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## Six-year distribution pattern of hepatitis C virus in Turkey: a multicentre study

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### ABSTRACT

Hepatitis C infection is a public health problem. The aim of this retrospective study was to determine the distribution of hepatitis C virus (HCV) genotypes in seven regions of Turkey, by evaluating 7002 patients with chronic HCV in a six-year period. During the 2009–2014 period, serum/plasma samples from 7002 new consecutive HCV RNA positive patients were collected. The female patients were 3867 (55.2%). The genotype distribution of HCV patients was evaluated by ages and years. Statistical analysis was performed by using the Mann–Whitney test and the  $\chi^2$  analysis. During the six-year period, genotype 1b was the most common genotype (67.7%) followed by untypeable genotype 1 (7.7%), genotype 4 (7.3%) and genotype 3 (6.7%). In 2014, genotype 3 was the second most common one (11.3%) and genotype 4 was the third most common one (9.8%). In the group with <25 years old patients, genotype 1b was most common (78.48%, 62/79) between the years of 2009 and 2011, whereas genotype 3 (34.8%, 86/247), between the years of 2012 and 2014. Genotype 1b was the most common in the groups between 26 and 35 years, 36 and 45 years, 46 and 55 years, 56 and 65 years. The rate of genotype 3 was increased from 4.78% to 10.06% and the rate of genotype 4 was increased from 1.3% to 3.84%, from 2009–2011 to 2012–2014. In recent years, genotypes 3 and 4 have gained importance. New therapeutic strategies and survey studies may be required for the modified HCV genotype pattern.

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### Introduction

Hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus. It is a member of the *Hepacivirus* genus in the family *Flaviviridae*. [1] Hepatitis C infection is a significant worldwide public health problem. [2–4] The estimated HCV prevalence is 2.2% and it affects over 200 million people globally. [5] HCV accounts for 27% of the cirrhosis cases and 25% of the hepatocellular carcinoma (HCC) cases worldwide. [6,7] Major transmission routes of HCV include intrafamilial transmission, direct blood contact, mother to child transmission, organ transplantations, needle-stick injuries, medical and dental procedures, intravenous drug use and shaving kits sharing. [6,8] HCV shows high genetic heterogeneity and it is divided

into six distinct genotypes throughout the world, with multiple subtypes in each genotype class. In the United States, 70% of the HCV cases are genotype 1 and the second most common genotype is genotype 2 (20%). [9] Genotype 1 is also the most prevalent in South America and Europe. [10] HCV subtype 1b is the most encountered type worldwide. [11,12] In Europe, the most common subtype 1b is followed by subtype 2a/2c and genotype 3. [2] Genotypes 1a and 3a are observed in the North American and European countries. Genotype 2 is prevalent in the Mediterranean countries, Far East and Western Africa. Genotype 4 is mainly found in Middle East and Central Africa. Genotypes 5 and 6 are observed in South Africa and South East Asia, respectively. [2,13] Genotype 4 is mainly seen

in Egypt, where it represents 90% of all HCV cases.[14] Dental care and wound treatment are related to genotype 4 infections.[14]

Turkey, which is a transcontinental Eurasian country, is divided into seven census regions: Marmara, Aegean, Black Sea, Central Anatolia, Eastern Anatolia, Southeastern Anatolia and the Mediterranean. In previous studies, genotype 1b was reported as the most prevalent subtype in Turkey.[15–18] In recent years, improvement in health-care-related standards, eradication of blood transfusion-related infections and increase in visits between the countries may lead to changes in the distribution of HCV genotypes.[19–21] There are no available data that reflect the epidemiological changes of HCV over the years in Turkey. Therefore, the aim of this multicentre study was to determine the distribution of HCV genotypes in seven regions of Turkey by evaluating 7002 chronic hepatitis C patients in a period of six years.

### Materials and methods

During the 2009–2014 period, serum/plasma samples from 7002 new consecutive HCV RNA positive patients were collected from eight hospitals located in seven regions of Turkey, including Marmara, Aegean, Black Sea, Central Anatolia, Eastern Anatolia, Southeastern Anatolia and the Mediterranean (Figure 1). The numbers of samples, according to provinces of Turkey, were as follows: 2888 were collected from Istanbul, 1550 were taken from Kayseri, 480 were from Mersin, 444 were from Trabzon, 359 were taken from Zonguldak, 322 were from

Malatya, 308 were from Izmir, 291 were taken from Konya, 192 were from Ankara, 120 were from Diyarbakir and 48 were taken from Van (Table 1). Among the enrolled patients, 3867 were female (55.2%) and 3135 (44.8%) were male. The patients were divided into six groups according to their age as follows: <25 years, 26–35 years, 36–45 years, 46–55 years, 56–65 years, >65 years. The genotype distribution of HCV patients was evaluated according to the ages of the patients and the years (2009–2014).

