Genome Immunobiology RIKEN Hakubi Research Team
RIKEN Hakubi Team Leader: Nicholas Parrish (M.D., Ph.D)

(0) Research field

CPR Subcommittee: **Biology**

Keywords: Endogenous viral elements,
Viral immunity, Genome engineering, Transposon

(1) Long-term goal of laboratory and research background

My research focuses on virus-host symbioses established upon integration of viral genetic material into the genome of the host. This has been a significant driver of human genome evolution, as over 50% of the human genome is derived from endogenous retroviruses and other mobile genetic elements. My team is currently studying host-integrated viral sequences derived from two human pathogens which do not encode integration enzymes; thus host-derived machinery was required for integration of these viral sequences into our genome: Borna disease virus, a recently emerging cause of human encephalitis, and human herpesvirus 6, a ubiquitous human pathogen responsible for roseola in infants and implicated in a number of serious neurological disorders including multiple sclerosis. The goal of my research is to understand and harness mechanisms of natural human genome plasticity for new treatments and resistance to disease.

(2) Current research activities (FY2021) and plan (until Mar. 2025)

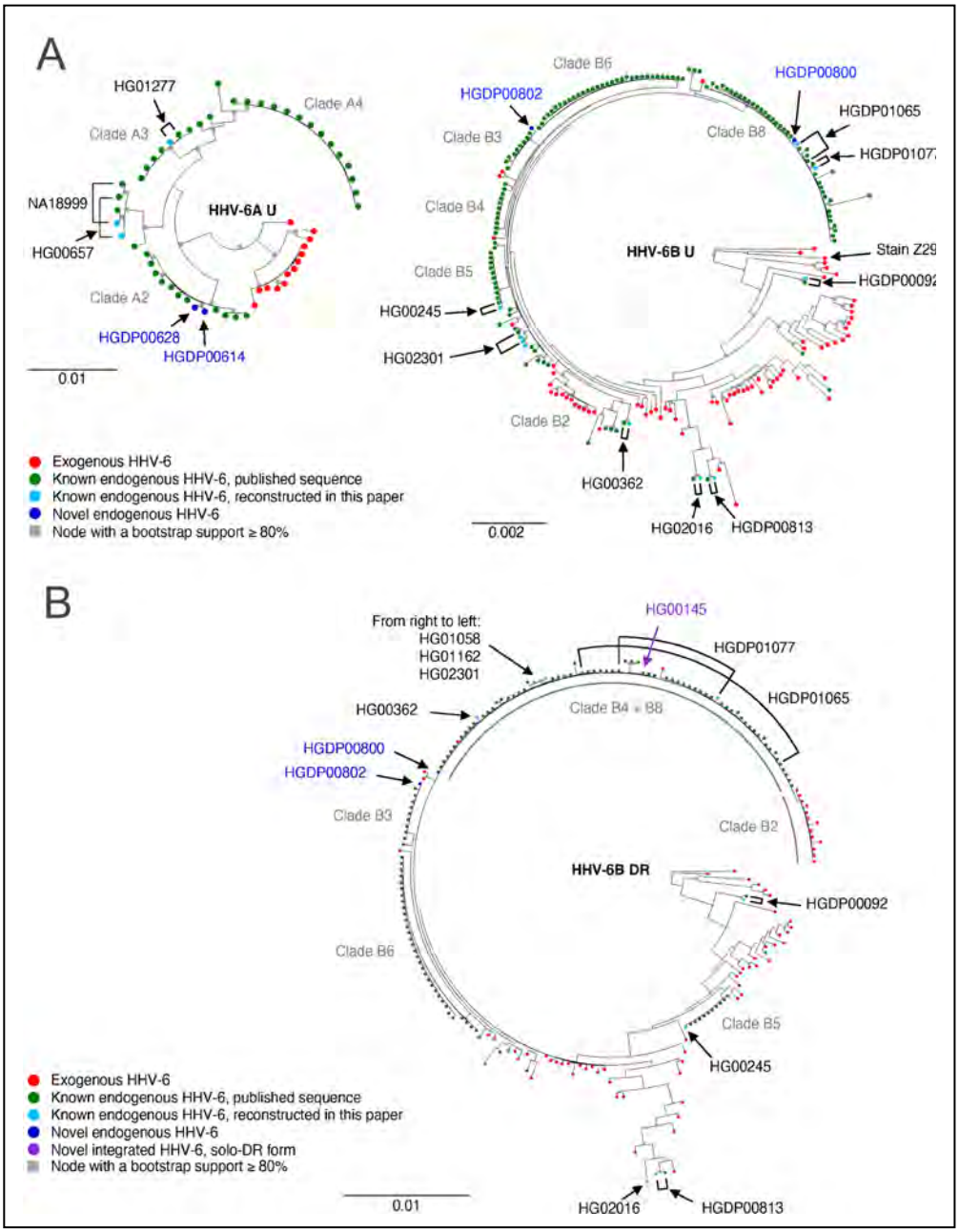
We study endogenous viral elements (EVEs), which are viral sequences that have become integrated into the genomes of their hosts. We are especially interested in how mammalian EVEs function in antiviral immunity. EVEs are often transcribed and processed into small RNAs called piRNAs, which can guide RNA interference (RNAi) against complementary sequences. We are testing if piRNA-guided RNAi functions as antiviral immunity in eukaryotes, similar to the CRISPR/Cas adaptive immune system in prokaryotes. We previously showed that EVEs present in mouse and human genomes called endogenous bornavirus-like nucleoprotein elements (EBLNs) are transcribed and processed into piRNAs (Parrish NF et al., *RNA*. 2015). While piRNAs are known to guide RNAi against transposons, they have not been shown to function in antiviral immunity against exogenous viruses in mammals. Recent results suggest that piRNAs are involved in immunity to human herpesvirus 6 (HHV-6) (Liu S et al., *Cell*. 2018). Intriguingly, the HHV-6 genome sequence can be found in about 1% of all humans' germline genome; we have recently determined that these sequences are also EVEs, having stably co-evolved with human chromosomes since prehistory. We have termed this phenomenon "endogenous HHV-6" (eHHV-6) and have performed the most comprehensive analysis of such sequences using whole genome sequencing data from global populations (Fig 1, taken from Kojima S et al., *PLoS Genetics.* 2021).

