J Mol Evol (2005) 61:192–206
DOI: 10.1007/s00239-004-0346-7

JOURNAL OF MOLECULAR EVOLUTION

Diverse Evolutionary Trajectories Characterize a Community of RNA-Cleaving Deoxyribozymes: A Case Study into the Population Dynamics of *In Vitro* Selection

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Received: 7 December 2004 / Accepted: 31 January 2005

Abstract. Two parallel *in vitro* selections (denoted Selection A and Selection B) were conducted under different selection-pressure regimes, yielding a diverse community of RNA-cleaving deoxyribozymes. In Selection A, the reaction time was reduced four times (from 5 h to 5 s) over the course of 24 generations, while in Selection B the reaction time was maintained at 5 h for 30 rounds of selective amplification. Sequence alignment was conducted on more than 800 clones assembled from 18 generations that span both selections. Many prominent catalytic sequence classes, including some that extend across both selections, were identified and used to construct fitness landscapes depicting their rise and fall over time. The landscapes from both selections exhibit similar global trends despite differences in population dynamics. Some deoxyribozymes were predominant in the early rounds of selection but gave way to other species that dominated in the middle rounds. Ultimately, these middle classes disappeared from the landscape in favor of new and presumably more fit deoxyribozyme sequence classes. The shape of these landscapes alludes to the presence of many latent deoxyribozymes in the initial library, which can only be accessed by changes in the selection pressure and/or by adaptive mutations. Basic computer simulations provide theoretical corroboration of the experimentally observed pattern of staggered sequence-class transitions across the fitness landscapes. These simulations model the influence of one or more contributing factors, including catalytic rate, folding efficiency, PCR amplification efficiency, and random mutagenesis. This is the first study which thoroughly documents the topography of a deoxyribozyme fitness landscape over many generations of *in vitro* selection.

Key words: Deoxyribozyme — Population dynamics — RNA cleavage — *In vitro* selection — Sequence diversity — Reaction time

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Introduction

In vitro selection is a combinatorial screening technique used to isolate functional nucleic acids (including aptamers, ribozymes, and deoxyribozymes) from synthetic libraries of random-sequence DNAs or RNAs (Breaker and Joyce 1994; Ellington and Szostak 1990; Robertson and Joyce 1990; Tuerk and Gold 1990). *In vitro* selection is characterized by iterative cycles of selective amplification, a process that cumulatively acts to enrich a DNA or RNA population for functionally active molecules, while simultaneously reducing the inactive fraction. Individual molecules are selected on the basis of fitness, which is a reflection of their differential ability to survive and reproduce under the imposed selection constraints. *In vitro* selection is, therefore, in many respects analogous to Darwinian evolution.

Unfortunately, the complexities of Darwinian evolution are not lost in the microenvironment of a test tube DNA population undergoing *in vitro* selec-

tion. Despite more than a decade of use, relatively little is known about the *in vitro* selection process and the factors that govern its outcome. Ultimately, this lack of knowledge may serve as a major obstacle to finding nucleic acid–based catalysts, with protein-like rate enhancements.

Our research is motivated by a desire to better our understanding of the *in vitro* selection process and thereby facilitate the search for functional nucleic acids. In the current study, we wanted to examine the population dynamics of a community of RNA-cleaving deoxyribozymes evolving under different levels of selection pressure. Understanding how the composition and complexity of a population changes over time, under different selection pressures, and in response to both inherent and environmental factors could potentially yield significant insight on how to implement the most effective screening measures for the isolation of nucleic acids with greater functional aptitude. Consider, for example, the original selection conducted by Santoro and Joyce that led to the isolation of two very useful RNA-cleaving deoxyribozymes referred to as 8–17 and 10–23 (Santoro and Joyce 1997). The 8–17 motif was part of a subpopulation that dominated in rounds 6–8, but the 10–23 motif was isolated from a different subpopulation that ascended to dominance in rounds 9–10, at the expense of the former. If the selection had continued beyond generation 10, would other more useful catalytic motifs have eventually ascended to dominance at the expense of 10–23? This is just one type of question that could be addressed more easily if we could identify any patterns of behavior that characterize populations undergoing *in vitro* selection.

The population dynamics of *in vitro* selection have not been studied in great detail, despite the significance of this subject. A few studies have used mathematical simulations to provide guiding principles for the optimization of *in vitro* selection, but the validity of these theoretical studies may suffer from simplifying assumptions and a lack of experimental corroboration (Irvine et al, 1991; Sun et al 1996; Vant-Hull et al. 1998). Unfortunately, empirical data are rather scarce. Typically, only the constituents in the terminal pool of an *in vitro* selection experiment are cloned and sequenced to reveal a static portrait of the population. This scenario essentially precludes analysis of population dynamics. Some studies have employed alternative techniques including the evaluation of restriction digest patterns (Bartel and Szostak 1993) and C_0t analysis (Charlton and Smith 1999) to track changes in pool complexity and composition over time. However, these methods cannot provide detailed information on population dynamics, nor was it the intended focus of either study. Studies of the *Tetrahymena* ribozyme have provided some insight into the population dynamics of a pool of partially randomized variants as they undergo in vitro evolution for altered function (Beaudry and Joyce 1992; Lehman et al. 2000; Lehman and Joyce 1993a, b). However, to date, no study has thoroughly documented the dynamics of a completely random nucleic acid population evolving over multiple generations of *in vitro* selection.

Previously, we conducted an *in vitro* selection experiment that yielded a diverse pool of RNA-cleaving deoxyribozymes (Schlosser and Li 2004). We reasoned that the large genetic variation within this pool might provide an interesting case study to examine the population dynamics of many deoxyribozymes competing through in vitro selection. Additional rounds were conducted along two parallel but distinct paths to determine how the composition of each population would change in response to different levels of selection pressure. Multiple generations were selected for cloning and sequence analysis, and comprehensive fitness landscapes were constructed to trace the rise and fall of individual sequence classes over time.

Material and Methods

Materials and Common Procedure

Standard oligonucleotides were prepared by automated DNA synthesis using cyanoethylphosphoramidite chemistry (Keck Biotechnology Resource Laboratory, Yale University; Central Facility, McMaster University). Random-sequence DNA libraries were synthesized using an equimolar mixture of the four standard phosphoramidites. DNA oligonucleotides were purified by 10% preparative denaturing (8 *M* urea) polyacrylamide gel electrophoresis (PAGE) and their concentrations were determined by spectroscopic methods. Nucleoside 5′-triphosphates, [γ-^{32} P]ATP, and [α-^{32} P]dGTP were purchased from Amersham Pharmacia. *Taq* DNA polymerase, T4 DNA ligase, and T4 polynucleotide kinase (PNK) were purchased from MBI Fermentas. All chemical reagents were purchased from Sigma. The 50-nucleotide (nt) RNA substrate (R1) was produced by RNA transcription using T7 RNA polymerase and a double-stranded DNA template as described previously (Schlosser and Li 2004).

In Vitro Selection Procedure

Sequences of relevant DNA and RNA molecules are shown in Fig. 1A. Each round of *in vitro* selection consists of steps I–VIII as illustrated in Fig. 1B.

Step I: The 104-nt library L1 was ligated to the 64-nt A1-R1 substrate to yield 168-nt A1-R1-L1 constructs. The reaction mixture, containing 250 pmol of A1-R1, 250 pmol of L1, and 300 pmol of template T2, was heated at 90°C for 30 s, and then cooled to room temperature. A volume of 12.5 μl ligase buffer (10× stock supplied by the manufacturer) and 25 μl of T4 DNA ligase (5 units/μl) were added to the mixture (250-μl final volume). The resultant reaction mixture was incubated for 4 h at room temperature. It is noteworthy that the ligase buffer was used at a final concentration of 0.5× to minimize the activation of DNA catalysts by Mg^{2+} present in the buffer, because we found that T4 DNA ligase was as effective at the reduced metal ion concentration.

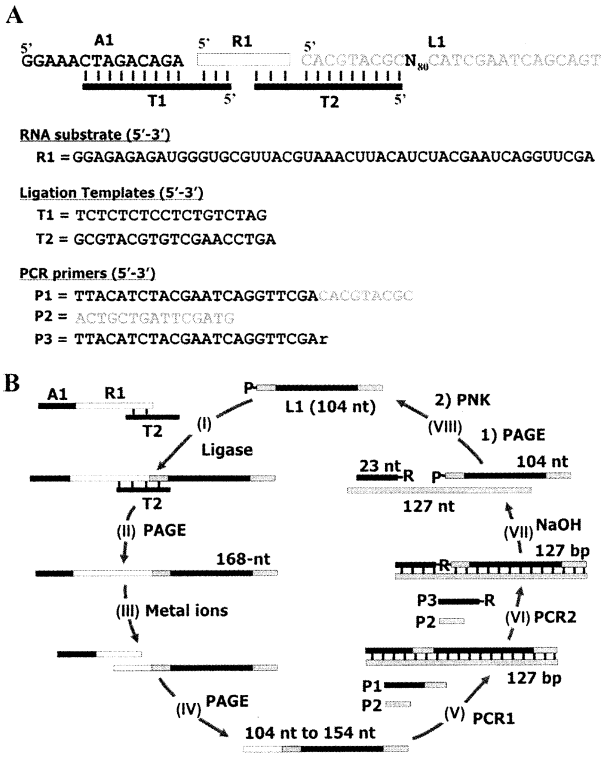

Fig. 1. Information on *in vitro* selection. **A** DNA sequences and their relationships. Each molecule in the library contains three key domains: a 14-nt DNA fragment (denoted A1) precedes a 50-nt RNA fragment (denoted R1), which in turn precedes another 104-nt DNA fragment (denoted L1). L1 contains 80 random-sequence nucleotides (N_{80}) that serve as the putative catalytic domain and provides initial sequence diversity. The N_{80} region of L1 is flanked by 9-nt and 15-nt fixed sequence domains at the 5′ end and 3′ end, respectively, which serve as primer-binding sites for PCR amplification. A1, R1, and L1 are ligated by T4 DNA ligase in the presence of templates T1 and T2. Sequences denoted by P1, P2, and P3 serve as primers during PCR (Ar, adenine ribonucleotide). **B** *In vitro* selection of RNA-cleaving deoxyribozymes. Each round of selection consists of steps I–VIII. In step I, the A1-R1-L1 chimeras are assembled by T4 DNA ligase involving the use of A1-R1, 5′-phosphorylated L1, and a synthetic DNA template T2. The resultant DNA–RNA–DNA molecules are purified by 10% denaturing PAGE (step II), followed by incubation with a selection buffer containing divalent metal ion cofactors (7.5 m*M* $MnCl_2$ and 7.5 m*M* $MgCl_2$) to promote catalytic activity (step III). The reaction is allowed to proceed for a designated amount of time before being stopped with the addition of the metal-chelating agent, EDTA. The resulting cleavage fragments are isolated by 10% denaturing PAGE (step IV). The isolated DNAs are amplified by two consecutive PCRs (steps V and VI). The first PCR used P1 and P2 as the primers. In addition to the 9-nt forward priming site, P1 contained 23 extra nucleotides at the 5′ end to introduce a new forward priming site for the second PCR, which used primers P2 and P3. Since P3 is a ribo-terminated primer, the DNA product from the second PCR can be digested under alkaline conditions to regenerate single-stranded deoxyribozyme sequences (step VII). The DNA mixture is subjected to 10% denaturing PAGE followed by DNA phosphorylation (step VIII), and the resulting phosphorylated 104-nt DNA is used to initiate the next round of selection.

Step II: A1-R1-L1 chimeras were recovered by ethanol precipitation and purified by 10% denaturing PAGE.

Step III: A 2× selection buffer was added to an equal volume of H_2O in which the DNA pellet from step II was dissolved. The resultant reaction mixture (with a DNA concentration of ~0.1 μ*M*) was allowed to stand at room temperature for the following designated times for Selection A: 5 h for G0–G7, 30 min for G8, 5 min for G9–G11, 30 s for G12–G14, and 5 s for G15–G24. For Selection B, the reaction time was maintained at 5 h. After the desired amount of time had elapsed, a 2× volume of 45 m*M* EDTA (pH 8.0) was added to the reaction mixture to stop the reaction. Selection buffer A (composed of 50 m*M* HEPES, pH 7.0, at 23°C, 400 m*M* NaCl, 100 m*M* KC1, 7.5 m*M* $MnCl_2$, 50 μ*M* $CuCl_2$, and 7.5 m*M* $MgCl_2$) was used from G0–G7, and selection buffer B (which was identical to selection buffer A with the exception that $CuCl_2$ was eliminated) was used for the remaining selection rounds.

Step IV: The above reaction mixture was subjected to 10% denaturing PAGE. The cleavage products of interest were excised from the gel and recovered by ethanol precipitation. All cleavage fragments of lengths between 104 and 154 nt were recovered during selection rounds G0–G5. Three dominant cleavage fragments, denoted DNA-I (112 nt), DNA-II (143 nt), and DNA-III (149 nt), were recovered separately in G6. The remaining selection rounds were conducted with only the DNA-II population, and the corresponding 143-nt cleavage product was recovered.

Steps V and VI: Two successive rounds of PCR were used to amplify the recovered cleavage fragments. P1 and P2 were used as the primer set for the first PCR, and P2 and P3 for the second PCR (Fig. 1). One percent of the double-stranded DNA product from the first PCR was used as the template in the second reaction. Both reactions were performed on a SmartCycler (Cepheid) and monitored in real-time using SYBR Green (Molecular Probes) as the reporter. The second PCR mixture contained 20 μCi [α-^{32} P]dGTP to introduce radiolabels into the amplified DNA products for visualization purposes. The second PCR also used a ribo-terminated primer (P3) so that the 104-nt putative catalytic DNA molecules could be regenerated by alkaline digestion.

In generation 8, a 15-nt extension was engineered onto the existing 3′ primer-binding site of the population in Selection A, and a new P2 primer (5′ CCA TCA GGA TCA GCT) employed accordingly during subsequent rounds of PCR. The 15-nt extension was created during PCR2 using P3 and an elongated 30-nt primer composed of the old and new P2 primer sequences (5′ CCA TCA GGA TCA GCT ACT GCT GAT TCG ATG). The same procedure was also used for the population in Selection B using a different P2 primer (5′ TCA TCA GCT CCA GGT) for subsequent rounds of PCR and a different 30-nt primer for PCR2 (5′ TCA TCA GCT CCA GGT ACT GCT GAT TCG ATG).

Step VII: The amplified DNA from the second PCR above was recovered by ethanol precipitation, 90 μl of 0.25 *M* NaOH was added to the DNA pellet, and the resultant solution was heated at 90°C for 10 min, followed by the addition of 10 μl of 3 *M* NaOAc (pH 5.2 at 23°C). This alkaline treatment serves to cleave the embedded RNA linkage.

Step VIII: The 104-nt cleavage fragments were purified by 10% denaturing PAGE. The recovered DNA molecules were incubated with 10 units of polynucleotide kinase (PNK) at 37°C for 1 h for DNA phosphorylation in a 100-μl reaction mixture containing 50 m*M* Tris–HCl (pH 7.8 at 23°C), 40 m*M* NaCl, 10 m*M* $MgCl_2$, 1 mg/ml BSA, and 0.5 m*M* ATP. The 5′-phosphorylated DNA (denoted G1) was used for the second round of selection. Steps I–VIII were repeated 24 times for Selection A and 30 times for Selection B, using the same procedure described for the first round of selection except that the ligation reaction scale in step I was reduced 10-fold (i.e., 25 μl final volume; however, all reaction components were maintained at the same concentrations as in round 1).

Cloning and Sequencing of Selected DNA Populations

DNA sequences from a relevant selection round were amplified by PCR and cloned into a vector by the TA cloning method. Plasmids containing individual catalysts were prepared using the Qiagen

Mini-Prep Kit. DNA sequencing was performed on a CEQ 2000XL capillary DNA sequencer (Beckman-Coulter) following the manufacturer's recommended procedures.

Quantification of Observed Sequence Identity

Sequences were aligned based on the location of their fixed primer-binding sites with the aid of the Bioedit Sequence Alignment Editor computer program, which is available free of charge over the internet at www.mbio.ncsu.edu/BioEdit/bioedit.html

Once aligned, individual sequences were grouped into common sequence classes by visual inspection, under the minimum requirement of approximately 90% sequence identity within the same generation and approximately 85% sequence identity across generations and across two selections. After the initial bulk sorting of individual sequences into common classes, the alignment was run through the ClustalW multiple alignment algorithm (with default parameters) provided in Bioedit to help identify previously undetected sequence matches due to misalignment from deletions or insertions. A sequence identity matrix was generated for sequences in each generation, using Bioedit. The sequence identity matrix is simply an $N \times N$ matrix (where N = number of sequences in a given class) that shows the sequence identity (expressed as a number between 1 and 0, where 1 represents identical sequences and 0 represents no identical bases in their current alignment) for each pairwise permutation of all sequences being considered (in this case for all sequences within a class). This identity matrix was used to determine the average sequence identity within classes by considering all constituents of the class, as well as the maximum and minimum sequence identity observed between any two sequences within the class. Likewise, the matrix was used to determine the average, maximum, and minimum sequence identity between classes for each generation. To calculate the sequence identity statistics between the 215 classes across generations and across both selections, the sequence of a single clone from each class was used to construct the identity matrix. This simplifying strategy was applied with three different data sets (using different randomly chosen sequences from each class) and yielded very similar results in every case.

Kinetic Analyses

A typical reaction involved the following steps: (1) heat denaturation of the A1-R1-DNA pool construct in water for 30 s at 90°C, (2) incubation for RNA cleavage at room temperature in selection buffer B for a designated time, (3) addition of EDTA to 30 mM to stop the reaction, (4) separation of cleavage products by denaturing 10% PAGE, and (5) quantitation using a PhosphorImager and ImageQuant software. For deriving the catalytic rate constants, aliquots of an RNA cleavage reaction solution were collected at different reaction time points that were under ~30% completion and the rate constant for the reaction was determined by plotting the natural logarithm of the fraction of DNA that remained unreacted vs. the reaction time. The negative slope of the line produced by a least-squares fit to the data was taken as the rate constant.

Simulations

Definitions and Equations

$X_{C,N}$: Number of copies of a given deoxyribozyme sequence class (or the noncatalytic class) in a given generation *before* the selection step. Note: Subscript C = class number; subscript N = generation or selection round.

$Y_{C,N}$: Number of copies of a given deoxyribozyme sequence class (or the noncatalytic class) in a given generation *after* the selection step.

$$X_{C,N} = Y_{C,N-1} \times AF_{C,N} \quad (1)$$

$AF_{C,N}$: Amplification factor (the fold amplification of each sequence class during PCR).

$$AF_{C,N} = Z \div \Sigma(Y_{C,N-1}) \quad (2)$$

Z: Total number of molecules (catalytic and noncatalytic) in the population in a given generation after the PCR step.

$\sum(Y_{C,N})$: Total number of molecules (catalytic and noncatalytic) in the population in a given generation after the selection step.

$$Y_{C,N} = X_{C,N} \times SR_{C,N} \quad (3)$$

$SR_{C,N}$: Surviving ratio (the fraction of a given sequence class that survives the selection step, $0 \leq SR_{C,N} \leq 1$).

$FR_{C,N}$: Fraction of the population composed of a given deoxyribozyme sequence class (or noncatalytic class) in a given generation.

$$FR_{C,N} = Y_{C,N}/\Sigma(Y_{C,N}) \quad (4)$$

$SR_{C,N}$ is determined by one or more contributing factors. When multiple factors are considered, the overall $SR_{C,N}$ can be taken as the product of each individual factor. For example, if three factors collectively influence the surviving ability of a given deoxyribozyme class, $SR_{C,N}$ can be computed by Eq. (5):

$$SR_{C,N} = (SR_{C,N})_1 \times (SR_{C,N})_2 \times (SR_{C,N})_3 \quad (5)$$

For simulation 1 (Fig. 7), $SR_{C,N} = (SR_{C,N})_{Rate} = k_C/k_t$, where k_C = catalytic rate of a given sequence class (min^{-1}), $k_t = 1/t$ = minimum threshold rate imposed by the reaction time (t; minutes).

For simulation 2 (Fig. 8), $SR_{C,N} = (SR_{C,N})_{Rate} \times (SR_{C,N})_{Folding}$, where $(SR_{C,N})_{Folding}$ is the "folding factor" or the fraction of a given deoxyribozyme sequence class that folds into a catalytically active conformation ($0 \leq (SR_{C,N})_{Folding} \leq 1$).

