The Origin of Hepatitis C Virus

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Abstract The origin of hepatitis C virus (HCV) can be conceptualised at several levels. Firstly, origins might refer to its dramatic spread throughout the Western world and developing countries throughout the twentieth century. As a blood-borne virus, this epidemic was fuelled by new parenteral transmission routes associated with medical treatments, immunisation, blood transfusion and more recently injecting drug use. At another level, however, origins might refer to the immediate sources of HCV associated with its pandemic spread, now identified as areas in Central and West sub-Saharan Africa and South and South East Asia where genetically diverse variants of HCV appear to have circulated for hundreds of years. Going back a final step to the actual source of HCV infection in these endemic areas, non-human primates have been long suspected as harbouring viruses related to HCV with potential cross-species transmission of variants corresponding to the 7 main genotypes into humans. Although there is tempting analogy between this and the clearly zoonotic origin of HIV-1 from chimpanzees in Central Africa, no published evidence to date has been obtained for infection of HCV-like viruses in either apes or Old World monkey species. Indeed, a radical rethink of both the host range and host-specificity of hepaciviruses is now required following the very recent findings of a non-primate hepacivirus (NPHV) in horses

Contents

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and potentially in dogs. Further research on a much wider range of mammals is needed to better understand the true genetic diversity of HCV-like viruses and their host ranges in the search for the ultimate origin of HCV in humans.

This review is written at a highly significant time in evolutionary studies of HCV and its origins. The discovery of closely related viruses to human HCV in horses and possibly dogs termed non-primate hepacivirus (NPHV) (Burbelo et al. 2012; Kapoor et al. 2011) throws an entirely new light on the species distribution of hepaciviruses and their host range. Despite the significance of these very recent discoveries, however, in many ways it is a particularly difficult time to write a review of HCV origins and evolutionary history. Frequent infection of horses worldwide with a virus reasonably similar to HCV breaks a key assumption of much previous research that the closest relative of HCV would be found in non-human primates. In its place we now have total uncertainty; domestic horses seem an incongruous host species and the suspicion must be that hepaciviruses are much more widely distributed in other mammals. At present, however, we simply do not know what these are. More importantly, we do not know whether viruses more similar to human HCV than NPHV exist and what species these may infect. Discovering a zoonotic source for the epidemic of HCV infection that has swept through the human population in the last century would be a truly important step in our understanding of host relationships, adaptation and pathogenicity.

This review of HCV origins therefore concentrates initially on the better characterised recent epidemic transmission of HCV in the twentieth century and the existence of suspected source areas for infection in sub-Saharan Africa and South-East Area. Some aspects of the much less well understood history of HCV before this recent spread will be speculatively discussed, as will the existence of HCV-like viruses in non-human species. Inevitably any comments made about the latter will, through further research, be revealed as either hopelessly cautious or naively overstated in a very short space of time, errors for which I apologise in advance. However, the findings cannot be simply omitted from a review with this title and I hope that they spur a greater interest in the wider group of hepaciviruses and whether the attributes of HCV that make it such an important human pathogen (persistence and hepatotropism) are shared with other members of the genus.

1 HCV Genetic Diversity and Genotype Classification

HCV is classified as the type member of the genus *Hepacivirus* within the virus family *Flaviviridae* (Fig. 1) (Bukh 1995; Simmonds et al. 1993, 2005). Although variants of HCV show substantial genetic diversity from each other, the 7 currently classified genotypes are all classified as one species under current ICTV rules notwithstanding their considerably antigenic variability and geographical differences in distribution (Simmonds et al. 2011). Until recently, the only other virus classified as a hepacivirus was GBV-B, a virus recovered from a laboratory

