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Review Article
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Current and Future Prospects of Torque Teno Virus

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Abstract

Human health has a significant importance and it is directly affected by a number of factors like different diseases including microbial and viral infections. Up till now we have paid attention to the disease causing viruses and pathogens and less has been investigated about the usefulness of normal viral flora. One such orphan virus is Torque Teno Virus (TTV). The virus is present in healthy as well as diseased population, indicating its high prevalence. The virus is ubiquitous to human body as it is present in almost all tissues and organs and this is the property that can be utilized for targeted drug delivery. Another potentially useful property of this virus is TTV derived Apoptosis Inducing protein that can be a hope for the affectees.

Keywords: Torque Teno Virus; Genotypes; Phylogenetics; Apoptosis

Introduction

Viruses are small, tiny infectious agents that use the host cell machinery for replication. The first ever virus to be identified and reported was Tobacco Mosaic Virus. The word "virus" is derived from Latin word meaning "poison". It is believed by certain schools of thoughts that viruses have co-evolved with humans. Viruses are composed of two essential parts i.e. Viral Genome composed of DNA or RNA which could be either single stranded or double stranded and a protein coat which surrounds the genome and its symmetry can be either helical, icosahedral or complex, In some viruses the protein coat is embedded by a lipid bilayer derived from host cell making third part of their structure [1,2].

Hepatic Human Viruses and Historical Background of TTV

There are many factors that are responsible for causing over 100 known forms of liver ailments ranging from host range of infants to adults. Alcohol consumption and the use of certain drugs have a stereotypical association with hepatic diseases. Hundreds of thousands of humans are affected by hepatitis worldwide. Intensity of disease and treatment outcomes depends upon the causative agent. One of the major cause of hepatic disorders are hepatitis viruses. Five reported viral agents causative for this are Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis D Virus (HDV) also known as delta agent and Hepatitis E Virus (HEV). On the other hand there are certain other agents that are associated with hepatocytes but their clear association with hepatitis is not established yet and they are Hepatitis G Virus (HGV) and Torque Teno Virus (TTV) [3,4]. Human TTV is also known an orphan virus (viruses that are not associated with any disease but may cause pathogenicity).

Discovery of Torque Teno Virus

TTV (a single stranded DNA virus) was first reported in 58 years old patient with recent history of blood transfusion (35 Units) suffering from non A-G hepatitis in 1997 from Japan and was detected in the serum sample taken during hepatitis treatment. Clone of approximately 500 bp was obtained and then matched with already present sequences in databases but it showed no similarities. DNA of TTV was detected in blood of hepatitis patient when a liver enzyme ALT (alanine aminotransferase) was at its peak [5,6].

At first it was named after the initials of the patient from which it was originally reported i.e. TT. But later the basis of its most common transmission mode and circular nature of its genome it was design named as Transfusion-transmission virus [7].

This human DNA virus has an approximate length of 3739 bp and 1.26 g/cm^3 density in sucrose gradient [8]. Post transfusion Hepatitis was supposed to be associated with TTV in the beginning [5]. But later it was found that TTV is a common virus in human with a high prevalence in healthy population. Intravenous Drug Users (IDUs) and patient suffering from non A-G hepatitis, non A-G cirrhosis, haemodialysis patients, liver transplant recipients and hemophilic patients are common hosts for this virus [9-12].

TTV displays similarity with the members of the family *parvoviridae* and *circoviridae* [13]. Initially it was placed in *circoviridae*, but it was different from other members of the family i.e., Porcine Circo Virus (PCV), Beak and Feather Disease Virus (BFDV) of parrots and Chicken Anemia Virus (CAV) in its nucleotide sequence, being positive stranded and genomic size of 3.8 kb [14], Later on, based on its genome organization, TTV was proposed as a member of a new family named "*Circoviridae*" and its genus is "*anneloviridae*" [11]. Genomic structure of TTV has more similarity with chicken anaemia virus that is the member of genus Gyrovirus, however the similarity is very minimum of a short stretch of nucleotides from 3816-3851 [15].