For simulation 3 (Fig. 9), $SR_{C,N} = (SR_{C,N})_{PCR} \times (SR_{C,N})_{Folding,\ where\ (SRC,N)PCR}$ is the "PCR efficiency" or the fraction of a given deoxyribozyme sequence class that is amplified during PCR ($0 \leq (SR_{C,N})_{PCR} \leq 1$).

Simplifying Assumptions and Conditions.

1. The initial random DNA library contains 10^{14} different molecules.
2. Each catalytic sequence class survives the initial round of selection despite having only single-copy representation in the initial library.
3. The gel-based selection method permits 0.8% of noncatalytic DNA molecules to survive each round (independent of the reaction time), and all these molecules are treated as a single class (NC).
4. A total of 10^{13} molecules are generated after each PCR ($Z = 10^{13}$).
5. Some form of mutational event(s) leads to a change in the overall surviving ratio of a given deoxyribozyme sequence class ($SR_{C,N}$).
6. The phenotypic properties (catalytic rate, folding factor, PCR efficiency) of specific deoxyribozyme sequence classes were chosen arbitrarily but within reasonable limits for deoxyribozyme standards.

With the preceding simplifying assumptions and conditions taken into consideration, the computer program Microsoft Excel was used to generate a spreadsheet of $FR_{C,N}$ values for all deoxyribozyme sequence classes versus each generation.

We will use simulation 1 (Fig. 7) as an example to illustrate the method by which the fraction of population ($FR_{C,N}$) was calculated for each sequence class in our computer simulations.

For G0: The initial library contains 10^{14} different molecules, and therefore each of the seven deoxyribozyme sequence classes is represented by only a single molecule. Thus, $X_{C,0}$ is equal to 1 molecule. Each deoxyribozyme must pass the first round of selection, so the product pool will also contain one copy of each deoxyribozyme. Therefore, $Y_{C,0}$ is also equal to 1 molecule. Noncatalytic DNA molecules are represented by a single class (class NC) with a surviving ratio (SR_{NC}) of 0.008. Therefore, the number of molecules of the noncatalytic class carried into the product pool will be: $Y_{NC,0} = 10^{14} \times 0.008 = 8 \times 10^{11}$ molecules. The total number of molecules in the product pool of G0 will be $\sum(Y_{C,0}) = 1 + 1 + 1 + 1 + 1 + 1 + 1 + 8 \times 10^{11} \approx 8 \times 10^{11}$. The $FR_{C,N}$ value for each deoxyribozyme class will be $FR_{1-7,0} = Y_{C,0} / \sum(Y_{C,0}) = 1 / (8 \times 10^{11}) \approx 1.25 \times 10^{-12}$. The $FR_{NC,0}$ of class NC is equal to 1.

For G1: The amplification step will generate 10^{13} molecules from 8×10^{11} input molecules, therefore $AF_{1-7,1} = 10^{13} \div \sum(Y_{C,0}) = 10^{13} / (8 \times 10^{11}) = 12.5$. For simulation 1 (Fig. 7) we assumed that every sequence class has the same PCR efficiency, and therefore $X_{C,1}$ (for each of the seven deoxyribozyme classes, C = 1–7) $= 1 \times 12.5 = 12.5$, and $X_{NC,1} = 8 \times 10^{11} \times 12.5 = 1 \times 10^{13}$. The k_C values for all seven deoxyribozyme classes (0.004, 0.01, 0.045, 0.1, 0.25, 0.6, and 2 min^{-1} for classes 1–7, respectively) are larger than the minimum threshold rate constant in G1 ($k_{5h} = 1/300\ min^{-1} = 0.0033\ min^{-1}$), therefore $SR_{1-7,1} = 1$. After the selection step, $Y_{1-7,1} = X_{1-7,1} \times SR_{1-7,1} = 12.5 \times 1 = 12.5$ copies and $Y_{NC,1} = 10^{13} \times 0.008 = 8 \times 10^{10}$ molecules. The total number of molecules in the product pool of G1 is $\Sigma(Y_{C,1}) = 12.5 + 12.5 + 12.5 + 12.5 + 12.5 + 12.5 + 8 \times 10^{10} \approx 8 \times 10^{10}$. The fraction of the population represented by each deoxyribozyme class in G1 is $FR_{C,1} = Y_{C,1} / \Sigma(Y_{C,1}) = 12.5 \div 8 \times 10^{10} \approx 1.56 \times 10^{-10}$. The $FR_{NC,1}$ of the noncatalytic group is equal to 1.

For the next generation ($N+1$), first calculate $AF_{C,N+1} = 10^{13} \div \Sigma(Y_{C,N})$, then compute $X_{C,N+1} = Y_{C,N} \times AF_{C,N+1}$; then determine $SR_{C,N+1} = k_C/k_t$ (if $k_C/k_t > 1$, $SR_{C,N+1}$ is taken as 1). After obtaining $Y_{C,N+1}$ for each sequence class by $Y_{C,N+1} = X_{C,N+1} \times SR_{C,N+1}$ and $Y_{NC,N+1} = X_{NC,N+1} \times 0.008$, the total number of molecules in the product pool of $G(N+1)$ is $\Sigma(Y_{C,N+1})$. The fraction of the population represented by each deoxyribozyme class in generation ($N+1$) is $FR_{C,N+1} = Y_{C,N+1} / \Sigma(Y_{C,N+1})$.

Results and Discussion

Continuation of Two Parallel Selections Initiated in a Prior Study

Our laboratory has recently initiated a research program to systematically investigate the in vitro selection methodology, which has gained considerable recognition over the last decade for its ability to isolate deoxyribozymes and other functional nucleic acids from synthetic DNA and RNA libraries. Previously, we conducted a study to examine the relationship between catalytic sequence diversity and the length of the reaction time imposed during *in vitro* selection (Schlosser and Li 2004). We devised a selection strategy to isolate RNA-cleaving deoxyribozymes from a library of single-stranded DNA molecules coupled to a long RNA substrate and performed two parallel experiments using different selection pressure. In the current study, we sought to characterize the population dynamics of this community of RNA-cleaving deoxyribozymes. A brief recap of the relevant experimental details from the previous study will first be addressed. Approximately 10^{14} different DNA sequences were used in the starting library (generation 0 or G0), which is illustrated along with the *in vitro* selection scheme in Fig. 1. A single selection was initially carried out from G0 to G7. There was no detectable cleavage product(s) in G0–G4. However, three different cleavage bands were seen in G5, each corresponding to a unique cleavage site along the 50-nt RNA substrate. In G6, each DNA band was carefully excised, and the eluted DNA was amplified separately. One of these three DNA bands in G7, named DNA-II, was used as the common starting pool for two subsequent parallel selections. In Selection A, the reaction time was progressively decreased from 5 h (G7), to 30 min (G8), to 5 min (G9–G11), to 30 s (G12–G14), and, finally, to 5 s (G15). In Selection B, a constant reaction time of 5 h was used for each round of selection from G7 to G15. It is noteworthy to mention that the risk of cross-contamination between these two parallel selections was minimized by a design strategy, which introduced different primer-binding sites onto the existing common 3′ end of each DNA population in G8. Approximately 50 clones from G7, G8, G10, G13, and G15 of each selection were sequenced, and the change in sequence diversity was reported for both selections.

In order to create a more meaningful characterization of the potential evolutionary scenarios occurring during *in vitro* selection, we decided to conduct 9 more rounds of Selection A and 15 more of Selection B. These additional rounds of selection would broaden the evolutionary timescale and increase the sensitivity of our system for detecting slow or latent evolutionary trajectories. As an experimentally imposed selection pressure, the reaction time was set at 5 s for the remainder of Selection A and 5 h for the remainder of Selection B. Once again, approximately 50 clones were sequenced from G18, G21, G24 (for both Selection A and Selection B), G27, and G30 (for Selection B).

Sequence Classification Statistics for Selections A and B

The sequences of all clones were analyzed and grouped into classes, and the data are presented in Table 1 (for Selection A) and Table 2 (for Selection B). In Selection A, a total of 393 clones were sequenced and 113 unique classes were revealed. The diversity ratio is a measure of the sequence diversity within each population and is defined as the ratio of unique sequence classes over the total number of sequenced clones. The observed maximum, minimum, and average sequence identity between individual clones *within* classes, as well as the observed maxi-

Table 1. Summary statistics for Selection A

	Generation							
	G7	G8	G10	G13	G15	G18	G21	G24
Time (min)	300	30	5	0.5	0.083	0.083	0.083	0.083
Total sequences	48	49	49	50	49	49	48	51
Unique sequences	43	35	28	23	8	12	4	9
Diversity ratio	0.90	0.71	0.57	0.46	0.16	0.24	0.08	0.18
Sequence distribution & frequency	39 × 1	26 × 1	20 × 1	13 × 1	3 × 1	6 × 1	1 × 1	5 × 1
	3 × 2	7 × 2	5 × 2	5 × 2	1 × 4	1 × 2	1 × 3	1 × 3
	1 × 3	1 × 3	1 × 3	2 × 3	1 × 5	2 × 3	1 × 9	1 × 6
		1 × 6	2 × 8	1 × 5	1 × 8	2 × 7	1 × 35	1 × 9
				1 × 7	1 × 14	1 × 21		1 × 28
				1 × 9	1 × 15			

Note. Summary statistics for Selection A. A total of 393 clones were taken from multiple generations and sequenced. The sequence diversity ratio is a measure of the sequence diversity within each population and is defined as the ratio of unique sequence classes over the total number of sequenced clones. The sequence distribution and frequency for each generation are indicated as (number of different sequence classes) × (number of sequenced clones in each class).

Table 2. Summary statistics for Selection B

Generation	G7	G8	G10	G13	G15	G18	G21	G24	G27	G30
Time (min)	300	300	300	300	300	300	300	300	300	300
Total sequences	48	47	47	48	49	55	50	55	52	61
Unique sequences	43	41	39	35	32	29	23	24	15	16
Diversity ratio	0.90	0.87	0.83	0.73	0.65	0.53	0.46	0.44	0.29	0.26
Sequence distribution & frequency	39 × 1	36 × 1	33 × 1	26 × 1	21 × 1	17 × 1	14 × 1	9 × 1	5 × 1	4 × 1
	3 × 2	4 × 2	4 × 2	6 × 2	7 × 2	4 × 2	3 × 2	7 × 2	5 × 2	2 × 2
	1 × 3	1 × 3	2 × 3	2 × 3	2 × 3	4 × 3	2 × 3	5 × 3	1 × 4	3 × 3
				1 × 4	2 × 4	3 × 4	1 × 4	2 × 4	2 × 6	1 × 4
						1 × 6	1 × 5	1 × 9	1 × 8	2 × 5
							1 × 6		1 × 13	1 × 6
							1 × 9			1 × 7
										1 × 8
										1 × 9

Note: Summary statistics for Selection B. A total of 512 clones were taken from multiple generations and sequenced. The sequence distribution and frequency for each generation are indicated as (number of different sequence classes) × (number of sequenced clones in each class).

mum, minimum, and average sequence identity *between* classes is tabulated for each generation and presented in Supplementary Table 1. These sequence classification statistics clearly indicate that individual clones fall into very distinct sequence classes. On average, clones within a given sequence class are more than 90% identical, while the maximum identity observed between any two classes does not exceed 60%.

Table 2 summarizes the sequencing results of Selection B. In total, 512 clones were sequenced (including the 48 common G7 clones) and 172 unique classes were revealed. Once again, clones within a given sequence class are more than 90% identical on average, while the maximum identity observed between any two classes does not exceed 60%. Across Selections A and B, 215 sequence classes were identified. The average sequence identity observed *within* the 215 classes is also more than 90%, while the maximum identity observed *between* the 215 classes (based on a single representative clone from each class) does not exceed 60%.

The fraction of the population that belongs to single-clone sequence classes and to various multiple-clone classes are illustrated in Fig. 2. Comparison of Selection A with Selection B reveals some interesting trends. In both cases the fraction of the population made up of single-clone sequence classes declines with increasing rounds of selection. However, the rate of decline in Selection A is greater than in Selection B, which is understandable given the additional selection pressure (i.e., reduced reaction time) imposed in Selection A. An opposite trend is observed in the fraction of the population composed of sequence classes containing three or more clones, which appears to increase with increasing rounds of selection. Again, the rate of increase in Selection A is greater than in Selection B. Dominant sequence classes (i.e.,

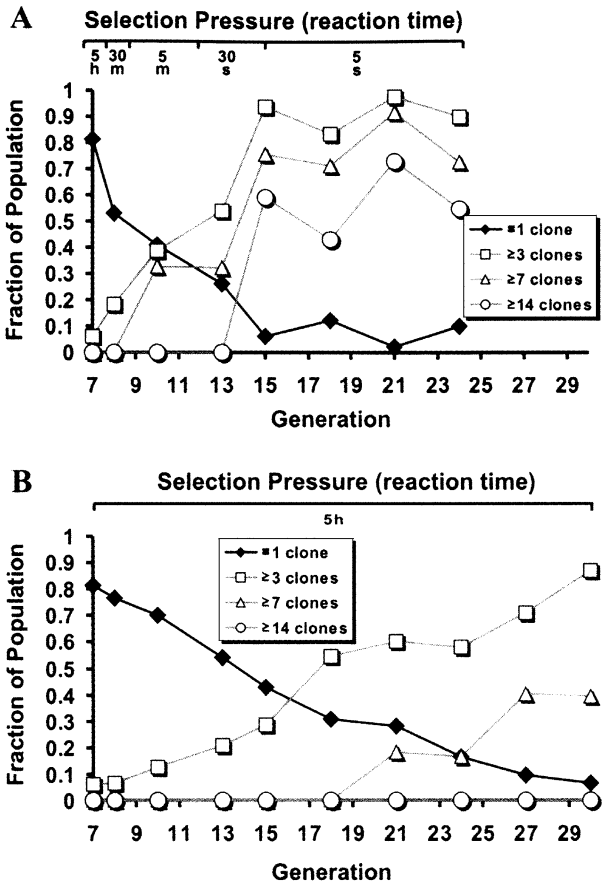

Fig. 2. General trends in population distribution over selection rounds. Changes in the fraction of the population composed of single-clone and various multiple-clone sequence classes are illustrated as a function of the generation. **A** Selection A. Increasing selection pressure was imposed on the population by incrementally decreasing the reaction time over the course of the experiment as shown above the graph. G0–G7, 5 h; G8, 30 min; G9–G11, 5 min; G12–G14, 30 s; G15–G24, 5 s. **B** Selection B. The reaction time was maintained at 5 h for every generation.

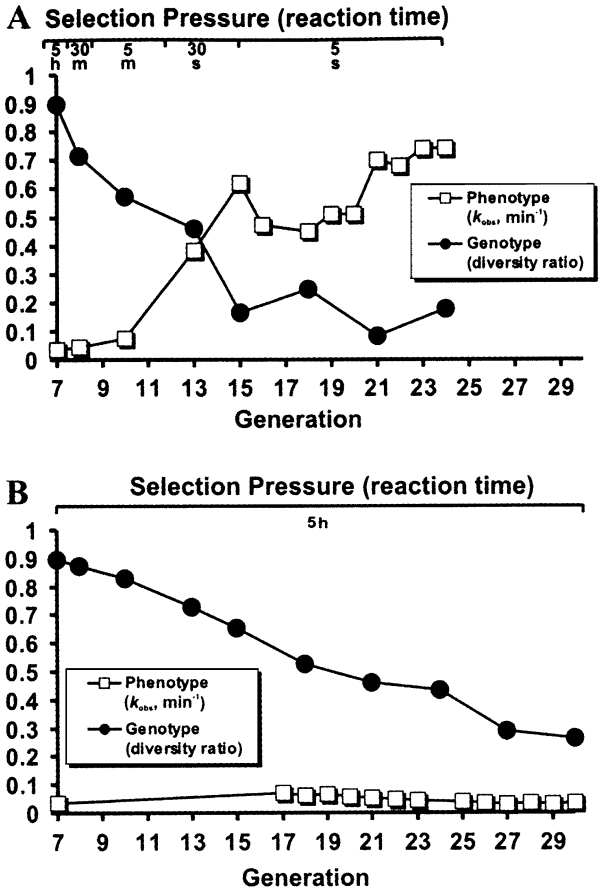

Fig. 3. Phenotypic and genotypic progression of the composite populations. The catalytic rate, k_{obs}, is used as one measure to describe the phenotypic character of the population, while the sequence diversity ratio is used to describe the genotypic character of the population. The diversity ratio is a measure of the sequence diversity within the population and is defined as the number of unique sequence classes divided by the number of sequenced clones. **A** Selection A. Increasing selection pressure was imposed on the population by incrementally decreasing the reaction time over the course of the experiment as shown above the graph. G0–G7, 5 h; G8, 30 min; G9–G11, 5 min; G12–G14, 30 s; G15–G24, 5 s. **B** Selection B. The reaction time was maintained at 5 h for every generation.

containing seven or more clones) begin to emerge by G10 in Selection A but do not emerge until around G21 in Selection B. The pool complexity in Selection A continues to diminish in favor of a few dominant classes, with nearly 60% of the population represented by classes with 14 or more clones. In contrast, the population in Selection B maintains a larger fraction of moderately dominant classes, with no representation by classes containing 14 or more clones. The fluctuations observed in G18 and G24 of Selection A, as well as G24 of Selection B, may be due to random genetic drift or sampling error.

Changes in the Phenotypic and Genotypic Character of Two Evolving Populations

Figure 3 traces the change in the phenotypic (catalytic rate, k_{obs}) and genotypic (diversity ratio) character of the composite population over the course of *in vitro* selection. In Selection A, the reduction in reaction time is paralleled by a rapid decrease in the diversity ratio and a dramatic increase in the catalytic rate. By G15, the population as a whole exhibits a catalytic rate of 0.62 min^{-1}, which represents an approximate 17-fold increase over the 0.036 min^{-1} catalytic rate observed in G7. Interestingly, the diversity ratio appears to plateau (with some fluctuations) after G15 when the reaction time was held constant for the remainder of the study. This observation suggests that selection is no longer acting on the remaining members of the population because they are phenotypically equivalent (or nearly equivalent) under the imposed selection pressure. A further reduction in the reaction time, however, may lead to a further reduction in the diversity ratio. The rate of increase in the catalytic rate also appears to roughly

level off after G15, which is consistent with the preceding analysis.

An entirely different scenario is observed in Selection B, where the reaction time was maintained at 5 h for every round of selection. Interestingly, the catalytic rate does not appear to increase between G7 and G30. Nevertheless, there is a steady decrease in the diversity ratio, which suggests that selection is still acting to reduce the variability in some secondary phenotypic trait(s). Alternatively, the observed decrease in the diversity ratio may be a general artifact of the *in vitro* selection method, which typically involves some degree of subsampling of the evolving population during every round. For instance, only a fraction of the total product from PCR1 is used to seed PCR2, and only a fraction of the DNA pool is recovered after each PAGE purification step. The subsampling that occurs with each of these laboratory manipulations decreases the effective population size, which in turn may lead to a decrease in genetic diversity. This bottleneck effect may be prominent during the initial rounds of selection when there are very few copies of each sequence variant. However, by G7 there should be numerous copies of each sequence variant that should act as a buffer against random changes in the overall genetic diversity. Therefore, the steady decrease in the diversity ratio observed in Fig. 3B is not likely to be explicitly caused by sampling bottlenecks, although this effect may facilitate the process by hastening the extinction of classes that have already dwindled in copy number due to less competitive secondary phenotypic characteristics.