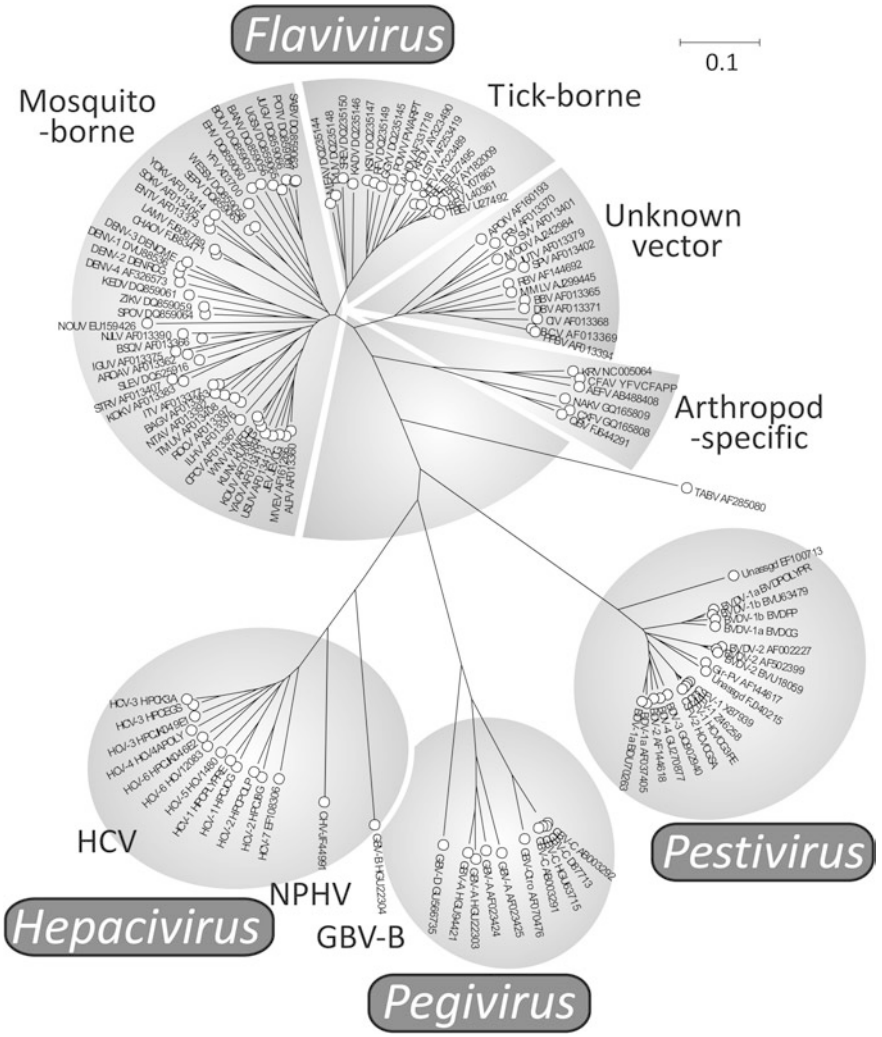

Fig. 1 Phylogenetic tree of members of the family *Flaviviridae* showing its primary division into four genera. The tree was based on comparison of conserved regions of the RNA polymerase sequences (positions 7704–8550 numbered as in the HCV-1 genome, AF011751) from representative variants within each genus and species. The unrooted phylogenetic tree was constructed by neighbour-joining of (uncorrected) amino acid p-distances. A divergence of 0.1 (10 % amino acid sequence divergence) is depicted on the scale bar. Variants variously described as GBV-A, GBV-C and hepatitis G virus have been assigned to the new proposed genus, *Pegivirus* as recently proposed (Stapleton et al. 2011)

housed tamarind [New World primate; (Simons et al. 1995; Muerhoff et al. 1995)]. Only the one isolate of GBV-B has been identified to date and its ultimate origin (primate or non-primate) remains unclear.

Members of the *Hepacivirus* genus are distinct genetically and in genome organisation from members of the recently assigned *Pegivirus* genus (Stapleton et al. 2011) (Fig. 1). This group comprises a number of non-pathogenic viruses infecting humans apes (Adams et al. 1998; Birkenmeyer et al. 1998), non-human primates (Simons et al. 1995) and more recently, bats (Epstein et al. 2010). The recent proposal to re-designate these viruses as human, simian and bat pegiviruses (Stapleton et al. 2011) was designed to dispel the confusion in their original nomenclature (terms such as GB virus C and hepatitis G virus have both been applied to pegiviruses infecting humans) and to differentiate these viruses clearly from GBV-B, a member of the *Hepacivirus* genus.

