

**Evolution's Footsteps: Reconstructing *in vitro* and *in vivo* Evolutionary Trajectories via Massively Parallel Sequencing and Profiling**

by

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*for my parents*

*&*

*in memory of my grandmother*

*Dorothy Frankel*  
*December 14, 1921 – July 13, 2012*



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## **Abstract**

Understanding how phenotypes evolve through natural selection is a fundamental question of biology. Microbial evolution studies provide the rare opportunity to experimentally elucidate the changes that allow an organism to adapt to novel conditions. In an *in vitro* experimental evolution system, cells evolve in response to a lab-controlled selective environment. In such experiments, the evolved strains may have no fitness-gain in non-stressed conditions, but outperform their progenitors in the selective growth conditions. A complementary *in vivo* system is monitoring the evolution of drug resistance in microbial pathogens.

Identifying the mutations underlying such evolved phenotypes have typically been limited to the identification of regions of interest by low-resolution techniques such as classical genetics or microarray mapping followed by sequencing, and many relevant genes may remain undetected. The recent development of technologies for cost-effective whole-genome re-sequencing offers the opportunity to comprehensively study evolution in action.

Here, I present a combined experimental and computational strategy to detect and study recurrent genetic aberrations accompanying adaptive evolution in *Saccharomyces cerevisiae* and *Candida albicans* by whole-genome re-sequencing of evolved strains using Illumina technology. We sequence parental and evolved strains from multiple evolutionary trajectories under the same selective pressure. Our computational approach focuses on the detection of recurrent aberrations – ranging from SNPs to larger variations. We remove variants present in parental strains as background and catalogue subsequent aberrations that persist and co-occur with phenotypic changes. Likely functional changes are identified by recurrence across independent evolutionary time courses.

In *S. cerevisiae* we identify those mutations that are responsible for evolved, adaptive phenotypes, as well as demonstrate that independently arising adaptive alleles, when in the same genetic background, reduce hybrid viability. In *C. albicans*, we show both large and small recurrent variations that are highly associated with acquisition of fluconazole resistance. Our approach elucidates the function and evolution of key systems in a key model organism and an human pathogen. More generally, our methodology is applicable to a broad range of species, allowing us to trace phenotypic evolution from bacteria to human cancers.

**Thesis Supervisor: Aviv Regev**

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## **Introduction**

## Overview

In his paper, *Nothing in Biology Makes Sense Except in the Light of Evolution*, Theodosius Dobzhansky wrote, “in the light of evolution, biology is, perhaps, intellectually the most satisfying and inspiring science. Without that light it becomes a pile of sundry facts some of them interesting or curious but making no meaningful picture as a whole.” [1] From understanding the nature of microbial antibiotic resistance[2-4], to the clonal origin of metastatic malignancy[5-8], to understanding more about ourselves and the biological diversity of our world[9, 10], the dynamics of evolution are core to furthering our understanding of biology.

There are two approaches by which we can study evolutionary processes. In the first approach, we can characterize extant species or populations and *infer* their evolutionary history. In the second approach, we monitor a starting population and trace evolution *as it occurs*. The latter approach is termed “forward evolution”, and it is often coupled to a response to stress serving as the known selective pressure. Forward evolution can occur in the laboratory (i.e. *in vitro*), such as the case of *Escherichia coli* grown under nutrient limitation. For example, whereas *E. coli* is defined by its inability to metabolize citrate under oxic conditions[11], Blount *et al.* show *de novo* evolution of the ability to metabolize it as a carbon source[12]. Similarly, we can monitor forward evolution in applications of human health (i.e. *in vivo*), such as resistance to chemotherapy arising between primary and recurring cancer[13].

Historically, experimental forward evolution was largely conducted by fly geneticists[14], but during the 1980’s it gained more widespread popularity among microbiologists[15, 16]. Advantages for using model organisms in experimental forward evolution include[14]: (1) populations that are easy to grow and enumerate for particular traits; (2) short doubling times, allowing experiments to be run for many generations; (3) in microbial

evolution, a progenitor population and intermediates that may be retained by frozen suspension for direct comparison at a later date; and (4) *in vitro* conditions that are easy to control and guarantee clonally derived progeny. These experiments help to elucidate which mutations are adaptive or how they occur, or allow one to compare the relative fitness of a trait mutation to many others[17-19].

Forward-evolution experiments require follow-up characterization in order identify the genetic changes underlying the evolved trait. Historically, mapping experiments for identifying the mutations underlying these evolved phenotypes have been limited to the identification of regions of interest by low-resolution methods such as classical genetics or microarray mapping followed by sequencing of selected regions[20, 21]. Most studies have focused on large-scale aberrations[22, 23] or candidate genes[24] and do not provide a comprehensive view of the genetic basis of evolved phenotypes. Thus, many relevant regions may remain undetected. With the advent and development of sequencing[25-28] and profiling technologies[20, 29, 30], the landscape for how these experiments could be conducted and analyzed has changed.

In this thesis, I present our contribution to the identification of mutations for species of fungi grown in both *in vivo* and *in vitro* settings under conditions of strong selection and the resulting biology we learn in the process. First, I describe a system in which a single strain of *Saccharomyces cerevisiae* was evolved for 500 generations in parallel in high salinity or low glucose conditions[31]. I demonstrate how we use sequencing and expression profiling data to identify the genes responsible for evolved phenotypes and, likely, for early speciation events. Next, I describe how I use this methodology to trace evolutionary trajectories of drug resistance in *in vivo* time series collections of the pathogen *Candida albicans*. And finally, I describe the

infrastructure developed for rapid, customizable, and parallelizable analysis of genomic sequence data.

To provide context, I begin by briefly reviewing the relevant concepts of population genetics and evolution, spanning from predictive arguments made prior to current knowledge of heritability as it relates to DNA to current theory and application. Next, I discuss the progression of sequencing methodology, highlighting how progression in this arena facilitates a broader understanding of evolution and populations genetics. Finally, I present the specific contributions of this thesis, integrating current sequencing and profiling technologies in a way that uniquely lends insights into evolving systems.

## **Evolution: Selection and Speciation**

### **Darwin and Selection**

In *The Origin of Species*, Darwin says, “I have called this principle, by which each slight variation, if useful, is preserved, by the term Natural Selection.”[32] Hartl and Clark distill Darwin’s definition as follows[33]:

1. More offspring are produced than can survive to procreate.
2. At least part of why individuals do not survive or procreate is due to genetic variation.
3. Genotypes associated with survival and reproduction are over-represented at time of reproduction.

Thus, while genetics concerns itself with Mendelian laws of inheritance, population genetics concerns itself with inheritance of traits across populations of organisms, and the governing force is selection. The degree to which a genotype affects survivability or fecundity is measured by fitness. Fitness can either be measured in absolute or relative terms, whereby the former is a

measure of the difference in members having a trait before and after selection, and the latter is a measure of the difference in ratios between two genotypes before and after selection[17]. While typically these observations are considered within the context of Mendelian genetics in a sexually reproductive species, they also apply to haploid, asexual organisms and those with non-Mendelian inheritance patterns. When all members of the population become carriers of a particular allele, the trait is “fixed”. If selection is strong, fixation can happen in comparatively few generations; this type of selection is termed “purifying”[33]. However, selection may also be “diversifying” – keeping the number of traits diverse and preventing any one trait from fixing[33]. Further, genetic drift may also cause a trait to fix, wherein purely stochastic events cause a neutral or deleterious trait to fix within a population, even though it has no, or negative, effect on fitness, respectively. Further nuances exist within these frameworks, such as genetic draft, wherein an allele for a gene that is physically close to a different allele under selection will “hitchhike” off that selected gene. This can happen even when that gene is selectively neutral or deleterious. Selection can also be artificially applied within the context of a laboratory to test hypotheses about how evolution functions in the wild. Some examples of selective conditions commonly applied in lab settings include thermal[34-36], nutritional[12, 37] or high salt[38]. The selective conditions can mimic harsh, naturally occurring environments.

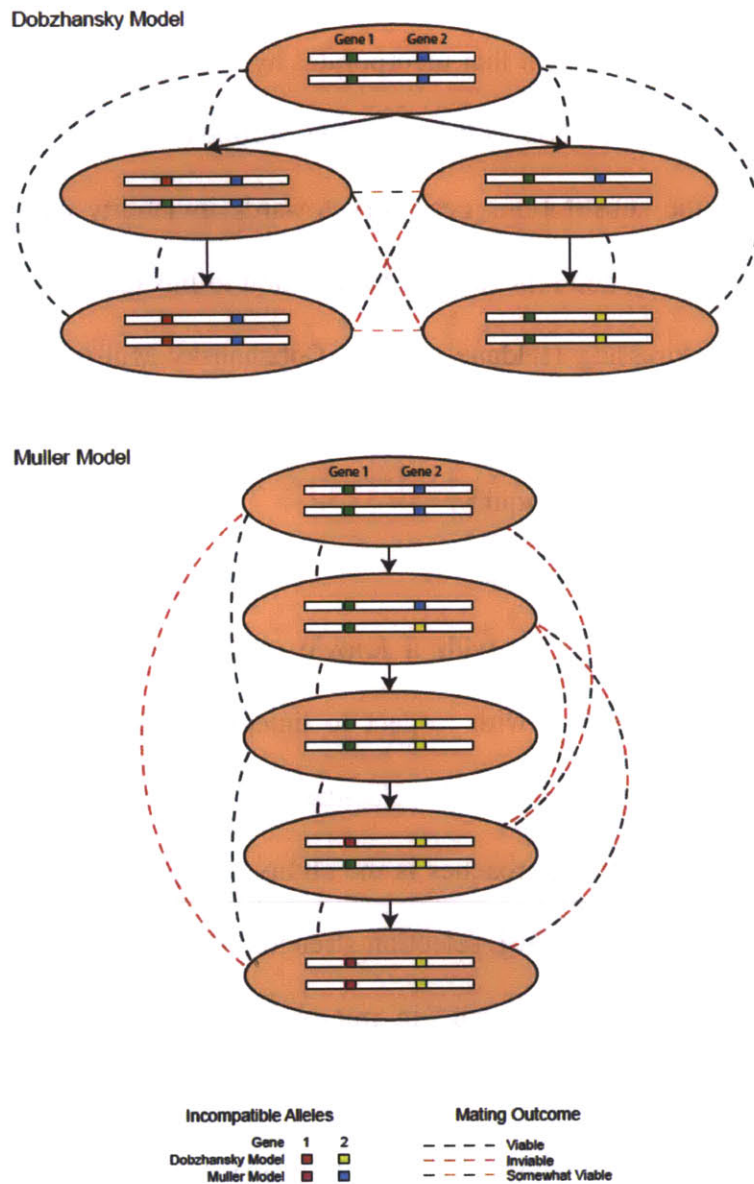
### **Speciation**

Selection is one of many possible mechanisms that can give rise to speciation[39]. Speciation is the evolutionary process by which one group of individuals becomes reproductively isolated from another[40]. This can be due to geographical isolation (allopatry)[41], changes in behavior or selection that isolate different groups within a population (sympatry)[41], or variations therein[41]. Due to reproductive isolation, the lack of gene flow gives rise to genomic

changes that will ultimately cause one species to diverge from another. This reproductive isolation is generally classified as prezygotic and postzygotic[41]. Prezygotic barriers might include behavioral differences that would prevent two individuals from mating, or mechanical barriers in the organisms themselves that cause physiological incompatibility. Postzygotic barriers might include hybrid sterility, where mating might be successful, but the resulting offspring cannot reproduce, or hybrid inviability altogether. JBS Haldane noted of interspecies crosses that, “When in the  $F_1$  offspring of a cross between two animal species or races one sex is absent, rare, or sterile, that sex is always the heterozygous sex.”[42] This phenomenon is observed in animals as well as plants[43], though the mechanism underlying this observation varies.