Fitness Landscapes of Selection A

Fitness is a measure of an individual's ability to survive and reproduce in a given environment. In 1932, Sewell Wright (1932) first introduced the idea of visualizing the distribution of fitness values within a population as a kind of landscape in order to study evolution. To examine the population dynamics of our model system, we have correlated the fitness of a particular sequence class to the number of clones observed in that class and constructed several fitness landscapes to trace changes in population composition and complexity over the course of *in vitro* selection. These fitness landscapes are not intended to convey any specific phenotypic information. The landscapes were constructed by grouping individual clones into common sequence classes as previously described and then normalizing the absolute number of clones in a given class by the total number of clones sequenced in that particular generation. This normalized number represents the fraction of the population (by generation) composed of a particular sequence class. In an effort to emphasize the pattern

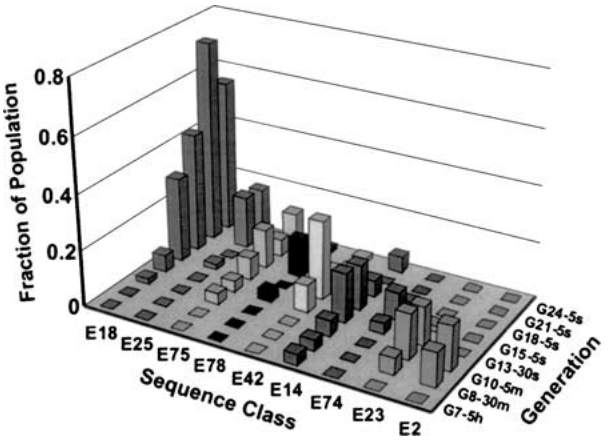

Fig. 4. Deoxyribozyme fitness landscape for Selection A. Changes in the composition and distribution of dominant sequence classes are illustrated. The fraction of population values is calculated by dividing the number of observed clones in a given class by the total number of clones sequenced in that generation. Sequence classes were arbitrarily arranged to illustrate the evolutionary succession of competing classes, and the order does not reflect any homology between classes, except by chance. The color scheme (gray scale) is arbitrary and intended only to facilitate viewing.

of dominant sequence classes and minimize the clutter created by transient classes with few clones, we imposed an arbitrary cumulative threshold value of 0.1 for inclusion into the landscape. In other words, if the sum of the fraction-of-population values across all generations is greater than or equal to 0.1, the sequence class was included in the fitness landscape. This requirement was imposed after the fraction-of-population values were calculated for all sequence classes. It should be noted that the sequence classes were arranged in such a manner as to illustrate a general progression in the level of fitness, and does not reflect any homology between the sequence classes (except by chance).

Figure 4 shows a fitness landscape composed of nine dominant sequence classes from Selection A. The landscape is characterized by a transition among three general species: those that dominate near the beginning of the selection, those that dominate during the middle of the selection, and those that dominate at the end of the selection. In addition to their absolute location on the landscape, these species also differ in distribution (i.e., broad vs. narrow peaks) and in their maximum amplitudes. Only one sequence class, E18, appears to rise steadily and predictably to dominance. The E18 sequence class is first observed in G10 and then quickly propagates to as much as 70% of the population by G21, before declining slightly to ~55% in G24. This decline may be an artifact of the relatively small sample set of clones that were sequenced in each selection round or it may simply reflect stochastic fluctuations in the composite population. Another noteworthy feature of this landscape is the staggered appearance of the sequence

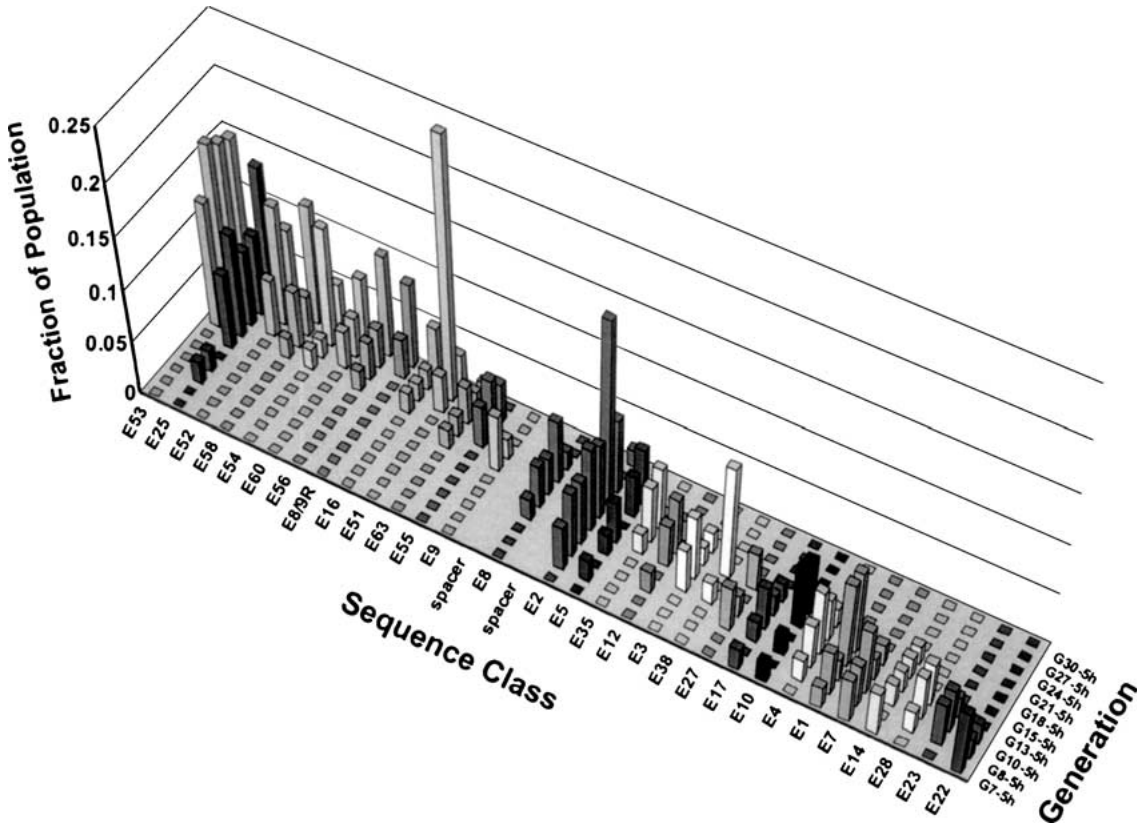

Fig. 5. Deoxyribozyme fitness landscape for Selection B. Changes in the composition and distribution of dominant sequence classes are illustrated. The fraction of population values is calculated by dividing the number of observed clones in a given class by the total number of clones sequenced in that generation. Sequence classes were arbitrarily arranged to illustrate the evolutionary succession of competing classes, and the order does not reflect any homology between classes, except by chance. ''Spacer'' intervals were inserted into the chart to separate certain classes for more convenient viewing as well. The color scheme (gray scale) is arbitrary and intended only to facilitate viewing.

classes across generational time. One possible explanation for this observation is the contribution of a secondary factor such as differential folding efficiency between classes. This issue will be addressed further in a subsequent section using computer simulations.

Fitness Landscapes of Selection B

The fitness landscape corresponding to 29 prominent sequence classes from Selection B is shown in Fig. 5. Interestingly, the pattern of staggered starting positions for the sequence classes observed in Fig. 4 is also preserved in this landscape, even though the reaction time was never reduced during the entire course of *in vitro* selection. In this situation, the catalytic rate of individual clones becomes largely irrelevant assuming that all clones in question possess activity above the minimum threshold value of 0.0033 min^{-1} (100% cleavage in 300 min or 1/300). Other factors, such as differential folding ability, differential PCR efficiency, and spontaneous mutagenesis during PCR, are likely to be the major forces dictating the survival and propagation of specific deoxyribozyme sequence classes. The influence of these factors on the shape of the fitness landscape can be modeled through simple computer simulations and will be addressed in a subsequent section.

It is interesting to note that a particular sequence class, named E8/9R, is likely the product of a recombination event between members of the E8 and the E9 sequence classes. E8/9R is an unusual class because it exhibits extensive sequence homology to both E8 and E9, which is contrary to the general trend observed in our sequence classification statistics. On average, the sequence identity between all other classes is ~32% with a maximum observed value of ~56%. In contrast, the average sequence identity between E8 and E8/9R is 62%, and that between E9 and E8/9R is 81%. The ''parent'' E8 and E9 classes are on average only ~48% identical. A sequence alignment reveals that the 3′ segment of E8/9R (Supplementary Fig. 1) is very similar to the 3′ end of E9, while the 5′ end of E8/9R closely resembles the 5′ end of E8. Even more suggestive is the middle G-rich motif of the E8/9R class, which shows a very high degree of sequence homology to *both* E8 and E9. Based on these observations, we suspect that E8/9R could very well have arisen from E8 and E9 as a result of recombination during PCR. Recombination can occur as a result of template switching by the poly-

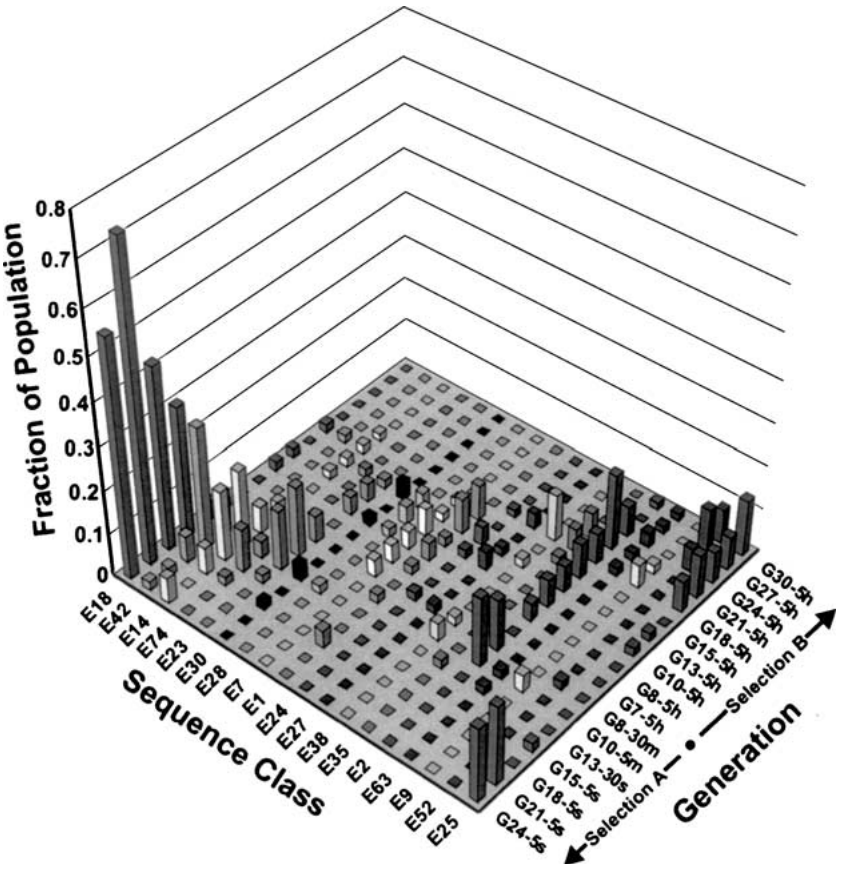

Fig. 6. Deoxyribozyme fitness landscape across both Selection A and Selection B. Changes in the composition and distribution of dominant sequence classes observed in both selections are illustrated. The fraction of population values was calculated by dividing the number of observed clones in a given class by the total number of clones sequenced in that generation. Sequence classes were arbitrarily arranged to illustrate the evolutionary succession of competing classes, and the order does not reflect any homology between classes, except by chance. The color scheme (gray scale) is arbitrary and intended only to facilitate viewing.

merase in the extension phase, or alternatively, prematurely terminated products can anneal to nonidentical but similar templates and be extended to completion in the next cycle. Such mechanisms of PCR-induced recombination have been described elsewhere (Meyerhans et al. 1990; Odelberg et al. 1995). The recombination event may have occurred between G18 and G21 when E9 and E8 represented a significant proportion of the population. Interestingly, both parent classes appear to die out at about the same time as the manifestation of E8/9R in G27, which suggests that the recombination event served to increase the fitness of E8/9R over either parent species. This observation alludes to the possibility for the extreme antiquity of recombination in an RNA world scenario as described by Lehman (2003).

Deoxyribozyme Fitness Landscapes Across Selection A and Selection B

Figure 6 shows the fitness landscape corresponding to 16 prominent sequence classes identified in both Selections A and B. This landscape is also characterized by three general categories of species: those that dominate in one selection but are only observed transiently in the other; those that appear transiently in both selections; and those that show signs of dominance at both ends of selection. The majority of sequence classes falls into the first two categories. The general lack of recurrence observed between the two selections is consistent with theoretical expectations (Lehman 2004) and is largely predicted to be due to the disparity in selection pressure. However, these results may be confounded by the presence of different 15-nt 3′ primer binding sites on either population.

Interestingly, the E18 class that clearly dominates Selection A is observed only transiently in generations 8, 10, and 15 of Selection B. This suggests that sequences are not being selected on the basis of catalytic rate in Selection B, which is consistent with the rate data observed in Fig. 3B. E25 is another interesting sequence class, which appears to dominate toward the end of both selections. Based on the observation that the phenotypic character of the terminal population in Selections A and B differed substantially (as measured by the catalytic rate; large k_{obs} in Selection A vs. small k_{obs} in Selection B), we suspected that variations in the genotypic character (in the form of base mutations) had evolved under the different selection regimes. A sequence alignment of all E25 sequence variants (Supplementary Fig. 2) indeed indicates that different base mutations in the 5′ half of sequences have been selected along each selection pathway. It is worthwhile to comment that the appearance of many AT-to-GC mutations along

the Selection B pathway may indicate that Selection B favors the evolution of deoxyribozymes that exhibit stable folding as a key phenotypic trait.

Theoretical Fitness Landscapes

Computer simulations were conducted to provide some theoretical justification for the population dynamics observed in the experimentally derived fitness landscapes of Selections A and B. These simulations model the shape of the fitness landscape when selection acts against one or more phenotypic characteristics.

Selection A Simulations

In order to survive the selection step, each deoxyribozyme molecule (*cis*-acting and only capable of single-turnover) has to cleave itself within the allotted reaction time (t, in minutes) imposed during each selection round. In Selection A, five different reaction times were imposed, each with an associated minimum threshold rate, k_t, that is equal to $1/t$. The five k_t's (min^{-1}) are 0.0033 ($t = 5$ h), 0.033 ($t = 30$ min), 0.20 ($t = 5$ min), 2.0 ($t = 30$ s), and 12 ($t = 5$ s).

In simulation 1 (Fig. 7), we assumed that the ability to cleave above the minimum threshold rate is the only factor that determines the fate of DNA molecules during *in vitro* selection. The fraction of the population that survives the selection criterion is denoted by the "surviving ratio," $SR_{C,N}$, which is based on the following equation:

$$SR_{C,N} = (SR_{C,N})_{Rate} = k_C/k_t$$
$$\text{where } 0 \leq SR_{C,N} \leq 1$$

For simplicity, we decided to trace the progress of just seven different deoxyribozyme sequence classes having catalytic rate constants (k_C) ranging between 0.004 and 2 min^{-1}. A "noncatalytic" class (NC) was also included to represent all inactive sequences. During the first seven rounds of selection, all seven deoxyribozyme sequence classes have an $SR_{C,N}$ of 1 (because they all possess a rate that exceeds the minimum threshold rate), while the noncatalytic class is assumed to have a constant $SR_{C,N}$ value of 0.008 (as an artifact of the gel-based selection strategy). Therefore, the only competition during these initial rounds exists between the catalytic and the noncatalytic classes. By G7, the noncatalytic class is largely eliminated.

From G8 onward, the seven deoxyribozyme sequence classes begin to exhibit differential levels of surviving ability. When the selection pressure increases in G8 (i.e., the reaction time is reduced from 5 h to 30 min), only classes 3–7 will stay highly competitive because they have a catalytic rate that exceeds the minimum threshold rate of 1/30 min^{-1}. In contrast, the first two classes have rates that fall below this minimum threshold and will, therefore, rapidly approach extinction as their copy numbers decrease with every successive generation. When the reaction time is further reduced to 5 min in G9–G11, to 30 s in G12–G14, and to 5 s in G15–G24, class 3 is the first class to become noncompetitive, followed by class 4, class 5, and class 6. Sequence class 7 represents the most catalytically proficient deoxyribozyme and is predicted to take over the selection by G13 and become the overwhelmingly dominant class in subsequent rounds.

The preceding simulation indicates that if deoxyribozyme sequences were selected solely on the basis of their catalytic rate, we would expect each class to be represented about equally at the beginning of

A

Sequence class		1	2	3	4	5	6	7	NC
k_C, min^{-1}		0.004	0.01	0.045	0.1	0.25	0.6	2.0	<3.3x10^{-4}
G0-G7 5h	$SR_{C\,0\text{-}7}$	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.008
G8 30m	$SR_{C,8}$	0.12	0.3	1.0	1.0	1.0	1.0	1.0	0.008
G9-G11 5m	$SR_{C\,9\text{-}11}$	0.02	0.05	0.23	0.5	1.0	1.0	1.0	0.008
G12-G14 30s	$SR_{C\,12\text{-}14}$			0.025	0.05	0.12	0.3	1.0	0.008
G15-G24 5s	$SR_{C\,15\text{-}24}$					0.021	0.05	0.17	0.008

B

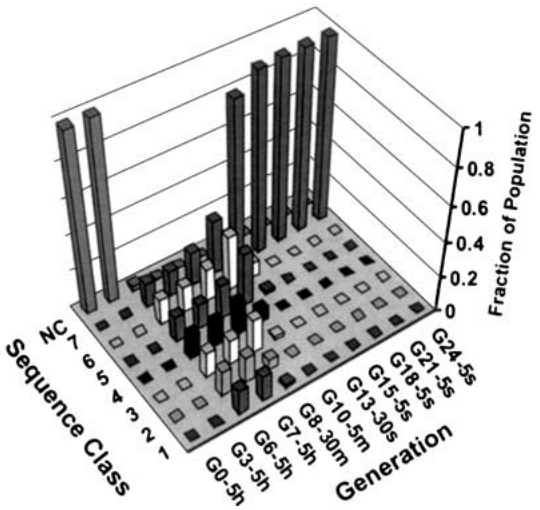

Fig. 7. Simulation 1 of Selection A using a one-parameter model. **A** Data table. **B** Simulated fitness landscape. Selection A is simulated under the assumption that selection is acting on only one phenotypic trait: the catalytic rate, k. All other phenotypic traits between classes are assumed to be equal. The progress of seven different catalytic sequence classes and a group of noncatalysts (NC) are followed over generational time, in terms of their surviving ratio (SR). The surviving ratio ($0 \leq SR \leq 1$) is defined as the fraction of a given sequence class that can survive the selection step (cleaving the attached RNA substrate in the allotted time frame). Changes in the SR are emphasized by large font. Blank squares indicate that the SR of a given sequence class has diminished to a level comparable with the noncatalyst group. Sequence classes were arbitrarily arranged to illustrate the evolutionary succession of competing classes, and the order does not reflect any homology between classes, except by chance. The color scheme (gray scale) is arbitrary and intended only to facilitate viewing.

selection and to follow the same pattern of growth until differences in their catalytic rate become manifest in response to changes in the selection pressure. Although this simulation does explain the progressive disappearance of less competitive deoxyribozyme classes under increasing selection pressure, it fails to account for the staggered starting appearance of individual deoxyribozyme classes observed across the landscape in Fig. 4. This analysis suggests that one or more other factors may also influence the outcome of Selection A. These factors may include differential folding ability, PCR efficiency, and spontaneous mutagenesis during PCR. A given sequence could potentially adopt multiple conformations that differ in catalytic activity, a phenomenon that has been well documented (Been et al. 1992; Carrigan et al. 2004; Gottlieb et al. 1994; Uhlenbeck 1995). Therefore, those sequences that have a greater tendency to fold into an active conformation would enjoy a selective advantage. Similarly, a sequence class that is more easily amplified by Taq DNA polymerase will produce more sequence copies during the PCR step. In addition, spontaneous mutations are routinely introduced by Taq DNA polymerase. If an originally less competitive deoxyribozyme acquires some adaptive mutations that significantly enhance its surviving ability (a higher catalytic rate, better PCR or folding efficiency, or some combination thereof), it will appear on the fitness landscape at some later point during the selection.

Based on the preceding discussion, we decided to perform a second simulation (Simulation 2, Fig. 8) that takes three factors into consideration: catalytic rate, structural folding efficiency, and random mutagenesis. We introduced a ''folding factor'' for each sequence class used in Simulation 1, such that the surviving ratio of each class can now be calculated as the product of the two individual factors (under nonmutagenic conditions):

$$SR_{C,N} = (SR_{C,N})_{Rate} \times (SR_{C,N})_{Folding}$$

The folding factor is defined as the fraction of a given deoxyribozyme sequence class that folds into a catalytically active conformation. To address the potential role of random mutagenesis, we have arbitrarily chosen sequence class 1 to receive adaptive mutations in G7, which boost its surviving ability from an initial value of 0.009 to 0.4 throughout the remaining selection rounds (G7–G24).