HCV genotypes are substantially divergent in sequence from each other and fall into 7 phylogenetic clades, designated as genotypes (Fig. 2). Within these, a variable number of sub-groupings are apparent. HCV variants circulating in Western countries have been designated as subtypes, of which 1a, 1b, 2a, 2b, 3a, 4a and 6a are the most frequently identified. HCV subtypes are epidemiologically distinct, with differences in risk group targeting and geographical distributions that reflect their recent epidemic spread. As examples, genotype 3a (along with 1a) typically infects injecting drug users in Northern Europe and 4a in most frequently found in the Middle East. Genotypes

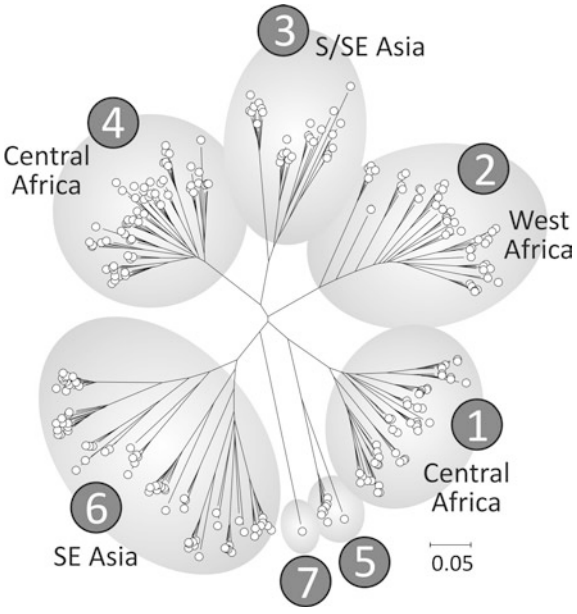

Fig. 2 Evolutionary tree of NS5B sequences of HCV genotypes 1–7 (positions 8276–8615 as numbered as in the H77 reference sequence). High diversity areas in sub-Saharan Africa and South East Asia contain a large number of variants additional to subtypes such as 1a, 1b and 3a found in Western countries, displaying an endemic pattern of diversity. The tree was constructed by neighbour-joining using maximum composite likelihood distances as implemented in the MEGA 4 program (Tamura et al. 2007). The scale bar depicts an evolutionary distance of 0.05

1b, 2a and 2b infections are in contrast most prevalent in older population groups throughout Europe and Asia and are most frequently linked to past blood transfusions.

A distinct pattern of viral diversity is observed in areas such as sub-Saharan Africa and South East Asia, where infections with individual genotype predominate over large geographical areas (such as genotype 1 in Central Africa, genotype 2 in West Africa and genotype 6 in South East Asia), within which there is substantial genetic diversity. The pattern of diversity observed within HCV is thus both the consequence of its very recent epidemic spread into new risk groups, overlaid on top of the much older "endemic" circulation of HCV in sub-Saharan Africa and South East Asia. These different ways to conceptualise "origins" of HCV are discussed in the next two sections.

2 The Recent Spread of HCV

The discovery of HCV in 1989 (Choo et al. 1989) was a remarkable achievement that heralded the use of molecular methods for virus aetiological studies refractory to previously used virus isolation methods. The very active research programme throughout the 1970s and 1980s that culminated in the discovery of HCV was primarily driven by pressing concerns of clinicians and epidemiologists who increasingly recognised chronic non-A, non-B hepatitis associated with blood transfusion and therapy with plasma-derived blood products (Prince et al. 1974; Feinstone et al. 1975; Alter et al. 1975). Since the development of effective diagnostic tests for HCV, the full scale of the spread of HCV became rapidly apparent. It is currently thought that HCV chronically infects 170 million people worldwide, 3 % of the world's population and creates a huge disease burden from chronic progressive liver disease (Pawlotsky 2003; Hoofnagle 2002; Seeff 2002). In addition to recipients of blood transfusion and medical treatment with unsterilised needles, diagnostic screening has identified the extensive spread of infection through needle-sharing drug abuse, an epidemic starting in the 1960s or earlier in Western countries and the primary route of ongoing transmission of infection following the introduction of effective blood donor screening and blood product inactivation steps in the 1990s (Nelson et al. 2011).