Structure and Genomic Organization of Torque Teno Virus

Nishizawa et al. in 1997 [5], using polymerase chain reaction (PCR) technique, presented that the genome of TTV was DNA in nature and after treating it with DNAse I it was evident that virus was en-capsidated putative virus. The single stranded nature of the DNA of this virus was proved by Mushahwar et al. in 1999 [16]. They treated the virus with Mung Bean Nuclease and restriction enzymes which showed that this

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virus is sensitive to both [16]. Since detergent has no effect on virus it is a non-enveloped virus [11] with a size of 30-50 nm in diameter [16]. Primarily when TTV genome was first sequenced by Okamoto et al. [11], it was considered as a single stranded linear DNA virus. But later studies have identified the GC rich region that proved the circular nature of this virus genome.

Genome

The genome of TTV is single stranded and circular in nature and 3.8 kb in length, which contains both coding and non-coding regions with sizes 2.6 kb and 1.2 kb respectively. It also contains some conserved regions [17,18]. Interestingly, the conserved regions are present in the non-coding area of the genome (UTRs). The conserved regions are GC rich region, a poly A sequence downstream and a TATA box upstream of the coding region [17,19,20]. Spanning approximately one third of TTV genome, the GC rich region is about 113 nt long [21]. Approximately 2-3 Open Reading Frames (ORFs) are present in TTV genome [11,16].

In order to check the transcribed ORFs, the Kamahora et al. cloned the TTV genotype-1 isolate. They identified 3 mRNA species. All the 3 mRNA species used the same TATA box to initiate the transcription and they all used the same poly A tail at the end [22]. The lengths of these mRNA species are 3.0 kb 1.2 kb and 1.0 kb respectively. The 2nd and 3rd mRNA species are further spliced into two or more ORFs, [21] thus showing that the genome of TTV undergoes alternative splicing. The UTR is used as a transcription factor control because TATA box and the poly A tail sequences are found in the UTR [21,23,24]. The general genomic organization is shown in the Figure 1.

Proteins

The TTV genome is negative sense ssDNA so its mRNA is transcribed from the complementary strand. The 3 mRNA species are translated into 3 or more proteins. The predicted length of ORF1 is 719-770 amino acids, and it is considered to encode a capsid protein [17,25-27]. In some TTV isolates, a stop codon is present at the center of the ORF1 [25,28,29]. TTV genotypes have higher variation at amino acid level than at the nucleotide level, but still there is a similarity in the functions of proteins encoded by different genotypes. ORF1 encodes a capsid protein and it is the longest open reading frame. ORF1 contains hyper variable regions (HVRs), the occurrence of mutations in ORF1 is much higher than any other proteins of TTV in which change in nucleotides (mutations) leads to amino acid changes and it occurs more frequently than in other protein parts. These HVRs help the virus to

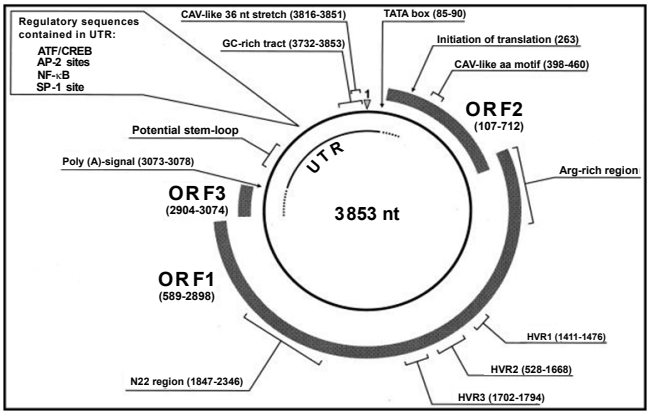

Figure 1: The Genome organization of TTV [58].

evade the immune system [16,30,31]. The protein encoded by ORF1 has an Arginine-rich N-terminus [11,16,32,33]. It is considered that this Arginine-rich N-terminus may function in binding of DNA during the process of packaging of viral DNA into capsid [25].

