An update on circulating Hepatitis delta virus genotypes in Australia

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Background

Hepatitis delta virus (HDV) is a small satellite RNA virus which requires the presence of the HBsAg in order to propagate and therefore infects only individuals infected with HBV.

HDV infection may occur simultaneously with HBV, or later as a superinfection. Recent estimates have suggested 12 million individuals have been infected with HDV, with prevalence and genotype distribution varying globally [1].

A previous study has shown three out of eight recognised HDV genotypes circulated in Australia from 2010 to 2016; genotype 1 (80.5%), genotype 5 (16%), and genotype 2 (3.5%) [2]. This current study expands on this knowledge and assesses the distribution of HDV genotypes over the period of 2017 to 2024.

Methods

Patient samples from across Australia were sent to VIDRL for HDV RNA testing; positive samples were then reflexed to HDV genotyping, if not previously performed at earlier collection points.

A region spanning the hepatitis D virus large antigen region was amplified and characterised by population-based sequencing to determine genotype. 167 patient HDV sequences were aligned with 65 representative HDV sequences from Genbank using MAFFT. A maximum likelihood phylogenetic tree was constructed using the GTR + G + I substitution model with 1,000 bootstrap replicates using MEGA v12.

HDV Genotype Distribution

The predominant HDV genotype in Australia (Table 1) is HDV Genotype 1, which has a global distribution. This is followed by genotype 5, then genotype 2, which are largely seen in Africa and Asia, respectively. The majority of patients infected with HDV in Australia are male.

	2010-2016	2017-2024	Total
Genotype 1	**136** (80%)	**141** (84%)	**277** (82%)
Genotype 2	**6** (4%)	**6** (4%)	**12** (4%)
Genotype 5	**27** (16%)	**20** (12%)	**47** (14%)
Total	**169** (69% male)	**167** (74% male)	**336** (72% male)

Table 1. HDV genotype distribution across Australia.

Twenty-three samples were received from correctional facilities over the period 2017-2024, of which 21 were HDV genotype 1 (16 from NSW, 5 from VIC), many of which cluster closely with other samples from correctional facilities (see Fig. 2). Further analysis may identify if these are related to incarcerated persons in the earlier study.

