Decoding sequence recognition code of nucleic acid-binding proteins of human-infecting DNA viruses

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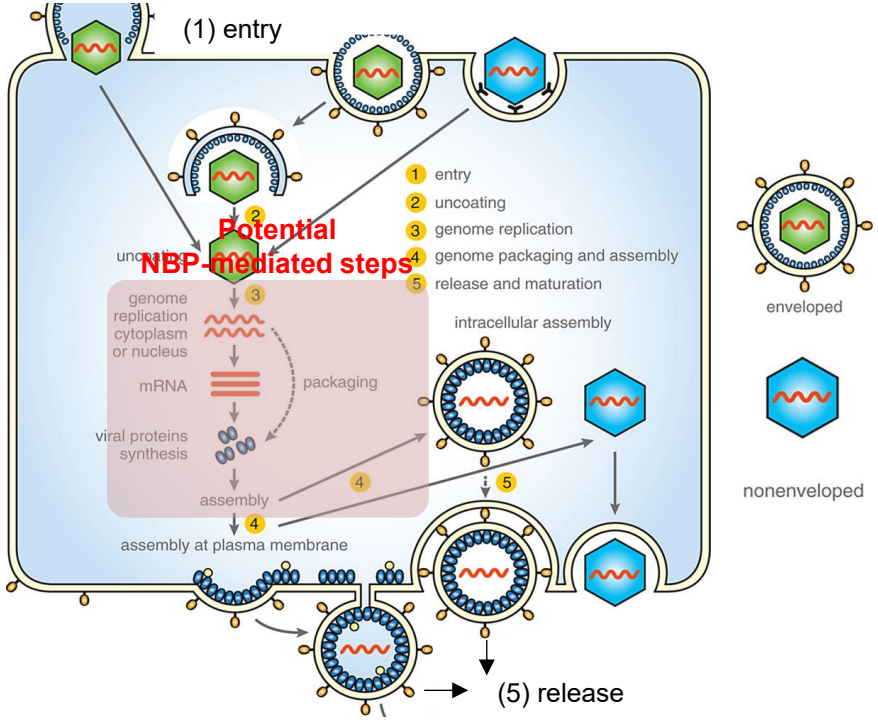
https://doi.org/10.1002/imt2.70170

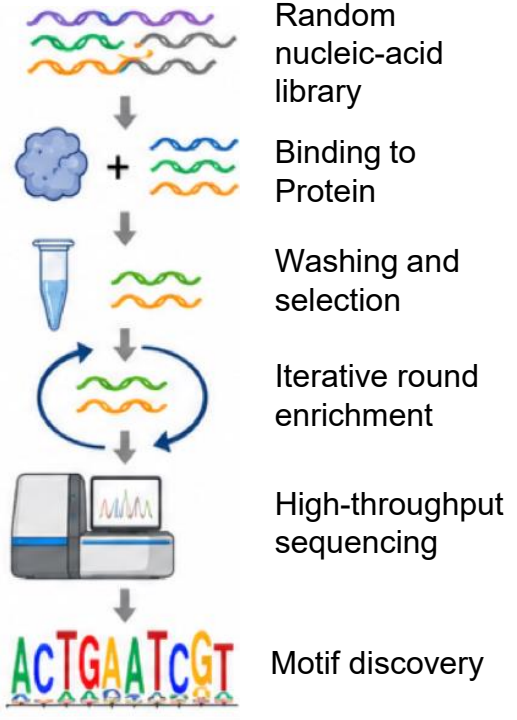
Background

1 Viral Genome Recognition and Packaging Are Key Steps in the Viral Life Cycle



Rumlová, M., et al. ***Biotechnology Advances***, 2018.

2 SELEX enables systematic motif discovery



Jolma, A. et al. ***Cell***. 2013.

3 Current limitations

- DNA-binding specificity has been characterized for **only a few DNA viral proteins**.
- **Systematic profiling** of NBP–DNA recognition across human-infecting DNA viruses **remains lacking**.

