

Norovirus - an overview

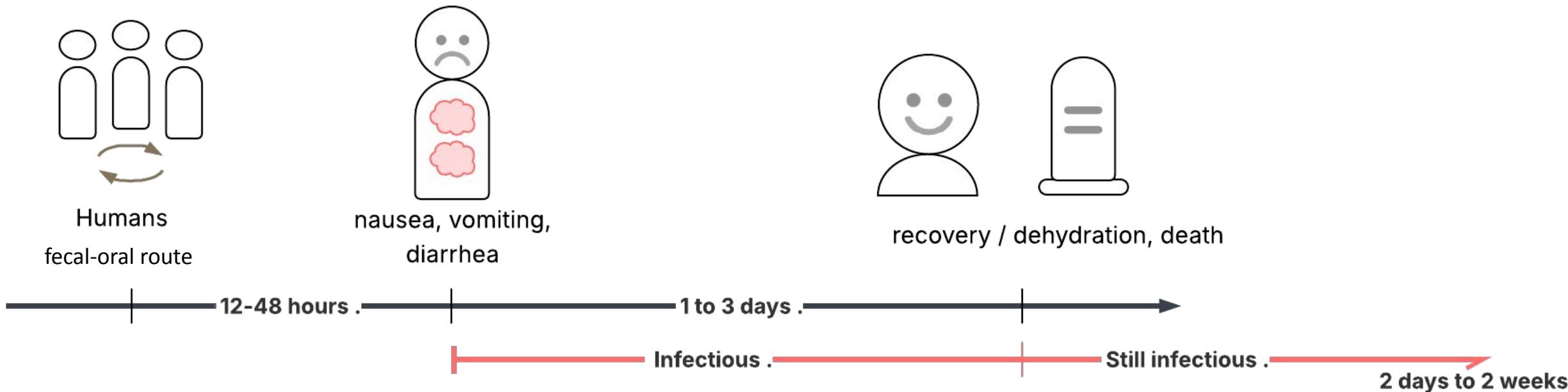
- Bedford Lab Meeting -

Jennifer Chang, Ph.D.

Bioinformatic Analyst III

Fred Hutchinson Cancer Center

"Winter Vomiting Disease"

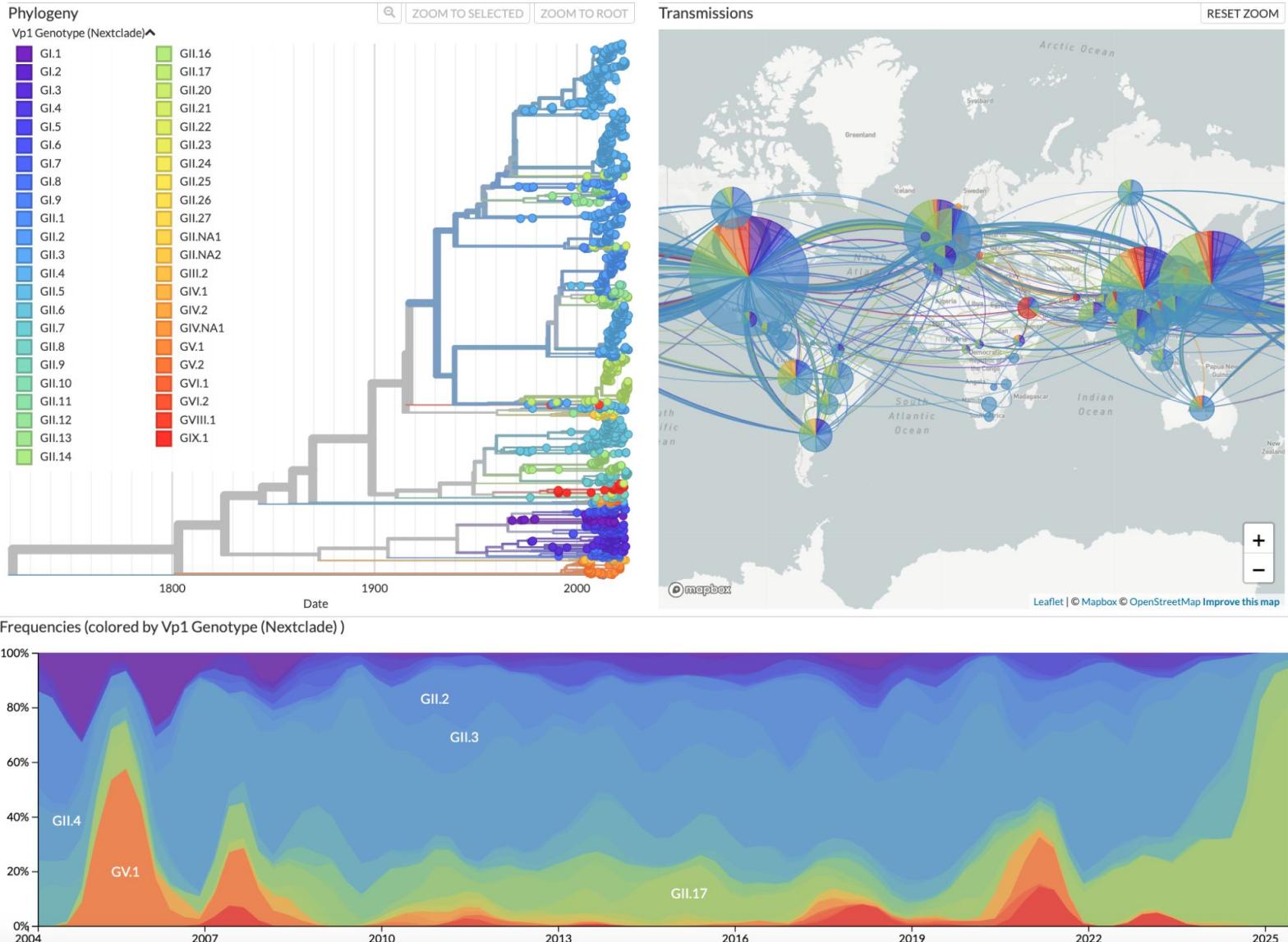


No approved FDA Norovirus vaccine
Wash hands and surfaces
Drink plenty of fluids

[CDC: About Norovirus](#)

Nextstrain dataset

Norovirus Nextstrain Dataset

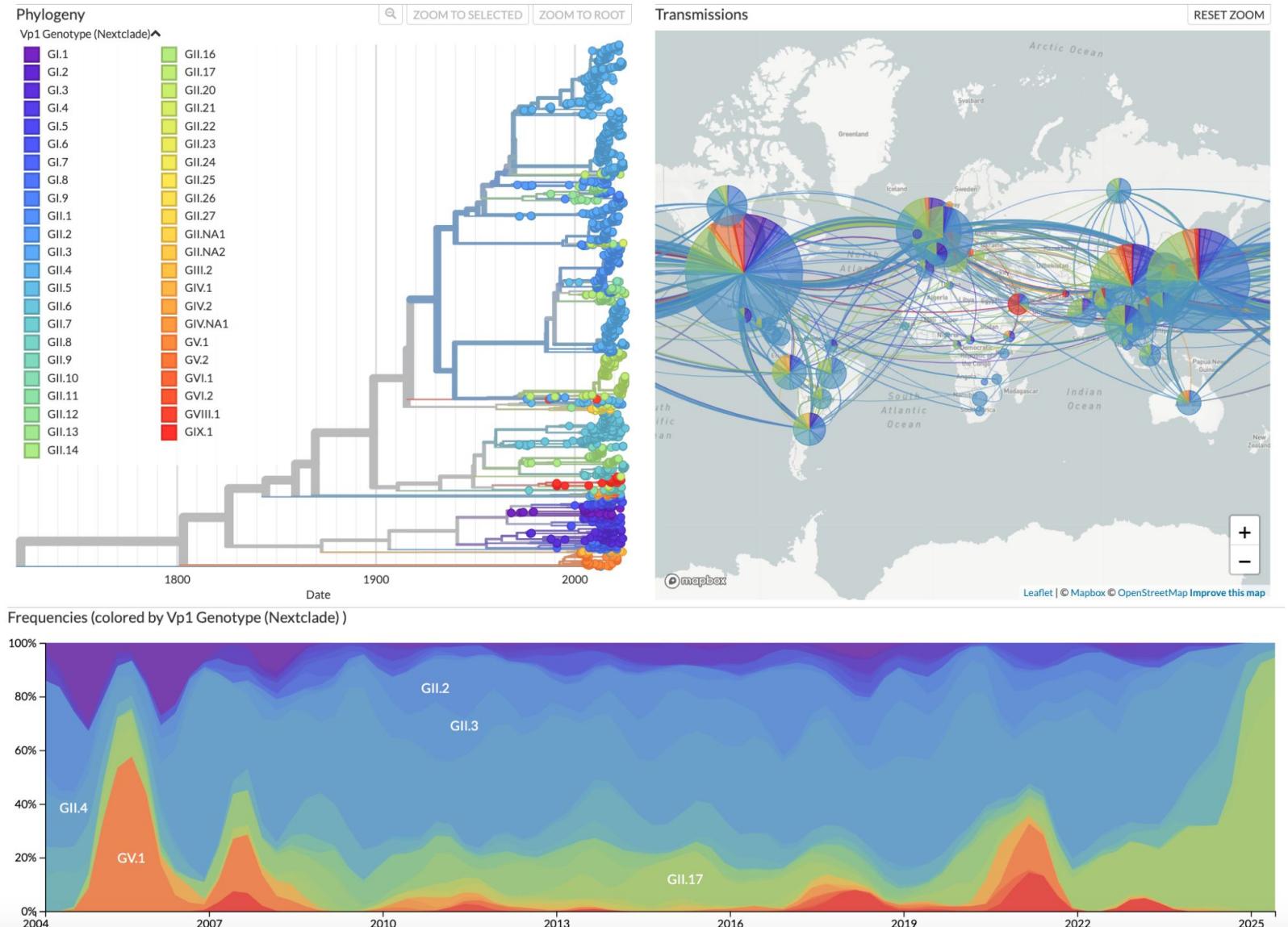


We maintain 14 views of norovirus evolution:

group	genome	p48	NTPase	p22	VPg	3CLpro	rdrp	VP1	VP2
all	genome	p48	NTPase	p22	VPg	3CLpro	rdrp	VP1	VP2
GII.2	genome								
GII.3	genome								
GII.4	genome								
GII.6	genome								
GII.17	genome								

<https://nextstrain.org/norovirus>

Norovirus Nextstrain Dataset



Acknowledging prior work from:

- Allison Li
- Katie Kistler
- John Huddleston
- Trevor Bedford

We maintain 14 views of norovirus evolution:

group	genome	p48	NTPase	p22	VPg	3CLpro	rdrp	VP1	VP2
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GII.6	genome								
GII.17	genome								

<https://nextstrain.org/norovirus>

2025-26 Season: GII.4 or GII.17

<https://www.cdc.gov/norovirus/php/reporting/calicinet-data.html>

https://wwwnc.cdc.gov/eid/article/31/7/25-0524_article

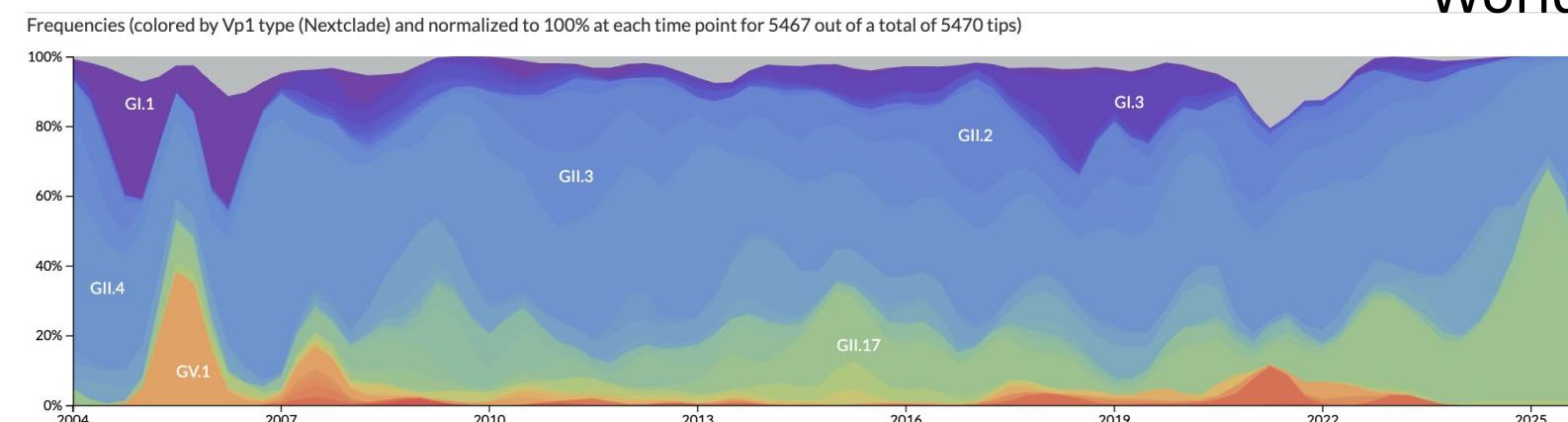
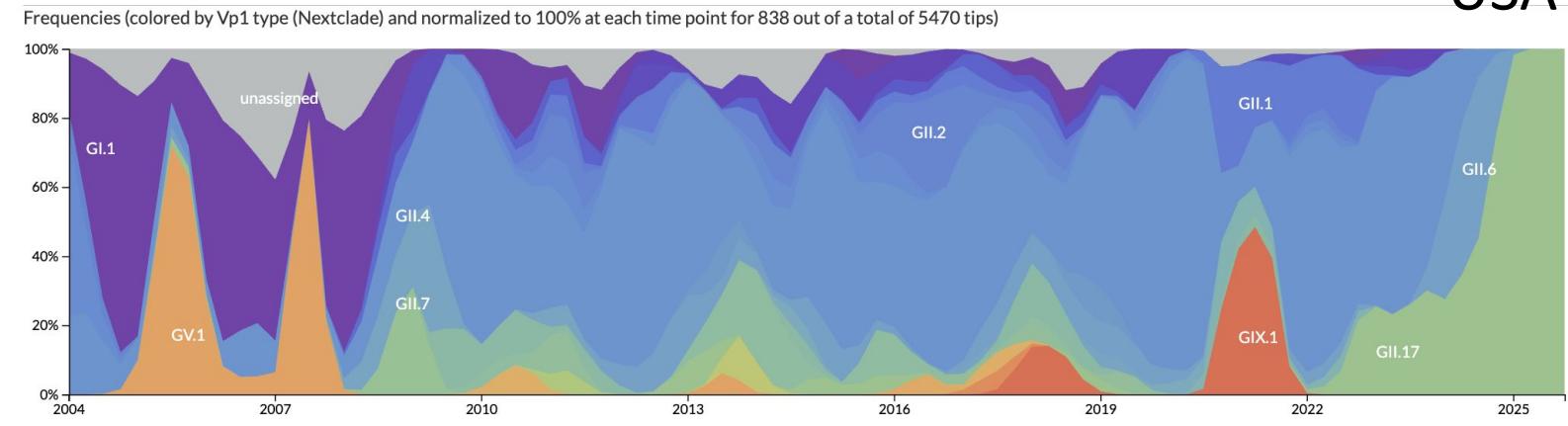
Data Table: September 1, 2025 – November 30, 2025 (n=11)