HDV Phylogenetic Analysis

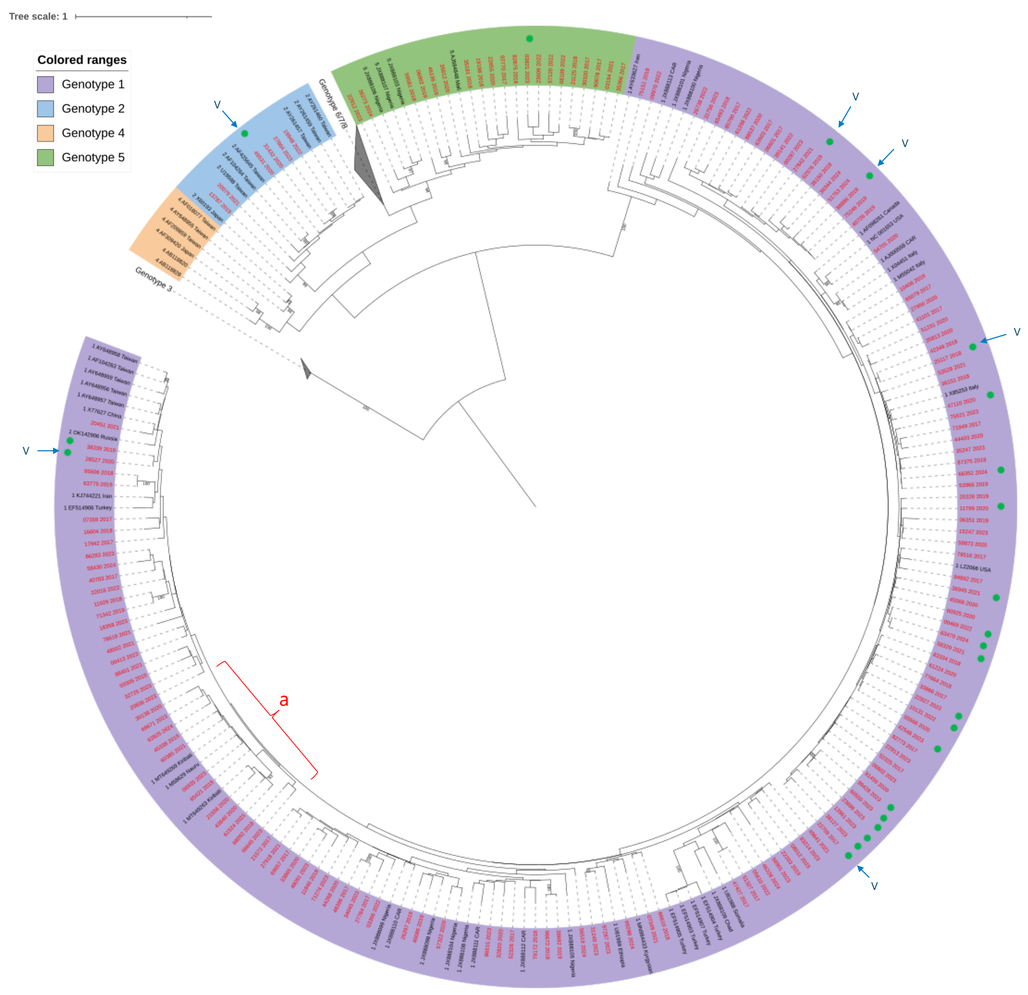

Figure 1. A maximum likelihood phylogenetic tree of the hepatitis D virus (HDV) large antigen region (421nt) showing the inferred relationship between the HDV sequences isolated from this study, and HDV sequences of known genotypes retrieved from Genbank. The tree was constructed using the model GTR + G + I, and branches are annotated with bootstrap support (1,000 replicates). Significant bootstrap values (>90%) are included. Accession numbers and country of origin of the sequences downloaded from Genbank are indicated on the tree. Genotypes are indicated by colour. The HDV sequences from this study are depicted in red. Individuals from correctional facilities are highlighted with a green dot. CAR, Central African Republic.

Whilst there is a high level of diversity in HDV, particularly within HDV-1, there are some areas of the tree that are more genetically related than others and may be of further interest.

Ten patients cluster closely with sequences from the Pacific Islands (Fig 2; a); of these 2 are residents of Pacific Islands. Six of the remaining patients reside in QLD, which itself has a high number of people of Pacific Island ethnicity.

Of the non-HDV-1 patients, six are HDV-2, which is a common genotype in South-East Asia, and 20 are HDV-5, which has origins in Africa. When looking at the state of residence, there is no difference between the distribution of these genotypes when compared to the overall study.

Epidemiological data is not included on referrals to VIDRL, and when analysing data from the phylogenetic tree, any inferred ethnicity would be an assumption. However, all patients with HDV-2 have surnames which indicate they are of South-East Asian origin and 80% of patients with HDV-5 surnames common to African nations.

There is more diversity seen in VIC correctional facilities (annotated with 'v' on map) than in NSW, potentially indicating transmission is occurring more frequently in NSW prisons.

Discussion

The distribution of HDV genotypes seen within Australia is likely a reflection of immigration patterns in Australia, alongside local transmission in PWID. The relevance of HDV genotypes is not well understood and may need to be assessed alongside host factors to determine an individual's response to treatment [3]. There is a low level of discrimination within HDV genotypes, however further classification into subtypes may allow for predicting disease progression [4].

Even without subtype classification, our phylogenetic analysis has shown distinct clusters which we may be able to further assess. For example, we have shown that a group of Australian patients cluster with a distinct subset of HDV-1, previously identified as the Pacific clade [5]. Further investigation of other clusters may link sequences with other distinct geographical areas. Epidemiological information such as country of birth would strengthen our data set and could lead to further studies with the aim to assess treatment response in Australian patients.

We have the capacity to perform contact tracing and investigate transmission when required. This may be of interest in settings such as correctional facilities, as close associations can be seen, particularly in samples received from NSW.

Once discrimination of HDV subtypes and the associated patient outcomes are better understood, there is the potential that clinicians will be seeking this data for their patients' care, and there may be a stronger case for HDV testing to be covered by Medicare.

By analysing the data over the period 2017-2024, and combining with the data accrued from 2010-2016, we have expanded our understanding of the genotypes currently circulating in Australia.

References

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