The class 2 deoxyribozyme has a relatively small catalytic rate compared to the other sequence classes (except class 1) but has the best folding ability, with a value of 0.8. This class is most competitive during the early stages of selection when the allotted reaction time is 5 h. Classes 3–6 all have better folding abilities than class 7, but possess lower catalytic rates, and

A

Sequence class		1	2	3	4	5	6	7	NC
k_C, min^{-1}		0.004	0.01	0.045	0.1	0.25	0.6	2.0	<3.3x10^{-4}
Folding factor		0.009	0.8	0.6	0.5	0.3	0.3	0.2	N/A
G0-G6 5h	$SR_{C,0-6}$	0.0009	0.8	0.6	0.5	0.3	0.3	0.2	0.008
G7 5h	$SR_{C,7}$	0.4	0.8	0.6	0.5	0.3	0.3	0.3	0.008
G8 30m	$SR_{C,8}$	0.4	0.24	0.6	0.5	0.3	0.3	0.2	0.008
G9-G11 5m	$SR_{C,9-11}$	0.4	0.04	0.14	0.25	0.3	0.3	0.2	0.008
G12-G14 30s	$SR_{C,12-14}$	0.4		0.015	0.025	0.038	0.09	0.2	0.008
G15-G24 5s	$SR_{C,15-24}$	0.4					0.015	0.033	0.008

B

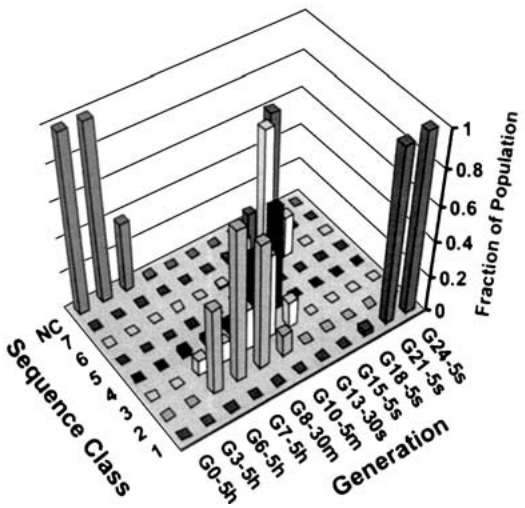

Fig. 8. Simulation 2 of Selection A using a three-parameter model. **A** Data table. **B** Simulated fitness landscape. Selection A is simulated under the assumption that selection is acting against two phenotypic traits (the catalytic rate and a folding factor) for most classes and a third factor (spontaneous mutagenesis) for class 1. The folding factor is represented by the fraction of a given sequence class that folds into a catalytically active conformation. The progress of seven different catalytic sequence classes and a group of noncatalysts (NC) is followed over generational time, in terms of their surviving ratio (SR). Sequence classes were arbitrarily arranged to illustrate the evolutionary succession of competing classes, and the order does not reflect any homology between classes, except by chance. The color scheme (gray scale) is arbitrary and intended only to facilitate viewing.

therefore are more competitive in the middle rounds of the selection. Class 7 is the most competitive in the later rounds of selection because it can exploit its superior catalytic rate under the more stringent reaction time, which is reflected as a better compounded surviving ability. Class 1 is the worst-performing class at the beginning of the selection but becomes very competitive after acquiring some advantageous mutations in the seventh generation. However, this class takes about 10 rounds to manifest because of its relatively small representation in the early stages of the population, when it was not competitive at all.

Simulation 2 (Fig. 8) is consistent with the patterns of ascending and descending catalytic species and the overall staggered shape of the landscape

illustrated in Fig. 4. It is easy to predict that the population dynamics of such a selection will continue to fluctuate until the emergence of a class that best meets the given selection constraints.

Selection B Simulation

Since no significant change in the catalytic rate was observed throughout Selection B, we conclude that the catalytic rate is at best only a minor contributing factor in the progress and outcome of Selection B. In other words, there is no ostensible selection pressure favoring deoxyribozyme sequences with particularly large catalytic rates. For example, there is no significant advantage for a deoxyribozyme class with a rate constant of 10 min^{-1} versus those with a rate constant of just 0.01 min^{-1}. Both deoxyribozymes should catalyze the RNA-cleavage reaction to completion within the allotted 5-h time frame. Other factors, including productive folding ability, PCR efficiency, and spontaneous mutagenesis during PCR, must have dictated the selection of individual deoxyribozyme classes in Selection B. Spontaneous mutagenesis is likely to be a very important contributing factor, or the fitness landscape is expected to be very simple: one or many deoxyribozymes with similar traits will emerge after just a few rounds of selection; after that, the population dynamics will become largely static and the landscape will remain unchanged because the selection pressure is constant throughout.

To provide a theoretical explanation, we performed a third simulation (Simulation 3; Fig. 9) that takes into account the following three factors: folding efficiency, PCR efficiency, and spontaneous mutational effects. Once again, seven catalytic sequence classes were used and their respective folding factors and PCR efficiency values are given in the table in Fig. 9. The $SR_{C,N}$ of each sequence class can be calculated (under nonmutagenic conditions) as the product of the PCR efficiency and folding factor:

$$SR_{C,N} = (SR_{C,N})_{PCR} \times (SR_{C,N})_{Folding}$$

$(SR_{C,N})_{Folding}$ is the fraction of a given deoxyribozyme class that folds into a catalytically active conformation and $(SR_{C,N})_{PCR}$ represents the corresponding PCR efficiency. We intentionally assigned similar $(SR_{C,N})_{PCR}$ values (0.5–0.75) and widely varied the folding factors (0.02–0.5) among the seven sequence classes in order to emphasize the potential influence of the folding parameter. We also assumed that one or more favorable mutational events (which result in different levels of enhancement of the surviving ability of a concerned class) have occurred to the following classes at different stages in the selection: one event for classes 2–5, two events for class 6, and three events for class 7.

A

Sequence class		1	2	3	4	5	6	7	NC
PCR efficiency		0.75	0.75	0.7	0.75	0.56	0.5	0.5	N/A
Folding factor		0.5	0.48	0.4	0.3	0.25	0.02	0.02	N/A
G0-G1 5h	$SR_{C\,0\text{-}1}$	0.37	0.36	0.28	0.22	0.14	0.01	0.01	0.008
G2-G3 5h	$SR_{C\,2\text{-}3}$	0.37	0.36	0.28	0.22	0.14	0.1	0.01	0.008
G4-G5 5h	$SR_{C\,4\text{-}5}$	0.37	0.36	0.45	0.22	0.14	0.4	0.4	0.008
G6-G8 5h	$SR_{C\,6\text{-}8}$	0.37	0.36	0.45	0.55	0.65	0.4	0.75	0.008
G9 5h	$SR_{C\,9}$	0.37	0.36	0.45	0.55	0.65	0.4	0.85	0.008
G10-G23 5h	$SR_{C\,10\text{-}23}$	0.37	0.36	0.45	0.55	0.65	0.75	0.85	0.008
G24-G30 5h	$SR_{C\,24\text{-}30}$	0.37	1.0	0.45	0.55	0.65	0.75	0.85	0.008

B

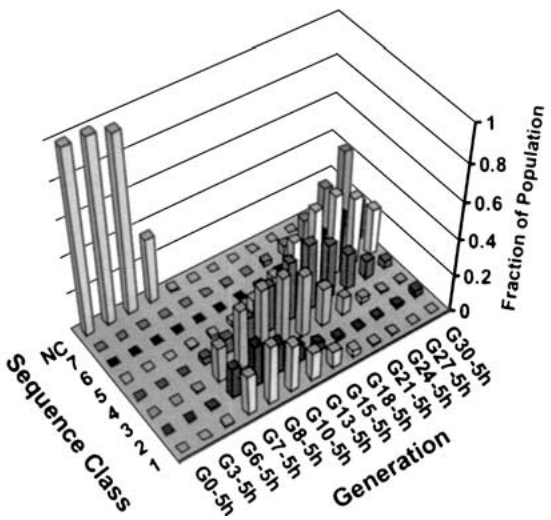

Fig. 9. Simulation 3 of Selection B using a three-parameter model. **A** Data table. **B** Simulated fitness landscape. Selection B is simulated under the assumption that folding efficiency, PCR efficiency, and spontaneous mutagenesis during PCR collectively act to shape the evolutionary fitness landscape. The folding factor is represented by the fraction of a given sequence class that folds into a catalytically active conformation. The progress of seven different catalytic sequence classes and a group of noncatalysts (NC) is followed over generational time, in terms of their surviving ratio (SR). Sequence classes were arbitrarily arranged to illustrate the evolutionary succession of competing classes, and the order does not reflect any homology between classes, except by chance. The color scheme (gray scale) is arbitrary and intended only to facilitate viewing.

Simulation 3 produces a landscape that largely parallels the fitness landscape given in Fig. 5: a continually changing population in which less fit classes disappear in favor of more fit classes. The fitness improvement for a given class is the cumulative result of one or more adaptive mutagenic events. The population dynamics of such a selection will be characterized by continual changes in the dominating species as long as higher-fitness classes can be produced along the evolutionary pathway. In the end, an individual or group of classes with the highest degree of fitness under the given conditions will "hijack" the selection. At this point, the fitness landscape will no

longer experience drastic changes, that is, until a new selection pressure is imposed.

Concluding Remarks

Herein, we sought to provide additional insight into the *in vitro* selection process. The population dynamics of a community of RNA-cleaving DNAzymes was studied in an effort to identify characteristic patterns of behavior. Identification of these patterns, or lack thereof, may improve our understanding and ability to predict the distribution of function in sequence space, the majority of which has yet to be explored and continues to represent a very daunting challenge. The most comprehensive information on population dynamics can be obtained by directly sequencing many individual clones over multiple rounds of selection. The resulting data can then be conveniently visualized by constructing the corresponding fitness landscapes.

The experimentally derived fitness landscapes presented in Figs. 4 and 5 illustrate two very different evolutionary paths. In Selection A (Fig. 4), the population complexity decreases rapidly in favor of just a few sequence classes, with one class in particular clearly dominating (comprising as much as ~70% of the population). This behavior can be attributed to the sharp reduction in reaction time, which causes Selection A to undergo directional selection in favor of those sequences at one end of the phenotypic spectrum (i.e., the fastest enzymes). This leads to a landscape with a relatively narrow and peaked distribution. In contrast, the population complexity of Selection B decreases at a far slower pace and is characterized by a larger number of classes of similar fitness. The landscape of Selection B appears broad and relatively flat, with most sequence classes occupying less than 15% of the population at any given time and only one class transiently comprising as much as 25% of the total population. Interestingly, both populations are characterized by a continuous transition in the dominating species, giving rise to the staggered appearance of "new" sequence classes across the fitness landscape. This observation alludes to the presence of many latent deoxyribozymes in the initial library, which will only manifest when the composite population is challenged with different selection pressure (as in Selection A) or through the acquisition of one or more adaptive mutations (as in Selection B). It is important to recognize the role of these latent deoxyribozyme species during in vitro selection, because all too frequently an implicit assumption is made that the dominant species at one moment in time (usually taken to be the "terminal" population) also represents the optimum solution at other moments in time before and after.

In vitro selection is frequently used for the expressed purpose of isolating nucleic acids with catalytic ability. The results of Selection B should serve as a cautionary tale; simply selecting for catalytic activity is not necessarily sufficient to yield a good catalyst. Evidence for this scenario has appeared elsewhere as well. Schmitt et al. selected for variants of a ligase ribozyme under decreasing Mg^{2+} conditions during *in vitro* evolution (Schmitt and Lehman 1999) and obtained a variant that did not possess a higher first-order catalytic rate constant but was, nevertheless, more active than the wild type. They suggested that the variant ribozyme was more active than the wild type because it was less likely to misfold into inactive conformers. The k_{obs} of the composite G30 population of Selection B indicates that no enhancement in catalytic activity has occurred despite many rounds of selective amplification. Although it is possible that individual clones within the G30 population may possess high catalytic rates, the k_{obs} of the composite population suggests that such species would exist as a minority. Moreover, we suspect that the weak selection pressure may actually help to decrease the representation of fast catalysts, by allowing the propagation of mildly deleterious mutations. For instance, an enzyme that incurs a mutation or series of mutations that cause its catalytic rate to drop from 10 to 0.01 min^{-1} will still survive under the imposed 5-h time constraint in our experiment. Since the number of possible deleterious mutations likely exceeds the number of possible beneficial mutations, this effect could potentially be quite substantial, especially for those employing *in vitro* evolution protocols that boast higher mutagenesis rates.

The current study has focused on the accumulation and analysis of large amounts of genotypic data. However, it would be very interesting to conduct a multivariable characterization of the phenotypic properties of specific clones within and between sequence classes, throughout the entire fitness landscape. This characterization represents the objective of a future study, which aims to assess the contribution of various factors including PCR amplification efficiency, folding efficiency, and catalytic rate in order to create a meaningful genotype-to-phenotype map. In the meantime, this study should be of immediate interest to those employing in vitro selection techniques and may also be of general interest to those studying population dynamics, optimization theory, and evolution.

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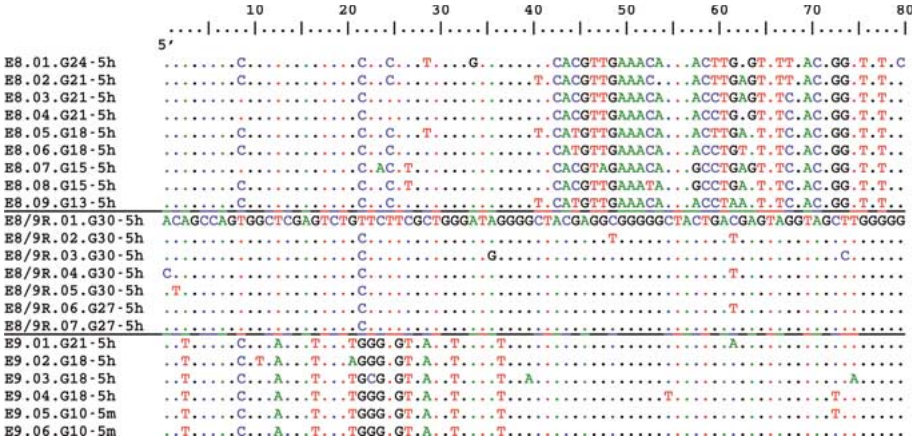
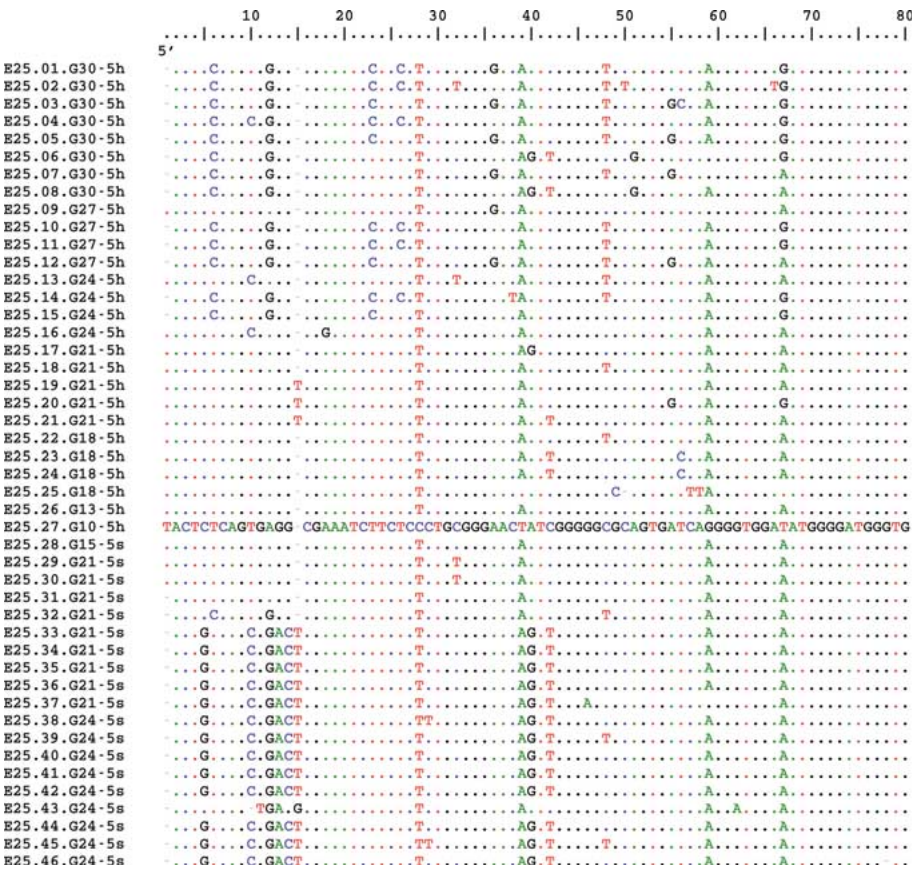


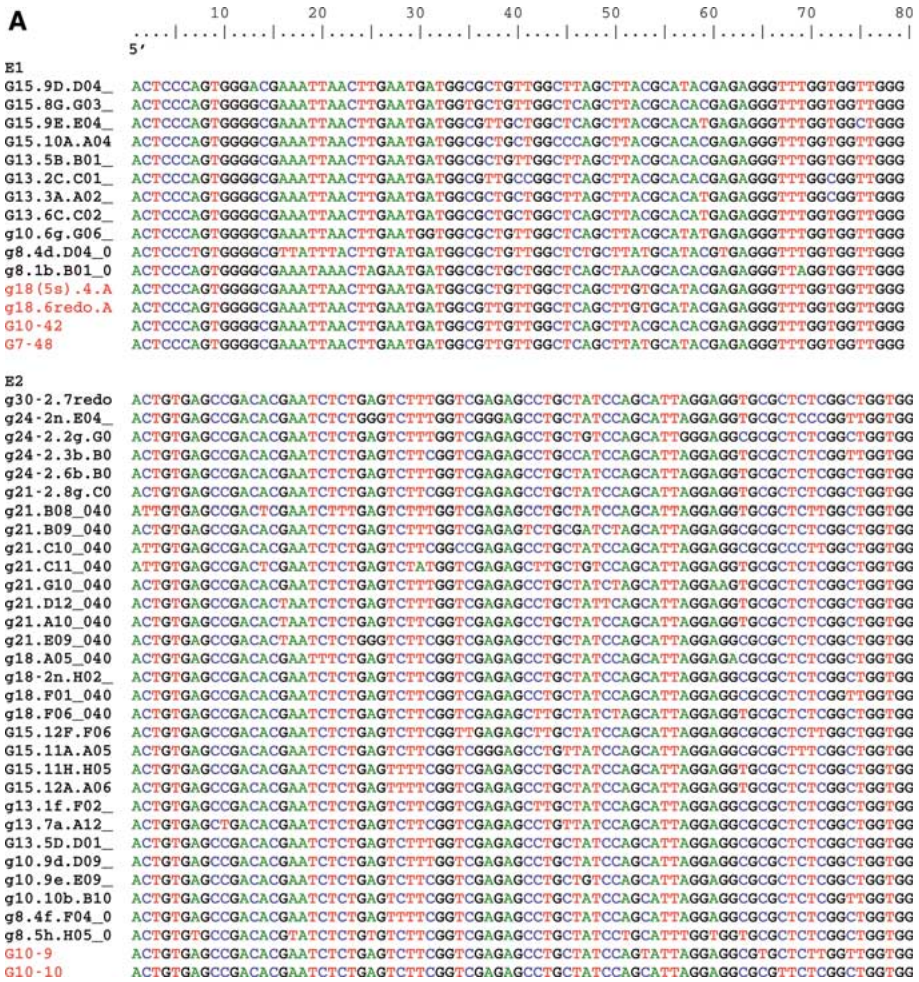
Supplementary Fig. 1. Sequence alignment of E8, E8/9R, and E9 sequence classes. Each clone is described by a title that denotes its sequence class (i.e. E8), a clone specific number within the class, followed by the generation (i.e. G24) from which it was derived and the corresponding reaction time. Clone, E8/9R.01.G30-5h, was used as the reference point to which all other clones are compared. Sequence identity is indicated by a dot. Only the 80-nt random-sequence domain is shown for simplicity. The average sequence identity within classes is as follows: E8 = 92%; E8/9R = 97%; E9 = 96%. The average sequence identity between classes is as follows: E8-E8/9R = 62%; E8-E9 = 48%; E9-E8/9R = 81%.