Genotype	Number of Outbreaks
GII.4 Sydney[P16]	5
GI.3[P13]	2
Other Genotypes	4

The Other Genotypes category includes genotypes from outbreaks that each make up less than 5% of the total number of outbreaks. These genotypes are: GI.3[P3], GII.1[P33], GII.17[P17], GII.7[P7].

Data Table: September 1, 2024 – August 31, 2025 (n=406)

Genotype	Number of Outbreaks
GII.17[P17]	301
GII.4 Sydney[P16]	43
GII.6[P7]	16
Other Genotype	46



Literature review - collect papers

- What is the **earliest study** identifying Norovirus as a viral disease?
- When was it first **sequenced**, and which genome region was published?
- When was the first Norovirus **vaccine** developed, and how effective was it?
- Have there been major updates to the vaccine? What prompted them?
- What **genotype** system has been used for Norovirus virus strains?
- What are some of the **key open questions** in recent Norovirus virus research?

Literature review - collect papers

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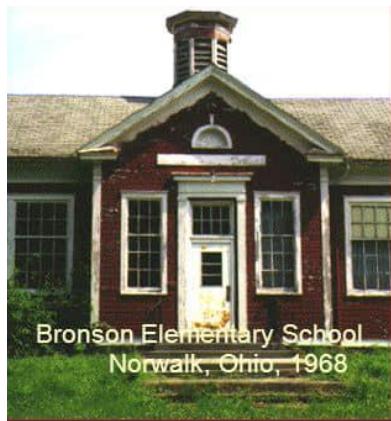
Why don't we have a norovirus vaccine yet?

Literature review - collect papers

- What is the **earliest study** identifying Norovirus as a viral disease?
 - Jordan et al, 1953; Adler, 1969; Kapikian et al, 1972, 2000;
- When was it first **sequenced**, and which genome region was published?
 - 1989, most of the full genome
- When was the first Norovirus **vaccine** developed, and how effective was it?
 - ...attempts made, not effective or not for long, Moderna mRNA vaccine Trials
- Have there been major updates to the vaccine? What prompted them?
 - ...multiple attempts made
- What **genotype** system has been used for Norovirus virus strains?
 - Tatusov et al, 2021; Zheng et al, 2006; Chhabra et al, 2019; Eden et al, 2013
- What are some of the **key open questions** in recent Norovirus virus research?
 - recombination, Fut2 host-factors secretors/non-secretors, MALT

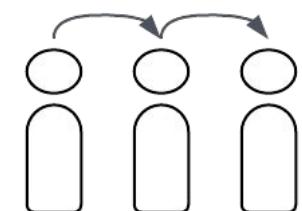
Literature review

Norovirus - the "Norwalk" virus

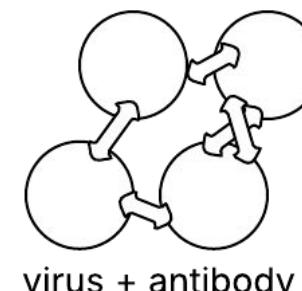
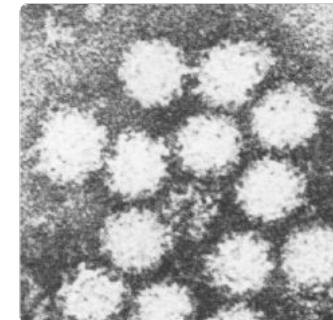


elementary school

cell culture ✗
tissue culture ✗
animal models ✗



human passaged



virus + antibody



1968 - Norwalk Ohio Outbreak
samples collected

[\(Adler & Zickl, 1968\)](#)

1972 - Immunoelectron Microscopy
aggregate viral particles by antiserum

[\(Hayashi et al, 2024\)](#)

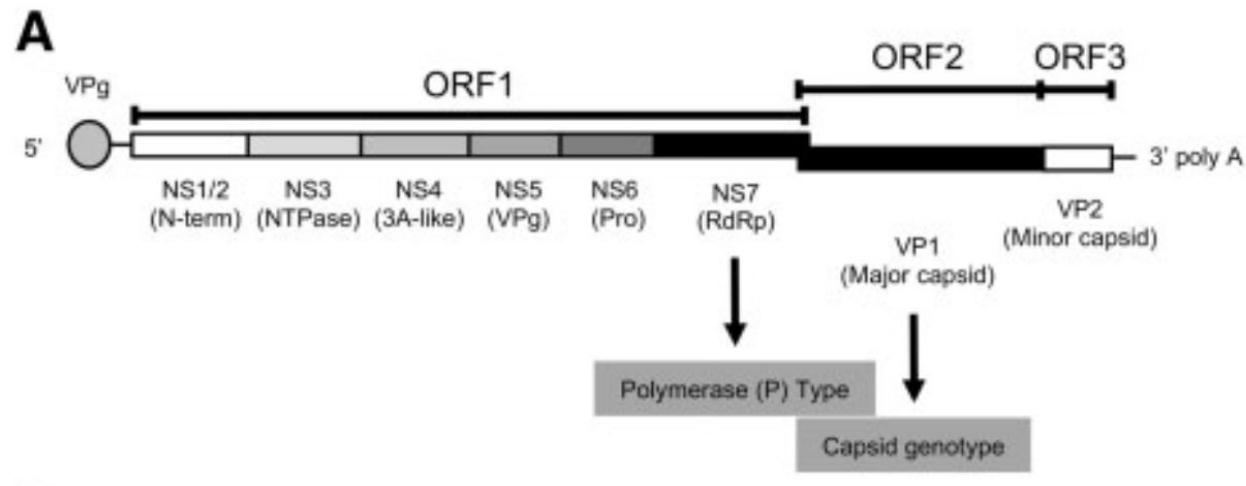
[\(Kapikian et al, 1972\)](#)

1989 - First sequenced
(described in 1993, Jiang et al)

[\(Jiang et al, 1993\)](#)

Genome Structure

Genome Structure - VP1

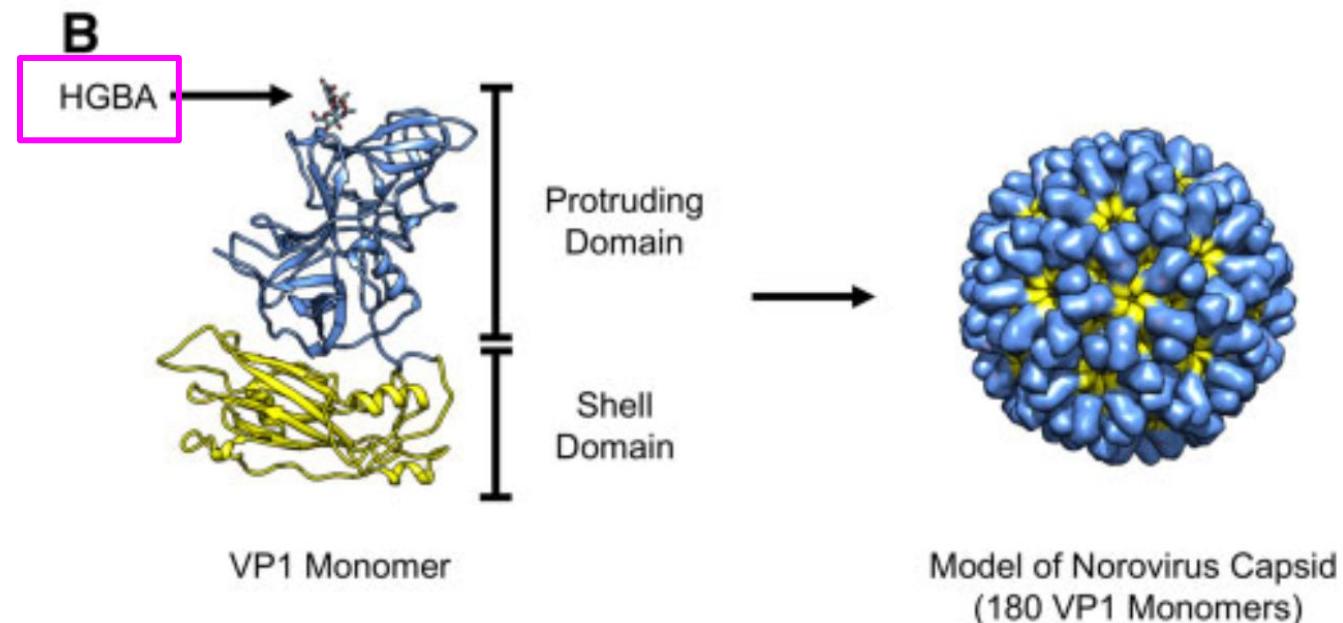


Protein coat - more robust than lipid

HBGA - Histo-Blood Group Antigen

If FUT2 is inactive - HBGA not available, person has protection against norovirus

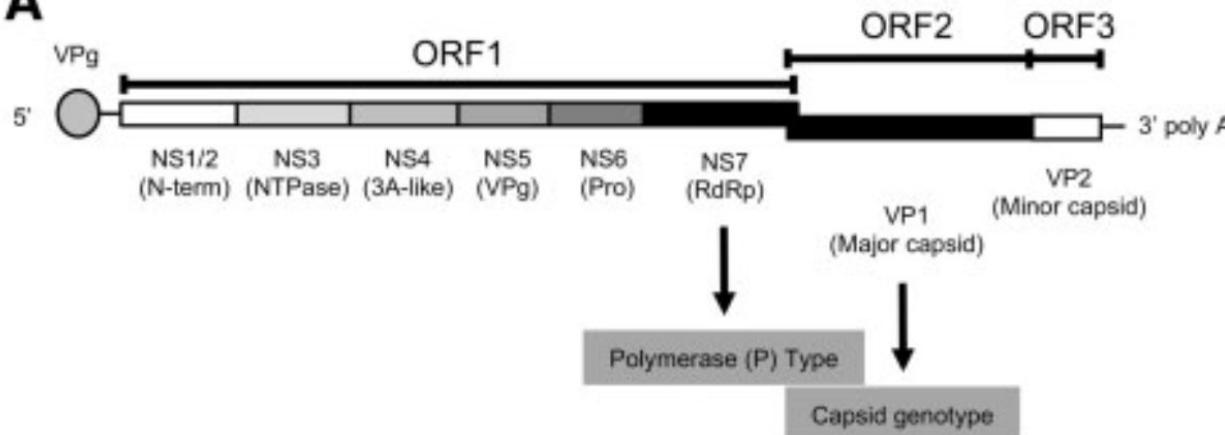
([Lindesmith et al, 2003](#))



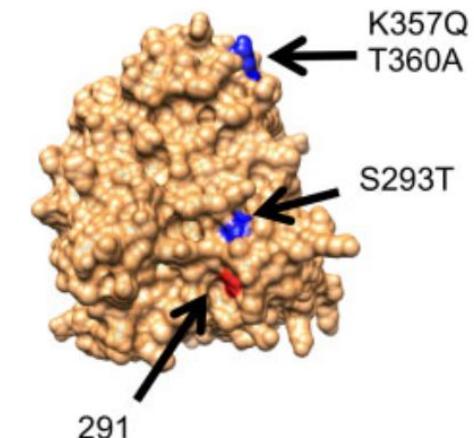
Parra, G.I., 2019. **Emergence of norovirus strains: A tale of two genes.** Virus Evolution, 5(2), p.vez048.