Of particular interest in this thesis (Chapter 1) are the events that occur early in the process of speciation. It has been referred to as Darwin’s Paradox[44]: “how could something as patently maladaptive as the evolution of sterility or inviability be allowed by natural selection?” Orr demonstrates this as follows[44]: for a given gene, if one population has a genotype of  $AA$ , and another population has a genotype of  $aa$ , and if the heterozygous genotype for this gene,  $Aa$ , is infertile, how could these populations have shared a common ancestor? At some point, there would have had to be a heterozygous genotype from the ancestral genotype, and that individual would have been infertile, and, thus, unable to reproduce and propagate the new allele. The solution to this problem, as proposed by Dobzhansky[45], is that instead of a single locus, at least two loci are required. The corollary to the previous example would then look as follows (Figure 1): a starting population has a genotype  $aabb$ . The first population acquires the  $A$  allele, and individuals would then be either  $Aabb$  or  $AAbb$ , both of which are fertile.  $A$  may be either selectively neutral or adaptive. In a second population, the opposite occurs;  $B$  evolves such that





**Figure 1. The Dobzhansky-Muller models of speciation**

Both models assert that incompatibility must arise from at least two genes, although it may be more. In Dobzhansky’s model (top), the alleles arising in the progeny are incompatible with each other, and will lead to increased reproductive isolation between the two populations. In the Muller model (bottom), the progenitor population does not change, but some progeny, forming their own population, become reproductively isolated from the progenitor.

individuals are either  $aaBb$  or  $aaBB$ . Both of these individuals are fertile, and  $B$  may be either selectively neutral or adaptive, as well. If the  $A$  and  $B$  alleles are incompatible within the same individual, then a model for speciation that incorporates hybrid sterility is resolved, thus serving as a solution to Darwin's Paradox. Muller further refined Dobzhansky's hypothesis by contributing that all of the substitutions necessary towards inviability can occur in the same lineage as opposed to two[44], and related this phenomenon to linkage to the X chromosome (in XY species), thus also addressing Haldane's Rule. Dobzhansky-Muller incompatibilities have been identified principally in *Drosophila*[46], with much work remaining to be characterized in other species; this is an area of open inquiry.

### **Forward experimental evolution**

Experimental evolution begins with a known set of genotypes and then follows a genotypic and phenotypic trajectory with respect to time[47] often during the application of selective pressure. This approach directly elucidates the dynamics of evolving adaptive mechanisms. An asset to *in vitro* approaches is the ability to replicate experiments and control parameters such as mutation rate[48-50], selection strength[50], population size[50] and genetic recombination[50]. This is especially true in microbial populations because of their large population sizes and short generation times.

Early work in this field includes the seminal experiment of Luria and Delbrück[51], which demonstrated that natural selection acts on genetic mutations that arise spontaneously in a population and then are selected, rather than mutations arising in response to stress. Also conducted in *E. coli* is classic work in forward evolution by Richard Lenski[18, 52, 53]. In his earlier work, Lenski showed that *E. coli* strains grown at a continued, elevated temperature stress for 200 generations acquired mutations that gave rise to an increase in fitness. It is important to

note that these mutations do not arise because of stress, but rather, they are rapidly selected for once they occur. Lenski's work also includes longitudinal studies, in which he has grown *E. coli* in nutrient (glucose) limiting conditions for many (recently, 50,000) generations[18, 54, 55]. These studies have yielded insights in convergent evolution, the uniformity of acquisition of advantageous mutations and the variable acquisition of neutral mutations, as well as the acquisition of new metabolic abilities that were strongly selected for in glucose limitation.

Experimental evolution is not limited to work in bacteria. Fungi, unicellular yeasts in particular, are excellent model organisms for experimental evolution for the same reasons described of bacteria, namely large population sizes and rapid generation cycles. Further, as eukaryotes, and having diverse genomic states such as both haploid and diploid members, yeast can offer different insights into evolutionary processes. For example, in conditions similar as those described for Lenski's work, Ferea *et al.* evolved *Saccharomyces cerevisiae* in glucose limiting conditions[56]. This work showed not only amplification of genes associated with hexose transport[57], which allowed strains to more effectively acquire glucose from the environment, but also that there were similar genomic rearrangements that occurred in parallel in response to persistent selection[58]. This approach has also been used to study other diverse phenotypes, such as mating selection preference[59] and divergent evolution[31], both as a means to study the progression of speciation, as well as a means to monitor evolutionary dynamics in competing populations[60-62].

### **Evolution of drug resistance**

The efficiency with which selection gives rise to individuals adapted to their environment has some unfortunate implications for human health. Classic examples of this include penicillin and chloroquin. Penicillin, identified by Alexander Fleming in 1928[63], is the most broadly-

used class of antibacterials[64]; by 1947, the first resistant strains emerged in the clinic[65]. Similarly, chloroquine was identified[66] as an alternative anti-malarial to quinine. The World Health Organization attempted to eradicate malaria from 1955-1969 [66], and by the late 1950s, chloroquin resistant strains of *Plasmodium falciparum* were present in Asia and South America[67]. Drug resistance is also a model system to trace evolution in action. Very recently, such studies have begun in prokaryotes[68, 69].

The trend toward rapid drug resistance is also true of the dimorphic fungal pathogen, *Candida albicans*. *C. albicans* exists as part of normal human flora as a commensal and is not found in environmental reservoirs[70]; however, it is opportunistic and can be pathogenic. Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States[71], with *C. albicans* accounting for nearly 65%[72, 73] of candida infections. Systemic infection is associated with a mortality rate as high as 50%[74]. Resistance arises during long-term prophylactic treatment regimes[75, 76] that are sometimes indicated in immunocompromised patients (BMT[77], HIV[78]). There are several classes of antifungals, including: polyenes, azoles, and allylamines, which target ergosterol or its synthesis[47]; and echinocandins and nikkomycins, which affect cell wall integrity via inhibiting glucan[79] and chitin[80] synthesis, respectively. Azoles are typically favored for their low occurrence of host toxicity[81].

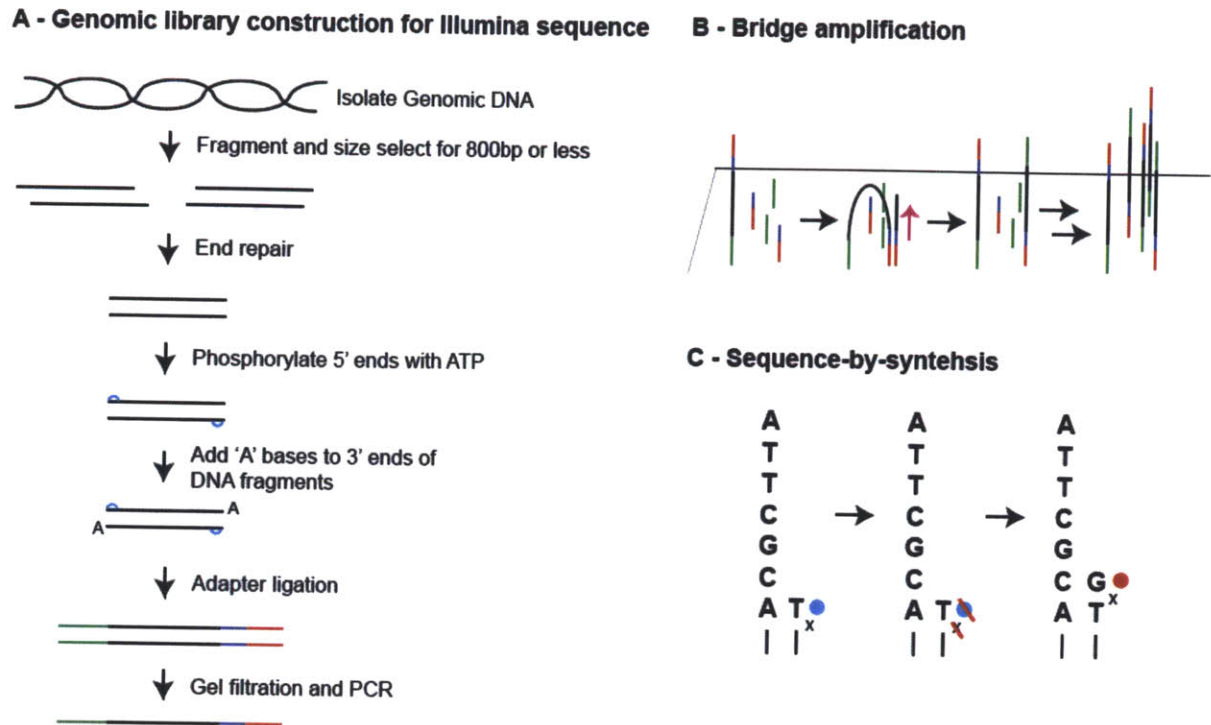
Both *in vitro* and *in vivo* systems are used to study *C. albicans* resistance because they provide an extensive trace of the evolutionary process by way of sampled strains throughout the evolutionary time course. In an *in vitro* experimental evolution system, 12 strains of *C. albicans* were evolved from a single drug-sensitive cell via daily serial transfer for 330 generations; six regularly exposed to twice their minimal inhibitory concentration of fluconazole as the selective

pressure, and six without any fluconazole exposure[82]. The six populations that were exposed to fluconazole all evolved resistance to the drug, whereas the six that were not exposed remained sensitive. Expression analysis of these populations indicated that genes known to be involved with resistance were induced[82]. While studies such as this one help to shed light on mechanisms of resistance, and while parameters can be tightly controlled *in vitro*, the laboratory environment in which resistance evolves is not a perfect proxy for how resistance evolves in a human patient. Thus, *in vivo* patient sampling methods are used to augment understanding of drug resistance acquisition.

There are many reasons to sample clinical isolates from patients. Sampling patients over time and/or with respect to different regions can be used to document emergence of resistance, or document changes in sensitivity with patient compliance to therapy[47]. Serial isolation of *C. albicans* from patients over the course of drug treatment, in particular, can be helpful in identifying mechanisms for increasing resistance[76, 83-85]. While quantities like mutation rate, selection intensity, and effective population cannot be known from these systems, the value of the “wild” environment and its effect on drug resistance evolution cannot be ignored. Previous studies of resistant strains have shown that this is mediated by multiple mechanisms including segmental aneuploidy[86], increased expression of drug pump genes[87], loss of heterozygosity (LOH) across chromosomes or regions of chromosomes[87, 88], mutations in ergosterol biosynthetic genes[89], and deviations facilitated by the heat shock protein Hsp90[90]. However, previous studies were also limited by their assumed clonality of sample strains as well as their limited ability to survey genomic changes.

## **Illumina Sequencing**

The first major innovation made in sequencing was by Fred Sanger[25, 91]; Sanger's "first-generation" dideoxy-sequencing dominated sequencing throughout the 1990's[92, 93]. Sanger sequencing would serve as the inspiration for massively parallel sequencing technologies such as Solexa/Illumina. Illumina sequencing (Figure 2) uses deoxynucleotide triphosphates (dNTPs) with reversible termination and fluorophores that distinguish one base from another[94]. DNA preparation consists of shearing, size selection, and ligation of adapters that will serve as templates for DNA polymerase as well as promote binding onto a glass flowcell (Figure 2a). The DNA is separated into single strands and annealed to the flowcell. The first round of DNA replication copies the reverse complement of the annealed strand onto a covalently attached adaptor. The annealed strand is then removed, and subsequent rounds of PCR replication are termed "bridge-amplification." Bridge amplification creates a clonal "patch" of DNA on the flowcell in proximity to the first attached DNA strand (figure 2b) by folding over (i.e. forming a "bridge") and annealing to another covalently attached adaptor. PCR templates off of that adaptor and copies the DNA strand's reverse complement onto the new adaptor. In a given round of bridge amplification, each single strand of DNA will act as a template for its own reverse complement. After several rounds of replication, the result is a clonal patch of DNA localized to the initial annealed single strand of DNA. Because the adapters are not reverse complements of each other, sequencing can preferentially target one strand in a patch (single-end) or both strands in a patch, though as distinct cycles of sequencing (paired-end). The actual sequencing then occurs by serially incorporating DNA via PCR with dNTPs that have reversible terminators in the 3' position. Fluorescent imaging is conducted, where each patch is read as one of 4 different fluorophores. The fluorophore and reversible terminator are then cleaved. This



## Figure 2. Illumina DNA sequencing

**A. Genomic DNA preparation for Illumina sequencing.** DNA is first sheared via nebulizer to fragments less than 800 base-pairs. The DNA fragments are end repaired to form blunt ends using T4 DNA polymerase and E. coli DNA Polymerase I Klenow fragment. An adenine is added to the blunt phosphorylated DNA fragments via the Klenow fragment's polymerase activity; this facilitates adapter ligation, which have a thymine overhang at the 3' end. Gel purification for size selection is followed with PCR amplification with both sets of primers such that only those constructs with both sets of adaptors undergo exponential amplification. The DNA is then melted to single-stranded DNA to anneal to the covalently linked adaptor-complements embedded in the flowcell.

