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A Review on The Global Widespread of TTV Infection Among Humans Population

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Abstract – Torque Teno Virus (TTV) is a human-infected virus that is present ubiquitously in nature. Globally, it infects up to 95% of the healthy individuals without any clinical manifestations. The widely used laboratory diagnosis of TTV infection is Polymerase chain reaction (PCR). Nevertheless, several other methods have been developed. The rapid growth of TTV variants over time has posed a challenge in estimating the global TTV infection as none of the PCR protocol has the ability to detect the entire spectrum of TTV variants. Multiple TTV epidemiological studies have been conducted among Asian population, whereas other continents showed a limited number of studies. The horizontal and vertical transmission of TTV among humans population, as well as interspecies transmission are potentially related to the global widespread of TTV infection.

Keywords: Torque Teno Virus (TTV), Untranslated region (UTR), N22-region, TTV variants, global TTV infection, intra- and interspecies transmission

Introduction

A metagenomics analysis has revealed a variety of novel human-blood virome, and interestingly, 70% of the total human virome detected was a single-stranded Anellovirus DNA where in particular, 95% of the total Anellovirus DNA belongs to TTV (De Vlaminck et al., 2013). A study on TTV has begun two decades ago after a group of researchers has successfully isolated this novel DNA virus from a serum of a Japanese patient with hepatitis of unexplained aetiology (Nishizawa et al., 1997). This small (30 to 50 nm in diameter), non-enveloped virus (Okamoto et al., 1998a; Mushahwar et al., 1999; Itoh et al., 2000) has been assigned into the genus *Alphatorquevirus*, a member of *Anelloviridae* family, and there are other 11 genera that have been assigned into this family (*Table 1*). TTV and the other two closely related genera, *Betatorquevirus* and *Gammatorquevirus*, are known as a human-infected virus, while the other genera are classified as animal-infected virus (ICTV, 2015).

Soon after the discovery of TTV, a number of publications exist investigating the molecular aspect of TTV as well as determining the prevalence of TTV DNA in various types of clinical specimens. However, this so-called orphan virus has long been ignored probably due to the absence of an efficient culture system. Many aspects of this virus are still poorly understood and the growing literature on the epidemiological aspect of TTV demonstrated that the prevalence of this virus is geographically variable independent of sociodemographic factors of the studied population (Massaú et al., 2012; Mazzola et al., 2015).

Table 1: The members of *Anelloviridae* family (Source: ICTV, 2015)

Genus	Species	Infected host
Alphatorquevirus	Torque teno virus	Human, chimpanzee
Betatorquevirus	Torque teno mini virus	Human, non-human primate
Deltatorquevirus	Torque teno tupia virus	Tupaias
Epsilontorquevirus	Torque teno tamarin virus	Tamarin
Etatorquevirus	Torque teno felis virus	Cat
Gammatorquevirus	Torque teno midi virus	Human, chimpanzee
Gyrovirus	Chicken anemia virus	Chicken
Iotatorquevirus	Torque teno sus virus 1	Swine
Kappatorquevirus	Torque teno sus virus k2	Swine
Lambdatorquevirus	Torque teno zalophus virus 1	Sea lion
Thetatorquevirus	Torque teno canis virus	Dog
Zetatorquevirus	Torque teno douroucouli virus	Douroucouli

At present, no definite answers on the replicative sites of TTV have yet been defined, nor does a firm evidence exists on the involvement of this virus in disease pathogenesis. While T lymphocyte has been listed as a potential replicative site for TTV (Focosi et al., 2015), there was no evidence on the specific receptor that could interact with specific proteins present on TTV to allow the viral entry. Besides, TTV has been suspected to be a causative agent of hepatitis with early studies supporting the involvement of TTV with hepatitis as well as with liver disease (Charlton et al., 1998; Naoumov et al., 1998). However, given the presence of TTV DNA in non-hepatitis patients including patients with respiratory diseases, cancer, haematological and autoimmune diseases as reviewed by Spandole et al. (2015), as well as with no significant association recently reported between TTV and hepatitis (Hussain et al., 2012; AbuOdeh et al., 2015), the pathogenic potential of TTV as causative agent of hepatitis and liver disease seems to be very weak. Apart from diseased patients, healthy individuals have been reported to be infected with TTV (Vasilyev et al., 2009; Mazzola et al., 2015) and until now, infection with TTV does not result in any sign and symptom, suggesting the non-pathogenic property of TTV to human populations.