ORF2 encodes for proteins of almost 200 amino acids. A stop codon in some genotypes divides ORF2 into smaller ORF2a and ORF2b coding areas. ORF2b has less conserved amino acids than ORF2a. ORF2b has a CAV like conserved amino acid motif $WX_7HX_3CX_1CX_5H$, [18,26,27,33,34]. This conserved sequence is similar to Protein-Tyrosine Phosphatase (PTPase) and it is considered that this protein might be involved in the cellular or viral protein regulation during infection [35]. ORF3 encodes protein of approximately 280 amino acids long and it encodes protein that is similar to a non-structural protein 5A (NS5A) of hepatitis C virus. This protein functions in regulation of cell cycle and suppress the antiviral resistance induced by interferon. It has a serine-rich domain at C-terminus [18,36] and its function is still not known.

ORF2-5 encodes a protein of approximate 280 amino acids long. It has some similarities with transcription factor protein. At the C-terminus of this protein, a conserved motif of unknown function is present. The sequence of this conserved motif is $EX_8RX_2RX_6PX_{12-19}FX_1L$ [18,37]. There is another protein called TTV-derived-Apoptosis-Inducing protein (TAIP), which is a putative protein of 105 amino acids long. TAIP induces apoptosis in cellular carcinoma cells [30]. It is said that due to Intra-genomic rearrangement and by alternative splicing more ORFs have been raised [38,39] thus increasing the variability of TTV isolates.

Replication Mechanism of TTV

A large number of healthy humans worldwide have TTV in their serum, therefore it is important to knowhow TTV replicates in human cells. The major aspects of TTV life cycle are still unknown. It is yet to be known that which type of cells provide replication machinery for TTV, however some studies have shown the presence of mRNA forms and double stranded DNA of TTV in bone marrow, in various human organs and in tissues which indicates that they can be an active replication sites of TTV. It is still uncertain where this virus attaches itself on host cell surface and how it maintains high viral loads in the blood of the infected hosts [40]. Peripheral blood acts as reservoir for TTV. The rich phylogenetic diversity of TTV makes it difficult to understand its biological functions and laboratory culturing of TTV is not yet successful [41].

In bone marrow cells three types of mRNA's of TTV (2.9 kbp, 1.2 kbp and 1.0 kbp) have been detected that are produced by alternative splicing. These mRNA's were also obtained when the whole genome of TTV was transfected into African green monkey cells. These mRNA's when Identified helped in understanding the functionality of ORF1 and ORF2 and also confirmed presence of ORF's other than these. When full length TTV clone was transfected into human embryonic kidney cells it confirmed the presence of these three mRNA's and also revealed the expression of six different proteins produced by alternative splicing strategy [42].

Phylogenetic Variation of TTV

The sequence of TTV genome is very diverse in nature. Uptill now 61 different isolates are known worldwide [7]. It is still unknown that what is the cause and mechanism for this great genomic variation. As TTV is a DNA virus low mutation rate is expected than RNA viruses. But there are many possible reasons which suggest higher than expected rate of mutation in TTV. It could be due to the presence of HVRs in

ORF1 [28], Intra genomic rearrangement [38] or due to Recombination [43,44]. Such a great genomic variation may be due to the co-evolution of this virus with humans [20,45,46].

Genotypes of TTV

Presently more than 30 genotypes of TTV have been classified under 5 genogroups [47]. The genotypes 1, 2, 3 and 4 seem to be frequently distributed across the world, but the prevalence of genotype 5 has not been completely established [36,48]. Few subtypes (1a, 1b, 2a, 2b) have also been identified. The genogroups are uniquely distributed in various regions across the world with G1 and G2 TTV common in the USA and in Italy in patients with hepatic disorders and in blood donors, while G4 is also reported but is less common [49]. Although any serious health problem is not correlated with TTV yet but several genotypes are believed to be responsible for human diseases [47].