**B. Bridge amplification.** ssDNA genomic constructs are allowed to anneal to the flowcell, where they may undergo bridge amplification. The result is clustered clonal DNA patches on the flowcell, with about 10 million clusters per lane, with eight lanes per flowcell.

**C. Sequencing.** Following bridge-amplification, sequence-by-synthesis reactions are carried out between 30-100 iterations. Modified bases with reversible terminators and unique fluorophores are incorporated. After laser recording of the base, the fluorophore and terminator are cleaved and the next iteration of base incorporation is catalyzed.

process is then repeated (current approaches may go for upwards of 120 iterations). Each patch's "color" sequence represents the DNA sequence. It is at the completion of the first round of sequencing that paired-end sequencing can occur; the process is repeated for the reverse complement of the strand that was previously sequenced.

Both because of the increase in throughput in massively parallel sequencing approaches, and also because of the relatively large size differences in some organisms, it may be advantageous to put more than one sample in a single lane of a flowcell. Thus, it is important to have the ability to deconvolute sequence data from these sources. One such method is indexing, which adds a sample-specific barcode during sample preparation[95]. The first few sequenced nucleotides in such a sequencing reaction are the barcode, and these reads can be binned, accordingly.

### **Genome Re-Sequencing using Illumina**

While massively parallel sequencing *can* be used for *de novo* assembly, most high-throughput sequencing approaches are intended for re-sequencing. Re-sequencing uses large numbers of short reads by way of alignment to a reference genome. Re-sequencing is both cheaper and faster than *de novo* reconstruction[96] while allowing detection of variants. Both alignment and variant detection rely on a quality metric; a method to determine both the quality of individual bases, as well as a measure for how well short-reads map to particular locations along the genome. Thus, we can summarize the challenges associated with re-sequencing as (1) quality scoring, (2) read mapping, and then (3) variant discovery.

Quality scoring is defined in relation to the probability of error of a particular base being mis-called or a read being mis-aligned. Specifically, the relationship is defined as  $Q = -10\log_{10} P$  where  $Q$  is the quality score and  $P$  is the probability of error[97, 98]. Quality measures for re-



sequencing data are not new to second generation sequencing platforms; they are a borrowed concept from Sanger sequencing[97]. Quality scoring is determined in a chemistry/platform-specific manner (usually in real-time by the sequencer). A related concept to base quality is mapping quality; an assessment of how well a read is aligned to a reference genome. This score integrates raw base quality as well as the degree of mismatching and gapping needed to allow a read to map to a particular location. Reads that cannot be aligned uniquely are either not mapped at all, or they are aligned at random with a mapping quality of 0. Both base quality and mapping quality are required for most methods of variant detection[99].

There are many different approaches with which one can align short reads: the two most common methods are indexing short reads[100, 101] or performing a Burrows-Wheeler transformation on the genome[102-104] for rapid read alignment. Short read indexing aligners, such as MAQ, index input reads and scan the reference genome, retaining the best hits and reporting their quality[101]. By contrast to indexed short read aligners, Burrows-Wheeler aligners require a pre-processing step on the reference genome creating a database. Once the reference genome is indexed, short reads are hashed against the database, and their best hits are retained. Similarly, if a read cannot be mapped uniquely, it will be assigned a mapping quality of zero.

Once reads are aligned to a reference genome, there are many methods that can be applied to detect variants. Methods to discover single nucleotide polymorphisms (SNPs) and small insertions and deletions (indels)[105], structural variants[106], and copy-number variations (CNVs)[107, 108] integrate base quality, mapping quality, and the frequency of repeated events in order to accurately indicate the existence of variations. Discovery of these variations can then be coupled to phenotypic variations for further analysis.

## Contributions of this thesis

In this thesis, we leverage massively parallel sequencing to study *in vivo* and *in vitro* evolutionary time courses with at unprecedented detail. Having arrived on this scene relatively early, our goals were to use existing technology and innovate around challenges as necessary.

Chapter 1 describes how we used this technology to explore experimentally evolved lineages of *S. cerevisiae*, all arising from a single clone. In this chapter we (1) map and identify new mutations arising from parallel experimentally evolved lines; (2) characterize the effects of mutation on relative fitness and transcriptional phenotypes; and (3) integrate these data and demonstrate the Dobzhansky-Muller interaction that could be a cause of incipient speciation.

In Chapter 2, we extend our approach to *in vivo* forward evolution by studying clinically derived time series of *C. albicans*. In this chapter, we demonstrate that: (1) persistent loss of heterozygosity on the right arm of chromosome 3 or the left arm of chromosome 5 occur simultaneously with strains acquiring resistance to fluconazole within time series; (2) polyploidy and isochromosome formation, while observed, do not seem to associate with increased drug resistance, nor are they retained within the time series we sequenced; (3) correlation structure, both positive and negative, exists in highly recurrent, persistent mutations that suggest that some mutations are likely to co-occur or preclude some subset of mutations from occurring; and (4) while the majority of previously isolated clinical isolates are clonally derived, this is not uniformly true, which affects previous understanding of time series data and reinforces the need for NGS-resolution data.

Finally, in Chapter 3, I present a general description of the procedures undertaken in both the *in vivo* and *in vitro* projects described in subsequent chapters. These procedures include alignment and refinement of alignment, variant detection and filtration, and novel approaches for

**variant annotation.**

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## **Chapter 1: Determinants of divergent adaptation and Dobzhansky-Muller interaction in experimental yeast populations**

We use functional genomics to investigate the incipient speciation of experimentally evolved yeast populations. We identify the underlying strain-specific mutations; assess their contributions to growth, fitness, and expression phenotypes; and ultimately demonstrate that the mechanism with which hybrid fitness is reduced is via a Dobzhansky-Muller incompatibility.

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## Abstract

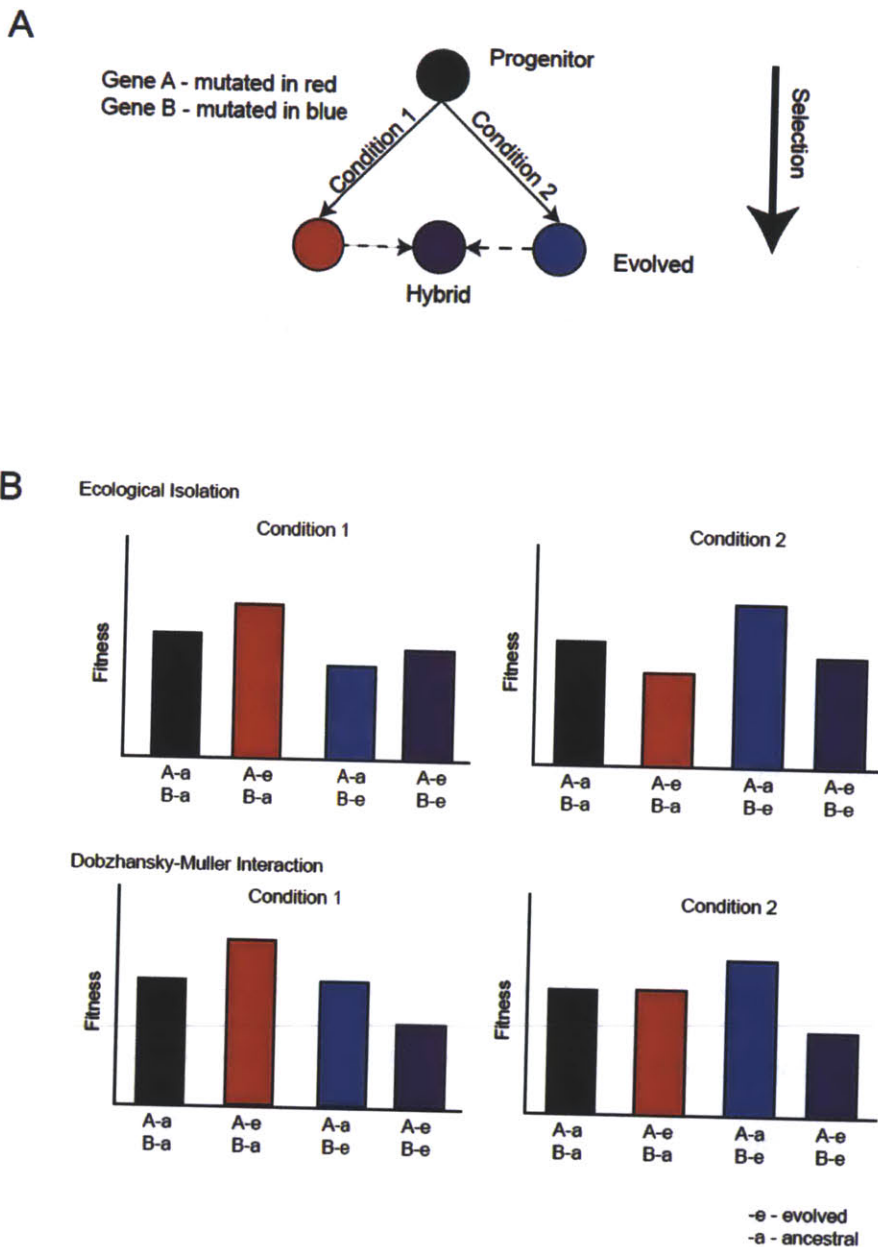
Divergent adaptation can be associated with reproductive isolation in the process of speciation[1]. We recently demonstrated the link between divergent adaptation and the onset of reproductive isolation in experimental populations of the yeast *Saccharomyces cerevisiae* evolved from a single progenitor in either a high-salt or a low-glucose environment[2]. Here, we used whole-genome re-sequencing of representatives of three populations to identify 17 candidate mutations, six of which explained the adaptive increases in mitotic fitness in the two environments. In two populations evolved in high salt, two different mutations occurred in the proton efflux pump gene *PMA1* and the global transcriptional repressor gene *CYC8*; the *ENA* genes encoding sodium efflux pumps were over-expressed once through expansion of this gene cluster and once due to mutation in the regulator *CYC8*. In the population from low glucose, one mutation occurred in *MDS3*, which modulates growth at high pH, and one in *MKT1*, a global regulator of mRNAs encoding mitochondrial proteins, the latter recapitulating a naturally-occurring variant. A Dobzhansky-Muller (DM) incompatibility between the evolved alleles of *PMA1* and *MKT1* strongly depressed fitness in the low-glucose environment. This DM interaction is the first reported between experimentally evolved alleles of known genes and shows how reproductive isolation can arise rapidly when divergent selection is strong.

