2020) on the identification, molecular analysis and characterization

of *Echinococcus* spp., a total of 85 isolates (cattle, n=66 and sheep, n=19) were collected in the Elazığ slaughterhouse in sheep and cattle. The gDNA isolation of all samples and the PCR products of the mt-CO1 gene (446 bp) were sequenced. Out of 85 isolates, 84 were accepted as *E. granulosus* sensu stricto and it was determined that one sheep isolate was *E. canadensis* (G6/G7), which was first described in Turkey.<sup>[41]</sup> In order to determine the genetic variability in G1 and G3 genotypes of *E. granulosus* sensu stricto in 2020, a total of 119 samples were collected from 48 cattle and 71 sheep in Ankara, Ordu, Adana and Mersin. For molecular characterization of G1 and G3 genotypes, two gene regions (full mt-CO1 gene sequence and partial mt-nad5 gene sequence) were amplified and haplotype analysis and protoscolices of fertile cysts were morphologically measured. Although there was no statistically significant difference between genotypes in terms of hook number, hook length, hook wing length, but a statistically significant difference was found in width.<sup>[42]</sup> In a study conducted in Elazığ in 2021 to determine the haplotypic profile of partial mt-CO1 gene in bovine lung hydatid cyst samples, 39 of 40 sequences were identified as *E. granulosus* sensu stricto. However, one of these gene profiles was identified as *Echinococcus canadensis* (G6/G7).<sup>[43]</sup> Finally, morphological and molecular characterization of cyst isolates obtained from wild boar and mule infected with hydatid cyst in 2021 were performed. Comparing the mt-CO1 gene sequences with the reference sequences in GenBank showed 100% similarity with the *E. granulosus* sensu stricto (G1-G3) sequences.<sup>[44]</sup>

## CONCLUSION

It has been stated that the geographical location of Turkey may have an effect on these possible outcomes. The identification of G6/7 in addition to the sheep genotype G1 indicated that pigs and camels in this region play a role in the transmission and distribution of *E. granulosus* to humans.

## ETHICAL DECLARATIONS

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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