We are testing for interactions between viruses and their related EVEs in mammalian genomes using two systems: 1) Borna disease virus/EBLNs and 2) human herpesvirus 6/endogenous human herpesvirus 6. We have engineered mutant mice which lack piRNA-generating EBLNs and will soon challenge them with Borna disease virus. We have knocked-in sequences from modern Borna disease virus into piRNA-generating loci, to simulate the acquisition of a new EBLN-like EVE; we hypothesize these mice will show heightened resistance to Borna disease virus.

We have undertaken bioinformatic studies of the distribution and evolutionary patterns of eHHV-6 in diverse humans, focusing on Japanese individuals sampled in the BioBank

Japan project. We are studying how these EVEs influence human genome structure and gene expression using cell lines and tissues from subjects who carry endogenous HHV-6. Finally, we are studying diverse human genomes on large scales, up to 100,000 whole genome sequences, to find previously-undetected genetic variants related to viruses. We will determine if these variants influence variation in human phenotypes including disease risk (Kojima et al., *bioRxiv* 2022).

F i g . 1 Phylogenetic analysis of HHV-6 and eHHV-6



A) Phylogenetic trees inferred from Unique (U) regions of HHV-6A and B. The publicly available sequences of endogenous and exogenous HHV-6 as well as ones reconstructed in the present study were used. B) Phylogenetic tree inferred from Direct Repeat (DR) regions of HHV-6B. The publicly available sequences of endogenous and exogenous HHV-6B, as well as ones reconstructed in the present study, were used. B, C. Clade names defined in the phylogenetic analysis in Aswad et al. are shown.

(3) Members as of Aug, 2022

(RIKEN Hakubi Team Leader)
Nicholas Parrish
(Postdoctral Researcher)
Rie Koide
(Special postdoctoral researcher)
Steven Heaton, Shohei Kojima
(Part-timers, Master's course student and Undergraduate Students)
Yuka Saito, Kei Hayakawa, Taichi Harimoto
(Technical Staff)
Asami Fujii,

(4) Representative research achievements

1. "Virus-derived variation in human genomes." Kojima, S., Kamada, A.J., Parrish, N.F. *PLoS Genetics* (2021) 17(4): e1009324.
2. "Comprehensive discovery of CRISPR-targeted terminally redundant sequences in the human gut metagenome: Viruses, plasmids, and more." Sugimoto, R., Nishimura, L., Nguyen, P.T., Ito, J., Parrish, N.F., et al. (2021) *PLOS Computational Biology* 17(10): e1009428.
3. "Mammalian antiviral systems directed by small RNA." Takahashi, T., Heaton, S.M., Parrish, N.F. (2021) *PLOS Pathogens* 17(12): e1010091.
4. "A hominoid-specific endogenous retrovirus may have rewired the gene regulatory network shared between primordial germ cells and naïve pluripotent cells." Ito, J., Seita, Y., Kojima, S., Parrish, N.F., et al. (2022) *PLOS Genetics* 18(5): e1009846.
5. "Mobile elements in human population-specific genome and phenotype divergence." Kojima, S., Koyama, S., Ka, M., Saito, Y., Parrish E.H., Endo, M., Takata, S., Mizukoshi, M., Hikino, K., Takeda, A., Gelinas, A.F., Heaton, S.M., Koide, S., Kamada, A.J., Noguchi, M., Hamada, M., Biobank Japan Project Consortium, Kamatani, Y., Murakawa, Y., Ishikagi, K., Nakamura, Y., Ito, K., Terao, C., Momozawa, Y., Parrish, N.F. (2022) *bioRxiv* https://doi.org/10.1101/2022.03.25.485726.

Laboratory Homepage

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