TTV is distinguished by its high degree of strain heterogeneity. The regional specificity of viral genotypes suggests frequent community transmission. Studies have shown that in Czech republic the most common genotype was 2 (54%), followed by 1 (13%) [50]. Presence of TTV not only in hepatitis patients but also in healthy individuals strongly suggest that its transmission can be through oral fecal route. TTV is found everywhere in the environment across the world. In Brazil about 92.3% water samples were contaminated with TTV with the highest concentration of 7.46×10^5, which is equivalent of per 100 ml [51].

TTV-Like Viruses and Relatives of TTV

Three other types of TTV-like viruses have also been discovered, since the discovery of TTV. They are: Torque TenoMinivirus (TTMV), Small Anellovirus (SAV) and Torque TenoMidivirus (TTMDV).

Torque teno mini virus

TTMV has smaller genome size and diameter than TTV [52,53]. TTV in CsCl has buoyant density of 1.31-1.33 g/cm^3 and TTMV has density of 1.27-1.28 g/cm^3. TTV mini virus was discovered accidentally by PCR of human plasma samples in which TTV specific primers were used that primarily matched with the sequences and generated a shorter stretch than TTV [42].

TTMV's genome is circular ssDNA with negative polarity and length of about 28-29 kb and diameter of 30 nm. It has a great resemblance with TTV in many ways; it has a GC-rich region, a coding region, CAV like motif in ORF 2 region and an Arginine-rich N-terminus [52,54]. A serine rich C-terminus is present in the ORF 1 of TTMV, which is believed to play an important role in replication process as it has some homology with topoisomerase 1 protein [53].

Like TTV, TTMV is also distributed across the world among healthy population [52]. The prevalence of TTMV among blood donors is about 48% to 72% [42].

Small anellovirus

SAV also share some common characters with TTV. It contains a GC-rich region, a coding area and a CAV like motif [55]. Similar to TTV, SAV isolates form a large phylogenetic tree and is common across the world among healthy population [56].

Torque teno midi virus

In recent past during the amplification of SAV sequence in human sera the amplicons attained were longer than expected and their length was 3242-3253 nt and these amplicons have all the properties of TTV like viruses. These newly recognized amplicons were named as Torque TenoMidivirus (TTMDV). Upon analyzing the different TTMDV sequences it was observed that they form a large group of isolates that have different lengths as well as sequence aspect. At nucleotide level it has 31% divergence and at amino acid level it has 61% divergence [42]. Torque Teno Midi Virus has many common characteristics with other TTV like viruses such as in ORF1 three replication motifs were recognized and stem loop structure was identified in GC rich region [57,58].

Prevalence and Sociodemography of TTV

TTV is observed in almost all the tissues and body fluids except in RBCs and in platelets. The cells of immune system are also infected by TTV [59,60]. It is also reported in cancer cells, in addition to normal cells [61]. The age and gender of a person and genogroup of virus is kept in mind when studying the prevalence of TTV. In one study in Brazil, the occurrence rate of TTV was reported to increase with age i.e. 17% in children under age of 11 years and 57% in individuals older than 50 years [62].

The infection may occur at a particular age group, for example according to Salakova et al. little children were infected by TTV in two age groups i.e. either at the age of two years or after start of primary school [63]. In one research in Mangolia to check the incidence of TTV infection, 83 samples of hepatic disorder patients (36 males and 47 females) were collected, out of them 50 (60.2%) were positive which include included 23 (46%) males and 27 (54%) females. The age of these patients was from 2-40 years [64].

Depending on the genogroups, rate of prevalence of TTV differ among age. The positivity rate of genogroup 2 after nPCR was 80% in young ones, 60.3% in sub adults and 58.3% in adults. For genogroup 1 of TTV no differences were detected by age. Likewise the positivity rate of TTV genogroup 2 according to gender was 74.2% females and 57.0% males, on the other hand no differences in genogroup 1 prevalence were observed on the basis of gender [65]. The occurrence of TTV across the world among the healthy blood donors greatly varies from between 1% and 2% in Scotland and U.S, 12% to 14% in Japan and Spain and upto 36% in Thailand [66]. TTV viremia is common among Iranian blood donors. Its prevalence in Iran is 22.4% or less comparable to China (28%) but lower than Thailand (37%) and Italy (42.4%) [67].