Supplementary Fig. 2. Sequence alignment of the E25 class. Each clone is described by a title that denotes its sequence class (i.e. E25), a clone specific number within the class, followed by the generation (i.e. G30) from which it was derived and the corresponding reaction time. Clone, E25.27.G10-5h, was used as the reference point to which all other clones are compared. Sequence identity is indicated by a dot, gaps in the alignment are indicated by a dash. Only the 80-nt random-sequence domain is shown for simplicity.

Supplementary Table 1. Sequence classification statistics. The average, minimum, and maximum sequence identity observed within classes, as well as the average, maximum, and minimum sequence identity observed between classes is tabulated per generation, and across all generations in both Selection A and B.

	Selection B										Selection A							Selection A + B
Time	5h	5h	5h	5h	5h	5h	5h	5h	5h	5h	30m	5m	30s	5s	5s	5s	5s	5h-5s
Generation	30	27	24	21	18	15	13	10	8	7	8	10	13	15	18	21	24	G30...G7...G24
Observed Sequence Identity Within Classes (%)																		
Average	95.2	95.0	95.2	93.9	93.2	93.9	94.5	94.8	92.4	95.0	95.7	95.6	96.9	93.2	94.9	91.2	94.0	94.0
Minimum	87.1	85.0	87.3	86.2	85.0	90.0	90.0	88.7	82.2	92.5	92.5	90.0	91.2	86.0	83.5	85.0	87.3	78.4
Maximum	100	100	100	100	100	100	98	98	100	100	98	100	100	100	100	100	100	100
Observed Sequence Identity Between Classes (%)																		
Average	31.2	29.1	29.5	31.0	33.6	33.4	33.7	31.4	31.4	31.5	33.0	35.0	32.3	37.5	39.4	36.3	40.1	~32
Maximum	51.2	50.0	48.7	50.0	53.7	50.6	56.2	52.5	52.5	50.6	50.0	52.5	51.2	50.0	53.1	47.5	48.7	~56
Minimum	17.5	12.5	12.5	15.0	16.0	15.0	16.2	12.5	13.7	12.5	12.5	20.0	15.0	17.5	22.2	17.5	27.5	~9



Supplementary Fig. 3. The sequences of all 857 clones are grouped into sequence classes. Each sequence class containing more than 1 clone is denoted by a number (i.e. E#). Within each sequence class individual clones are represented by a number (i.e. G# or g#) that indicates the generation from which it was recovered, followed by an alpha-numeric designation to identify specific clones. Clones from Selection B are represented by black titles, while red titles indicate clones from Selection A. Only the ~80-nt random-sequence domain of each clone is illustrated.

B

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G10-11          ACTGTGAGCCGACACGAATCTCTGGGTCTTCGGTCGAGAGCCTGCTATCTAGCATTAGGAGGCGCGTTCTCGGCTGGTGG
G10-12          ACTGTGAGCCGACACGAGTCTCTGAGTCTTCGGTCGAGAGCCTGCTATCCAGCATTAGGAGGCGCGCTCTTGGCTGGTGG
G10-13          ACTGCGAGCCGACACGAATCTCTGAGTCTTCGGTTGAGAGCCTGCTATCCAGCATTAGGAGGCGCGCTCTCGGCTGGTGG
G10-14          ACTGTGAGCCGACACGAGTCTCTGAGTCTTCGGTTGAGAGCCTGCTATTCAGCATTAGGAGGCGCGTTCTCGGCTGGTGG
G10-15          ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTATCCAGCATTAGGAGGCGCGCTCTCGGCTGGTGG
G10-16          ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTATCCAGCATTAGGAGGCGCGCTCTCGGCTGGTGG
G8-1            ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTATTCAGCATTAGGAGGCGCGCTCTCGGCTGGTGG
G8-2            ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTATCCAGCATTAGGAGGCGCGCTTTCGGCTGGTGG
G8-3            ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTGTCCAGCATTAGGAGGCGCGCTCTCGGCTGGTGG
G8-4            ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGTCTGCTATCCAGCATTAGGAGGCGCGCTCTCGGTTGGTGG
G8-5            ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTATCCAGCATTAGGAGGCGCGTTCTCGGCTGGTGG
G8-6            ACTGTGAGCCGACACGAATCTCTGAGTCTTCGGTCGAGAGCCTGCTATCTAGCATTAGGAGGTGCGCTCTCGGCTGGTGG

E3
g21.E10_040     ACTCCTAGCAGGGCGAAATCTTTCTGACGGGAGCTGAACCTTAAGCCCTGGATTTAGAGATTCTGTGACTGTGGCTGG
g18-2.4e.F0     ACTCCTAGTAGGGCGAAATCTTTCTGACGGGAGCTGAACCTTAAGCCTTGGATTTAGAGGTTCTGTGACCGTGGCCGG
G15.8F.F03_     ACTCCTAGCAGGGCGAAATCTTTCTGGCGAGAGCTGAACCTTAAGTCCTGGACTTAGAGGTTCTGTGACTGTGGCCGG
G15.10D.D04     ACTCCTAGCAGGGCGAAATCTTTTTGACGAGAGCTGAACCTTAAGTCCTGGATTTGGAGGTTCTGTGACTGTGGCCGG
g15.7e.E12_     ACTCCTAGCAGGGCGAAATCTTTCTGACGAGAGCTGAATCTTAAGCCTTGGATTTAGAGGCTCTGTGACTGTGGCCGG
G13.2F.F01_     ACTCCTAGCAGGACGAAATCTTTCTGACGAGAGCTGAACCTTAAGCCCTGGATTTAGAGGTTCTGTGACTGTGGCCGG
G13.4B.B03_     ACTCCTAGCAGGGCGAAATTTTTCTGACGGGAGCTGAACCTTAAGTTCTGGATTTAGAGGTTCTGTGACTGTGGCCGG

E4
g18.G04_040     ACTATGAGCCATACGATGTCTCTCTCCAGCGCCGCATGTAGCAGAACGTAGGTGTAGGATCCTTTTAGTGGCTCGGGTGG
G15.12H.H06     ACTATGAGCCATACGACGTCCCTCTCCAGCGCCGTATGAAGTAGAATGTAGGTGAAGGATCCCTTAAGTGGCTCGGGTGG
G15.10F.F04     ACTATGAGCCATACGATGTCCCTCTCCAGCGCTGCATGGAGCAGAACGCAGGTGAAGGATCCCTTAAGTGGCTTGGGTGG
g13.7b.B12_     ACTATGAGCCATACGACGTCCCTCTCTAGCGCCGTATGAAGTAGAATGCAGGTGAAGGATCCCTTAAGTGGCTCGGGTGG
G13.6G.G02_     ACTATGAGCCATACGACGTCTCTCTCCAGCGCTGCATGAAGCAGAACGCAGGTGAAGGATCCCTTAAGTGGTTTGGGTGG
G13.6H.H02_     ACTATGAGCCATACGACGTCCCTCTCCAGCGCCGCATGAAGCAGAACGTAGGTGAAGGATCCCTTAAGTGGCTCGGGTGG
g10.7c.C07_     ACTATGAGCCATACGACGTCCCTCTCCAGCGCTGCGTGAAGCAGAACGCAGGTGAAGGATCCCTTAAGTGGCTTGGGTGG
g10.11c.C11     ACTATGAGCCATACGATGTCCCTCTCCAGCGCCGCATGAAGCAGAACGCAGGTGAAGGATCCCTTAAGTGGCTCGGGTGG
g8.3b.B03_0     ACTATGAGCCATACGACGTCCCTCTCTAGTGCCGCATGAAGCAGA-CGTAGGTGAAGGATCCCTTAAGTGGCTCGGGTGG

E5
g24-2.4h.H0     ACTGTTAGTAACACGAGTCACCTCCTCGGCAGAGCTGCAGCCATCGGCTTCGTGAGGGGGTGTGGACCTGTTGGGAGGG
g24-2.5g.G0     ACTGTTAGTAACACGAGTCACCTCCTCGGCAGAGCTGCAGTCATCGGCTTCGTGAGGGGGTGTAGACCTGTTGGGGGGG
g24-2n.G04_     ACTGTTAGTAACACGAGTCACCTCCTCGGCAGAGCTGTAGCCATCGGCTTCGTGAGGGGGTGTAGACCTGTTGGGGGGG
g21-2n.A03_     ACTGTTAGTAACACGAGTCATCTCCTCGGTAGAGCTGCAGCCACCGGCTTCGCGAGGGGGTGTAGACCTGTTGGGGGGGG
g21-2.7g.B0     ACTGTAAGTAACACGAGTCATCT----GGCAGAGCTGCAGCCAT-GGCTTCGTGAGGGGGTGTGGACCTGTTGGGGGGG
G15.9C.C04_     ACTGTTAGTAACGCGAGTCACCTCCTCGGCAGAGCTGCAGCTATCGGTTTCGCGAGGGGGCGTAGACCTGTTGGGGGGGG
g15.12g.G01     ACTGTTAGTAACACGAGTCACCTCCTCGGCAGAGTTGCAGCCATCGGCTTTGCGAGGGGGCGTAGACCTGTTGGGGGGG
G13.4H.H03_     ACTGTTAGTAACACGAGTCACCTCTTCGGCAGAGCTGCAGTCATCGGTTTCGCGAGGGGGCGTAGACTTGTTGGGGGGGG
g8.4b.B04_0     ACTGTAAGTAACACGAGTCAACTACTCGGCAGAGCTGCAGCCATCGGCTACGCGAGGGGGCGTAGACCTGTAGGGGGGGG

E6
G15.8E.H03_     ACTATAAGCAATACGAATCTCGAGGGCGCGGTGGAGGTGACCGGTCGGGCAATTCAAGAGCCGCTTTCTGGAACGATGGG
G15.12D.D06     ACTATTAGCAATACGAATCTCGAGGGTGCGGTGGAGGTGACCGGTCGGGCAATTCAAGAGCCGTTTTCTGGAACGATTGG
g13.12f.F01     ACTATAAGCAATACGAATCTCGAGGGCGCGGTGGAGGTGACCGGTCGGGCAATTCAAGAGCCGCTTTCTGGAACGATTGG
G7-39           ACTATTAGCAATACGAATCTCGAGGGCGCGGTGGAGGTGACCGGTCGGGCAATTCAAGAGCCGCTTTCTGGAACGGTTGG

E7
G15.9H.H04_     ACTAGGAGCCGCTACGAATCTCAGCAGTCACTTTGATGTGAAGGTTAAAATGAGATCTGACGTTGGTGTAACTTCGTGGG
G13.3G.G02_     ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTCTGACGTGAAGGTTTAAATGAGGTCTGACGTTGGTGTAACTCCGTGGG
g10.8f.F08_     ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTTGATGTGAAGGTTAAAATGAGATCTGACGTTGGTGTAACTCCGTGGG
g10.9h.H09_     ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTTGACGTGAAGGTTTAAATGAGATCTGACGTTGGTGTAATTCTGTGGG
g10.10e.E10     ACTAGGAGCCGCTACGAATTTCAGCGGTCGCTCTGACGTGAAGGTTAAAATGAGATTTGACGCTGGTGCAACTCCGTGGG
g8.6d.D06_0     ATAAGGAGCCGCTACGAATCTCAGCAGTCGCTTAGACGTGAAGGTTAAAATGAGATCTGACGTTGGTGTAACTCCGTGGG
g8.1d.D01_0     ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTAGGTGTGAAGGTTAAAATGAGATCTGACGTTGGTGTAACTCCGTGGG
G8-12           ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTTGACGTGAAGGTTAAAACGAGATCTGACGTTGGTGTAACTTCGTGGG
G8-13           ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTTGACGTGAAGGTTAAAATGAGATCTGACGTTGGTGTAATTCCGTGGG
G7-1            ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTTGACGTGAAGGTTAAAATGAGATTTGACGTTGGTGTAACTTCGTGGG
G7-2            ACTAGGAGCCGCTACGAATCTCAGCAGTCGCTTTGACGTGAAGGTTAAAATGAGATCTGACGTTGGTGTAACTCCGTGGG
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C

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E8
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g21.H09_040   ACAGCCAGTGGCTCGAGTCTGCTCTTCGCTGGGATAGGGGCTCACGTTGAAACACTAACCTGAGTTTCGACGGGTTGTGG
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g18-2.3a.B0   ACAGCCAGCGGCTCGAGTCTGCTCCTCGTTGGGATAGGGGTTCATGTTGAAACACTAACTTGAATTTCGACGGGTTGTGG
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G15.10H.H04   ACAGCCAGTGGCTCGAGTCTGCTACTTGCTGGGATAGGGGCTCACGTAGAAACACTAGCCTGAGTTTCGACGGGTTGTGG
G15.11F.F05   ACAGCCAGCGGCTCGAGTCTGCTCCTTGCTGGGATAGGGGCTCACGTTGAAATACTAGCCTGAATTTCGACGGGTTGTGG
G13.4C.C03_   ACAGCCAGCGGCTCGAGTCTGCTCCTCGCTGGGATAGGGGTTCATGTTGAAACACTAACCTAAATTTCGACGGGTTGTGG

E8/9R
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g27-2.G08_0   ACAGCCAGTGGCTCGAGTCTGCTCTTCGCTGGGATAGGGGCTACGAGGCGGGGGCTACTGATGAGTAGGTAGCTTGGGGG
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E9
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E10
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E11
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G15.12B.B06   GCACTATCAGCGATTCGATTCGGGATCTATGTCTAGGGAACGGTAAGGCGAATGGTCACGTATGGGAAAAAGGGGGACG

E12
g21.E07_040   ACTATCAGCTGATACGAATCTATGGTGGGGCTGCTCTAATGGGAGTCGGAACGCGTGGTGGCAGAAGTTGAGTGGTGGG
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G15.9G.G04_   ACTATCAGCTGATACGAATCTTTGGTGGGGCTGCTCTAATGGGAGTCGGAACGCGTGGTGGCAGAAGT-GAGTGGTGGG
G15.10C.C04   ACTATCAGCTGATACGAATCTTTGGTGGGGCTGCTCTAATGGGAGTCGGAATGCGTGGTGGCAGAAGTTGAGTGGTGGG
g10.7b.B07_   ACTATCAGCTGATACGAATCTATGGTGGGGCTGCTCTAATGGGAGTCGGAACGCGTGGTGGCAGAAGTTGAGTGGTGGG

E13
g15.7g.G12_   ACTGTTAGTAACACGAAGTCTTTCTGCAACGGTGTATGGATGCCATTCAGCGCGGGACGTCGGGAATTCTAAGGTGGTCG
G15.11G.G05   ACTGTTAGTAACACGAAGTCTTTCTGCAACGGTGAATGGACGCCATTCAGCGTGGGACGTCAGGAATCCAAAGGTGGCCG
g10.10d.D10   ACTGTAAGTAACACGAAGTCTAACTGCAATGGTGAATGGACGCCATACAGCGTGGGACGTCAGGAATCCAAAGGTGGTCG

E14
g18-2n.C02_   A-CTGCTAGCAGCCCGAAATCGCTCTCCCAATATGGGCTTTCGGGG-AAGACGGTAATAGGAGAAATGGTGCTATGTCCGTG
g15.7h.H12_   A-CTGCTAGCAGCTCTTAATCGCTCTCCCTATATGGGCTTCCGGGG-ATTACGGTTATAGGAGTTATGGTGCCTTGTCCGTG
G13.5G.G01_   A-CTGTTAGCAGCTCGAAATCGCTCTCCCAATATGGGCTTCCGGGG-AAGACGGTAATAGGAGAAATGGTGCCTTGTCTGTG
g10.9a.A09_   A-CTGCTAGCAGCCCGAAATTGCTCTCCCAATATGGGCTTCCGGGG-AAGACGGTAATAGGAGAAATGGTGCCTTGTTTGTG
g24.3.D10_0   A-CTGCTAGCAGCTCGAAATCGCTCTCCCAATGTGGCCTTCCGGGG-AAGACGGTAATAGGAGAAATGGTGCCCTGTCCGTT
g24.6.B04_0   A-CTGCTAGCAGCTCGAAATCGCTCTCCCAATGTGGCCTTCCGGGG-AAGACGGTAATAGGAGAAATGGTGCCCTGTCCGTT
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D

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g24n.C03_04   A CTGCTAGCAGCTCGAAATCGCTCTCCCAATGTGGCCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCCTGTCCGTT
g18(5s).5.B   A CTGCTAGCAGCTCGAAATCGCTCTCCCAATATGGGTTTCCGGGG AAGACGGTAATAGGAGAAATGGTGTCTTGTCCGTG
g18.A01_040   A CTGCTAGCAGCTCGAAATCGCTCTCCCAATATGGGCTTCCGGGG AAGACGGTAATAGGAGGAATGGTGTCTTGTTCGTG
g18n.F01_04   A CTGCTAGCAGCTCGAAATCGCTCTCCCAATATGGGTGTTCCGGGGAAGATGGTAATAGGAGAAATGGTGTCTTGTCCGTG
G15-39        A CTGCTAGCAGCTCGAAATCGCTCTCTCAATATGGGCTTTCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
G15-40        A CTGCTAGCAGCTCGAAATCGCTCTTCCGATATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTTCGTG
G15-41        A CTGCTAGCAGCTCGAAATCGCTCTCCCAATATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
G15-42        A CTGCTAGCAGCTCGAAATCGCTCTCCTAATATGGGTTTCCGGGG AGGACGGTAATAGGAGAAATGGTACCTTGTCCGTG
G15-43        A CTGCTAGCAGCTCGAAATCGCTCTCCCAATATGGTCTTCCGGGG AAGACGGTAATAGGAGGAATGGTGTCTTGTCCGCG
G15-44        A CTGCTAGCAGCTCGAAATCGCTCTCTCAATATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTTCGTG
G15-45        A CTGCTAGCAGCTCGAAATCGCTCTCCCAATATGGTCTTCTGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCTGTG
G15-46        A CTGCTAGCAGCTCGAAATCGCTCTCCCGATATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
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G10-17        A CTGCTAGCAGCCCGAAATCGCTTTCCCAATATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
G10-18        A CTGCTAGCAGCTCGAAATCGCTCTCTCAATATGGGCTTTCGGGG AAGATGGTAATAGGAGAAATGGTGTCTTGTCCGTG
G10-19        A CTGCTAGCAGCCCGAAATCGCTCTCCCAATATGGTCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
G8-18         A CTGCTAGCAGCCCGAAATCGCTCTCCCAGTATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGTCTTGTCTGTG
G8-19         A CTGCTAGCAGCCCGAAATCGCTCTCCCAATATGGGCTTCTGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
G7-15         A CTGCTAGCAGCCCGAAATTGCTCTCCCAATATGGGCTTCCGGGG AAGACGGTAATAGGAGAAATGGTGCCTTGTCCGTG
G7-13         A CTGCTAGCAGCCCGAAATCGCTTTCCCCATATGGGCTTTCGGGGGAAGACGGTAATAGGAGAAATGGTGTCTTGTCCGTG

E15
G15.10E.E04   ATATCCTAGCAGGCCGAGTCTCTCTTAGACGTCGGCACGAGTCGCCCGATAGTCATCTGGGCTGGAGTTGGTCCCATAGG
g8.2b.B02_0   ATATCCTAGCAGGTCGAGTCTCTTTTAGACGTCGGCACGAGTCGCCCGATAGTCATCTGGGCTAGAGTTGGTCCCATAGG

E16
g30-2.7redo   ATGTCCTAGCAGGGCGAGTCTCTAGAATGGTGTGGTGGGCTAGGGCAAGGCCAGCGGCGGTTGAGGTATGAAGGATGTGC
g30-2.A08_0   ACTTCCTAGCAGGGCGAGTCTCTTGAATGACGTGGTGGGTTAGGGCAAGGCCAGCGGCGGTTGGGGTATGGAGGATGTGC
g30-2.D12_0   ACTTCCTAGCAGGGCGAGTCTCTTGAATGACGTGGTGGGTTGGGGTAAGGCCGGCGGCGGCTGAGGTATGAAGGATGTGC
g27-2.A08_0   ACTTCCTAGCAGGGCGAGTCTCTTGAATGACGTGGTGGGCTAGGGCAAGGCTAGCGGCGGCTGAGGTATGAGGGATGTGC
g24-2.3e.E0   ACTTCCTAGCAGGGCGAGTCTCTTGAATGACGTGGTGGGCTAGGGCAAGGTCAGCGGCAGTTGGGGTGTGAAGGATGTGC
g21.H11_040   ACTTCCTAGCAGGGCGAGTTTCTTGAATGACGTGGTGGGCTAGGGCAAGGCCAGTGGCAGCTGAGGTATGGAGGATGTGC