## Introduction

Speciation is one of the most fundamental problems of biology, as it is the process by which biodiversity is generated[3]. Fungi are excellent models for the study of eukaryotic speciation[4] and divergent adaptation is one such method by which this may occur. Divergent adaptation of populations may be associated with the evolution of reproductive isolation in two different ways: ecological isolation[5, 6] and Dobzhansky-Muller (DM) interaction[7] (Figure 1). Under ecological isolation, populations adapt to divergent environments through the accumulation of genetic changes that result in increased fitness. If formed, hybrid populations are genotypically intermediate and therefore sub-optimally matched to any environment in which adaptation occurred. Reduced fitness in hybrids retards, if not prevents, gene flow between populations, contributing to speciation. With DM interaction, there is negative interaction in hybrids among alleles that have never been tested together by natural selection.

Among fully-fledged species, the majority of genes identified as components of DM interactions are unrelated to adaptation[8]. An exception is the DM interaction between a nuclear gene *AEP2* in *Saccharomyces bayanus* and a mitochondrial gene *OLI1* in *S. cerevisiae*[9]. It is unknown whether any of the DM incompatibilities identified to date among existing species drove the ancient speciation events.

To separate initial events from subsequent evolutionary change in extant species, we focused on the earliest mutations conferring adaptation and reproductive isolation in experimental populations of yeast under strongly divergent selection. In a previous work, Dettman *et al.* studied experimental populations of *S. cerevisiae* that evolved from a single progenitor (P) in either a high-salt (S) or a low-glucose (M) environment [2]. These populations were propagated as batch-transferred cultures with population size fluctuating daily between  $10^6$



**Figure 1. Fitness effects due to purely ecological isolation compared to DM interaction.**

(A) Starting from a founding population, sub-populations are evolved separately in disparate selective conditions. These evolved populations will be adapted to the selective condition in which they are grown. These adaptations may be deleterious in the alternate selective condition (B, top) independently (ecological isolation), or there may be a negative interaction between the evolved alleles that causes fitness deficits in the selective condition (B, bottom) (Dobzhansky-Muller interaction).

(‘bottleneck size’) and  $10^8$  individuals. After 500 generations, each of the evolved populations had adapted to their selective environment compared to the progenitor as assessed by relative fitness. This adaptation was environment-specific, as the evolved strains did not show increased fitness in either the permissive or alternate selective environments. Consistent with this observation, the **S/P** and **M/P** hybrids showed reduced fitness relative to the **S** and **P** populations in their respective selective environments but not the permissive environment. While this was also true of the **S/M** hybrids, the **S/M** hybrids presented an even *lower* fitness than the progenitor hybrids (**S/P** and **M/P**) in their selective environments. Dettman *et al.* concluded that the fitness reduction in hybrids was due to both ecological isolation and a DM interaction. The short time frame of this study was in contrast to other studies of genes involved in speciation [7-12] and of isolating mechanisms among extant species [13-15].

In this work, we wanted to determine the genetic and molecular basis of both the adaptation and the reproductive isolation observed among these different yeast populations. Our first objective was to identify which mutations arose in each line. We sequenced the haploid progenitor (**P**), and haploid cells representing two of the populations evolved in high salt (**S2** and **S6**) and one of the populations evolved in low glucose (**M8**). In order to identify the causes for ecological adaptation, we mated the evolved strains to the progenitor (**S2XP**, **S6XP**, **M8XP**) and genotyped their segregants as well as compared their fitness to the progenitor and evolved strains. We then profiled the expression of each strain in permissive and selective environments to identify the molecular relationship between the genotypes and evolved phenotypes. Finally, to evaluate the cause of the DM interaction, we measured the fitness of **S2XM8** segregants carrying the adaptive alleles from **S2**, **M8**, or both.



## Results

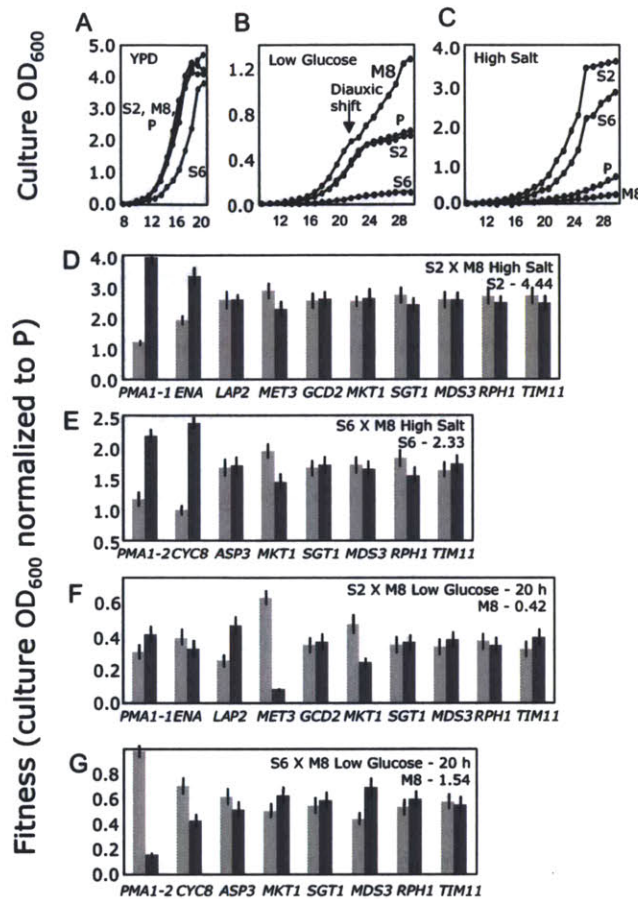
### **Illumina sequencing of progenitor and evolved strains identifies seventeen candidate mutations**

To identify the evolved mutations, we conducted whole-genome re-sequencing of single haploid representatives from two populations evolved in high salt (**S2** and **S6**), one population evolved in low glucose (**M8**), and their common progenitor (**P**). The three evolved strains had increased fitness in the respective environments in which they evolved (Figure 2). We mapped all sequenced reads to the finished *S. cerevisiae* S288C genome, and located mutations unique to each evolved strain (Experimental Procedures).

Seventeen candidate mutations were confirmed by PCR, conventional sequencing, and comparative genome hybridization analysis (Tables S1 and S2). These included: in **S2**, non-synonymous point mutations in the coding sequence of *PMA1*, *GCD2*, *MET3*, and *LAP2*, a point mutation in the intergenic region 3' to *SEC13* and *PNP1*, and an expansion of the *ENA* gene cluster; in **S6**, non-synonymous point mutations in the *PMA1* and *CYC8* coding sequences, point mutations in the *YBP2* and *CAB3* promoters, and a contraction of the *ASP3* gene cluster; and in **M8**, non-synonymous mutations in the coding sequences of *TIM11*, *RPH1*, *MDS3*, *MKT1*, and *SGT1*, and a synonymous mutation in *UBI4*. We note that two other studies have identified mutations in genome-wide screens from experimental yeast populations[16, 17].

### **Assessing the contribution of each evolved allele to fitness in the adaptive environment**

To assess the contribution of these mutations to adaptation, we measured the fitness effects of each of the mutations unique to **S2**, **S6**, and **M8** (Tables S1 and S3-S7) by monitoring culture density during growth (Experimental Procedures). We compared the fitness of the



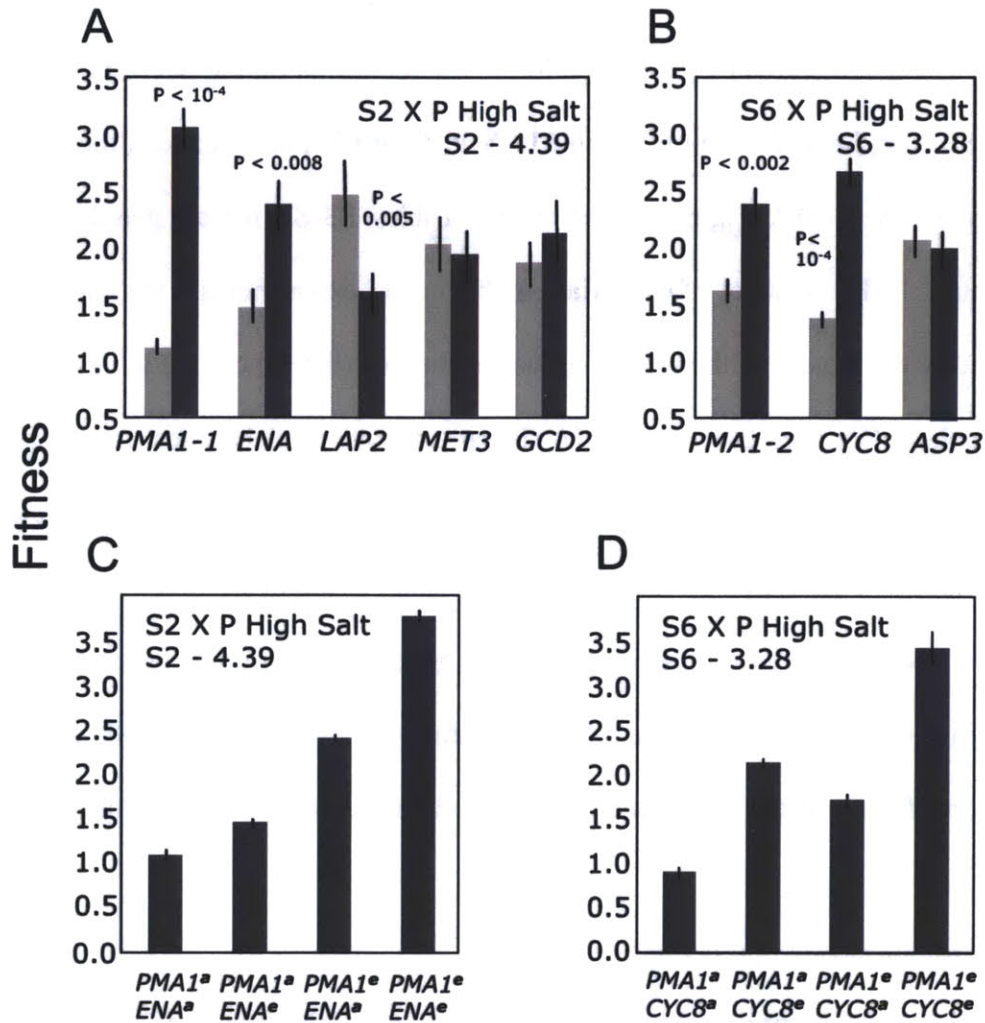
**Figure 2. Growth of the progenitor and evolved haploid strains and average fitness effects of variant loci.**

(A - C) Three haploid strains were isolated from evolved populations (S2, S6 from high salt, and M8 from low-glucose) and one haploid strain was isolated from the progenitor (P) for whole genome sequencing and fitness assays. S2 and S6 have a fitness advantage in high salt (C); M8 has an advantage in low glucose (B); S6 has a general growth defect in YPD (A) and low-glucose (B). (D - G) Shown are fitness measurements (OD<sub>600</sub>, mean and standard error, normalized to the progenitor value) for 96 progeny – fully genotyped for all coding alleles identified by sequencing – from each of the crosses S2 X M8 (A, C, 10 loci) and S6 X M8 (B, D, 8 loci) in high salt (A, B) and low glucose (C, D). Data are aggregated by specific alleles, as marked. Full genotypic and fitness data appear in Tables S3-S7 and P-values of all statistical tests appear in Table S8. Light gray bars, ancestral alleles; dark bars, evolved alleles. Fitness of evolved parent is shown at the upper right corner. Note that values in (C) average well below the progenitor (at 1.0). This was in part due to the high-salt evolved allele of *MET3*, which confers complete absence of growth in low glucose. Note also that the values in (D) average below that of the progenitor; here this was due to the salt-evolved allele of *PMA1-2*, which confers a severe growth deficiency in low glucose.

progenitor (P) and evolved (S2, S6, and M8) strains, in both high-salt and low-glucose environments, to that of progeny genotyped for all the identified mutations from crosses with the progenitor (S2 X P, S6 X P, Figure 3, and M8 X P, Figure 4), and between the evolved strains (S2 X M8 and S6 X M8, Figures 2 and 5, see Tables S3-S7 for all genotypes and fitness measurements). To control for variation between experiments, we normalized each measurement by the fitness of the progenitor as a reference (the fitness value of the progenitor is 1.0 in all graphs). We used 2-way ANOVA (linear, additive model) to test for the fitness effect of each evolved and ancestral allele and for interactions between every pair of alleles ( $P < 0.05$ , Bonferroni multiple hypothesis correction; Experimental Procedures, Table S8). Since several of the candidate SNPs involved regulatory genes (the general transcription factor *CYC8* in S6 and the chromatin modifier *RPH1* and the RNA regulatory protein *MKT1* in M8), we also profiled the expression of each of the progenitor and evolved strains in YPD, high-salt and low-glucose (Figure 6).