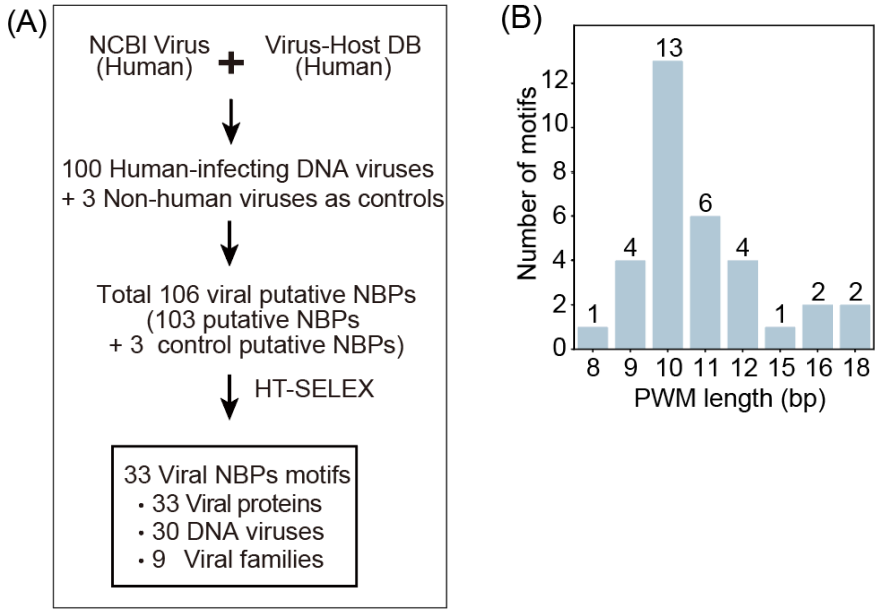
NBPs, nucleic acid-binding proteins

Scientific Question

What are the DNA recognition specificities of human-infecting viral NBPs?

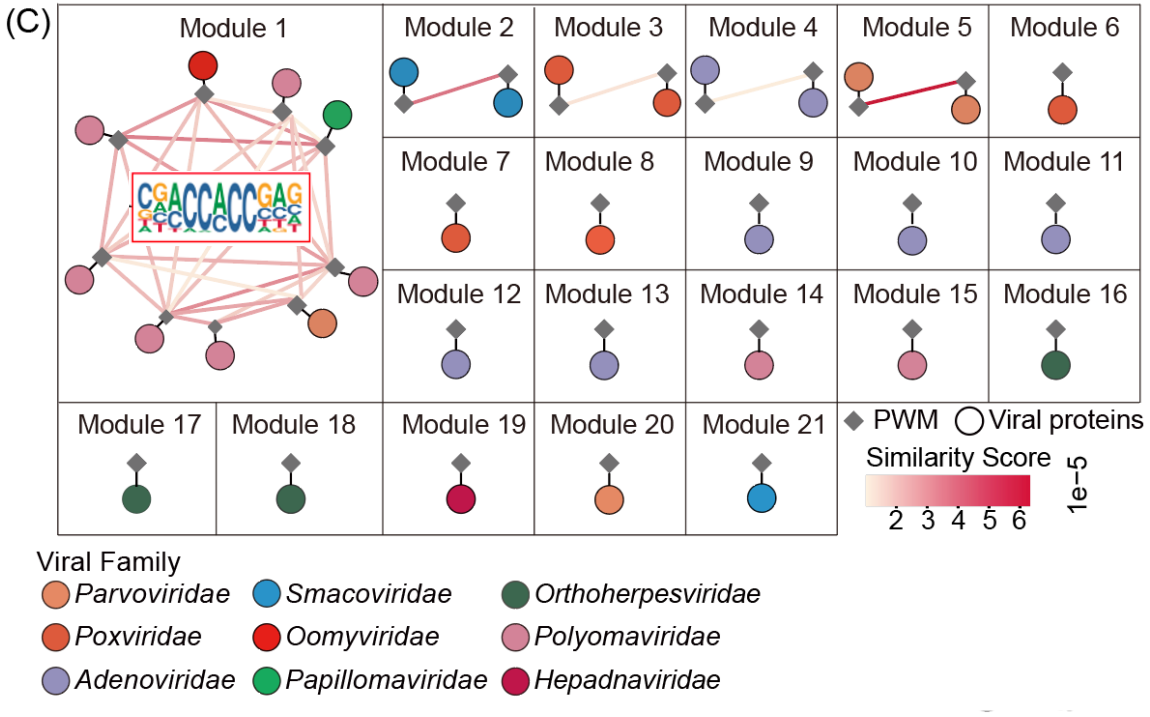
Systematic HT-SELEX Profiling of Human-infecting DNA Viral NBPs

1 Systematic HT-SELEX Profiling



HT-SELEX, High-throughput Systematic Evolution of Ligands by Exponential Enrichment

