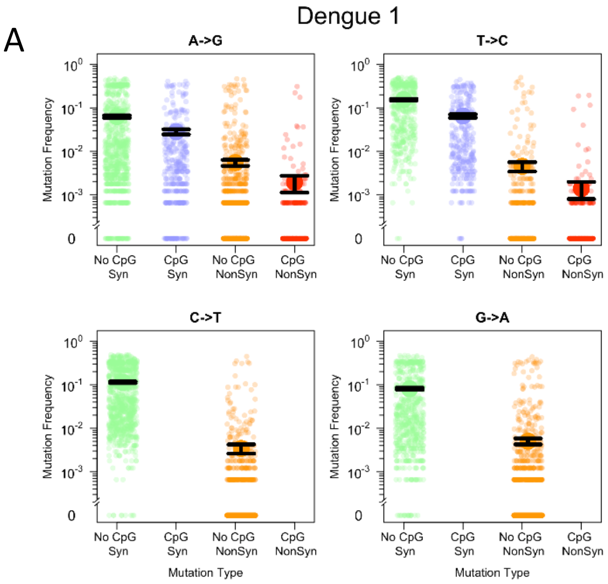
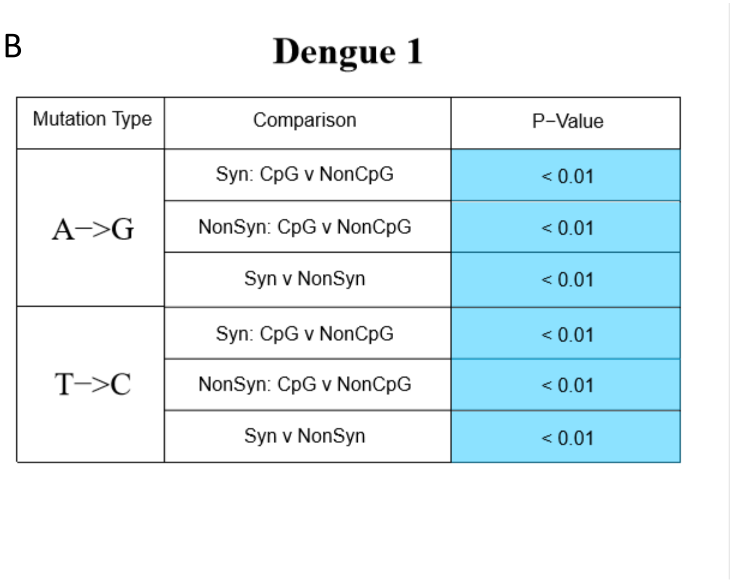
Dengue 1



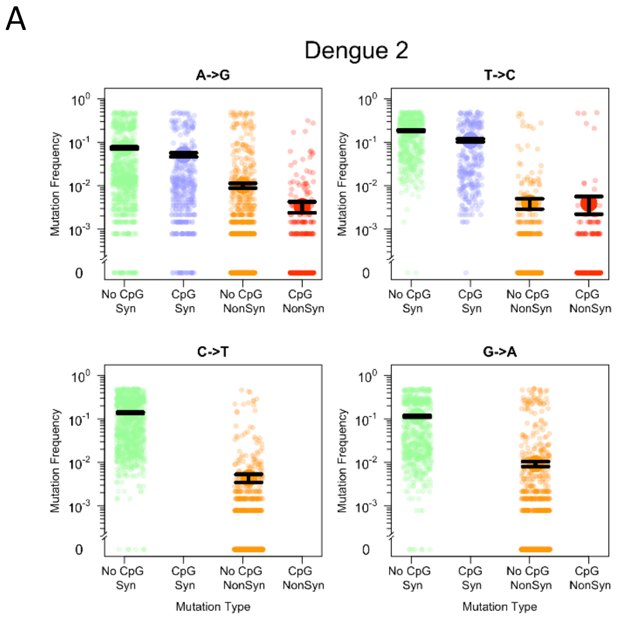


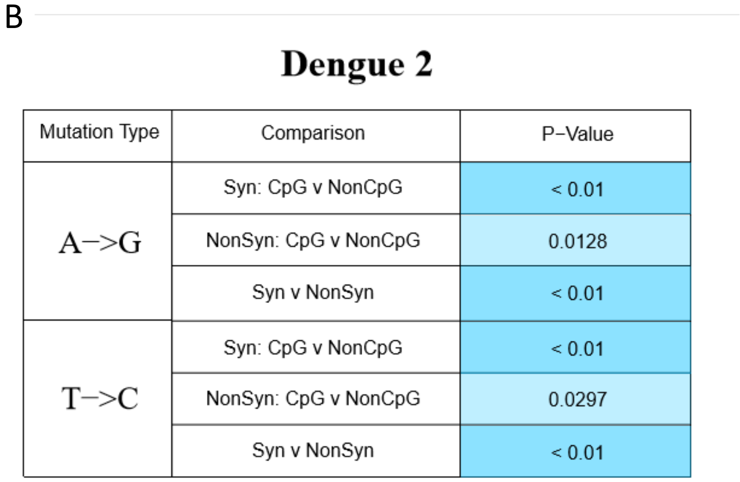
**Dengue 1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 1.** (a) Transition mutation frequencies for the analysis of Dengue 1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Dengue 2



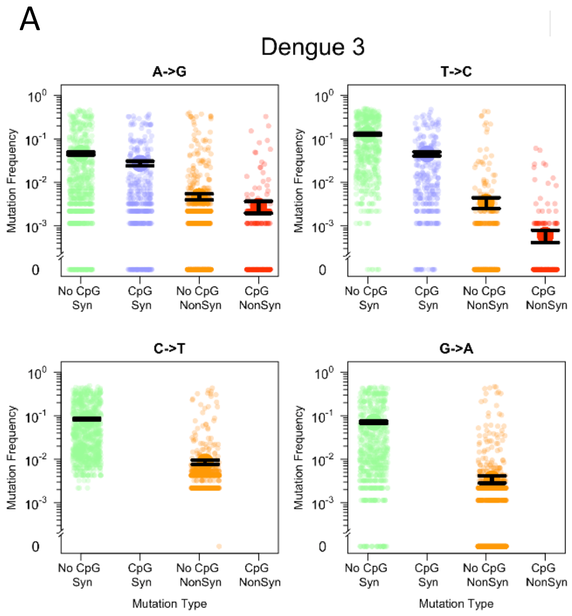


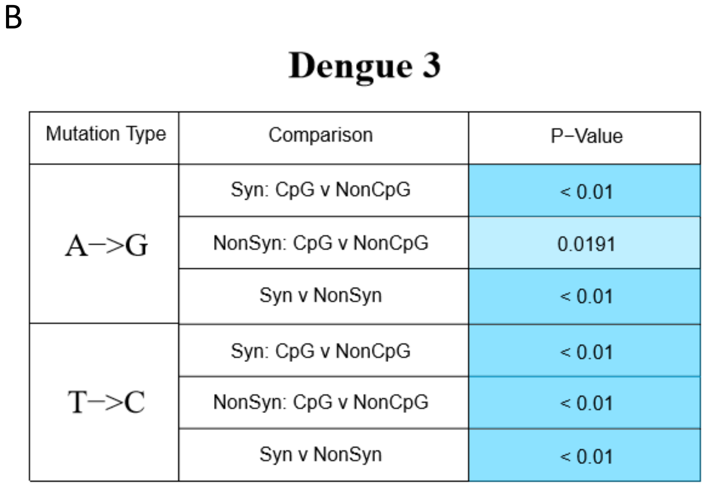
**Dengue 2**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0128 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0297 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 2.** (a) Transition mutation frequencies for the analysis of Dengue 2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Dengue 3



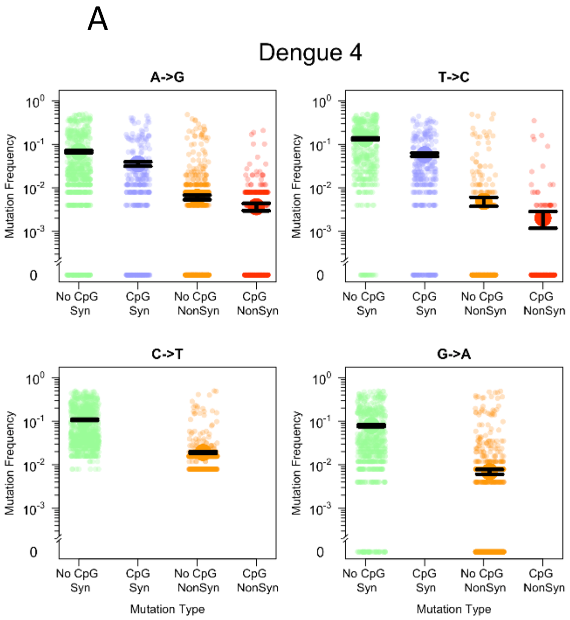


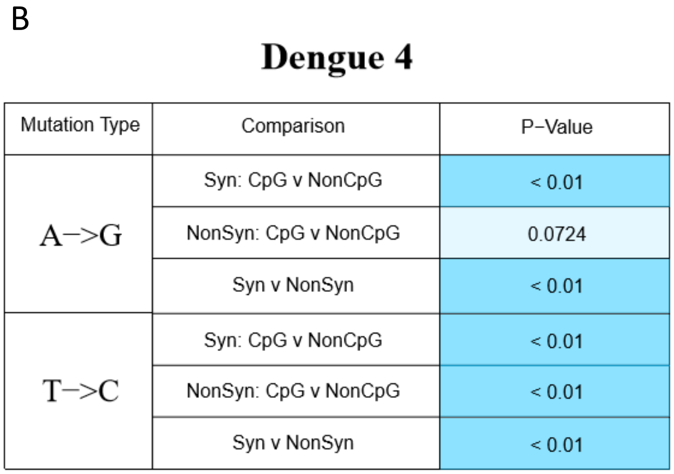
## Dengue 3

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0191 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 3.** (a) Transition mutation frequencies for the analysis of Dengue 3 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Dengue 4

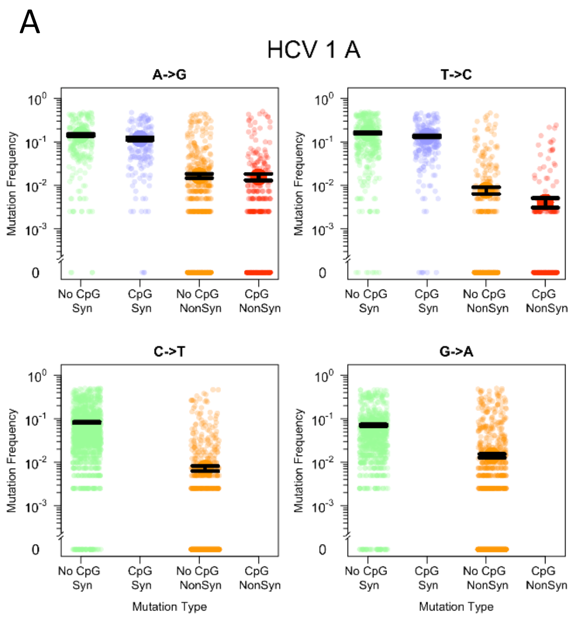


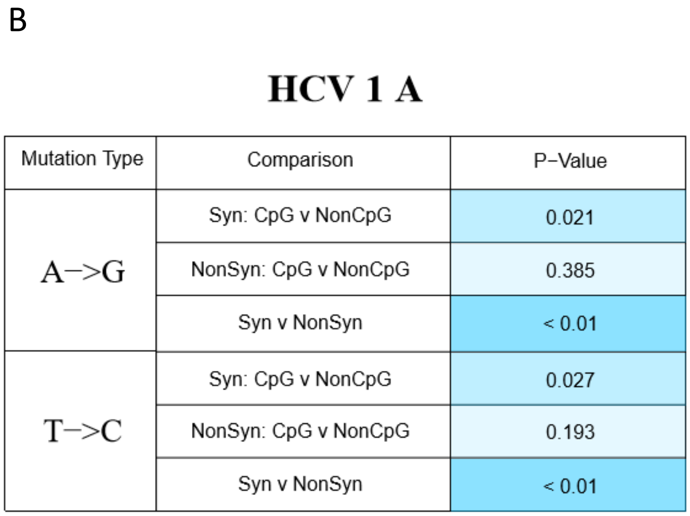


| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0724 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 4.** (a) Transition mutation frequencies for the analysis of Dengue 4 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HCV1 A



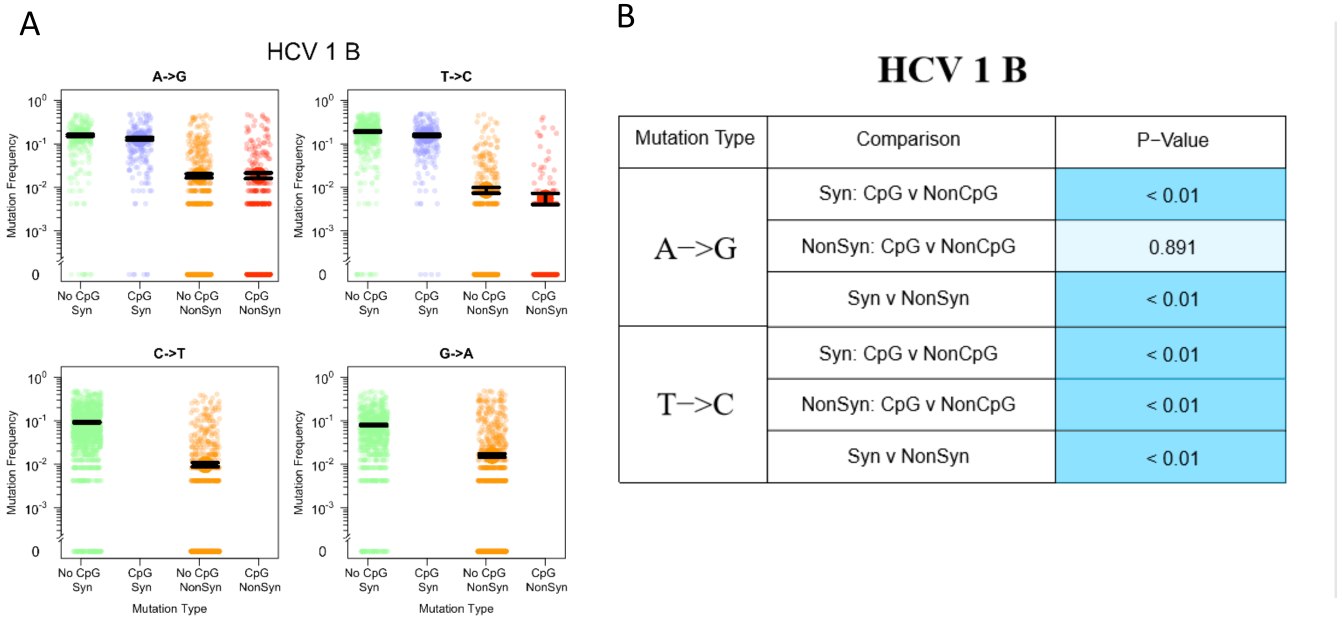

B

HCV 1 A

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.021 |
| | NonSyn: CpG v NonCpG | 0.385 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.027 |
| | NonSyn: CpG v NonCpG | 0.193 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 5.** (a) Transition mutation frequencies for the analysis of HCV 1 A with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

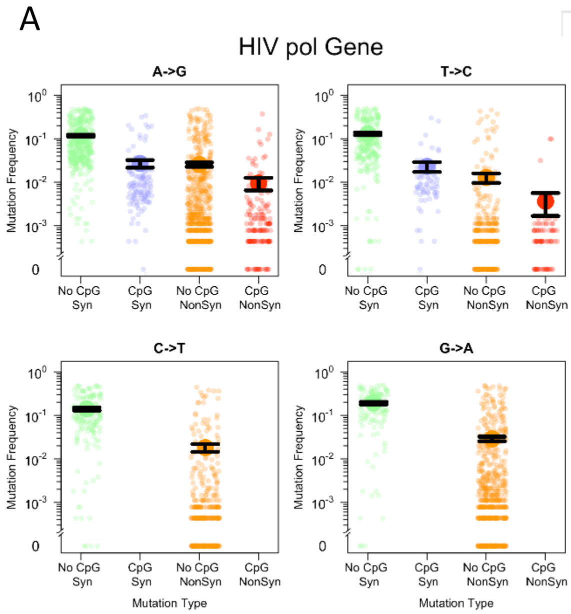
HCV 1 B

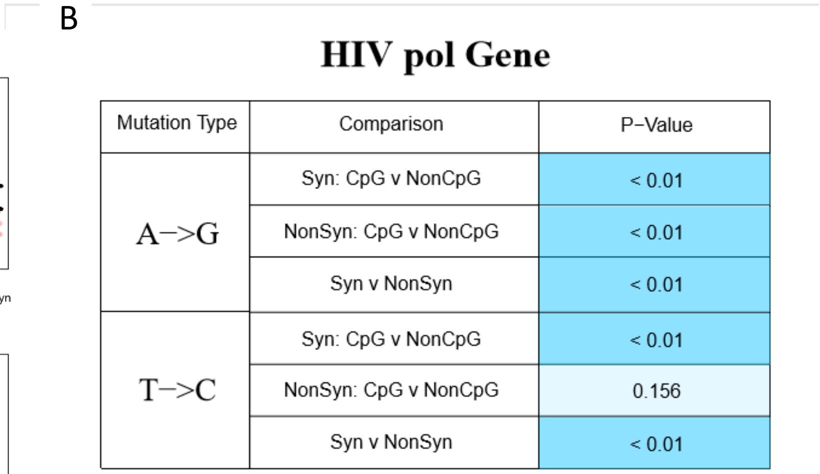


| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.891 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 6.** (a) Transition mutation frequencies for the analysis of HCV 1 B with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HIV pol Gene




B

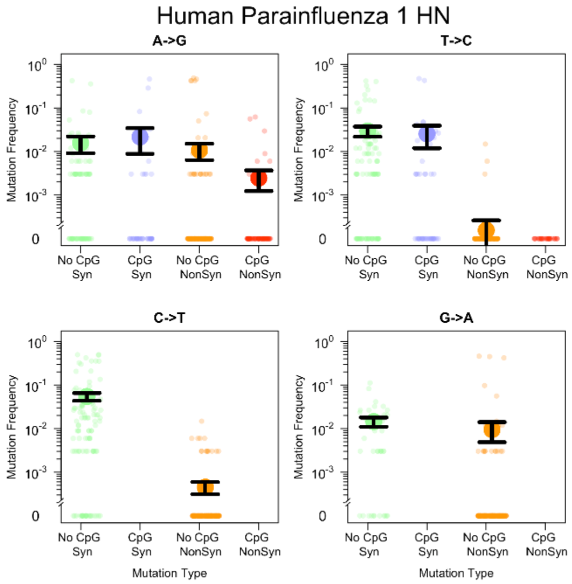
## HIV pol Gene

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.156 |
| | Syn v NonSyn | < 0.01 |

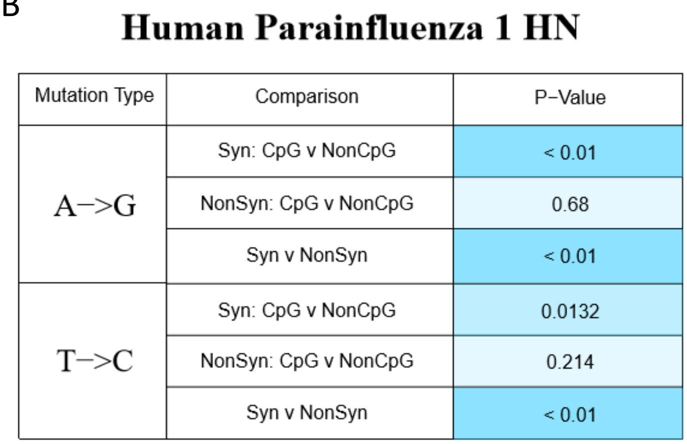
**Supplementary Fig 7.** (a) Transition mutation frequencies for the analysis of HIV Pol with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Human Parainfluenza 1 HN

A



B

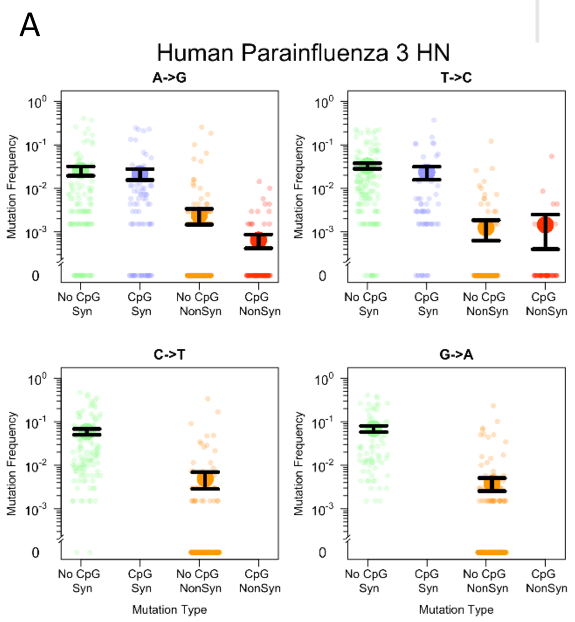


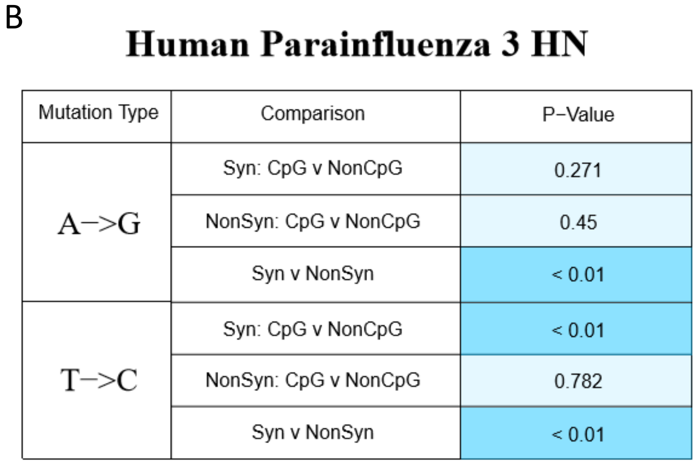
**Human Parainfluenza 1 HN**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.68 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.0132 |
| | NonSyn: CpG v NonCpG | 0.214 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 8.** (a) Transition mutation frequencies for the analysis of Human Parainfluenza 1 HN with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Human Parainfluenza 3 HN





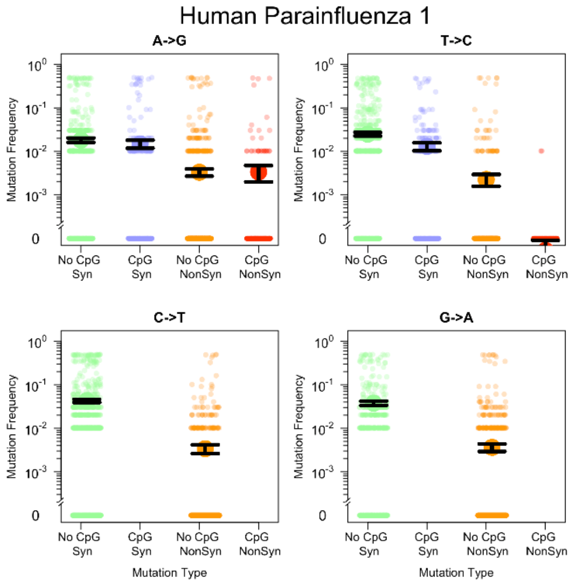
**Human Parainfluenza 3 HN**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.271 |
| | NonSyn: CpG v NonCpG | 0.45 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.782 |
| | Syn v NonSyn | < 0.01 |

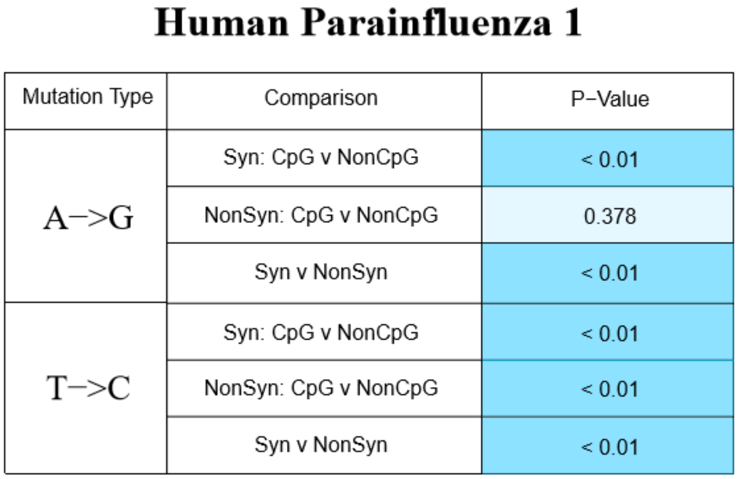
**Supplementary Fig 9.** (a) Transition mutation frequencies for the analysis of Human Parainfluenza 3 HN with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Human Parainfluenza 1

A



B

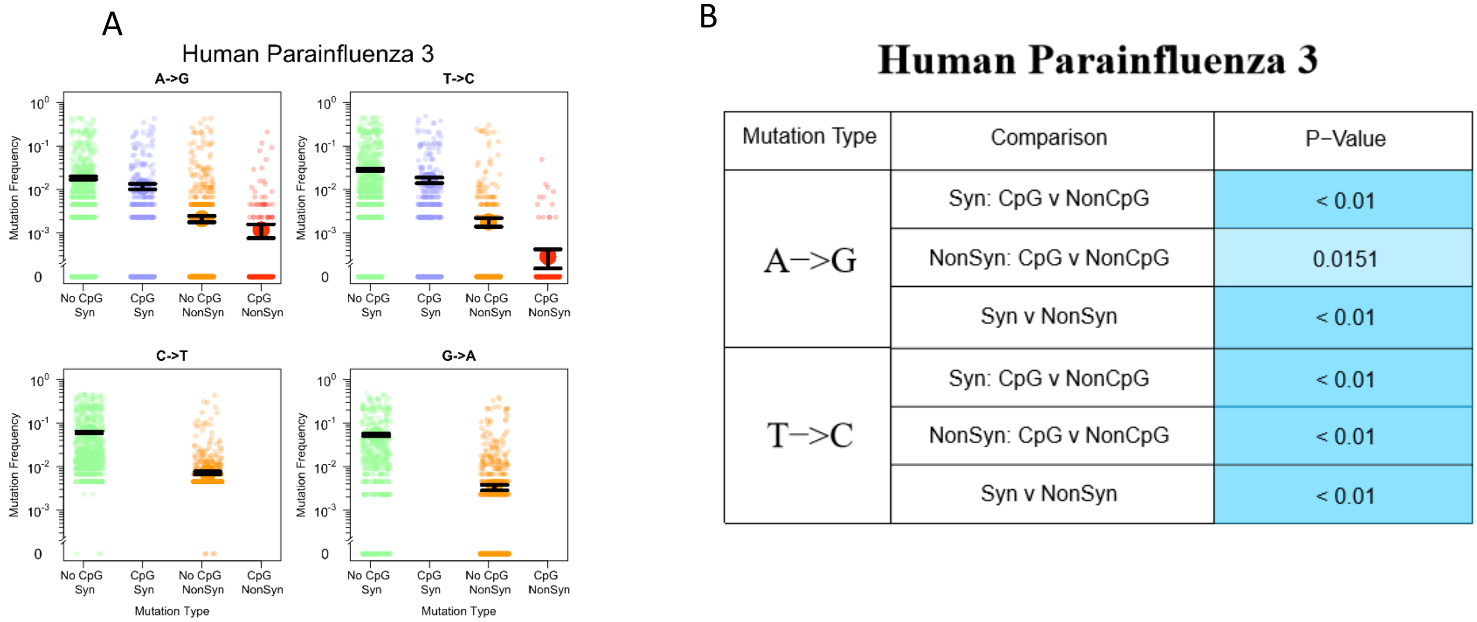


## Human Parainfluenza 1

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.378 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 10.** (a) Transition mutation frequencies for the analysis of Human Parainfluenza 1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Human Parainfluenza 3

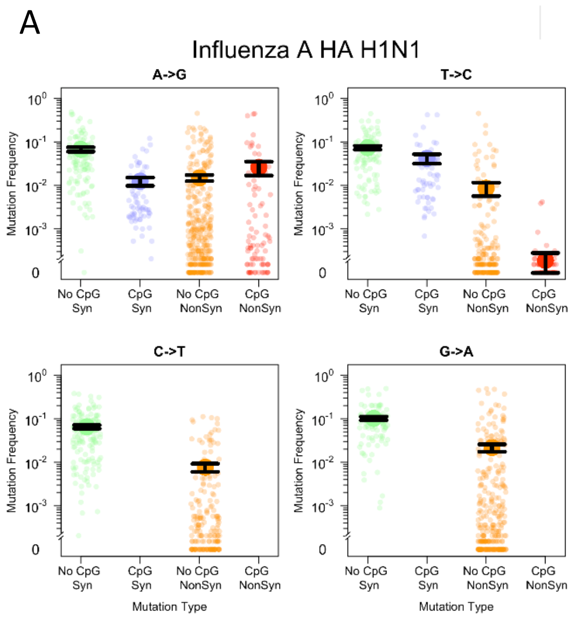


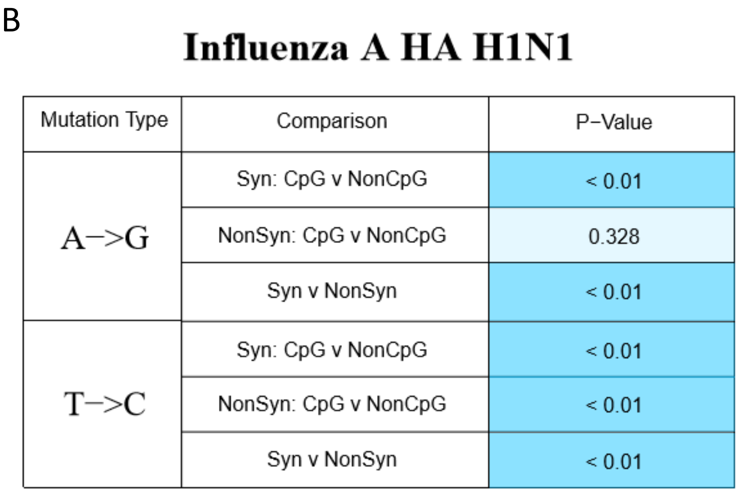
## Human Parainfluenza 3

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0151 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 11.** (a) Transition mutation frequencies for the analysis of Human Parainfluenza 3 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Influenza A HA H1N1



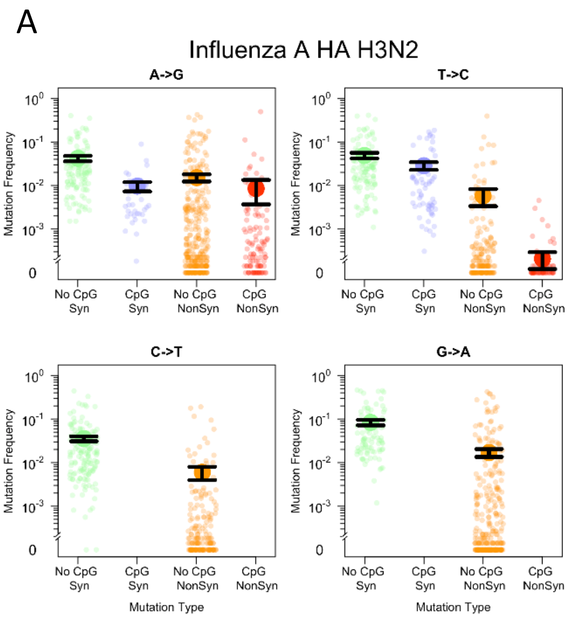


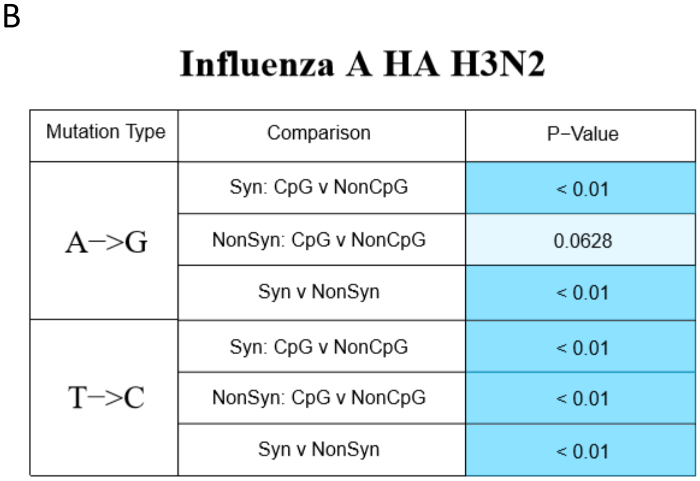
**Influenza A HA H1N1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.328 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 12.** (a) Transition mutation frequencies for the analysis of Influenza A HA H1N1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Influenza A HA H3N2