Both the time of initial spread of HCV into Western countries and the population dynamics of the epidemic can only be indirectly inferred. However, available evidence is consistent with relatively recent dates for its worldwide spread although it likely preceded the AIDS epidemic by some decades. A lack of samples available for screening collected before the Second World War has prevented a direct demonstration of this hypothesis and reconstruction of the HCV epidemic has been largely based on modelling evolutionary histories of currently circulating variants and by identifying historical factors such as widespread use of blood transfusion and other parenterally delivered treatments and vaccinations that facilitated HCV transmission.

In epidemiological terms, transmission of HCV through sexual contact or from mother to child is inefficient and infrequent (Wasley and Alter 2000; Pradat and Trepo

2000; Thomas 2000). The restriction of HCV transmission through primarily parenteral routes therefore implicates medical treatment with unsterilised needles (including large-scale vaccination programmes), blood transfusion and more recently injecting drug use as routes as the principal means of HCV spread and a relatively recent timescale (Drucker et al. 2001). None of these risk factors were common before the Second World War and supports the current model for the spread of genotypes 1b and type 2 subtypes from the 1940s–1950s, overlaid by more recent transmission among IDUs from the 1960s onwards (Pybus et al. 2001; Cochrane et al. 2002).

This scenario is strongly supported by genetic analysis of HCV genotypes and subtypes most frequently detected among IDUs and those infected previously through medical treatment. A recent large-scale coalescent analysis of 1a and 1b subtypes demonstrated relatively small and constant population sizes for both subtypes from the early twentieth century followed by an exponential period of population growth between the 1940s and 1980s in the USA (Magiorkinis et al. 2009). The slowing of population growth thereafter is additionally consistent with reductions in blood transfusion risk through HIV-1 followed by HCV screening and the expansion of needle exchange programmes that have led to significant falls in HCV incidence among IDUs. Emphasising the global nature of the recent spread of HCV, parallel phylogeographic analyses have revealed similar demographic histories of these subtypes in Brazil, Indonesia and Japan (Nakano et al. 2004). A detailed analysis of reconstructed population sizes of HCV and the emergence of parenteral routes of exposure in Japan Egypt and the USA further strengthens these conclusions (Mizokami et al. 2006), including the close links between HCV emergence and parenteral antischistosomal therapy in Japan and subsequently in Egypt. In the latter, the extremely high population prevalence of HCV is dominated by genotype 4a, whose spread can be reconstructed to have occurred between the 1930s–1950s, a period that coincides with targeted extensive antischistosomal injection campaigns using largely unsterilised injection equipment (Pybus et al. 2003).

Collectively, these and several further combined phylogenetic and epidemiological reconstructions provide a convincing narrative for the spread of HCV worldwide. Although earlier by some decades, its spread is paralleled by the explosive worldwide spread of HIV-1 from Africa from the 1980s onwards leading to the current AIDS pandemic. In one sense, the question of the origins of HCV has likely already been answered. However, where HCV was before then and what factors led to its emergence are much less well understood and are discussed in the next section.