Genome Structure - VP1 and RdRp

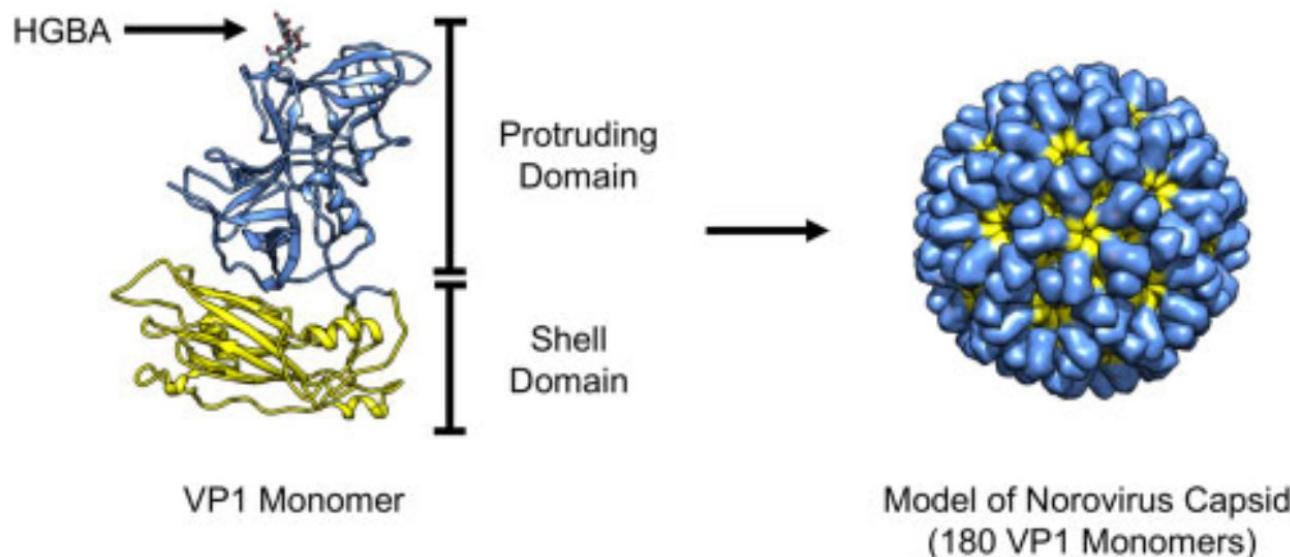
A



RdRp Side View



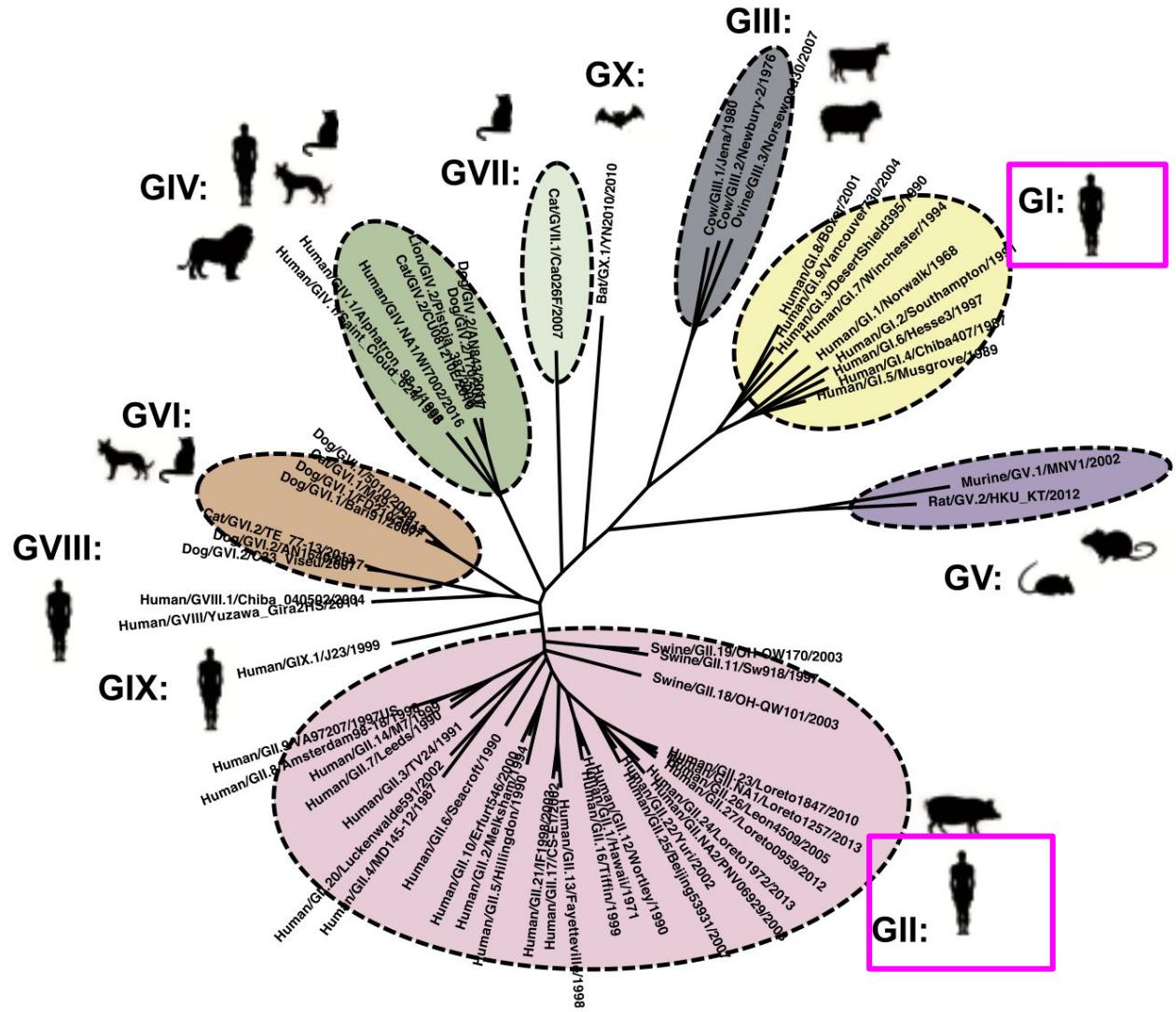
B



Parra, G.I., 2019. **Emergence of norovirus strains: A tale of two genes.** Virus Evolution, 5(2), p.vez048.

Nomenclature

Norovirus - Genogroups (VP1)



Groups tend to be host specific, with limited cross-protection

Human infections usually associated with groups **G1** and **GII**

Parra, G.I., 2019. Emergence of norovirus strains: A tale of two genes.
Virus Evolution, 5(2), p.vez048.

Norovirus - splits into genotypes

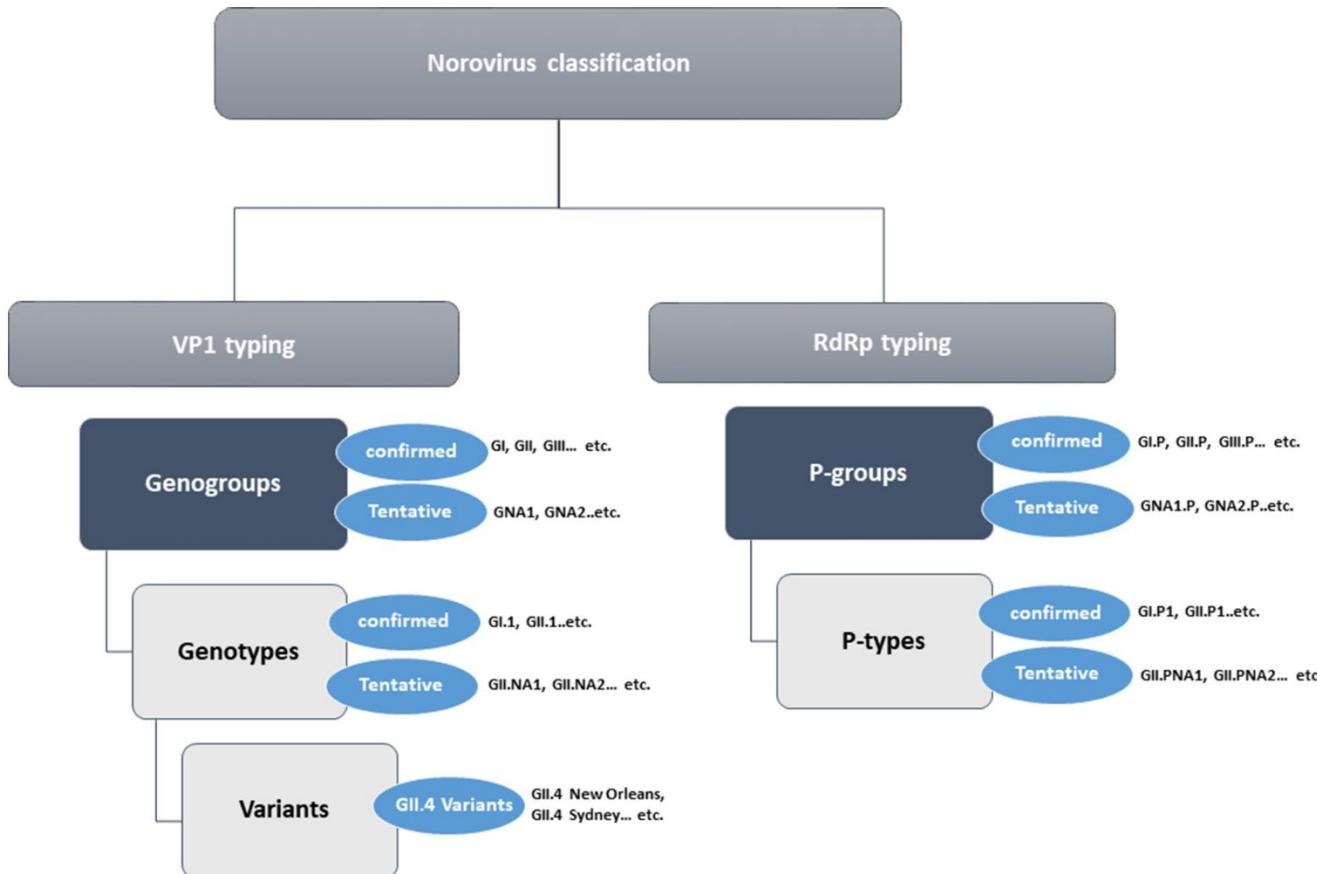


Fig. 1. Classification of noroviruses into genogroups, genotypes, variants, P-groups and P-types. Tentative genogroups, genotypes, P-groups and P-types are currently represented only by a single sequence or multiple non-identical sequences from a single geographic location and are therefore named as non-assigned (NA).

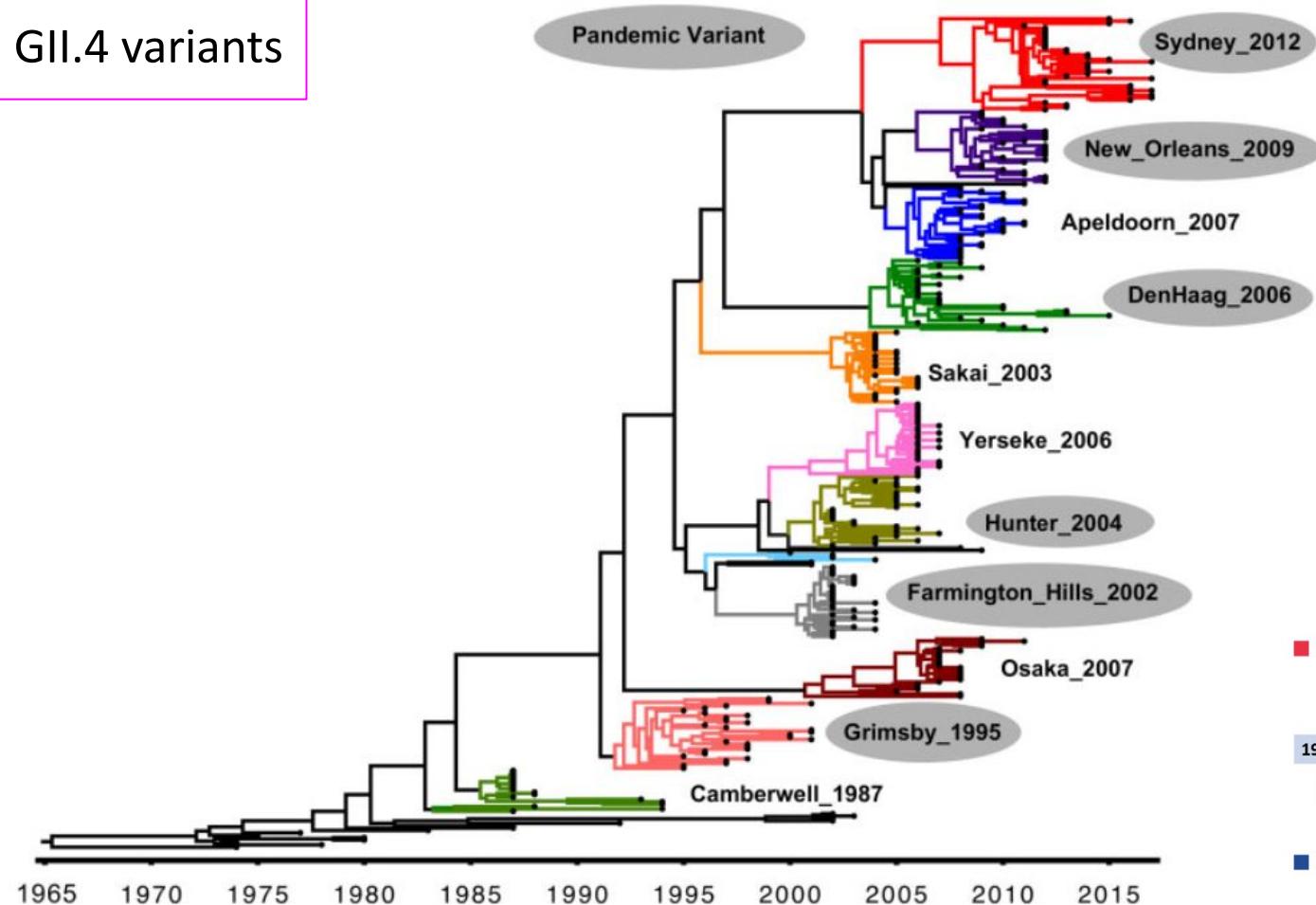
Chhabra, P., de Graaf, M., Parra, G.I., Chan, M.C.W., Green, K., Martella, V., Wang, Q., White, P.A., Katayama, K., Vennema, H. and Koopmans, M.P., 2019. **Updated classification of norovirus genogroups and genotypes.** Journal of General Virology, 100(10), pp.1393-1406.