The epidemiological and demographic characteristics of the patients were recorded in this study. Data of risk factors for the development of HCV infection, including blood transfusions, surgical interventions, medical and dental procedures and injection drug use, were collected. Kits and systems used for the molecular analysis were the Cobas AmpliPrep/Cobas TaqMan HCV test (Roche Diagnostics, Milan, Italy), Versant HCV genotype 2.0 assay (LIPA) (Siemens, Healthcare Diagnostic Inc., Tarrytown, NY, USA), Rotor-Gene 6000 (Corbett Research, Sydney, Australia), INNO LIPA HCV (Ampliquality HCV-TS; AB-Analitica, Italy), ABI 3130 genetic analyser (Applied Biosystems Inc., Foster city, CA, USA). Statistical analyses were performed by using the Mann–Whitney test and  $\chi^2$  analyses of the study differences were considered significant at  $P < 0.05$ .

### Results and discussion

Turkey is a bridge country between Asia and Europe. In recent years, there has been a refugee movement in the



Figure 1. Turkey provinces included in the study (map of Turkey).

**Table 1.** Distribution of HCV genotypes by hospitals.

Hospital no.	Hospital	1b	2a/2c	3	4	1a	1*	2*	2b	1a/1b	5	6	Other (mixed <sup>#</sup> )	Untypeable HCV	Total
(1)	Acibadem University Hospital, Istanbul	1480	0	280	104	210	0	172	0	0	4	0	0	0	2250
(2)	Katip Celebi University Hospital, Izmir	177	0	15	5	20	73	8	0	1	0	0	9	0	308
(3)	Necmettin Erbakan University Hospital, Konya	250	4	8	6	4	8	9	0	2	0	0	0	0	291
(4)	Bulent Ecevit University Hospital, Zonguldak	0	0	19	2	0	335	3	0	0	0	0	0	0	359
(5)	Yuzuncu Yil University Hospital, Van	40	0	3	0	5	0	0	0	0	0	0	0	0	48
(6)	Atatürk Training and Research Hospital, Ankara	149	2	8	7	10	12	4	0	0	0	0	0	0	192
(7)	Erciyes University Hospital, Kayseri	936	32	15	359	76	103	29	0	0	0	0	0	0	1550
(8)	Mersin University Hospital, Mersin	376	3	29 (3a)	5 (4a)	29	9	17	4	5	0	1	0	2	480
(9)	Karadeniz Technical University	386	0	21	6	21	0	7	0	3	0	0	0	0	444
(10)	Inonu University	306	4	7	1	4	0	0	0	0	0	0	0	0	322
(11)	Istanbul University Cerrahpasa Medical Faculty	540	31	59	8	0	0	0	0	0	0	0	0	0	638
(12)	Dicle University	101	0	3	11	4	0	0	0	0	0	1	0	0	120
Total		4741	76	467	518	383	540	249	4	11	4	2	9	2	7002

Note: untypeable genotype 1 (1\*); untypeable genotype 2 (2\*).

<sup>#</sup>mixed – multiple HCV genotypes.

South borders of the country. HCV subtype 1b is the most encountered type in Turkey and worldwide. [19–21] Various studies conducted in countries, bordering with Turkey, showed that the frequency of HCV genotypes, other than genotype 1, had increased. In a study held in Syria, genotyping of HCV was performed in 636 consecutive HCV patients over a three-year period.[22] In this study, genotype 4 was the most frequent genotype (59%), followed by genotype 1 (28.5%) and genotype 5 (10%). The majority of genotype 5 patients (87%) lived in the North of Syria, including 21 cases (33%) from Azaz, a small city close to Turkey.[22] In an Iranian study, conducted between June 2007 and June 2012, with 142 viremic patients, 71 (50%) patients were infected with HCV subtype 1a, 43 patients (30.3%) had subtype 3a, 20 patients (14.1%) were infected with subtype 1b, 3 patients (2.1%) with subtype 4d, 2 patients (1.4%) with subtype 4a, 1 patient (0.7%) was infected with subtype 2b and 1 (0.7%) patient had subtype 6a.[23] A different