Although TTV is currently considered to be non-pathogenic, it is possible that, probably due to mutation, certain TTV genotypes or species are either a key player of a particular disease or may act as co-factor in the progression of any disease. Knowledge on the trend and global widespread of TTV infection as well as TTV genetic diversity have a profound impact on the production of vaccine and antiviral drug, and the development of drug resistance in the future. Therefore, this review attempts to gather the epidemiological data on TTV prevalence among both healthy individuals and diseased patients, while at the same time discusses the molecular diagnostics used in TTV detection as well as the possible mode of TTV transmission contributing to the high TTV prevalence in the certain studied populations.

Genomic Characterization of TTV

The genome of TTV is made up of circular, negative sense, single-stranded DNA (Miyata et al., 1999; Mushahwar et al., 1999), with total length varies among TTV genotypes, which are between 3.8kb to 3.9kb. *Figure 1* displays the schematic illustration of the genomic organisation of TTV, which is conserved among various TTV isolates. There are two main regions of TTV genome namely the protein-coding region (~2.6kb) and the untranslated region (UTR) (~1.2kb). The occurrence of TTV sequence divergence is not evenly distributed throughout the genome; however, UTR is highly conserved compared to the protein-coding region. The protein-coding region consists of several open reading frames (ORFs), N22-ORF 1 region, hypervariable region (HVR) and N-terminal arginine-rich motif (Okamoto et al., 1998a; Muljono et al., 2001; Hussain et al., 2012; Hsiao et al., 2016). TTV has

been shown to produce up to four messenger RNAs (mRNA) and the expression of protein results in two main ORFs, which are ORF 1 and ORF 2 with several shorter ORFs. The splice site connects the distant ORFs and creates new ORFs, such as ORF 3 and ORF 4 (Muljono et al., 2001; Qiu et al., 2005; Kakkola et al., 2008; Mueller et al., 2008). It is noteworthy that ORF 1 constitute the longest coding sequence and due to a premature stop codon, its expression resulted in a shorter ORF 1 as occurred in a few TTV isolates (Jelcic et al., 2004; Hussain et al., 2012). These proteins coding-gene highly diverge at nucleotides and amino acids level between isolates, and they encode a different length of protein in different isolates (Spandole et al., 2015). The highly conserved region of UTR, which stretches from polyadenylation signal to the initiation codon of ORF 2, comprises GC-rich tract and several elements important for transcriptional regulation (Okamoto et al., 1998a; Okamoto et al., 1998b; Mushahwar et al., 1999; Muljono et al., 2001; Kamada et al., 2004; Hussain et al., 2012; Hsiao et al., 2016).