Rate of occurrence of TTV varies across the world [68]. On the whole moderate occurrence rates were reported in U.S and Northern Europe, intermediate in Asia and higher in Africa and South America with an average prevalence of about 80%. Similarly a survey of sera conducted by Matsumoto and his coworkers in Greater Washington and Chesapeake reported that the rates of prevalence of TTV were higher amongst the Asians and African Americans [69,70].

The occurrence of TTV differs in different regions of the world [71,72]. For example, the prevalence of TTV is 51.6%-82.7% in Turkey [68,69,73] 53.3% in China [72], 46-62% in Brazil [65,74], 92.0% in Japan [75], 25.0% in Egypt [76] and 2.6% in Iran [77], 52.6% in Czech Republic [63] and 54% in Congo [78]. With the discovery of new variants of TTV, its prevalence changes all the times [79,80].

Modes of Transmission of TTV

The route of spread of TTV is still uncertain. The prevalence of TTV is strongly associated with populations having history of transfusion of blood or blood products [81,82], and it is thought that TTV is

transmitted via blood transfusion. Two more groups of population that are strongly associated with TTV are haemodialysis patients and intravenous drug users (IVDUs) [83]. Presence of TTV is also reported in the sera of those individuals who have not received any blood transfusion yet, so like many other viruses other routes of transmission may also exist [68].

The qualitative and quantitative PCR analysis showed the presence of TTV in feces [11,84-86], in fresh water and waste water [87,88], in saliva and throat swabs [85,89,90], in semen and cervical swabs [91-93], in amniotic fluids, cord cells [94-96] and Breast Milk [97-99] so the other probable modes of spread may be oral fecal, water borne, respiratory tract, sexual transmission and Mother-Child transmission respectively.

The least efficient transmission mode of TTV is sexual transmission while the most efficient transmission is through Mother-Child. If a person acquires TTV by Mother-Child transmission then the virus would have been in the body since early days of life. In the case of vertical transmission, the effects of TTV on developing fetus are unclear. A study reported the increased prevalence of TTV in Drug users with multiple sex partners and liver diseases [100]. In mother to child transmission of TTV horizontal infection is more common than vertical transmission, because of its presence in breast milk, it is prominent mother to child infection mode [95]. Chikasue et al. were successful to find out that this virus might have an air borne route that makes it successfully transmissible in persons occupying the same room (18 cm distance). They also reported the virus in exhaled breath and its infection catching period was infancy [101].

TTV Immunology

The knowledge about immune responses of TTV infection is limited because TTV produces only 4-5 proteins, which provoke little immune response. TTV specific antibodies have been detected in the sera of infected individuals by Tsuda et al. [102]. Tsuda et al. used the technique of immunoprecipitation to establish, that after the clearance of TTV DNA, short term antibodies IgM appeared in the blood and after them long lived IgG antibodies showed up [102].

ORF1 N and C terminus specific antibodies have also been detected in the blood of infected individuals [103,104]. TTV immunocomplexes have been detected in the sera of TTV positive individuals [102,105]. These immunocomplexes have been found in case of prolonged infections but not in acute infections [31]. The immune system clears about 90% viral particles a day [59] but it is still a point to ponder that how TTV outpace the immune response and immune system is incapable to exterminate it. An immunogenic protein (low detection of IgG) is produced by ORF2; immunogenicity of this protein is not specific but varies from genotype to genotype. Antibodies formed as a result of TTV infection, do not cross react and neutralize. Therefore it is not for sure that weather this protein can be used to develop genotype and genogroup detection assays for TTV [106]. A study was aimed to find out the correlation between elevated ALT levels and TTV viremia but no association was found [67].