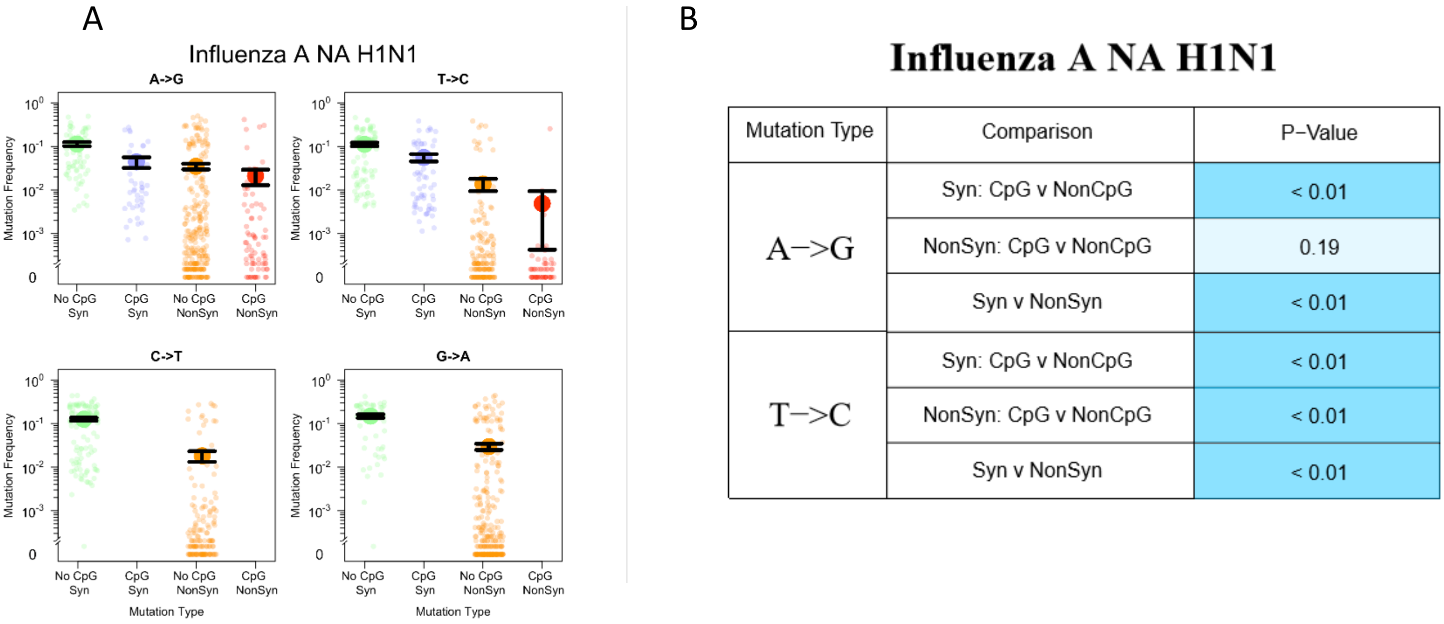

B

**Influenza A HA H3N2**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0628 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 13.** (a) Transition mutation frequencies for the analysis of Influenza A HA H3N2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Influenza A NA H1N1

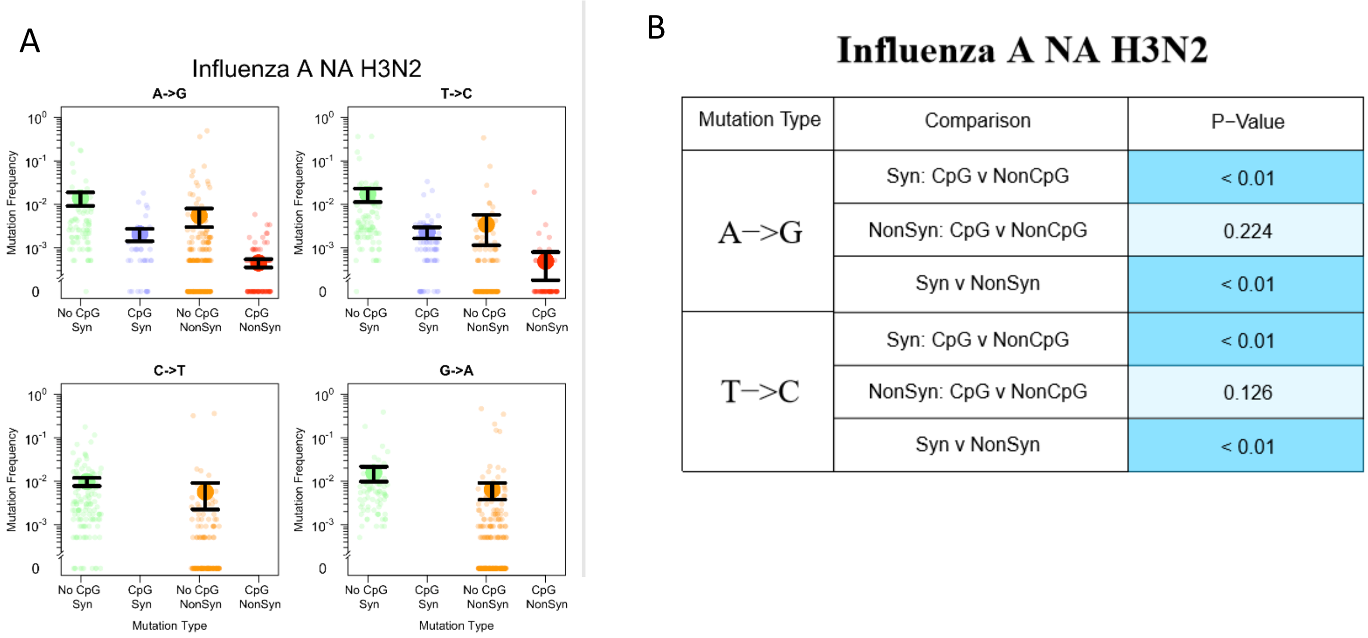


**Influenza A NA H1N1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.19 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 14.** (a) Transition mutation frequencies for the analysis of Influenza A NA H1N1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Influenza A NA H3N2

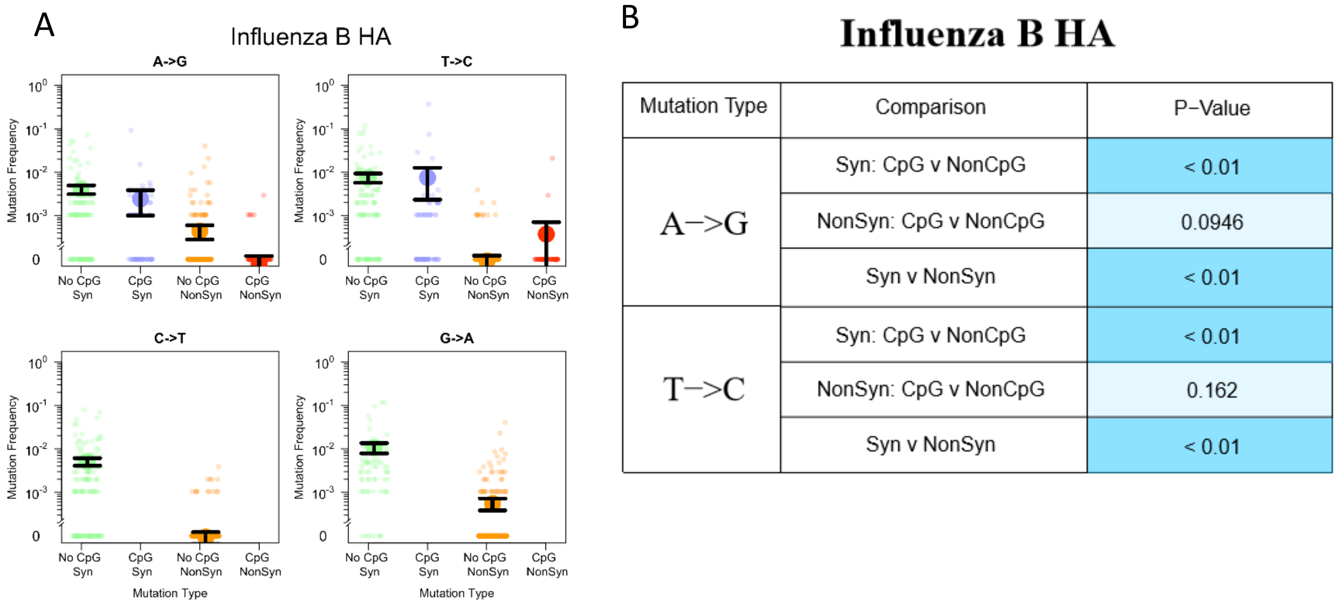


Influenza A NA H3N2

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.224 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.126 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 15.** (a) Transition mutation frequencies for the analysis of Influenza A NA H3N2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Influenza B HA

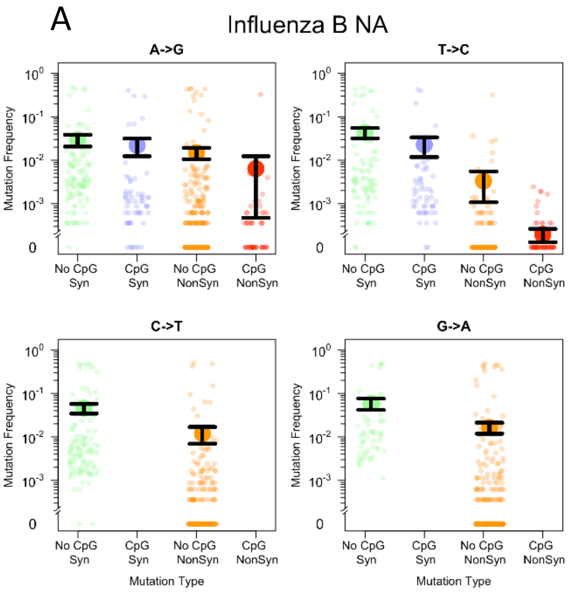


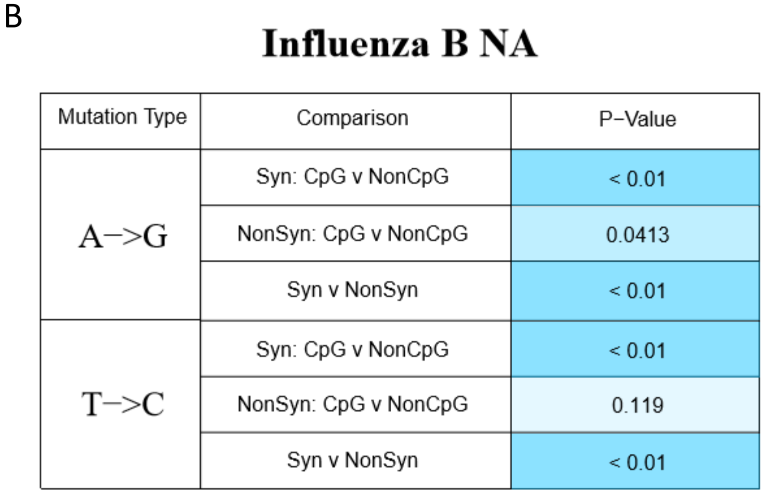
**Influenza B HA**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0946 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.162 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 16.** (a) Transition mutation frequencies for the analysis of Influenza B HA with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Influenza B NA



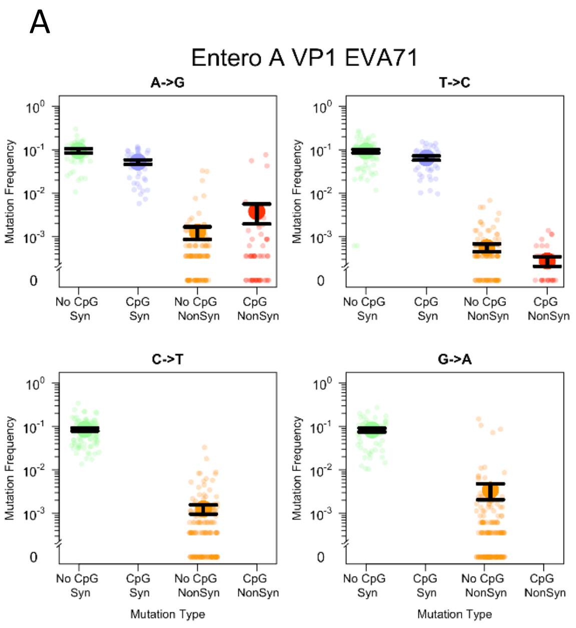

B

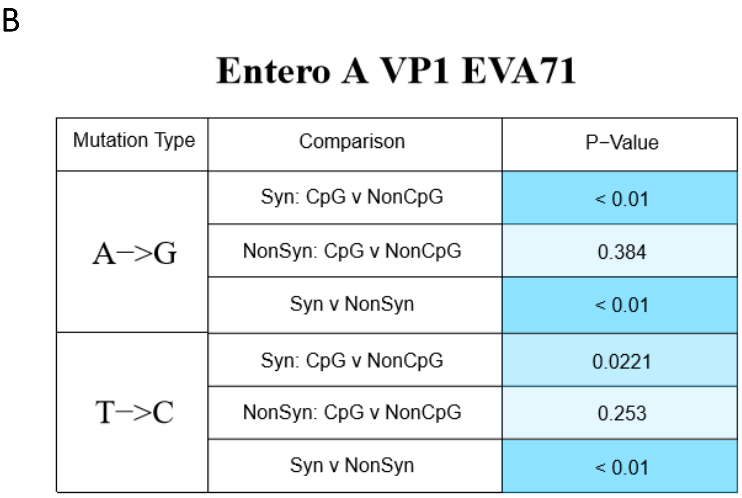
Influenza B NA

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
|  | NonSyn: CpG v NonCpG | 0.0413 |
|  | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
|  | NonSyn: CpG v NonCpG | 0.119 |
|  | Syn v NonSyn | < 0.01 |

**Supplementary Fig 17.** (a) Transition mutation frequencies for the analysis of Influenza B NA with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Entero A Vp1 EVA71



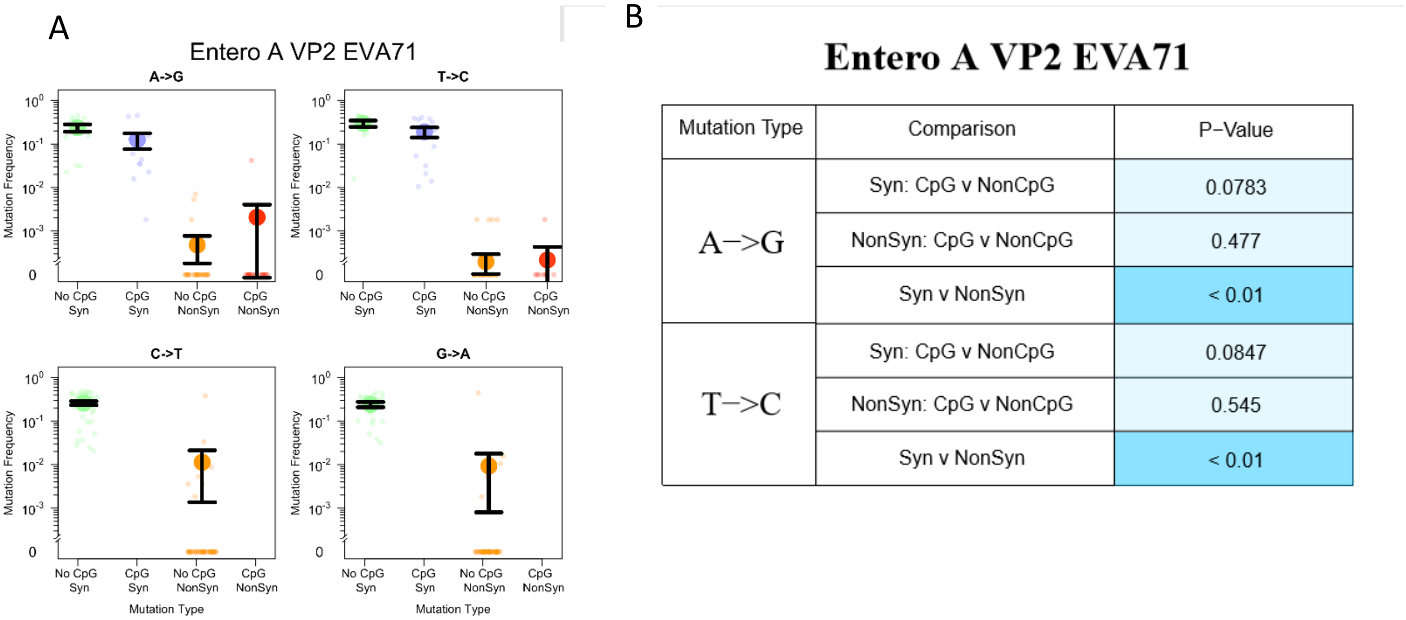


## Entero A VP1 EVA71

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.384 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.0221 |
| | NonSyn: CpG v NonCpG | 0.253 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 18.** (a) Transition mutation frequencies for the analysis of Entero A VP1 Eva71 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Entero A Vp2 EVA71

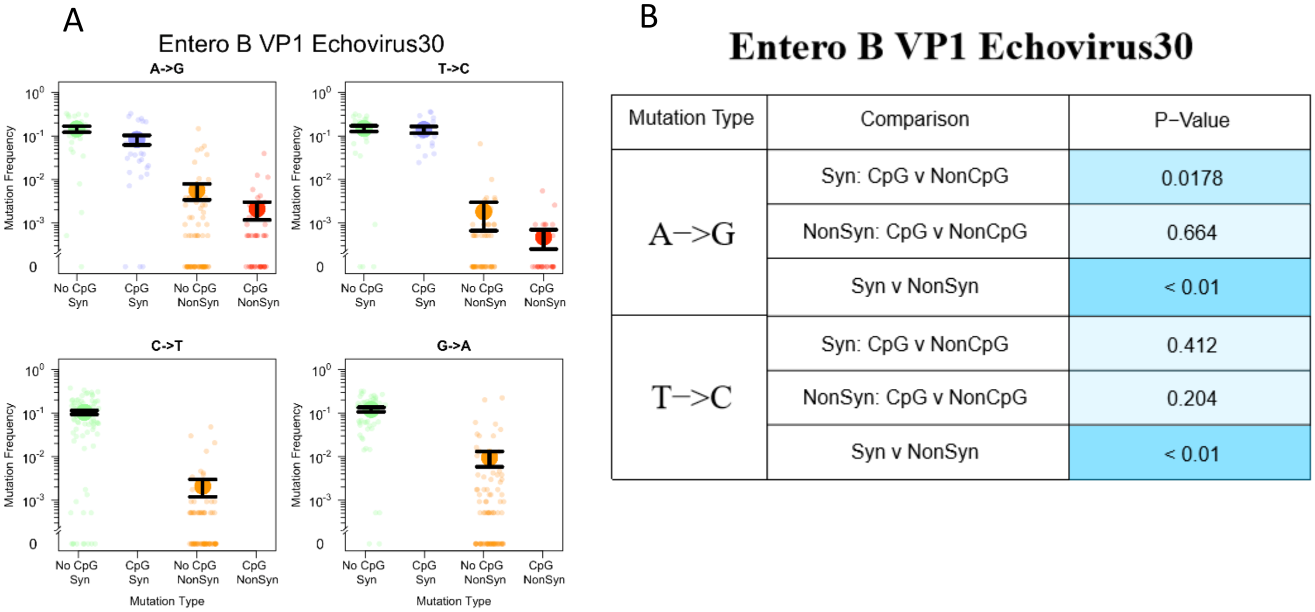


## Entero A VP2 EVA71

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.0783 |
| | NonSyn: CpG v NonCpG | 0.477 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.0847 |
| | NonSyn: CpG v NonCpG | 0.545 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 19.** (a) Transition mutation frequencies for the analysis of Entero A VP2 Eva71 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Entero B Vp1 Echovirus30

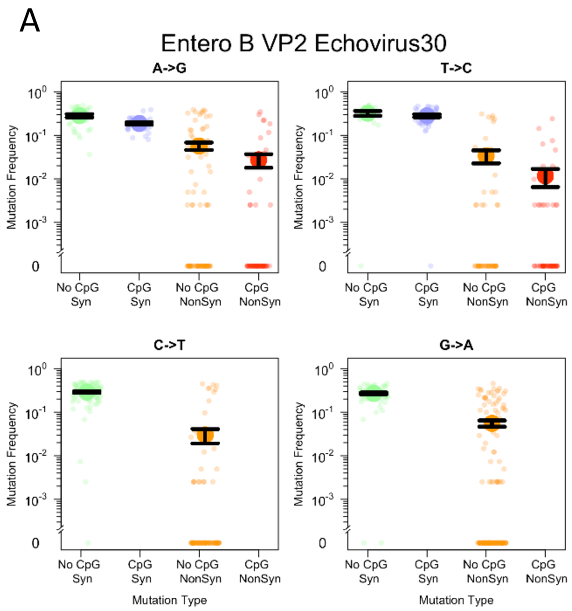


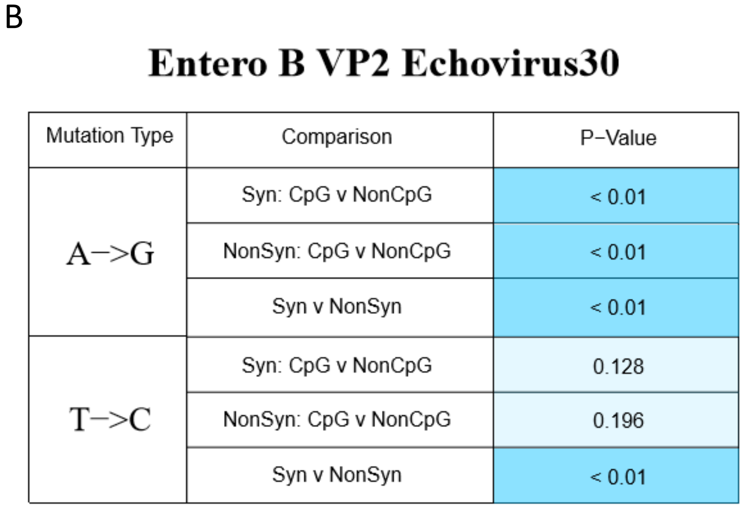
## Entero B VP1 Echovirus30

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.0178 |
| | NonSyn: CpG v NonCpG | 0.664 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.412 |
| | NonSyn: CpG v NonCpG | 0.204 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 20.** (a) Transition mutation frequencies for the analysis of Entero B VP1 Echovirus30 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Entero B Vp2 Echovirus30



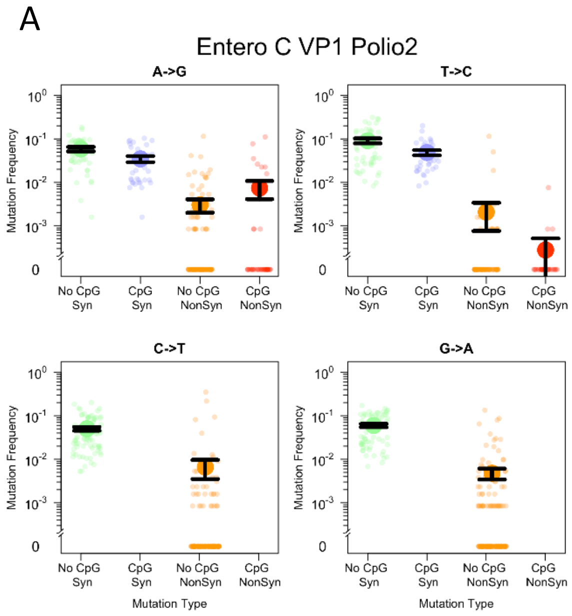


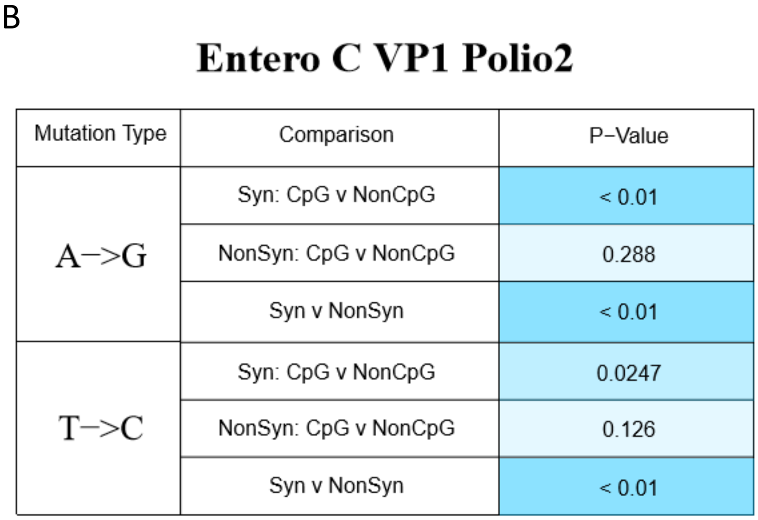
## Entero B VP2 Echovirus30

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.128 |
| | NonSyn: CpG v NonCpG | 0.196 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 21.** (a) Transition mutation frequencies for the analysis of Entero B VP2 Echovirus30 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Entero C VP1 Polio2



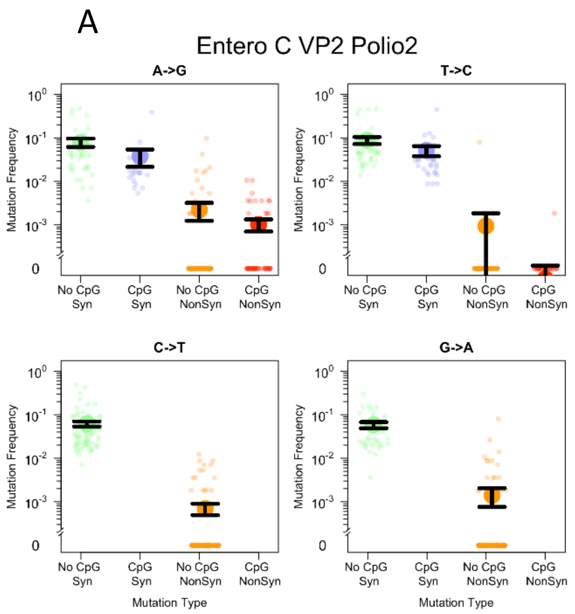


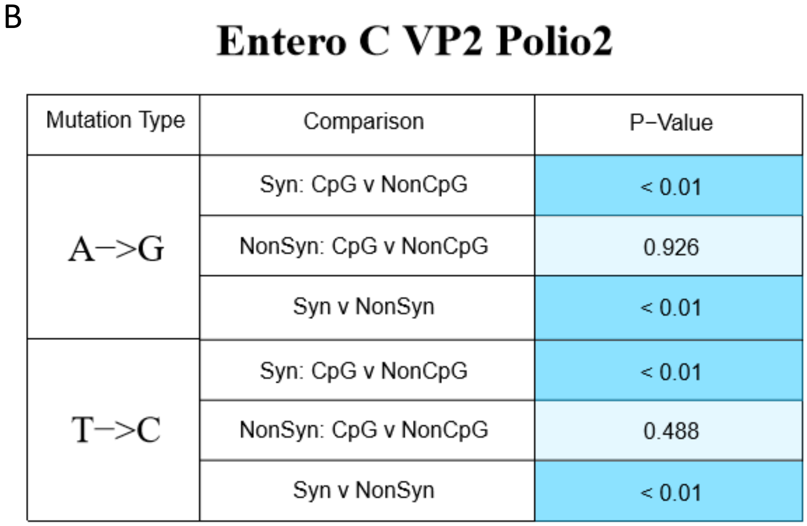
## Entero C VP1 Polio2

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.288 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.0247 |
| | NonSyn: CpG v NonCpG | 0.126 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 22.** (a) Transition mutation frequencies for the analysis of Entero C VP1 Polio2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Entero C VP2 Polio2



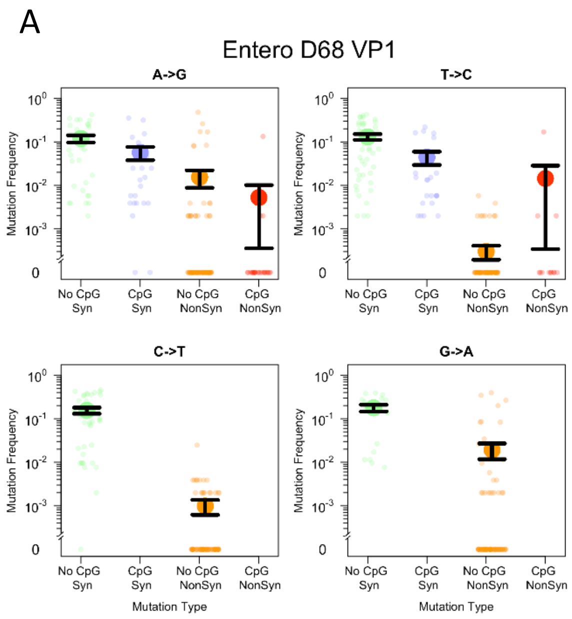


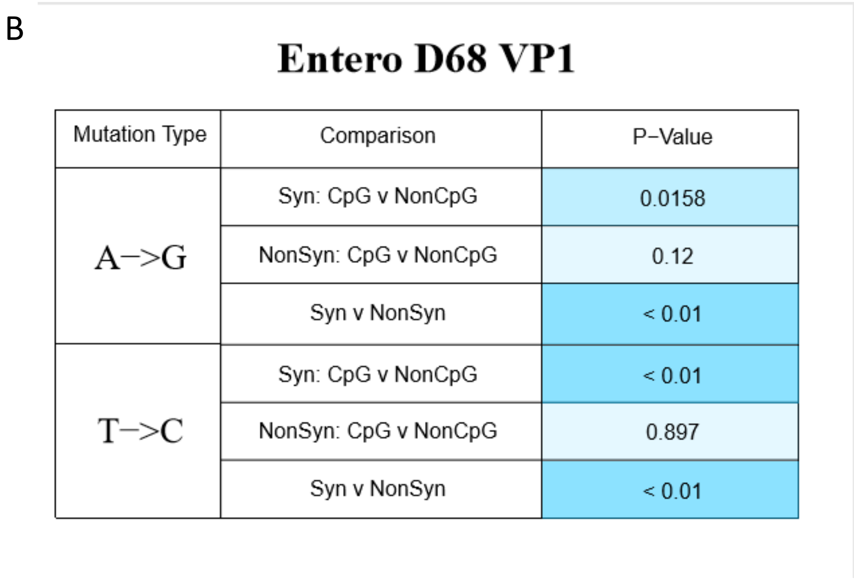
## Entero C VP2 Polio2

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.926 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.488 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 23.** (a) Transition mutation frequencies for the analysis of Entero C VP2 Polio2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

## Entero D68 VP1



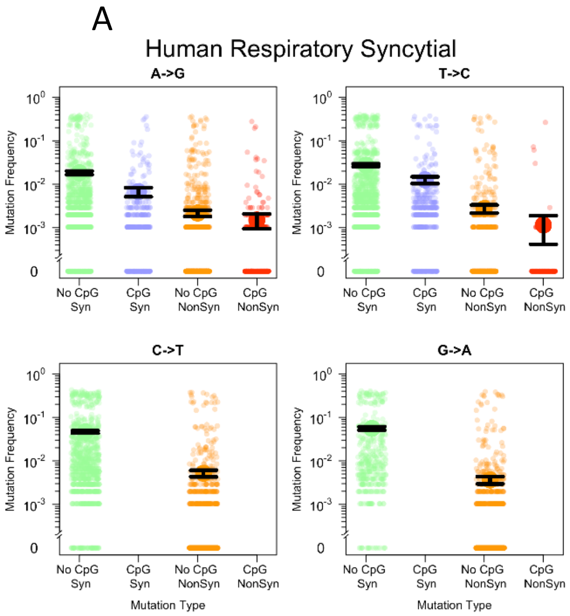


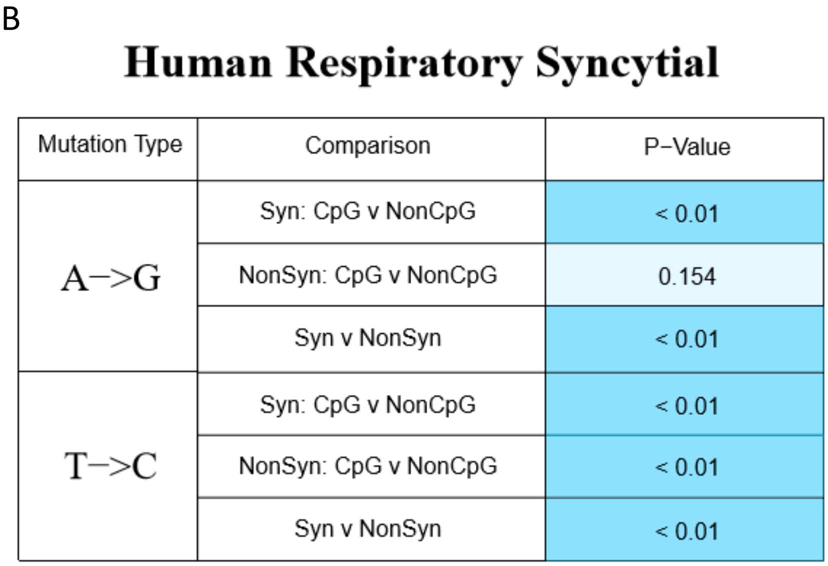
**Entero D68 VP1**

| Mutation Type | Comparison | P-Value |
|---|---|---|
| A->G | Syn: CpG v NonCpG | 0.0158 |
| | NonSyn: CpG v NonCpG | 0.12 |
| | Syn v NonSyn | < 0.01 |
| T->C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.897 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 24.** (a) Transition mutation frequencies for the analysis of Entero D68 VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Human Respiratory Syncytial