E17
g18-2.3g.H0   ACTTATAGCATTACGAATCCGACACAAGACGCTGGAAAACTTGGGAGCCTGAGGGGCTTTTGTTTGTAGTTGTCTTTGG
G15.11B.B05   ACTAATAGCATTACGAATCTGACATAAGACGCTGGGAAACTTGGAAGCCTGAGGGGCTTTTGTTTGTAGTCGTCCTTGG
G13.2A.A01_   ACTAATAGCATTACGAATCCGACATAAGACGCTGGAAAACT GGAAGCCTGAGGGGCTCTTGTTTGTAGTCGTCCTCGG
G13.3B.B02_   ACTAATAGCATTACGAATCCGACATAAGACGCTGGAAAACTTGGAAGCCTGAGGGGCTTTTGTTTGTAGTCGTCCTTGG
g10.9g.G09_   ACTAATAGCATTACGAATCCGACACAAGACGTTGGAAAATTTGGAAGTCTGAGGGGCTTTTGTTTGTAGTCGTCCTTGG
G7-28         ACTAATAGCATTACGAATCCGACATAAGACGCTGGAAAACTTGGAAGCCTGAGGGGCTTTTGTTTGCAGTCGTCCTTGG

E18
G15.11D.D05   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCAGGTATGACCAGGGAAGAATGGGTGGACACAAATTGATGGTGTTGGG
g10.6h.H06_   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCAGGTATGACCAGGGTAGTATGGGTGGACACTTATTGATGGTGTCGGG
g8.3f.F03_0   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCAGGTATGATTAGGGAAGAATGGGTGGACACAAATTGATGGTGTCGGG
g24.6.A04_0   ACTTCCAGCGGATCGATTCTCTTTCCCGTTGCGGGTATGACCAGGGAGGAGTGGGTGGACACAGGTTGATGGTGTCGGG
g24n.H03_04   ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTGTGACCAGGGAGGAGTGGGTGGACACGGATTGATGGTGTTGGG
g24.6.C04_0   ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGGTTGATGGTGTTGGG
g24.6.E04_0   ACTTCCAGCGGATCGATTCTCTTTCCCGTTGTGGGTATGATCAGGGAGGAATGGGTGGACATAGGTTGATGGTGTCGGG
g24.6.F04_0   ACTTCCAGCGGATCGATTCTCTTTCCTGTCGCGGGCATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTCGGG
g24.6.H04_0   ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTGTGACCAGGGAGGAGTGGGTGGGCACAGATTGATGGTGTTGGG
g24n.B03_04   ACTTCCAGCGGATCGATTCTCTTTCCCGTTGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
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g24.5.F12_0   ACTTCCAGCGGATCGATTCTCTTTCCCGTTGTGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g24.1.A08_0   ACTTCCAGCGGATCGATTCTCTTTCCCGTTGCGGGTATGACCAGGGAGGAATGGGTGGACATAGGTTGATGGTGTTGGG
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g24.1.B08_0 ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGGCCAGGGAGGAGTGGGTGGACACAGATTGATGGTGTTGGG
g24.1.E08_0 ACTTCCAGCGGATCGATTCTCTTTCCCGTTGCGGGTATGACCAGGGAGGGATGGGTGGACACAGATTGATGGTGTCGGG
g24.2.A09_0 ACTTCCAGCGGATCGATTCTCTTTCCCGTCGTGGGTATGACTAGGGAGGAATGGGTGGACACAGATTGATGGTGTCGGG
g24.2.B09_0 ACTTCCAGCGGATCGATTCTCTTTCCCGTAGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTCGGG
g24.2.D09_0 ACTTCCAGCGGATCGATTCTTTTTCCCGTCGCGGGTGTGACCAGGGAGGAGTGGGTGGACACAGATTGATGGTGTTGGG
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g21.10.H05_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGGCCAGGGAGGAATGGGTGGATACAGATTGATGGTGTCGGG
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g21.11.E06_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGTGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
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g21.11.G06_ ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAACGGGTGGACACAGGTTGATGGTGTCGGG
g21.11.H06_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGGTTGATGGTGTTGGG
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g21.12.E07_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g21.12.F07_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAAGGATGGGTGGACATAAATTGATGGTGTTGGG
g21(5s).9.G ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAAGAATGGGTGGACACAGGTTGATGGTGTCGGG
g21(5s).8.D ATTCCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTGTGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g21(5s).8.E GCTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACATAGATTGATGGTGTTGGG
g21(5s).8.G ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACATAAATTGATGGTGTTGGG
g21(5s).9.C ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACATAGATTGATGGTGTTGGG
g21(5s).9.D ACTTCCAGCGGATCGATTCTCTTTCTCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACGCAGATTGATGGTGTCGGG
g21(5s).9.E ACTTCCAGCGGATCGATTCTCTTTCCCGTTGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g21.7h.H01_ ATTTCCAGCGGATCGATTCTTTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g21.7g.G01_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGCGGACACAGATTGATGGTGTTGGG
g21.7a.A01_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g21.7b.B01_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAGTGGGTGGACACAGATTGATGGTGTCGGG
g21.7d.D01_ ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAGTGGGTGGACGCAGATTGATGGTGTCGGG
g21(5s).8.A ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGGTTGATGGTGTTGGG
g21(5s).8.H ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAAGAATGGGTGGACATAAGTTGATGGTGTTGGG
g18(5s).5.H ATTTCCAGCGGATCGATTCTATAACCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGATACAGATTGATGGTGTTGGG
g18(5s).5.G ATTTCCAGCGGATCGATTCTCTTTCCCGTCGTGGGTATGACTAGGGAGGAATGGGTGGGCATAAATTGATGGTGTTGGG
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g18.H01_040 ATTTCCAGCGGATCGATTCTCTTTCCCGTCGTGGGTATGACCAGGGAGGAATGGGTGGACACAAATTGATGGTGTCGGG
g18(5s).2.C ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTCGGG
g18(5s).2.E ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCAGGTATGACTAGGGGAGAATGGGTGGACATAGATTGATGGTGTTGGG
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g18(5s).5.C ATTTCCAGCGGATCGATTCTCTTTCCCGTTGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTCGGG
g18(5s).5.D ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGATCAGGGAGGAATGGGTGGACATAAATTGATGGTGTTGGG

F

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g18(5s).3.D   ATTTCCAGCGGATCGATTCTCTTTCCTGTTGTAGGTATGATCAGGGAAGAATGGGTGGACATAAATTGATGGTGTCGGG
g18(5s).5.A   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g18(5s).2.F   ACTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACTAGGGAGGAATGGGTGGACACAGGTTGATGGTGTTGGG
g18(5s).3.E   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAAGAATGGGTGGACACAAATTGATGGTGTTGGG
g18(5s).4.B   ACTTCCAGCGGATCGATTCTCTATCCCGTCGCAGGTATGACCAGGGAAGAATGGGTGAACACAAATTGATGGTGTCGGG
g18(5s).4.C   ATTTCCAGCGGATCGATTCTCTTTCTAGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g18.E01_040   ACTTCCAGCGGATGCATTCTCTTTCCCGTCGCGGGTATGATCAGGGAGGAATGGGTGGAGACAAATTGATGGTGTCGGG
g18.6redo.H   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g18.F01_040   ACTTCCAGCGGATCGATTCTCTTTCCTGTTGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g18.6redo.D   ATTTCCAGCGGATCGATTCTCTTTCTTGTCGTGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTTGGG
g18n.E01_04   ATTTCCAGCGGATCGATTCTCTTTCCCGTCGCGGGTATGACCAGGGAGGAATGGGTGGACACAGATTGATGGTGTCGGG
G15-1         ATTTCCAGCGGATCGATTCTCTTTCCCGTCGTAGGTATGACCAGGGAAGAATAGGTGGACATAAATTGATGGTGTCGGG
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E19
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E20
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g8.2d.D02_0   GCACTCTCAGTGAGCCGAGTCTCTCTCAGGGATGTCCTGTATCTTGTTGAGTAGTGTGCATTTCTGGCGGTCGGTTTGG
g8.1f.F01_0   GCACTCTCAGTGAGCCGAGTCTCTCTCAGGGATGTCCTGTATCTTGTTGAGTAGTGTGCATTTCTGGCGGTCGGTTTGG

E21
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g8.1c.C01_0   ATGTCAGCAGACACGATATCTGTCGCCTTGTGTATGGTTAACTATAACCTGAGTATGTGGTTTGGTTTCGTCTTCGGGGG
G7-26         ATGTCAGCAGACACGATATCTGTCGCCTCGTGCATGGTAAACTATAACCTGAGTATGTGGTTTGGTTTCGTCTTCGGGGG

E22
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E23
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g10.11b.B11   ACTGCCAGCGGCGCGATTCACTGTCGGAGACTAGTTGCTGCTTTCGGCTTGGAAGGATAAAACTTTTGTCATAGCGTGGG
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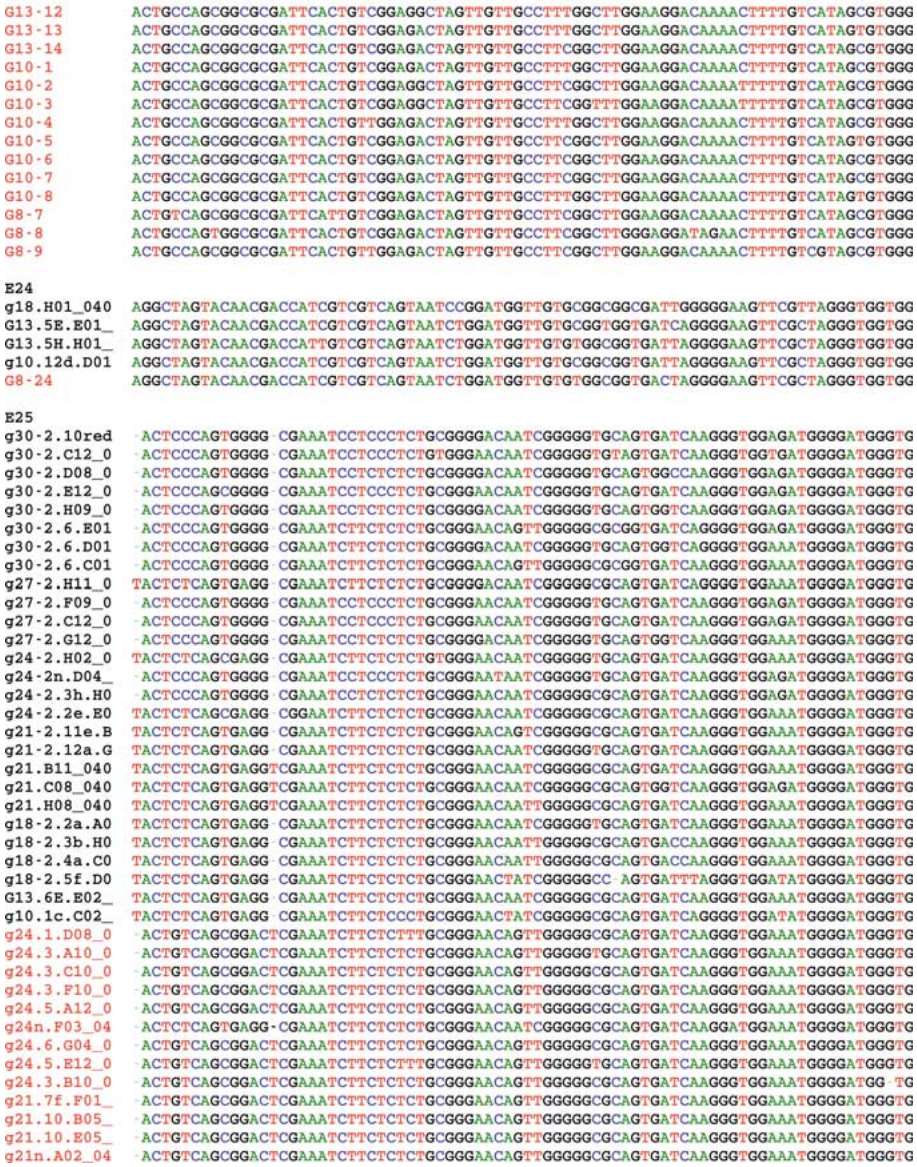
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E43
G15.9F.F04_     ACTATCAGCGATACGAAGACTATGCTCCTATGCTATGCCTGACATTAATGGGGTTAGTCCCCATGTTGGGCGGGTTGG
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E44
G13.6B.B02_     ATTTATAGTATTACGAGTCTCTGATAATTGGATAGGTTCCAGTATATCAGTAAGGGTAGTGCGGCTAGTCTGGTTCTGGG
G8-16           ATTAATAGCATTACGAGTCTCTGATAATTGGATAGGTTCCAGTATATCAGTAAGGGTAGTGCGGTTAGTTTGGTTCTTGG
G8-17           ATTAATAGCATTACGAGTCTCTGATAATTGGATAGGTCCCAGTGTATCAGTAAGGGTAGTGCGGCTAGTCTGGTTCTTGG

E45
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E46
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G10-21          ACTATCAGCGATGCGAATTCTCATACAGCATGTGTTTACTCCGAGGTAGGTGCATGGGTTGAAGATCGCTAGTCCCGTGG
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E47
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E48
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E49
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E50
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E51
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g27-2.B09_0     TGGAGGAGACGGCGGCTTGGGGGTGTGGACCACCGGGCCTACGATGGGGTTATCTAGGATGGATAGGGTTTGGATGG
g27-2.E09_0     TGGAGGAGACGGCGGCTTGGGGGTGTGGACCACCGGGCCTACGATGGGGTTATCTAGGATGGATAGGGTTTGGATGG
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g27-2n.F05_     TGGAGGAGATGGCGGCTTGGGGGTGTGGACCACCGGGCCTACGATGGGGTTATCTAGGATGGATAGGGTTTGGATGG
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E52
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g24-2.2b.B0   CAGGCAGGGTCGAGGTGGGATCGGACGATGTATTGTAACGGCACTCTCAGTGAGGCGGGTCGCTCTCCGTGGTTGGG
g24-2n.B04_   CAGGCAGGGTCGAGGTAGGATCGGACGATGTATTGTAACGGCACTCTCAGTGAGGCGGGTCGCTCTCCGTGGTTGGG
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E53
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g27-2.B12_0   ATTGCCAGCGGCGCGAATCGACTCTGGGCGGATCCGGTCACCGGACCAAGGACGGAGGATTTGGGAGGTCTAGTTTAGG
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g27-2.A12_0   ACAGCCAGCGGCGCGAATCGACTCTAGGCGGATCCGGTCACCGGACCAAGGATGGAGGATTCGGGAGGTCTAGTTTAGG
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E54
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g24-2.4a.A0   GGAGGGGACGGAGGGTGGGGGGCGTATTGCACTCTTAGCGAGCCGAAATCTCGGGAGGCTGGGTTTGTGTTTTGTGGG
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E55
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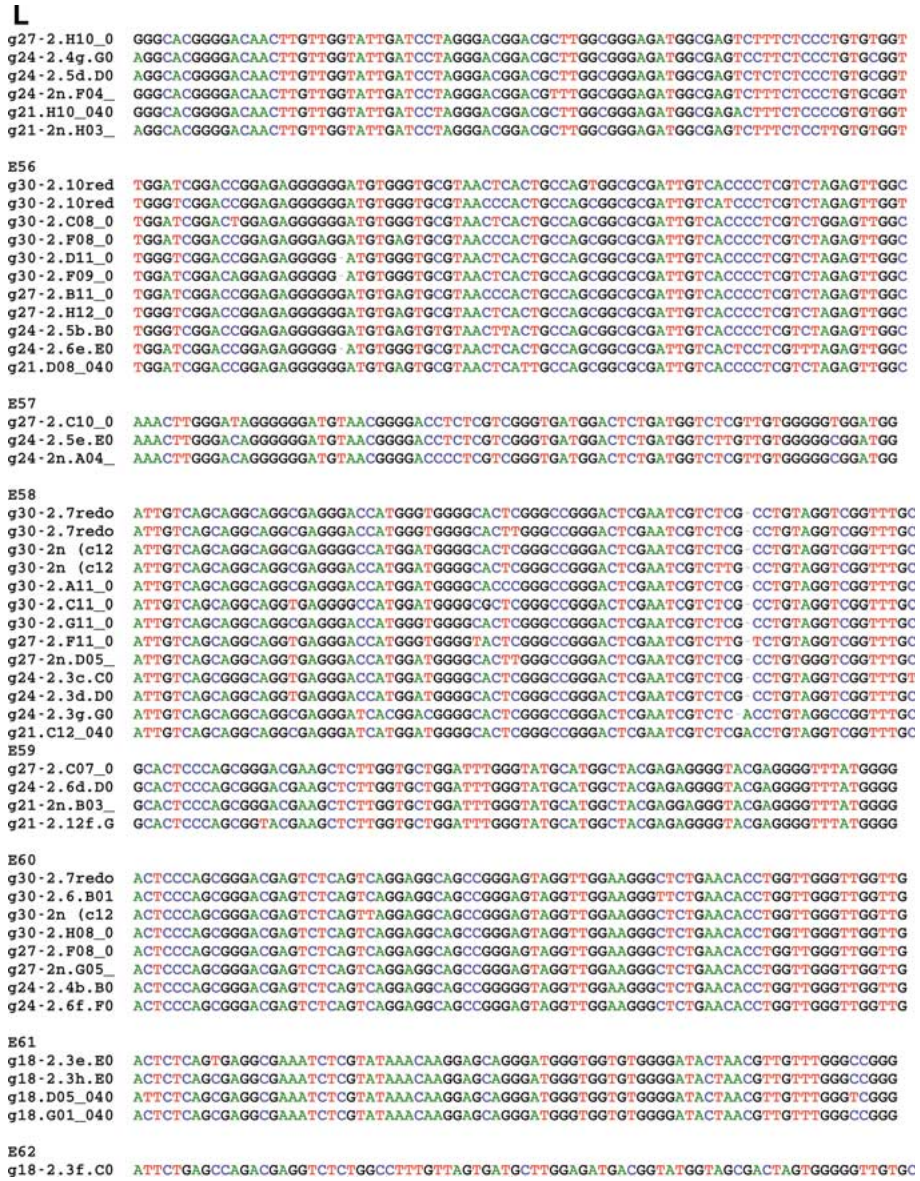
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g24-2.4b.B0 ACTCCCAGCGGGACGAGTCTCAGTCAGGAGGCAGCCGGGGGTAGGTTGGAAGGGCTCTGAACACCTGGTTGGGTTGGTTG
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E65
g18-2.5b.A0  ATAGCTAGCAGCACGAATCAACTCTGAGGCATGATGGTCGGTGGTGGCTAGTAGGAACTAAGTTCGTTACGAGGTCGTGG
g18.B01_040  ACTACTAGCAGGACGAATCAACTCTGAGGCATGATGGTTGGTGGTGGCCCGTAGGAGCTAAGCTCGTAACGGGGTTGTGG

E66
g24-2.2h.H0  ACTATCAGCCGATCCGAATCCCCCATGACCAAACGGTGCGGTCGTTGGTGGTGGGGTAGACCTCCTCTGGTACTCTGGTG
g21-2n.E03_  ACTATCAGCCGATCCGAATCCCCCACGATCAAACGGTGCGGTCGTTGGTGGTGGGGTAGACCTCCTCTGGTACTCTGGTG
g18-2.5g.A0  ACTATCAGCCGATCCGAATCCCCCATGACCAAACGGTGTGGTCGTTGGTGGTGGGGCAGATCTCCTTTGGTATTTTGGTG

E67
g21-2.11a.F  ATTCCCAGCGGGTCGAGTCTTCGGGGGGTTAGGAGGGAGTCGCAAGCGTTGTGCGACGGTAGCCGTCTGTCTAGGCCGG
g21.G12_040  ATTCCCAGCGGGTCGAGTCTTCGGGGGGTTAGGAGGGAGTCGCAAGCGTTGTGCGACGGTAACCGTCTGTCTAGGCCGG
g21.F07_040  ATTCCCAGCGGGTCTAGTCTTCGGGGGGTTAGGAGGGAGTCGCAAGCGTTGTGCGACGGTAGCCGTCTGTCTAGGCCGG
g21-2n.G03_  ATTCCCAGCGGGTCGAGTCTTCGGGGG-TTAGGAGGGAGTCGCAAGCGCTGTGCGACGGTAGCCGTCTGTCTAGGCCGG

