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**Human parechovirus cluster in the UK, 8 May to 2 August 2016 – sequence analysis**

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**Highlights**

- Human parechovirus 3 (HPEV 3) was detected in a UK cluster of neonatal sepsis
- These UK HPEV sequences clustered closely with others from Europe and Australia
- As with enteroviruses, HPEV should be included in routine hospital diagnostic testing
- Currently not all commercially available PCR kits routinely include HPEV as a target

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**Dear Editor,**

We recently described an unexpected cluster of human parechovirus (HPEV) cases involving hospitalised neonates and infants (n=26) presenting with symptoms of sepsis in population in the Midlands, UK [1].

Briefly, HPEV usually causes self-limiting, mild gastroenteritis and respiratory infections, though more severe neurological and cardiovascular complications are possible [2]. In this population, HPEV RT-PCR testing on cerebrospinal fluid (CSF) was part of the routine septic work-up for any neonate or infant admitted to hospital presenting with any combination of fever, lethargy or drowsiness, rash, poor-feeding, tachycardia or irritability. In this cluster occurring between May and August 2016 there were 15 male and 11 female neonatal or infant cases (aged 8-197 days, median 47 days) [1]. The CSF PCR testing was

performed using a combination of multiplex PCR assays: a commercial polymerase chain reaction (PCR) assay for the detection of enterovirus and HPEV (FTD EPA, Fast-track diagnostics Ltd, Sliema, Malta), and in-house assays for the other targets (herpes simplex virus 1 and 2, varicella zoster virus) [3,4]. No other viral CNS infections were detected in any of the HPEV-positive cases.

Since then we have sequenced a region of the HPEV genome covering the VP3-VP1 junction from those samples with sufficient concentration of viral RNA to allow PCR amplification of this region, using a previously described protocol [5].

In total seven (3 males, 4 females) of the 26 CSF samples were successfully sequenced (GenBank accession numbers MF136612 to MF 136618). Four of the HPEV sequences from cases in our cluster formed a monophyletic clade with good branch support (SH-like test support value 0.94, **Fig 1**). Two HPEV virus sequences clustered closely with 2015 CSF HPEV sequences from an outbreak in neonates with fever and diarrhoea in Queensland, Australia [8], and the remaining sequence clustered closely with a diagnostic 2014 serum HPEV sequence from Austria [9], which also included some older 2010 CSF HPEV sequences from Scotland [10]. All of these viruses belonged to HPeV genotype 3, which is the genotype most commonly associated with human disease in this age group [11, 12].