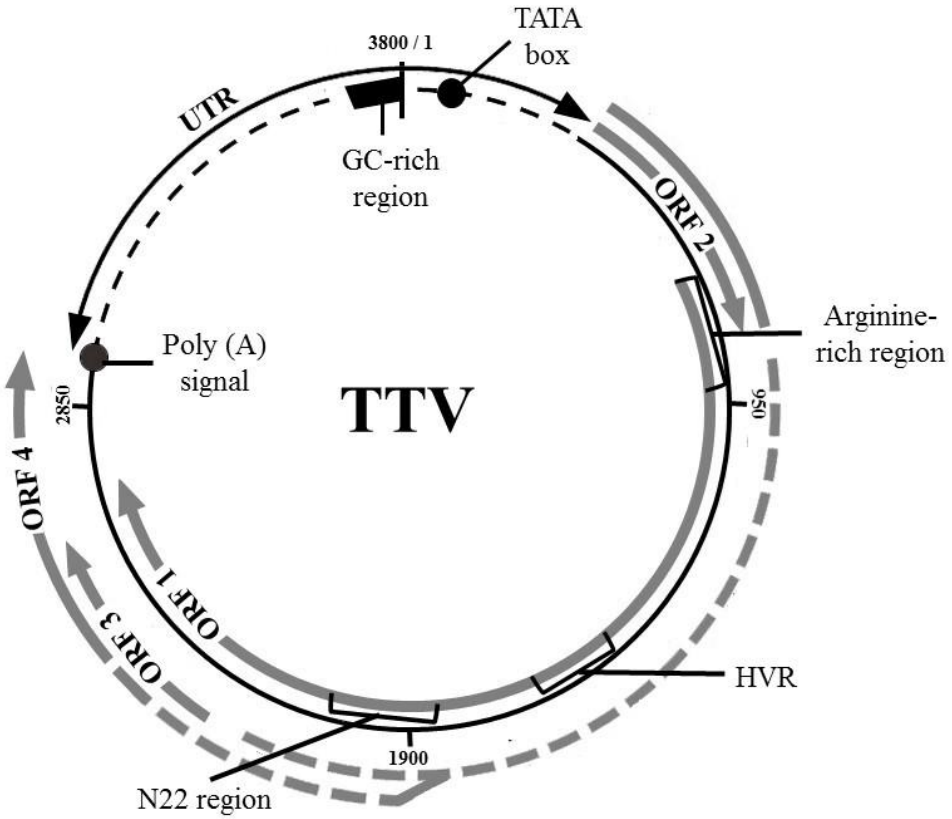

Figure 1: The schematic illustration of the genomic organisation of TTV. (Source: Okamoto et al., 1998a; Miyata et al., 1999; Muljono et al., 2001; Kamada et al., 2004; Hussain et al. 2012; Hsiao et al., 2016)

According to International Committee on Taxonomy of Viruses, ICTV (2015), there are 29 reported TTV species and more than 6000 sequences currently available in the National Center for Biotechnology Information (NCBI) database that belong to TTV. The cut-off value of the nucleotide sequence identity is 50% among TTV species, 30% between the TTV genotypes, 15% to 29% among TTV subtypes (Manzin et al., 2015). Phylogenetic analysis of the TTV genome demonstrated that, the TTV species and genotypes were classified into five different phylogenetic groups (Hussain et al., 2012; Mi et al., 2014), however, an additional two groups were recently reported clustering the TTV variants into seven groups (Hsiao et al., 2016). Since TTV is made up of a small, single-stranded DNA genome, it is likely that the generation of a large number of TTV variant is driven by the high mutation rate, which is closer to RNA virus (Sanjuán & Domingo, 2016).

Laboratory diagnosis of TTV infection

To date, none of the laboratory method used for disclosure of TTV epidemiology has the ability to detect the entire spectrum of TTV genotypes. The growing number of TTV variants demands a development of more sensitive and effective methods in providing the accurate estimation of TTV infection. Here, several laboratory methods used in the previous studies were addressed.

PCR is the most prominent method used in TTV detection, which includes standard PCR, nested or semi-nested PCR and real-time PCR. Although PCR is a fast and inexpensive technique, in the case of TTV, the selection of TTV genomic region targeted for amplification is the most crucial part due to its sequence heterogeneity among TTV variants. Detection of the entire spectrum of TTV genotype is impossible using only a single set of primer.

Due to historical reason, N22-ORF 1 region has been targeted for amplification (N22 PCR) in a number of studies (Muljono et al., 2001; Irshad et al., 2008; El-taher et al., 2015). The use of degenerate primers and/or the increase of annealing or extension times can increase TTV detection rate of N22 PCR (Biagini et al., 2000). Improvement on the PCR protocol has been done by considering the highly conserved region of TTV genome. As evidenced by the previous studies, the amplification of 5' or 3' UTR (UTR PCR) increased TTV detection rate as compared to amplification of N22-ORF 1 region (Koohi et al., 2012; Peng et al., 2015), which will be further discussed in the following section.