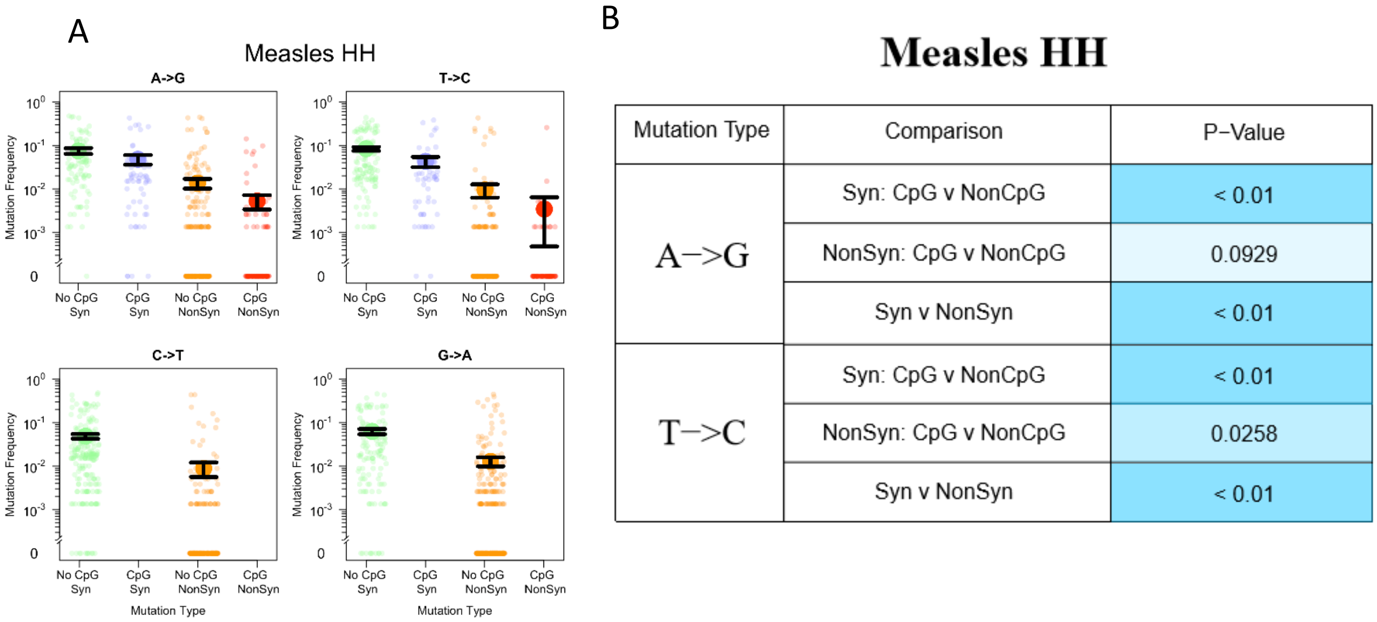


Human Respiratory Syncytial

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.154 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 25.** (a) Transition mutation frequencies for the analysis of Human Respiratory Syncytial with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Measles HH

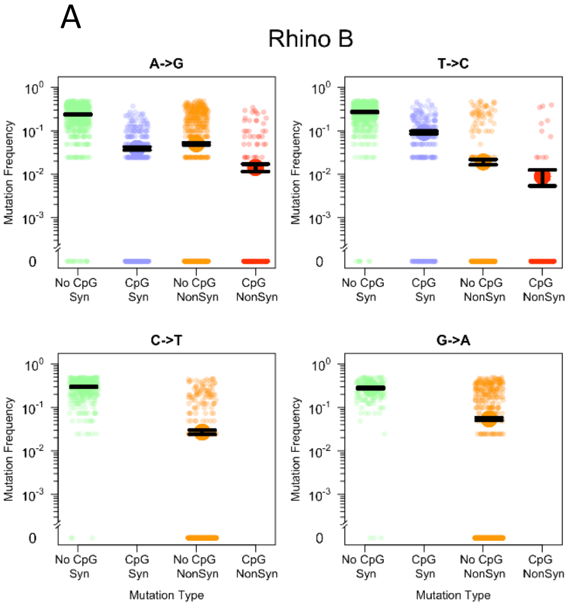


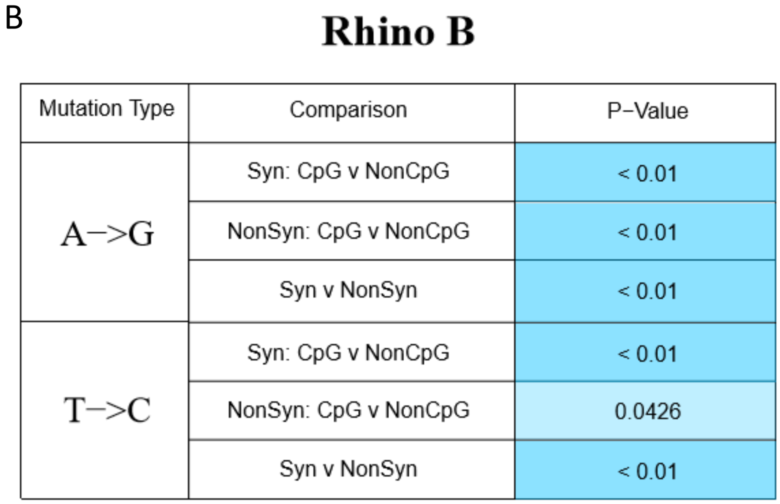
**Measles HH**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0929 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0258 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 26.** (a) Transition mutation frequencies for the analysis of Measles HH with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Rhino B



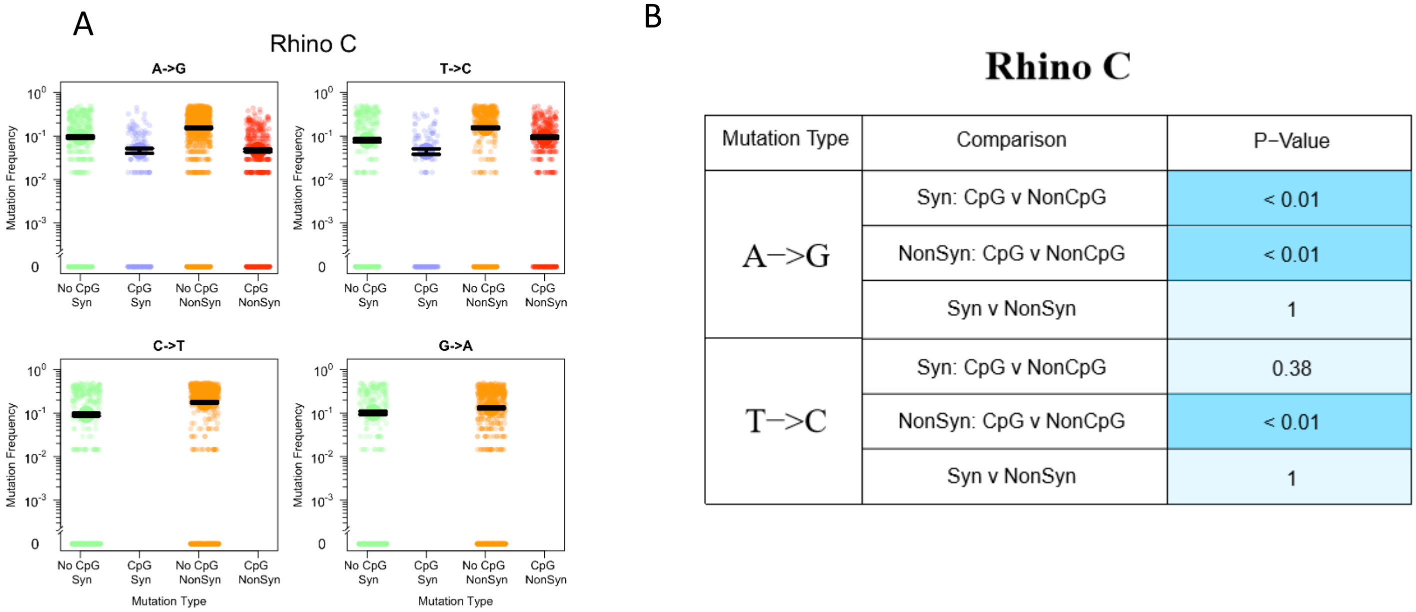


**Rhino B**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0426 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 27.** (a) Transition mutation frequencies for the analysis of Rhino B with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

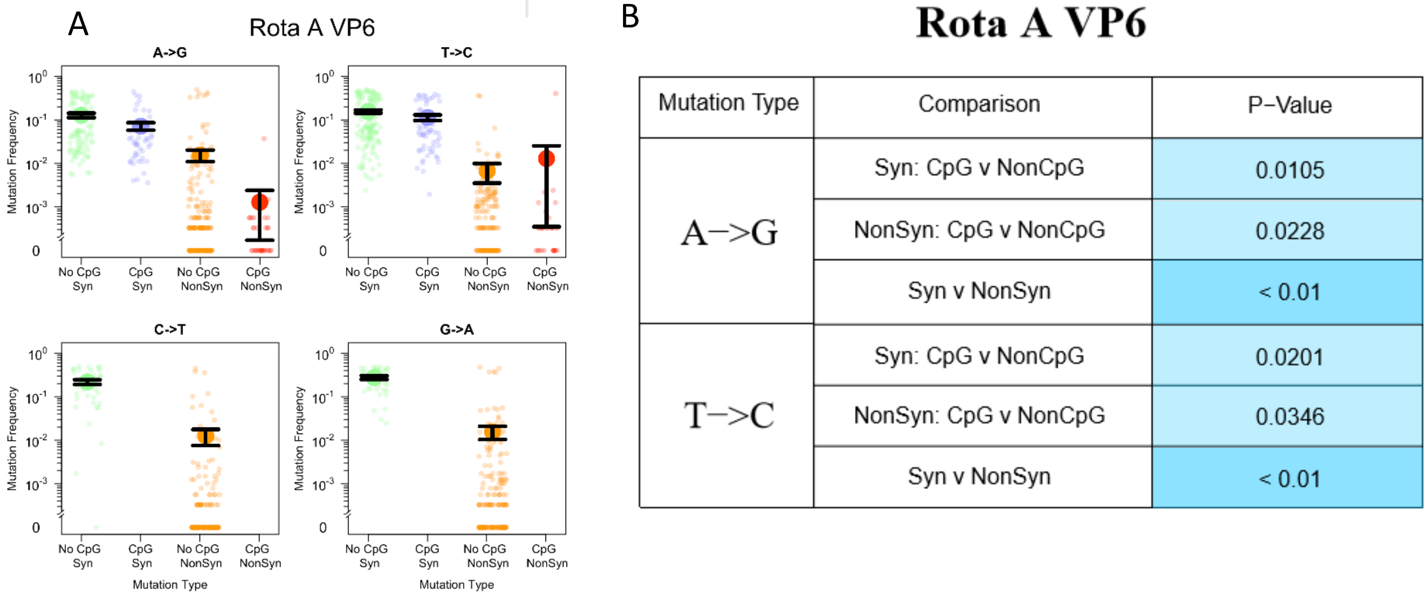
Rhino C



| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 1 |
| T−>C | Syn: CpG v NonCpG | 0.38 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 1 |

**Supplementary Fig 28.** (a) Transition mutation frequencies for the analysis of Rhino C with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

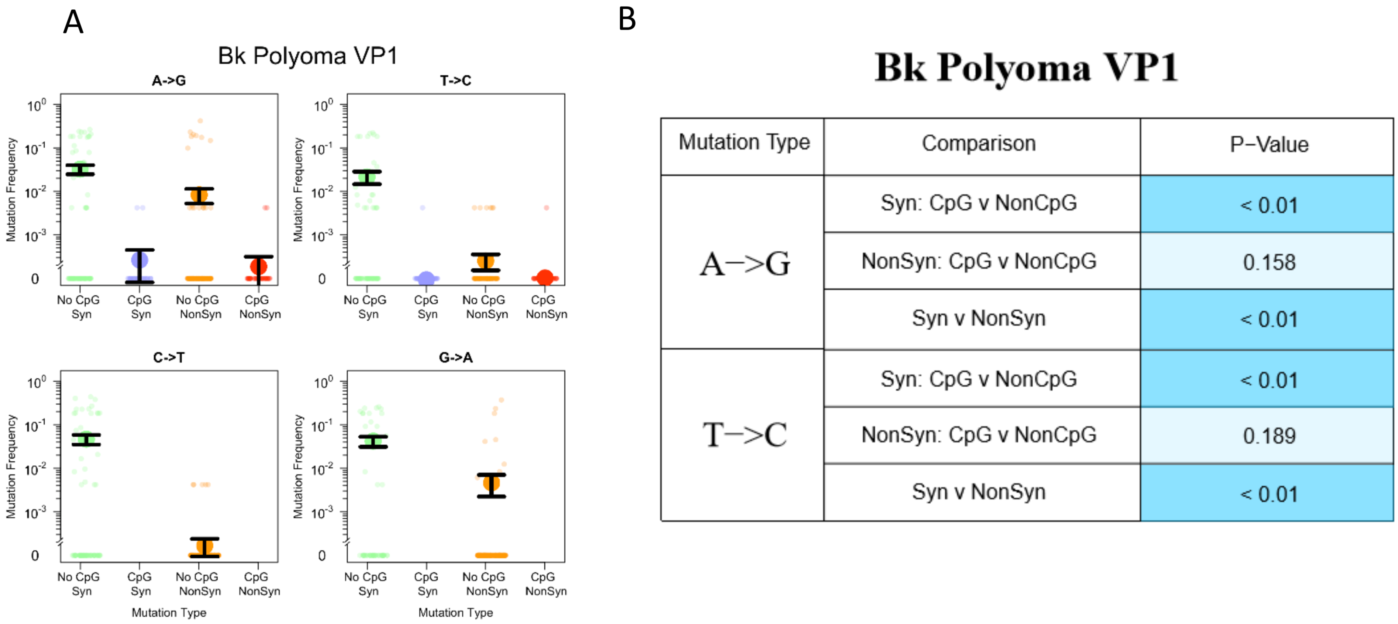
# Rota A VP6



| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.0105 |
| | NonSyn: CpG v NonCpG | 0.0228 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.0201 |
| | NonSyn: CpG v NonCpG | 0.0346 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 29.** (a) Transition mutation frequencies for the analysis of Rota A VP6 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

BK Polyoma VP1

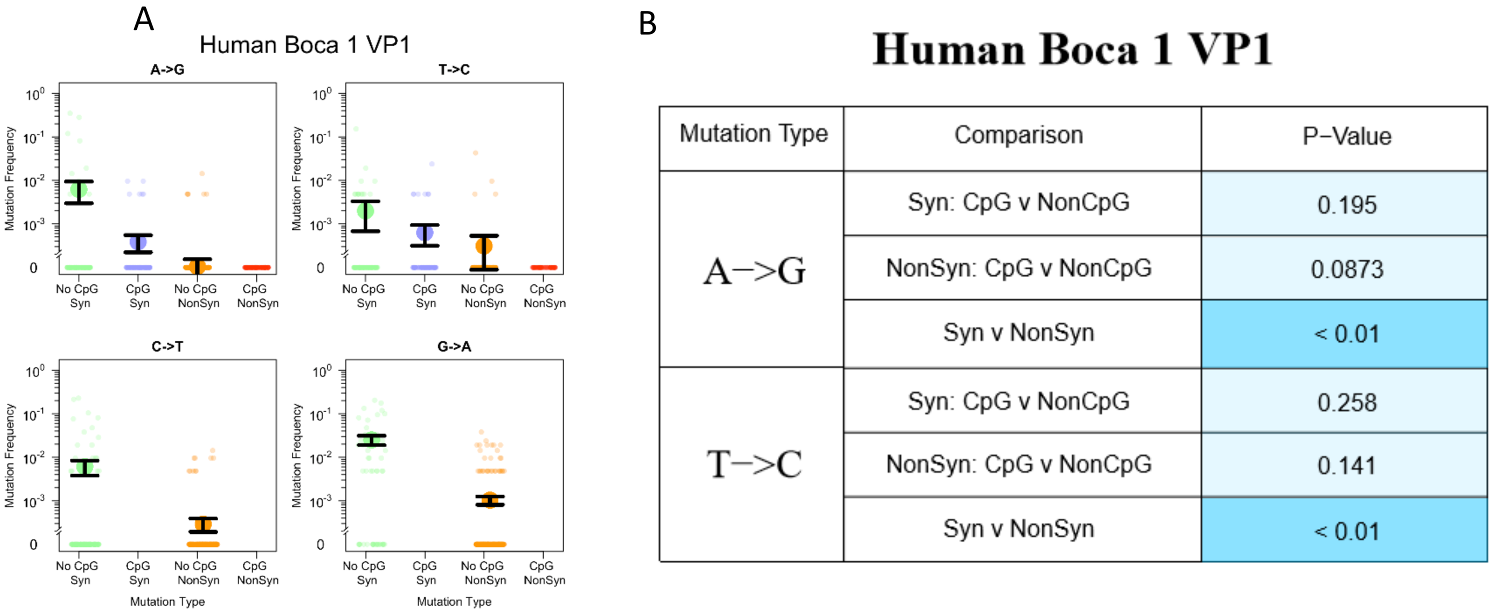


## Bk Polyoma VP1

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.158 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.189 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 30.** (a) Transition mutation frequencies for the analysis of BK Polyoma VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

## Human Boca VP1

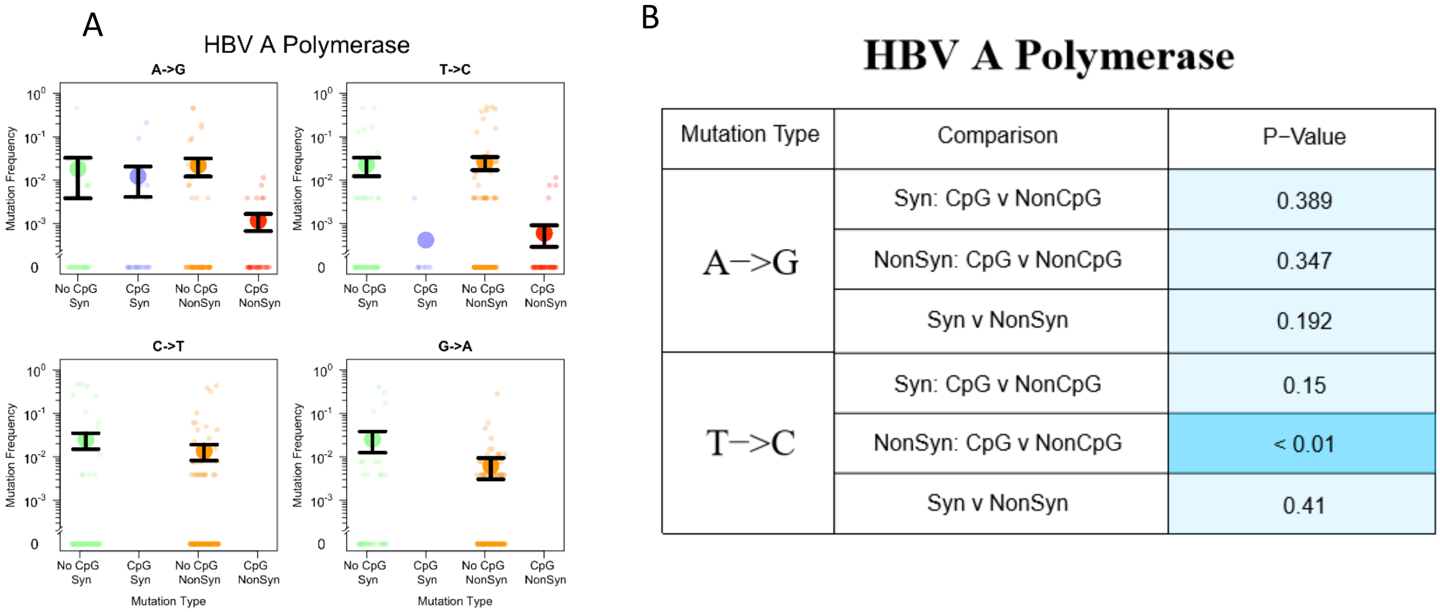


Human Boca 1 VP1

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.195 |
| | NonSyn: CpG v NonCpG | 0.0873 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.258 |
| | NonSyn: CpG v NonCpG | 0.141 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 31.** (a) Transition mutation frequencies for the analysis of Human Boca VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HBV A polymerase

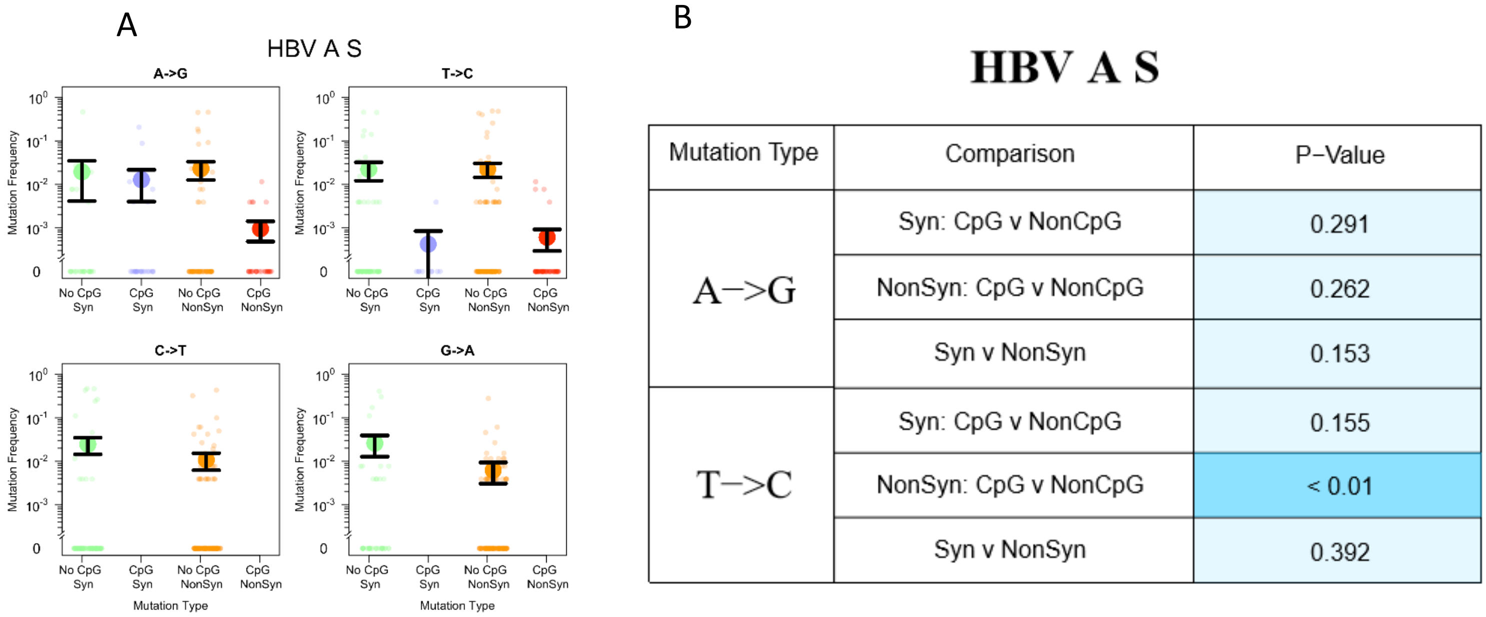


HBV A Polymerase

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.389 |
| | NonSyn: CpG v NonCpG | 0.347 |
| | Syn v NonSyn | 0.192 |
| T−>C | Syn: CpG v NonCpG | 0.15 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 0.41 |

**Supplementary Fig 32.** (a) Transition mutation frequencies for the analysis of HBV A Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HBV A S

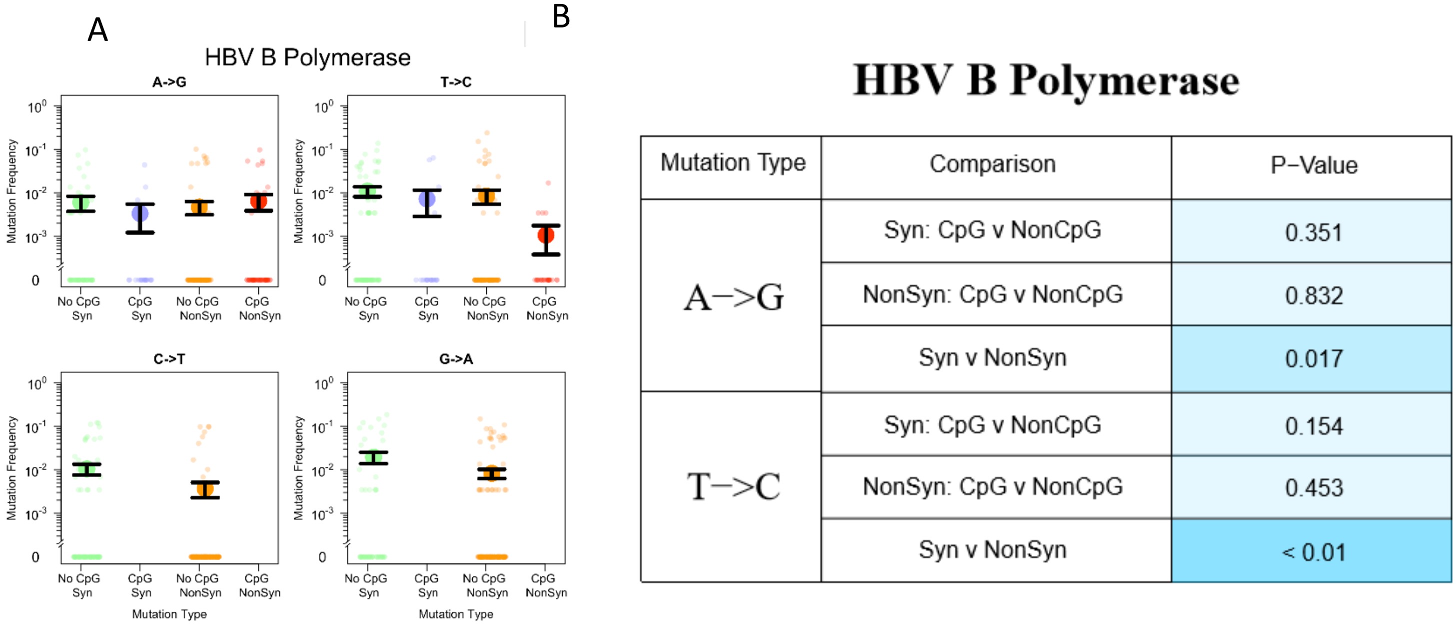


**HBV A S**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.291 |
| | NonSyn: CpG v NonCpG | 0.262 |
| | Syn v NonSyn | 0.153 |
| T−>C | Syn: CpG v NonCpG | 0.155 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 0.392 |

**Supplementary Fig 33.** (a) Transition mutation frequencies for the analysis of HBV A S with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

# HBV B Polymerase

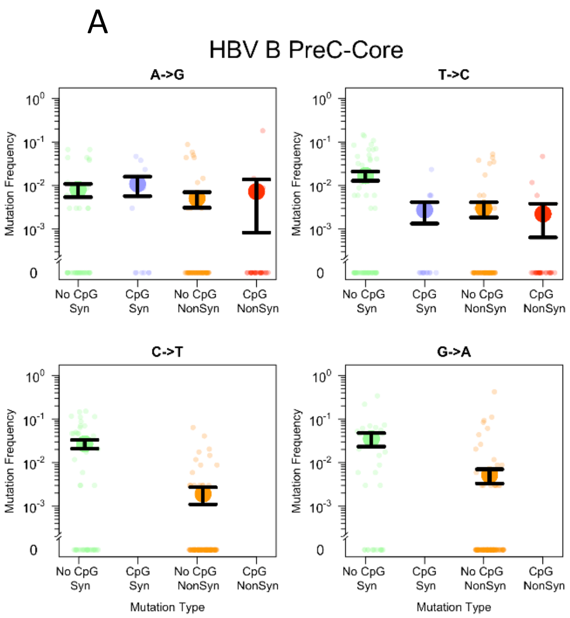


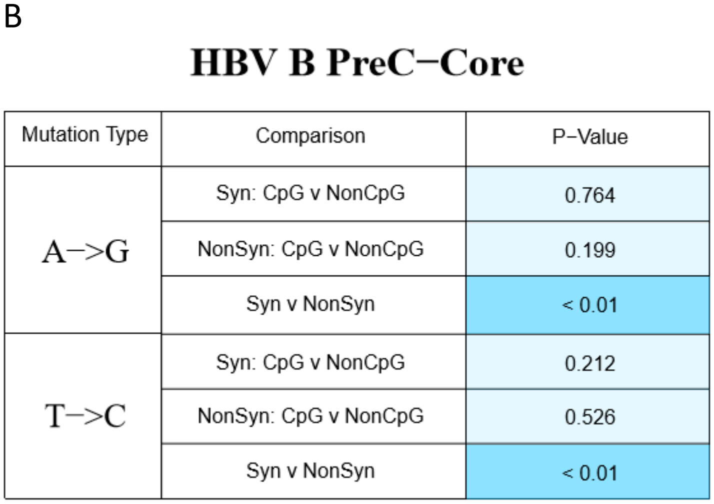
HBV B Polymerase

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.351 |
| | NonSyn: CpG v NonCpG | 0.832 |
| | Syn v NonSyn | 0.017 |
| T−>C | Syn: CpG v NonCpG | 0.154 |
| | NonSyn: CpG v NonCpG | 0.453 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 34.** (a) Transition mutation frequencies for the analysis of HBV A Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HBV B PreC-Core



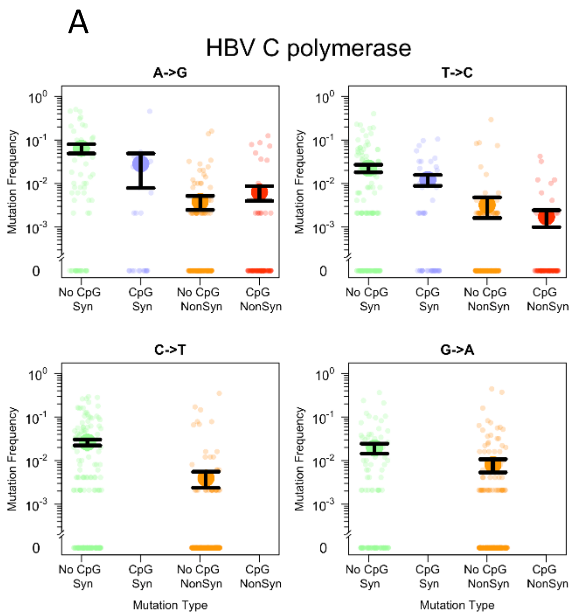


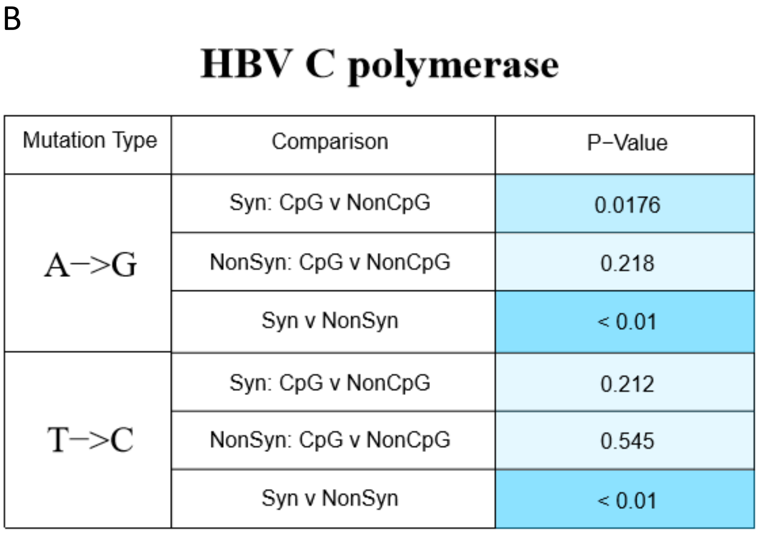
HBV B PreC−Core

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.764 |
| | NonSyn: CpG v NonCpG | 0.199 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.212 |
| | NonSyn: CpG v NonCpG | 0.526 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 35.** (a) Transition mutation frequencies for the analysis of HBV B PreC-Core with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HBV C Polymerase