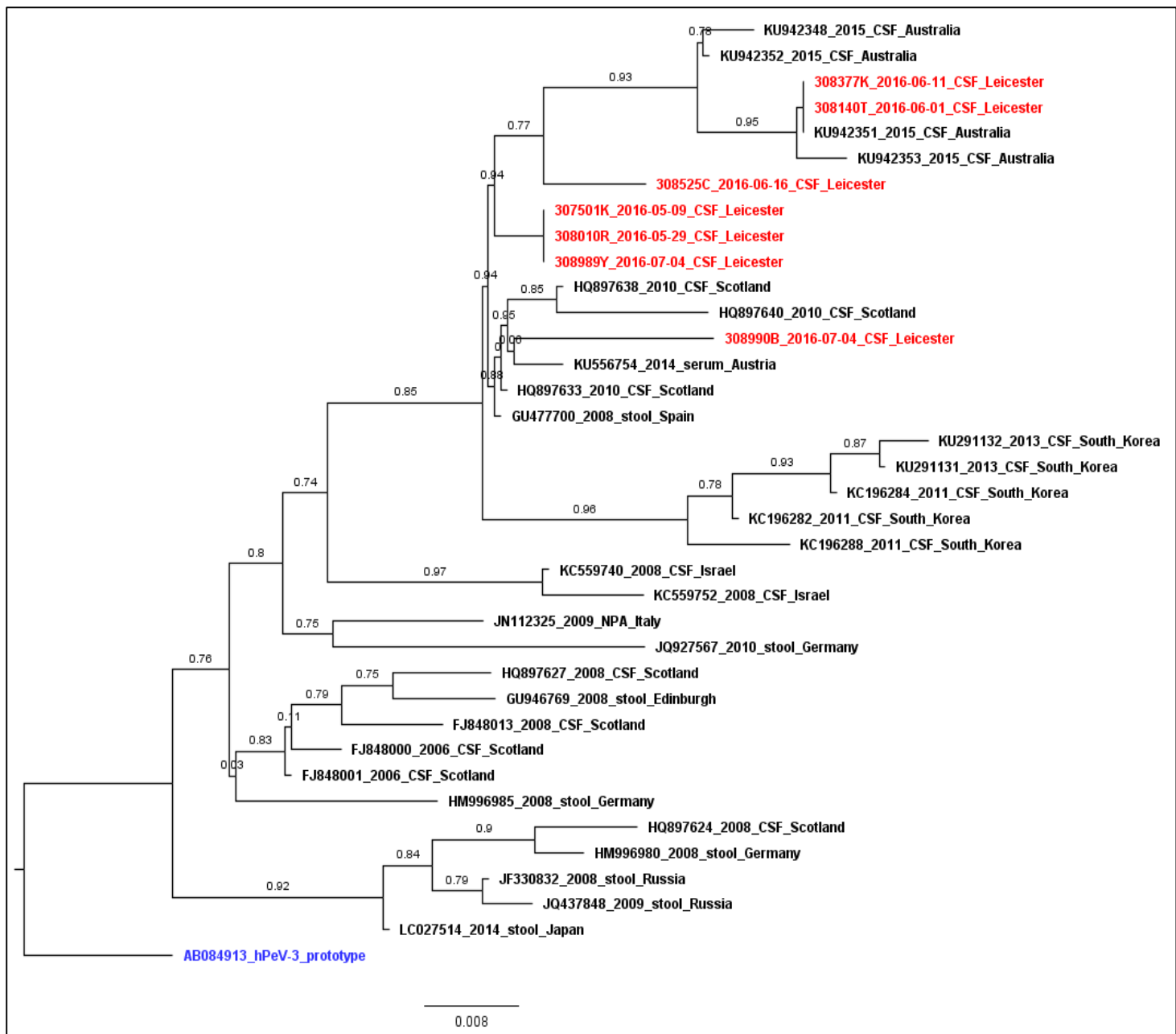
This and other studies [2, 5, 9-12] clearly demonstrate the importance of HPEV as a cause of neonatal and infant sepsis, and this virus should be screened for (along with enteroviruses) routinely in such cases presenting hospital. Commercial kits are now available for such testing. Many of these cases are diagnosed on CSF samples but stool and blood samples are also useful clinical sample types to detect HPEV infection, which may also be taken routinely as part of the septic work-up in these very young children. Although the management of such cases is mainly supportive, as there are no specific antivirals (though intravenous immunoglobulin may be helpful [13]), a diagnosis of HPEV infection as the cause of sepsis, where no other pathogen is detected, may reduce the use of unnecessary antimicrobials. In addition, due to the mostly self-limiting nature of HPEV infections, early discharge home is possible once a diagnosis of HPEV infection has been made, as was the case in our cluster [1].

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**Fig 1.** Maximum likelihood tree of 7 HPEV sequences (256 bp covering the VP3-VP1 junction of the polyprotein gene obtained from the CSF of these neonatal and infant patients from Leicester 2016 and representative HPEV sequences from the NCBI GenBank database. Sequences were aligned and edited in BioEdit v.7.2.5 [6] to a final length of 256 bp. The phylogenetic tree was drawn using FastTree v.2.1.7 SSE3 [7] under a GTR model of evolution with Shimodaira-Hasegawa (SH-like) test for branch support.