For the purpose of genotyping, one of the most widely utilised methods is the phylogenetic analysis based on either the sequence spanning ORF 1 region or the sequence spanning 5' or 3' UTR. Determination of TTV genotypes based on the partial sequence of N22-ORF 1 region might not represent the real distribution since amplification of the N22 region mainly detects group 1 TTV genotype (Peng et al., 2002). Apart from that, PCR using group-specific primers corresponding to the five TTV genogroups as well as the restriction fragment length polymorphism (RFLP) in determining TTV genogroups were developed. These group-specific primers were designed based on one TTV isolate representative of each TTV genogroup. The group-specific primer has been used either in standard PCR or multiplex PCR protocol to determine the most widely distributed genogroup (Devalle & Niel, 2004; Devalle & Niel, 2005; Wei et al., 2015). In contrast to phylogenetic analysis, group-specific primer and RFLP have the ability to demonstrate the occurrence of co-infection with multiple TTV genotype within the studied population.

While PCR has the ability to detect the presence of TTV DNA, the method used for diagnosis of TTV infection based on detection of TTV antibodies such as immunoblotting, immunoprecipitation, immunocapture and Enzyme immunoassay (EIA) has been also developed. The N-terminal and C-terminal of ORF 1, and ORF 2 protein have been employed as an antigen against circulating TTV antibody, and in contrast to PCR, antibody-based detection is able to detect the resolved TTV infection (Tsuda et al., 1999; Handa et al., 2000; Ott et al., 2000; Tsuda et al., 2001; Kakkola et al., 2008).

The prevalence of TTV

TTV is ubiquitous in the human population; however, its prevalence is varied across different regions of the world. The estimated TTV prevalence was mostly based on the detection of TTV DNA. In this section, the discussion focuses on TTV prevalence and its genotype distribution by PCR using UTR-specific and ORF-specific primer for six different continents. In this discussion, amplification of the nucleotide sequence spanning UTR is referred to as UTR PCR, whereas the amplification of nucleotide sequence spanning ORF 1 is referred to as ORF PCR.

Africa

The data on TTV infection rate among African populations is very limited. Based on the data provided by Smuts et al. (2003) and Hafez et al. (2007), 17% to 84% of African populations are infected with TTV regardless of individual's health status and detection method employed (*Table 2*).

The high prevalence of TTV among rural populations in South Africa as reported by Smuts et al. (2003) can be linked with the sanitation level as those who live under poor sanitary conditions may have a greater chance to be infected by this virus (Pujol et al., 2005).

Table 2: The prevalence and genotype distribution of TTV in Africa

Countries	References	Subjects	Prevalence of TTV (%)		Major group / genotypes detected
			UTR PCR	ORF PCR	
Qoluobia	Hafez et al. (2007)	Healthy individuals	-	36.7	Genotype 1, 5
		Hepatocellular carcinoma	-	46.7	
		Liver cirrhosis	-	40	
South Africa	Smuts et al. (2003)	Rural community	84	17	Genotype 1, 2

Asia

Asian continent presents the largest data on TTV prevalence compared to the other continents. Meanwhile, the estimated TTV prevalence among Asian population is ranging from 6.67% to 100% (*Table 3*). A few studies have been conducted in Pakistan, Taiwan and Thailand, and based on the data reported by Hussain et al. (2012) and Hsiao et al. (2016), TTV infection rate in Pakistan and Taiwan was seen to be high, while, Urwijitaroon et al. (2007) reported a low TTV infection rate among Thais. While TTV epidemiological study was reported to be limited in a few countries, multiple epidemiological studies have been conducted in Iran with up to 92% of the Iranian infected by TTV as reported by Koohi et al. (2012). Variability in TTV prevalence among Iranian was noted and might be due to the different regions of the TTV genome targeted for amplification as UTR-specific primer may result in higher detection rate compared to ORF-specific primer. Interestingly, three studies conducted by Koohi et al. (2012), Mousavi-Nasab et al. (2013) and Izadi et al. (2016) showed a decreasing number of TTV infection rate although they detected the presence of TTV DNA using similar set of primer targeted at 5' UTR (Okamoto et al. 1999). The difference in TTV detection rate could be due to several reasons including the growing number of TTV variants over time, the medications used that affect TTV replication and low TTV titre of the test samples that may give negative results (Chris D et al., 2002; Izadi et al., 2016). In China, Peng et al. (2015) reported that half of the infants enrolled in the study were tested TTV positive while the adults showed a high percentage of TTV infection rate ranging from 97.5 to 100% as detected using UTR PCR. Nevertheless, the detection rate of TTV tended to be lower using ORF PCR (Peng et al., 2015). TTV prevalence reported by Wei et al. (2015) was much lower compared to the reported prevalence by Peng et al. (2015) possibly due to the group-specific primer used by Wei et al. (2015). The group-specific primer was design based on the nucleotide sequence of one TTV genotype representative from each TTV genogroup (group 1 to 5) and due to the high sequence heterogeneity between TTV genotype, certain TTV genotypes could not be detected leading to negative results.