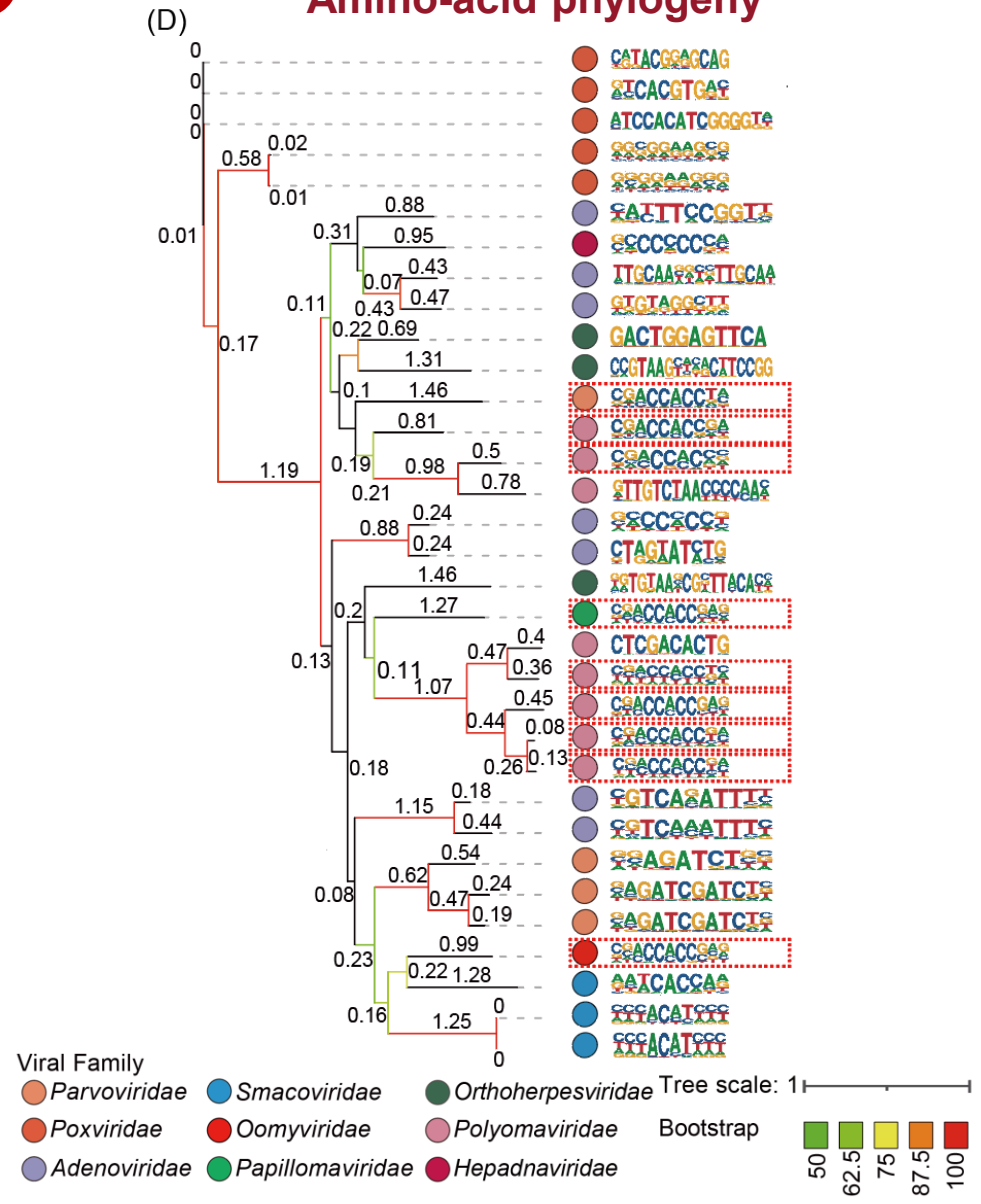
2 Motif similarity network



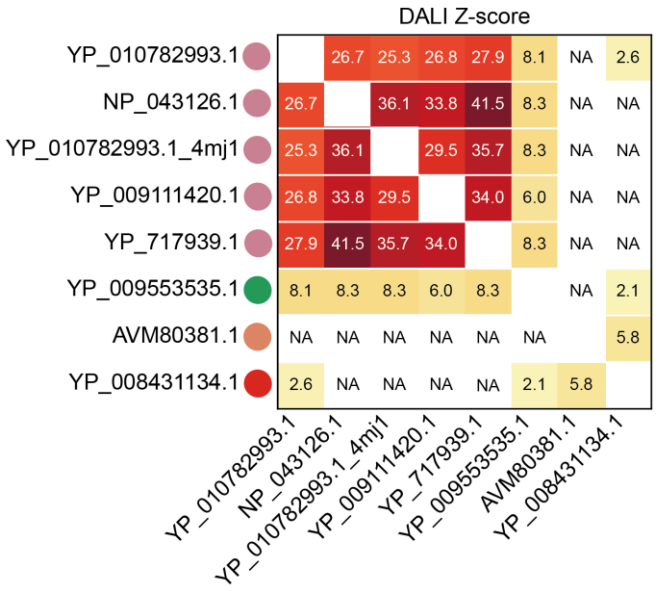
Module 1 clusters 9 NBPs from diverse viral families sharing a conserved CCACC core motif.