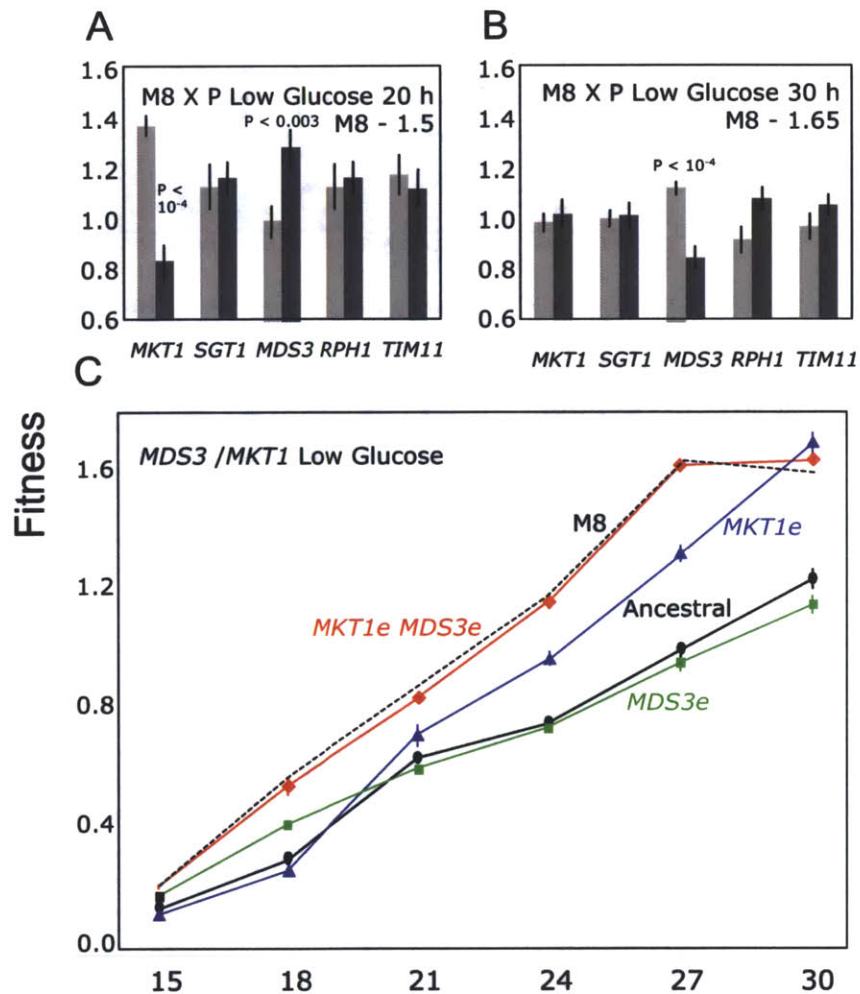
### **Recurrent mutations in *PMAl*, and phenocopy mutations in *ENA* and *CYC8* contribute the majority of the observed fitness effects in high salt**

Analysis of the 48 S2 X P progeny showed that the main adaptive determinants for the higher fitness of S2 in salt are the *ENA* gene-cluster expansion (mean fitness relative to progenitor: *ENAl<sub>e</sub>* segregants – 2.35, *ENAl<sub>a</sub>* segregants – 1.54,  $P < 0.008$ ) and the evolved allele of *PMAl* (mean fitness relative to progenitor: *PMAl<sub>e</sub>* segregants – 3.03 *ENAl<sub>a</sub>* segregants – 1.16,  $P < 10^{-4}$ ), with the *PMAl* allele having a more pronounced effect (Figure 3A and Table S3). *PMAl* encodes an essential ATP-driven proton pump responsible for maintaining the pH gradient across the cell membrane[18], and the *ENA* genes encode three paralogous ATP-driven



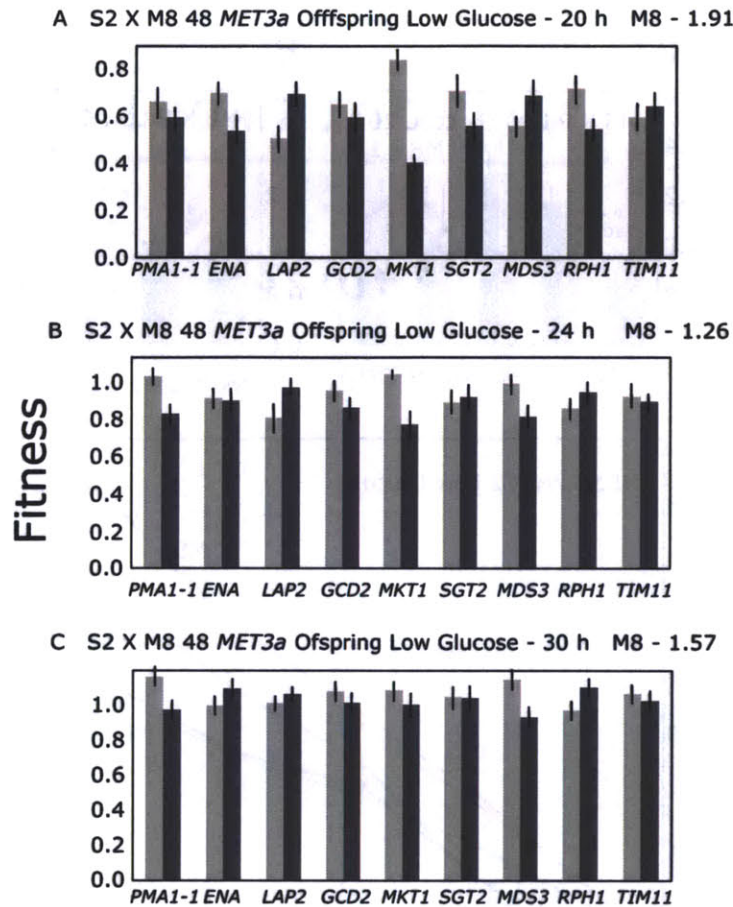
**Figure 3. Contribution of S2 and S6 evolved alleles to fitness in high salt**

Shown are fitness measurements ( $OD_{600}$ , mean and standard error, normalized to the progenitor value) for 48 offspring fully genotyped for all coding alleles identified by sequencing – from each of the crosses S2 X P (A, C, 5 loci) and S6 X P (B, D, 3 loci). Data are aggregated by specific alleles as marked (in each marked category, e.g. “*PMA1-2*”, the other alleles are segregating). Full data (including intergenic loci) are available in Tables S3 and S4. (A, B). The bars represent the average fitness effect of each variant across all offspring. Light gray bars, ancestral alleles; dark bars, evolved alleles. Fitness of evolved parent is shown at the upper right corner. Significant differences are noted with *P*-value. (C, D) Average pair-wise effects of the two most advantageous mutations in each strain. Shown are the same data as in A and B, but averaged for two-locus genotypes showing positive interaction. Superscript *a* = ancestral allele; superscript *e* = evolved allele. Interaction was tested by ANOVA; all *P* values appear in Table S8.



**Figure 4. Contribution of M8 evolved alleles to fitness in low glucose**

(A, B) Average fitness effect of each variant across the segregant offspring at log-phase (20h) and post-diauxic shift (30h) during growth in low-glucose. Shown are fitness measurements (OD<sub>600</sub>, mean and standard error, normalized to the progenitor value) for 48 progeny from an M8 X P cross – fully genotyped for all five coding loci identified by sequencing, at 20h (A) and 30h (B) of growth on glucose. Data are aggregated by specific alleles, as marked (in each marked category, e.g. “MKT1”, the other alleles are segregating). Full data are available in Table S5. Light gray bars, ancestral alleles; dark bars, evolved alleles. Fitness of evolved parent is shown at the upper right corner. Significant differences are noted with P-value. All P values appear in Table S8. (C) Evolved alleles of *MDS3* and *MKT1* (*MDS3e* and *MKT1e*) account for the M8 phenotype. Shown are growth curves (OD<sub>600</sub>) from three tetrads from each of two independent crosses segregating for *MDS3* and *MKT1*, and no other evolved alleles (based on full genotyping). The number of replicates for each time course varied between four and eight, reflecting independent assortment. The evolved allele of *MDS3* (green) confers a benefit early, while that of *MKT1* (blue) confers a benefit late in the growth cycle, relative to the ancestral genotype (black). Together these two alleles produce a phenotype (red) that matches that of the M8 strain (dashed).



**Figure 5. Average fitness effects in low glucose of each variant across segregants from the S2XM8 cross that had the ancestral *MET3* allele for prototrophy**

Shown are fitness measurements ( $OD_{600}$ , mean and standard error, normalized to the progenitor) in low glucose for 48 fully genotyped progeny from the crosses S2 X M8 that had the ancestral *MET3* allele for prototrophy. Data are aggregated by specific alleles, as marked. Full genotypic and fitness data appear in Tables S3-S7 and P-values of all statistical tests appear in Table S8. Light gray bars, ancestral alleles; dark bars, evolved alleles. Fitness of evolved parent is shown at the upper right corner. (A) 20h; (B) 24h; (C) 30h.

sodium efflux pumps [19] (a similar *ENA* gene-cluster expansion has been observed previously [20] with adaptation to high salt). *ENA* and *PMA1* also had the only significant additive interaction (ANOVA,  $P < 10^{-4}$ , Figure 3C), although this interaction was only marginally significant on a logarithmic scale (ANOVA of  $\log(\text{fitness})$ ,  $P < 0.07$ ). Nevertheless, the individual effects of the evolved alleles of *ENA* and *PMA1* in increasing fitness act in an unreduced (non-interfering) manner when together in the same haploid genotype. This is consistent with a reduction of H<sup>+</sup> efflux associated with the evolved allele of *PMA1*, and a greater Na<sup>+</sup> efflux by the expanded *ENA* gene cluster. Together, the evolved allele of *PMA1* and the *ENA* expansion conferred nearly the full fitness increase of the S2 haploid over the progenitor. Subsidiary minor effects of other mutations are summarized in Table S1..

S6 revealed a pattern of adaptation remarkably parallel to that of S2 (Figure 3B and Table S4). A mutation in *PMA1* distinct from that in S2 and another in *CYC8*, a general transcriptional repressor that acts together with *TUP1*, each conferred large gains in fitness (mean fitness relative to progenitor: *PMA1e* segregants – 2.40; *PMA1a* segregants – 1.64,  $P < 0.002$ ; *CYC8e* segregants – 2.68; *CYC8a* segregants – 1.39,  $P < 10^{-4}$ ). A pairwise interaction between *PMA1* and *CYC8* (Figure 4D), was positive and marginally significant on an additive scale (ANOVA,  $P < 0.0074$ , significance threshold of  $P = 0.0083$  with 6 comparisons), but not on a logarithmic scale ( $P < 0.023$ , significance threshold of  $P = 0.0083$  with 6 comparisons). The fitness effects of the evolved alleles of *PMA1* and *CYC8* are non-interfering when together in the same haploid genotype. The growth defect of S6 (Figure 2A and B) was due to the mutation in *PMA1*; all genotyped strains with the evolved allele grew poorly in YPD and in low glucose (Figure 2G).