TTV Pathogenicity

At the time of discovery of TTV it was considered as a hepatitis virus [5]. However after numerous studies it was found to be present in 90% of healthy individuals.TTV neither exhibits seasonal variations nor has any epidemic yet been reported [51,87,88].

The infection caused by TTV can be either temporary or permanent. Although the association of TTV with post transfusion hepatitis is known, but its role as a pathogen is yet unclear [58]. Nevertheless, a great genetic variation among TTV genotypes suggest that only some of these genotypes may be disease causing. Some studies have shown relationship between TTV genotype 1 and raised levels of serum transaminase in humans, [5] recent studies proposed this genotype to be more pathogenic than any other, in children with hepatic disorders due to unknown cause [107].

The viral genotypes exhibit geographical clustering which leads to frequent community transmission [108] and co-infection with different viral genotypes is also common [109-111] established that a TTV infection, especially infection with some genotypes like genotype 1, can aggravate thrombocytopenia in patients of choronic hepatic disorders such as chronic hepatitis C, chronic hepatitis B and hepatitis of unknown etiology regardless of extent of liver fibrosis.

Some studies have proposed that TTV viremia was about three times greater in patients with a recent or past history of hepatitis B as compared to normal healthy people ($P<0.05$) [50]. However some studies have suggested that no correlation exist between high titer of TTV and fulminant hepatitis [99]. Studies have shown the presence of TTV in liver tissue, particularly in the hepatic cells of chronic hepatitis patients, the virus appears to be localized in the cell, however the under lying reason for this is unknown [92,112].

TTV Co-infection

Although TTV has absence of apparent pathogenicity, yet, many studies have been done to examine the correlation of TTV with many other diseases [41,58,113]. The phenomenon of co-infection is common in TTV, it has been detected in co-infection with many other viral species and is known to aggravate various infections like liver disorders, cancer of pancreas, asthma, rhinitis, and inflammatory idiopathic myopathies [114].

A lot of studies have been done to find the association between TTV and all hepatic diseases, because TTV was first identified in the person suffering from Hepatitis of unknown etiology. Many studies which have shown the increase in ALT level with increasing titer of TTV, claim that there is a correlation between hepatitis and TTV infection [5,9,115]. On the other hand many other investigators claimed that there is no association between TTV and hepatic diseases, as they have verified that increasing ALT level is independent of TTV loads [10,20,71,116].

According to some studies there may be a link between severity of respiratory tract infection and TTV positivity, as high titer of TTV was detected in nasal swabs of these patients [117]. Some investigators claimed that TTV has an association with progress of asthma. According to them, the Th2 signaling mechanism, which plays an important role in pathogenesis of asthma, get disturbed because of TTV replication [118]. A few studies have shown an association between Human Papiloma Virus and TTV [90]. It has also been suggested that TTV has an association with *Helicobecter pylori,* because high TTV titer was found in gastric tissues of Gastritis patients [119].

Some genotypes of TTV have been found to have a higher occurrence in AIDS patients than in normal persons [120]. It has been proposed that as the HIV infection progresses, the TTV titer also increases [120-122]. The presence or absence of TTV, appear to have no impact on immunological or clinical level of HIV infection [123]. In recent past a boy (10 years age) developed co infection of acute hepatitis and TTV with lymphocytopenia ($CD4^+$ T-lymphocytes). The patient had a marked difference in CD4/8 ratio. After two months the

patient suffered from hepatitis-associated aplastic anemia. Still a clear association of TTV with both idiopathies is unclear [124].

García-Álvarez et al. aimed to find out association between liver diseases, TTV and Torque Teno Mini Virus (TTMV). HCV/HIV coinfected individuals were targeted for quantification of TTV and TTMV and found a high prevalence of both TTV and TTMV infections in HIV/HCV-coinfected patients, rendering these anelloviruses to be associated with advance grade of liver fibrosis. Therefore the potential role of these viruses in the development of hepatic diseases in HIV/HCV coinfected individuals cannot be over looked [125].