Genotypes have limited cross-protection

Human infections usually associated with genotypes **GII.4** and **GII.17**

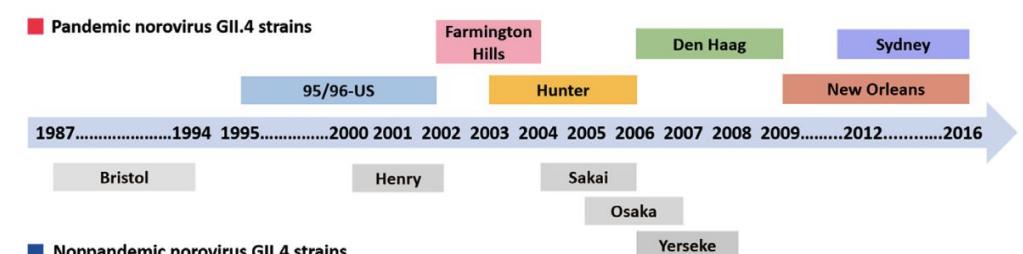
Norovirus - variants (outbreaks)

GII.4 variants



Parra, G.I., 2019. **Emergence of norovirus strains: A tale of two genes.** Virus Evolution, 5(2), p.vez048.

Chan, M.C., Kwan, H.S. and Chan, P.K., 2017. **Structure and genotypes of noroviruses.** In The norovirus (pp. 51-63). Academic Press.



Norovirus - clusters?

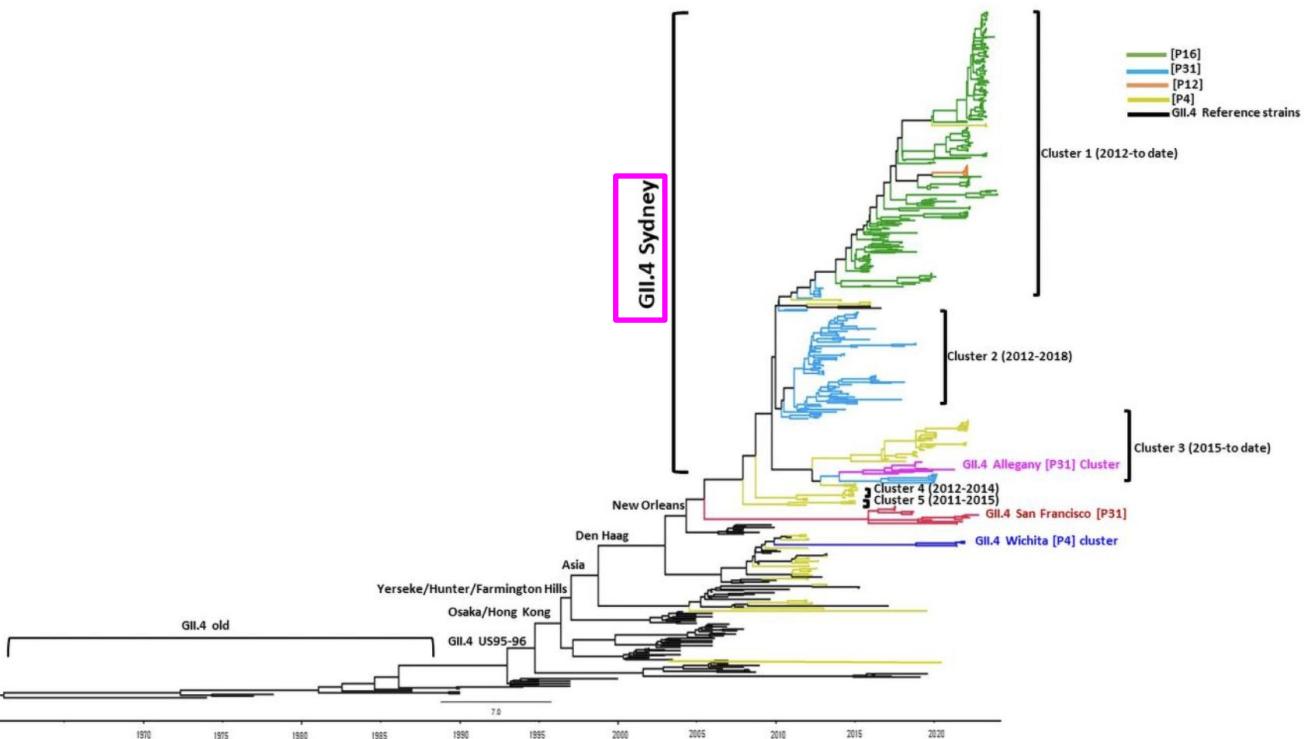
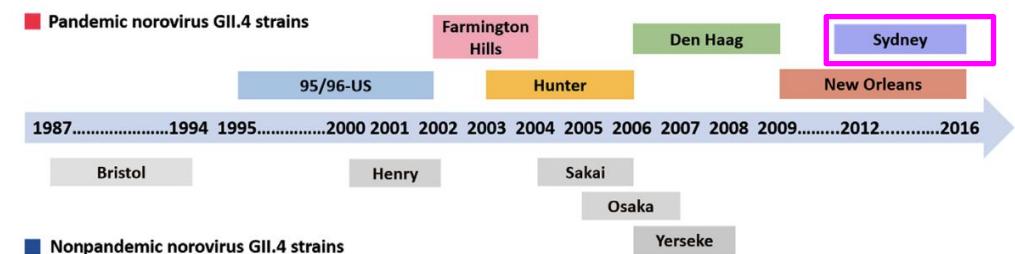


Figure 2. Time-scaled phylogenetic tree of complete GII.4 VP1 nucleotide sequences constructed by the bayesian MCMC method (BEAST version 1.10.4) is shown. GTR + G + I substitution and the uncorrelated relaxed clock model with constant coalescence were used to examine rate heterogeneity across branches based on a log-normal prior distribution of 4.3×10^{-3} substitutions per site per year and an SD of 0.1 [32]. Five MCMC replicate runs were performed with chain lengths of 150 000 000 and sampling every 10 000 steps. Results were analyzed with Tracer version 1.7.2 [33] to confirm effective sample size values ≥ 200 . To reach convergence, trees were combined by LogCombiner version 1.10.4 resampling 45 000 [22]. The mean estimated rate of GII.4 molecular evolution per TempEst was 5.56×10^{-3} substitutions per site per year. The most common recent ancestor for all GII.4 viruses was estimated to occur in 1961 (1961.18). The time-scaled evolution of GII.4 Sydney viruses involved 5 sublineages (1–5). All branches from the United States GII.4 strains that clustered with known variants are colored per their corresponding P-types. Abbreviation: MCMC, Markov chain Monte Carlo.

Barclay, L., Montmayeur, A.M., Cannon, J.L., Mallory, M.L., Reyes, Y.I., Wall, H., Baric, R.S., Lindesmith, L.C., Vinjé, J. and Chhabra, P., 2025. **Molecular Evolution and Epidemiology of Norovirus GII. 4 Viruses in the United States**. The Journal of Infectious Diseases, p.jiaf100.

Chan, M.C., Kwan, H.S. and Chan, P.K., 2017. **Structure and genotypes of noroviruses**. In The norovirus (pp. 51-63). Academic Press.



Norovirus - epitopes

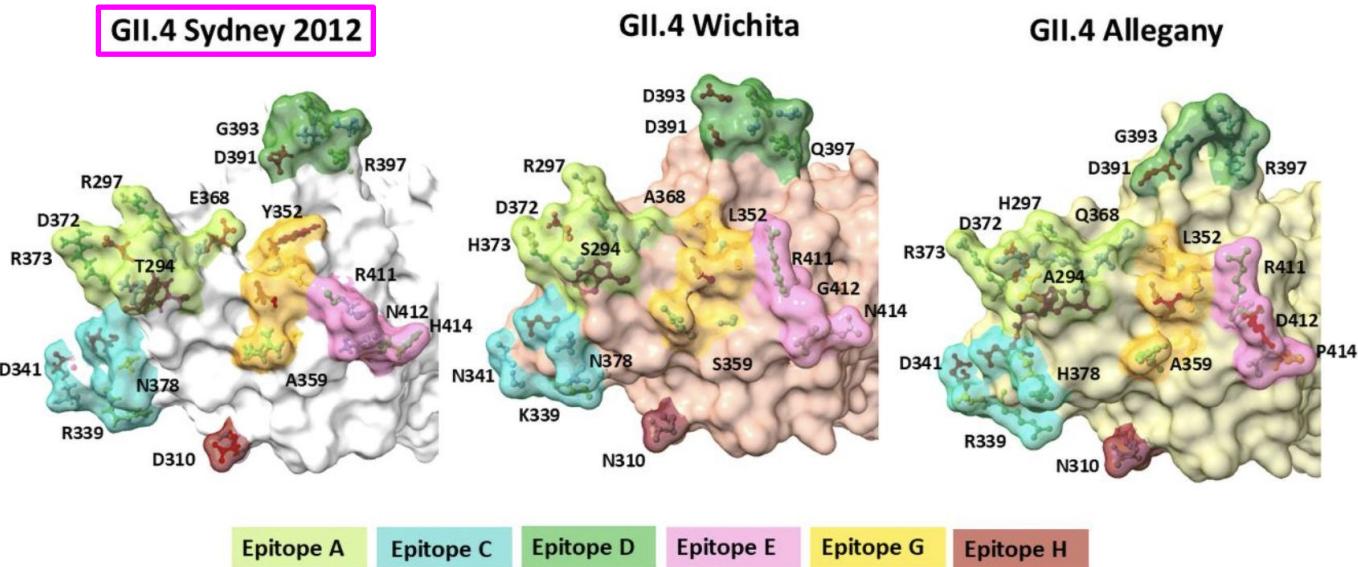
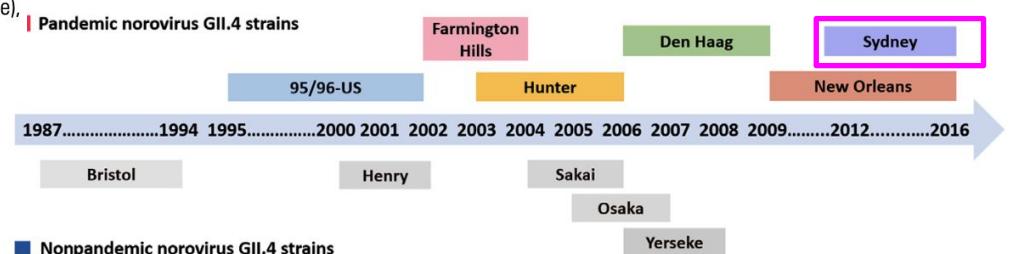


Figure 5. P-domain structure and homology models for novel GII.4 Allegany and GII.4 Wichita viruses are compared with the GII.4 Sydney (Protein Data Bank 4OP7) P-domain as the backbone (GenBank JX459908). The amino acid side chains are colored according to chemistry: negative (red), positive (green), polar uncharged (blue), hydrophobic (yellow), and proline (orange).

Barclay, L., Montmayeur, A.M., Cannon, J.L., Mallory, M.L., Reyes, Y.I., Wall, H., Baric, R.S., Lindesmith, L.C., Vinjé, J. and Chhabra, P., 2025. **Molecular Evolution and Epidemiology of Norovirus GII. 4 Viruses in the United States.** The Journal of Infectious Diseases, p.jiaf100.

Chan, M.C., Kwan, H.S. and Chan, P.K., 2017. **Structure and genotypes of noroviruses.** In The norovirus (pp. 51-63). Academic Press.



