**Supplementary file 3. Prevalent sequence clusters over the course of evolution.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Round | Cluster | Nucleotides 9–17 | Nucleotides 83–95 | Frequency (%) |
|  6 |  wild type | CCGCACAAA | AUAGCG--CCAAC | 91.2 |
|  6 |  6.1 | CCGCACAAA | AUGGCG--CCAAC | 1.2 |
|  8 |  wild type | CCGCACAAA | AUAGCG--CCAAC | 64.0 |
|  8 |  8.1 | CCGCACAAA | CAAGCG--CCAAC | 4.8 |
|  8 |  6.1 | CCGCACAAA | AUGGCG--CCAAC | 3.5 |
|  8 |  wild type | CCGCACAAA | AUAGCG--CCAUC | 2.1 |
|  8 |  8.2 | CCGCACAGA | AUGGCG--CCAAC | 1.6 |
|  8 |  wild type | CCGCACAAA | ACAGCG--CCAGC | 1.6 |
|  8 |  8.3 | CCGCACAGA | AUAGCG--CCAAC | 1.5 |
|  8 |  8.4 | CCGCACAAA | AUAGCG--CCAGC | 1.5 |
|  8 |  8.5 | CCGCACGAA | AUAGCG--CCAAC | 1.1 |
|  8 |  wild type | CCGCACAAA | AUAGCG--UCAAC | 1.1 |
|  11 |  11.1 | CCGCACUAA | AUAGUG--CCAAC | 27.1 |
|  11 |  wild type | CCGCACAAA | AUAGCG--CCAAC | 24.8 |
|  11 |  11.2 | CCGCACAAA | AUGGCU--CGAAG | 16.1 |
|  11 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 7.4 |
|  11 |  11.3 | CCGCACAAA | AUUGUG--CCACC | 6.1 |
|  11 |  8.1 | CCGCACAAA | CAAGCG--CCAAC | 2.4 |
|  11 |  11.1 | CCGCACUAA | AUAGUG--CCACC | 1.5 |
|  11 |  24-3 | CCGCACGAA | AUCGUG--CCAAC | 1.3 |
|  11 |  11.4 | CCGCACAAA | AUCGCG--CCACC | 1.2 |
|  11 |  11.5 | CCGCACAGA | ACUGUG--CCACC | 1.1 |
|  11 |  11.4 | CCGCACAAA | AUCGCG--CCAAC | 1.0 |
|  12 |  11.1 | CCGCACUAA | AUAGUG--CCAAC | 45.2 |
|  12 |  11.3 | CCGCACAAA | AUUGUG--CCACC | 13.7 |
|  12 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 13.6 |
|  12 |  wild type | CCGCACAAA | AUAGCG--CCAAC | 7.2 |
|  12 |  11.2 | CCGCACAAA | AUGGCU--CGAAG | 7.1 |
|  12 |  wild type | CCGCACAAA | AUAGCG--CCAUC | 2.1 |
|  12 |  11.1 | CCGCACUAA | AUAGUG--CCACC | 1.6 |
|  12 |  24-3 | CCGCACGAA | AUCGUG--CCAAC | 1.1 |
|  14 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 63.4 |
|  14 |  11.3 | CCGCACAAA | AUUGUG--CCACC | 10.1 |
|  14 |  wild type | CCGCACAAA | AUAGCG--CCAAC | 9.3 |
|  14 |  11.2 | CCGCACAAA | AUGGCU--CGAAG | 6.6 |
|  14 |  11.1 | CCGCACUAA | AUAGUG--CCAAC | 2.5 |
|  14 |  24-3 | CCGCACGAA | AUCGUG--CCAAC | 2.1 |
|  14 |  14.1 | CCGCACAAA | -U-GUG--CCACC | 1.3 |
|  16 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 73.1 |
|  16 |  14.1 | CCGCACAAA | -U-GUG--CCACC | 14.9 |
|  16 |  11.5 | CCGCACAGA | ACUGUG--CCACC | 1.7 |
|  16 |  24-3 | CCGCACGAA | AUCGUG--CCAUC | 1.4 |
|  18 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 69.9 |
|  18 |  14.1 | CCGCACAAA | -U-GUG--CCACC | 16.2 |
|  18 |  24-3 | CCGCACGAA | AUCGUG--CCAUC | 2.2 |
|  18 |  11.3 | CCGCACAAA | AUUGUG--CCAAC | 2.1 |
|  18 |  18.1 | CCGCACGAA | UUCGUG--CCACC | 2.1 |
|  18 |  18.2 | CCGCACUAA | UUAGUG--CCACC | 1.0 |
|  18 |  18.1 | CCGCACGAA | UUCGUG--CCAUC | 1.0 |
|  21 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 75.4 |
|  21 |  14.1 | CCGCACAAA | -U-GUG--CCACC | 18.3 |
|  21 |  14.1 | CCGCACAAA | AU-GUG--CCACC | 1.4 |