Divergent and Convergent DNA-Recognition Patterns

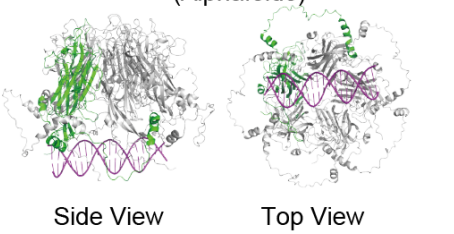
1 Amino-acid phylogeny



2 Predicted structural similarity



(E)



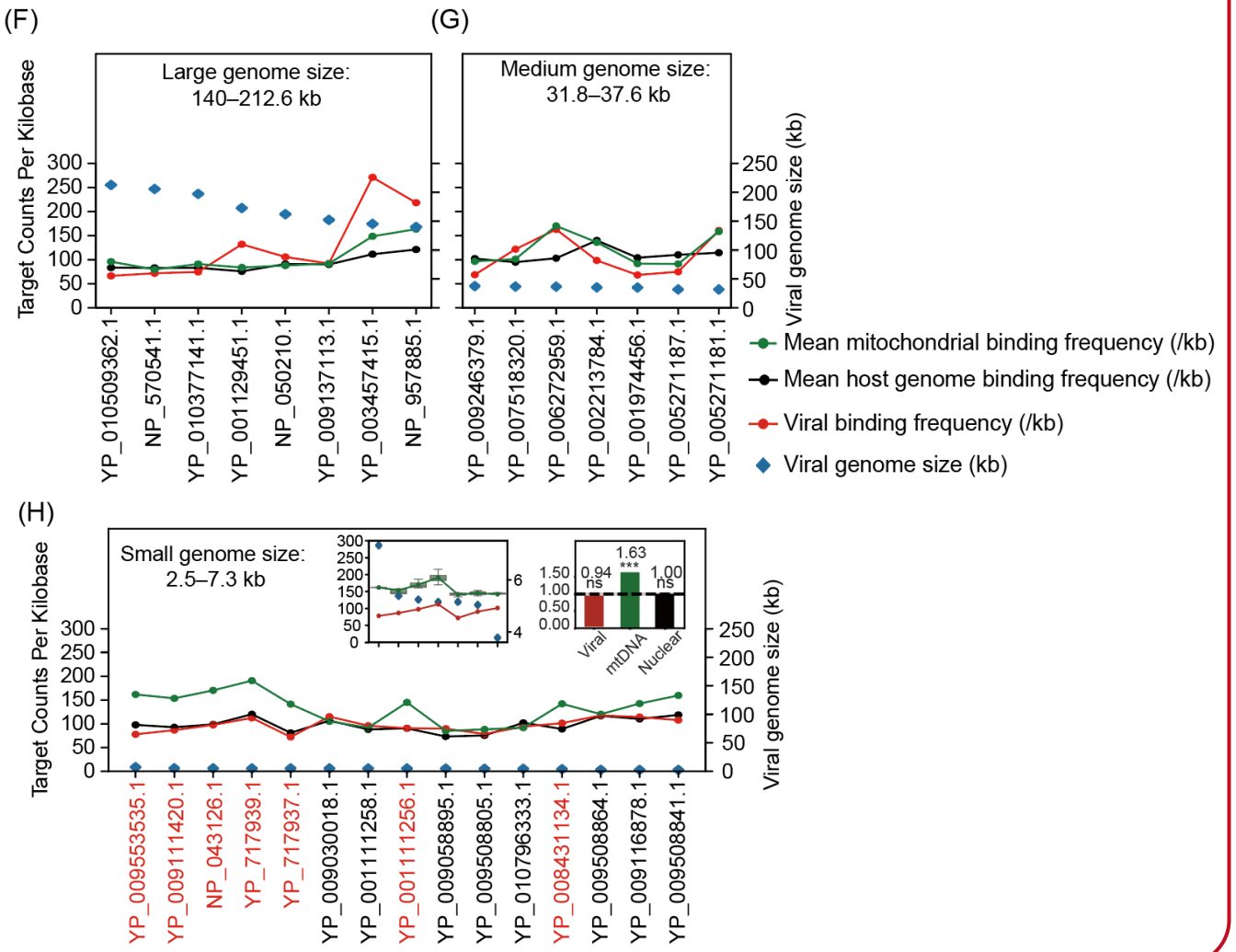
Probe AATTGCTCCCACCACATATC
TTAACGAGGGTGGTGTATAG

Pentameric structure of viral NBP YP_717939.1 (PDB: 4MJ1) ;
See Figure S7 for details.