E68
g24-2.2d.D0  ACTTCCAGCGGAACGAATTTCTGACCTCGGTGGGTTGTTAAGGCTGGCTTCTGGTGAGTCCGGGTGTGCCAGCCGTTGTG
g21.F08_040  ACTTCCAGCGGAACGAATCTCTGACCCTGGTGGGCTGTTAAGGCTGGCTTCTGGTGAGTCCAGGTGCGCCAGCCGTTGTG

E69
g24-2.5f.F0  ACTCCTAGCATG-GACGATTCGAATCTCCTCCTGAGGGCAAAGGGTTTCGTCTGGGCACGGCGTCAGCCTGTGGTGGGG
g24-2.4c.C0  ACTCCTAGCATG-GACGATTCGAATCTCCTCCTGAGGGCAAAGGGTTTCGTCTGGGCACGGCGTCAGCCTGTGGTGGGG
g21-2.9g.D0  ACTCCTAGCATGTGACGATTCGAATCTCCTCCTGAGGGCAAAGGGTTTCGTCTGGGCACGGCGT-AGCCTGTGGTGGGG

E70
g30-2n (c12  AC-TCCTAGCTAGGACGAATCGATCTCTGTGGTTGGGGCTACCTCTGAGGCGCTGCCGATCCGGGATGGGGCAGTGTGGG
g24-2.6c.C0  AT-TCCTAGCTAGGACGAATCAATCTCTGTGGTCGGGGCTACCTCTGGGGCGCTGTCGATTCGGAGTGGGGCAGTGTGGG
g24-2n.C04_  AT-TCCTAGCTAGGACGAATCAATCTCTGTGGTCGGGGCTACCTCTGGGGCGTTGTCGATCCGGAGTGGGGCAGTGTGGG
g24-2.A02_0  ATGTCCTAGCTAGGACGAATCAATCTCTGTGGTCGGGGTTACCTCTGGGGCGTTGTCGATCCGGAGTGGGGCAGTGTGGG
E71
g18.D04_040  ACTGTGAGCTCACACTATTCTTATTGAGTCAGGCGGGGGACCCGGGGAAGGTGCTCGGAGAGTAGTAGCTGGGTGTTG
G13-40       ACTGTGAGCTCACACGATTCTTATTGAGTCAGGCGGGGGCCCGGGGAAGGTGCTCGGAGAGTAGTAGCTGGGTGTTG

E72
g24-2.G02_0  TGGTTTGGCCTGCGGGTGGTAGGTGGAAATCGAGTTTCGGTACCGCACTGCCAGCGGCGCGAGCTCTGAGTGGGTCTTGG
g24-2n.H04_  TGGTTTGGCCTGCGGGTGGTAGGTGGAAATCGAGTTTCGGTAACGCACTGCCAGCGGCGCGAGCTCTGAATGGGTCTTGG

E73
g30-2.G08_0  TGATGAGTAGGATAAGGTGCGCACTGCCAGCGGCGCGATGTCTCGGTACTGTGACTGCTGGCTAGGTACGGGGTGGGAGG
g30-2.7redo  TGATGAGTAGGGTAAGATGTGCACTGCCAGCGGCGCGATGTCTCGGTACTGTGACTGCTGGCTAGGTACGGGGTGGGAGG
g24-2.4e.E0  TGATGAGTAGGGTAAGGTGTGCACTGCCAGCGGCGCGATGTCTCGGTACTGTGATTGTTGGCTAGGTACGGGGTGGGAGG

E74
G13.6F.F02_  ACCTCAATAGCAGCGCTAACAAAAAGTTTCGAGAAAGCGAATCACCTAACAGTGGTGACTCCATTGGCCTTTTGGGTGGG
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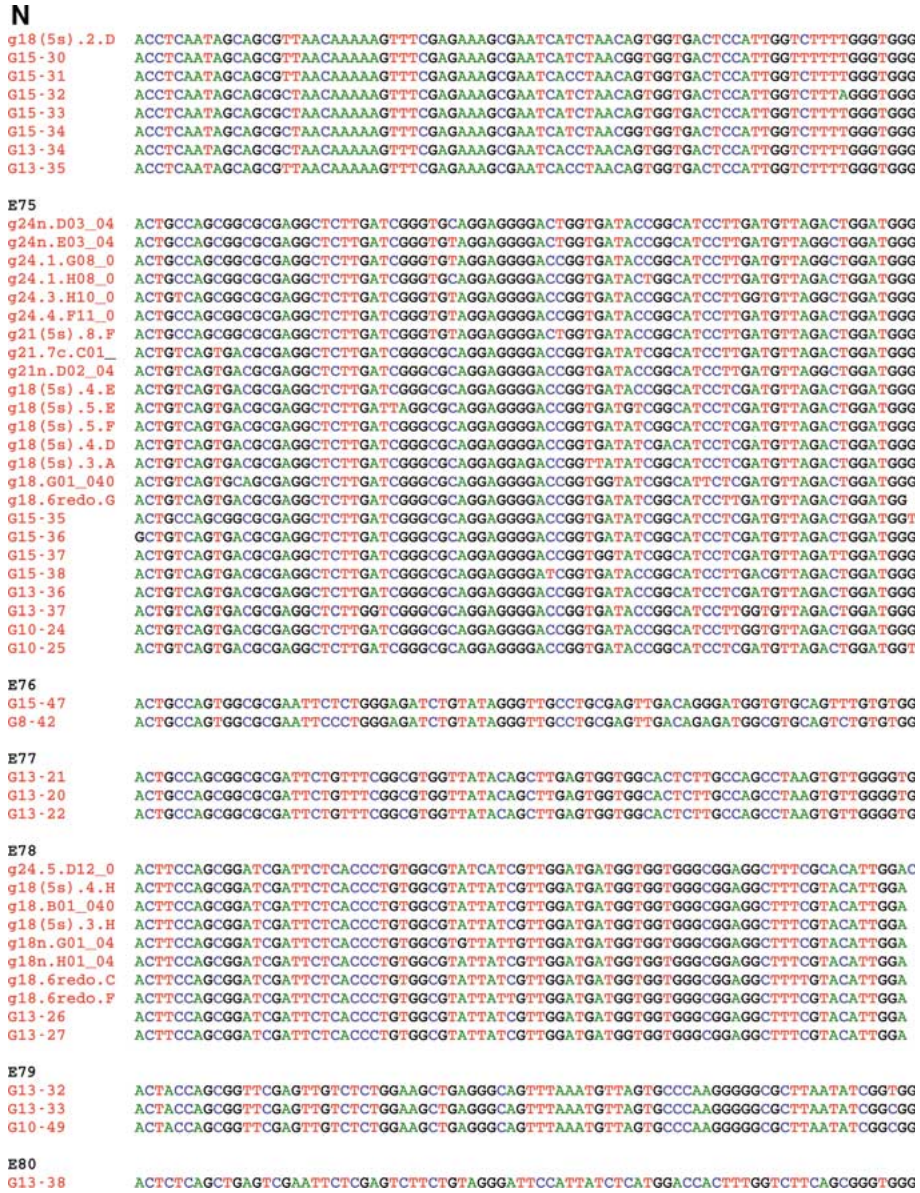
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G15-30 ACCTCAATAGCAGCGTTAACAAAAAGTTTCGAGAAAGCGAATCATCTAACGGTGGTGACTCCATTGGTTTTTTGGGTGGG
G15-31 ACCTCAATAGCAGCGTTAACAAAAAGTTTCGAGAAAGCGAATCACCTAACAGTGGTGACTCCATTGGTCTTTTGGGTGGG
G15-32 ACCTCAATAGCAGCGCTAACAAAAAGTTTCGAGAAAGCGAATCATCTAACAGTGGTGACTCCATTGGTCTTTAGGGTGGG
G15-33 ACCTCAATAGCAGCGCTAACAAAAAGTTTCGAGAAAGCGAATCATCTAACAGTGGTGACTCCATTGGTCTTTTGGGTGGG
G15-34 ACCTCAATAGCAGCGCTAACAAAAAGTTTCGAGAAAGCGAATCATCTAACGGTGGTGACTCCATTGGTCTTTTGGGTGGG
G13-34 ACCTCAATAGCAGCGCTAACAAAAAGTTTCGAGAAAGCGAATCACCTAACAGTGGTGACTCCATTGGTCTTTTGGGTGGG
G13-35 ACCTCAATAGCAGCGTTAACAAAAAGTTTCGAGAAAGCGAATCACCTAACAGTGGTGACTCCATTGGTCTTTTGGGTGGG
E75
g24n.D03_04 ACTGCCAGCGGCGCGAGGCTCTTGATCGGGTGCAGGAGGGGACTGGTGATACCGGCATCCTTGATGTTAGACTGGATGGG
g24n.E03_04 ACTGCCAGCGGCGCGAGGCTCTTGATCGGGTGTAGGAGGGGACTGGTGATACCGGCATCCTTGATGTTAGGCTGGATGGG
g24.1.G08_0 ACTGCCAGCGGCGCGAGGCTCTTGATCGGGTGTAGGAGGGGACCGGTGATACCGGCATCCTTGATGTTAGGCTGGATGGG
g24.1.H08_0 ACTGCCAGCGGCGCGAGGCTCTTGATCGGGTGCAGGAGGGGACCGGTGATACTGGCATCCTTGATGTTAGACTGGATGGG
g24.3.H10_0 ACTGTCAGCGGCGCGAGGCTCTTGATCGGGTGTAGGAGGGGACCGGTGATACCGGCATCCTTGGTGTTAGGCTGGATGGG
g24.4.F11_0 ACTGCCAGCGGCGCGAGGCTCTTGATCGGGTGTAGGAGGGGACCGGTGATACCGGCATCCTTGATGTTAGACTGGATGGG
g21(5s).8.F ACTGCCAGCGGCGCGAGGCTCTTGATCGGGTGTAGGAGGGGACTGGTGATACCGGCATCCTTGATGTTAGACTGGATGGG
g21.7c.C01_ ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATATCGGCATCCTTGATGTTAGACTGGATGGG
g21n.D02_04 ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATACCGGCATCCTTGATGTTAGGCTGGATGGG
g18(5s).4.E ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATACCGGCATCCTCGATGTTAGACTGGATGGG
g18(5s).5.E ACTGTCAGTGACGCGAGGCTCTTGATTAGGCGCAGGAGGGGACCGGTGATGTCGGCATCCTCGATGTTAGACTGGATGGG
g18(5s).5.F ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATATCGGCATCCTCGATGTTAGACTGGATGGG
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g18.G01_040 ACTGTCAGTGCAGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGGTATCGGCATTCTCGATGTTAGACTGGATGGG
g18.6redo.G ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATATCGGCATCCTTGATGTTAGACTGGATGG
G15-35 ACTGCCAGCGGCGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATATCGGCATCCTCGATGTTAGACTGGATGGT
G15-36 GCTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATATCGGCATCCTCGATGTTAGACTGGATGGG
G15-37 ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGGTATCGGCATCCTCGATGTTAGATTGGATGGG
G15-38 ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGATCGGTGATACCGGCATCCTTGACGTTAGACTGGATGGG
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G10-24 ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATACCGGCATCCTTGGTGTTAGACTGGATGGG
G10-25 ACTGTCAGTGACGCGAGGCTCTTGATCGGGCGCAGGAGGGGACCGGTGATACCGGCATCCTCGATGTTAGACTGGATGGT
E76
G15-47 ACTGCCAGTGGCGCGAATTCTCTGGGAGATCTGTATAGGGTTGCCTGCGAGTTGACAGGGATGGTGTGCAGTTTGTGTGG
G8-42 ACTGCCAGTGGCGCGAATTCCCTGGGAGATCTGTATAGGGTTGCCTGCGAGTTGACAGAGATGGCGTGCAGTCTGTGTGG
E77
G13-21 ACTGCCAGCGGCGCGATTCTGTTTCGGCGTGGTTATACAGCTTGAGTGGTGGCACTCTTGCCAGCCTAAGTGTTGGGGTG
G13-20 ACTGCCAGCGGCGCGATTCTGTTTCGGCGTGGTTATACAGCTTGAGTGGTGGCACTCTTGCCAGCCTAAGTGTTGGGGTG
G13-22 ACTGCCAGCGGCGCGATTCTGTTTCGGCGTGGTTATACAGCTTGAGTGGTGGCACTCTTGCCAGCCTAAGTGTTGGGGTG
E78
g24.5.D12_0 ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATCATCGTTGGATGATGGTGGTGGGCGGAGGCTTTCGCACATTGGAC
g18(5s).4.H ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATCGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
g18.B01_040 ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATCGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
g18(5s).3.H ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATCGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
g18n.G01_04 ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTGTTATTGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
g18n.H01_04 ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATCGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
g18.6redo.C ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATCGTTGGATGATGGTGGTGGGCGGAGGCTTTTGTACATTGGA
g18.6redo.F ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATTGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
G13-26 ACTTCCAGCGGATCGATTCTCACCCTGTGGCGTATTATCGTTGGATGATGGTGGTGGGCGGAGGCTTTCGTACATTGGA
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E79
G13-32 ACTACCAGCGGTTCGAGTTGTCTCTGGAAGCTGAGGGCAGTTTAAATGTTAGTGCCCAAGGGGGCGCTTAATATCGGTGG
G13-33 ACTACCAGCGGTTCGAGTTGTCTCTGGAAGCTGAGGGCAGTTTAAATGTTAGTGCCCAAGGGGGCGCTTAATATCGGCGG
G10-49 ACTACCAGCGGTTCGAGTTGTCTCTGGAAGCTGAGGGCAGTTTAAATGTTAGTGCCCAAGGGGGCGCTTAATATCGGCGG
E80
G13-38 ACTCTCAGCTGAGTCGAATTCTCGAGTCTTCTGTAGGGATTCCATTATCTCATGGACCACTTTGGTCTTCAGCGGGTGGG

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G7-11          ACTCTCAGCTGAGTCGAATTCTCGAGTCTTCTGTAGGGATTCTATTATTTCATGGACCATTTTGGTCTTCAGCGGGTGGG

E81
G13-42         ACTCTCAGTGAGTCGAATCTCTAGGCCAGGCAGCGGGAGAATGTTTACGCAGAGTTGCTCTGGGGGTTAAGGTTGTGCGG
G10-41         ACTCTCAGTGAGTCGAATCTCTTGGTCAGGCAGCGGGAGAATGTTTACGCAGAGTTGCTCTGGGGGCTAAGGTTGTGTGG

E82
g18(5s).3.F    ACTTCCAGCGGATCGATTCATGGTTCTGAGGGCTATGTTAGGTAGGGAGGCTAGGTTAGATCGTGGATCGGTATGGGGGG
G13-44         ACTTCCAGTGGATCGATTCATGGTTCTGAGGGCTATGTTAGGTAGGGAGGCTAGGTTAGATCGTGGATCGGTATGGGGGG

E83
G13-48         ACGTCTGAGCCCAGTCGAGTCTCTCTAAGCGCATACAAGGGTCACGGTAGTGGTCGACAAGCTGTCCTGTAGCGTGGTGG
G10-22         ACGTCTGAGCCCAGCCGAGTCTCTCTAAGCGCATACAAGGATCACGGTAGTGGTCGACAGGCTGTCCTGTAGCGTGGTGG
G10-23         ACGTCTGAGCTCAGCCGAGTCTCTCTAAGCGCATACAAGGATCACGGTAGTGGTCGACAAGCTGTCCTGTAGTGTGGTGG
G8-46          ACGTCTGAGCCCAGTCGAGTCTCTCTAAGCGCATACAAGGATCACGGTAGTGGTCGACAAGCTGTCCTGTAGCGTGGTGG

E84
G10-32         AGCTAAGATAGCTAGAACGCGGCACTCTCAGCGAGACGATTCTACTTTCACATTTGCAGGGTTGGCTGCATTGGGCTGGG
G7-38          AGCTAAGATAGCTAGAATGCGGCACTCTCAGCGAGACGATTCTACTTTCATATCTGCAGGGTCGGCTGCATTGGGCTGGG

E85
g24n.A03_04    ACCTAAAATAGCCCGGTTGGTGTGACTTGAGGATTAAGCGAATCGCTGTCCTGGTCTAGGGAATGTGTCCGCGGTGTTGG
g18(5s).2.A    ACCTCAAATAGCCCGGCTGGTGTGACTCGAGGATTAAGCGAATCGCTGTCCTGGTCTAGGGAATGTGTCTGTGGTGTTGG
G8-10          ACCTGAAATAGCCCGGCTGGTGTGACTTGAGGATTAAGCGAATCGTTGTCCTGGTCTAGGGAATGTGTCCGTGGCGTTGG
G8-11          ACCTGAAATAGCCCGGCTGGTGTGACTCGAGGATCAAGCGAATCGCTGTCCTGGTCTAGGGAATGTGTCCGTGGTGTTGG

E86
G8-20          TCTGCCAGCCGGCGCGATTCTTAACTTCACGTACGTTGAGGGTGAGGCATGTTGGGACTGGCGGAGGGCAGTCTCCAGGG
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E87
G8-38          ATTCTTAGCAAGACGATTCTGTCTTCGGGGCGTGGGTTTTTGTGCTGTGCGTATGAATGCTGTGAACGTCGTGTTGTGGG
G7-3           ATTCTTAGCAAGACGATTCTGTCTTCGGGGTGTGGGTTTTTGTGCTGTGCGTATGAGTGCTGTGAACGTCGTGTTGTGGG
G7-4           ATTCTTAGCAAGACGATTCTGTCTTCGGGGCGTGGGTTTTTGTGCTGTGCGTATGAATGCTGTGAACGTCGTGTTGCGGG

