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Diagnostically untypable hepatitis C virus variants: It is time to resolve the problem

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Abstract

Pakistan is a low income country with more than 10 million hepatitis C virus (HCV) infections and the burden is on continuous raise. Accurate viral genotyping is very critical for proper treatment of the infected individuals as the sustained virological response of the standard antiviral interferon therapy is genotype dependent. We observed at our diagnostic center that 15.6% of HCV patient's samples were not genotypeable by using Ohno *et al* method. The genotyped samples showed that 3a (68.3%) is the major prevalent genotype in Pakistan followed by 2a (10.3%), 3b (2.6%), 1b (1.5%), 2b (1.2%) and 1a (0.5%). Presence of large number of untypable HCV variants in the current study highlights an important issue of health care setup in Pakistan. Untypable HCV cases create difficulties in treatment of these patients. The problem of routine diagnostics setup of Pakistan should be addressed on priority basis to facilitate the medical professionals in patient's treatment and to help in achieving the maximum sustained virological response.

Key words: Hepatitis C virus; Genotypes; Diagnostics; Untypable variants; Antiviral interferon therapy; Pakistan

Core tip: Hepatitis C virus (HCV) is a major health issue in Pakistan. Accurate HCV genotyping is very critical for the treatment of a patient because the duration and efficacy of standard antiviral therapy depends on viral genotype. We observed a large proportion (15.6%) of untypable HCV isolates during routine diagnostic. As HCV genotype information is mandatory prior to standard interferon ribavirin therapy, it is very important to be clear about the viral genotype. It is highly needed that the mystery of diagnostically untypable HCV variants in Pakistan should be resolved on priority basis to insure the proper treatment of the patients.

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TO THE EDITOR

Hepatitis C virus (HCV) with more than 200 million infections worldwide[1] and over 10 million in Pakistan is one of the leading causes of morbidity and mortality[2]. HCV genome, due to error prone nature of viral polymerase, has mutation rate of approximately 10^{-3} per nucleotide per replication[3]. Due to these mutations, HCV results in higher quasi-species circulation in the infected population. During routine genotype diagnostic test[4] at Genomic Research Labs and Diagnostics Center,

Table 1 Prevalence of diagnostically untypable hepatitis C virus variants in Pakistan *n* (%)

Ref.	Year	Untypable
Waqar *et al*[6]	2014	66 (12)
Ali *et al*[7]	2014	21 (17.35)
Waqar *et al*[8]	2014	52 (13.87)
Safi *et al*[9]	2012	2 (1.7)
Ali *et al*[10]	2011	50 (16.4)
Mahmood *et al*[11]	2011	9 (2.25)
Ali *et al*[12]	2011	34 (17)
Inamullah *et al*[13]	2011	70 (37.8)
Idrees *et al*[14]	2011	2 (6)
Rehman *et al*[15]	2011	9 (14.3)
Khan *et al*[16]	2011	1 (4.34)
Ahmad *et al*[17]	2010	35 (2.5)
Ali *et al*[18]	2010	116 (27.95)
Ahmad *et al*[19]	2010	34 (2.5)
Rauf *et al*[20]	2010	3 (12)
Abbas *et al*[21]	2009	34 (17)
Asif *et al*[22]	2009	11 (52.4)
Afridi *et al*[23]	2009	9 (32.14)
Ahmed *et al*[24]	2009	8 (3.6)
Idrees *et al*[25]	2008	201 (5.99)
Akhund *et al*[26]	2008	52 (15.11)
Hakim *et al*[27]	2008	8 (3.84)
Ijaz *et al*[28]	2008	5 (3.22)
Ahmed *et al*[29]	2007	6 (7)
Iqbal *et al*[30]	2007	106 (6.42)

Rawalpindi, we observed 15.6% of HCV samples did not match any genotype. Out of 736 HCV patient blood samples screened at our diagnostic center, 115 were untypable. The prevalence of known genotypes 3a, 3b, 2a, 2b, 1a and 1b was 503 (68.3%), 19 (2.6%), 75 (10.3%), 09 (1.2%), 04 (0.5%) and 11 (1.5%) respectively. A recent conclusive report by Butt *et al*[5], based on results of 20552 HCV patient samples during 2000-2009 showed that 17% samples were untypable and the pattern indicated that it is going to increase with the passage of time. Other reports published from Pakistan during last 8 years also clearly suggested that significant numbers of samples were not genotyped successfully (Table 1)[6-30].

There is constant emergence of quasi-species in infected patients. Genotyping is done from highly conserved part of HCV genome and mutations in this part of genome result in loss of genotyping capability of the method used. This changing pattern is multi-factorial and might be due to high viral genome mutation rate[31], host immunological pressure[32], drug pressure[33], viral[34]/host immune escape mechanism[35,36], changes in transmission route[37], abroad traveling[38] and several other unknown factors.

Pakistan is a developing country with poor socioeconomic conditions. HCV standard interferon therapy is very costly and its effectiveness varies against different genotypes. Without knowing the causative genotype, it is difficult for health care workers to start and manage the therapy especially in poor countries like Pakistan. In Pakistan HCV burden is very high and with large number of untypable HCV in circulation. It is highly needed to sequence the untypable HCV quasi-specie to know exactly the underlying mechanisms behind this problem. Sequence analysis can give us information about the changing pattern in HCV clades and will be highly effective in determining the course of standard interferon therapy. A lot of efforts and money can be saved by solving the mystery of untypable HCV quasi-species in Pakistan. By exploring this phenomenon it will be easy for health care professional to manage the HCV patient's disease progress and therapy efficacy.

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