study, evaluating HCC patients, indicated that the most prevalent genotype was genotype 1b, followed by genotype 4 in Iraq.[24] The determination of therapeutic recommendations and the duration of treatment in combination with therapy depends on the genotype. [25,26] For instance, genotypes 1 and 4 are less responsive to interferon-based treatment than genotypes 2, 3, 5 and 6. The duration of standard interferon-based therapy for genotypes 1 and 4 is 48 weeks, whereas the treatment for genotypes 2 and 3 is completed in 24 weeks. Sustained virological responses occur in 70% of genotype 1 cases, in ~90% of genotypes 2 and 3 cases, in ~65% of genotype 4 cases and in ~80% of genotype 6 cases.[13,27] There are insufficient data about the pattern change of HCV molecular epidemiology in Turkey over the years. In this study, during a six-year period, genotype 1b was the most common genotype (67.7%), followed by the untypeable genotype 1 (7.7%), genotype 4 (7.3%) and genotype 3 (6.7%) (Table 2). There was no

**Table 2.** Distribution of HCV genotypes by years.

Year	1b	2a/2c	3	4	1a	1*	2*	2b	1a/1b	5	6	Other (mixed <sup>#</sup> )	Untypeable HCV	Total
2009	455	6	15	38	19	37	6	0	0	0	0	0	0	576
2010	731	12	37	79	36	96	12	0	2	0	1	2	0	1008
2011	811	17	53	61	67	114	28	0	5	0	1	6	0	1163
2012	871	11	107	62	87	77	58	3	2	0	0	0	0	1278
2013	1152	17	122	159	114	160	77	1	1	2	0	1	2	1808
2014	721	13	133	115	60	56	68	0	1	2	0	0	0	1169
Total	4741	76	467	514	383	540	249	4	11	4	2	9	2	7002

Note: untypeable genotype 1 (1\*); untypeable genotype 2 (2\*).

<sup>#</sup>mixed – multiple HCV genotypes.

statistically significant difference between male's and female's rates.

The second most prevalent genotype was the untypeable genotype 1 in 2009, 2010, 2011 and 2013 with a prevalence of 6.4%, 9.5%, 9.8%, 4.79%, respectively. In 2014, genotype 3 was the second most common genotype with a prevalence of 11.3% and genotype 4 was the third most common genotype with a prevalence of 9.8% (Table 2). Data of HCV genotype/subtype prevalence among different age groups could be obtained only in 5120 HCV RNA-positive patients. These patients were evaluated in two time periods (2009–2011; 2012–2014), as shown in Table 3. Most of the patients (29.37%) were found in the 56–65 years group (Table 3).

In <25 years old group, genotype 1b was the most common, with a prevalence of 78.48% (62/79) between 2009–2011, whereas genotype 3 was the most common genotype, with a prevalence of 34.8% (86/247) between 2012–2014.

In 26–35 years old group, genotype 1b was the most common one with a prevalence of 69.8% (141/202) between 2009–2011 and 43.8% (176/401) between 2012–2014. In the same group, genotype 3 was the second most common genotype between 2012–2014 with a prevalence of 28.4% (114/401) (Table 3).

In 36–45 years, 46–55 years and 56–65 years old groups, genotype 1b was the most common genotype. The genotype distribution rates in 1839 HCV patients in 2009–2011 were as follows: genotype 1b – 75.8%, genotype 1\* – 10.54%, genotype 3 – 4.78%, genotype 1a – 4.13%, genotype 2\* – 1.95%, genotype 4 – 1.3%. The genotype distribution rates in 3281 HCV patients in 2012–2014 were as follows: genotype 1b – 67.5%, genotype 3 – 10.06%, genotype 1a – 6.4%, genotype 2\* – 5.36%, genotype 1\* – 5.21%, genotype 4 – 3.84%. Our study indicated that although genotype 1 was a predominant subtype, in recent years, the rates of prevalence of genotypes 3 and 4 have increased. The rate of genotype 3 was increased from 4.78% to 10.06% and the rate of genotype 4 was increased from 1.3% to 3.84%, from 2009–2011 to 2012–2014, respectively. The genotype distribution of our study was similar to other European studies.[2,22,15] For instance, in a study of Marascio et al.,[2] subtype 1b was reported as the most common subtype, followed by subtypes 2a/2c and genotype 3. The study found that subtype 1b was prevalent in elderly patients with some risk factors, such as transfusions and surgical procedures.[2] An Italy study with 3577 patients also showed that subtype 1b was the most prevalent type, followed by subtype 2c and genotypes 3 and 4.[22] To this day, there have not been any multicentre large-scale Turkey studies analysing the changing pattern of HCV genotypes in a long period of