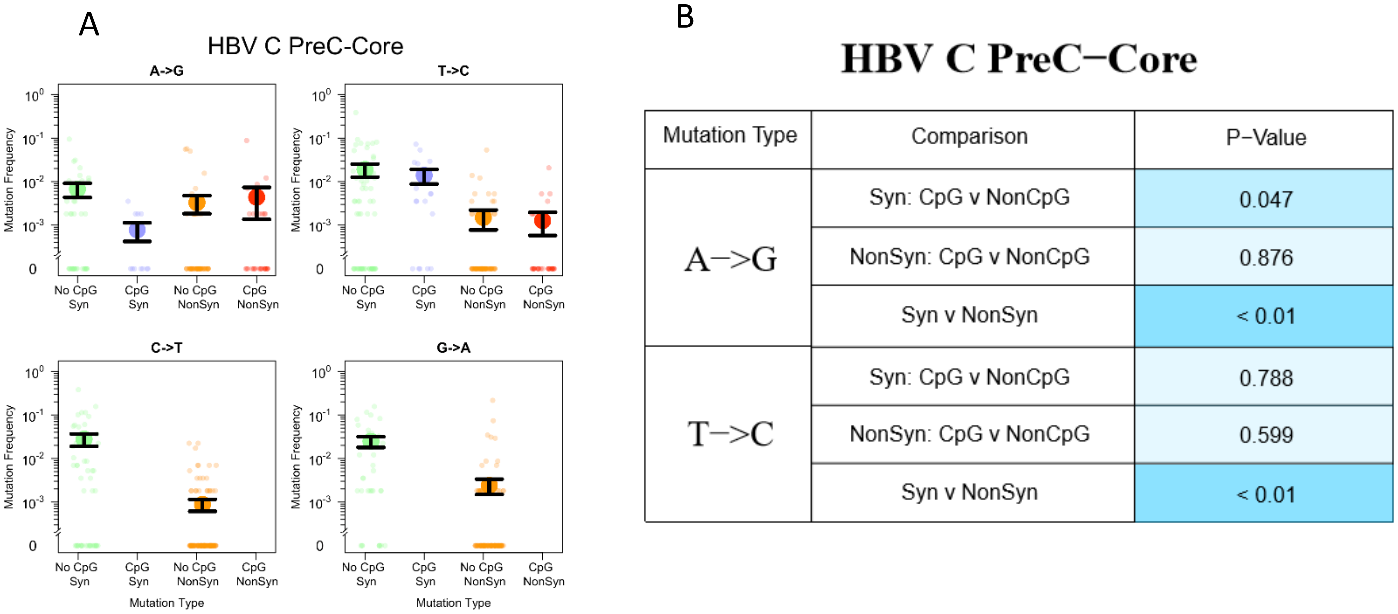

B

HBV C polymerase

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.0176 |
| | NonSyn: CpG v NonCpG | 0.218 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.212 |
| | NonSyn: CpG v NonCpG | 0.545 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 36.** (a) Transition mutation frequencies for the analysis of HBV C Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HBV C PreC-Core



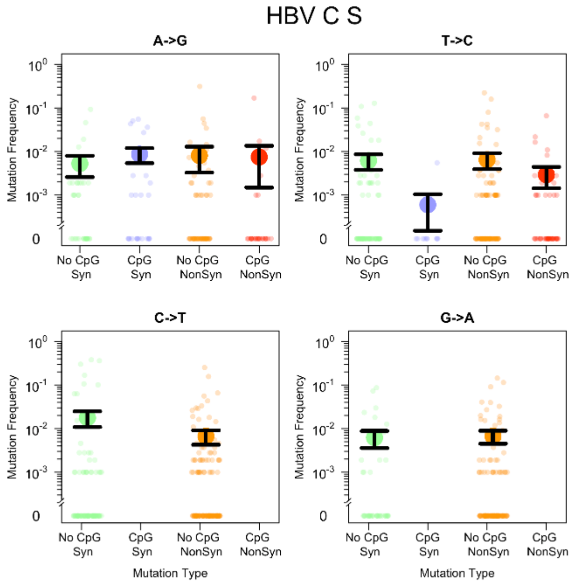
**HBV C PreC−Core**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.047 |
| | NonSyn: CpG v NonCpG | 0.876 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.788 |
| | NonSyn: CpG v NonCpG | 0.599 |
| | Syn v NonSyn | < 0.01 |

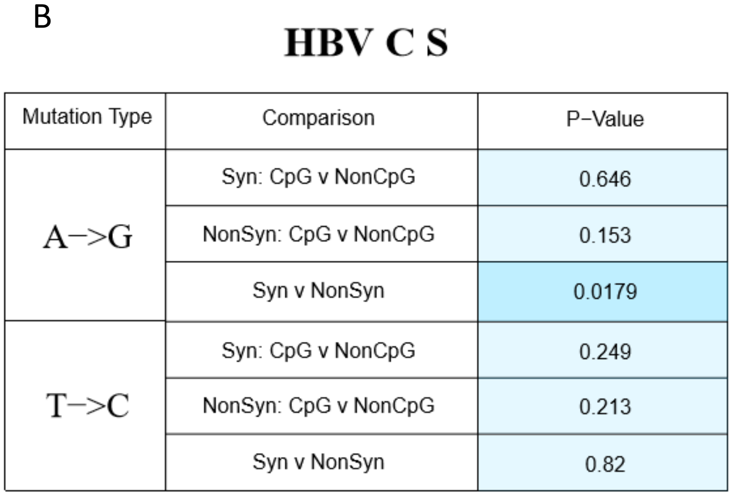
**Supplementary Fig 37.** (a) Transition mutation frequencies for the analysis of HBV C PreC-Core with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

HBV C S

A



B

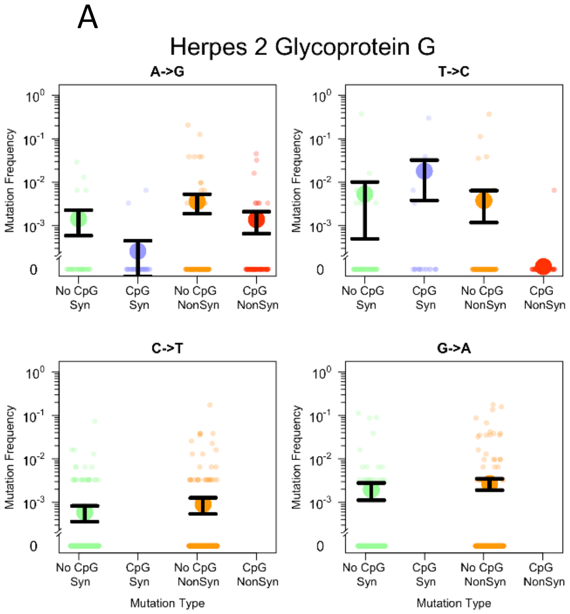


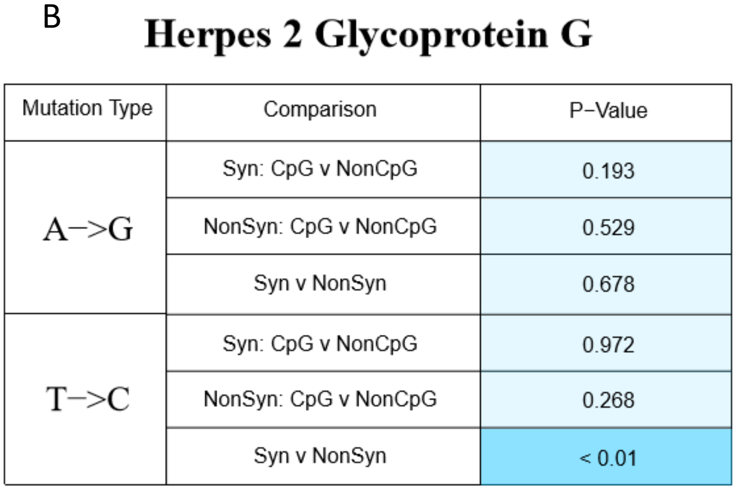
HBV C S

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.646 |
| | NonSyn: CpG v NonCpG | 0.153 |
| | Syn v NonSyn | 0.0179 |
| T−>C | Syn: CpG v NonCpG | 0.249 |
| | NonSyn: CpG v NonCpG | 0.213 |
| | Syn v NonSyn | 0.82 |

**Supplementary Fig 38.** (a) Transition mutation frequencies for the analysis of HBV C S with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Herpes 2 Glycoprotein G




B

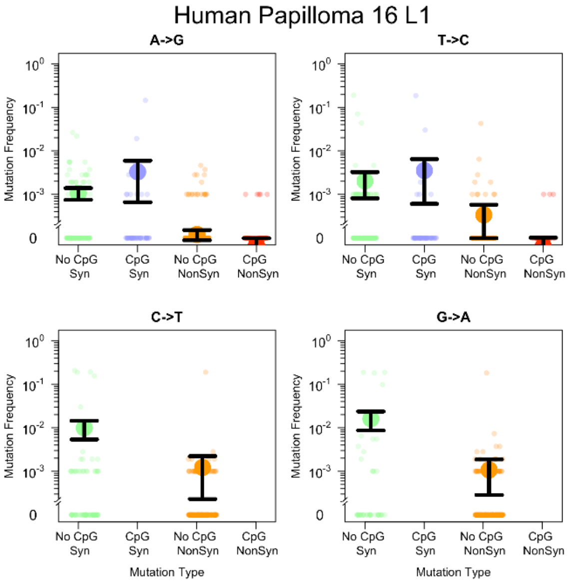
Herpes 2 Glycoprotein G

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.193 |
|  | NonSyn: CpG v NonCpG | 0.529 |
|  | Syn v NonSyn | 0.678 |
| T−>C | Syn: CpG v NonCpG | 0.972 |
|  | NonSyn: CpG v NonCpG | 0.268 |
|  | Syn v NonSyn | < 0.01 |

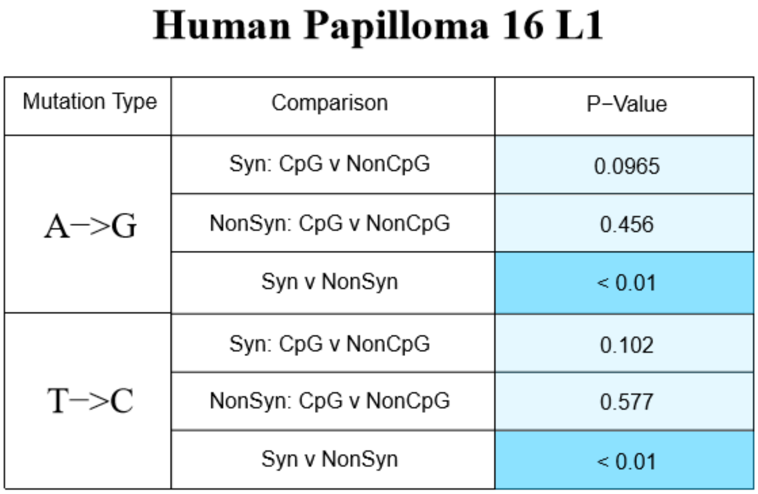
**Supplementary Fig 39.** (a) Transition mutation frequencies for the analysis of Herpes 2 Glycoprotein G with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Human Papilloma 16 L1

A



B

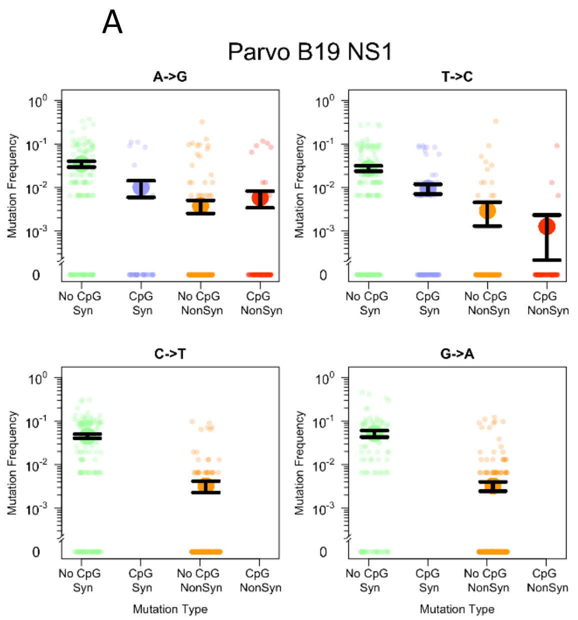


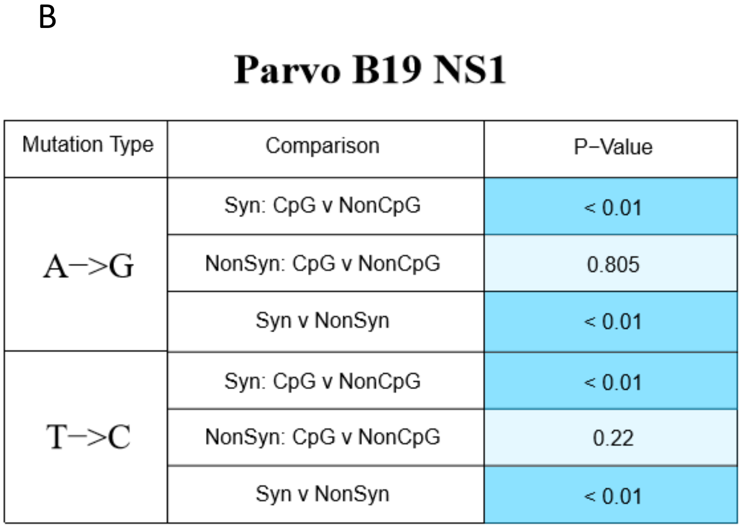
Human Papilloma 16 L1

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.0965 |
| | NonSyn: CpG v NonCpG | 0.456 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.102 |
| | NonSyn: CpG v NonCpG | 0.577 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 40.** (a) Transition mutation frequencies for the analysis of Human Papilloma 16 L1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Parvo B19 NS1



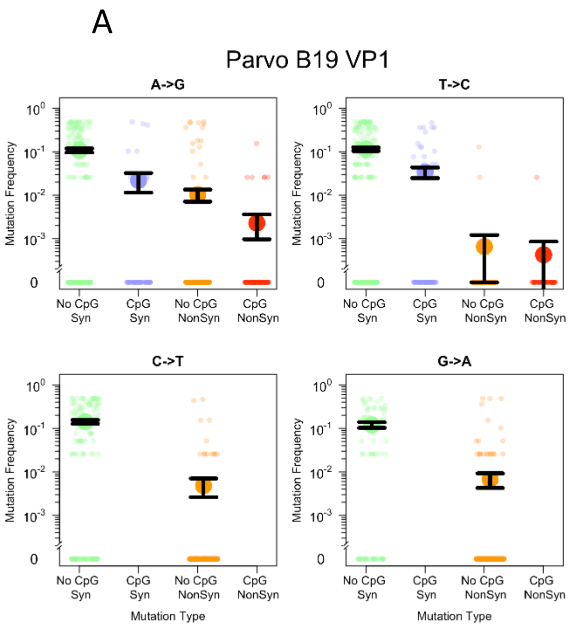

B

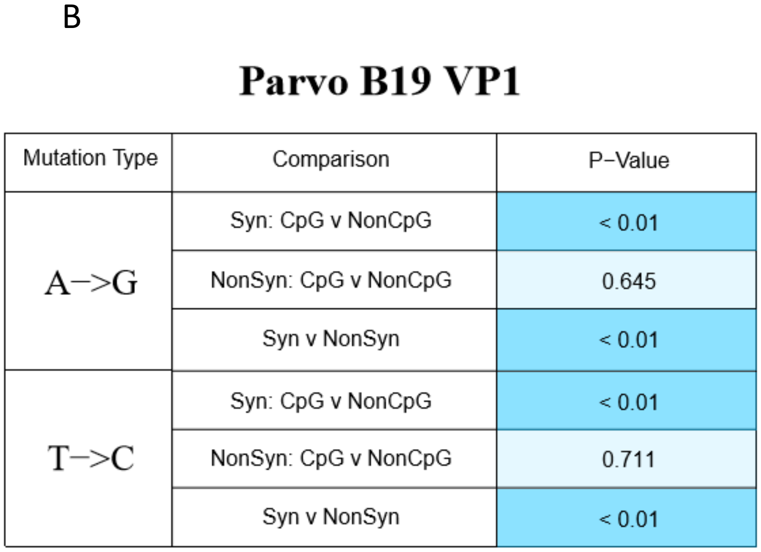
Parvo B19 NS1

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.805 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.22 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 41.** (a) Transition mutation frequencies for the analysis of Parvo B19 NS1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

Parvo B19 VP1



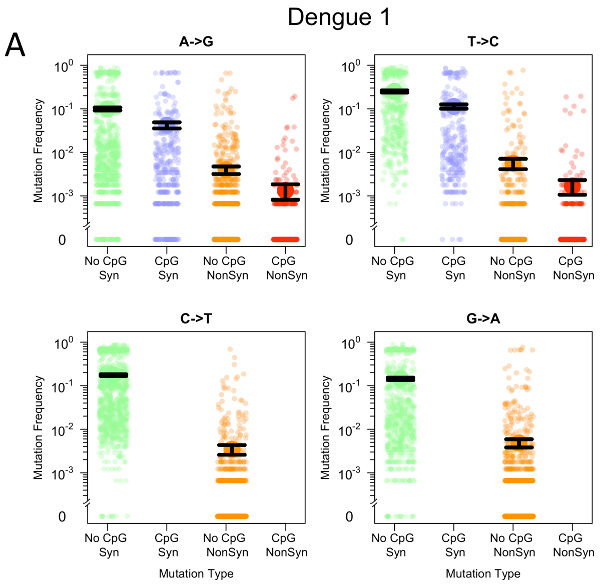


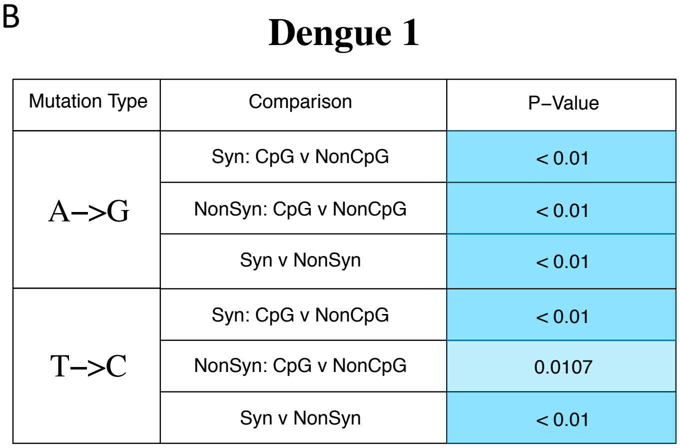
**Parvo B19 VP1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A->G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.645 |
| | Syn v NonSyn | < 0.01 |
| T->C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.711 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig 42.** (a) Transition mutation frequencies for the analysis of Parvo B19 VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results.

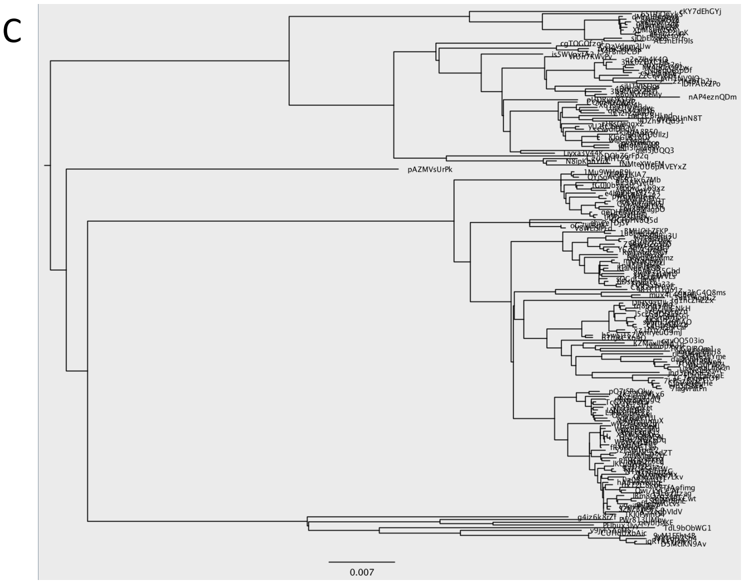
## Ancestral Dengue 1





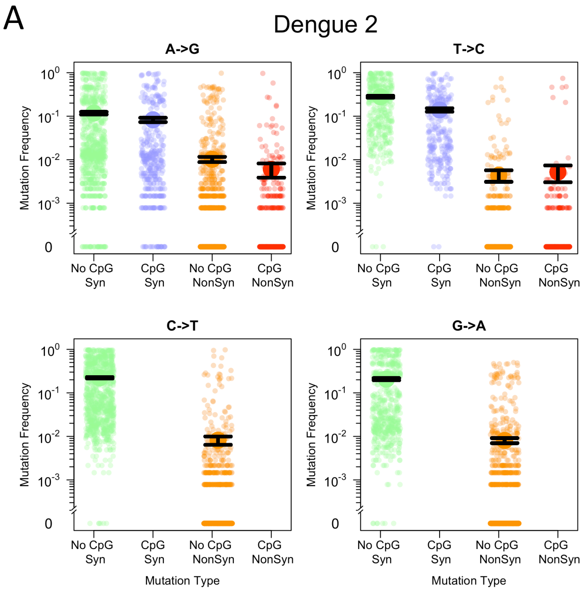
### Dengue 1

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0107 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 43** (a) Transition mutation frequencies for the ancestral analysis of Dengue 1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

## Ancestral Dengue 2

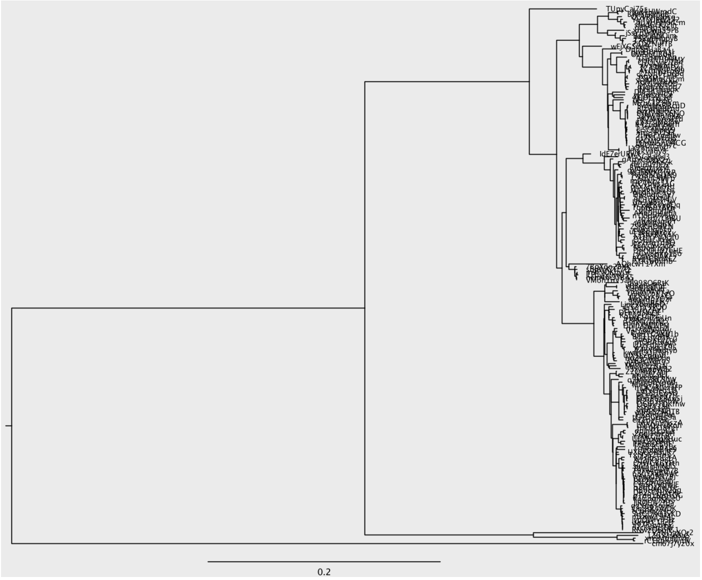


B

### Dengue 2

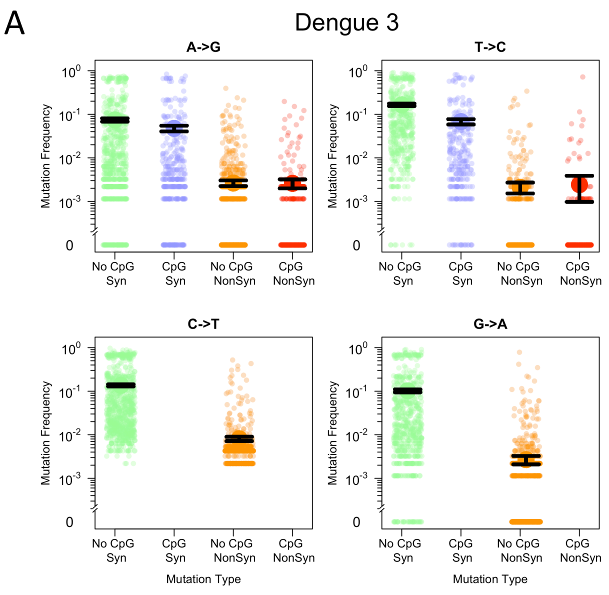
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0174 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0198 |
| | Syn v NonSyn | < 0.01 |

C



**Supplementary Fig. 44** (a) Transition mutation frequencies for the ancestral analysis of Dengue 2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

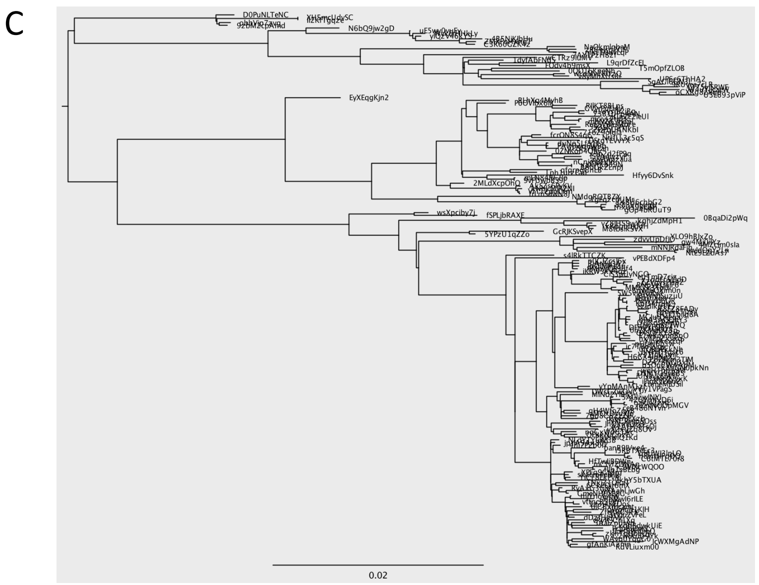
Ancestral Dengue 3



B

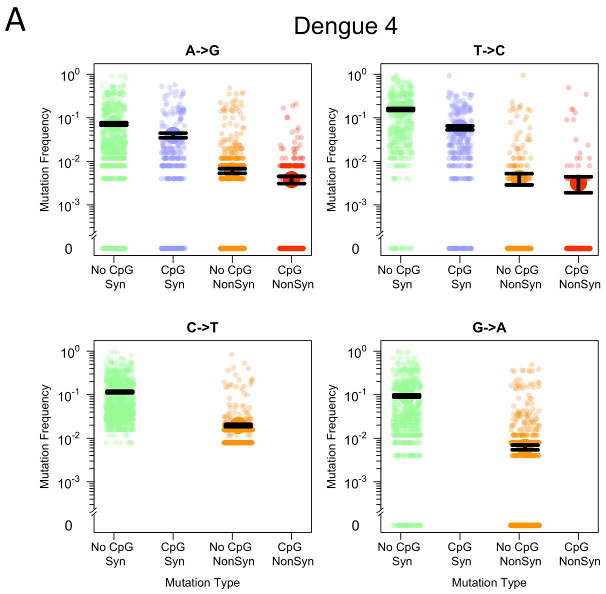
**Dengue 3**

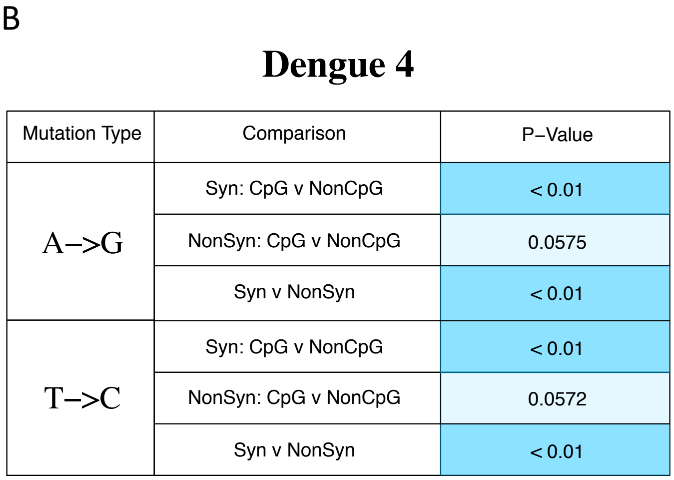
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0677 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0168 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 45** (a) Transition mutation frequencies for the ancestral analysis of Dengue 3 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

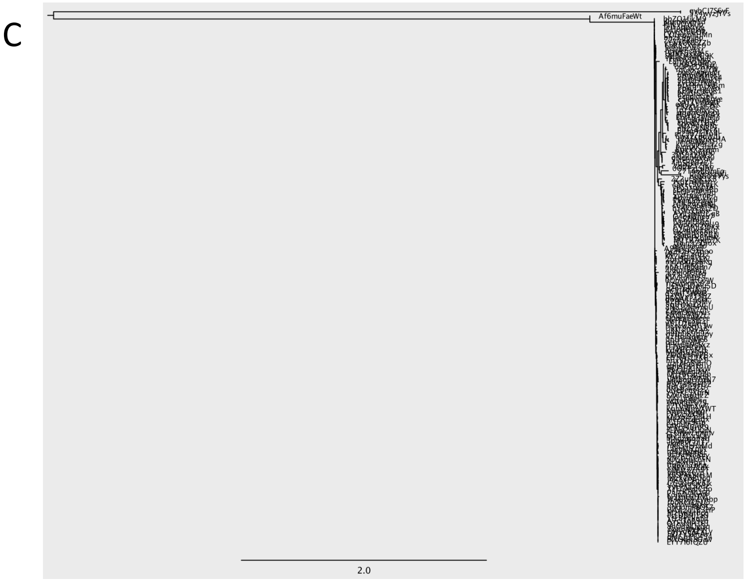
Ancestral Dengue 4




B

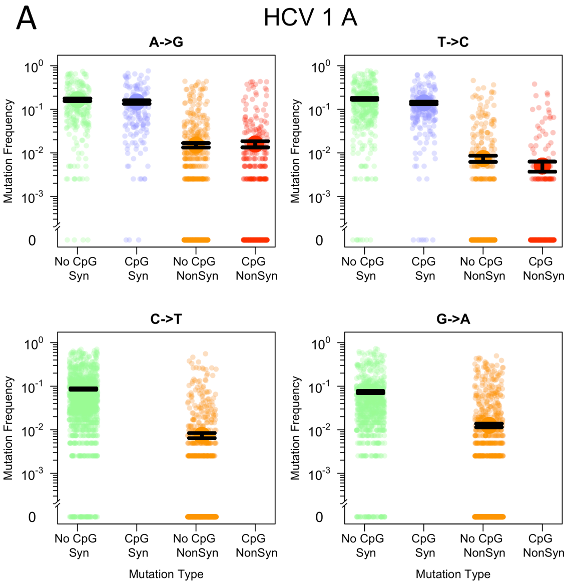
**Dengue 4**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0575 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0572 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 46** (a) Transition mutation frequencies for the ancestral analysis of Dengue 4 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral HCV 1 A

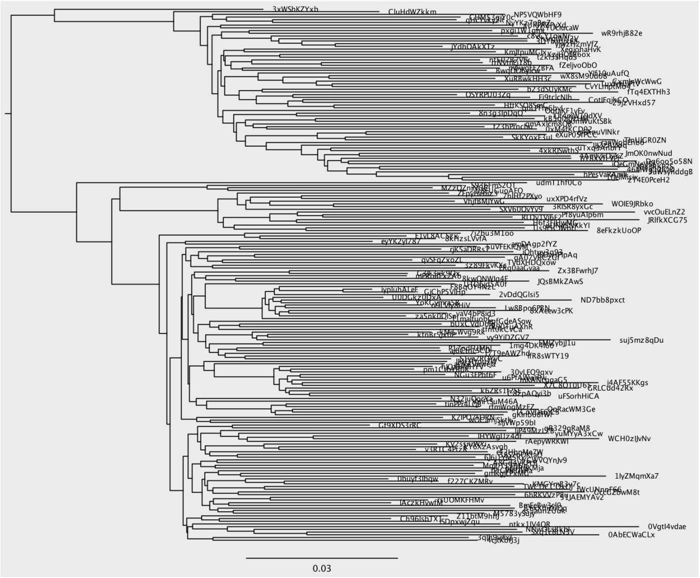


B

**HCV 1 A**

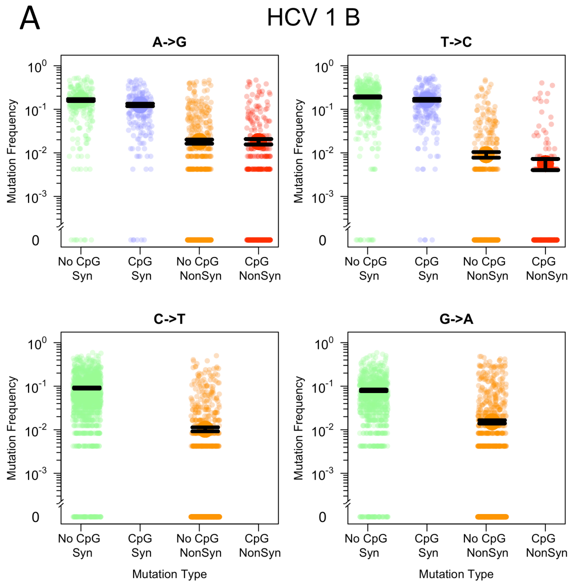
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.0649 |
| | NonSyn: CpG v NonCpG | 0.602 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.0143 |
| | NonSyn: CpG v NonCpG | 0.189 |
| | Syn v NonSyn | < 0.01 |