3 Endemic Circulation of HCV

While the epidemic spread of HCV is associated with specific, very prevalent subtypes such as 1a, 1b, 3a and 4a, these represent a small part of the diversity existing with HCV. In sub-Saharan Africa and South East Asia, a quite distinct pattern of genetic diversity exists (Fig. 2). Discounting recent introductions, infections in large, geographically contiguous areas among several countries in Central Africa or the South East Asian peninsula are dominated by individual genotypes

(genotypes 1 and 6 respectively in these examples). Individual variants within these genotypes show striking genetic diversity from each other matching the genetic divergence observed between subtypes such as 1a and 1b found in Western countries. For example, sequence characterisation of genotype 2 variants infecting 23 blood donors in Ghana (West Africa) revealed the presence of 20 highly diverse variants that would merit their assignment as new subtypes, as divergent from each other as 2a is from 2b (≈25 % nucleotide sequence divergence) (Candotti et al. 2003). Although far from fully mapped systematically, infections throughout Western Africa are predominantly by genotype 2 (Candotti et al. 2003; Jeannel et al. 1998; Mellor et al. 1995; WansbroughJones et al. 1998; Ruggieri et al. 1996), while those in Central Africa, such as the Congo, Cameroon and Gabon are by genotypes 1 and 4 (Mellor et al. 1995; Bukh et al. 1993; Fretz et al. 1995; Stuyver et al. 1993; Menendez et al. 1999; Xu et al. 1994; Ndjomou et al. 2003; Li et al. 2009, 2012). Genotype 3 and 6 are typically found in the Indian sub-continent and South East Asia (Mellor et al. 1995; Tokita et al. 1994, 1994, 1995; Lu et al. 2008). It is further suspected, although with very limited data that genotypes 5 and 7 are concentrated in Central/Southern Africa.

The extensive genetic heterogeneity of HCV in these regions has been described as an "endemic" pattern of diversity and is consistent with its long-term presence and diversification in these populations. As such, it is currently hypothesised that they represent source areas fuelling the worldwide spread of HCV in the last 100–200 years. Indeed, the distinct subtypes that have been described in Western countries such as 1a, 1b and 3a might simply represent the explosive expansion of certain variants within new risk groups for infection. Although we do not know and may never be able to reconstruct their ultimate origins and initial transmission pathways, 1a, 1b, 3a and others may simply happen to be the most successful of variants that entered previously unexposed and highly susceptible individuals exposed parenterally. In the same way that HIV-1 subtype B entered and spread within male homosexuals and IDUs in the USA and subsequently in Europe (Gao et al. 1999), our current collection of classified subtype might similarly represent founder viruses that were among the first to spread epidemically in the last century in Western countries where HCV was first genetically characterised.

Supporting this model are the more recently described examples of introductions and varying degrees of local spread of a range of otherwise undescribed "subtypes" of HCV. As examples, substantial diversity and restricted distributions of genotype 2 variants infecting have been described in Europe (Thomas et al. 2007), Indonesia (Utama et al. 2010) and throughout the Caribbean (Sulbaran et al. 2010; Martial et al. 2004), the latter examples in particular perhaps representing the shipment of infected West Africans through the slave trade in the eighteenth and nineteenth centuries (Markov et al. 2009). The more recent spread of genotype 4 variants within Cameron and Egypt through medical treatment (Pybus et al. 2003; Pepin and Labbe 2012), into Mediterranean countries and the recent rapid spread of genotype 4 variants among IDUs in Southern Europe (Nicot et al. 2005; de Bruijne et al. 2009) provide further examples of this model (Ndjomou et al. 2003).

What remains unexplained is the nature of the "endemic" circulation of HCV in these implicated source areas and in particular the transmission routes that have

sustained long-term circulation of HCV in what have been until recently relatively frequently highly isolated human communities. As discussed, transmission by either sexual contact or from mother to child is inefficient at least in areas where it has been studied (Wasley and Alter 2000; Pradat and Trepo 2000; Thomas 2000) and various factors that may enhance transmission have been proposed. Examples include sexually transmitted infections (STIs), circumcision, excision and scarification practices (Shepard et al. 2005) which at least in Central Africa show associations with HCV infection and more remote possibilities such as mosquito or other arthropod vectors (Pybus et al. 2007). These various hypotheses are yet to be resolved.