Viral NBPs show both intra-family conservation and cross-family CCACC motif convergence.

Predicted Binding-Site Distributions Are Associated with Genome Size

Genome Size-Associated Binding Patterns



Grouped by viral genome size relative to mtDNA (~16.6 kb):

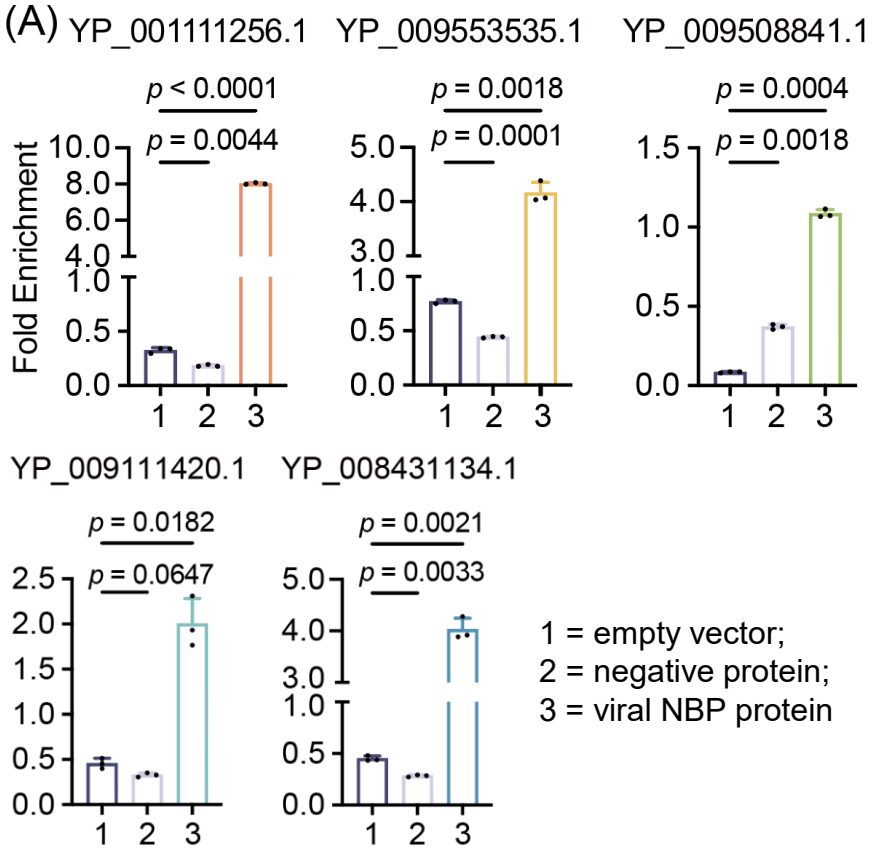
- Large (140–212.6 kb; > 8×): enriched on cognate viral genomes;
- Medium (31.8–37.6 kb; ~1.9–2.3×): no clear enrichment bias;
- Small (2.5–7.3 kb; < 0.5×): enriched on host mtDNA, especially Module 1 CCACC-motif NBPs.

Large-, medium-, and small-genome viral NBPs show distinct predicted genomic contexts.