The cluster of genes whose expression is specifically induced in S6 (Figure 6B) is enriched for targets of the Tup1-Cyc8 complex (140 common genes between 837 Tup1-Cyc8

targets and 240 genes in the S6 up-regulated cluster, out of 5728 genes in array,  $P < 1.5 \times 10^{-58}$ ), suggesting that the evolved *CYC8* allele encodes a less potent transcriptional repressor than the ancestral allele. Furthermore, these genes – repressed by Tup1-Cyc8 in YPD [21] and specifically induced in S6 – are enriched for known genes induced in the osmotic stress response [22] (53 common genes between 259 OSR genes and 240 genes in the S6 up-regulated cluster out of 5728 genes in array,  $P < 1.52 \times 10^{-23}$ ). Among the Tup1-Cyc8 target genes that are de-repressed in S6 are the glycerol biosynthesis enzyme *HOR2* (important for high salt tolerance) and the *ENA1* and *ENA2* genes, phenocopying the effect of the genetic expansion of the *ENA* cluster in S2.

### **Mutations in *MKT1* and *MDS3* contribute to increased fitness in distinct growth phases in low-glucose**

The contribution of the M8 evolved alleles to increased fitness and reproductive isolation in low-glucose depended on growth phase (Figure 4 and Table S5). At 20 h, when the cultures were growing exponentially by fermentation, only the *MDS3* allele conferred a significant fitness advantage (mean fitness relative to progenitor: *MDS3e* segregants – 1.3; *MDS3a* segregants – 0.99,  $P < 0.003$ ) among the M8 X P offspring (Figure 4A), and there were no significant allele interactions. *MDS3* is necessary for growth under alkaline conditions [23], consistent with the fitness benefit it conferred when culture pH was highest (near neutrality). In contrast, the evolved allele of *MKT1* – a major regulator of the mRNAs encoding mitochondrial proteins [24] – conferred a fitness disadvantage at this phase (mean fitness relative to progenitor: *MKT1e* segregants – 0.83; *MKT1a* segregants – 1.36,  $P < 10^{-4}$ ). The effect of each of these alleles was reversed after the diauxic shift from fermentation to respiration (30h, Figure 4B), when the



evolved *MDS3* allele conferred a fitness disadvantage (mean fitness relative to progenitor: *MDS3e* segregants – 0.82; *MDS3a* segregants – 1.12,  $P < 10^{-4}$ ) and the evolved *MKT1* allele was nearly neutral (mean fitness relative to progenitor: *MKT1e* segregants – 1.00; *MKT1a* – 0.97).

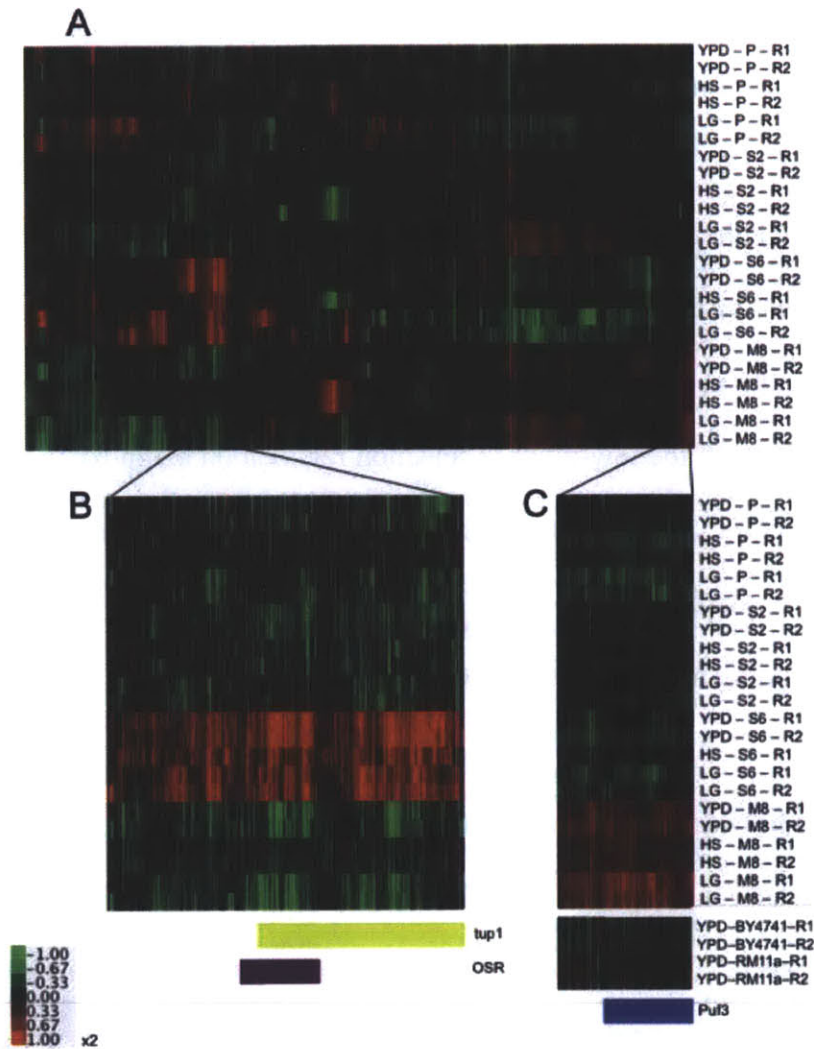
To explore the stage-dependent effects of *MDS3* and *MKT1*, we used 24 genotyped offspring of two crosses (three tetrads from each cross) segregating only for the evolved and ancestral alleles of *MDS3* and *MKT1* and for no other evolved SNPs. The evolved allele of *MKT1* alone showed no deficit relative to the progenitor in early time points (Figure 4C), but had a strong increase in fitness late in the growth cycle. This is in contrast to the aggregate effect of *MKT1* in the presence of other segregating SNPs (Figures 4A and B), where we found a fitness deficit early and near neutrality late. Nevertheless, in both experiments, the effect of *MKT1e* had the same directionality: it performs better late in the growth cycle than early. The evolved allele of *MDS3* showed the opposite directionality, performing better early than late. Importantly, genotypes carrying only the evolved alleles of both *MDS3* and *MKT1* closely approximated the growth curve of the **M8** haploid strain, accounting for the adaptation observed in low glucose (Figure 4C).

A competitive fitness assay over a 24 h period provided a third, independent, measure of the individual fitness effects in low glucose of the evolved alleles of *MDS3* and *MKT1*. This period matched the daily batch-culture regimen in the original 500 generation experiment [2], which included both fermentative and respirative energy production. Each mutation conferred a fitness advantage over the progenitor alleles (*MDS3*,  $1.25 \pm 0.1$  SE  $n=9$  and *MKT1*  $1.10 \pm 0.2$  SE  $n=6$ ). We conclude that our experimental regimen selected for alleles conferring advantages at distinct phases of the yeast growth cycle.

Finally, the evolved alleles of the mitochondrial protein *TIM11* and the chromatin modifier gene *RPH1* conferred smaller, non-significant growth increases at 30h (post-shift, Figure 4B, Tables S5 and S8). This effect is consistent with the role of the *RPH1* paralog in regulating gene expression post-diauxic shift [25]. However, the evolved *RPH1* allele was not essential to reconstitute the full **M8** phenotype.

### **The *MKT1* allele reverted to a wild allele during experimental evolution**

The evolved *MKT1* allele of **M8** is identical to the allele (89G) observed in strains of *S. cerevisiae* of diverse environmental origin and of *S. paradoxus* [26], leading to a non-conservative amino acid change from aspartate (**P**) to glycine (**M8**). *MKT1* encodes a major component in the interaction between Puf3, a sequence-specific RNA binding protein targeting mRNAs involved in mitochondrial function, and P-bodies, which control sequestration and expression of certain mRNAs [24]. The cluster of genes of elevated expression in **M8** strains (Figure 6C) is highly enriched for mitochondrial genes (62 common genes between 588 mitochondrial genes and 90 genes in the **M8** upregulated cluster out of 5728 genes in array,  $P < 2.7 \times 10^{-41}$ ), including aerobic respiration genes (10 common genes between 64 aerobic respiration genes and 90 genes in the **M8** upregulated cluster out of 5728 genes in array,  $P < 4.2 \times 10^{-8}$ ), and in particular known Puf3 targets (59 common genes between 137 Puf3 target genes and 90 genes in the **M8** upregulated cluster out of 5728 genes in array,  $P < 9.7 \times 10^{-79}$ ). Furthermore, the **M8** cluster includes genes more highly expressed in the vineyard strain RM-11 than the lab strain BY (Figure 6C, bottom). The eQTLs for these genes were previously found to be closely linked to the *MKT1* allele that segregates in the BY X RM-11 cross [24].



**Figure 6. Global expression changes in evolved strains associated with the adaptive genetic changes**

(A) Genome wide expression profiles from P, S2, S6, and M8 strains grown in YPD, low glucose (LG), and high salt (HS) environments. Red – induced compared to mean of all strains in that condition; green – repressed compared to mean of all strains in that condition. (B) Genes with high expression specific to S6 across all conditions are enriched for Cyc8-Tup1 targets and for osmotic response genes. Shown is a zoomed in cluster from (A). Yellow bar – genes whose expression is induced in a deletion of the *TUP1* gene [19]; purple bar – genes whose expression is induced during the Osmotic Stress Response (OSR) to high salt [20]. Genes are re-ordered by the *TUP1* and OSR annotations. (C) Genes with high expression specific to M8 across all conditions are induced in the RM-11 wine strain and enriched for Puf3 targets. Top panel – zoomed in cluster from (A). Bottom panel – expression of the same genes in the laboratory strain BY and in the wild wine strain RM. Blue bar – genes in the Puf3 module [22], whose eQTL in a cross between BY and RM has been linked to the same genetic change in *MKT1* found also in the M8 strain. Genes are re-ordered by membership in the Puf3 module.

Taken together, the data suggest a past mutation from the allele (89G) uniformly present in wild strains to that of the laboratory standard (89A), carried by our **P** strain, followed by an exact reversion of that mutation at some point during the 500 generations of evolution from **P** to **M8**. Thus, the progenitor (**P**) laboratory reference strain carries a less potent form of *MKT1*, with lower expression of target genes, strongly selected for in lab experiments focusing on early or mid-log phase cells in which the wild allele (here the “evolved *MKT1*”) confers a growth disadvantage. In contrast, the low-glucose selection regimen on a 24h batch-transfer cycle used in this study may more closely approximate natural conditions in which growth more often approaches stasis, a condition that would favor the reversion to the naturally-occurring 89G allele, and corresponding higher expression of gene targets.