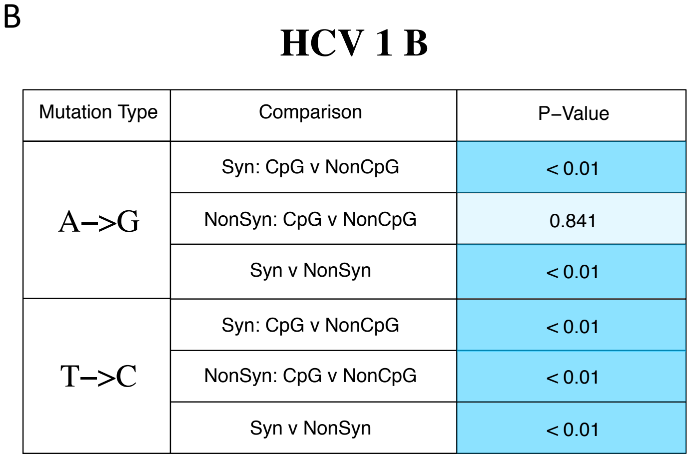
C



**Supplementary Fig. 47** (a) Transition mutation frequencies for the ancestral analysis of HCV 1 A with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

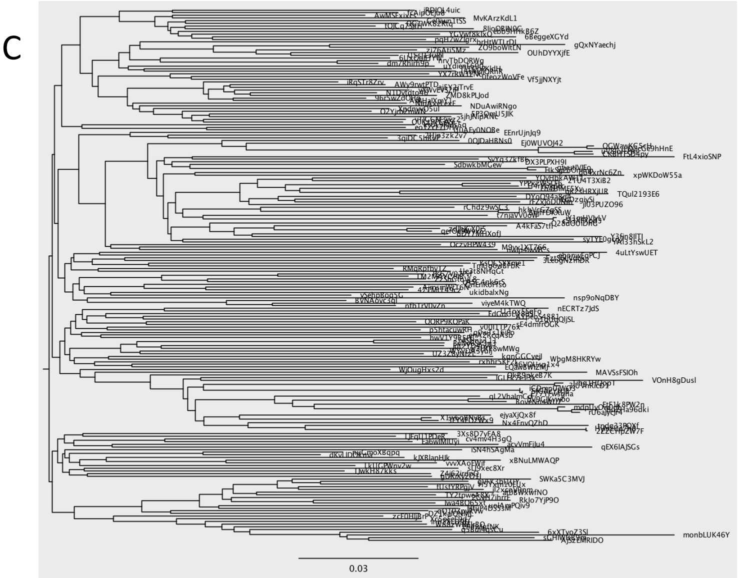
Ancestral HCV 1 B





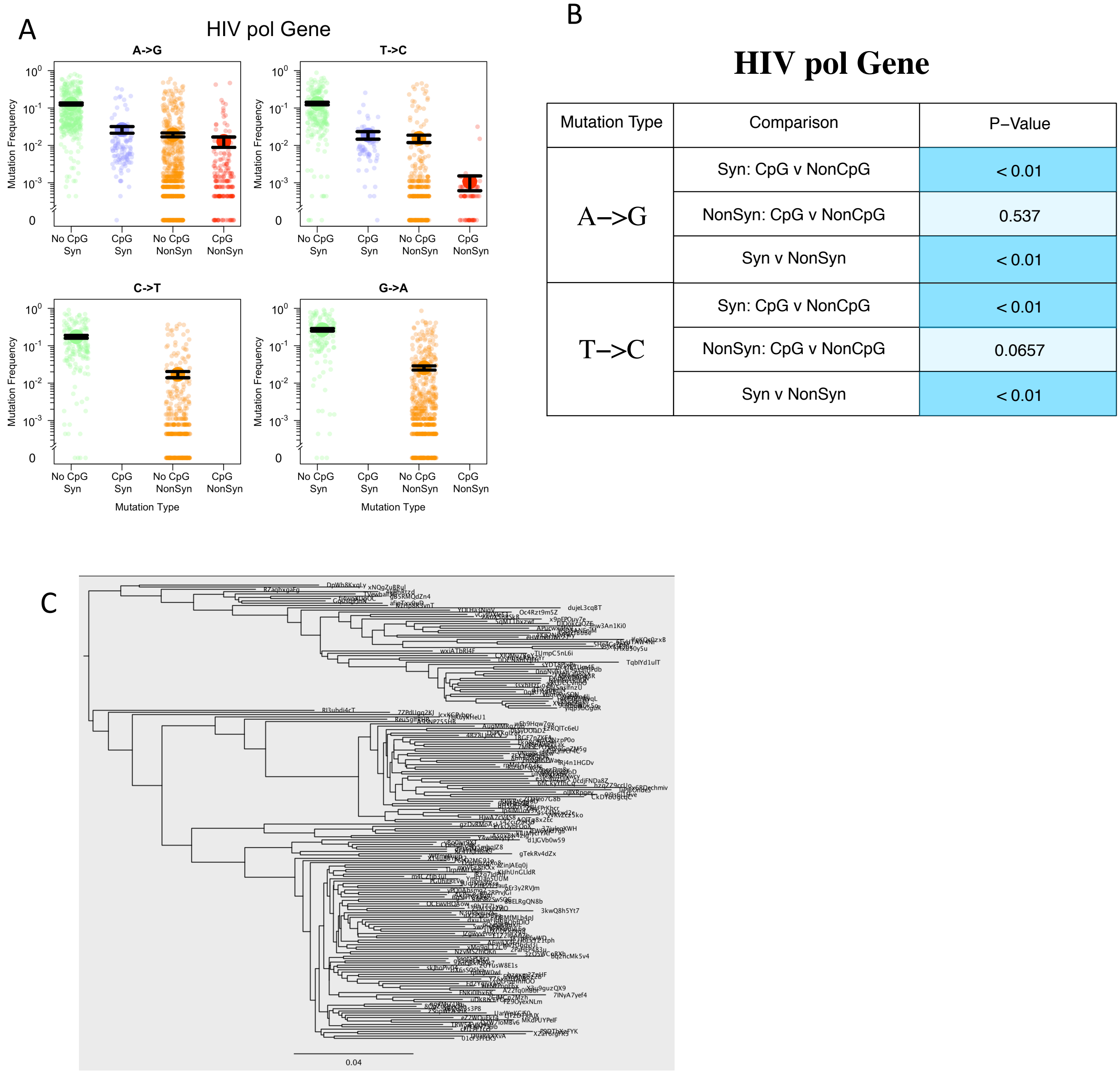
## HCV 1 B

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.841 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 48**(a) Transition mutation frequencies for the ancestral analysis of HCV 1 B with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

# Ancestral HIV pol Gene



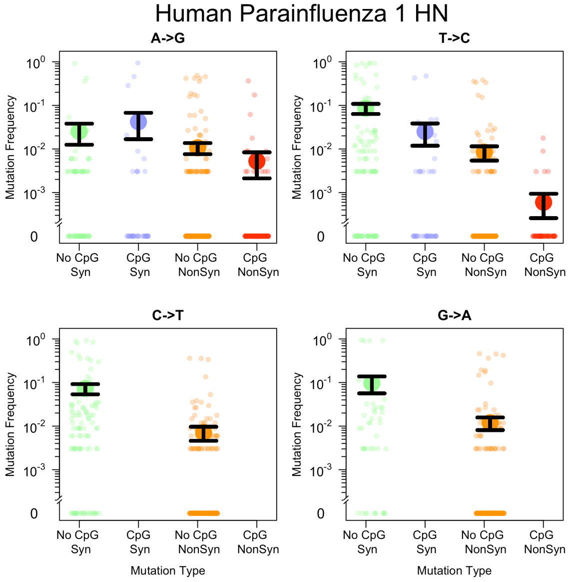
HIV pol Gene

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.537 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0657 |
| | Syn v NonSyn | < 0.01 |

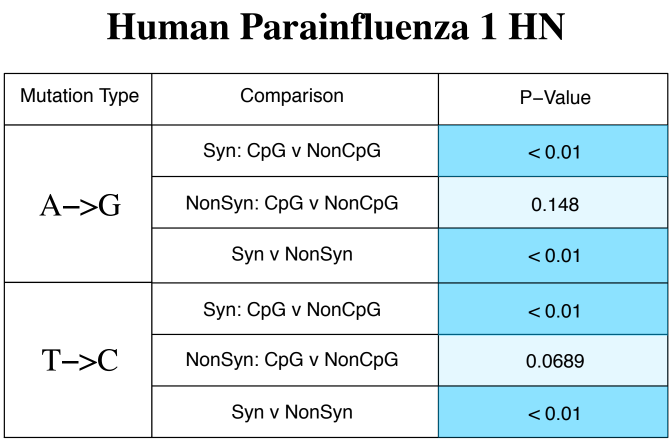
**Supplementary Fig. 49** (a) Transition mutation frequencies for the ancestral analysis of HIV Pol gene with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Human Parainfluenza 1 HN

A



B



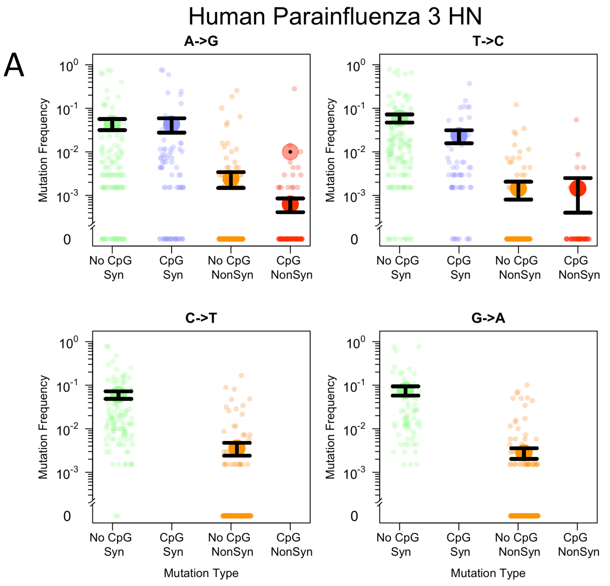
## Human Parainfluenza 1 HN

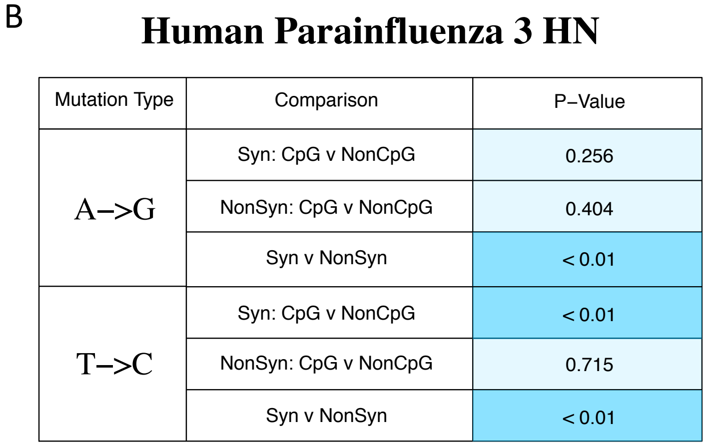
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.148 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0689 |
| | Syn v NonSyn | < 0.01 |

C

**Supplementary Fig. 50** (a) Transition mutation frequencies for the ancestral analysis of Human Parainfluenza 1 HN with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

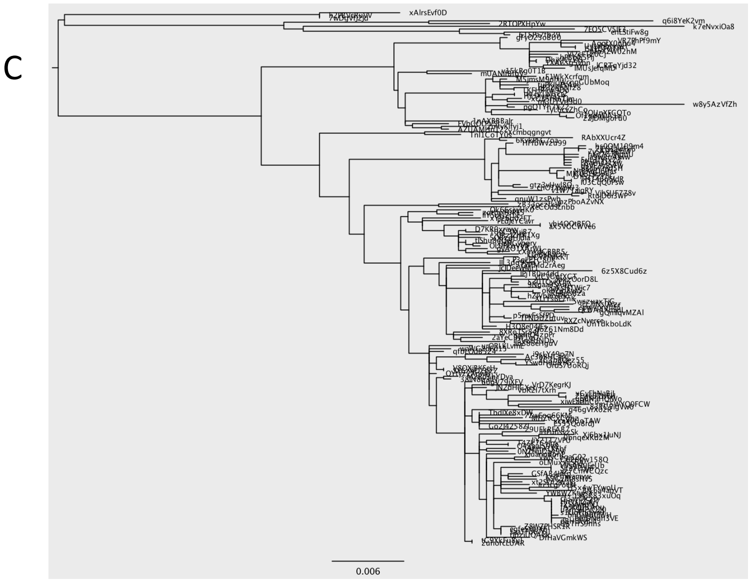
Ancestral Human Parainfluenza 3 HN





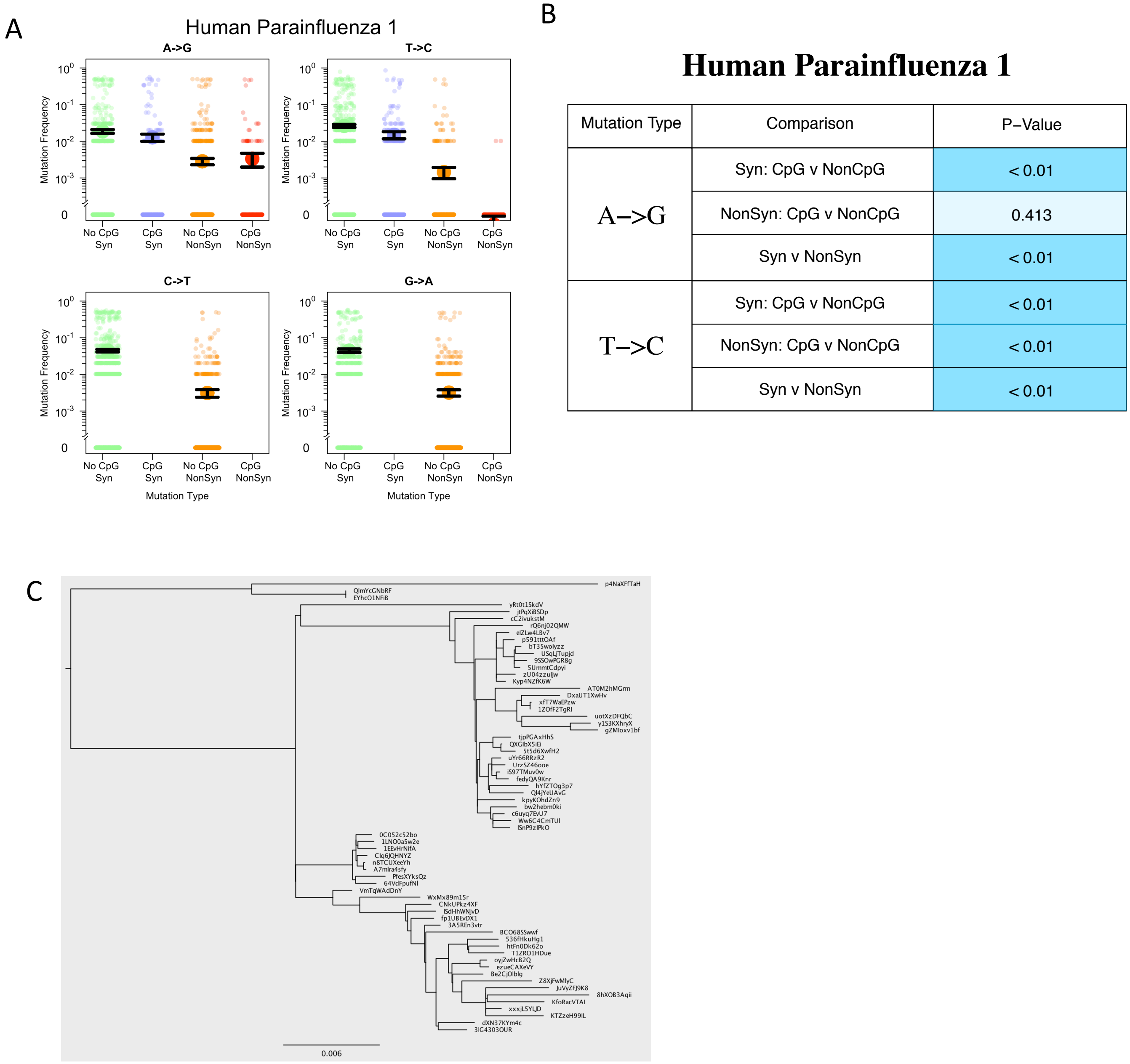
## Human Parainfluenza 3 HN

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.256 |
| | NonSyn: CpG v NonCpG | 0.404 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.715 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 51** (a) Transition mutation frequencies for the ancestral analysis of Human Parainfluenza 3 HN with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

# Ancestral Human Parainfluenza 1



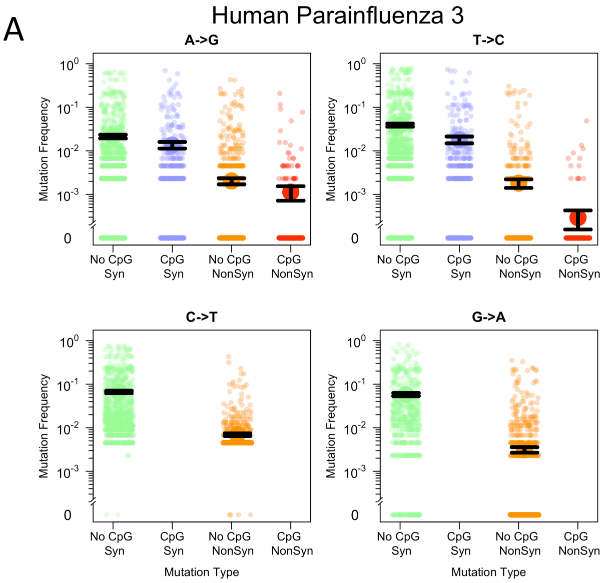
B

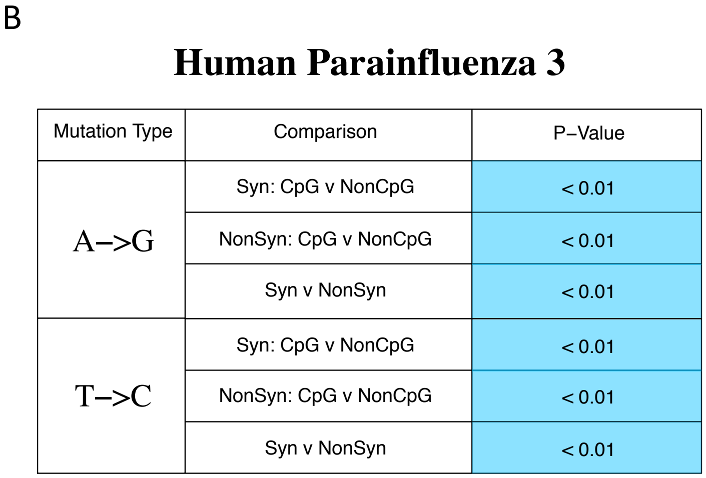
**Human Parainfluenza 1**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.413 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

**Supplementary Fig. 52** (a) Transition mutation frequencies for the ancestral analysis of Human Parainfluenza 1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

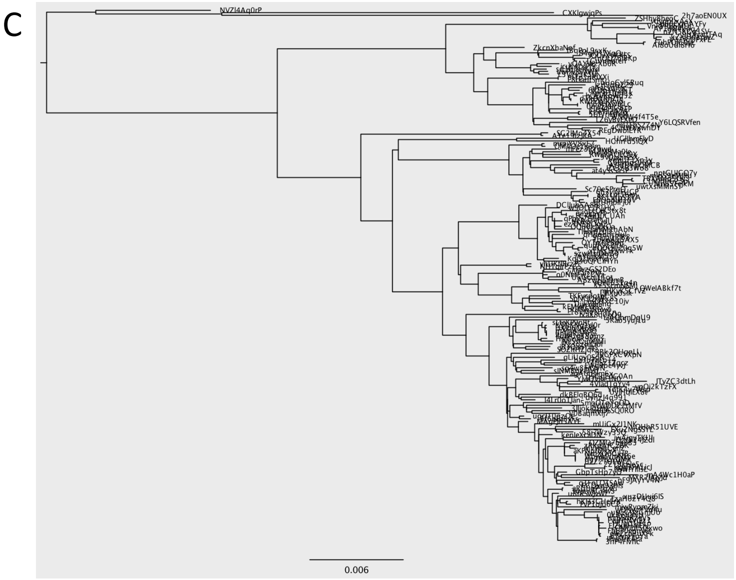
Ancestral Human Parainfluenza 3





## Human Parainfluenza 3

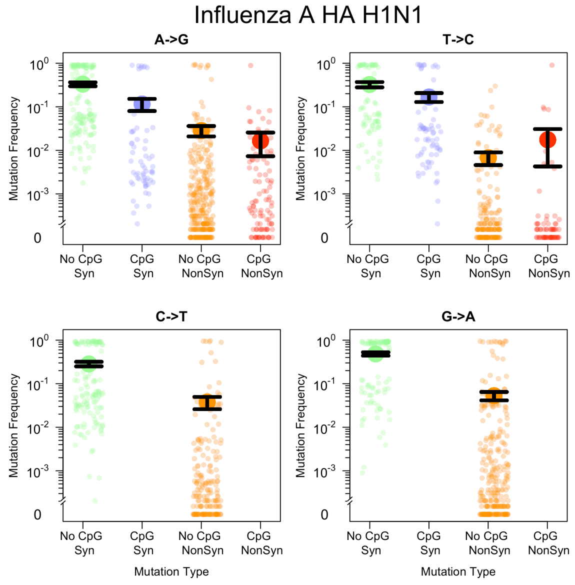
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |



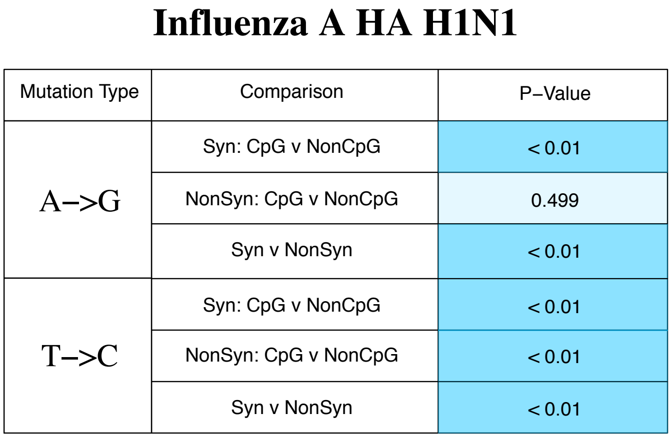
**Supplementary Fig. 53** (a) Transition mutation frequencies for the ancestral analysis of Human Parainfluenza 3 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Influenza A HA H1N1

A



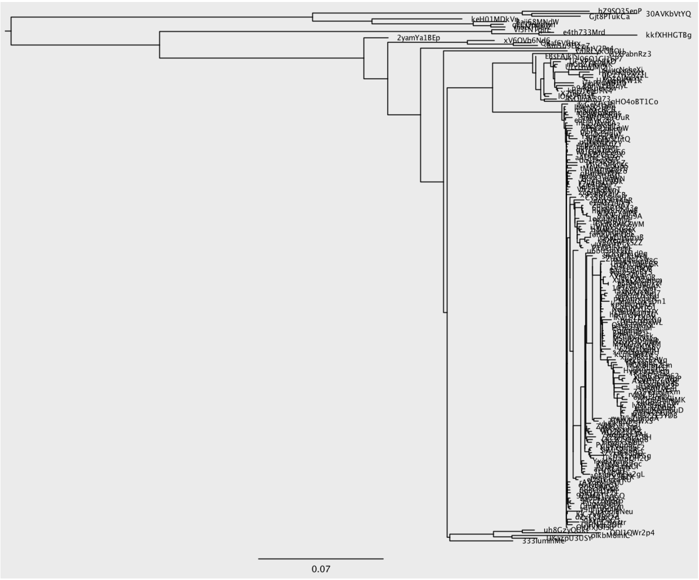
B



**Influenza A HA H1N1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.499 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

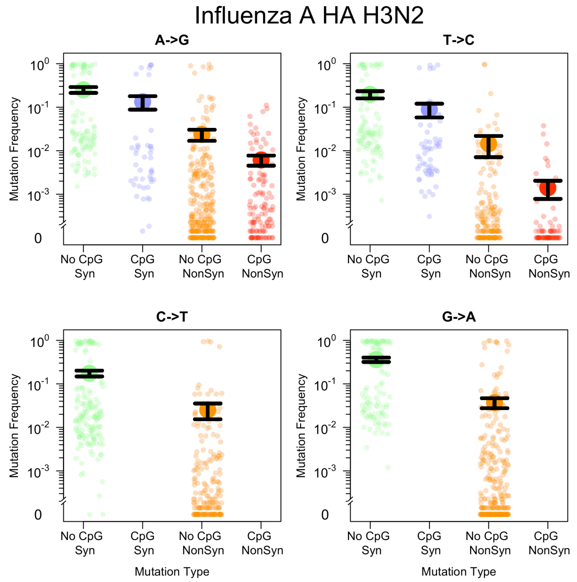
C



**Supplementary Fig. 54** (a) Transition mutation frequencies for the ancestral analysis of Influenza A HA H1N1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Influenza A HA H3N2

A



B

## Influenza A HA H3N2

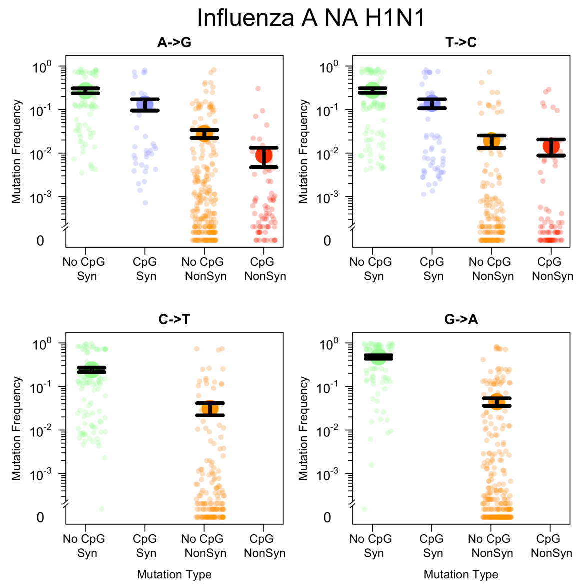
| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.486 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

C

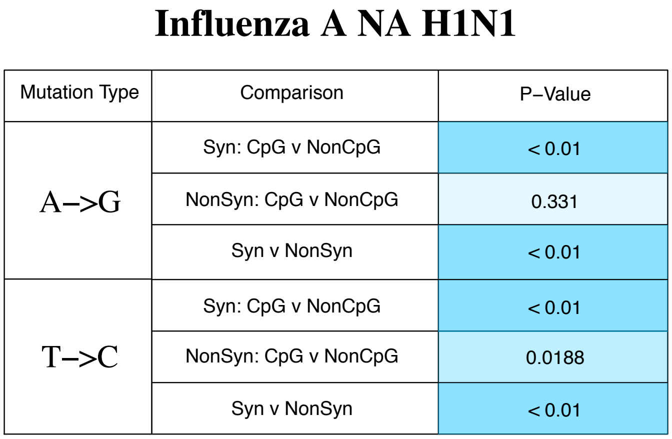
**Supplementary Fig. 55** (a) Transition mutation frequencies for the ancestral analysis of Influenza A HA H3N2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Influenza A NA H1N1

A

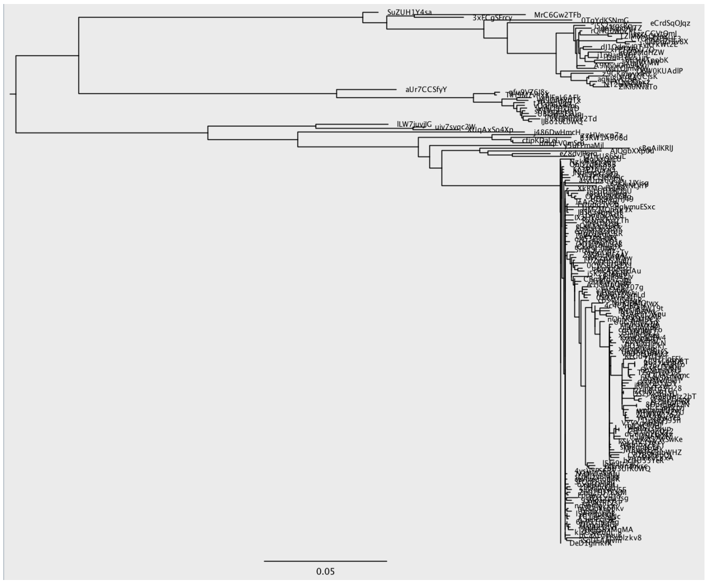


B


### Influenza A NA H1N1

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.331 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0188 |
| | Syn v NonSyn | < 0.01 |

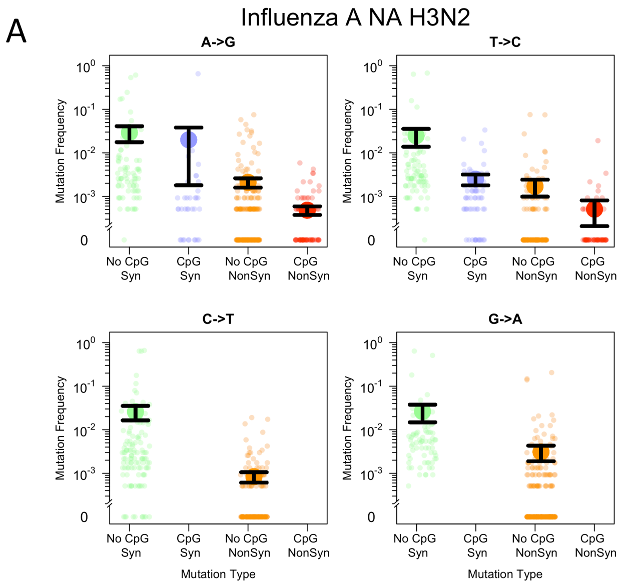
C



**Supplementary Fig. 56** (a) Transition mutation frequencies for the ancestral analysis of Influenza A NA H1N1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Influenza A NA H3N2

A

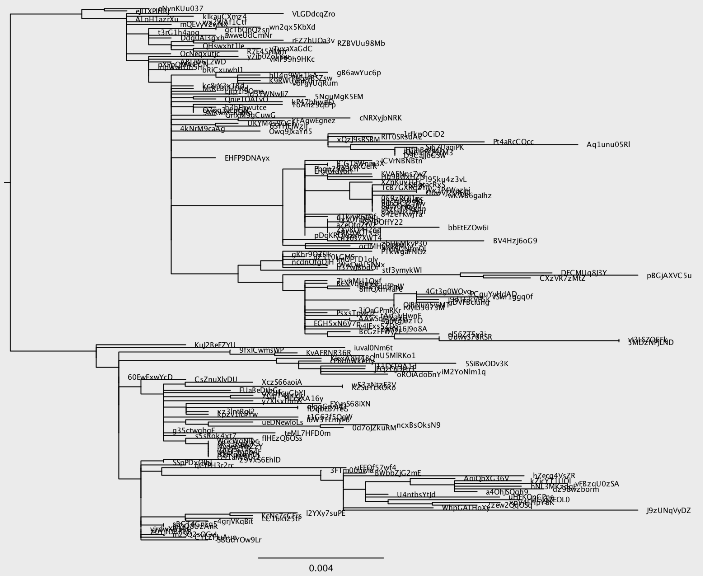


B

**Influenza A NA H3N2**

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.229 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.176 |
| | Syn v NonSyn | < 0.01 |