Norovirus - recombination

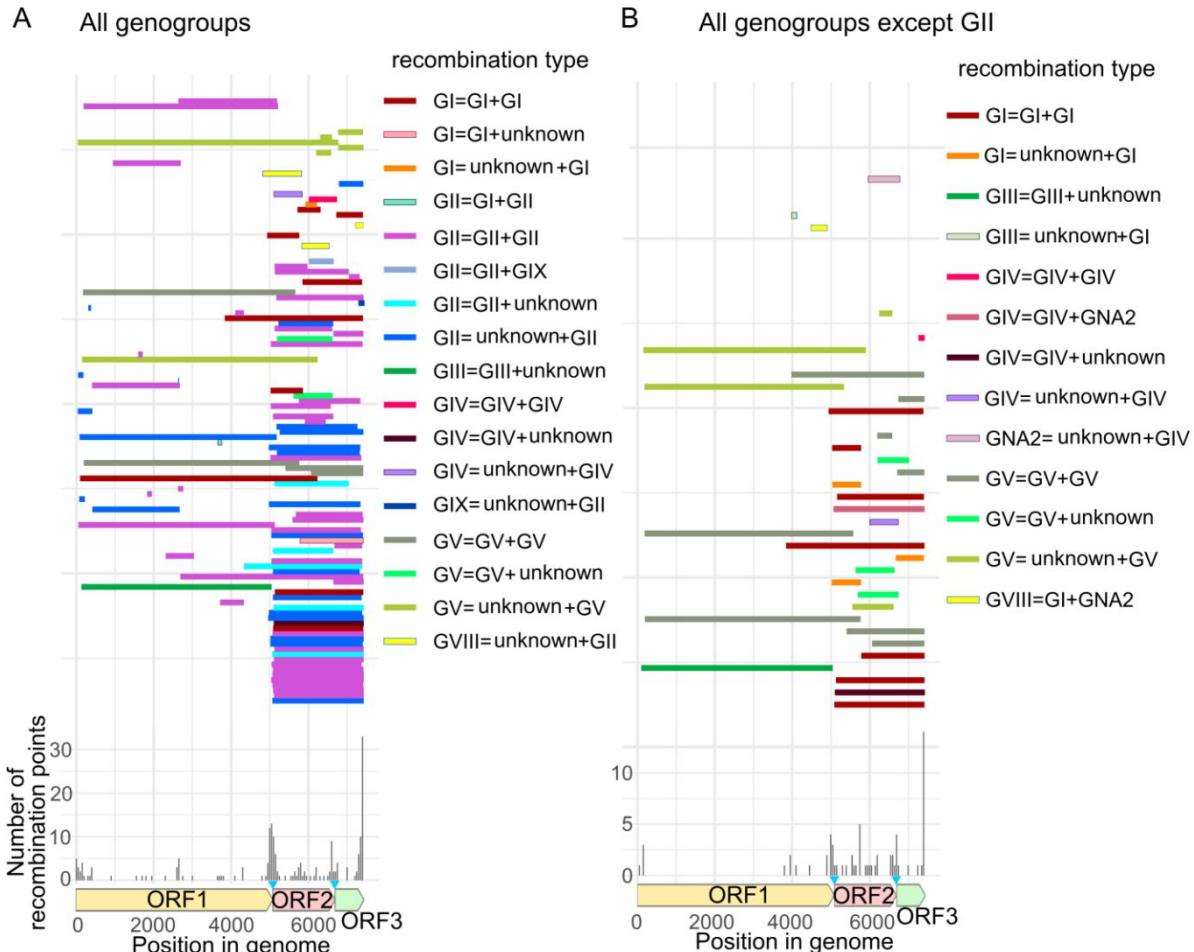


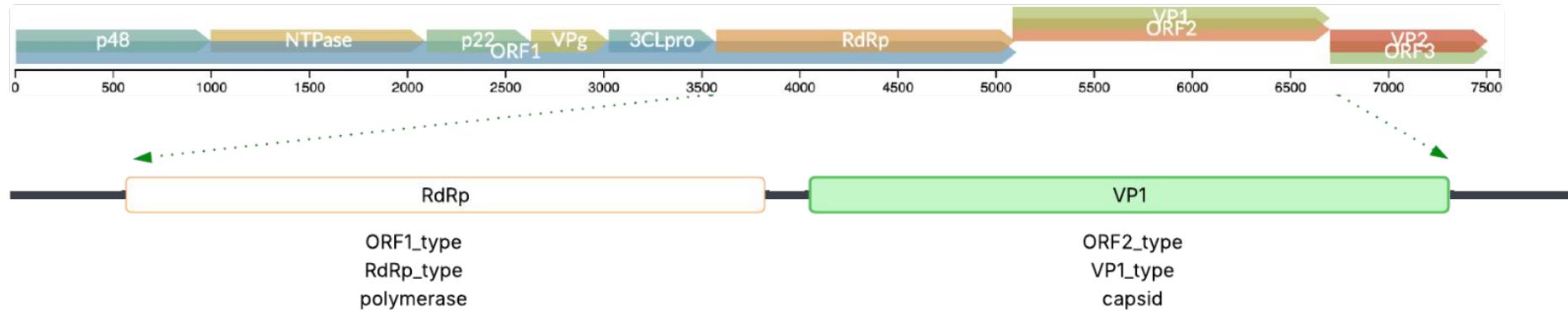
Figure 3. The distribution of recombinant fragments detected by at least four algorithms implemented in RDP4 in two datasets: (A)—the dataset that includes all norovirus genogroups; (B)—the dataset with all genogroups except GII. Blue triangles indicate the overlaps between ORF1 and ORF2 (17 nt), ORF2 and ORF3 (1 nt) that were duplicated in alignments of concatenated ORFs. Recombination type legend refers to the VP1 genogroups of a recombinant norovirus, and its minor and major parents (recombinant = minor parent + major parent). The lower panel shows the number of recombination breakpoints detected by RDP4 at each position of the alignment.

Vakulenko, Y.A., Orlov, A.V. and Lukashev, A.N., 2023. Patterns and temporal dynamics of natural recombination in noroviruses. *Viruses*, 15(2), p.372.

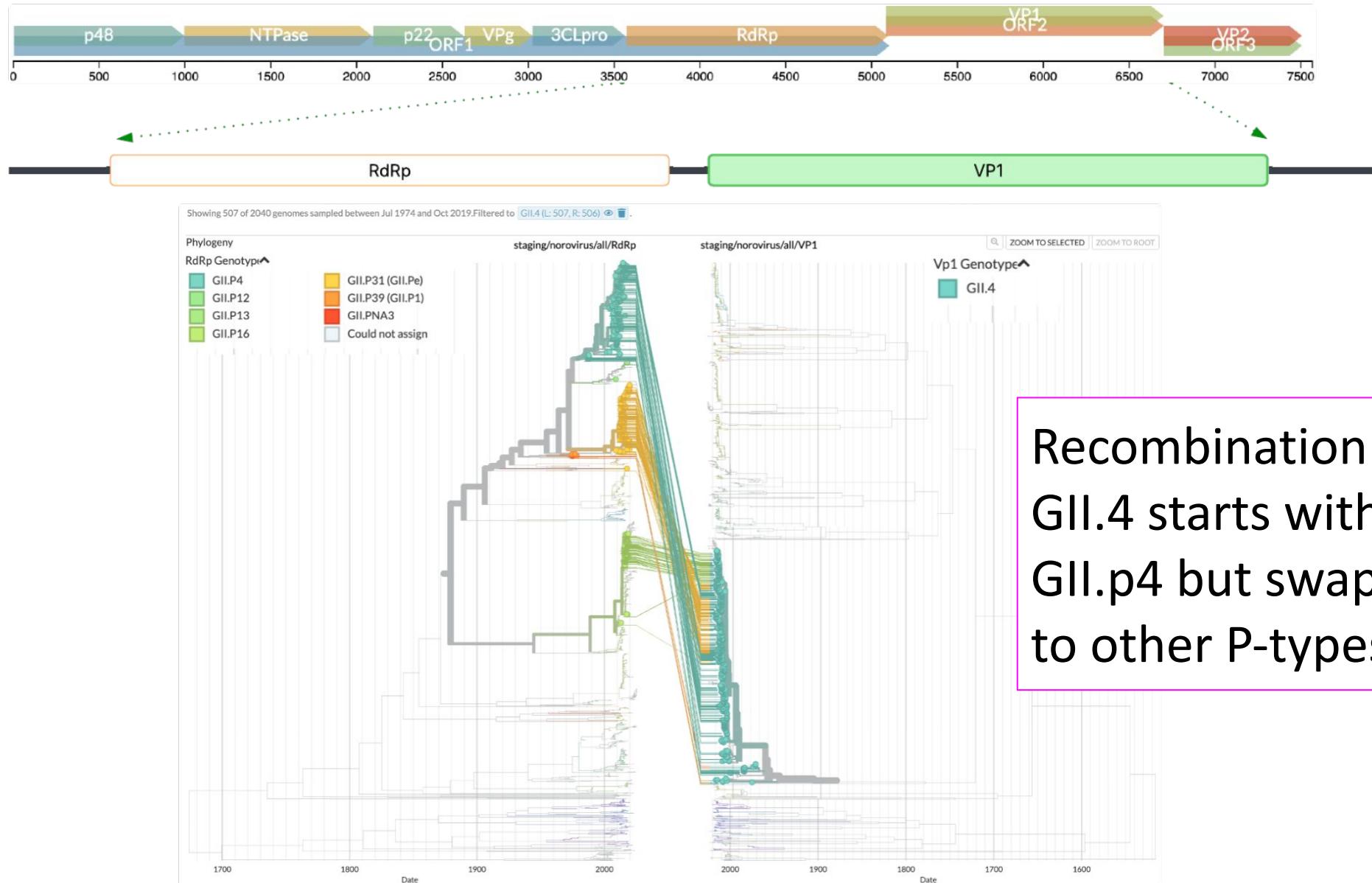
Okay, I need a summary...