Selection A (single clone classes)
g24.2.C09_0    ACTTCCAGCGGATCGAAATCTCTCTTTGCAGCTGGACTCGGAGGCCTGCTTCCACCAGTAGGGGGGTTTGTTCAGGGTGG
g24.4.B11_0    ACTGCCAGCGGCGCGATTCTCGGTCAACCTCCTCTGTGCTAGTGGCCGGCTGTGGAATGGGGGTGGGTGGTCCTGTGTG
g18(5s).4.F    ACTGTCAGCGGACTCGAAATCTTTCAACTCTGGTGAGTCTCATGGTAATGTTTCTGGTTCGGTACCAAATAGACGCTGGG
g18(5s).2.G    ACTGTTAGCAACTCGATTTGATCTTCTCGACGGTCGTGATGTGGGCAGGCAGTGGTTTAGACTTGGGGAGGCCCCGTGTG
G13-41         ACTGTACAGCCGACACGAATCTAAGGAATCTGGCTAGGAGCTCCTTCAGTGACGTGTGAGAAGGCACACTTGTTTGGGGA
G13-43         ATTACGAGCCGTTCGATTCTCAATACGATGAAATCGTTTCCGAATTCGGAGGCATGGGGATCCGCGGTTGTAGCAGGGGG
G13-50         CTGGTAGATTCGGTTTGGGTAAGTTCCTCGACCGCATTGTCAGCGACTTGAAATCAGAATCTTCTGTTGTGGTGTTGCGG
G10-30         ACTTCCAGCGGAACGATTCTTCCCCGCGAGTCCGAAGAATGGTGTACAGCCTATATGTTCGTAGTGATAGTTGGGGTGGT
G10-33         ATTGCCAGCGTGCGCGAGTTTGCTCGACTTATGCTCGTGGTTTCCCTACGATGTTTGGCGCGGCATATCTTCTGAGGTGG
G10-34         ACTGCCAGCGGGCGCGATTCTCATTGGTCGAGGAGATCCTGTACGGATTTAGGGGGTTCGGCCAACATCGCATGTCTTGG
G10-36         ACTCCCAGCGGGACGAGTCTCAGATTGGCATTGTGATGCTGCTATTCAAGAGAGGTGGTGTGTAATCCGGCGGTAGTTGG
G10-38         ACTGTCAGCTGACACGAGTTCGGCTCCAACCTTGGTCAGTGTTTGAGAATCATTTGTTGGGGTTTATCCGACACCATGGG
G10-39         ATTAGCAGCGGTGCGAGTCTCATGTGATGTCAGAGTTTGTGCGCATGCCCAGTTTCGCAGCTAGTGGTCGTGTTGTGGGC
G10-40         ACTTGTAGCATCAACGAGTCTTTCTCAGGTCAGTCGGTTGGCCTCCGTGGGGAATGGTGAGATTTGTAGGGGCGTGTTGG
G10-43         TTTGCCCGATGCTCGGTGCATCGGTCCTAGTAGGGCGATTCTCGGCTCCCCAGCTTTATGAGCTTTCTGCGATGTGTGGG
G10-45         ACTGCGAGCCGCGCGAAAAGTAACAACGGCTCTGTCTACTATGTTTGAAGGTGGGTCTGGTGTTACCTCCTGGTTGTGGG
G10-46         ACTGCCAGCGAGCGCGAAATCTCCCGATTGAGGTCGTGTAGTGTAGAGGTTAGGGAAAAAGAACTTTTGTGGGGGTTGGG
G10-47         ACTGCCAGCGGCGCGATTTGGCTCTACCGTTCATTCGGCTGTGTTGCCCTAGGTAGGGTTCAGCAGTGATTTTGGTGGGG
G10-48         ATTGTCAGCGACACGAATCCCGAGTCTGGGGGGTTTTCAGCGGCTGTATCCGATAGCGGTTAGCGTAAATACCCATATGG
G8-26          ATTCCCAGTGGGTCGAGTCCTTCTTCTCTGCAGCGTGTGGGTGTGATTCCGACGACACATGCGTAGGCTATATACGTTGG
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G8-37          ATTCCCAGTGGGGCGATTCTCCAAGGCCTCTGGATGCTCTTCGCTCCAGGCGAATATACTGGTAAGTTGCTAATGGGTGG
G8-41          ACTAGCAGCGGTACGAGGTCTCTTTAGTTCTGTCCTAGGGTAGGTCAAGCTCTGCTTAGGGGTGGAAGTCCTGCCTCGGG
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G8-44       GGTAGCTCTTCGGATGAAGAAGGGCCCTAGCATGATGTGCTTGAAGCGGCATGTGAGCCACACGATATCTCTCGAGCTGG
G8-45       GCTCTAAGCTAGACGATTCTACTCTGCTTGGTCGGTCACGATCGGTAACGCGTGAGTTGTTAGGGTTGCGCATGTTGGG
G8-47       ATTATCAGCGATACGAATTCTCTTTGTGCTATCGAAAAGGAATCTGATCACATTTTTGGAAGGTCGTCGTCGGGAGTGGG
G8-48       TGAGGAACCCTGCATTAGGCGTTGTCTTATGTCTCGCAATGCCAGCGGCTCGAATCTCGTTTGCTGTGTCGTTCATGGGG
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G7-7         ATTACGAGCCGTACGAGTCTCTCTTAAGGTGTGTTGCTCGTATGTCATCTAGCTGTGCGCGGGGGGGTGGTCGAGTGTGG
G7-9         ATTACCAGCGGTTCGAAATTGATCTGTCGGTCTTAGTTCGGTGGGCTGTCGGGCCGCGTATCCGGTGCTACTCATGGGGG
G7-10        ACTGTCAGCGACTCGAAATCTAATCAATCTCATCGGGGCCGGCGTGGTAGCATACACGACTGTTAGAGCCATTGTGCTGG
G7-12        ATTGTGAGCCACTCGAATCGTTTCTCCAATGGTATGAATGTTGTACAAACTCGGATGGTCGTGTACGTGCTTCGTGGG
G7-14        ATACCGACCGTGAGGGCATCTCGTTTCTGGTCTTTGGGCACAGGGTCGTACCGGTATGATACATTAGATCGGTTCGGGG
G7-16        ACTGCCAGCGGCGCGAACTTACCCTCATTGGTGCAGTAATAAGAGCAGATGTTGCGTTGTTCGGGAACGTAATGACGGTGG
G7-17        AACTCCGAGCCGGTCGAGTCGGCCGGTACCTGGATCGTTGGGGATGGCGGGGCTATTAGAGCGCGTTGCCTGGGTGTTGGTGG
G7-18        CGACCGTGAGGGCTTCTCGTCTGAGTTGGATAGGAGTAATATATAGTGTAAAGTGCGGATGTGTATGCGCTAGCCGGTGG
G7-20        ATTTCCAGCGGATCGAATTGTCATCTCATGAGCGTAGGGAGGTCTATTGTTGGGGGGCAGTGTATGATAGCAGGTGAG
G7-22        TGAGTATTGTTGCAAGTTCAGGTAGCTTTGTAATGATGTATGTTGCATTGCCAGCGGCACGATTCATGGCCCTCTGTGTG
G7-23        ATCCTAAGCTTAGACGAGTCTTTTTCGGGCACCTTGTGAACCTGTCAGGTAAGCACTATTCTGGCACGGGCGGTTGGTGG
G7-24        ACTATCAGCGATACGAAGCTCTTTGGCGAAGCGATAGATCCTAGGAGAGGGGGGACGCTGGTACTTTGGCGGTGTTAGG
G7-25        CGACCGAGAGGGCATCTCTTCTTCGGATGTTTGAACATCTTATCTAGATTGAGAGTTGCGCGGGTTGGTCCACCTCTAGG
G7-27        AGTTTGCGAACTGGGAACCTCGAGTCACTGACAGCGGCGGCGATTCTTTCTCCGTTAGGGGAGGGGTTTATGCGTGGGGG
G7-29        ATTCTCAGCGAGACGGCATTTTGTCCCTGCTATGCAGTCTGTTCGTGTCAACGGAGGATTAAGGCTGCCTCAGGTGTTGG
G7-30        GTGGGGTGTTGGTAGGTAAACGCACGGACAGCTGCCACGATATCTTTGCTCGTTTGTTTAAGTTATAACGTTTCCAGGGG
G7-31        ACTATTAGCATATACGAGTCTCTGTAGGGTCTGTCCGTAGAGTCGGCCTAGCGGGTTCGGTGTTTATGATCGGTGTGTGG
G7-32        ATTTTCAGCGAAACGAATTTTTTCTCGATGGCTGAATGTTGGGGGTGGTGTGGGGATGATACTTTTGGCAGGACTGTGG
G7-33        GAGTGTTGATTAAGGGTAGTGGTACATACGCACTTGCAGCGGCAACGAGTCTATCCTCCGTTCACGGCGTCCCTGTTGGG
G7-35        TGGCGGAGGGCAGCATTAGGTTTTGGATGTTGTCCGGGGTCATCTTCGATGGGAAGGCCACCTGGCAGTTGTAGTTGG
G7-36        ACTCCCAGCGGGACGATTCTATTCATCAGTAAGTCCCTTAGTCAAGTGGGTCCAAGCGGGACGCGATGCATTTAGGTGG
G7-40        ATTTTCAGCTGAAACGAGTGTCTCGCCGCTGTTCGTGGGGTGCGGTGGGCTCCGAGCACAGACTATTTTTCACCTGGG
G7-41        ACTACTAGCATGTGCGATTCTGGCTCCTGTTCAGGATCCGAGCGGGTGGTGCAAGAGCCAATTGGATAATAATGTGTGGG
G7-43        TCGACCTCGTGATCAGCAGCAGATTTAACGTACTCCCAGCGGGACGGGTCGCTCTCCCTATAGTTGTGGCTGGCGTGTGG
G7-44        ACTAGCAGCGGTGCGAAATCGCTTTCAACCAACGGCTGGATGTTTCGAGCGTTGTCGCGCGCATGGAACATTGACATTGG
G7-45        ATTCTCAGCGAGTCGAATCTGTCTTGCTGGGGTTGGCGGGATTCGTTGATTACCTCGGATAGGTCCTTTGCGTCTAGTGG
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Selection B (single clone classes)
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g24-2.2c.C0  ACTCCTAGCAGGGCGAATCTTTTACCCATAACACCCGGTACCAAGGCGTTGGCCTGGGCAGGTGGGTGGCTGGTTGTGGT
g21.F11_040  ATTAAGAGCCTTTGCTGAGTTGACTCCGAGTCTTCCGCGGGTGTGGTTGGAAGCAGCTGCGATCAAGCTTGGGATTGGG
g21-2.11d.C  ATTGCCAGCCGGCGCGAATCGGGATTTTGAGAGGCTAGTTCTCGGGGTCAGCACATGATGGACGTGAGGAGTTTGCATGC
g18.B04_040  ACTACTAGCAAGTCGTAGTCTACTTTACCAGGGATGCCGAGAGAAAATGGTGGGTACGCTGGGGTAGCTATAGTGATCGTGGG
g18-2.6c.G0  ACTCCCAGTGGGTCGAAATCTTCTCTAGGAAAAAATCCGGGCCATCAGTTCAAAGGCGGGCGGAATGTGGCATGAGTTG
g18.H02_040  ACTAGCAGCTGGTACGAATCTCTAGGAGGGATGCGCTTTGGCTGGTGACCTGGGTCGCGGAGGGAGCTATACATGGTGCA
G15.9A.A04_  ATTAACAGCGTTGCGATTCTCGCTCGGCGTCTAGCCCAGGTGGATGCATGGTTGCGTCTGGGCTCTGGATGGGGTTGTGC
G15.9B.B04_  ATTGTCAGTGACGCGAGTCTCTCAGCGGTTAGTGGCTCTAAACGGGAACGCACCGTGCGTAGGACGGACTGGGGGTGGG
g15.1g.G02_  ACTCCTAGCAGGGCGAGTCATACATCCCGTATCGCAACTAGCAGACCACTGGAGGGGGAATAGGTAGGGGGTAGTTGCTG
G15.8B.B03_  GGGTGAAATTAGCACAGTCAGCGACACGAATTGTCGCTCTTCATATGGCGTCGGGTGGCAGTATACGTCTGCGTGTGCGGG
G15.8D.D03_  GTATGGTGAGGCCTGTTTGAGAGAGTGAGAAGTTGGAGGAAACCGCACTCCCAGCGTGGGCGATGCAGACTCTTATTGG
g15.12h.H01  ATTGTGAGCCCACACGAATCAGTCTCCGCATGTCTGCTCAGCACGGACAAGCCCGTCAGTGAAGTTGTTGGGTTTTTGTG
g15-2n.C06_  ACTGTTAGCTAACACGAAGTCACGCTTCCGCGGTATTTTATAGGCGTGGTAACGTTCTTGAAGTTACCCGAGATGGCTGG
g15-2n.B06_  ACTGTGAGCCCACCCGAGTCTCTGTCATCAAGCAGGGATATCAATGATGAGAAGAGATTATATGTAGCAACGGTTTGTGC
G15.11C.C05  ACTTTCAGCGAACCGAGTCTCTCGGGGTCGAAAAGCCCTCGGGGGTTACTTGAAGAGGCAAAGCTATGGCATGTTGGGGG
G15.12E.E06  ACTATTAGCAATACGAATTTTCGACGATGCTGGCAGCACGGAAACCTGCGTAGGCTGAGTTGGAATGTGCATGTGGTGG
g13.12e.E01  ACTGTTAGCAACGCGAGTCACGCAACGATGGTCTAGTAGTGTTATGAGCGTGGACAAAATAGGGTTTATTTGCTCTCGGG
G13.5A.A01_  ATTATCAGCGATACGAAATTAACGGCGCTCTGGCAAGCGAATGGTCTTCGGCGGGAGGGAGTTTCTCGCCAATCCGGTGG
G13.5C.C01_  ACCTCTTAGCATAACGCAGGGCGTTAAACGACTGAACTACCTTGGCAGGTGGGAGGTAGACGAGTCTCTTTCACTTGTGG
G13.5F.F01_  ACTGTTAGCAACACGAAGTCCAGCCTCCTCGGCGTGGTCTAAAAGGAAGGGTAACCTGGATAAAGAGGTACCTATTTCGG
G13.2B.B01_  ACTAAAAGCTTTTACGAGTCTTTGCCGGGACTAGTCCAATGGTGGAAGGAGGTGTGGTGTGATCTTGGGAACCCTTGG
G13.2H.H01_  ACTTCTCAGCGAGACGAATCTGTGTGAATGTGTCGGGAGCGTCCTGAGTTCGGACGAGCCGGAACTAATACTCCTGGGTG
G13.3C.C02_  ACTGCCAGCGGCTCGAGGGCTCTCCGTAAGCAAAGTTTTCCTGGTTCGAATAAATAAAGGGTCGAAGGTCGGGTCTGTGG
G13.3D.D02_  ACTTCCAGCGGATCGGGATCTTTATCCACGTCAATTAGGGGGTTGTGGGTTGCTATGGGTAAGTACCTTGGTATGGA
G13.3E.E02_  ACTTTCAGCGAATCGAATTATATCTCGAGTGAATAGTACTCCGCCATGGGAACTGGGGTGGGGTGAACAGAAGCTTTGGG
G13.3F.F02_  ATTTTCAGCGAAACGAATCTTAGTGCCGGTCTGATGGGAGAGGTGTTATCCTTTGGAAGTAGGGCACAATTCTCTGGCGC
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G13.4A.A03_ ACTATGAGCTCAAACGAATCATCTCTACAGTGATTATCGCTGTGGTATAGGGTGGAGGGGCGCATGTTGGAAGGTTGGG
g10.7a.A07_ ATTTCAAGCTGAACGAATCTTGATGCCTTCTACTCGTTGTTGCAGGAGTGAGGATTTCCATGGGTTATTCGTCGGCGGG
g10.7e.E07_ TGTTTTGTATGTCAGTTTGGATGGGTGCTTTCCTAGCAGTGACGAGTCTCGCCTTCTCCGGGCTAGTAGTGTGTCGAGTGGG
g10.7g.G07_ ACAAATAGCATTACGAAATCTCTGGTTCAAATGAGCATTGTGCTTAATAAGCTGACAGTGGTAAGAAACGGTGCATAGG
g10.12c.C01 ATTAACAGTGTTGCGAAATCTATCGCCTGTGTATACTGGAAGGTCAGCGTGGAGCAATGTAGATTGACCATGGTTTGTGG
g10.11h.H11 ATTATCAGTGAGCGAGTCTTGCTTCCTTGGTTGTAGCGATCACCGCTTTACTAAGGTCCGTATTTCGGAGTGTGTTTGG
g10.6e.E06_ ATTGTGAGCCACTCGAATTTTTTTTCCAGCAACGCTGGCGGTTATGTCGTGAATAGGTAGATTTCACGCTGCTCGTTTAGG
g10.7h.H07_ ATAGCAGCGACTACGATATCGCTCTACGGGGCAAAGTGTCCAAGTTTCGGGTGATCGGCAGTGTAGAATCACGGGGTGGG
g10.8b.B08_ TCAATAGCAGATATAATACGAAAAGCGCCATCTAGTGTCCGCGTGAGTCGTTACGAATGGTTATAGATATATAATGTGGGG
g10-2n.D06_ GATTTGGAATCGTAAAGCACTATCAGCCGATACGATATCTTTTAGCTGAATTTGGAGGGGCCTAGGAGGGGGATTTGTGG
g10.8c.C08_ ACTGTTAGCTTACGCGTAAATCGCGACTCGGTAGTCCGTCATACTATGCTGCTCAGCTAGTTACGGGTAGTTATGGTGGG
g10.8h.H08_ ACAAATAGCATAACGAAGGATAACAACAACAGGCGCATGGAATAATGTAGGTGTGATGATAATACAAGCGAGTAGTGTGGG
g10.9b.B09_ ATAGCAAGCTGCACGAAATACATACGAGTCTGTCAGGACAAGGGATCGGTGGTCGCCACTAAGGGTATGGTATACCAGGG
g10.10c.C10 GCACTGTCAGCGACACGAATTTACGAATACATTATTGTCTTTGGGGTGGGTCTGGGCTTATGTCTAGCCAGCATGGGG
g10.10f.F10 ATTTCTAGCTAGAACGATTTTCTCTTTGCTGCACACCCGGTCCAATCGAATTCATAACCGGTAAACAAGGTATCGTTGGG
g10.10g.G10 ATTACTAGTAGTTCGAGTCTCTATCGATGTGGCGAAGGGCATAGCCAGTTTCACGAGTGCGGTGACATGGGGTATGGGG
g10.11d.D11 ATAAACAGCGTTGCGAAATTTACTACTAAAGTAGCCTTCTGGGTGTGGGCAATCATCAGGAATGATGTGCACCGGGGTCTGG
g10.11e.E11 ATTCTAAGCATAGACGATTCTCTAAAGTGATGGGAGAGAGTTGTCCTGGCAGCATTGTGGAACCGTCACGTTGGTTGGGG
g8.4c.C04_0 GCTACAAGCTGAACGAGTCTCTATAAAGCTGGTATGTTAAAGTGCGTAATGAGCATAGGGAGTTAAGAAAACTAGGTGGG
g8.1b.B02_0 ACAAATAGCATAACGAATCATGACACAAGACGCTGGAAAACTAGGAAGTCATGAGGGGCTAAAGTAAGTAGTCGTAATAGG
g8.12a.A01_ ATTAACAGCGTTGCGAATTCTCTCGCTCTTGTATTAGGGTGCTAGCTGTCTGAATGGACGCGGGAGGTGAGTGGGTGGG
g8.1a.A01_0 GCATTCTCAGCGAGACGAATCATTGTCCGGGTTGTTGTGAGGGGTCGGTGCTAACTTACGTGAGGTACACTATGGTGGG
g8.1e.E01_0 ACTATCAGTGATACGAGTCTCTCATTAAGTCTGGTCTACGGGCGGTGGCGCGGTATGACTTTGCATGGGTTGTCATGTGG
G8.4A.E07_0 ACACTCAGCGAGGCGAGTCTCTCTACCAGCCTGGTAGGAAGTTATAGGAGGCGATTATAAGTCGCGGGGAGTGGCCATGG
g8.1g.G01_0 ACGGCCAGCGGCGCGATTCCTGTCCGCGGGGGTTAGAATAGATAGCGAATAGATAGTACATAATATAGTGATGGTGGTGTGG
g8.5f.F05_0 ACTATCAGCGATACGATTTTCACGCCCTTGACAGTCAGAATTGCGGTGATCATATCATTCATGAACGATAACGCATGGGG
G8.5D.H07_0 TACTTTACAGTGAATCGAAATCTCATATATTCGCTGGTCATTGTTGGGAGGCGAGACCGCTGGGAATAGTGTTGGGGTGGG
G8.3A.B07_0 ACTGCCAGGGGCTCGAGTCGCTCTTTGTAGGGGACAGGATGTCCGGTGTGCTGCGACCTCAGTCTACTTATTTGTGGGG
G8.3E.C07_0 ATTCACAGCGGTGACGAGTCTCTTCCATTGGTTCTCACTTTTGCTTGGATTCATGGCGATGGATGCAAAAGGTGGTGTGG
G8.3H.D07_0 ATTTATAGCATAAACGAAGTCTCTGGTATGCATGTATAGAATAATACTGTGATCACCGCGGCGCGATGAGGTTGTGGGTTGGG
G8.4E.F07_0 GAGGTTCCTGCGATTTCTGCACTAACAGCTGTTACGAATCAACTCTTGATGGATTGGGCGTTTCTGGCGGTACCTTGGGG
g8-2n.H06_0 TTCCTGGTGCCTGGACGCCGGATAGTTATACGAGCACATCCCAGCGGGTCGATTTTCTCTTGGAGGAGGTTTGTTCTGGG
g8.2f.F02_0 ACAACCAGCGGTCCGAAATAGCTCACCGGTGTCGTGGTAGTCTCACTGCCGTCAGGCAAAGGAGTGCATAATAGGTTGGG
g8.2g.G02_0 ATACTGAGCCAGACGATACTCACTATACTAAGGAACTGTGGGCCTGTAAAATAACGGACCCTCATACTACGTAGCGGGGG
g8.2h.H02_0 ATTAGCAGCGCTGCGAGTCGCTCTTCGGGTTAGAGCATGGCGTGAGCTATTGGGTTGAATCGTATGTATTATCATGGG
g8.3c.C03_0 TCTAGTCAGTGATGCGAGTCTAACTCCTCTAACTCGTGTGAATACAAGGGAAGTCACAGGTGTTCGCGGGTGGTTTTGGG
g8.3d.D03_0 ACAGTACAGCCCATCGCGTGGATGCAACGATAGTACCATAGTAGCGTTGGAAGAGCGATTCCGGTACCTATGGCTAGTG
g8.12b.B01_ ATAAGCAGCTGTGCGAAATCTACTAAAGCTGGTCAATACTAAGTACCGCGTGCGGGCTGTAAAGCGGGGGTCTGGGTTGG
g8.3g.G03_0 ACTGTTAGCAGACACGAAATTCTTACTTTTAATCTAGCGGGTATTGAGCAGCGGACTAGTGGGACGAAGAGTACCGGTGG
G8.5B.G07_0 ATTGCCAGCGGCTCGGAGCTCTTTACCTGCATTGAGTATAAGGAGTTATGGCGATTCGGCTTGCTAGTTAAATCCGTTGG