**Table 3.** HCV genotype/subtype prevalence among different age groups (years) in a total of 5120 HCV RNA-positive patients, stratified in two time periods (2009–2011; 2012–2014).

Genotype	<25 years				26–35 years				36–45 years				46–55 years				56–65 years				>65 years				Sum of groups by Years 2009–2011	Sum of groups by years 2012–2014	Total 2009–2014
	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014	2009–2011	2012–2014							
1b	62	74	141	176	159	212	290	507	434	741	308	506	1394	2216	3610												
2a/2c	0	2	0	3	1	3	6	6	9	8	4	2	20	24	44												
3	9	86	28	114	10	56	18	53	15	32	8	7	88	348	436												
4	0	19	5	28	4	15	9	26	3	30	3	8	24	126	150												
1a	2	34	16	39	16	36	12	44	20	39	10	19	76	211	287												
1*	3	4	8	6	13	12	55	44	61	63	54	42	194	171	365												
2*	3	28	4	34	4	29	9	19	6	35	8	31	36	176	212												
1a/1b	0	0	0	0	2	2	0	1	5	0	0	1	7	4	11												
5	0	0	0	0	0	1	0	0	0	3	0	0	0	4	4												
6	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1												
Total	79	247	202	401	211	366	399	700	553	951	395	616	1839	3281	5120												

Note: untypeable genotype 1 (1\*), untypeable genotype 2 (2\*).

time. There have been only some local HCV epidemiological studies in Turkey.[15,17] In a study of Saglik et al., [15] it was found that out of 422 blood samples from HCV RNA positive chronic hepatitis C patients, genotype 1b was observed in 63.3%, genotype 1a in 14.7%, genotypes 3a and 2b in 0.9%, genotype 4e in 0.2%. Of the 422 patients, 40 were foreign-born (16 cases from Russia; 4 from Ukraine and Georgia each; 3 from Turkmenistan, Kyrgyzstan and Germany each; 1 from Tajikistan, Azerbaijan, Uzbekistan, Chechnya, Moldova, Switzerland and Romania each) and among these patients, genotype 3a was the most common genotype, followed by genotype 1b (42.5%).[15] In a southern Turkey study, genotype 1b was observed in 84.7% of the studied patients, and low rates of genotype 1a, 2b, 3a, 4a and genotype 6 were detected. [16] Aktaş et al. [17] also reported that genotype 1b was the most common genotype in the Black Sea Region of Turkey.[17] A Turkey phylogenetic analysis study reported that genotype 1 was the main genetic variant of HCV in Turkey, but did not reveal any Turkish indigenous phylogenetic cluster. Phylogenetic analysis showed that Turkish strains have their closest matches from both Asia (Japan) and Europe/USA.[18]

Previous studies have reported that genotypes 3 and 4 occurred in younger people and especially genotype 4 was found to be related to intravenous drug users' infections and sexual exposure.[2,25] The changing pattern in Turkey may be caused by changes in young people's sexual behaviour and refugee movements in the borders of Turkey. In addition to common transmission routes of HCV, a number of cultural or ritual practices have been proposed as a potential historical mode of HCV spreading, such as circumcision, genital mutilation, ritual scarification, traditional tattooing and acupuncture.[28] We suggested that with the increasing of travel, business tourism and emigrations between other countries, a change of HCV genotype distribution may be observed in our country. In the near future, spreading of genotypes 3 and 4 may be problematic in Turkey.

## Conclusions

In conclusion, a changed epidemiology profile of HCV infection in Turkey was observed in this study. It seems that subtypes, other than genotype 1, may gain importance in near future due to medical improvements and intercultural interactions. Furthermore, the modification of HCV genotype pattern will change treatment strategies and disease prevention measures.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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