The time depth of "endemic" circulation of HCV remains similarly uncertain. Molecular evolutionary reconstructions of the recent spread of HCV have produced robust and reproducible estimates of its substitution rate (see previous section). Substitution rates extrapolated to the much larger sequence distances that exist within genotypes (such as between subtypes 1a and 1b) have been used to provide some kind of estimate of the minimum period over which the observed "endemic" diversity developed (Pybus et al. 2001; Markov et al. 2009; Smith et al. 1997; Pybus et al. 2009). Reconstructed dates for the common ancestor of different genotypes vary but are estimated to be several hundred years ago for genotype 2 and even longer for genotype 6. In the opinion of the author of this review, such estimates should be treated with extreme caution and minimum estimates at best. Extrapolating substitution rates measured over short observation intervals to the much longer periods of subtype and genotype diversification makes assumptions about the evolutionary process that are not self-evidently justified. Factors such as extreme rate variation between sites, large-scale RNA secondary structure, greater selective constraints and fitness optimisation of viruses association with large population sizes may create substantial underestimates of the real period of virus diversification [reviewed in (Sharp and Simmonds 2011)]. While it is beyond the scope of the current article to discuss this in detail, what can be said is that the subtype diversification in HCV and thus the likely period of endemic circulation in sub-Saharan Africa and Southern Asia is prolonged and likely long before long distance travel and interactions with colonial powers. These genotypes are therefore likely to be truly indigenous to areas where they currently endemically circulate. This takes us a step further back to the question of the ultimate source of HCV. This much more speculative area will be reviewed in the next section.

4 Origins of Human Infections and HCV Homologues in Other Mammals

A compelling scenario which has driven much research endeavour in the last decade and a half is the hypothesis for a non-human primate source for HCV infections in humans. The theory makes epidemiological sense in that high diversity areas of endemic circulation in humans are those where human, ape and Old World monkey populations overlap. Before long range travel and the means for

wider dissemination, human infections acquired zoonotically from non-human primates may have remained geographically focussed and thus account for the specific association of each of the genotypes in defined areas of sub-Saharan Africa and Southern Asia. The idea of a non-human primate source for humans is additionally consistent with the observation of its poor transmissibility between humans, largely confined to parenteral routes and a reflection perhaps of its lack of host adaptation as might also be its severe, immune-mediated liver pathology.

This model is, of course, also driven by the tempting analogy with the origin of HIV-1, which similarly exploded worldwide out of Central Africa in the twentieth century through infections directly or indirectly from chimpanzees (Gao et al. 1999). As might be imagined for HCV, HIV-1 infections acquired through contact with Central African chimpanzees (*Pan troglodytes*) may have been occurring for centuries or millennia, but only in the last 50–70 years were demographic and societal changes suitable for its wider pandemic spread. Important differences from the HIV-1 model of origins would be the earlier spread of HCV worldwide and the existence of multiple potential source areas and possibly different primate species. These would be necessary to account for the distinct endemic distributions of HCV genotypes in different parts of sub-Saharan Africa and also South East Asia. Finally, into this model would come GBV-B, which might perhaps represent a much more divergent homologue of HCV in a New World primate species.

Despite the elegance, plausibility and potential medical relevance of the primate origin hypothesis, the fundamental problem has always been that HCV or homologues cannot be found in ape or monkey species, at least to the author's knowledge. Extensive screening programmes both published (Makuwa et al. 2003, 2006) and unpublished have failed to document either seropositivity or viral sequences in literally hundreds or thousands of plasma samples collected from different ape and monkey species. As a possibly related problem, GBV-B has to date never been recovered nor serological evidence for past infections obtained from any tamarind or other New World primate among wild populations in South America.

Without an obvious primate source for infection and the genetic evidence for circulation of HCV in what would have been largely isolated human populations in distinct parts of the world for centuries or more likely millennia, studies of the ultimate origins of HCV have reached something of a frustrating impasse. As with many other virus discoveries, however, its resolution is likely to be considerably stranger than could have been imagined even as recently as last year. By pure serendipity, attempts by Kapoor and colleagues to identify viral causes of respiratory disease in dog held in kennels by deep sequencing revealed the existence of an RNA virus extraordinarily similar to HCV (Fig. 3) but with suspected biological and epidemiological properties quite different from what had been previously described for both HCV and GBV-B (Kapoor et al. 2011).