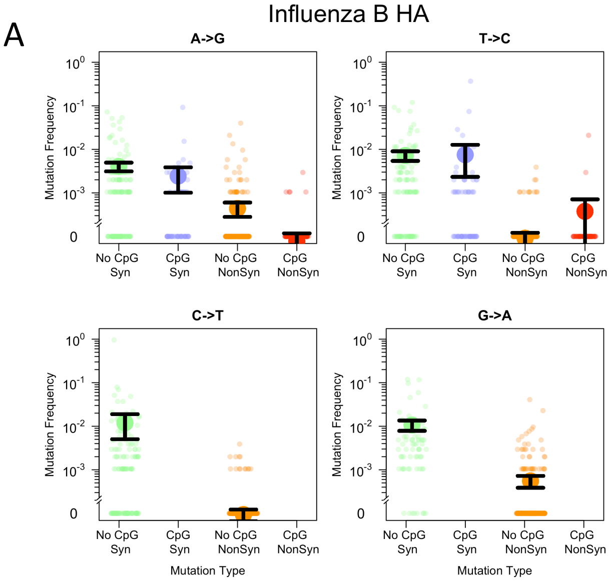
C



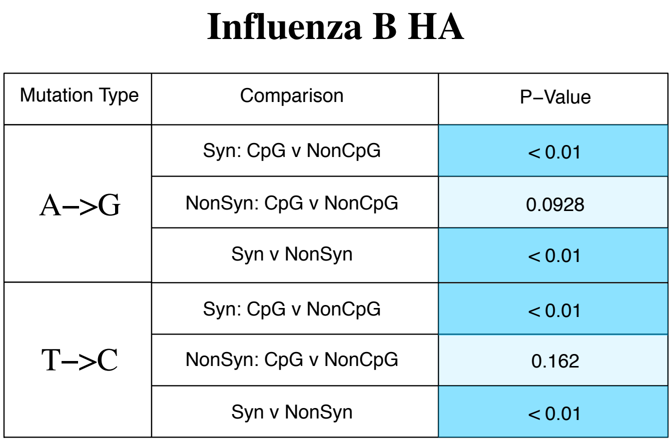
**Supplementary Fig. 57** (a) Transition mutation frequencies for the ancestral analysis of Influenza A NA H3N2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

# Ancestral Influenza B HA

A



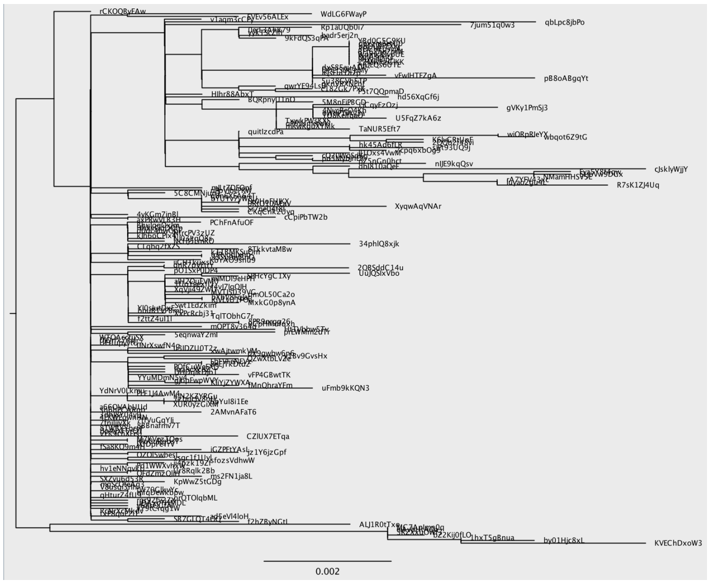
B



## Influenza B HA

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0928 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.162 |
| | Syn v NonSyn | < 0.01 |

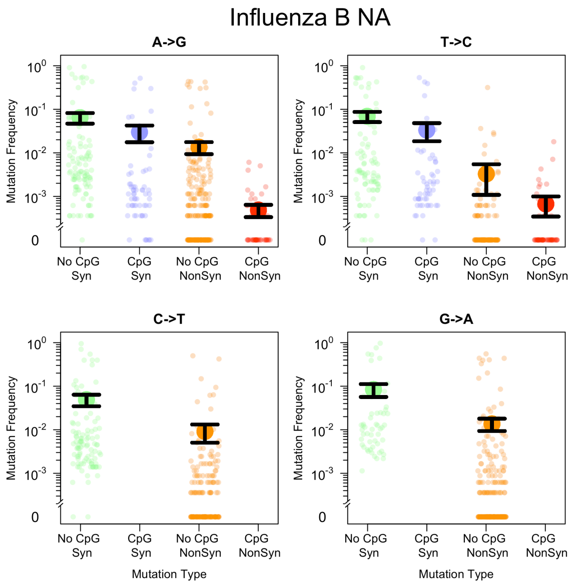
C



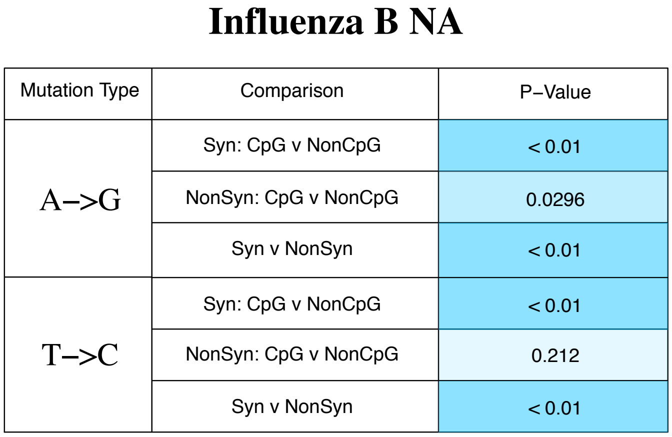
**Supplementary Fig. 58** (a) Transition mutation frequencies for the ancestral analysis of Influenza B HA with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Influenza B NA

A



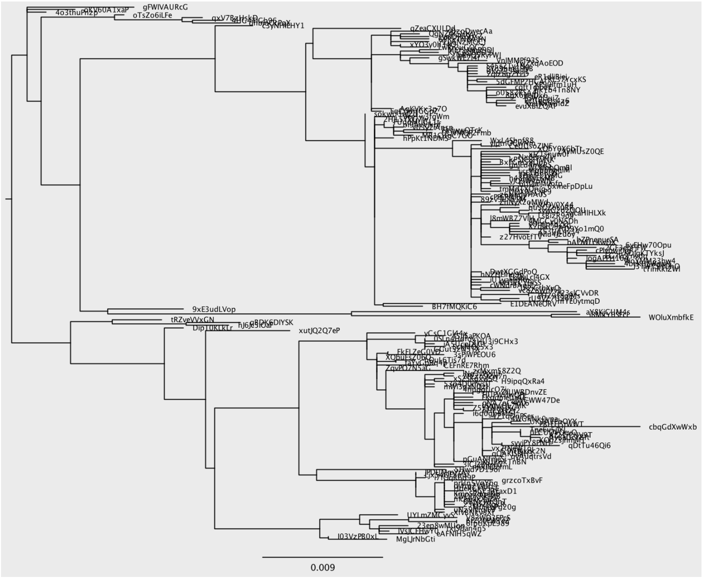
B



## Influenza B NA

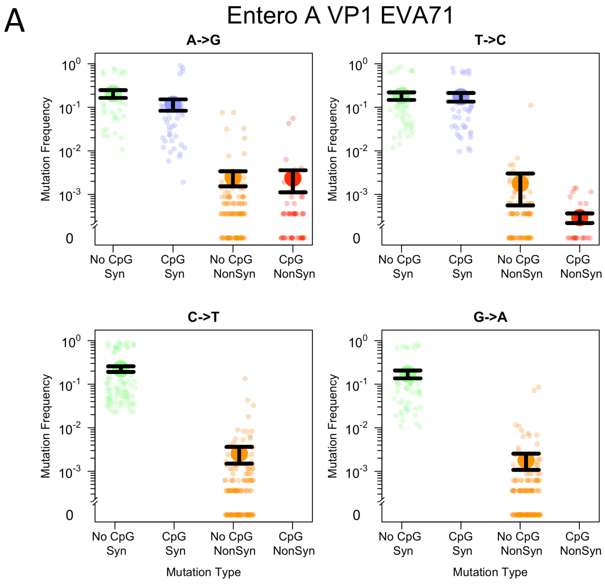
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0296 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.212 |
| | Syn v NonSyn | < 0.01 |

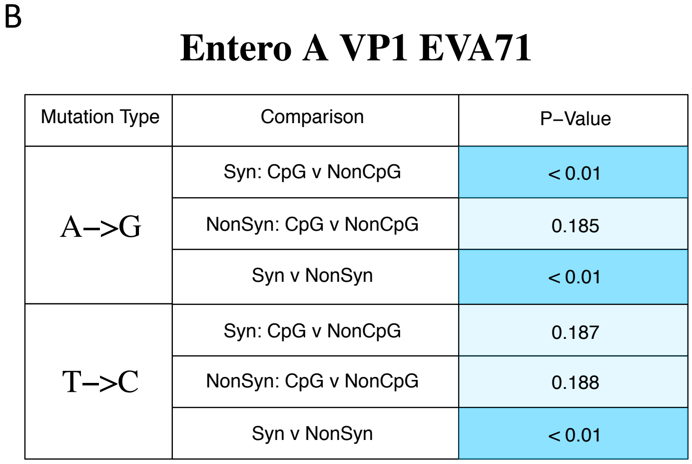
C



**Supplementary Fig. 59** (a) Transition mutation frequencies for the ancestral analysis of Influenza B NA with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

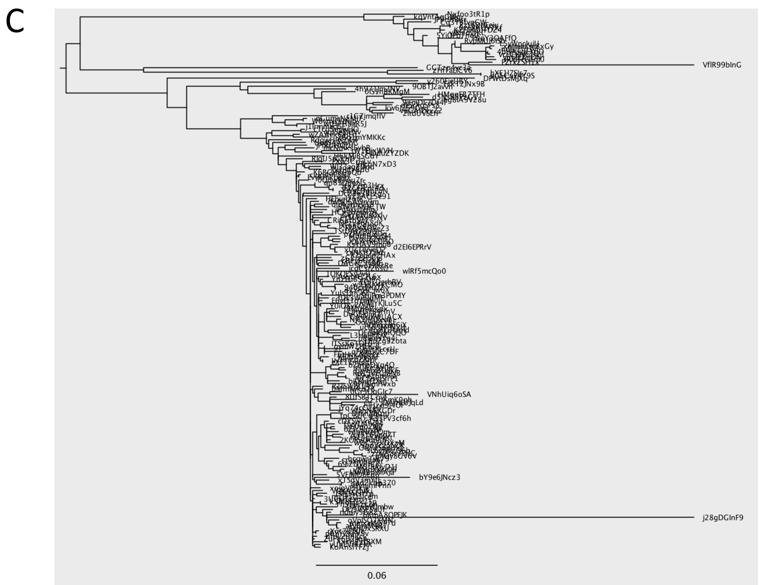
Ancestral Entero A VP1 EVA71





## Entero A VP1 EVA71

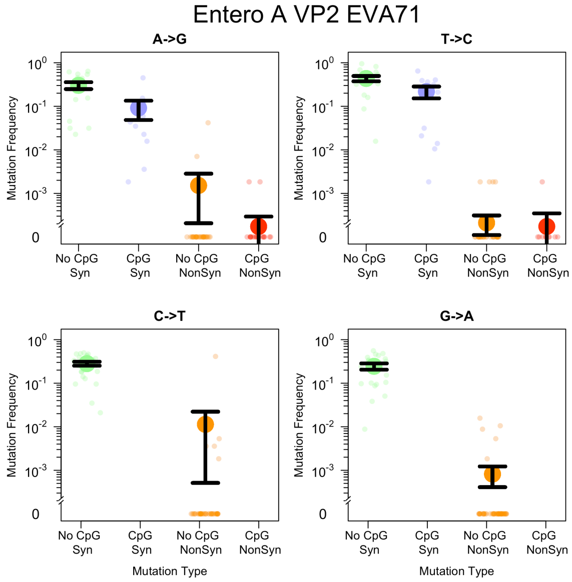
| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.185 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.187 |
| | NonSyn: CpG v NonCpG | 0.188 |
| | Syn v NonSyn | < 0.01 |



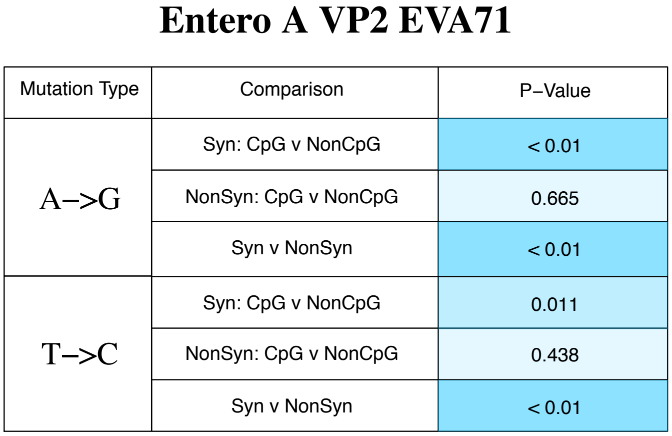
**Supplementary Fig. 60** (a) Transition mutation frequencies for the ancestral analysis of Entero A VP1 EVA71 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Entero A VP2 EVA71

A



B



**Entero A VP2 EVA71**

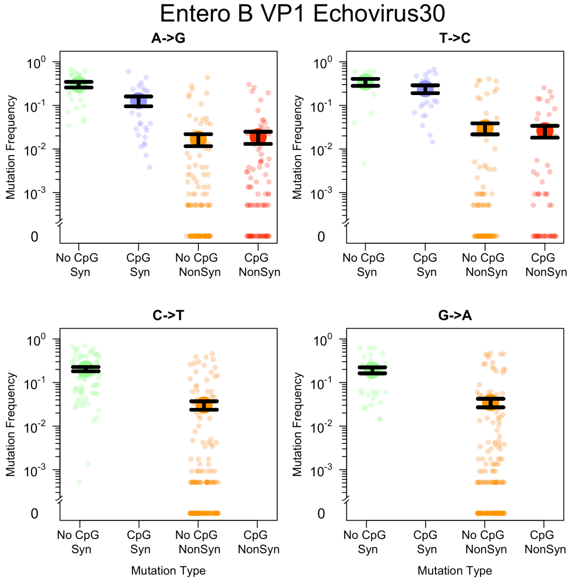
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.665 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.011 |
| | NonSyn: CpG v NonCpG | 0.438 |
| | Syn v NonSyn | < 0.01 |

C

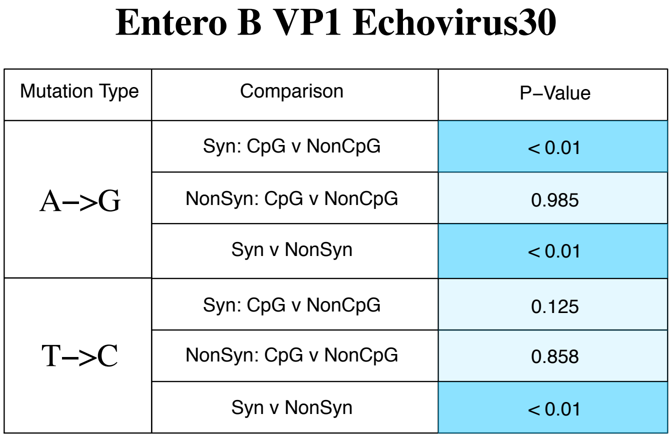
**Supplementary Fig. 61** (a) Transition mutation frequencies for the ancestral analysis of Entero A VP2 EVA71 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Entero B VP1 Echovirus30

A



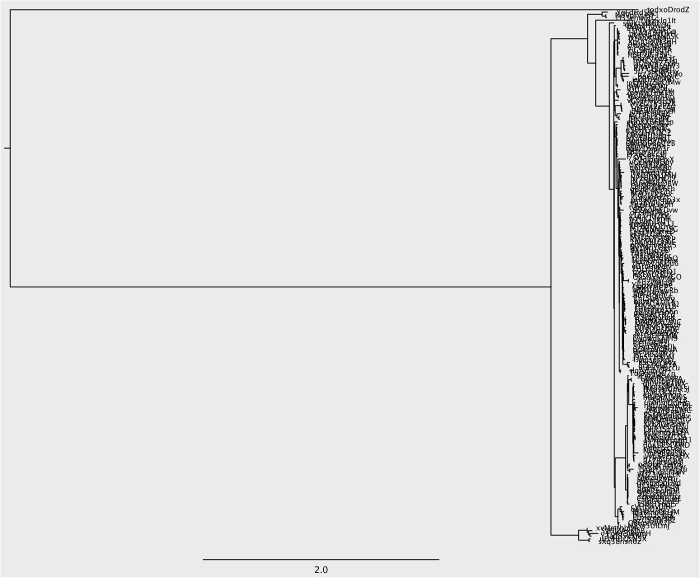
B



## Entero B VP1 Echovirus30

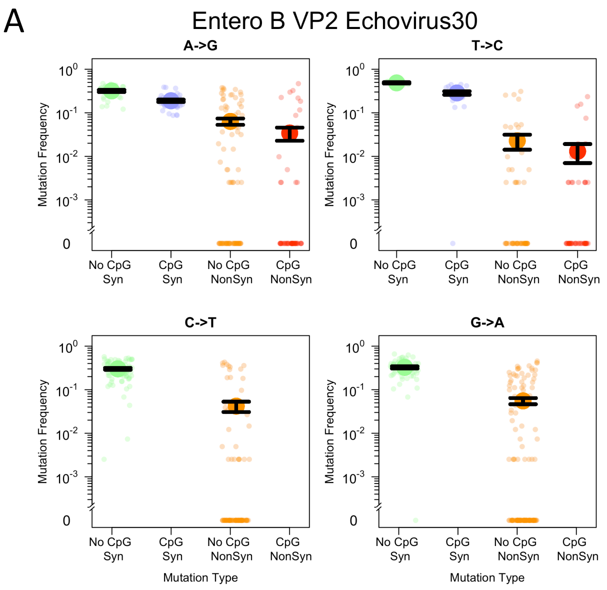
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.985 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.125 |
| | NonSyn: CpG v NonCpG | 0.858 |
| | Syn v NonSyn | < 0.01 |

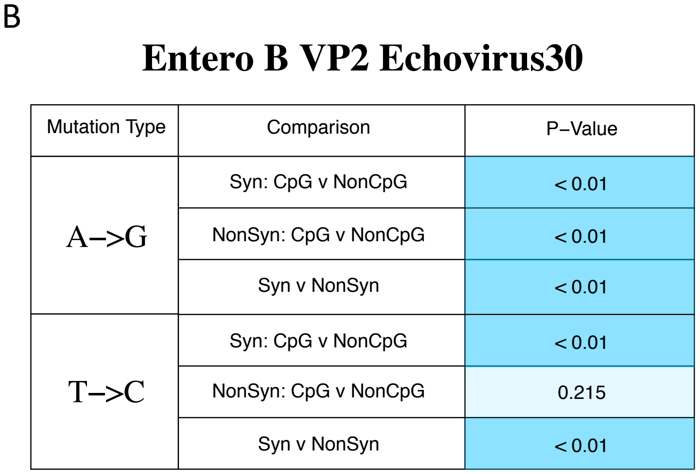
C



**Supplementary Fig. 62** (a) Transition mutation frequencies for the ancestral analysis of Entero B VP1 Echovirus30 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

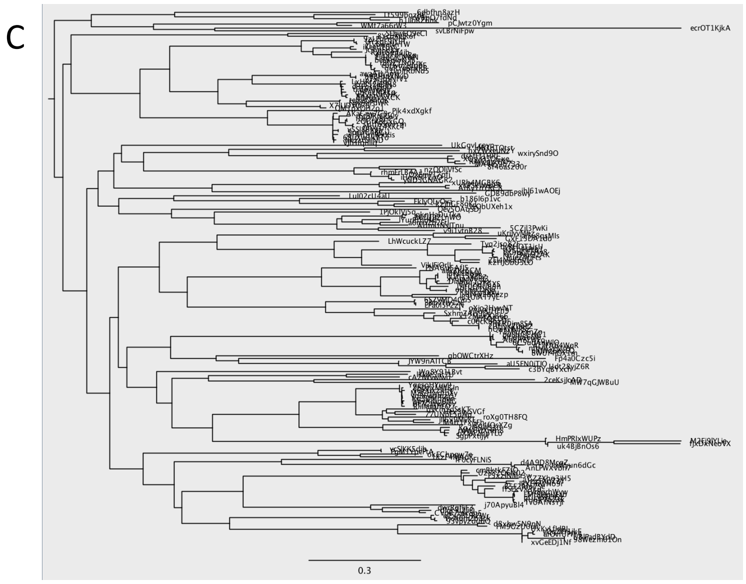
Ancestral Entero B VP2 Echovirus30





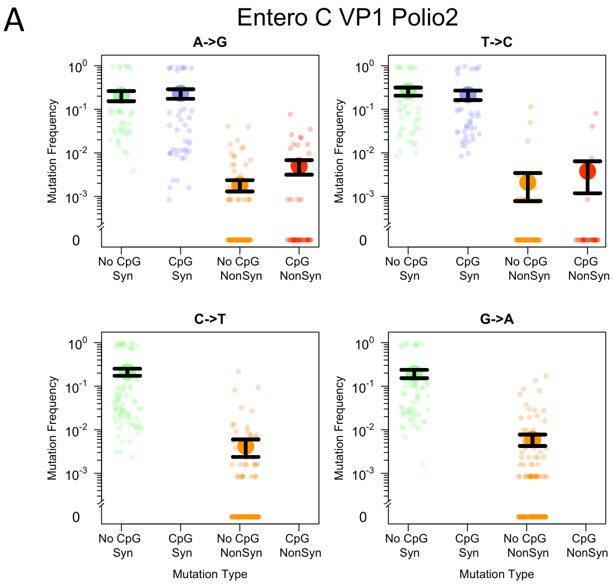
**Entero B VP2 Echovirus30**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.215 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 63** (a) Transition mutation frequencies for the ancestral analysis of Entero B VP2 Echovirus30 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

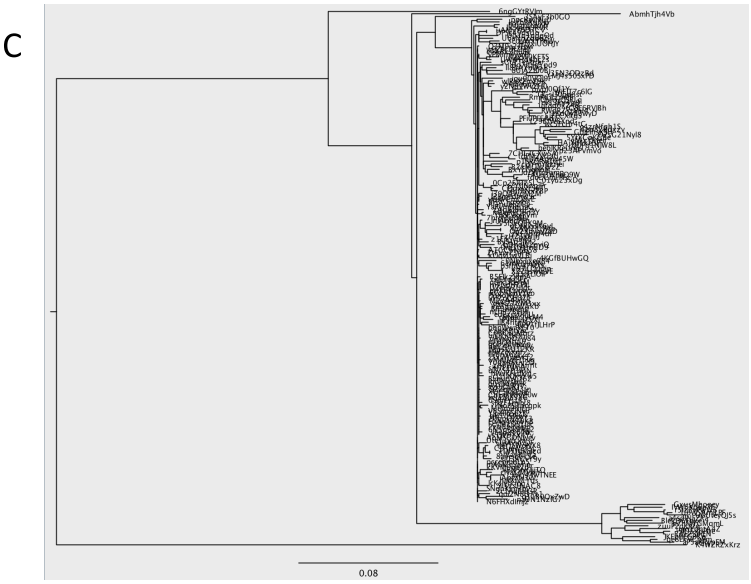
Ancestral Entero C VP1 Polio2



B

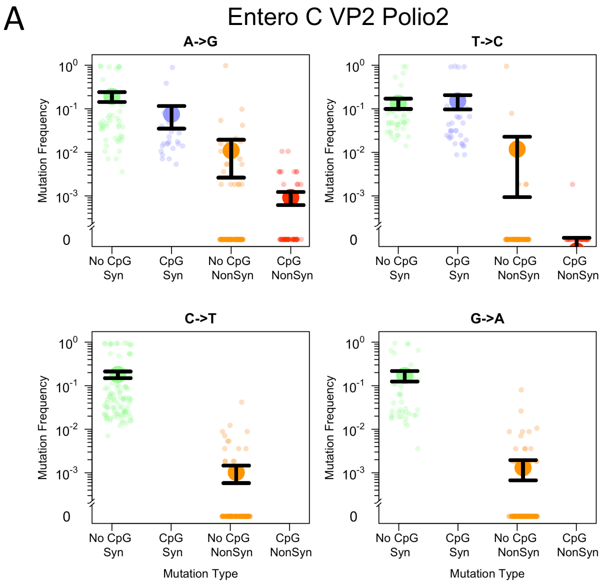
## Entero C VP1 Polio2

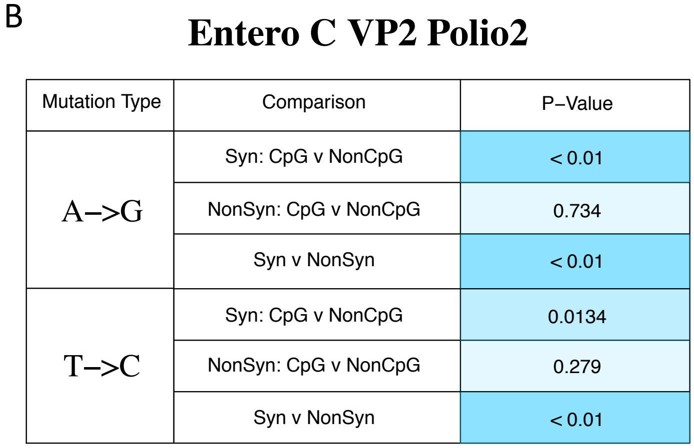
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.0246 |
| | NonSyn: CpG v NonCpG | 0.555 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.131 |
| | NonSyn: CpG v NonCpG | 0.206 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 64** (a) Transition mutation frequencies for the ancestral analysis of Entero C VP1 Polio2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

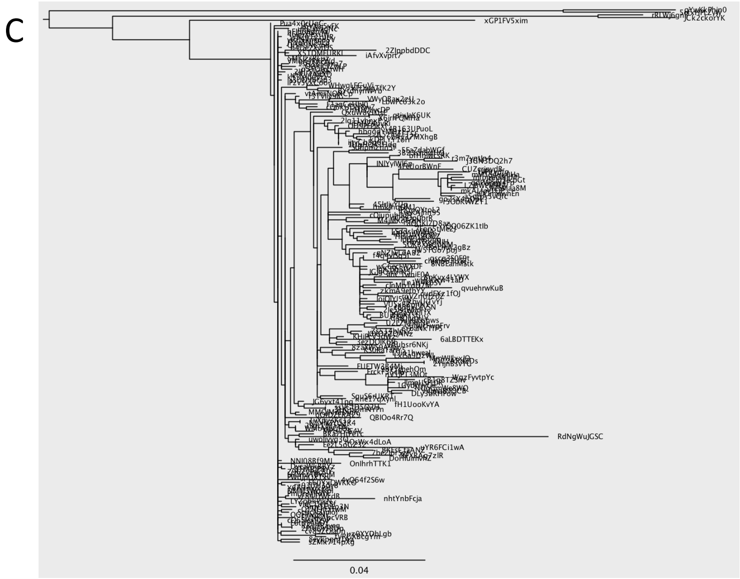
Ancestral Entero C VP2 Polio2





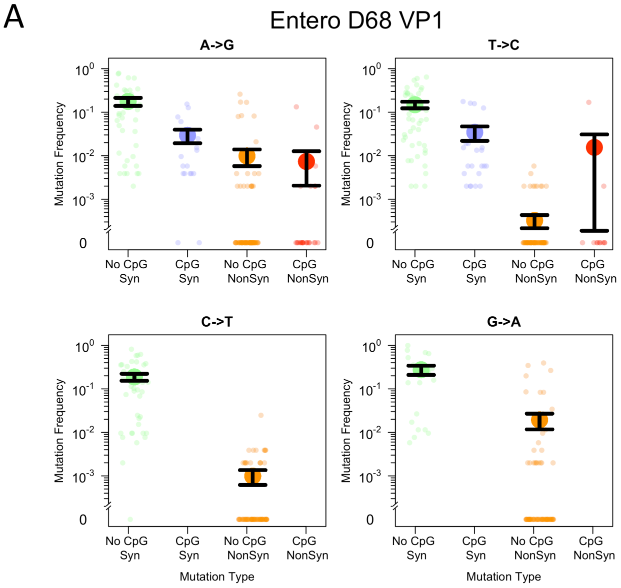
**Entero C VP2 Polio2**

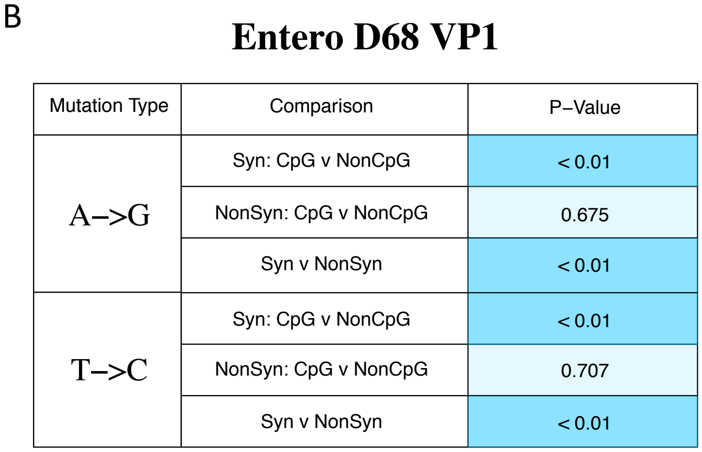
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.734 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.0134 |
| | NonSyn: CpG v NonCpG | 0.279 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 65** (a) Transition mutation frequencies for the ancestral analysis of Entero C VP2 Polio2 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

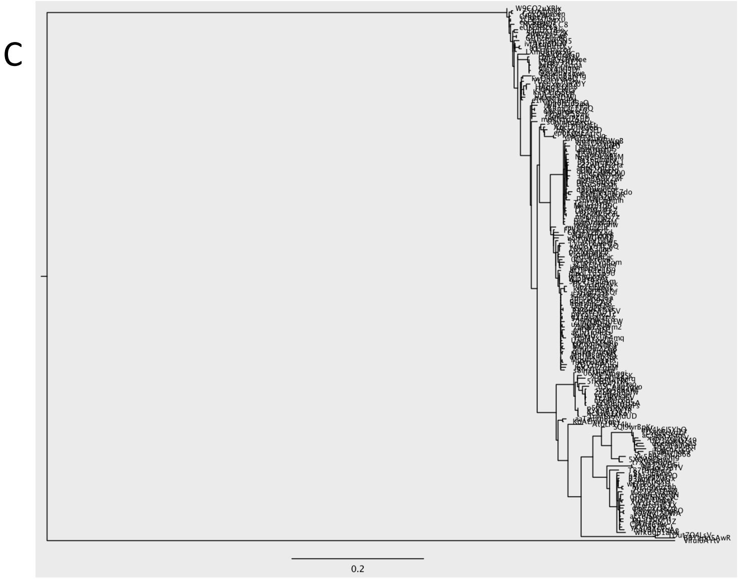
Ancestral Entero D68 VP1





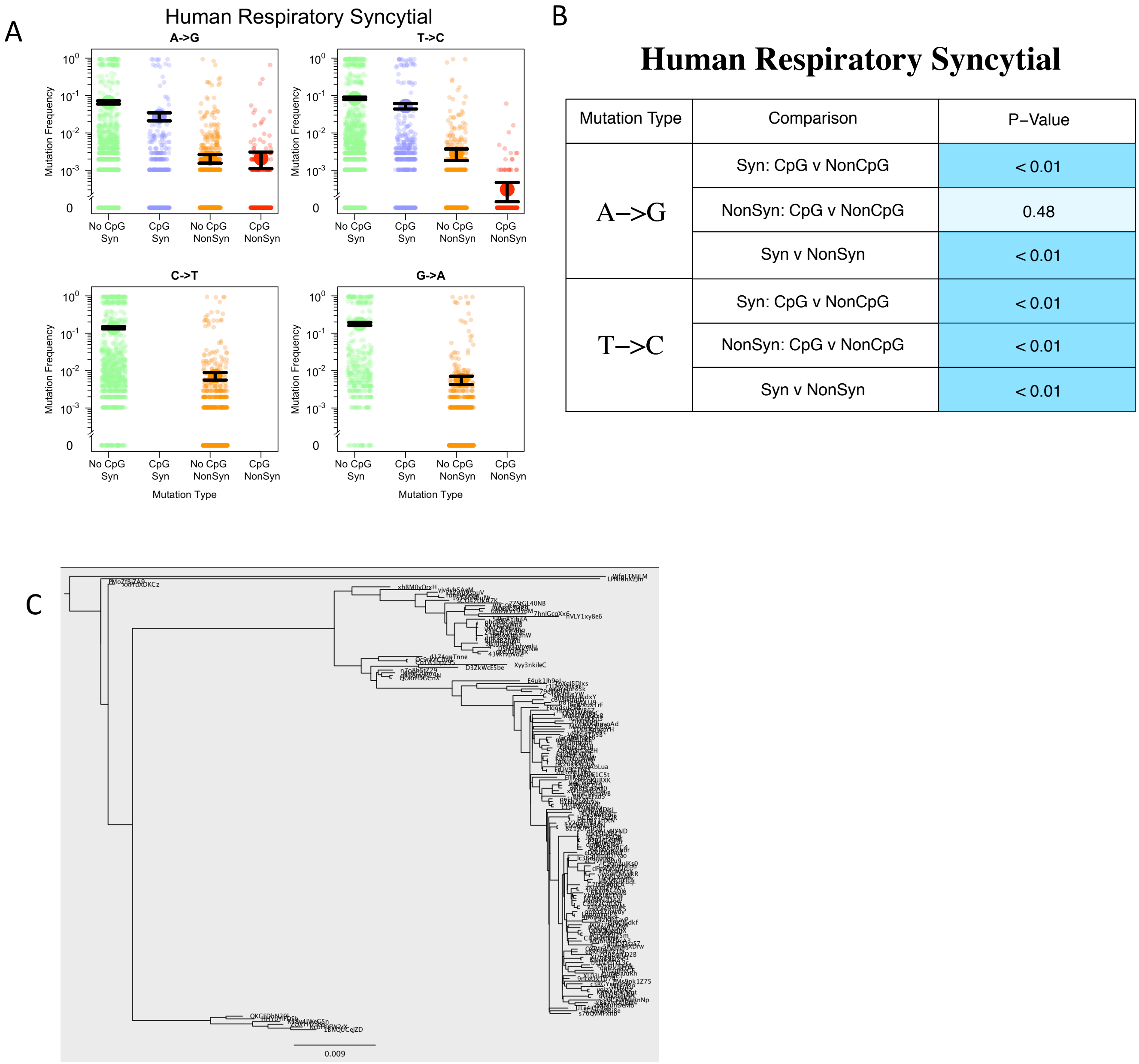
## Entero D68 VP1

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | < 0.01 |
|  | NonSyn: CpG v NonCpG | 0.675 |
|  | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | < 0.01 |
|  | NonSyn: CpG v NonCpG | 0.707 |
|  | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 66** (a) Transition mutation frequencies for the ancestral analysis of Entero D68 VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Human Respiratory Syncytial



