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From Virome to Biomarker: Insights into the Role of Torque Teno Virus in Health and Ecosystems

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Abstract

In virology, the term ‘virome’ refers to commensal viruses that typically replicate and persist within healthy individuals, without causing harmful effects to the host; this concept is familiar to microbiologists. Torque Teno Virus (TTV) is one of common commensal viruses which is very ubiquitous in the environment and infects both humans and animals. Multiple modes of transmission of TTV enhance the spreading of these viruses within ecosystems and infect new hosts. Recently, TTV has emerged as a promising biomarker for medical and environmental applications. This review article examines the widespread presence of the TTV and discusses its potential as a biomarker for exciting future uses. Also, explore the extensive global distribution of TTV, highlighting the intriguing variations in its frequency observed across diverse populations. By inspecting the factors contributing to these disparities, including geographical location, and host demographics, this review sheds light on the enigmatic nature of TTV’s prevalence.

Keywords Torque Teno Virus, Virome, Biomarker

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List of abbreviations: Ag = Antigen, DNA = Deoxyribonucleic acid, ELISA = Enzyme-linked immunosorbent assay, HAV = Hepatitis A virus, HBV = Hepatitis B virus, HCV = Hepatitis C virus, HPV = Human papilloma virus, HTTV = Human Torque Teno Virus, N22 = Region of TTV-genome, ORF = Open reading frame, PCR = Polymerase chain reaction, TTV = Torque Teno Virus, UT R= Untranslated regions

Introduction

Torque Teno Virus (TTV), is a small non-enveloped virus with single-stranded circular DNA. Unlike most viruses, TTV has a negative-sense viral genome enclosed within a spherical icosahedral capsid [(1)]. The size of viral genome ranges between 2.1 and 3.9 Kb [(2)]. TTV can resist detergents and dry heat because of the absence of lipid envelopes, which increases survival and widespread within the environment [(3)].

The viral DNA contains two important regions: untranslated regions (UTRs) and open reading frames (ORFs). UTRs are a highly conservative genomic region in 90 % of TTV isolates and contributed ideal targets for viral detection in clinical samples [(4)]. The TTV genome encodes three overlapping ORFs, with ORF1 encoding structural proteins which plays a vital role in TTV’s spread within the host, and ORF2 and ORF3 involved in replication and immune evasion. Taxonomic classification is currently based on the analysis of the entire ORF1 nucleotide sequence, with pairwise nucleotide sequence identity cut-off values of 35% and 56% to define a species and a genus, respectively [(5-7)].

TTV replicates by the mechanism called rolling-circle replication (RCR) [(8)]. Additionally, TTV has a remarkable feature, which is high genetic variation, it could be happened though several factors, including co-infections with different TTV strains in the same host, recombination events between isolates, and cross-infections with animal strains [9,10]. Furthermore, high mutation rate could be occurring, especially within the highly variable region (HVR) of ORF1, all these factors may enhance the genomic diversity [11,12].

History overview of TTV

In 1997, early human isolates of TTV "HTTV" was identified in a Japanese patient who had received over 25 blood units during heart surgery. After follow-up, the patient was suffering from an unknown etiology of hepatitis with a rising titer of alanine aminotransferase (ALT) in the serum sample [13]. This finding sparked further investigation, leading to the detection of TTV in animals and discover the other human isolate such as Torque Teno Mini virus (TTMV) and Torque Teno Midi virus (TTMDV) in a few years later [14-17].

At the beginning, researchers considered TTV a circovirus and classified it within the Circoviridae family because of the molecular level similarities between the two viruses [18]. However, the International Committee on Viruses (ICTV) eventually reclassified TTV into a new genus called "Anellovirus". While a new family called "Anelloviridae" was established in 2009 [19]. The acronym TTV is derived from the Latin words' "torque" and "tenuis " which mean necklace and narrow according to the genomic nature of the virus [20]. Recently, last update on viral taxonomy reveals that categorized Anelloviridae family into 31 genera, consisting of 156 species [21].

Epidemiology and genotype distribution:

TTV is a very ubiquitous virus in the environment, it could be found in the surfaces, air and water systems as well [22,23]. Also, it could be present within various hosts [24]. Generally, TTV infect healthy individuals as lifelong persists infection under control of the immune system without causing any undesirable effects. While high viral loads being observed within immunocompromised patients because of an inverse relationship between the level of immunosuppression and TTV viral load [25], among that many studies try using TTV viral load as a biomarker for assessing immune status of certain individuals, as we will explain later in this review. Interestingly, the physiological changes in women, particularly during pregnancy, have a role in increase TTV viral load, that means unbalanced immune systems reflect on TTV viral load [26]. Multiple studies have consistently demonstrated that TTV as part our human virome and detectable in most individuals regardless of any factors involving ages, sex, immune statuses, geographic locations, socioeconomic backgrounds, seasonal variations, underlying health conditions, physiological states, and occupational factors [27-30].