The virus, initially termed canine hepacivirus (CHV) showed approximately 50 % nucleotide sequence divergence from HCV. Data presented in that study demonstrated high viral loads in respiratory samples and an implied respiratory route of transmission and association with respiratory disease, none of which have been observed in HCV (or GBV-B) infections. Infections were found in dogs from

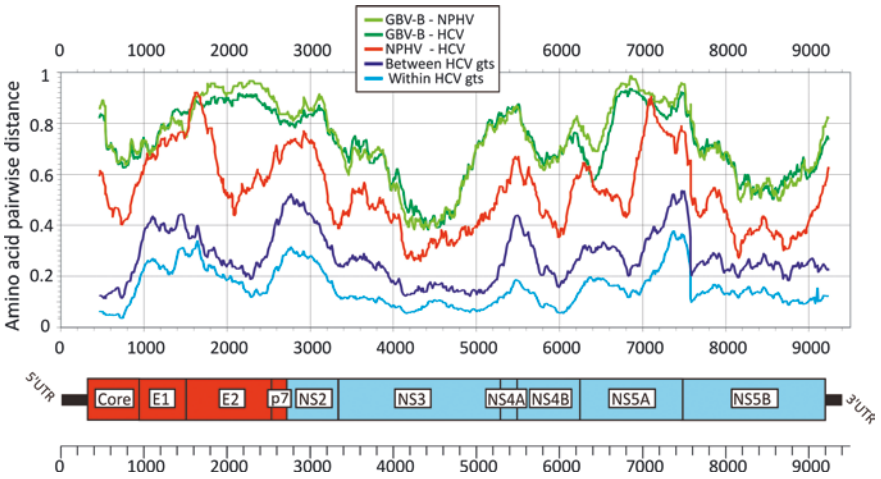

Fig. 3 Amino acid sequence divergence scan of members of the *Hepacivirus* genus, with genome diagram drawn to scale underneath plot. NPHV is more similar to HCV throughout the genome (*red line*) than GBV-B (*dark green line*). However, NPHV/HCV divergence is substantially greater than between genotypes (*dark and light blue lines* respectively). This figure has been adapted from Fig. 2 in (Kapoor et al. 2011). For details related to the HCV polyprotein and the cleavage products see chapter "Hepatitis C virus Proteins From Structure to Function" by Moradpour and Penin, this volume

different regions of the USA but partial genome characterisation demonstrated a virtual absence of genetic diversity that would be expected for an RNA virus like HCV. Whether the virus spread systemically or persisted was not demonstrated although imaging of viral RNA in liver by in situ hybridisation was presented.

More recently, further studies of the host range of hepaciviruses in a range of mammalian species were performed by the same group using a serological assay for antibodies to a peptide expressed from the NS3 region of the CHV genome (Burbelo et al. 2012). This produced further unexpected findings. From the 80 dogs, 81 deer, 84 cows, 103 horses and 14 rabbits screened, only horses showed frequent seropositivity (35 %) with one weak positive sample from a cow while, remarkably, all 80 dogs were seronegative. Of the 103 horse samples, 8 were PCR-positive (all seropositive) and from each of these near-complete genome sequences were obtained. Sequences showed moderate sequence diversity from each other (6.4–17.2 % nucleotide sequence divergence) with the CHV sequence grouping with horse-derived variants. As viruses similar to CHV were frequently found in horses, the investigators coined the name NPHV to describe this group.

The diversity of NPHV variants was somewhere between inter-subtype and within subtype divergence of HCV, certainly not the equivalent of HCV genotypes (Fig. 3). The high degree of amino acid sequence conservation did, however, contrast markedly with the degree of sequence variability at synonymous (non-coding) sites in the genome. The extraordinarily low ratio between synonymous to non-synonymous

substitutions (0.03–0.06) indicates however that its evolution has been more severely constrained and/or less subject to positive selection pressures than HCV. These low sequence distances are therefore not necessarily an indication of their recent divergence.