Visualize nomenclature of groups, types, and variants

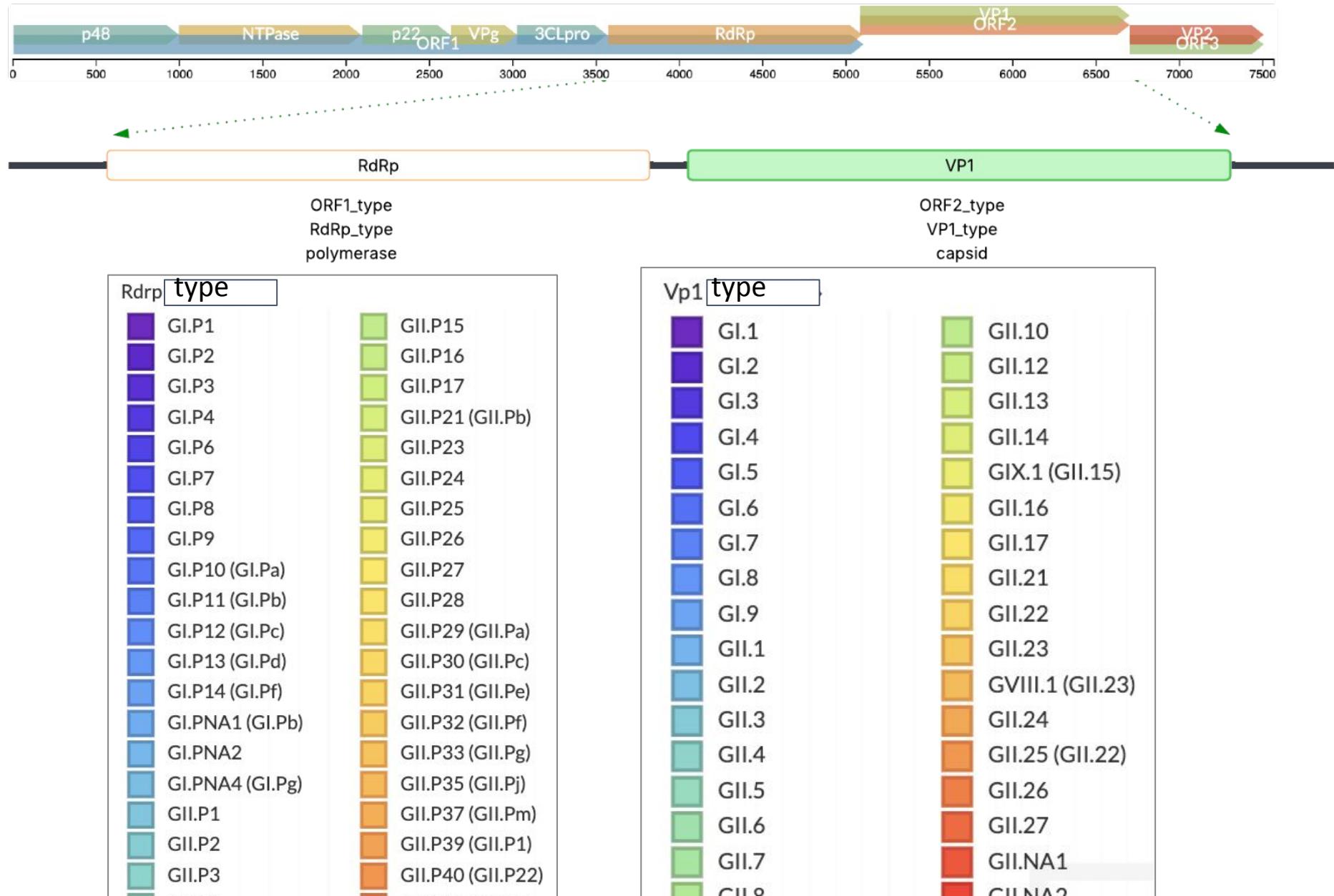
Norovirus nomenclature



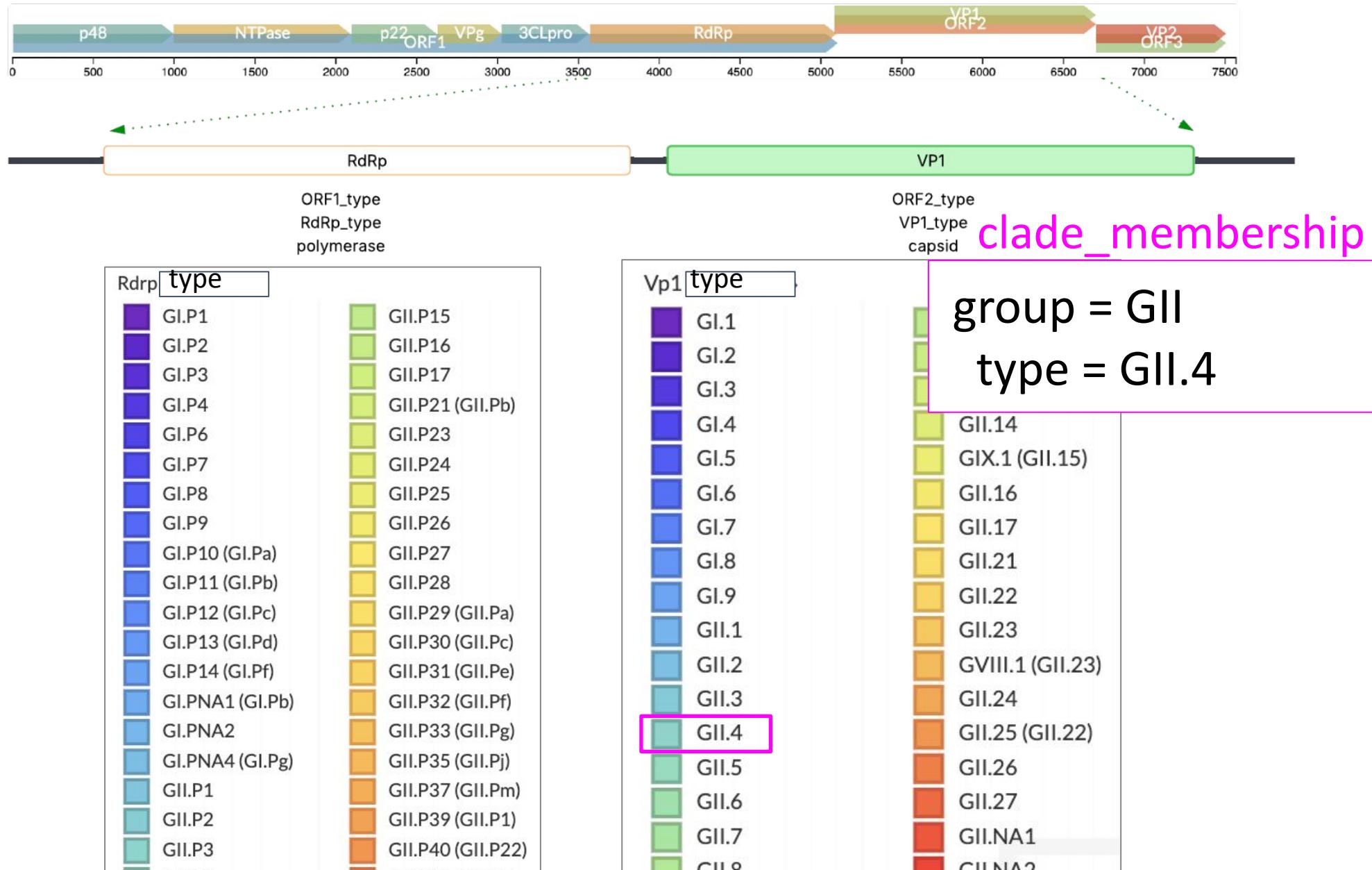
Norovirus nomenclature



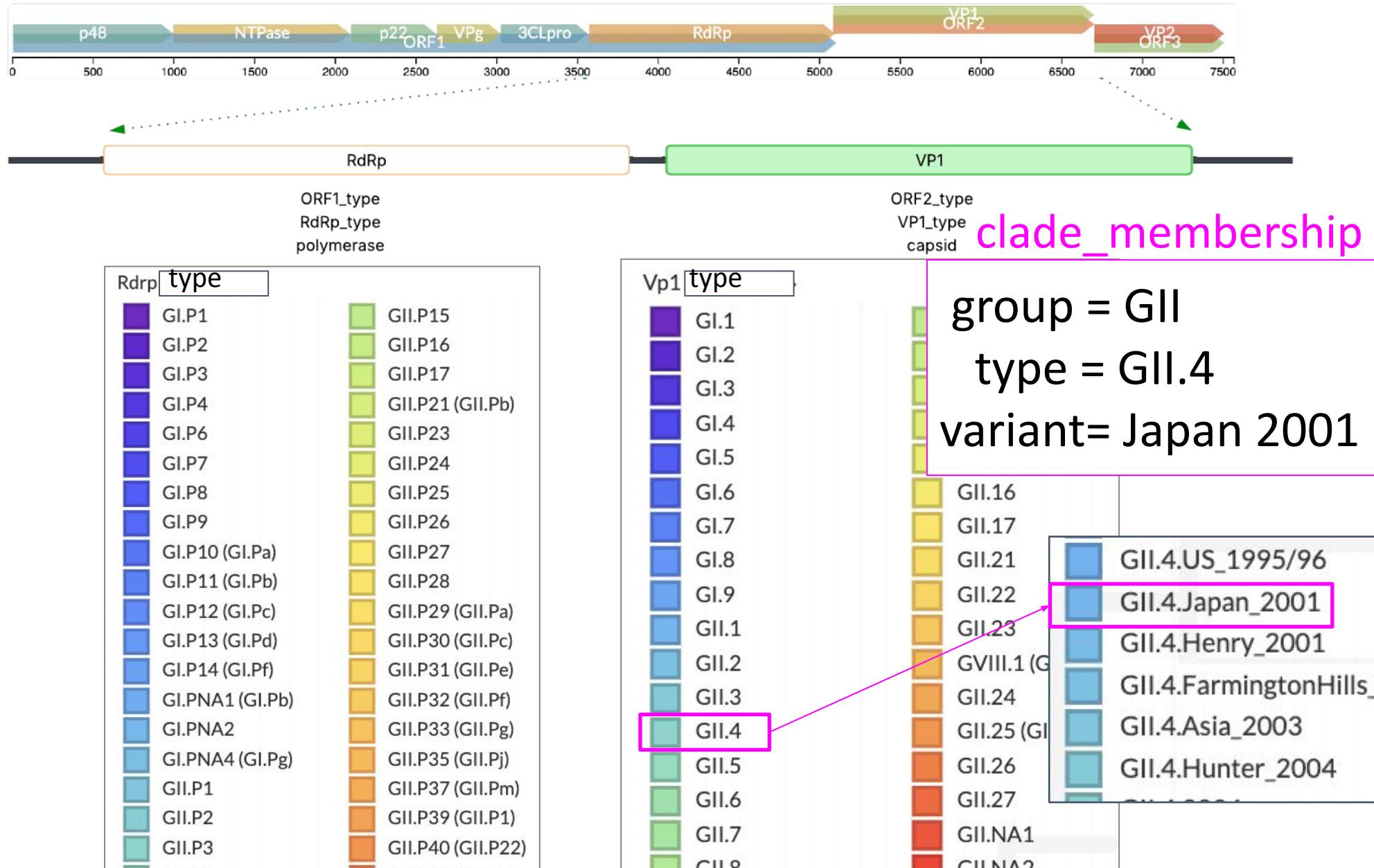
Norovirus nomenclature



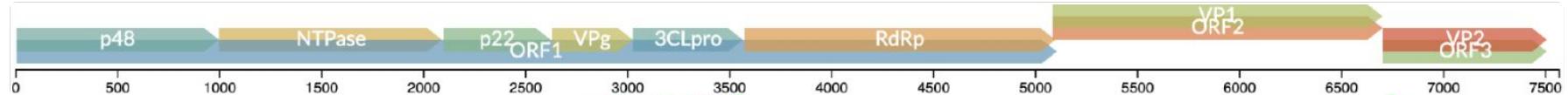
Norovirus nomenclature



Norovirus nomenclature



Norovirus nomenclature



reference

NC_039477 (GII.4)
NORO_226_06_01_2016 (GII.P16_GII.4)

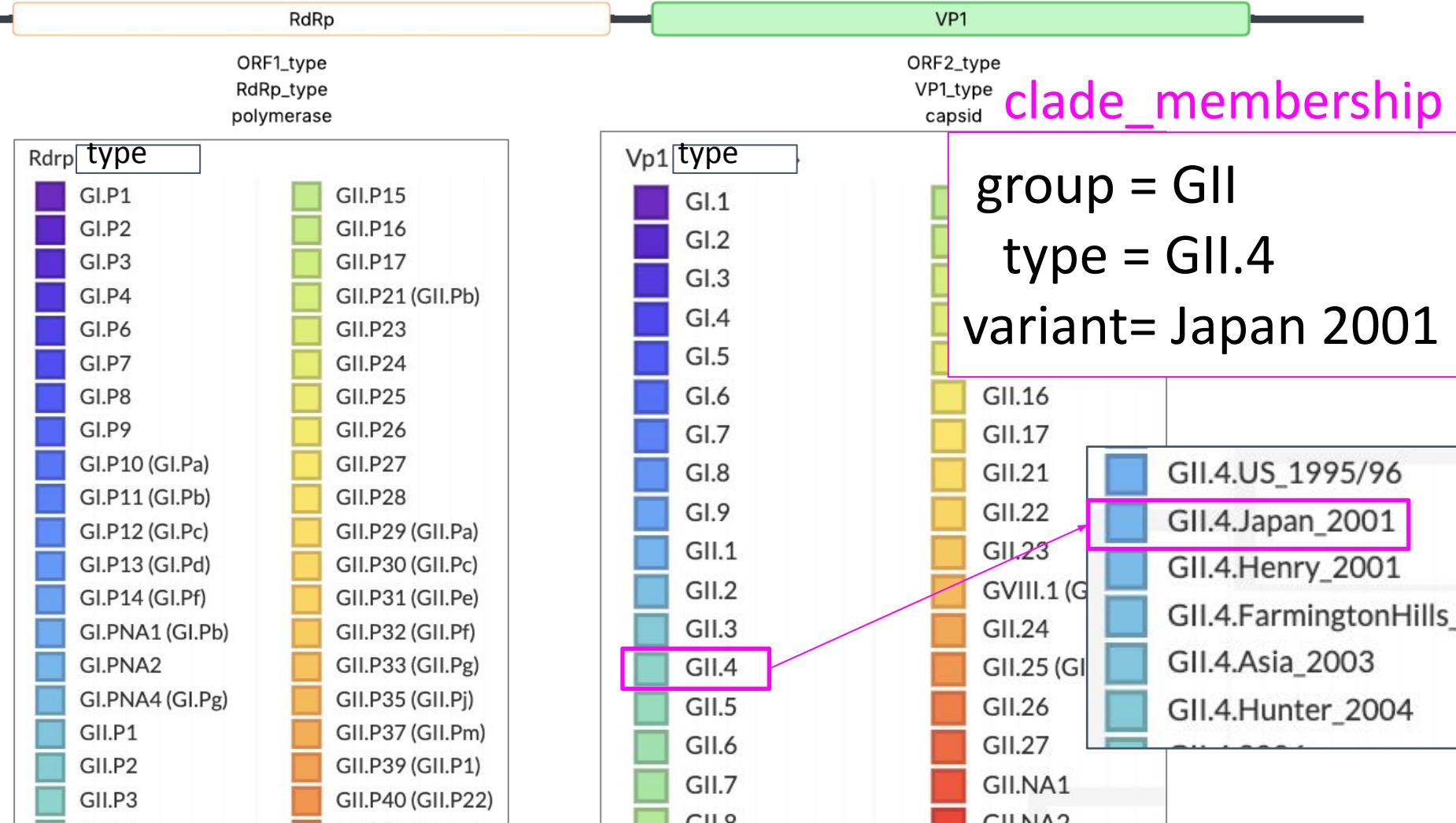
NC_039476 (GII.2)
Env/CHN/2016/GII.P16-GII.2/BJSMQ

JX846924 (GII.3)
Hu/GII.3/HK71/1978/CHN

NC_040876 (GII.6)
NORO_176-1_17_12_2015 (GII.P7_GII.6)

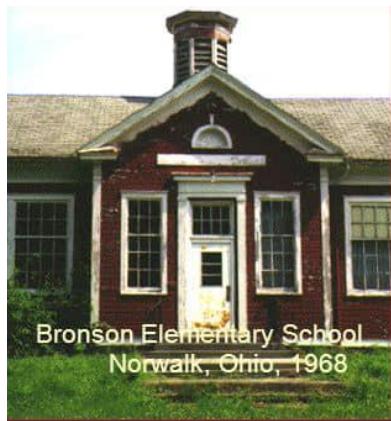
NC_039475 (GII.17)
Hu/GII.P17_GII.17/KR/2015/CAU-267

more info



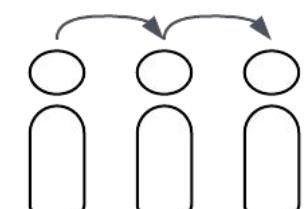
Back to our timeline

Norovirus - the "Norwalk" virus

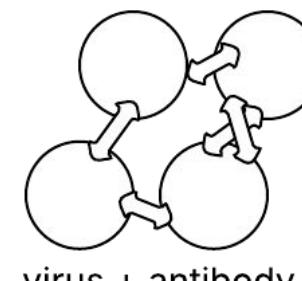
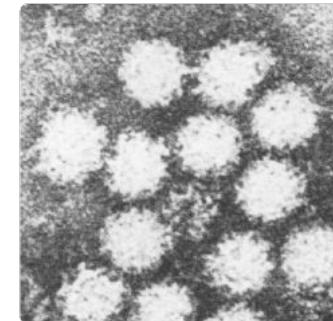


elementary school

cell culture ✗
tissue culture ✗
animal models ✗



human passaged



virus + antibody



1968 - Norwalk Ohio Outbreak
samples collected

[\(Adler & Zickl, 1968\)](#)

1972 - Immunoelectron Microscopy
aggregate viral particles by antiserum

[\(Hayashi et al, 2024\)](#)