Numerous epidemiological studies have documented the global prevalence and widespread distribution TTV across various populations, with significant variability in infection rates. These disparities in TTV frequency can be attributed to factors such as detection methods, specimen type, target gene, and host characteristics, including immune status, as illustrated in table (1). Studies have reported TTV infection rates in healthy individuals ranging from 4% to 98%, while in immunocompromised patients, the frequency can reach up to 100%. [31,32]. The range in Iraqi population for example is between 8% and 93.9% [11,27]. In contrast, studies conducted in Iran report a range is 26% to 96% [33], while Jordan shows a range between 17.9% and 95.5% [34,35]. Another study reported there is an association between race-based TTV and frequency by detecting a high infection rate among the black population compared to whites, but further studies are required [36].

According to phylogenetic analyses and geographical distribution of TTV genotypes. Studies report genotype 1 as the most common in Asia, followed by genotype 3 in Africa, and genotypes 5 and 2 prevalent in the Middle East [37,38].

Table 1. The frequency of TTV from different studies worldwide

Country	Subject	Frequency of TTV	Type of sample	Target gene	Detection method	Reference
China	Patients with chronic HBV infection Healthy Blood donors	100% 98%	Serum	UTR- and ORF1 - N22	PCR	(31)
Italy	Solid-organ transplant patients	97.5%	Serum	UTR	Real time PCR (TaqMan)	(38)
Tanzania	Febrile pediatric	97.2%	Serum	-	Metagenomic next-generation sequencing	(39)
Jordan	Blood donor	95.5%	Serum	5′-UTR	Nested PCR	(34)
Taiwan	General population	95%	Serum	UTR	PCR	(40)
Iraq	Blood donors HBV-positive patients	93.9% 89.2%	Serum	UTR	Nested PCR ELISA for detection of TTV Ag	(27) (41)
India	HBV-positive patients	87.6%	Serum	-	Real time PCR	(42)
Taiwan	General population	86.4%	Serum	UTR	PCR	(43)
Qatar	Blood donors	85.2%	Plasma	-	Nested PCR	(44)
Iran	Healthy children	83.3%	Urine	UTR	Real time PCR (TaqMan)	(33)
USA	Pregnant woman with second trimester	81%	Plasma	UTR	Quantitative Real-Time PCR TaqMan	(36)
Iraq	Hemodialysis patients	81%	Serum	UTR	Nested PCR	(45)
India	HAV and HCV-positive patients	77 %	Serum	-	Real-Time PCR	(42)
Italy	Healthy individuals	76%	Serum	UTR	Real-Time PCR TaqMan	(38)
Egypt	Hemodialysis patients	76%	Blood	ORF1-N22	Nested PCR	(46)
Iran	Healthy woman	75%	Blood	-	Nested PCR	(47)
India	Blood donors	72%	Serum	-	Real-Time PCR	(42)
Iran	Woman-with breast cancer	70%	Blood	-	Nested PCR	(47)
Russia	Healthy infants	67%	blood	-	Real-Time PCR	(48)
Italy	Healthy blood donors	65%	Plasma & whole blood	UTR	Real time PCR assay (TaqMan)	(49)
USA	Pregnant Woman-with	64%	Saliva	UTR	Quantitative Real-Time	(36)

	second trimester				PCR (TaqMan)	
Iran	β-Thalassemia	57.2%	Serum	ORF2	Nested PCR	[50]
Iraq	Renal transplant recipients	56.25%	Serum	-	Real-Time PCR (SYBR green)	[51]
Iran	HPV-positive woman	56%	Fresh cervical cyto-brush	5'-UTR and N22 region	Nested PCR	[52]
Iraq	Hemodialysis Patients	40.9%	Serum	-	ELISA for detection of TTV-Ag	[53]
Egypt	Hemodialysis Patients	38.9%	Serum	ORF1	Semi Nested PCR	[54]
Spain	Children-with acute respiratory infection.	38.3%	Nasopharyngeal aspirate	UTR	PCR	[55]
Iraq	HCV-positive patients	30.8%	Serum	-	ELISA for detection of TTV Ag	[41]
Iraq	Thalassemia patients	29.2%	Plasma	ORF1-N22	Real-Time PCR	[56]
Egypt	Hemodialysis Patients	28%	Serum	ORF1-N22	Semi-Nested PCR	[57]
Iraq	Healthy blood donors	23.3%	Serum	-	ELISA for detection of TTV Ag	[41]
Jordan	Healthy blood donors	17.9%	Serum	-	ELISA for TTV- Ag	[35]
Iraq	Hemodialysis patients	15%	Serum	ORF1-N22	Nested PCR	[58]
Iraq	Urinary-tract infected woman	8%	Urine	ORF1-N22	Nested PCR	[11]
Iran	Healthy individuals	4%	Serum	5΄-UTR and N22 regions	Nested PCR	[32]

Tropism and pathogenesis

TTV DNA has been found in several human clinical samples, including bodily fluids, such as whole blood, serum, plasma, saliva, tears, urine, sweat [48,49], cerebrospinal, synovial, bile, and seminal [59,60]. Also, in women's breast milk, amniotic fluid, and vaginal secretions [61]. Other researchers have found TTV in tissues, including gingival tissue, brain walls, and nasopharyngeal mucosa scrapes [62,63].