There was no information available on the clinical features of infection with NPHV in horses. To address this we have recently surveyed horses in Scotland by PCR and identified 3 viraemic horses from 136 screened (Lyons et al. 2012). Using veterinary records and further sampling, these have been evaluated for evidence of hepatitis or other systemic disease manifestations. Positive horses were originally referred for reasons such as lameness, foot abscess or respiratory infections with no evidence of the ill-health that might be associated with severe systemic infections. Although most liver indices were in the normal range, gamma glutamyl transferase (GGT) levels, a sensitive marker of liver inflammation were marginally or significantly elevated along with elevation in bile acids, perhaps providing some tentative evidence for an aetiological role of NPHV in hepatitis. Repeated sampling from one of the study horses demonstrated persistence over at least a 6-month period and viral loads comparable to those observed in HCV infections (7×10^4–5×10^7 RNA copies/ml). Respiratory samples and peripheral blood mononuclear cells from the infected horse have proven uniformly negative although no opportunity to perform a liver biopsy of the horse has yet presented itself. Overall, these more recent findings provide some reassurance that hepacivirus infections in horses are both persistent and potentially associated with mild liver disease rather than the respiratory disease and viral secretion found originally in dogs. However, large-scale PCR-based screening of other mammalian species using primers conserved between NPHV and HCV failed to detect hepaciviruses in dogs (nearly 200 screened), cats, pigs and rodents (Lyons et al. 2012), very much as found in the previous serology-based study (Burbelo et al. 2012).

This, to date, represents current published knowledge of non-human hepaciviruses, a series of findings that present several conflicting interpretations and difficulties. This author believes that, despite the negative results from screening so far, domestic horses are most unlikely to be the only mammalian species (other than human or tamarins) infected with hepaciviruses and there is clearly much to be learned in short term from more extensive screening.

5 Concluding Thoughts

Our understanding of the ultimate origins of HCV infection in humans will doubtless be hugely enhanced once proper mammalian screening for other hepaciviruses has been performed and the genetic diversity and, more importantly, the specificity of different hepaciviruses to individual host species is more clearly established. From such studies, it may well turn out that hepaciviruses are highly catholic in their host range perhaps capable of jumping between horses and dogs as suggested by the published screening data (Burbelo et al. 2012; Kapoor et al. 2011) and perhaps all species in-between. An ability of hepaciviruses to jump species is consistent

with the observation that the NPHV protease is able to cleave human MAVS and TRIF (Parera et al. 2012); this ability to prevent interferon signalling is essential for HCV replication (Foy et al. 2005) and may therefore function across species barriers and potentially favour zoonotic transmission. A wide mammalian host range is also characteristic of vector-borne flaviviruses and pestiviruses, the latter at least within ruminant species. In this scenario, HCV infections in humans may well have a zoonotic origin consistent with its relatively recent emergence (at least in Western countries). While being still relatively poorly adapted for infecting its new host, this may further account for its peculiar, inefficient transmission routes.

Alternatively, it may be that each hepacivirus species is uniquely adapted to one target species, HCV in humans, NPHV in horses and perhaps further hepaciviruses in other mammalian species waiting to be discovered. The ability of HCV to persist lifelong in humans, an attribute that greatly enhances its transmissibility and evidence for subtle virus/host interactions such as the enhancing role of human micro RNA, miR-122 expressed in liver on virus replication (Jopling et al. 2005) certainly hints at long-term virus/host co-adaptation. HCV may always have infected humans throughout their evolution and it is only through greater life expectancy, scope for epidemic transmission and better surveillance and understanding of causes of hepatitis that it has come to current medical attention. In that sense, HCV does not have an "origin", it is just one of those viruses like herpesviruses that have always infected humans and before them hominoids, proto-apes and potentially right back to the ancestor of mammals themselves.

Future research will be truly important in resolving these two diametrically opposed possibilities.

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