Table 3: The prevalence and genotype distribution of TTV in Asia

Countries	References	Subjects	Prevalence of TTV (%)		Group / Genotypes
			UTR PCR	ORF PCR	
China	Wei et al. (2015)	Cardiovascular disease	14		All group detected using group-specific primer
		Tumour	18.8		
		Gastroenteritis	26.7		
	Peng et al. (2015)	Adults	98	37.8	-
		Chronic hepatitis B	100	35	
		Chronic hepatitis C	97.5	42.5	
		Infants	54.7	17.4	

Iran	Doosti et al. (2011)	Healthy individuals		2.9	
		Hepatitis B		8.9	
		Hepatitis C		10.8	
	Koohi et al. (2012)	Chronic Hepatitis C patients	92.0	5.0	Genotype 1, 3, 11, 17, 22
	Mousavi-Nasab et al. (2013)	Healthy individuals	18.0		
		Hepatitis B	50.8		
		Hepatitis C	66.5		
	Izadi et al. (2016)	Chronic Hepatitis B patients	6.67	-	-
		Chronic Hepatitis C patients	13.3	-	
		Healthy individuals	10.0	-	
	Taheri et al. (2017)	Healthy individuals		11.0	
		HIV infected		18.8	
India	Irshad et al. (2008)	Healthy individuals	-	26.7	Genotype 1, 2
		Liver disease	-	27	
		Chronic renal failure	-	58.5	
	Magu et al. (2015)	Healthy individuals	72		-
		Hepatitis A	77.4		
		Hepatitis B	85.7		
		Hepatitis C	77		
		Non A-C hepatitis	92.8		
Indonesia	Muljono et al. (2001)	Healthy individuals	95	41.8	Genotype 1, 2, 3, 22, 23
Pakistan	Hussain et al. (2012)	Healthy individuals	92.5	-	Group 2
		Hepatitis B	89.7	-	
		Hepatitis C	90	-	
Thailand	Urwijitaroon et al. (2007)	Negative HBV and HCV	-	28	-
		Hepatitis B	-	25	
		Hepatitis C	-	29	
Taiwan	Hsiao et al. (2016)	Healthy individuals	95	-	Group 3, Group 6 and 7 (identified in this study)

Middle East

Based on the data gathered from three different countries located in the Middle East (*Table 4*), the high prevalence of TTV was reported among healthy individuals (81.4%) and hepatitis patients (84.9% to 90.75%) in Qatar (AbuOdeh et al., 2015), with no significant association between TTV infection and hepatitis. In Turkey, the high prevalence of TTV detected using UTR PCR was reported by Yazici et al. (2002) (82.7% to 86.4%); however, it is not comparable with the prevalence reported by Kalken et al. (2005) (16.8% to 53.1%). In addition, much difference in TTV prevalence detected using ORF PCR was observed between the study conducted by Erensoy et al. (2002) (51.6 to 80.0%) and Kalken et al. (2005) (12.0 to 31.9%). As stated above, the unspecificity of the primer used, different level of TTV titre of the tested samples as well as different background of the studied population might have an impact on the estimation of TTV infection. However, there is another issue that demands further investigation, which is the contribution of host's gene polymorphism against TTV infection. At present, there are only a few publications exist on the association of TTV infection with the host's gene polymorphism. TTV has been linked with *APOBEC3B* gene polymorphism, in