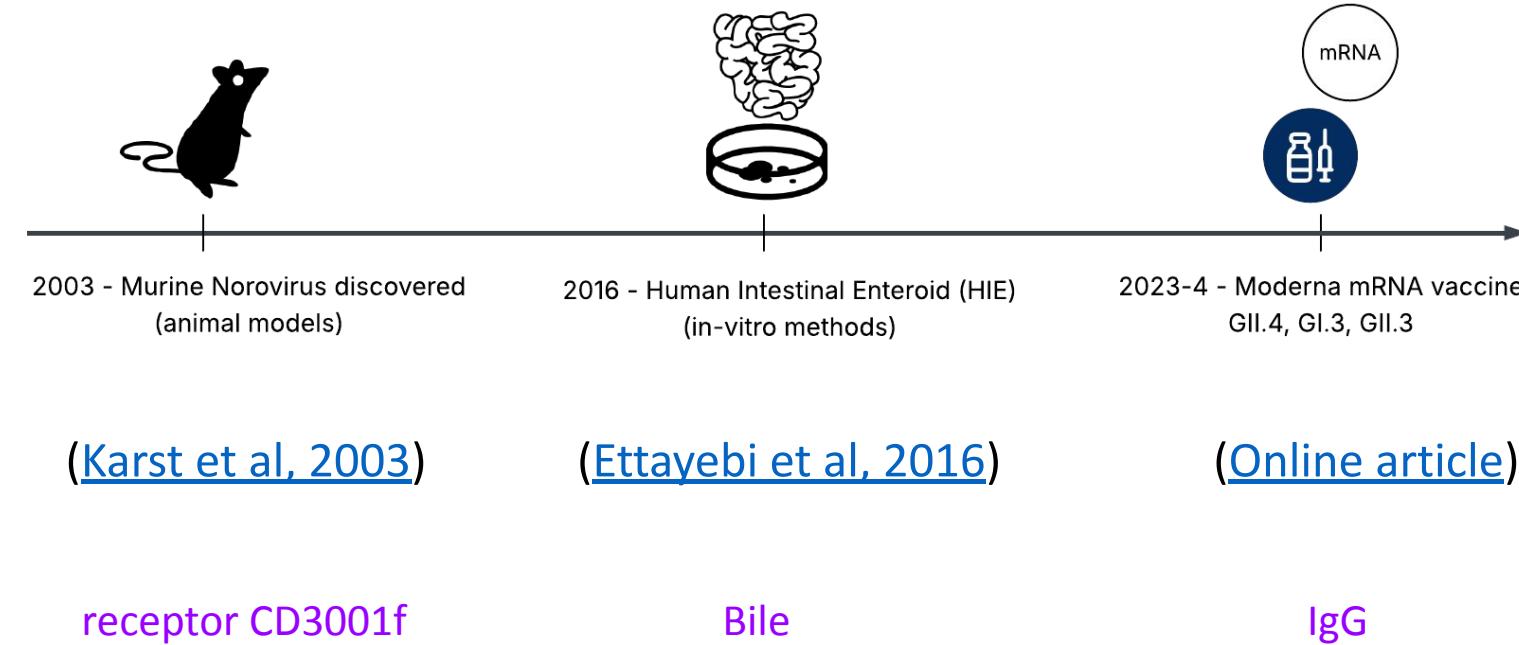
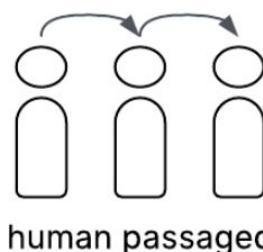
[\(Kapikian et al, 1972\)](#)

1989 - First sequenced
(described in 1993, Jiang et al)

[\(Jiang et al, 1993\)](#)

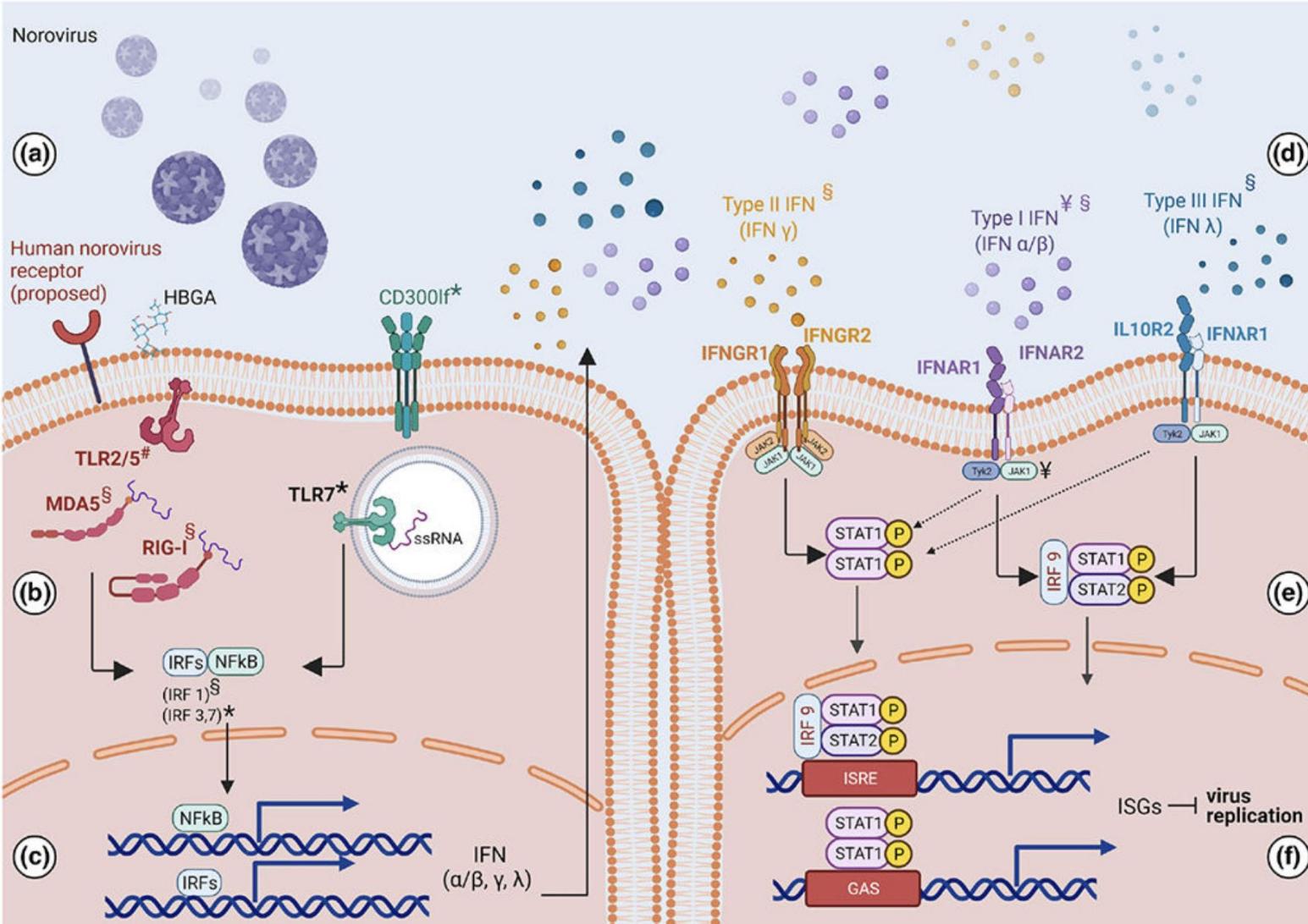
Norovirus - recent developments

cell culture x
tissue culture x
animal models x



([Adler & Zickl, 1968](#))

Host Response

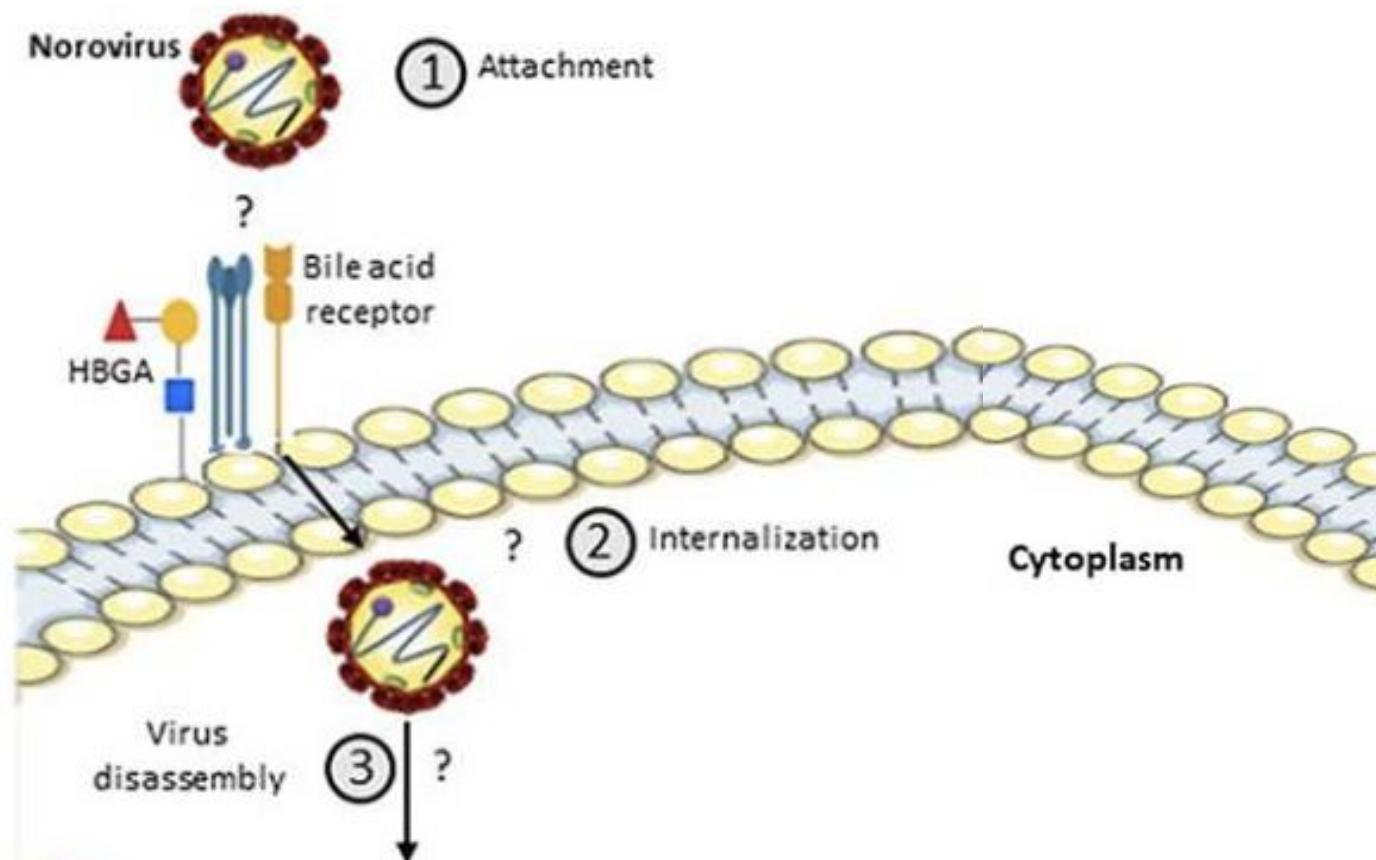


Mboko, W.P., Chhabra, P., Valcarce, M.D., Costantini, V. and Vinjé, J., 2022. **Advances in understanding of the innate immune response to human norovirus infection using organoid models.** Journal of General Virology, 103(1), p.001720.

Fig. 1.

The antiviral response in norovirus-infected cells. Norovirus infection induces an antiviral response that restricts virus replication. a. Human norovirus attachment is facilitated by human blood group antigens (HBGA) and a receptor that is yet to be identified. In mice the receptor is CD300lf [66]. b. Viral entry results in sensing of the virus and viral components by molecular sensors. The molecular sensors that are triggered during human norovirus infection have not been identified, however human norovirus virus-like particles (VLPs) have been shown to trigger TLR2 and TLR5 [70]. MDA5 and RIG-I are also involved in the

Host Response



Campillay-Véliz, C.P., Carvajal, J.J., Avellaneda, A.M., Escobar, D., Covián, C., Kalergis, A.M. and Lay, M.K., 2020.

Human norovirus proteins: implications in the replicative cycle, pathogenesis, and the host immune response. *Frontiers in immunology*, 11, p.961.