Cell Tropism

Former studies about TTV has shown its presence in different human samples like breast milk, serum, synovial fluid, peripheral blood, feces, saliva, bile juices [68]. A wide range of host cell tropism is exhibited by TTV, because its DNA is present in many organs and tissues of the host. The technique of in situ detection was used to locate the host cells of TTV and the DNA of TTV was found in various cells and tissues [126].

The cells which originate from haemopoetic stem cells are thought to be the most potential hosts for TTV. Some investigators claim salivary glands as a candidate for host of TTV, as they have found high TTV loads in saliva [89]. TTV has also been found in the cytoplasm of oral epithelial cells, through the technique of in situ hybridization [127].

Maggi et al. proved that TTV DNA titer was higher in nasal cavity than in sera hence they considered the nasal cavity as a basic location of TTV infection [119]. The most widely studied location for TTV infection is liver because formerly TTV was believed to be a hepatitis virus. In the patients of hepatic disorders TTV has been detected in cytoplasm and nucleus of hepatocytes by in situ methods [128].

TTV as a Commensal Virus

Since TTV is considered to lack any pathogenicity, many investigators have claimed that out of 500 species of commensal microbes of human intestine TTV is one [129,130]. It has been proposed that TTV is the first known human commensal virus [131]. To date, the described human commensal microbiota is majorly constituted by bacteria even though some fungi and certain protozoans also contribute to it, no other human commensal viruses are known yet [58]. The role of TTV as an enteric virus is also well established. The complete viral genome from water samples has been characterized in Brazil [132].

Animal Torque Teno Virus

In addition to being detected in humans TTV has also been found in the sera of non-human primates and domesticated farm animals, varying in genomic size and sequence TTV is extensively distributed among the animals across the world. The animals are usually targeted by TTV, which has a genome length smaller than human TTV [133]. It is yet unclear that how these organisms have acquired TTV infection. However, according to one study the genome sequences of TTV of gibbons held in human custody, had shown great resemblance with human TTV sequences suggesting the probable transmission through animal handlers [134].

The TTV responsible for infecting non-human primates is called simian TTV (s-TTV) [37,135]. The simian TTV was first discovered in 2003 in Japan [136]. The simian TTV has been detected in the apes, chimpanzees, African monkeys, gibbons and in tupaias [126,134]. Both the simian TTV and human TTV share closely related genome organization, having 85% sequence similarity [37,136]. The route of transmission from monkeys to humans is still unknown [136].

There is an evidence of simian TTV infection in humans, about 1.5% of healthy Japanese population and about 10.5% Japanese patients having hepatic disorders were infected by simian TTV [136]. TTV presence in domestic animals is also established and it was detected in dogs, cows, cats, chicken, sheep etc [37,79, 80,135,137,138].

Another very common animal TTV in addition to simian TTV is swine TTV [80]. For very long time Torque TenoSus viruses are circulating unchecked and are considered harmless. TTV Sus viruses are known to cause disease in pigs [139]. To date two genotypes of swine TTV have been identified in domestic as well as in wild pigs [140]. The two genotypes of swine TTV are widely distributed in pigs across the world [138,141].

In a study to check presence of swine TTV among seven breeds of pigs, 92-100% were found to be positive [142]. Martínez-Guinó et al. have established that swine TTV can transmit in both ways i.e. through sexual exposure as well as from mother to piglet, but no harmful effects were observed in the developing fetuses, so they concluded that TTV infection does not play any role in swine abortion [143]. A study has indicated that both types of swine TTV were present in almost all tissues of body and were highly prevalent among old pigs, the only pigs negative for TTV infection were fetuses, 5 days old and 5 weeks old pigs [144]. Wang and coworkers reported most divergent subtypes of genotype 1 in swine from China and divided them in two subtypes i.e. 1a and 1b [145].

Resemblance of TTV with Chicken Anemia Virus

Chicken Anemia Virus (CAV) is a member of family *Circoviridae*. This family consists of viruses infecting vertebrates and having ssDNA genome. Gyrovirus and Circovirus are 2 genus of *Circoviridae*. CAV a member of genus circovirus (a pathogen of chicken), has similarities in genome organization and transcription regulation sites with TTV. Both TTV and CAV have negative sense single stranded DNA circular genome [5,146].