which those subjects who were having intact allele, either heterozygous intact / deletion (I/D) or homozygous intact (I/I) was associated with high chance of developing TTV viremia compared to those who were having homozygous deletion (D/D) (Prasetyo et al., 2017). Besides that, recent study by Ramzi et al. (2017) which was conducted among hematopoietic stem cell transplantation patients demonstrated the association between cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene polymorphism with TTV infection. Among the four types of gene polymorphism, which include -17722 T/C, -1661 A/G, -318 C/T, and +49 A/G, the prevalence of active TTV infection after the transplantation was significantly related to CTLA-4 +49 A/G polymorphism, and among patients with low-grade acute GVHD, TTV infection could be linked with CTLA-4 -1661 A/G and CTLA-4 -318 C/T. The study conducted in Saudi Arabia demonstrated that TTV was prevalent among the haemodialysis patients (42.9%) compared to 19% of the control group (P<0.001) (El-taher et al., 2015).

Table 4: The prevalence and genotype distribution of TTV in Middle East

Countries	**References**	**Subjects**	**Prevalence of TTV (%)**		**Group / Genotypes**
			UTR PCR	**ORF PCR**	
Qatar	Abu Odeh et al. (2015)	Healthy individuals	81.4	-	Group 1,2,3,5
		Hepatitis B	90.75	-	
		Hepatitis C	84.9	-	
Turkey	Yazici et al. (2002)	Prostitute and homosexual men	86.4	-	-
		Healthy individuals	82.7	-	-
	Erensoy et al. (2002)	Healthy individuals	-	51.6	Genotype 1, 2
		Thalassemia	-	61	
		Fulminant hepatitis	-	80	
		Haemodialysis patients	-	75	
	Kalkan et al. (2005)	Healthy individuals	16.8	12	Genotype 1,2,3,4
		Mentally retarded children	30.6	22.7	
		Schizophrenic children	26.7	14.2	
		Leprosy cases	32.5	23.2	
		Chronic hepatitis B	31.3	19.6	
		Chronic hepatitis C	53.1	31.9	
Saudi Arabia	El-taher et al. (2015)	Haemodialysis patients	-	42.9	Genotype 1,2,3,4,5,6 (genotype 1 most common in both groups)
		Healthy individuals	-	19	

Europe

Similar to the African continent, a limited number of TTV epidemiological study among European was also observed (*Table 5*). Within this continent, 50.4% to 95% of patients with blood-borne

diseases, 91.8% of intravenous drug users and 62% of sex workers have been infected with TTV (Takács et al., 2003; Saláková et al., 2004), whereas the prevalence of TTV isolated from cancer patients was slightly lower, which was 24% to 50% (Hettmann et al., 2016). The high TTV prevalence (94%) was also reported among Russian population, which was much higher compared to healthy individuals of the Czech Republic (52.6%) (Saláková et al., 2004; Vasilyev et al., 2009).

Table 5: The prevalence and genotype distribution of TTV in Europe

Countries	**References**	**Subjects**	**Prevalence of TTV (%)**		**Group / Genotypes**
			UTR PCR	**ORF PCR**	
Czech Republic	Saláková et al. (2004)	Healthy individuals	52.6	-	Genotype 1a, 1b, 2b, 2c, 8
		Haemophilia patients	95	-	
		Intravenous drug users	91.8	-	
		Sex workers	62	-	
		Penitentiary prisoners	74	-	
		Healthy children (age 1-14)	67.8	-	
		Cord blood samples	0	-	
		Non A-E hepatitis	75	-	
		Hepatitis C	89.2	-	
		Blood donors with elevated ALT	60.8	-	
Russia	Vasilyev et al. (2009)	Healthy individuals	94		
Hungary	Hettmann et al. (2016)	Head and neck carcinoma	-	30 - 38	Genotype 1,2,3
		Oral carcinoma	-	24 - 50	
		Healthy individuals	-	5 - 14	
	Takács et al. (2003)	Healthy individuals	-	18.5	Group 1 (genotype 1,2,6); Group 2 (genotype 8, 17)
		Hepatitis patients unknown etiology	-	50.4	

