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 (FY2020) and plan (until Mar. 2025)

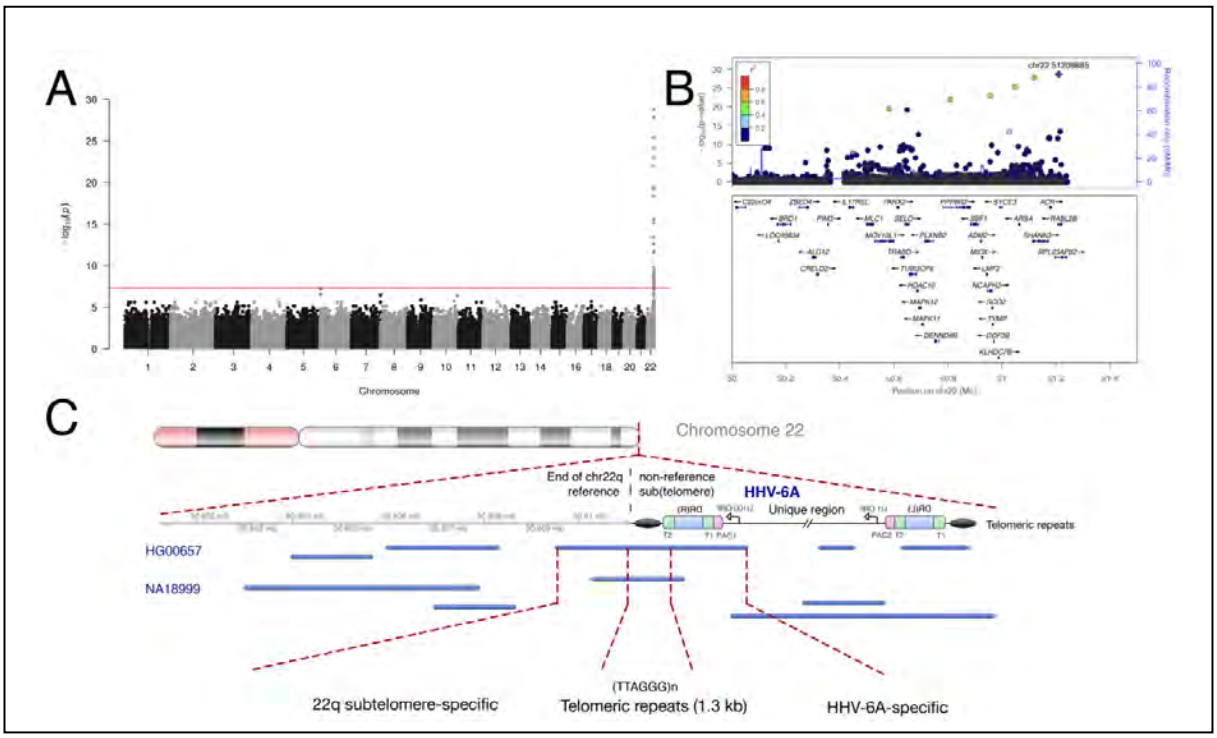
We study endogenous viral elements (EVEs), which are viral sequences that have become integrated into the genomes of their hosts. We are interested in how mammalian EVEs function in antiviral immunity. EVEs are often transcribed and processed into small RNAs called piRNAs, which can guide RNA interference (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 (Fig 1, taken from Liu X et al., *PLoS Genetics*. 2020).

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 this EVE 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.



F i g . 1 **An HHV-6A-derived EVE is integrated on chromosome 22q in East Asians.**
A) Manhattan plot showing an association between variants on distal chromosome 22q and Biobank Japan (BBJ) subjects who carry integrated endogenous HHV-6A (N = 12).
B) Regional association plot of the chromosome 22q region demonstrates that strength of association increases with proximity to the telomere, the preferred site of HHV-6 integration.
C) Long-read sequencing confirms integration of endogenous HHV-6A in chromosome 22q telomeric heterochromatin. Mapping of individual Oxford Nanopore sequencing reads (blue lines) to the chr22q reference sequence and to HHV-6A is depicted. Reads were obtained from lymphoblastoid cell lines derived from two East Asian subjects with HHV-6A-derived EVE. Reads that span the EVE integration site are highlighted.

(3) Members as of March, 2021

(RIKEN Hakubi Team Leader)
Nicholas Parrish
(Postdoctral Researcher)
Anselmo Jiro Kamada, Rie Koide, Shohei Kojima
(Special postdoctoral researcher)
Steven Heaton
(Technical Staff)
Asami Fujii, Erica Hammaker Parrish

(4) Representative research achievements

1. "Endogenous retroviruses drive species-specific germline transcriptomes in mammals." Sakashita, A., Maezawa, S., Takahashi, K., Alavattam, K.G., Yukawa, M., Hu, Y-C., Kojima, S., Parrish, N.F., Barski, A., Pavlicev, M., and Namekawa, S.H. *Nature Structural and Molecular Biology.* (2020) 27(10) pp.967-977.
2. "Endogenization and excision of human herpesvirus 6 in human genomes." Liu, X., Kosugi, S., Koide, R., Kawamura, Y., Ito, J., Miura, H., Matoba, N., Matsuzaki, M., Fujita, M., Kamada, A.J., Nakagawa, H., Tamiya, G., Matsuda, K., Murakami, Y., Kubo, M., Sato, K., Momozawa, Y., Ohashi, J., Terao, C., Yoshikawa, T., Parrish, N.F., Kamatani, Y.

PLoS Genetics (2020) 16(8): e1008915.
3. "Chromosomally-integrated human herpesvirus 6 and autoimmune connective tissue diseases." Kojima, S., Parrish, N.F., Terao, C. *Journal of Clinical Virology.* (2021) 134: e104714.
4. "Virus-like insertions with sequence signatures similar to those of endogenous non-retroviral RNA viruses in the human genome." Kojima, S., Yoshikawa, K., Ito, J., Nakagawa, S., Parrish, N.F., Horie, M., Kawano, S., Tomonaga, K. *Proceedings of the National Academy of Sciences, United States of America.* (2021) 118(5): e2010758118.
5. "Virus-derived variation in human genomes." Kojima, S., Kamada, A.J., Parrish, N.F. *PLoS Genetics* (2021) 17(4): e1009324.

Laboratory Homepage
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