Selected Small-Genome Viral NBPs Associate with mtDNA

1

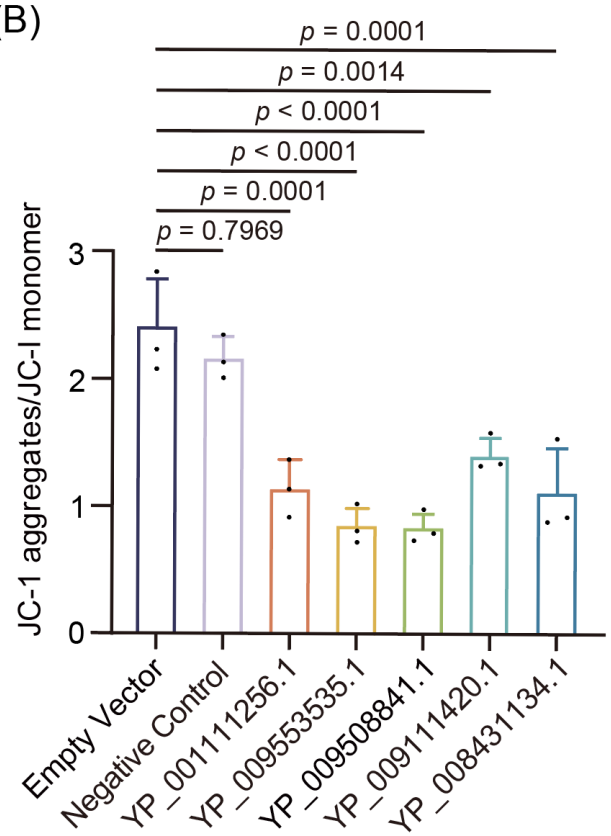
MitoChIP-qPCR



These NBPs were enriched at predicted mtDNA loci relative to controls.

2

JC-1 mitochondrial membrane potential assay



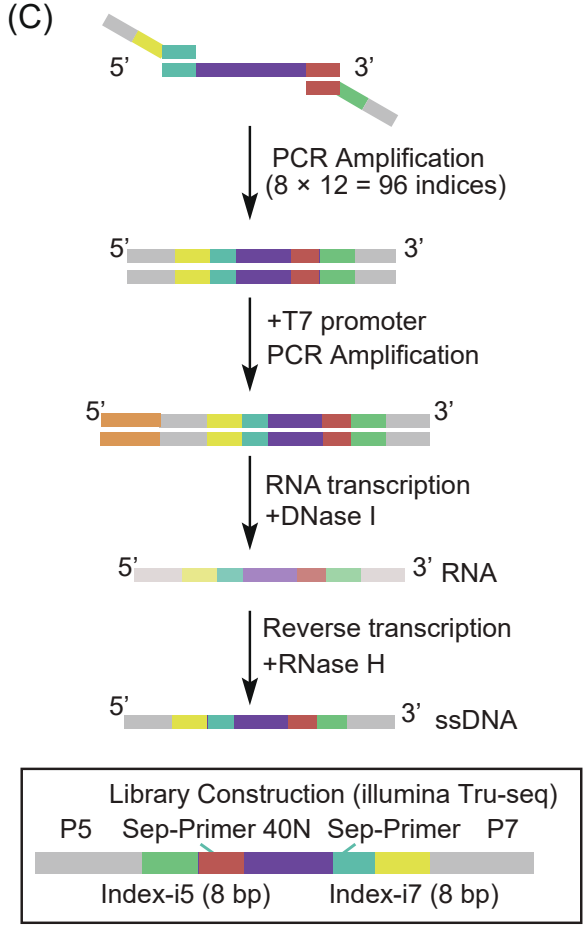
Reduced JC-1 aggregate/monomer ratios suggest mitochondrial depolarization.

These results support mtDNA association and mitochondrial depolarization, but not direct causality.

ssDNA-SELEX Expands Viral NBP DNA-Recognition Profiling

1 ssDNA-SELEX workflow

(C)

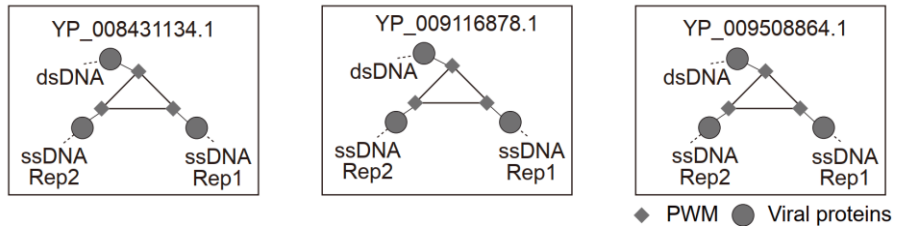


2 HT-SELEX vs ssDNA-SELEX motifs

(D)

Protein ID	HT-SELEX	ssDNA -SELEX Rep1	ssDNA -SELEX Rep2
YP_008431134.1			
YP_009116878.1			
YP_009508864.1			
YP_009508841.1		N/A	N/A
YP_009508805.1		N/A	N/A
YP_010796333.1		N/A	N/A
YP_009058895.1		N/A	N/A
AVM80381.1		N/A	N/A