North and South America

According to *Table 6*, epidemiological study conducted in Canada illustrated that 38.8% of the diarrheic individuals were positive for TTV in their stool samples as demonstrated by real-time PCR, and significantly high TTV load in stools of diarrhoeic individuals compared to non-diarrhoeic individuals (Brassard et al., 2015), thus supporting the hypothesis on the faecal-oral route of TTV transmission that will be further discussed in the following section. Meanwhile, in countries within South America, such as Brazil and Uruguay, the prevalence of TTV varied from 54% and 100% among hepatitis and HIV-1 patients and varied from 46% to 69% among healthy individuals regardless of the PCR protocol employed (Devalle & Niel, 2004; Mazzola et al., 2015; Cancela et al., 2016).

Table 6: The prevalence and genotype distribution of TTV in North and South America

Countries	References	Subjects	Prevalence of TTV (%)		Group / Genotypes
			UTR PCR	ORF PCR	
Canada	Brassard et al. (2015)	Diarrheic	38.8		-
		Non-diarrheic	18.4		-
Brazil	Mazzola et al. (2015)	Healthy individuals	-	69.0	–
	Devalle and Niel (2004)	Healthy individuals	46		All groups (1-5) were detected using group-specific primers
		Hepatitis B	54		
		HIV type 1 (HIV-1)	100		
Uruguay	Cancela et al. (2016)	Hepatitis patients	79.0	-	Group 3

Multiple Route of TTV Transmission

Widely distributed TTV infection among human populations might be explained by the multiple modes of transmission. TTV could be horizontally transmitted among human population via blood and excretory products, and vertically transmitted from mother to infants. Apart from human to human transmission, the zoonotic transmission should also be considered as this virus is also known to infect animals. Here, a brief description on the several possible routes of TTV transmission is presented.

Horizontal Transmission

Since hematopoietic cells have been hypothesised as the replicative sites for TTV, blood and blood products could be among the possible routes for TTV transmission (Zhong et al., 2002; Maggi et al., 2010). In line with Zhong et al. (2002) and Maggi et al. (2010), Focosi et al. (2015) suggested TTV as a T-lymphotropic virus evidenced by the reduction of TTV viremia in parallel with the absolute lymphocyte count (ALC) after the induction of immunosuppressive drug among the transplant recipients. Besides, TTV DNA was significantly detected in individuals exposed to infected blood or blood products including those receiving the blood transfusion or intravenous drug user (Saláková et al. 2004; El-taher et al., 2015).

According to Bendinelli et al. (2001), the widespread of TTV infection across different regions of the world, and among individuals with a number of conditions and variety of circumstances does not solely depend on blood-borne transmission. Given the presence of high TTV prevalence among healthy individuals and the worldwide distribution of TTV, it supports the hypothesis on the involvement of other modes of transmission in spreading the virus. TTV has been proposed to be transmitted via respiratory droplet and saliva through the air. The presence of TTV DNA in nasal secretion and saliva of infants as well as healthy adults indicate that the respiratory tract may act as a reservoir of TTV (Maggi et al., 2003; Naganuma et al., 2008), and this virus could be spread via exhalation (Chikasue et al., 2012).

As evidenced by the presence of TTV DNA in faeces of TTV-infected individuals, there is a possibility that this virus is shed into intestine and transmitted into the next host via faecal route (Okamoto et al., 1998b). This hypothesis is also in agreement with a recent study among diarrheic and non-diarrheic individuals reporting a significant association between TTV infection rate and viral load with enteritis (Brassard et al., 2015). In providing more evidence on the faecal-oral route of TTV transmission, a number of studies have been carried out on the detection and quantification of TTV genome in water from different sources. Low sewage treatment may contaminate food, water supplies

and living area, which contribute to the faecal-oral cycle of TTV (Dalla Vecchia et al., 2013). Analysis on the enteric virus presence in water samples in Brazil revealed that detection rate of TTV DNA in surface water and in effluent sample of sewage water by means of PCR were 28.57% and 12.5%, respectively (Vecchia et al., 2012a; Vecchia et al., 2012b). The shedding of TTV particles into faeces demonstrated that this non-enveloped virus might be highly resistant to water environment (Flint et al., 2015).