#### **A DM Interaction between *PMA1* and *MKT1***

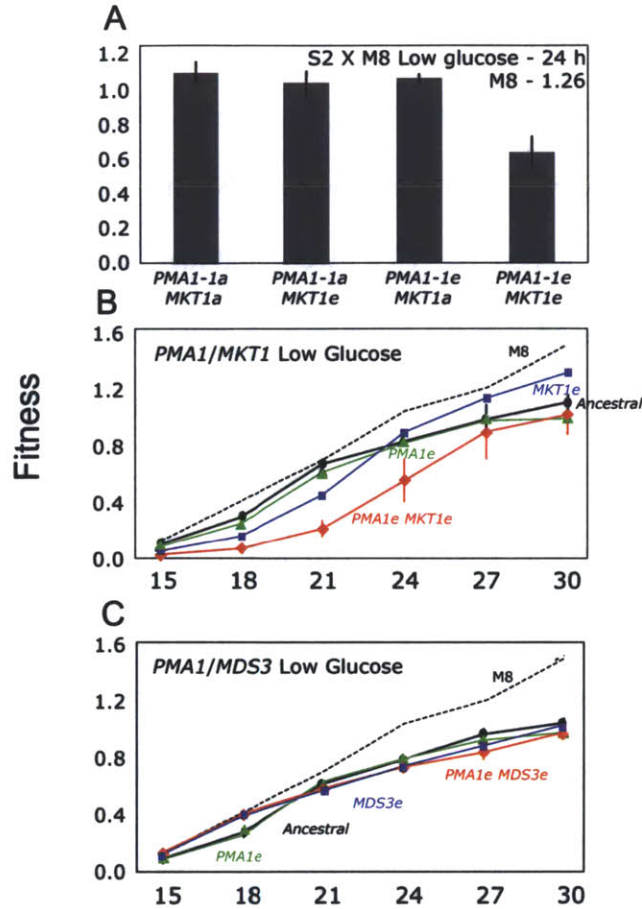
We next tested for the presence of DM interactions, defined as genetic incompatibilities between alleles independently evolved in the two environments. We measured the fitness, in the two selective environments, of 96 offspring from 24 tetrads from the **S2 X M8** and **S6 X M8** crosses (Figures 2 and 5). All progeny were fully genotyped for all segregating SNPs, gene-cluster size alterations, and mating type, all of which segregated ~1:1 in tetrads (Tables S6 and S7). As before, we tested each pairwise combination of loci for interaction by means of ANOVA (Table S8).

Among the offspring of the **S2 X M8** cross in the low-glucose environment at 24 hours (Figure 5A and Supplemental Table 6), we found only one marginal P-value of 0.015 for a *PMA1e-MKT1e* negative fitness interaction (in the presence of other segregating alleles). Since

the initial value was marginal, we tested this preliminary evidence for an interaction in two additional independent experiments.

In the first, we measured the fitness of 24 genotyped offspring of two crosses (three tetrads from each cross), that segregated at **only** the two SNP sites in *PMA1* and *MKT1* (no other evolved alleles were present in the cross). Here, we found that the fitness of offspring carrying both evolved alleles was depressed over the entire growth cycle in low glucose (Figure 7B), most prominently at the 21 and 24h time points (the same time point as in Figure 7A). At 24h, an overall ANOVA of additive variation over the four genotypes was statistically significant ( $P < 0.016$ , one test only) and a Tukey-Kramer HSD test indicated that the only difference was between the *PMA1a MKT1e* and *PMA1e MKT1e* genotypes. The reduction in the *PMA1e MKT1e* genotype is therefore due to the presence of the *PMA1e* allele, which is otherwise nearly neutral in the low-glucose environment and closely tracks the progenitor over the entire growth cycle. We further confirmed this result in three additional replicate experiments with the same strains at 24h, finding a significant interaction between the *PMA1* and *MKT1* alleles, when fitting a linear mixed model treating strain as a random effect and tested against a null model of no interaction between *PMA1* and *MKT1* (*PMA1aMKT1a*:  $0.69 \pm 0.02$ , *PMA1aMKT1e*:  $0.70 \pm 0.02$ , *PMA1eMKT1a*:  $0.66 \pm 0.01$ , *PMA1eMKT1e*:  $0.46 \pm 0.03$ ,  $P < 10^{-4}$ ). This interaction is also significant on log scale ( $P < 4 \times 10^{-5}$ ). This fulfills the criterion for a DM interaction [2]. Similar assays with offspring segregating for *MDS3* and *PMA1* showed no such negative interaction (Figure 7C).

We independently confirmed the negative interaction between the *PMA1* and *MKT1* genotypes in competition experiments in the low-glucose environment at an early time point (17h under conditions matching those in Figure 7B), showing a negative reduction in the number



**Figure 7. DM interactions between the evolved alleles of *PMA1* and *MKT1***

(A) DM interaction between the evolved alleles of *PMA1* and *MKT1* at 24h in low-glucose. Shown are the fitness measurements ( $OD_{600}$ , mean and standard error, normalized to the progenitor value) of 96 offspring of a cross between S2 and M8 in the low-glucose environment at 24h grouped by their two-locus genotypes for *PMA1* and *MKT1* (*e* - evolved allele; *a* - ancestral allele); note the depressed fitness of the genotype carrying both evolved alleles of these genes. ANOVA: evolved allele of *PMA1*,  $P < 10^{-4}$ ; evolved allele of *MKT1*,  $P < 10^{-4}$ ; and interaction of the evolved alleles of *PMA1* and *MKT1*,  $P < 0.015$ . Full data are available in Table S6 and all P values of all tests are listed in Table S8. (B) DM interaction between the evolved alleles of *PMA1* and *MKT1* along the growth curve. Shown are growth curves from three tetrads from each of two independent crosses segregating for *PMA1* and *MKT1*, and carrying no other evolved alleles (based on full genotyping). The number of replicates for each time course varied between four and eight, reflecting independent assortment. The genotype carrying the evolved alleles of *PMA1* and *MKT1* (red) shows poor growth at all time points (up to 27h) relative to the other genotypes. The other genotypes are marked as *PMA1e* (green); *MKT1e* (blue); ancestral (*PMA1a* *MKT1a*, black); and M8 (dashed). (C) Absence of an interaction between *PMA1* and *MDS3*; analysis as in B: *PMA1e* (green); *MDS3e* (blue), *PMA1e* *MDS3e* (red); ancestral (*PMA1a* *MDS3a*, black); and M8 (dashed).

of doublings in the *PMA1e MKT1e* genotype strain (*MKT1e*,  $0.87 \pm 0.01$  SE (n=3); *PMA1e*,  $0.89 \pm 0.02$  SE (n=3); *PMA1e MKT1e*,  $0.7 \pm .07$  SE (n=3) all relative to the doublings by the progenitor). As a control, we confirmed the expected beneficial effect of *MDS3e* in the competition assay ( $1.28 + 0.01$  SE (n=2)). The difference in fitness among the genotypes fell just short of significant ( $P < 0.061$ , one-way ANOVA, linear scale), likely reflecting the smaller sample size and the earlier (17h) time point. Nevertheless, each of these three experiments supported the conclusion of negative interaction between the evolved alleles of *PMA1* and *MKT1*, most notably at 24h. In contrast, there was no evidence for a DM interaction in the **S2 X M8** and **S6 X M8** offspring in high salt and the **S6 X M8** offspring in low glucose (Supplemental S7 and S8), where all adaptive determinants had effects similar to those in crosses of the evolved strains and the progenitor (Figures 2A and B).

## Discussion

In this study we used whole-genome sequencing of progenitor and evolved strains, along with genotyping, fitness assays, and mRNA profiling to identify and characterize the genetic and molecular basis of early events associated with divergent selection in experimental yeast populations. We found six key determinants, each of which contributes to ecological isolation in which genotypically mixed hybrids are not as well matched to either environment as the pure evolved strains.

The DM interaction between *PMA1* and *MKT1* is the first reported between evolved alleles of known genes in experimental populations derived from a common ancestor. Although it is tempting to speculate on how such an incompatibility might affect natural yeast populations, our study was limited to haploid effects. One possibility is that a DM incompatibility like that

reported here would quickly be eliminated with recombination. Conversely, such a DM interaction might present a strong reproductive isolation mechanism in nature under the low rate of outcrossing in *S. cerevisiae* [27]; in such a case the incompatibility would persist in hybrid populations. These possibilities remain to be investigated.

No consistent functional theme has yet emerged among the known “speciation genes” implicated in DM interactions among species in nature [7-12]. Here, we show that the adaptive mechanisms evolved in response to strong directional selection in two environments have substantial effects on gene regulation and phenotype and that at least two of the adaptive determinants produce an intrinsic clash resulting in a fitness reduction characteristic of a DM interaction. In extant species examined to date, the majority of DM incompatibilities occur in genes unrelated to ecological adaptation [8]. Our study, in which we experimentally set the conditions thought to foster incipient speciation, documents a counter example in which divergent adaptive changes themselves confer a DM incompatibility. It is possible that newly evolved adaptive mechanisms under other conditions will have similarly far-reaching consequences, with potential for DM incompatibility. We propose that the potential pool of speciation genes includes genes conveying adaptation under strong selection in the earliest stages of speciation – that functional diversity in speciation genes could reflect the diversity of adaptive mechanisms.



## **Experimental Procedures**

### **Strains**

We used haploid strains that were derived from the diploid experimental populations described by Dettman et al.[5]. Each strain was marked by replacement of the *URA3* open reading frame with either the NATr or G418r cassette flanked by two unique barcodes. Populations **S2** (G418<sup>r</sup>), **S6** (NAT<sup>r</sup>), and **M8** (NAT<sup>r</sup>) were allowed to sporulate and four complete tetrads were dissected from each. The **S2** and **S6** haploid offspring were assayed for fitness (see below) in high salt (YPD with 1.0 M NaCl), and those from **M8** in low glucose (Yeast Nitrogen Base with 2.5 g of glucose per L, rather than the standard 20 g). Strains with the highest values in the fitness test were selected as the representatives from each population. The progenitor **P** (G418<sup>r</sup>) was strain Sc3044. In array experiments we also used the standard laboratory strain BY4741 and the wine strain RM-11a.

### **Illumina sequencing**

We prepared genomic DNA from the progenitor (**P**) and evolved strains (**S2**, **S6**, and **M8**) and sequenced the DNA using single-end Illumina sequencing[28]. In the progenitor, we generated 843 Mb from 36-mer sequence reads. In the evolved strains, we generated an average of 688 Mb from 51-mer sequence reads. We then mapped the sequence data to the S288C reference genome (Saccharomyces Genome Database <ftp://ftp.yeastgenome.org/yeast/>) using the Maq alignment tool[29]; 622 Mb of the progenitor was mapped for a coverage of ~52x coverage, and an average of 447 Mb of the evolved strains was mapped for an average coverage of ~37x (Supplemental Table 2). Primary data are available at: <http://www.broadinstitute.org/regev/webdata/Anderson/>.

## **Identification of SNPs**

SNP calling was also conducted via Maq using default parameters. There are 554 SNP loci called in at least one strain (including the progenitor). We classified these SNPs given their location; 182 were noncoding, 81 were synonymous nucleotide substitutions, and 291 were non-synonymous nucleotide substitutions. From the total of 554 SNPs identified (Supplemental Table 2), 539 were interpreted as present in the ancestor and all four derived haploid strains. These SNPs represent mutations that occurred before the experimental evolution described by Dettman et al. [5] and were not relevant to this study. The 15 SNPs interpreted as unique to **S2**, **S6**, and **M8** included 12 coding, non-synonymous SNPs (four in **S2**, two in **S6**, six in **M8**) and three noncoding (one in **S2** and two in **S6**) SNPs. Each of these SNPs was confirmed by conventional PCR and Sanger sequencing, and were evaluated for their fitness effects.

## **SNP assays**

PCR amplicons ranging from 300 - 500 base pairs in size were transferred to nylon membranes and hybridized with 15 base oligonucleotide probes 5' end labeled with  $^{32}\text{P}$ . In each probe, the site of potential base mismatch was in the center. The hybridizations were done 2 - 4 C above the predicted  $T_m$  to ensure specificity. This method follows that described by Cowen et al.[30].

## **Comparative genome hybridization (CGH)**

Genomic DNA was prepared according to the protocol available at <http://genome-www.stanford.edu/rearrangements/aCGH1.html>. Genomic DNA (40-50  $\mu\text{g}$ ) was sonicated to obtain DNA fragments of roughly 100 basepairs to 10 kilobases and purified with a QIAquick PCR Purification Kit (Qiagen). The two DNA samples to be compared were labeled with Cy3 or

Cy5 using the Mirus Label IT® Nucleic Acid Labeling Kit (Mirus, Madison, Wisconsin, United States), according to the manufacturer's protocol with the following modification: half-sized reactions were used. The labeled genomic DNA was co-hybridized to *S. cerevisiae* microarrays obtained from the University Health Network Microarray Centre (Toronto, Ontario, Canada). A pre-soak for background reduction used the Pronto Background Reduction Kit (Corning) according to the manufacturer's instructions. QuantArray (PerkinElmer) was used to quantify the relative fluorescence of Cy3 and Cy5 for each spot on the array.