|  21 |  18.1 | CCGCACGAA | UUCGUG--CCACC | 1.1 |
|  24 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 60.2 |
|  24 |  14.1 | CCGCACAAA | AU-GUG--CCACC | 31.3 |
|  24 |  24.1 | CCGCACGAA | AU-GUG--CCACC | 2.1 |
|  24 |  24.2 | CCGCACAAA | AUCGUG--CCACC | 2.0 |
|  24 |  14.1 | CCGCACAAA | ---GUG--CCACC | 1.1 |
|  27 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 55.2 |
|  27 |  14.1 | CCGCACAAA | -U-GUG--CCACC | 31.1 |
|  27 |  24.1 | CCGCACGAA | -U-GUG--CCACC | 5.7 |
|  27 |  18.2 | CCGCACUAA | UUAGUG--CCACC | 2.1 |
|  27 |  24.2 | CCGCACAAA | AUCGUG--CCACC | 1.6 |
|  27 |  18.1 | CCGCACGAA | UUCGUG--CCACC | 1.1 |
|  28 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 81.1 |
|  28 |  18.2 | CCGCACUAA | UUAGUG--CCACC | 8.5 |
|  28 |  18.1 | CCGCACGAA | UUCGUG--CCACC | 4.0 |
|  28 |  14.1 | CCGCACAAA | -U-GUG--CCACC | 2.6 |
|  31 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 48.8 |
|  31 |  31.1 | CCGCACACA | AGUGUG--CCACC | 17.8 |
|  31 |  38-6 | CCGCACAAA | AUUGUGCACCACC | 12.0 |
|  31 |  18.1 | CCGCACGAA | UUCGUG--CCACC | 4.8 |
|  31 |  31.2 | CCGCACGGA | ACCGUG--CCACC | 4.2 |
|  31 |  18.2 | CCGCACUAA | UUAGUG--CCACC | 3.6 |
|  31 |  31.3 | CCGCACGAC | GUCGUG--CCAGC | 2.7 |
|  31 |  31.4 | CCGCACGAA | ----------ACC | 1.4 |
|  31 |  18.2 | CCGCACUAA | UUAGUG--CCAAC | 1.2 |
|  31 |  31.5 | CCGCACGAA | ----UG--CCACC | 1.2 |
|  34 |  31.3 | CCGCACGAC | GUCGUG--CCAGC | 46.1 |
|  34 |  38-6 | CCGCACAAA | AUUGUGCACCACC | 44.7 |
|  34 |  31.2 | CCGCACGGA | ACCGUG--CCACC | 3.5 |
|  34 |  31.1 | CCGCACACA | AGUGUG--CCACC | 1.8 |
|  34 |  24-3 | CCGCACGAA | AUCGUG--CCACC | 1.6 |
|  36 |  31.3 | CCGCACGAC | GUCGUG--CCAGC | 53.1 |
|  36 |  38-6 | CCGCACAAA | AUUGUGCACCACC | 42.7 |
|  36 |  31.2 | CCGCACGGA | ACCGUG--CCACC | 1.7 |
|  38 |  38-6 | CCGCACAAA | AUUGUGCACCACC | 50.0 |
|  38 |  31.3 | CCGCACGAC | GUCGUG--CCAGC | 47.0 |
|  38 |  31.2 | CCGCACGGA | ACCGUG--CCACC | 1.3 |
|  43 |  38-6 | CCGCACAAA | AUUGUGCACCACC | 43.5 |
|  43 |  31.1 | CCGCACACA | AGUGUG--CCACC | 38.3 |
|  43 |  31.2 | CCGCACGGA | ACCGUG--CCACC | 9.4 |
|  43 |  31.3 | CCGCACGAC | GUCGUG--CCAGC | 3.2 |
|  46 |  38-6 | CCGCACAAA | AUUGUGCACCACC | 79.4 |
|  46 |  52-2 | CCGCACCAA | AUGGUGCACCACC | 7.4 |
|  46 |  31.1 | CCGCACACA | AGUGUG--CCACC | 3.5 |
|  46 |  46.1 | CCGCACUAA | AUAGUGCACCACC | 2.6 |
|  49 |  52-2 | CCGCACCAA | AUGGUGCACCACC | 75.6 |
|  49 |  " | CCGCACCAA | AUGGUGCACCUCC | 17.5 |
|  49 |  " | CCGCACCAA | AUGGUGCCCCACC | 3.7 |
|  49 |  " | CCGCACCAA | AUGGUGCUCCACC | 1.1 |
|  52 |  52-2 | CCGCACCAA | AUGGUGCACCACC | 80.8 |
|  52 |  " | CCGCACCAA | AUGGUGCACCUCC | 9.6 |
|  52 |  " | CCGCACCAA | AUGGUGCCCCACC | 3.6 |
|  52 |  " | CCGCACCAA | AUGGUGCUCCACC | 1.7 |

Clusters representing >1% of the population in a given round are shown. Clusters that differ by only a single nucleotide outside the P8 stem are given the same name. Clusters that include the wild type, 24-3, 38-6, or 52-2 polymerase are given the name of that polymerase.