Vertical Transmission

Although scarce, some evidence exist on the vertical transmission of TTV from mother to child, either prenatal or postnatal (Davidson et al., 1999; Maggi et al., 2003; Ninomiya et al., 2008). Cord blood and amniotic fluid (transplacental transmission) (Gerner et al., 2000; Matsubara et al., 2001) may act as a vehicle in transmitting TTV DNA from mother to infant during the prenatal period. While Bagaglio et al. (2002) was able to demonstrate the presence of TTV DNA in infants at birth, which was in line with the study by Gerner et al. (2000) on TTV nucleotide sequence analysis isolated from mother-child pairs infected with TTV that showed the sequence homology, a few other studies demonstrated the lack of cord blood as well as amniotic fluid as a medium of TTV transmission (Kazi et al., 2000; Iso et al., 2001; Ninomiya et al., 2008; Tyschik et al., 2017). Ninomiya et al. (2008) failed to detect presence of TTV DNA within cord blood; however, they reported that the prevalence of infants infected with Anellovirus DNA increased with the number of months after birth with the first appearance was detected at 20 days of age (Ninomiya et al., 2008), indicating the postnatal acquisition of TTV. Several studies provided an evidence on the possibility of the breast milk to act as a medium in transmitting the virus during the postnatal period (Gerner et al., 2000; Schröter et al., 2000; Iso et al., 2001; Matsubara et al., 2001); however, it deserves further investigation since infants born to uninfected mothers who were refrained from breastfeeding their infants were positive for TTV DNA (Kazi et al., 2000).

Cross-species Transmission

The *Anelloviridae* family is not restricted to the human-infected virus. A number of Anellovirus species have been considered as the animal-infected viruses that infect animal such as pigs, dogs, macaque, tupaias, and non-human primates (ICTV 2015). Since it infects both human and animal, it owes the answer on the potential cross-species transmission of TTV. In an attempt to find the possible source of TTV infection among human, several studies conducted on non-human primates revealed that TTV variants are species-specific (Leary et al., 1999; Okamoto et al., 2000a; Okamoto et al., 2000b), with 66 to 90% of the nucleotide sequence of TTV genotype 1a (isolate TA278) similar to TTV isolated from chimpanzee, thus suggesting the possible cross-infection of TTV between human and chimpanzee (Okamoto et al., 2000). As reported by Iwaki et al. (2003), 10% of the Japanese patients who suffered from liver diseases are infected with simian TTV. The hypothesis for the possible cross-species infection of TTV is supported by the recent evidence provided by Ssemadaali et al. (2016). They reported that, most of the human sera tested were infected with both human TTV and swine TTV (TTSuV). Further investigation revealed that human PBMCs have the ability to support the TTSuV DNA replication and its respond towards immune stimulation significantly declined upon infection with TTSuV DNA (Ssemadaali et al., 2016). These findings may provide the fundamental knowledge on the possible interspecies transmissions of TTV. However, further studies are warrant to provide more significant evidence especially in the context of disease pathogenesis.

Conclusion

The study on TTV has started 20 years ago. Nonetheless, many aspects of this virus are still controversial. TTV prevalence is a geographically variable and there are certain regions of the world that are yet to be studied. Despite the presence of TTV DNA in individuals with a number of health conditions, TTV is also prevalent among healthy individuals. At present, the role of TTV in the pathogenesis of the disease is still unknown and infection with this virus result in no sign and symptom. Prevalence study on TTV may give the estimation on the ubiquity of TTV and widespread of its infection, however, a more efficient assay is needed to measure the impact of this virus on human health.

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