The ORF1 of TTV has arginine rich N-terminus like that in CAV [14], this arginine rich N-terminus plays an important role in binding and packaging of viral DNA in the capsid [42]. A conserved Amino Acid motif having sequence $WX_7HX_3CX_1CX_5H$ (the sequence for PTPase signature motif) is common in both TTV and CAV [18,20,33]. Another similarity between TTV and CAV is that TTV derived apoptosis inducing protein (TAIP, induces apoptosis in hepatic cancer cells) bear similarity to the apoptin protein of CAV (causes apoptosis in cancer cells) [30].

Resemblance of TTV with Hepatitis C Virus

ORF3 of TTV genotype 1a encodes a protein, which is quite similar to HCV non-structural protein 5A (NS5A). The NS5A plays an important role in suppressing the Interferon-induced anti-viral response [147]. TTV co infection with HCV has been studied across the world but it is yet to be known that whether TTV is an "accidental visitor", "helper" or "responsible cause" for HCV associated liver damage [148].

Epstein Bar Virus as Helper Virus for TTV

Association of Viral infections and multiple sclerosis pathogenicity is well known. Both Epstein-Barr virus (EBV) and TTV have been

frequently explored as a probable candidates. Actual mechanisms involved are still unknown. Borkosky et al. by using a series of EBV positive and negative lymphoblastoid and Burkitt's lymphoma cell lines, reported viral replication, by both genome amplification, as well as quantitative PCR of two TTV-HD14 isolates isolated from multiple sclerosis brain. A statistically significant boosted replication of TTV was observed in the EBV-positive cell lines, including the EBV converted BJAB line while quantitative analysis revealed negative results in comparison to the EBV-negative Burkitt's lymphoma cell line BJAB. This advocates a helper effect of EBV infections in the replication of TTV. Both the viruses might have a positive interaction in etiology and multiple sclerosis progression [149].

Vaccines, Enzymes and Drugs Contaminated with TTV

In porcine major genogroup of TTV i.e. TTV2 appears to be associated with a porcine circovirus disease (post-weaning multisystemic wasting syndrome). At the same time the importance of using pig materials in making porcine vaccines, commercial enzymes and products as well as human drugs is unavoidable. But a little is investigated globally about the probable presence of extraneous viruses, in products comprising of porcine-derived constituents. One such work was conducted by Kekarainen et al. in year 2009, by screening Human Drugs (total screened drugs 7, positive 1), Swine vaccines (screened 26 and over all 9 positive,4 against Mycoplasma hyopneumoniae, 3 against M. hyopneumoniae, 1 against porcine parvovirus and 1 against porcine reproductive and respiratory syndrome virus) and porcine origin enzyme products (screened 3 and positive 1), using PCR for the presence of Swine TTV geno groups TTV1 and TTV2. Therefore we can say that swine origin products should be screened for these viruses. The contamination of enzymes for laboratory use with such viruses can affect the results of experiments. Secondly if a nonhuman virus enters the human body what type of response will be observed in the immune system, is unpredictable yet [150]. In a recent report it was observed that host immune system and response development is effected by the Torque TenoSus Virus 1 (TTSuV1) natural infection. Another important and concerning thing is the immunization suppression by the PRRS MLV vaccine, and exacerbation of PRRS to a certain level in pigs [151]. The present link of Sus TTV with disease is the root of this virus' current significance [152].

TTV as a Potential Targeted Drug Delivery System

In recent era nanobiotechnology has emerged as a blessing for mankind and it has promising applications in the field of targeted drug delivery system. This is potentially a useful milestone towards the treatment of cancers especially breast cancer [153]. TTV TAIP protein can be used as a targeted drug delivery system as it has a property to induce apoptosis in cancer cells. Secondly as this virus has a big range of cell tropism, it can easily enter the target sites in selected cells as vector.

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