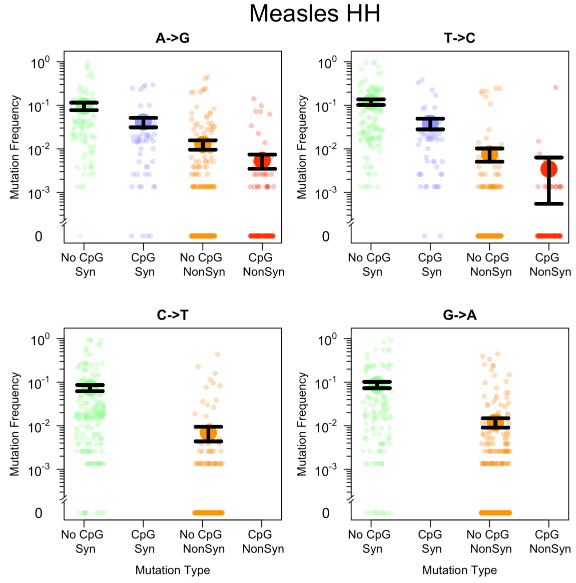
**Human Respiratory Syncytial**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.48 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |

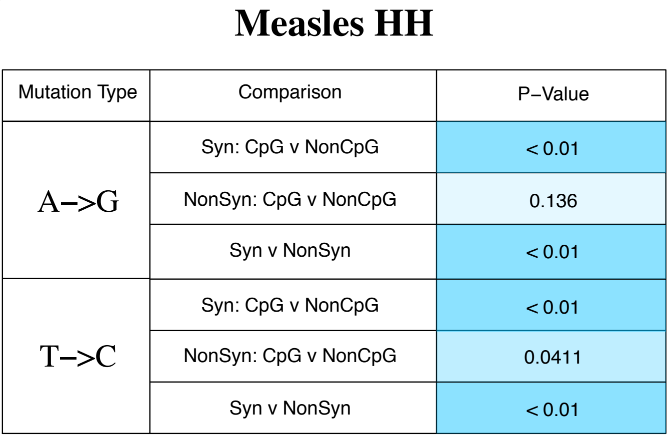
**Supplementary Fig. 67** (a) Transition mutation frequencies for the ancestral analysis of Human Respiratory Syncytial with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Measles HH

A



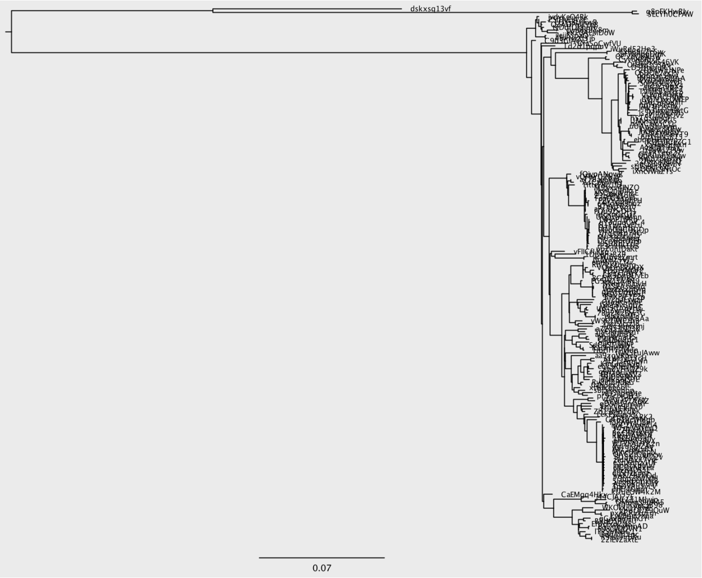
B



**Measles HH**

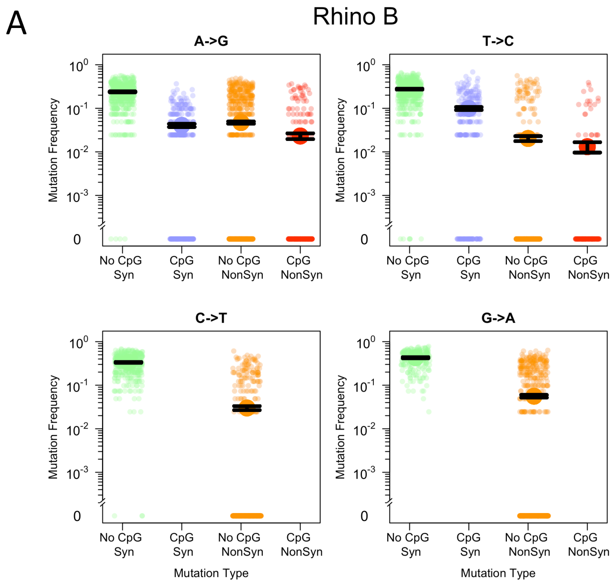
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.136 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.0411 |
| | Syn v NonSyn | < 0.01 |

C

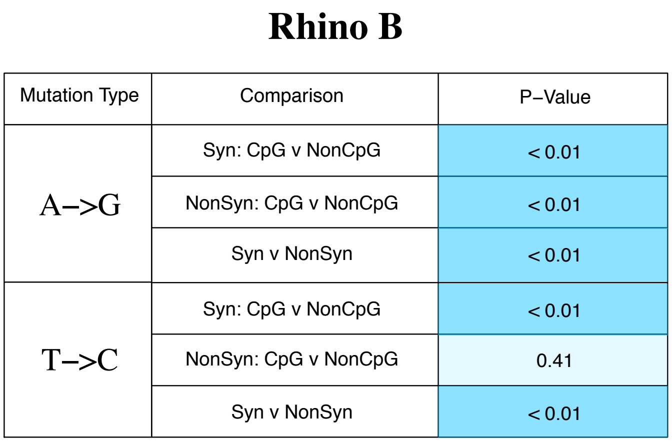


**Supplementary Fig. 68** (a) Transition mutation frequencies for the ancestral analysis of Measles HH with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Rhino B

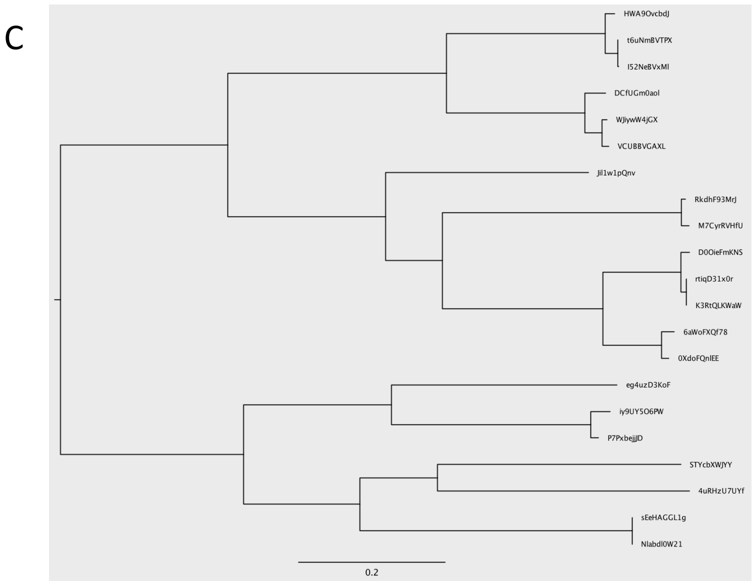


B



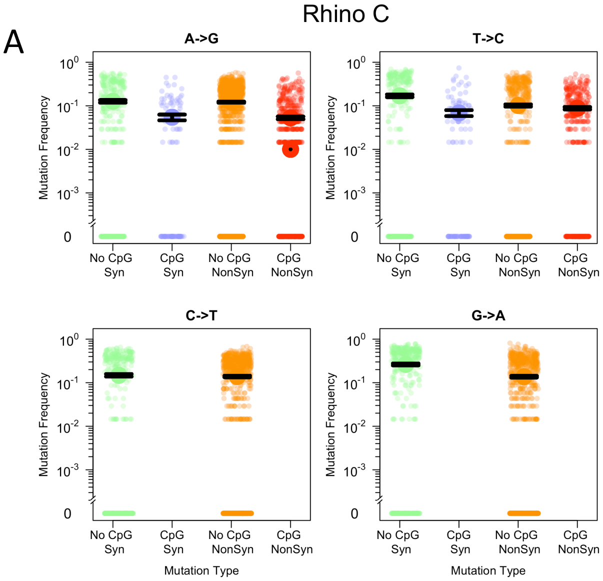
**Rhino B**

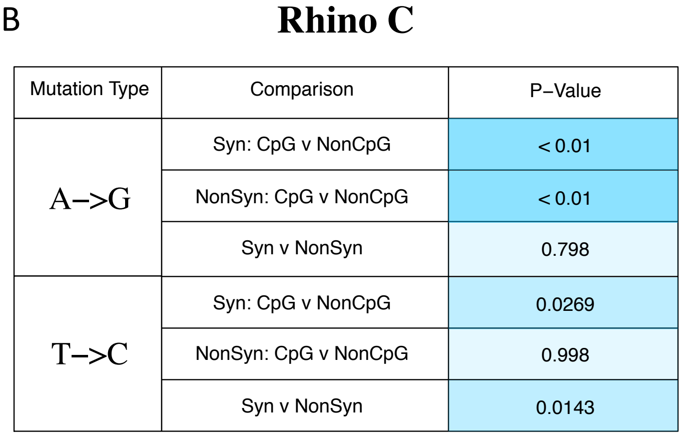
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.41 |
| | Syn v NonSyn | < 0.01 |



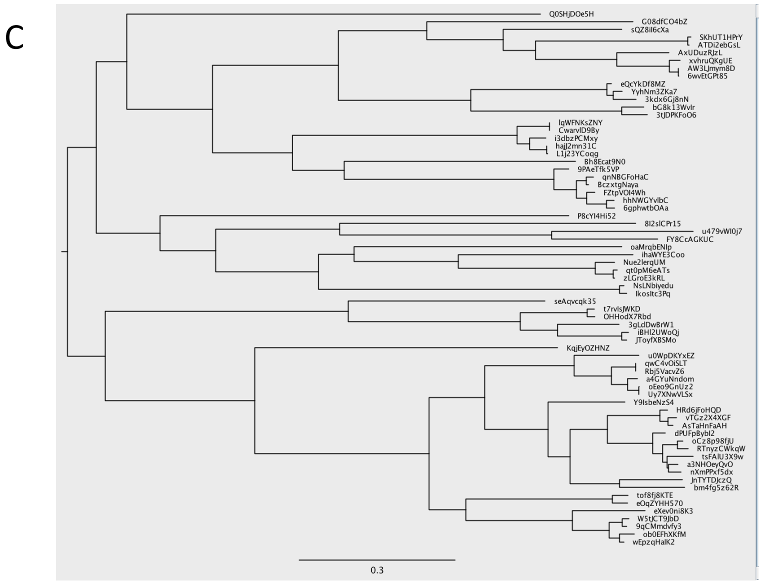
**Supplementary Fig. 69** (a) Transition mutation frequencies for the ancestral analysis of Rhino B with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

## Ancestral Rhino C



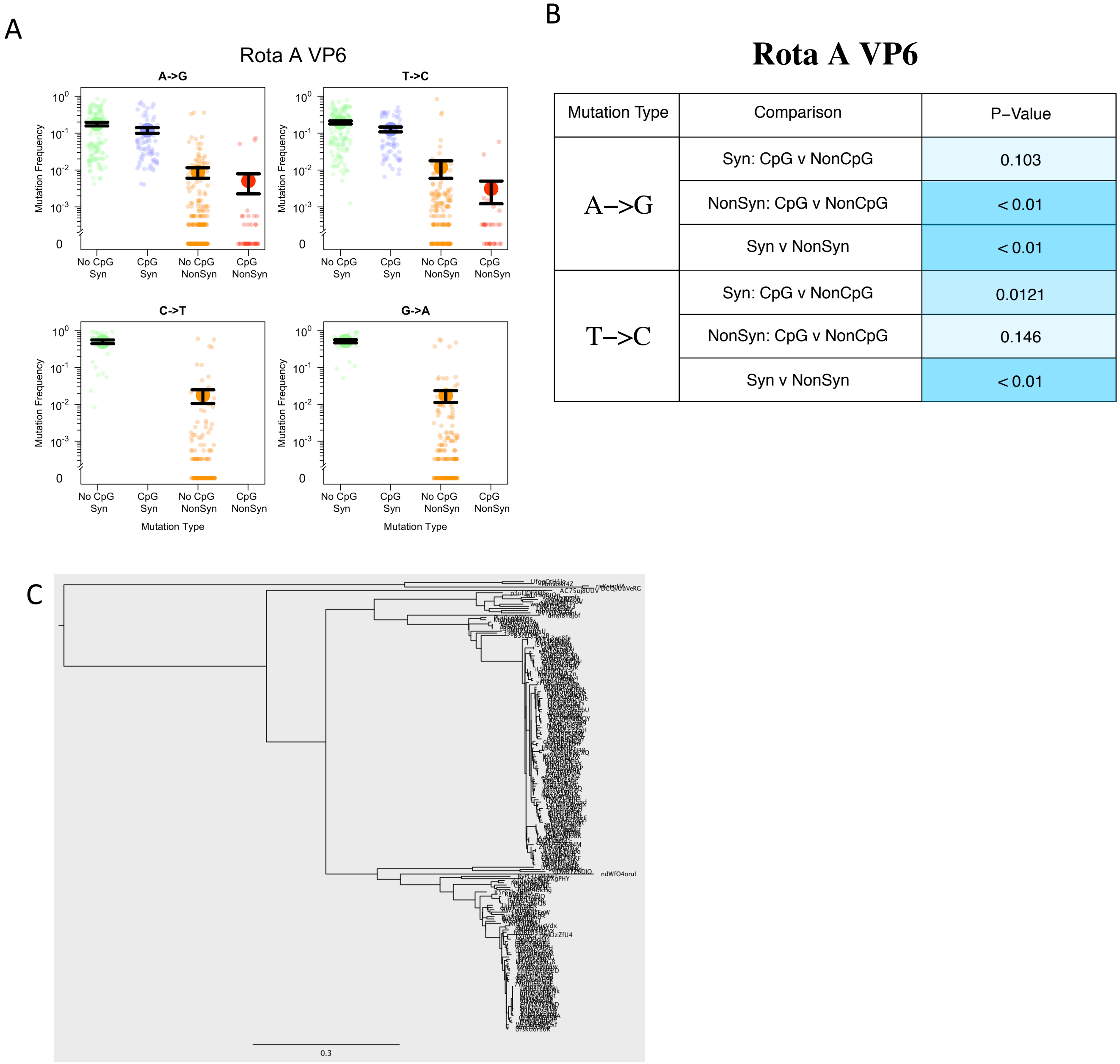


| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 0.798 |
| T–>C | Syn: CpG v NonCpG | 0.0269 |
| | NonSyn: CpG v NonCpG | 0.998 |
| | Syn v NonSyn | 0.0143 |



**Supplementary Fig. 70** (a) Transition mutation frequencies for the ancestral analysis of Rhino C with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Rota A VP6



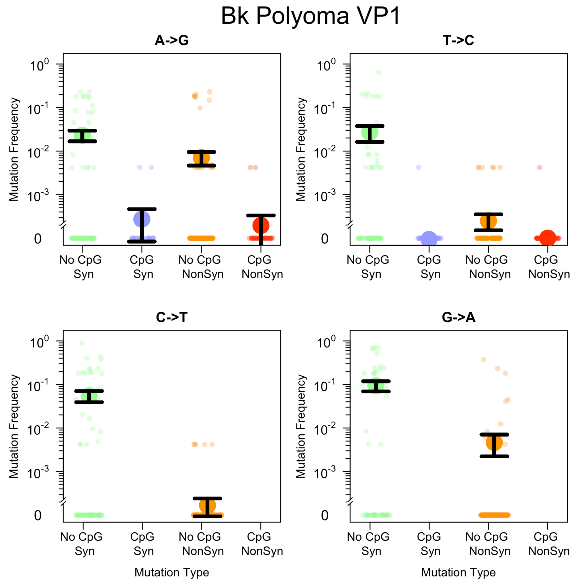
**Rota A VP6**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.103 |
|  | NonSyn: CpG v NonCpG | < 0.01 |
|  | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.0121 |
|  | NonSyn: CpG v NonCpG | 0.146 |
|  | Syn v NonSyn | < 0.01 |

**Supplementary Fig. 71** (a) Transition mutation frequencies for the ancestral analysis of Rota A VP6 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

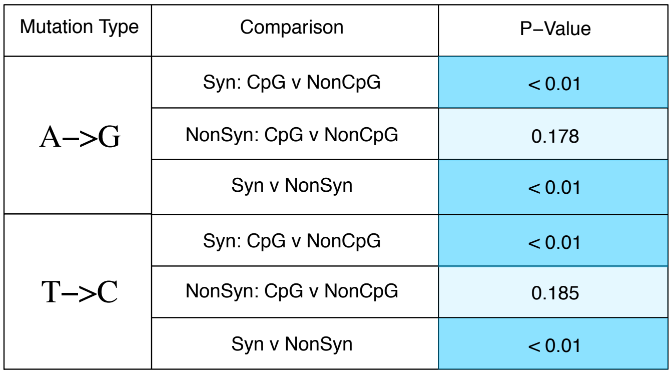
Ancestral Bk Polymerase

A



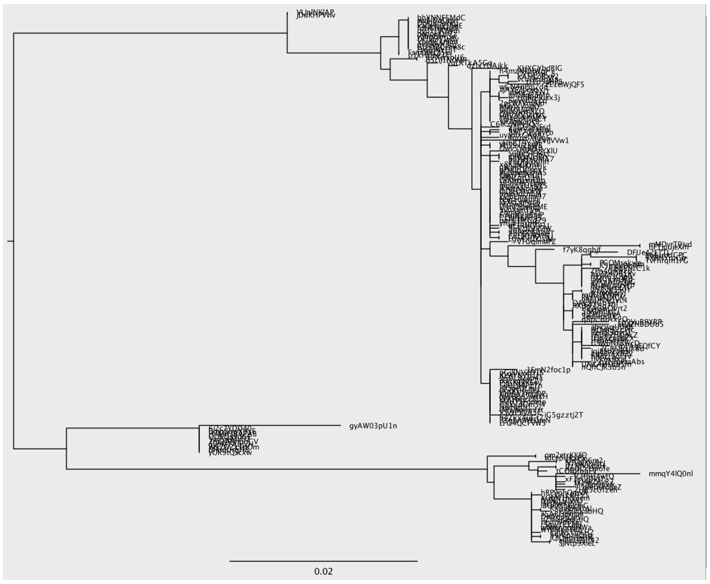
B

## Bk Polyoma VP1



| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.178 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.185 |
| | Syn v NonSyn | < 0.01 |

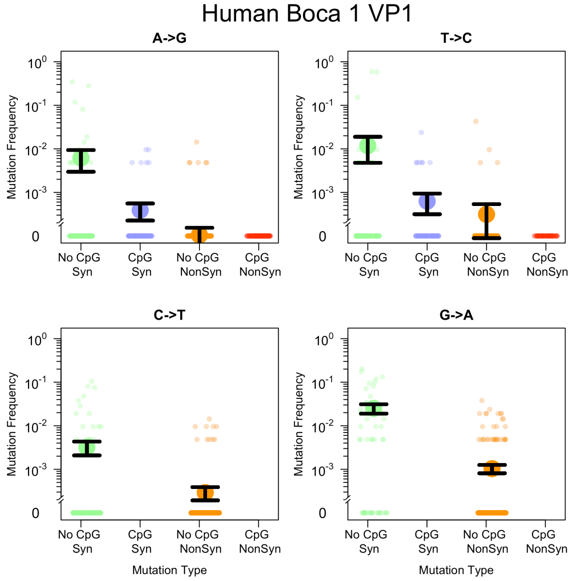
C



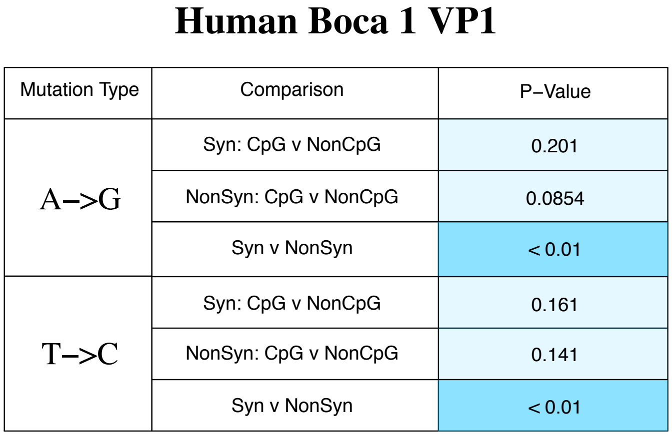
**Supplementary Fig. 72** (a) Transition mutation frequencies for the ancestral analysis of Bk Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Human Boca 1 VP1

A



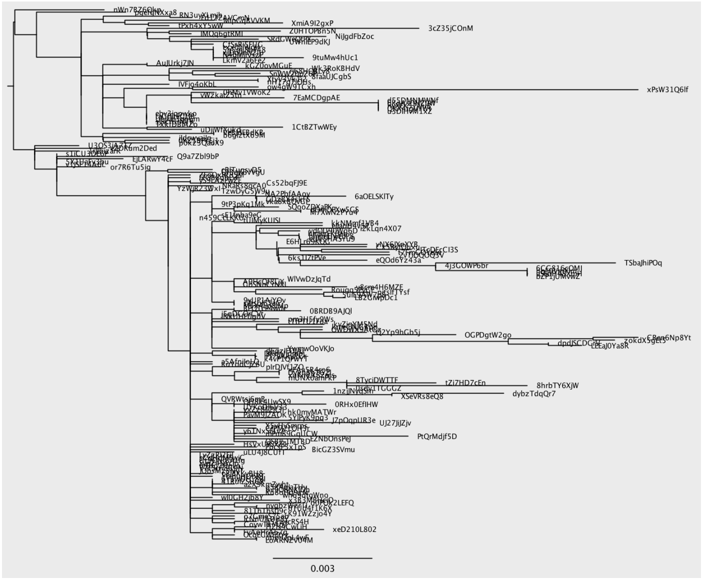
B



# Human Boca 1 VP1

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.201 |
| | NonSyn: CpG v NonCpG | 0.0854 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.161 |
| | NonSyn: CpG v NonCpG | 0.141 |
| | Syn v NonSyn | < 0.01 |

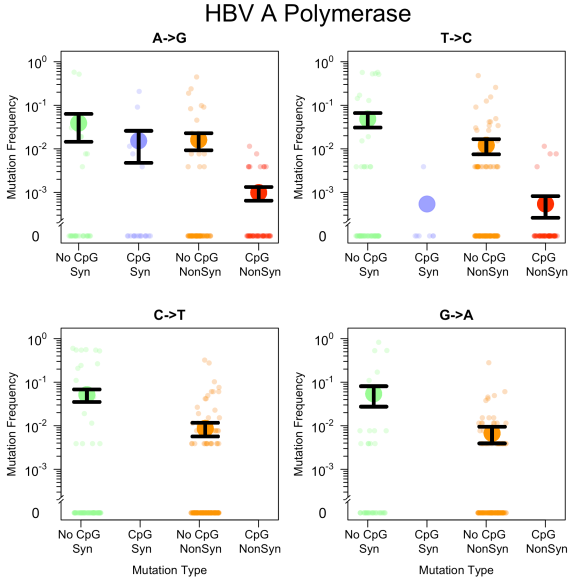
C



**Supplementary Fig. 73** (a) Transition mutation frequencies for the ancestral analysis of Human Boca 1 VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

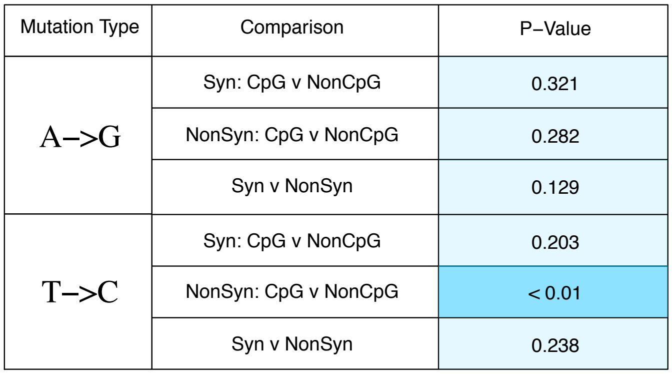
Ancestral HBV A Polymerase

A



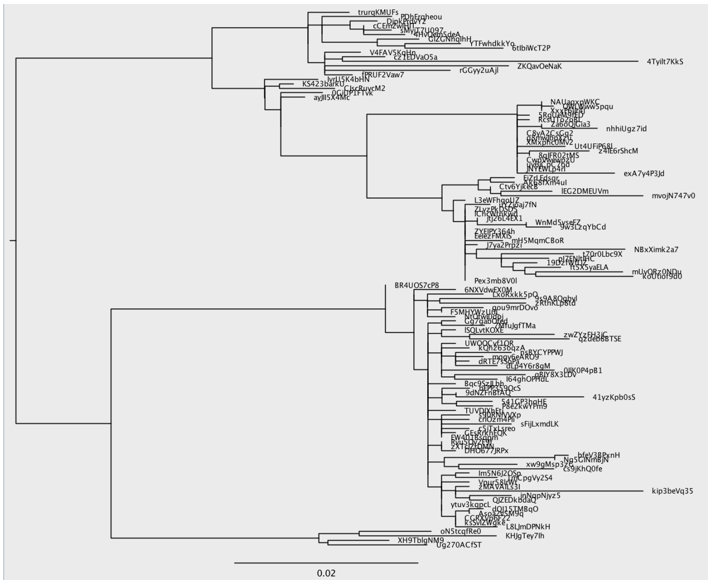
B

## HBV A Polymerase



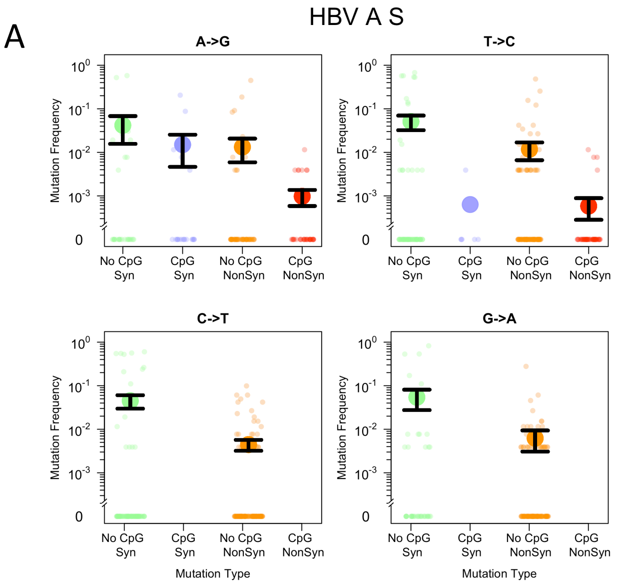
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.321 |
| | NonSyn: CpG v NonCpG | 0.282 |
| | Syn v NonSyn | 0.129 |
| T–>C | Syn: CpG v NonCpG | 0.203 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 0.238 |

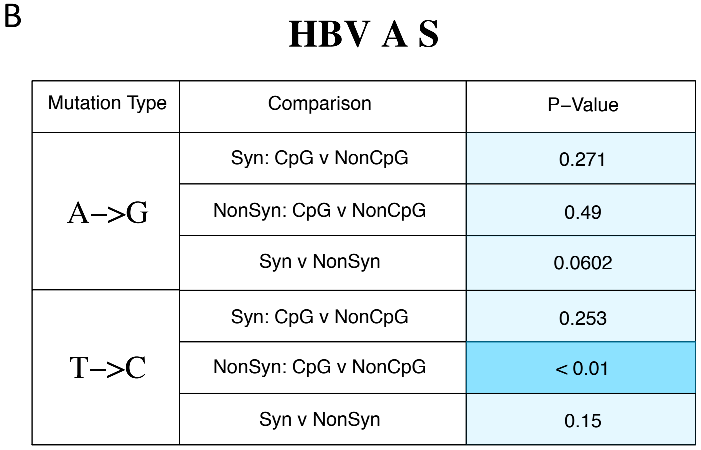
C



**Supplementary Fig. 74** (a) Transition mutation frequencies for the ancestral analysis of HBV A Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