The presence of TTV across various bodily fluids and tissues suggests a broad tropism of TTV, meaning the virus might infect a wide range of cells within the host with a lack of a strong preference for specific cell types warranting further investigation into the mechanisms underlying the ability to infect diverse tissues [28,64].

The pathogenicity of TTV remains controversial. As mentioned previously, TTV infection is commensal, nonpathogenic, and lacking a direct association with specific diseases [65-68], while other studies detected a potential role for specific TTV genotypes in exacerbating the severity of certain human diseases [55,69,70].

Potential routes of TTV transmission and inter-species spread

The pervasive nature of TTV is remarkable, its detection across a diverse range of hosts and through various transmission modalities likely contributes to its widespread prevalence. In humans, for example, TTV can spread through horizontal transmissions, such as respiratory droplets, fecal-oral routes, blood transfusions, and medical procedures. [71-73]. Sexual contact is also a potential transmission route, particularly among adults, due to found TTV in both vaginal secretions and seminal fluid [52,74].

Otherwise, TTV observed in neonates after birth raises the possibility of vertical transmission, either transplacentally during pregnancy or through breastfeeding [25,48].

A study supported this maternal transmission by demonstrating identical initial TTV genotypes in newborns and their infected mothers [39]. Beyond human-to-human spreading, zoonotic transmission is another potential route [75,76]. TTV is presence in wide range of animals, including wild species, livestock, farm animals, poultry, and even some marine creatures [21,77]. It would not surprise if each animal acquired a species-specific TTV strain [78,79]. Moreover, studies have reported varying infection rates in different animal hosts. For example, TTV in horses was 63%, followed by cows 42%, goats 36%, sheep 30%, chickens 28%, and dogs 10% [14,80–82]. While pigs had a higher infection rate, reaching up to 77%, addition to that the cross infection between human-animal TTV strain could be occur [79].

TTV applications

Potential role of TTV as immunological biomarker

A few years ago, studies started using TTV as a potential noninvasive biomarker for medical and environmental purposes. Because it is easily detectable and can be directly obtained from both clinical and environmental samples. Notably, research has explored the utility of TTV viral load as an immunological marker, particularly in immunocompromised patients [83-85]. Otherwise, studies suggest TTV could use as monitoring biomarker by clinicians in regimens and optimizing the dose of immunosuppressive drugs for recipient after organ transplantation, this approach might minimize the risk of opportunistic infections and organ rejection. Also, the development of commercially available real-time PCR kits enhancement further strengthens these uses [72,86,87].

Moreover, studies tried to use TTV as a promising biomarker for various health conditions to monitoring age-related immune dysfunction among older people [39,88]. Other investigation explored TTV viral load as a personalized guide therapy and disease control in HIV-positive patients [89]. In addition, another study proposed that TTV viral load could serve as a biomarker to predict female infertility in the future [90].

Emerging roles of TTV biomarker and SARS-CoV-2

After emergence of the SARS-CoV-2 pandemic, increased interest of TTV as a potential prognostic marker for detected the disease severity, particularly in SARS-CoV-2 patients who admitted to the intensive care unit compared to those with less severe illness, and there are significant differences in viral load in both groups [91,92]. As already mentioned, the unbalanced immune system due to diseases might raise the TTV viral load, but when someone has a severe case of SARS-CoV-2 infection, the opposite happens. This suggests that immune system of host and TTV coinfection may interact together, but the mechanism is still not clear [70]. In other studies, TTV holds promise as a virological biomarker for predicting vaccine effectiveness against SARS-CoV-2, potentially aiding in the assessment of immune response in vaccinated individuals [38,93]. TTV has the potential to serve as a prognostic biomarker in both viral infections and other inflammatory diseases [94-96].

TTV as a biomarker for fecal contamination in water sources

According to environmental biomarker, TTV could serve as an alternative marker indicator for monitoring water quality and fecal contamination in water systems. It reflects anthropogenic pollution levels in the environment [97-99]. High quantities of TTV could be disseminated within stool into water systems, and the frequency is also variable based on the type of water and geographical region [23]. The lowest reported frequency of TTV was 11.17% in clean tap water, while the highest reported frequency was 92.33% in polluted streams [100-102].

In conclusion, this review article on TTV presents promising potential for two significant applications; given its widespread prevalence and detection in a variety of clinical and biological samples, TTV emerges as a viable candidate for a novel biomarker, this application applies to medical settings where immunocompromised patients require close monitoring, furthermore, the presence of TTV could serve as an alternative biomarker for assessing water quality, providing a valuable tool for environmental surveillance.

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