HIO - Mboko et al, 2022

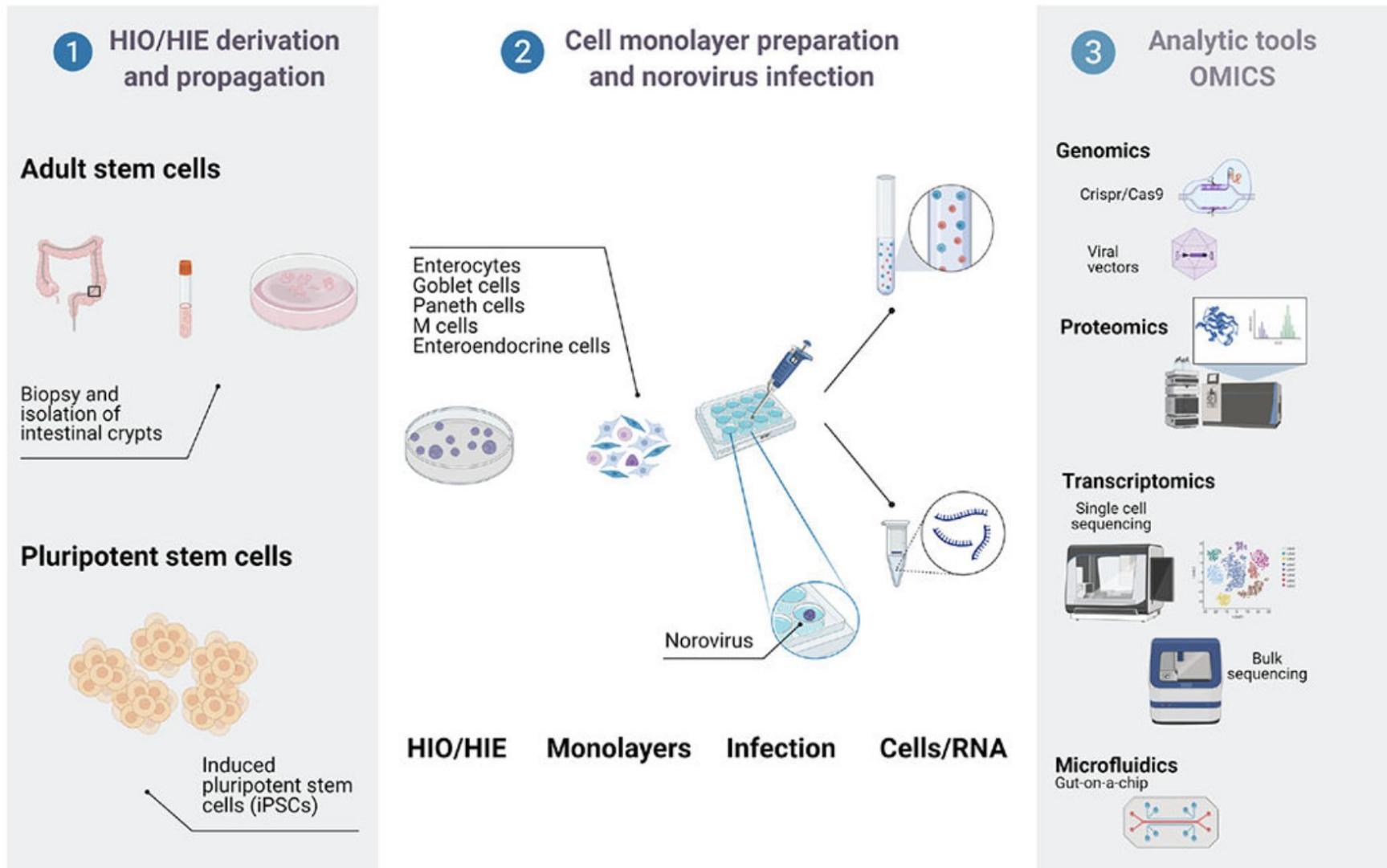
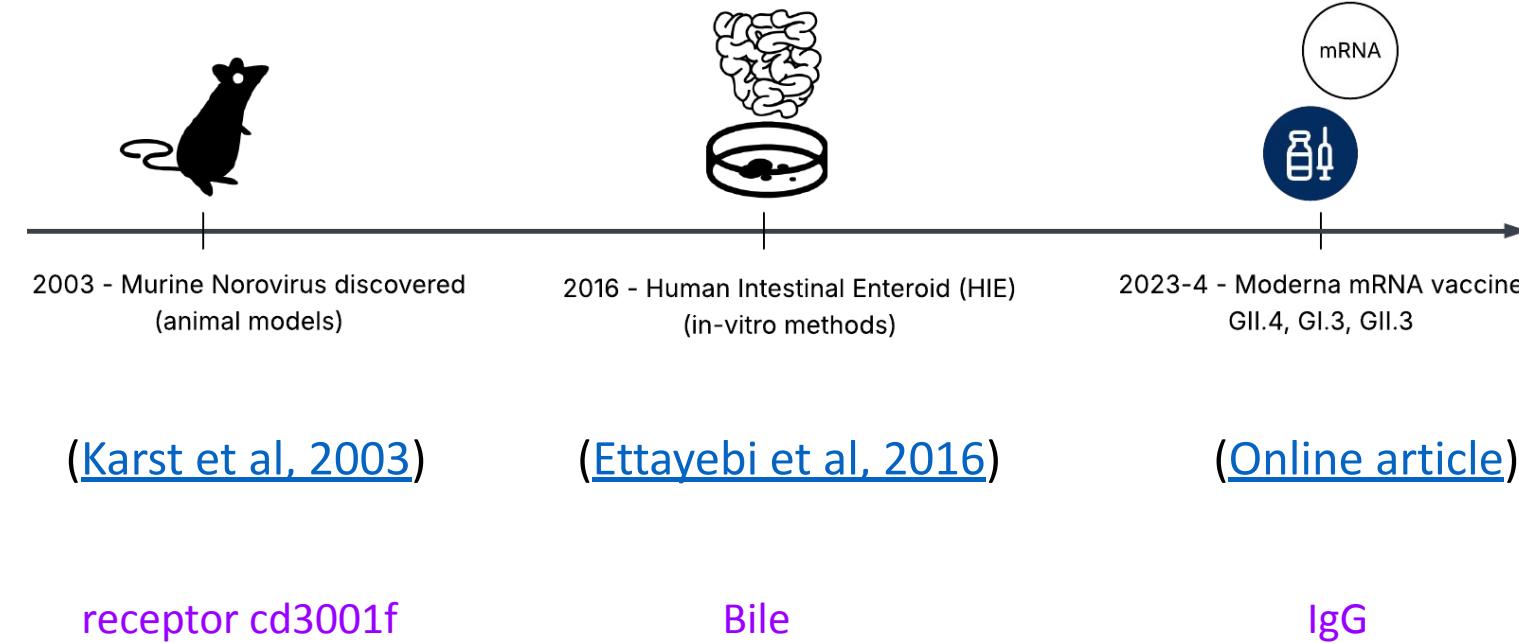
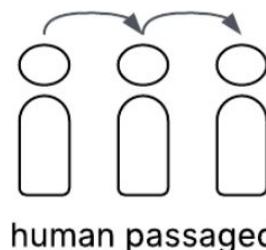


Fig. 2.

Application of human intestinal enteroids/organoids (HIE/HIO) in immune response to human norovirus infection. HIE/HIO can be used to investigate the immune response to norovirus infection and determine mechanisms that restrict norovirus replication. HIE and HIO are derived either from biopsies, or adult induced pluripotent cells (iPSCs). Once HIE/HIO are differentiated, they can be infected with human norovirus. The cells can be manipulated using CRISPR/Cas9 or viral vectors to create mutant strains that also be used in norovirus studies. Cells and RNA derived from infected HIE/HIO can be analysed for transcriptional changes using RNA sequencing. Single cell RNA sequencing can also be subjected to proteomics-based analyses to investigate effects on expression. Another potential application of HIE/HIO is measuring the immune response to norovirus infection using gut-on-a-chip technology. Created with BioRender.com on 12 October 2021).

Norovirus - recent developments

cell culture x
tissue culture x
animal models x



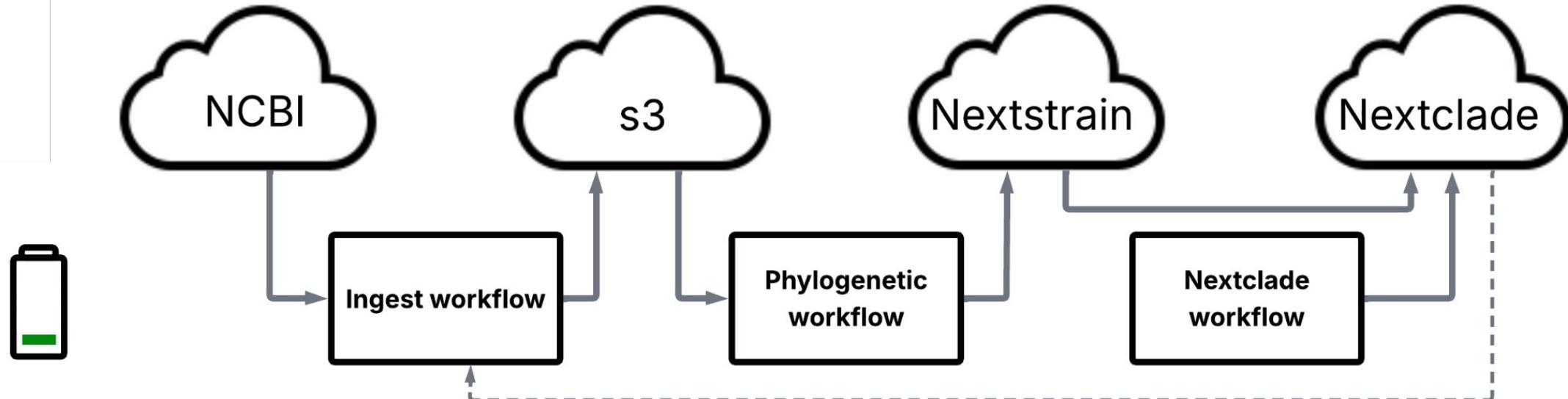
([Adler & Zickl, 1968](#))

Thank you!

Road Map

Remaining tasks

optional tasks



Norovirus NCBI Taxon ID: 142786
merge GenomeDetective.tsvs
calculate gene coverage

54 -> 14 builds
6 genotypes, 8 genes
GII.4 reference
Recombination

CDC References - Genome Detective
VP1 (ORF2), RdRp (ORF1)
Added missing GIII(bovine, GV(murine),
GVI and GVII (canine)

Pathogen-repo-guide

Why align to a pathogen repo guide?

Nextstrain GitHub Practices

Consistency and Reproducibility

Nextstrain's focus on pathogen genomics requires a high degree of consistency in data analysis workflows. By implementing best practices, particularly in Snakemake workflows, we ensure:

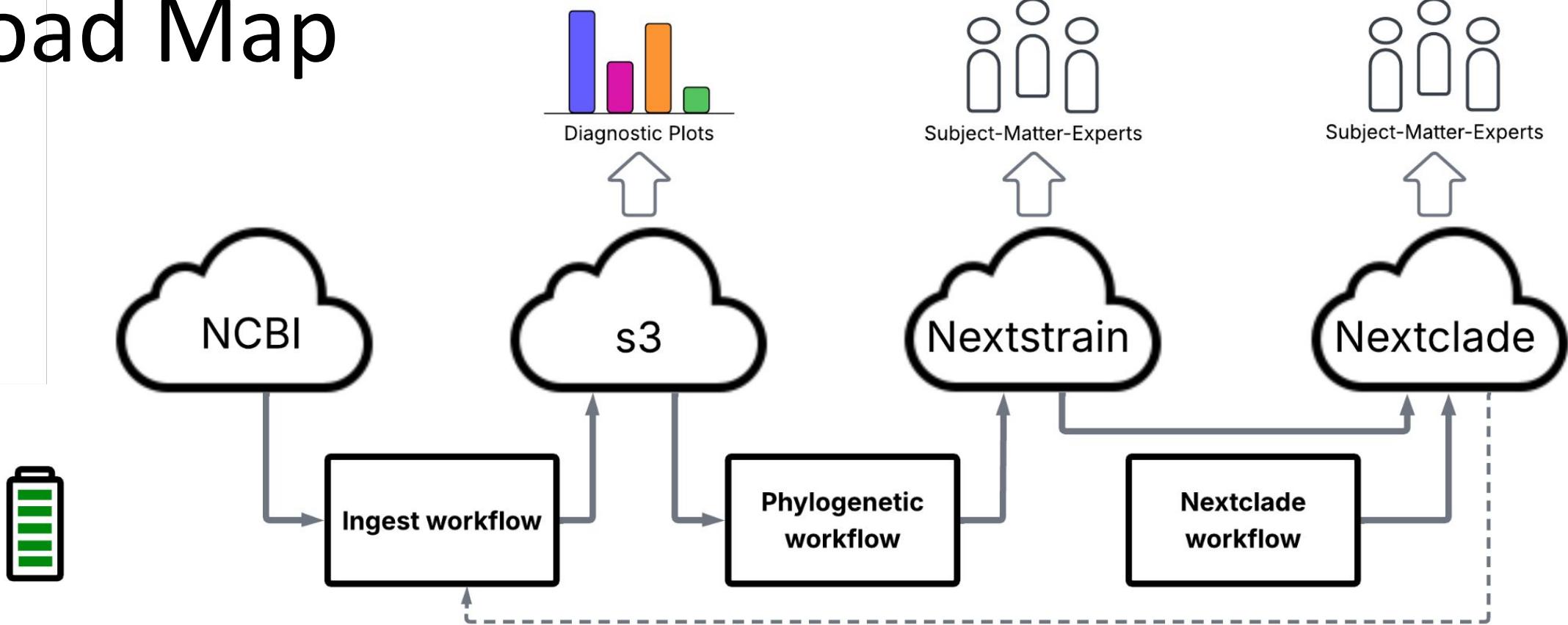
- Reproducible analysis across different datasets and pathogens
- Uniform coding standards that facilitate easier code review and maintenance
- Consistent file structures and naming conventions

Continuous Improvement and Adaptability

The field of pathogen genomics is rapidly evolving, and Nextstrain's best practice aims to collaboratively adapt and maintain high quality by:

- Regular review and updates to best practices to incorporate new tools and methodologies
- Some flexibility to adapt workflows for different pathogens and analysis requirements

Road Map



GitHub PRs - levels of effort for review



pathogen-repo-guide
(e.g. ingest workflow)



in another repo
(e.g. copy an existing script)



add a new standard
(e.g. add a new tool/feature)

Photos by [Leslie Saunders](#), [Jens Lelie](#), and [Joshua Earle](#) on [Unsplash](#)