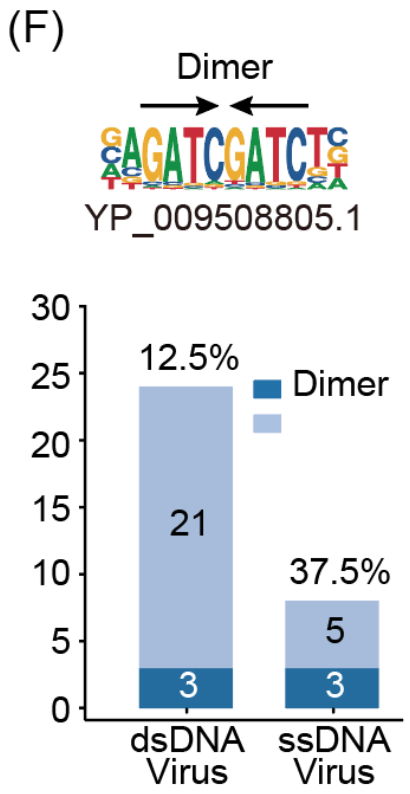
(E)

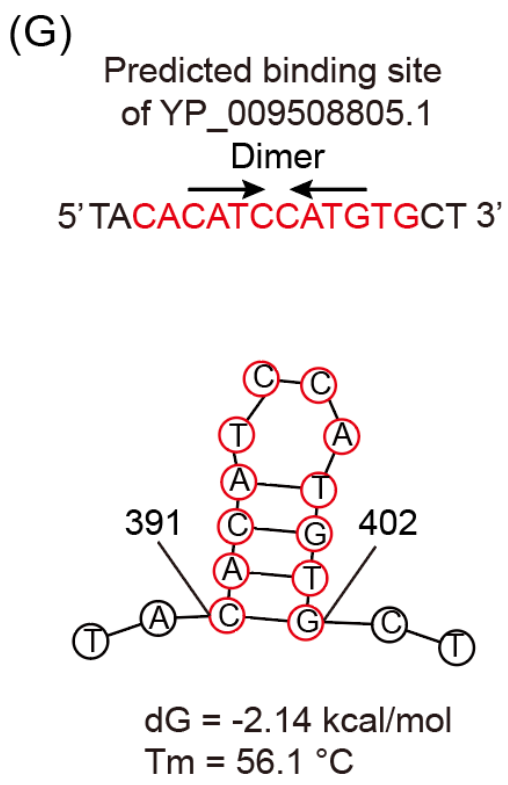


Three ssDNA-virus NBPs showed comparable core motifs between ssDNA-SELEX and HT-SELEX, suggesting strand-state-independent core recognition.