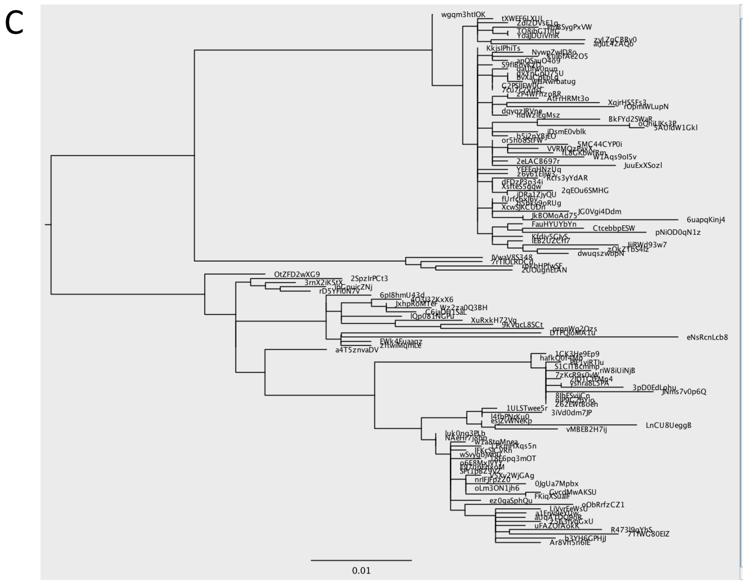
Ancestral HBV A S





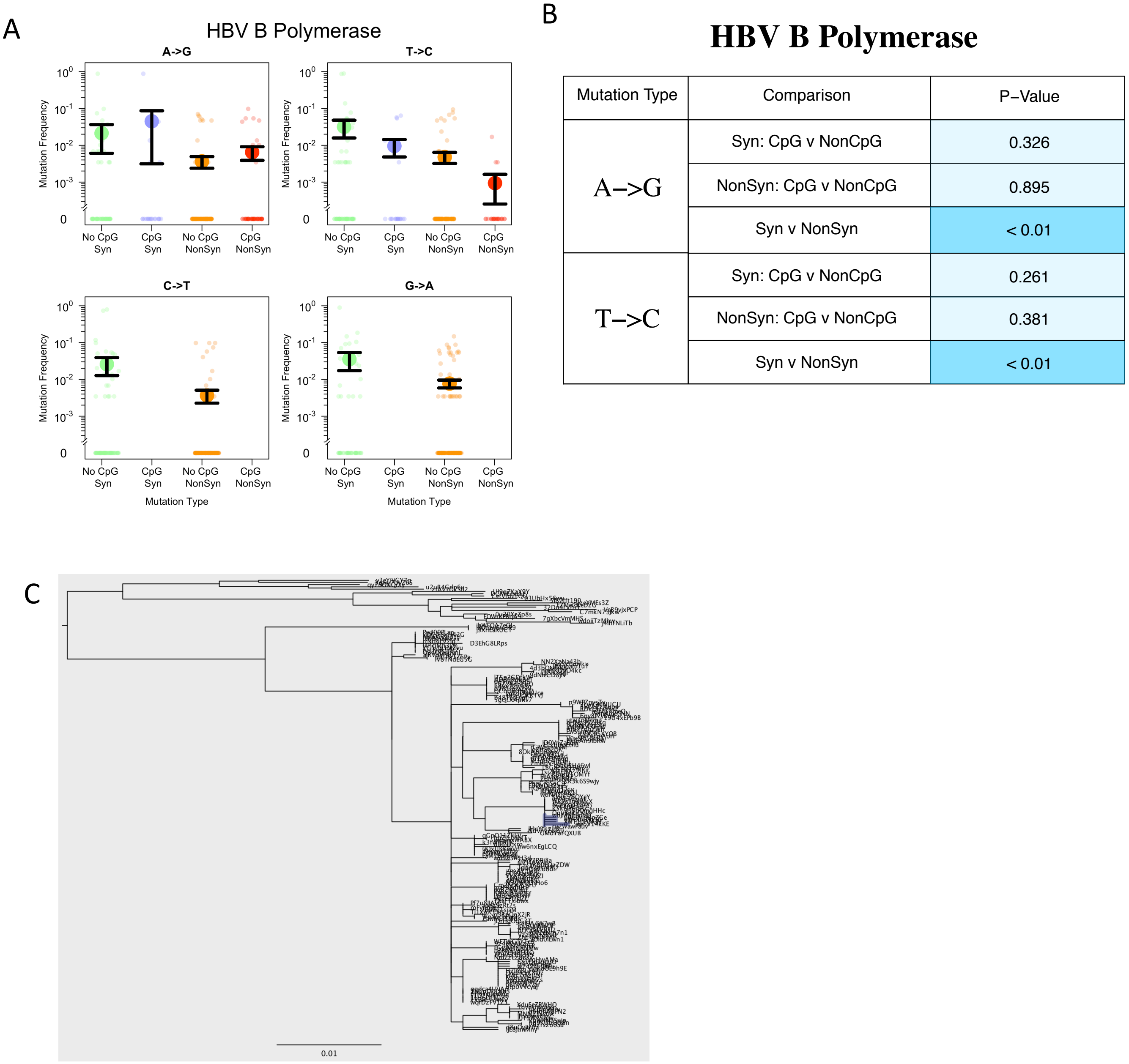
HBV A S

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.271 |
| | NonSyn: CpG v NonCpG | 0.49 |
| | Syn v NonSyn | 0.0602 |
| T–>C | Syn: CpG v NonCpG | 0.253 |
| | NonSyn: CpG v NonCpG | < 0.01 |
| | Syn v NonSyn | 0.15 |



**Supplementary Fig. 75** (a) Transition mutation frequencies for the ancestral analysis of HBV A S with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral HBV B Polymerase



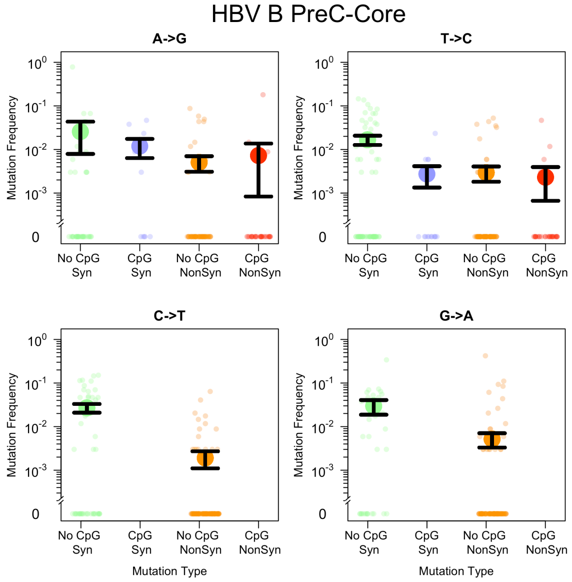
HBV B Polymerase

| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.326 |
| | NonSyn: CpG v NonCpG | 0.895 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.261 |
| | NonSyn: CpG v NonCpG | 0.381 |
| | Syn v NonSyn | < 0.01 |

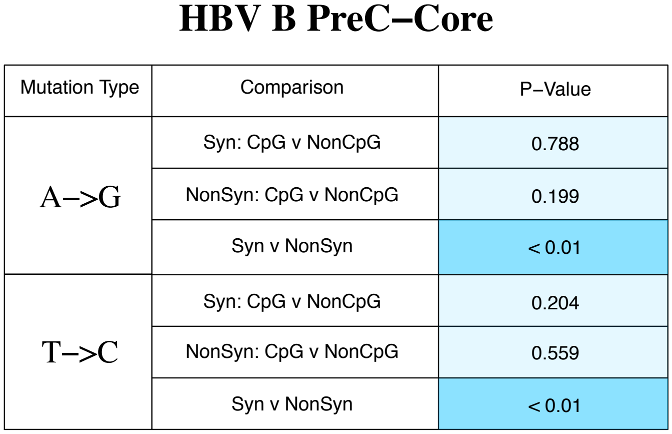
**Supplementary Fig. 76** (a) Transition mutation frequencies for the ancestral analysis of HBV B Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral HBV B PreC-Core

A



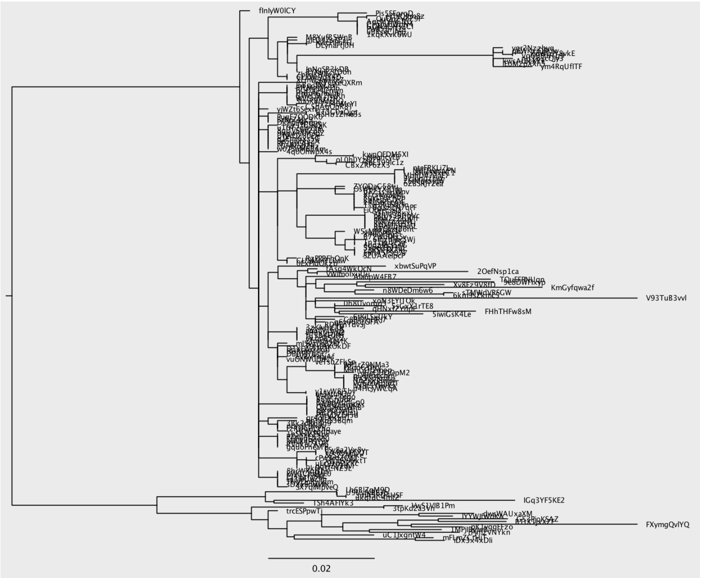
B



HBV B PreC−Core

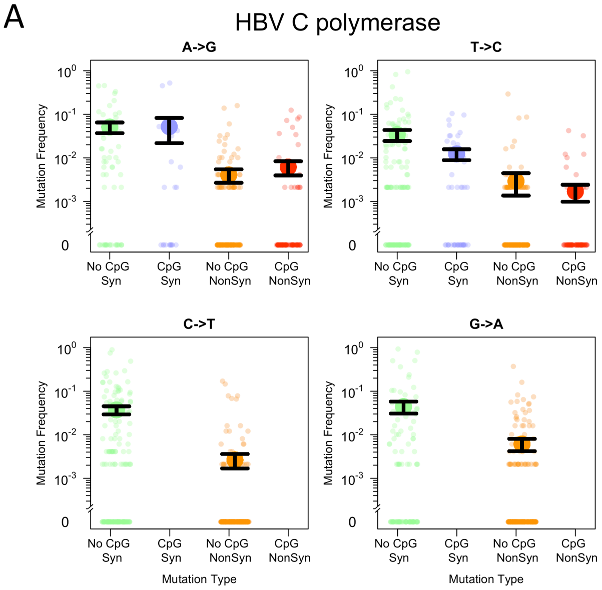
| Mutation Type | Comparison | P−Value |
|---|---|---|
| A−>G | Syn: CpG v NonCpG | 0.788 |
| | NonSyn: CpG v NonCpG | 0.199 |
| | Syn v NonSyn | < 0.01 |
| T−>C | Syn: CpG v NonCpG | 0.204 |
| | NonSyn: CpG v NonCpG | 0.559 |
| | Syn v NonSyn | < 0.01 |

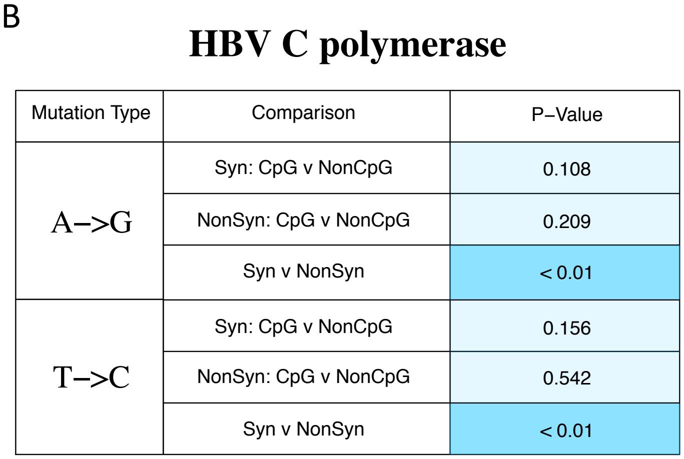
C



**Supplementary Fig. 77** (a) Transition mutation frequencies for the ancestral analysis of HBV B PreC-Core with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

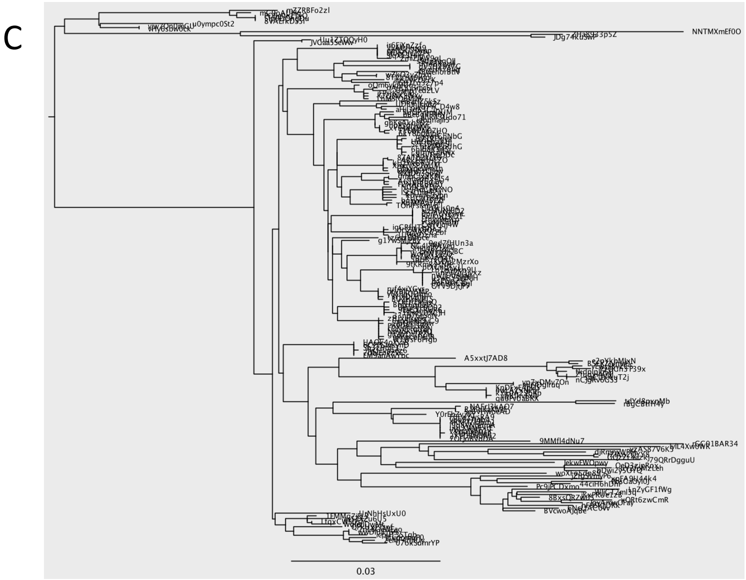
Ancestral HBV C Polymerase





## HBV C polymerase

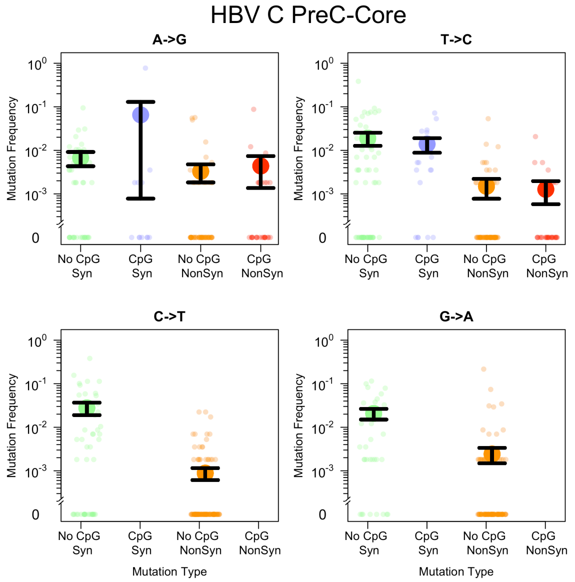
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.108 |
| | NonSyn: CpG v NonCpG | 0.209 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.156 |
| | NonSyn: CpG v NonCpG | 0.542 |
| | Syn v NonSyn | < 0.01 |



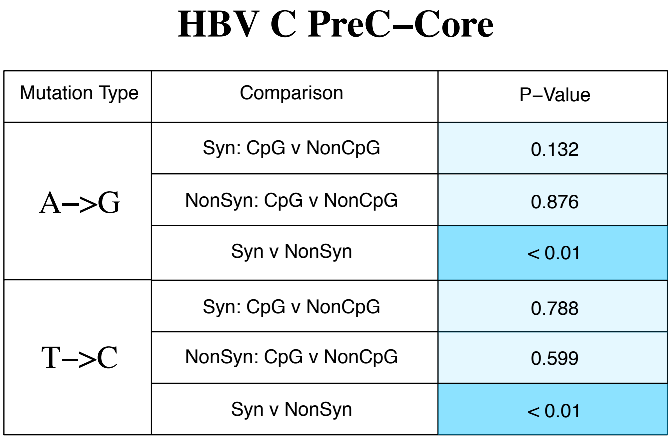
**Supplementary Fig. 78** (a) Transition mutation frequencies for the ancestral analysis of HBV C Polymerase with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral HBV C PreC-Core

A



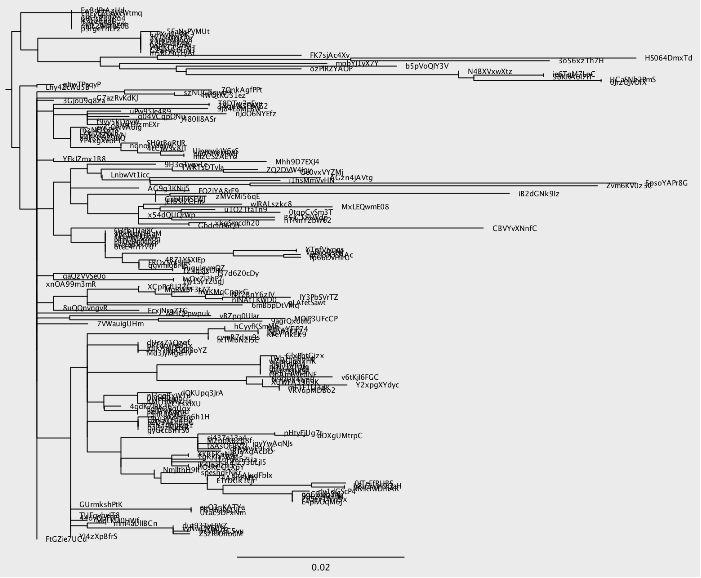
B



**HBV C PreC–Core**

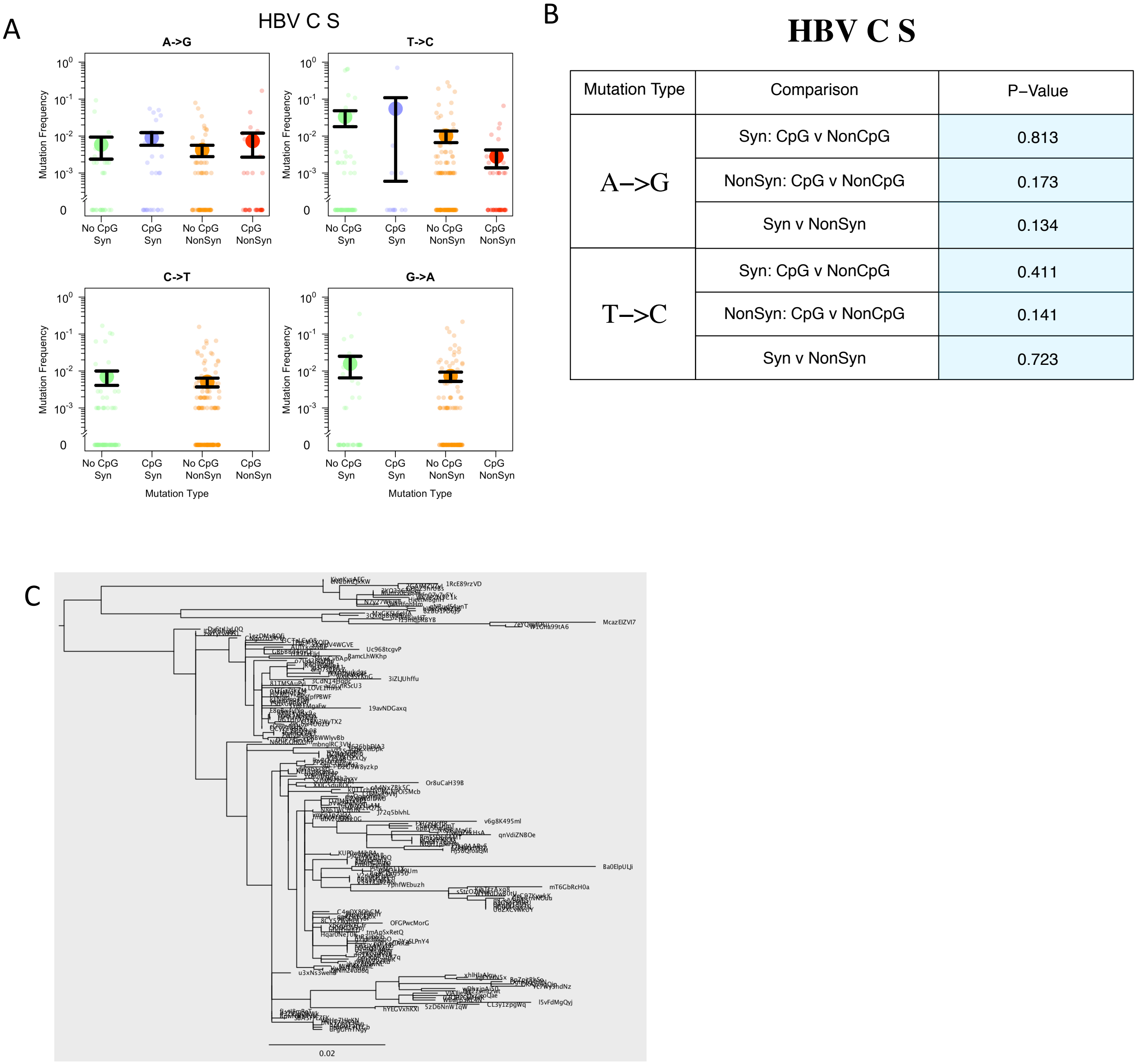
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.132 |
| | NonSyn: CpG v NonCpG | 0.876 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.788 |
| | NonSyn: CpG v NonCpG | 0.599 |
| | Syn v NonSyn | < 0.01 |

C



**Supplementary Fig. 79** (a) Transition mutation frequencies for the ancestral analysis of HBV C PreC-Core with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral HBV C S

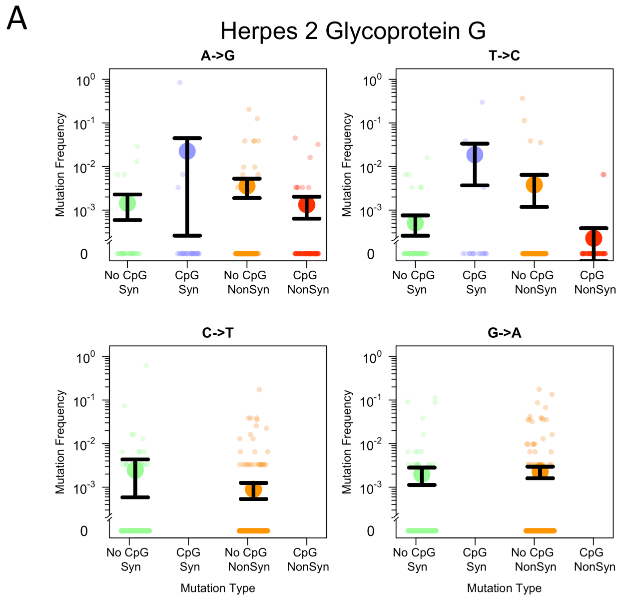


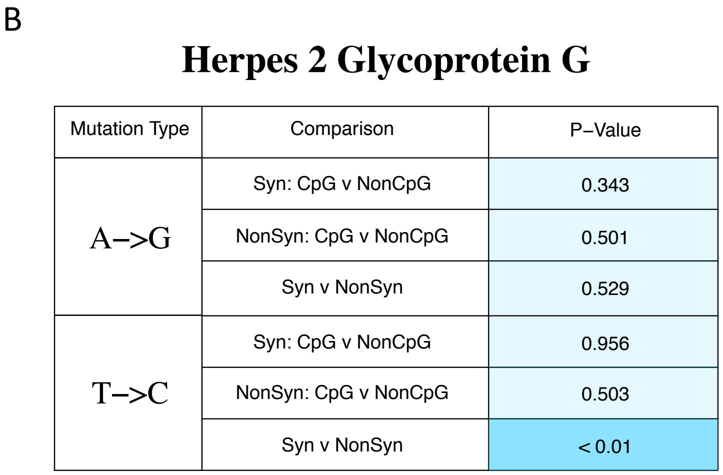
**HBV C S**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.813 |
| | NonSyn: CpG v NonCpG | 0.173 |
| | Syn v NonSyn | 0.134 |
| T–>C | Syn: CpG v NonCpG | 0.411 |
| | NonSyn: CpG v NonCpG | 0.141 |
| | Syn v NonSyn | 0.723 |

**Supplementary Fig. 80**(a) Transition mutation frequencies for the ancestral analysis of HBV C S with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

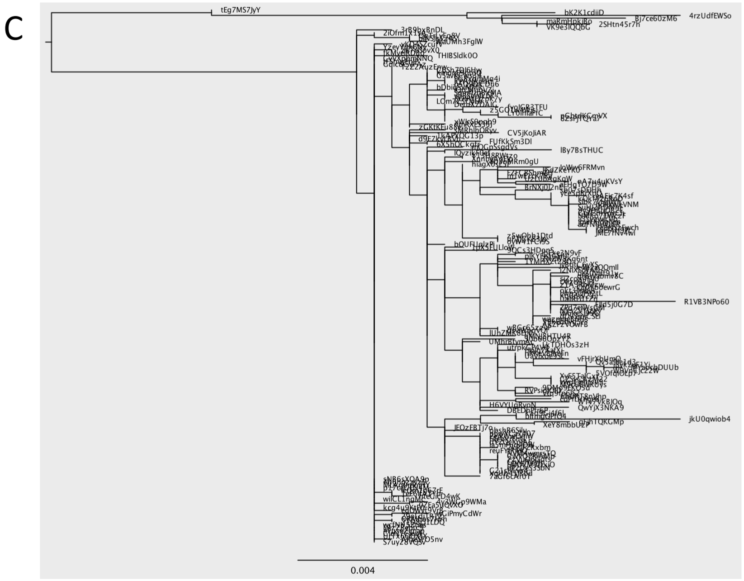
# Ancestral Herpes 2 Glycoprotein G





**Herpes 2 Glycoprotein G**

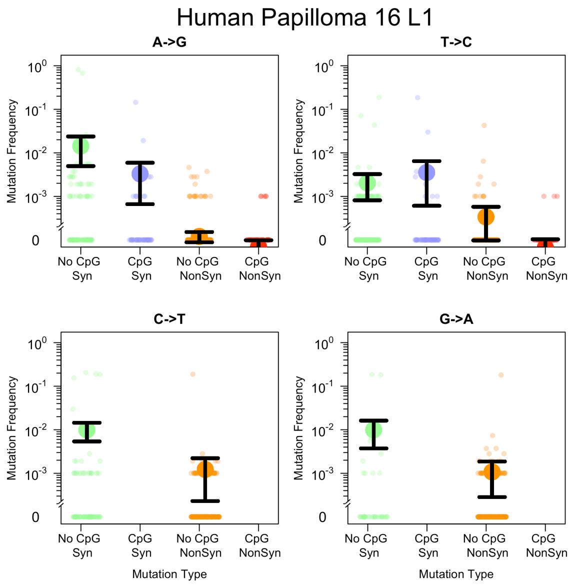
| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.343 |
| | NonSyn: CpG v NonCpG | 0.501 |
| | Syn v NonSyn | 0.529 |
| T–>C | Syn: CpG v NonCpG | 0.956 |
| | NonSyn: CpG v NonCpG | 0.503 |
| | Syn v NonSyn | < 0.01 |



**Supplementary Fig. 81** (a) Transition mutation frequencies for the ancestral analysis of Herpes 2 Glycoprotein G with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Human Papilloma 16 L1

A

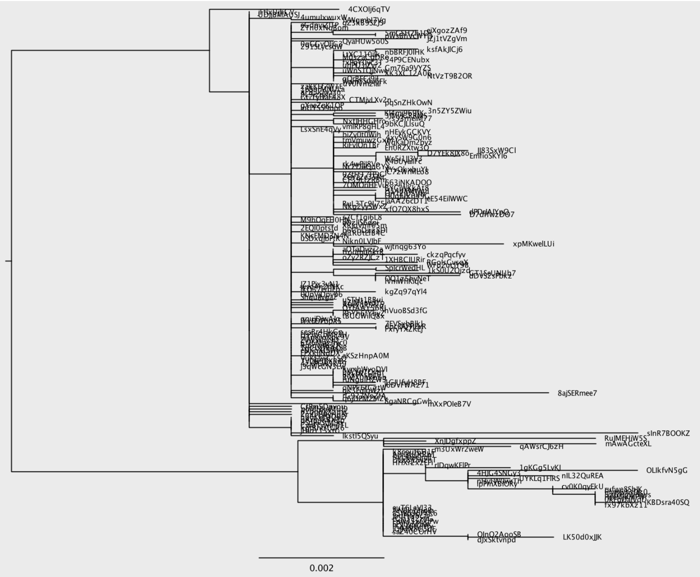


B

**Human Papilloma 16 L1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | 0.0665 |
| | NonSyn: CpG v NonCpG | 0.456 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | 0.102 |
| | NonSyn: CpG v NonCpG | 0.595 |
| | Syn v NonSyn | < 0.01 |

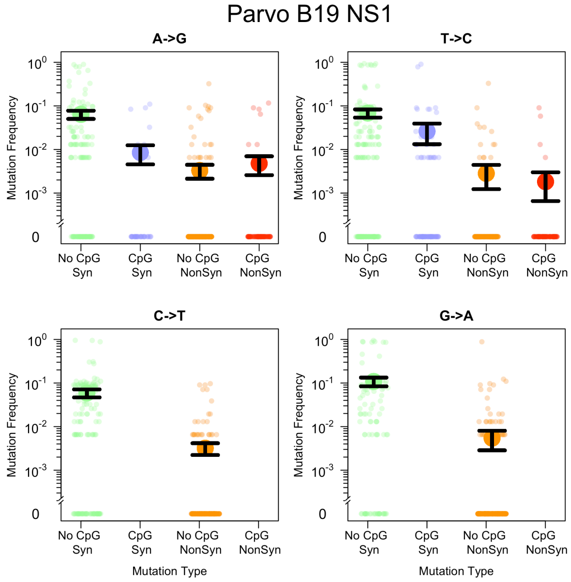
C



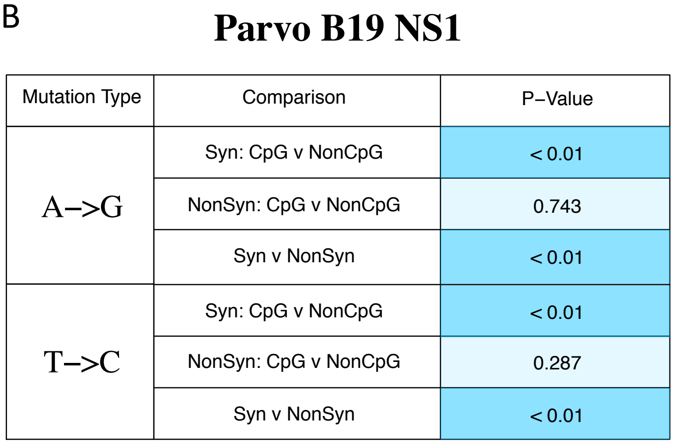
**Supplementary Fig. 82** (a) Transition mutation frequencies for the ancestral analysis of Human Papilloma 16 L1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Parvo B19 NS1

A



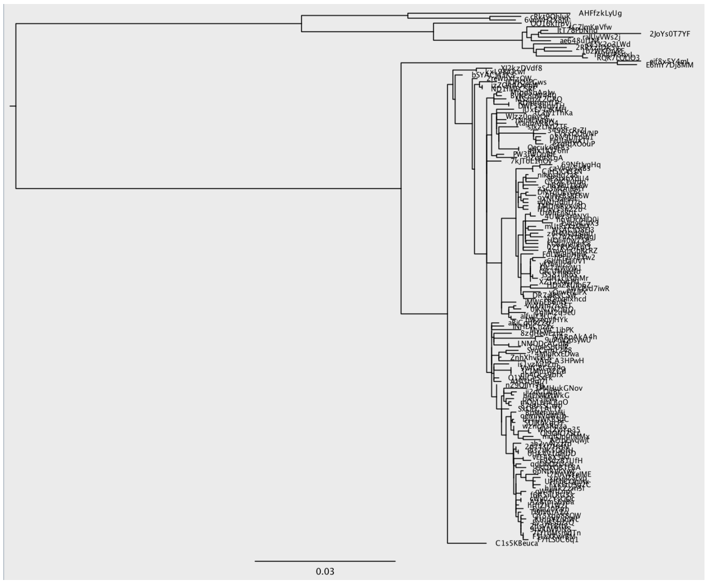
B



**Parvo B19 NS1**

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.743 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.287 |
| | Syn v NonSyn | < 0.01 |

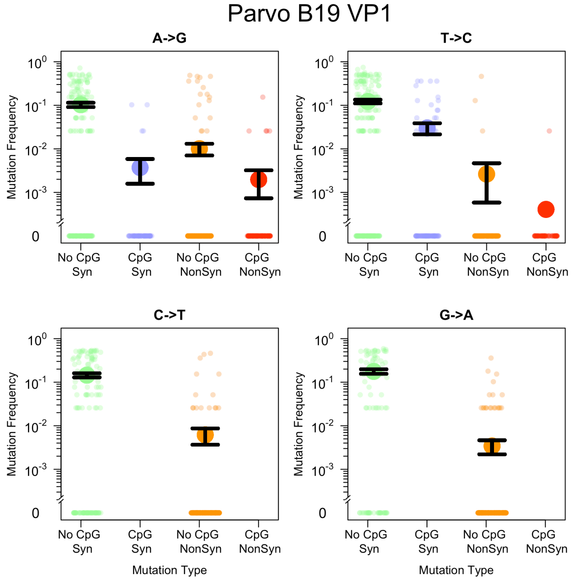
C



**Supplementary Fig. 83** (a) Transition mutation frequencies for the ancestral analysis of Parvo B19 NS1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.

Ancestral Parvo B19 VP1

A

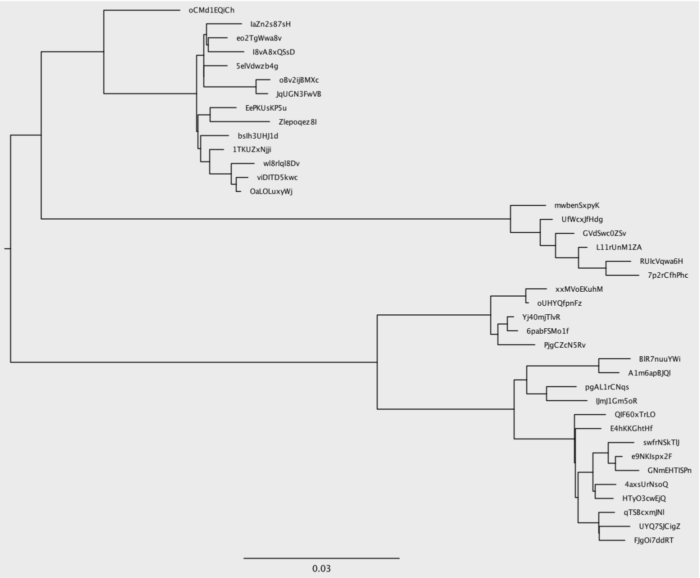


B

## Parvo B19 VP1

| Mutation Type | Comparison | P–Value |
|---|---|---|
| A–>G | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.343 |
| | Syn v NonSyn | < 0.01 |
| T–>C | Syn: CpG v NonCpG | < 0.01 |
| | NonSyn: CpG v NonCpG | 0.572 |
| | Syn v NonSyn | < 0.01 |

C



**Supplementary Fig. 84** (a) Transition mutation frequencies for the ancestral analysis of Parvo B19 VP1 with mean and standard error (black line). (b) Wilcoxon test results, where the shade of the blue in the P-value cell represents the significance level; darker the shade, the more significant the results. (c) Midpoint rooted tree from a sample size of 200.