ssDNA-Virus NBPs Show Dimer-Like Binding Modes

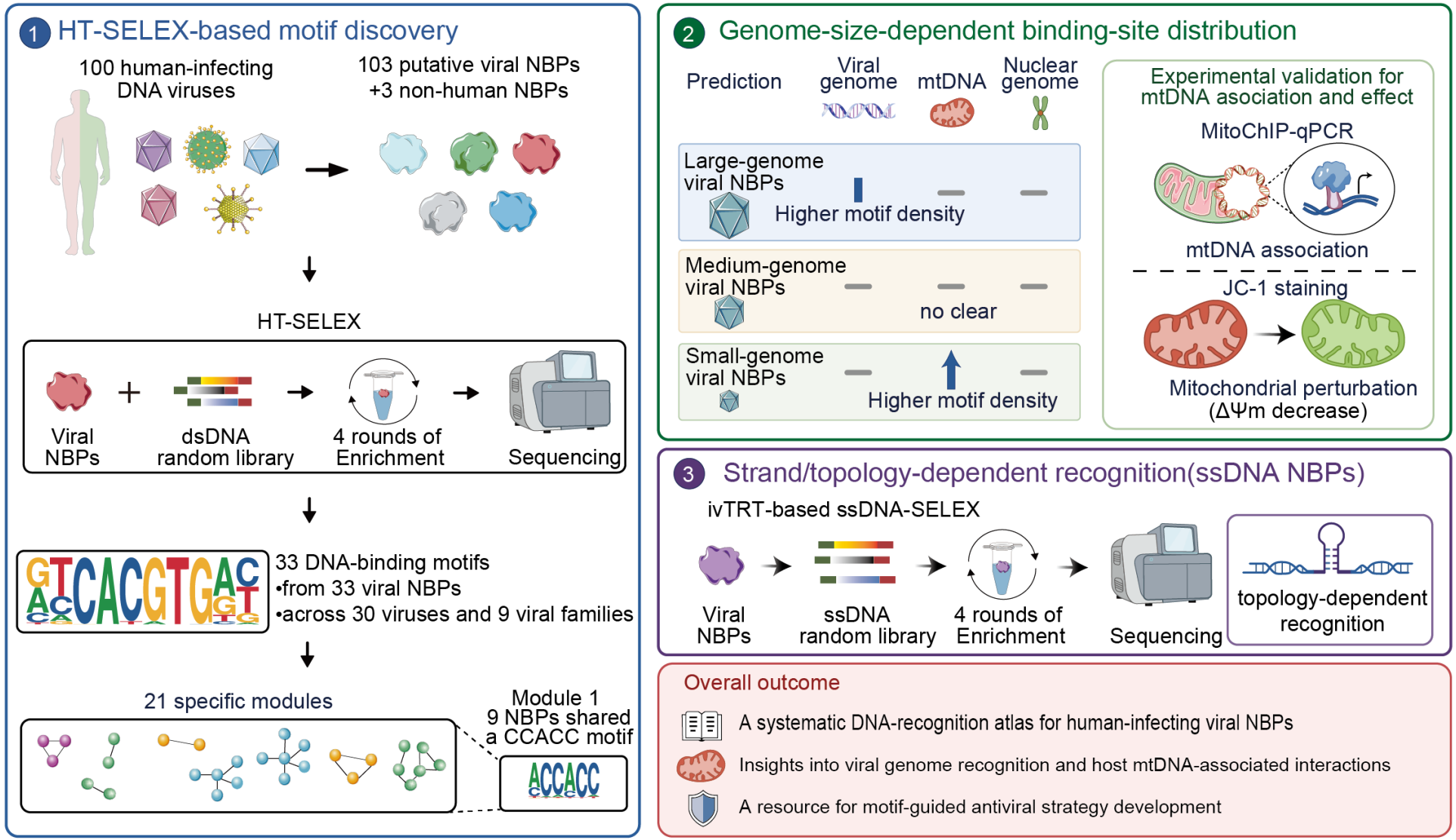
Monomer-Like and Dimer-Like Binding Patterns





Dimer-like motifs were more frequently observed in ssDNA-virus NBPs and may recognize inverted-repeat sequences capable of forming stem-loop structures.

Summary



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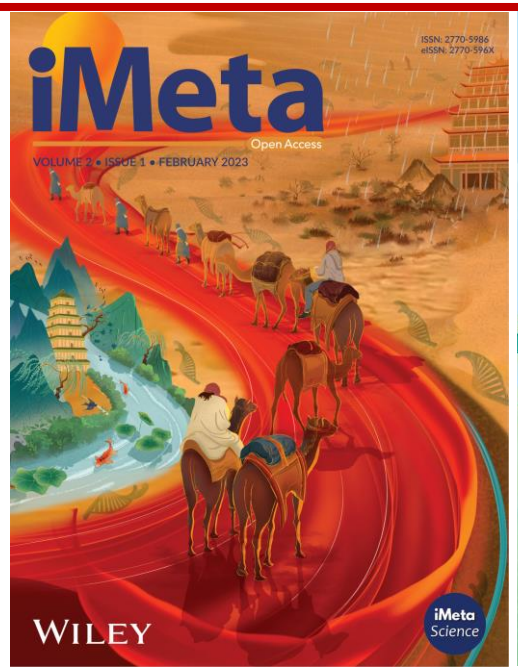

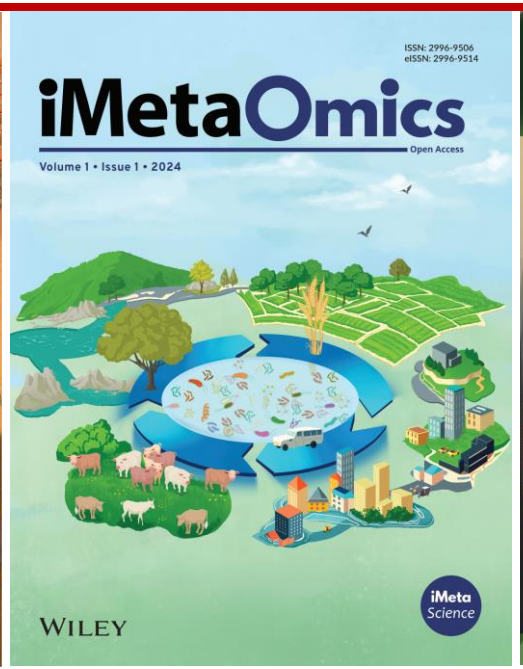

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