### **Confirmation of copy number changes**

In subsequent experiments, specific copy number variants were assayed by digesting genomic DNA with *EcoRI*, followed by electrophoresis and capillary transfer to a nylon membrane. The blots were probed with PCR products representing most of the open reading frame of the gene. Hybridization signal was quantified exactly as described by Anderson et al. [30]. This signal was normalized by hybridizing with a gene (*YEF3*) not showing copy-number variation, to correct for variation in the amount of genomic DNA loaded per lane.

### **Fitness measurements**

The measure of fitness for each strain was culture density after set periods of time following introduction of a standard volume of inoculum of an overnight culture (10  $\mu$ L for high-salt environment or 2  $\mu$ L for low-glucose environment) to 10 ml of fresh medium. The P, S2, and M8 haploid strains were included as controls. The fitness values of genotypes were highly consistent within experiments, but the overall scale of variation differed among experiments.

### **Statistical significance of allele effects and interactions**

We used 2-way ANOVA to test for the fitness effect of each evolved and ancestral allele and for interactions between every pair of alleles, and 3-way ANOVA to test for 3-allele interactions (only one significant interaction was found). We confirmed that each dataset was generally normally distributed based on Rankit (QQ plot), but for the lowest values (e.g., MET3e in Figure 2C) likely due to spectrophotometer error. For each test, we used a linear, fixed-effects, additive model, with a least squares fit, as implemented in JMP, The Statistical Discovery Software, version 5.1 (SAS Institute, Inc.). For each interaction test, there were three factors, one locus, the other locus, and their interaction. *P* values for the interactions are available in Supplemental Table 4. For each cross (S2XP, S6XP, M8XP, S2XM8, S6XM8), we used a significance threshold of  $0.05/N$  (Bonferroni correction), where *N* is the number of tests made.

### **Competition experiments**

Equal numbers of strains carrying evolved and ancestral alleles were mixed and followed over 13.2 generations (for *MDS3* and *MKT1* genotypes) or over 7-8 generations (*PMA1* and *MKT1* genotypes) as described by Anderson et al.[31] except that SNP frequencies, rather than bar codes, were monitored directly. For calibration standards, different strains were mixed to give allele frequencies of: 1.0, 0.98, 0.97, 0.94, 0.88, 0.75, 0.5, 0.25, 0.13, 0.64, 0.03, and 0.02; the correlation between pixel volumes on the phosphor screen after hybridization of PCR amplicons on Nylon membranes with allele-specific probes were always highly correlated with the known allele frequencies ( $R^2 > 0.99$ )

### **Effects of SNPs and *ENA* gene-cluster expansion on fitness**

For measuring the association of evolved alleles with fitness effects, four crosses were made: i) the *MATa* S2 haploid X a *MATa* P; ii) the *MATa* M8 haploid X a *MATa* P strain; iii) the *MATa* S2 haploid X the *MATa* M8; and iv) the *MATa* S6 X a the *MATa* M8. Diploids were recovered by simultaneous selection with NAT and G418. Sporulation and tetrad dissection were standard<sup>17</sup>.

### **RNA preparation, genomic DNA preparation and labeling**

Total RNA was isolated using the RNeasy Midi or Mini Kits (Qiagen) according to the provided instructions for mechanical lysis. Samples were quality controlled with the RNA 6000 Nano II kit for the Bioanalyzer 2100 (Agilent). Genomic DNA was isolated using Genomic-tip 500/G (Qiagen) using the provided protocol for yeast. Progenitor DNA samples were sheared using Covaris sonicator to 500-1000 bp fragments, as verified using DNA kit for the Bioanalyzer 2100 (Agilent). Total RNA samples were reverse transcribed and then labeled with Cy3 (cyanine fluorescent dyes) and genomic DNA samples were labeled with Cy5 using a modification of the protocol developed by Joe Derisi (UCSF) and Rosetta Inpharmatics (Kirkland, WA) that can be obtained at [www.microarrays.org](http://www.microarrays.org).

### **Microarray hybridizations**

Each Cy3 labeled cDNA biological replicate was mixed with a reference Cy5 labeled genomic DNA sample and hybridized on commercial *S. cerevisiae* two-color Agilent oligo-arrays in the 4x44K format (4-5 probes per target gene). Labeled genomic DNA was denatured at 95°C for 3

minutes, then snap-cooled on ice for 5 minutes prior to being combined with an RNA sample. After hybridization and washing per Agilent instructions, arrays were scanned using an Agilent scanner and analyzed with Agilent's feature extraction software version 10.5.1.1, excluding final normalization (below).

### **Microarray data processing**

For each probe, the median signal intensities were background-subtracted for both channels and combined by taking the log<sub>2</sub> of their ratio. To estimate the absolute expression values for each gene, we took the median of the log<sub>2</sub> ratios across all probes. Data was combined using quantile normalization to estimate the absolute expression level per gene. Finally, each gene's expression in each sample was normalized by subtracting its mean expression across all strains in the same condition (YPD, low glucose, or salt). The processed data was clustered using hierarchical agglomerative clustering. Functional enrichment was assessed by comparing to previously collected gene sets[32] and estimated using a hypergeometric test, as previously described [32]. Micro-array data are available at: <http://www.ncbi.nlm.nih.gov/geo/query> under accession number GSE20943.

### **Supplemental data**

Supplemental tables can be found on the journal's cite:

<http://www.sciencedirect.com/science/article/pii/S0960982210007670#appd002>

Supplemental tables can be found in Appendix 1 or at:

<http://www.broadinstitute.org/regev/webdata/Anderson/>

Gene Expression Omnibus Record is GSE20943.

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## **Chapter 2: The mutational landscape of gradual acquisition of drug resistance in clinical samples of *Candida albicans***

We use whole genome re-sequencing and phenotypic characterization of strains of *Candida albicans* derived from HIV patients with oropharyngeal candidiasis. We confirm the progression of the drug resistant phenotype and couple to recurrent, persistent changes in the genome sequence. We observe that increase in drug resistance can also be coupled to other phenotypes, and ultimately describe those changes.

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## Abstract

*Candida albicans* is both part of the healthy human microbiome and a major pathogen in immunocompromised individuals [1]. Infections are most commonly treated with azole inhibitors of ergosterol biosynthesis. Prophylactic treatment in immunocompromised patients [2, 3] often leads to the development of drug resistance. Since *C. albicans* is diploid and lacks a complete sexual cycle, conventional genetic analysis is challenging [4]. An alternative approach is to study the mutations that arise naturally during the evolution of drug resistance *in vivo*, using strains sampled consecutively from the same patient. Studies in evolved strains have implicated multiple mechanisms in drug resistance, but have focused on large-scale aberrations or candidate genes, and do not comprehensively chart the genetic basis of adaptation [5]. Here, we leverage massively parallel DNA sequencing to systematically analyze 43 strains serially collected from 11 oral candidiasis patients, ranging from two to 16 time points per patient. We find that most infections are clonal, allowing us to detect newly acquired mutations, including SNPs, copy-number variations and LOHs. Focusing on mutations that are both persistent within a patient and recurrent across patients, we identify an important and under-reported LOH event that co-occurs with increases in drug resistance and identify both well-known drug-related genes as well as poorly characterized, highly recurrent genes which may be functionally significant. Our work sheds new light on the molecular mechanisms underlying the evolution of drug resistance and host adaptation.

## Introduction

The dimorphic yeast *Candida albicans* is one of the most studied fungal pathogens. *C. albicans* is part of the healthy human microbiome as a commensal and is not found in environmental reservoirs[6], however it also exists as a major pathogen in immunocompromised individuals[1]. Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States[7], with *C. albicans* accounting for nearly 65%[8, 9] of *Candida* infections. Systemic infection is associated with a mortality rate as high as 50%[1]. Resistance arises during long-term prophylactic treatment regimes[10, 11] that are sometimes indicated in immunocompromised patients (e.g. bone marrow transplant[2] or HIV[3]). Previous studies of resistant strains have shown that this is mediated by multiple (possibly inter-dependent) mechanisms including segmental aneuploidy[12], increased expression of drug pump genes[13], loss of heterozygosity (LOH) across chromosomes or regions of chromosomes[13, 14], mutations in ergosterol biosynthetic genes[15], and deviations facilitated by the heat shock protein Hsp90[16]. Because *C. albicans* is diploid and lacks a complete sexual cycle, conventional genetic analysis is simply not possible, and has been a barrier for study despite its medical significance[4].

Both *in vitro* and *in vivo* systems provide an extensive trace of the evolutionary process, in the form of sampled strains throughout the evolutionary time course. Thus, they hold the promise of uncovering the evolutionary mechanism of stressor adaptation. However, previous studies have focused predominantly on large-scale aberrations or candidate genes, but not both, and therefore do not provide a comprehensive view of the genetic changes underlying adaptation[5]. The development and decreasing costs of high-throughput sequencing makes it possible to follow the genomic evolution of pathogens, but a challenge remains in distinguishing

between selection and drift when looking at variations. In the laboratory, this difficulty has been addressed by following several populations grown in parallel cultures under identical conditions; the adaptive nature of mutations is indicated by their recurrence in replicate experiments. In natural and clinical environments, such studies are more difficult and are only now being broached via genomic inquiry in prokaryotes[17].

In this work, we aimed to determine the entire mutational landscape of clinically derived strains of *C. albicans* that acquire drug resistance. We sequenced 43 strains from 11 HIV patients with oropharyngeal candidiasis; from each patient, there were two or more isolates. Our first objective was to determine whether each series was clonally derived. Following establishment of clonality, and removing non-clonal isolates, we identified and catalogued each mutation in each series, focusing particularly on newly arising mutations. Using recurrence between patients as an indicator of functional significance, we find both large, genome-level events as well as small, single base-pair substitutions that are likely players in drug resistance. Finally, we explore relating other changing phenotypes to genomic level events.

## Results

### Sequencing of *in vivo* isolates during evolution of drug resistance

To study the *in vivo* evolution of azole resistance in *C. albicans*, we analyzed 43 strains from 11 HIV-infected patients with oropharyngeal candidiasis[18, 19] (**Table 1**). The strains from each patient were isolated during incidences of infection and form a time series (**Figure 1, Figure 2a**). The first strain (progenitor) was isolated prior to any treatment with azole anti-fungals; the remaining strains were isolated at later, typically consecutive time points, culminating in the final ‘endpoint’ strain (**Table 1**). The progenitors are more sensitive to fluconazole than subsequent isolates, as defined by the minimum inhibitory concentration (MIC) (**Table 1, Methods**). Previous studies in some of these strains identified several mechanisms that may contribute to drug resistance, including segmental aneuploidy[12], increased expression of drug efflux genes[13], loss of heterozygosity (LOH) across large chromosomal segments[13, 14], mutations in ergosterol biosynthetic genes[15], and facilitation by the chaperone heat shock protein 90 (Hsp90)[16].

We sequenced the genomic DNA of each of the strains (and the *C. albicans* lab strain, SC5314), using Illumina sequencing (**Methods, Table 1**), identified point mutations and larger aberrations that occurred after the progenitor, and determined for each if it is *persistent* within a patient and *recurrent* across patients (**Figure 1, Supplementary Table 1**). All mutations were detected relative to SC5314, the *C. albicans* genome reference strain. *Background* mutations are common to all strains in the series (including the progenitor, **Figure 1, purple**). *Persistent* mutations are not present in the progenitor, but present consecutively from the isolate in which they arose throughout the remainder of the time course (**Figure 1, yellow**), presumably selected

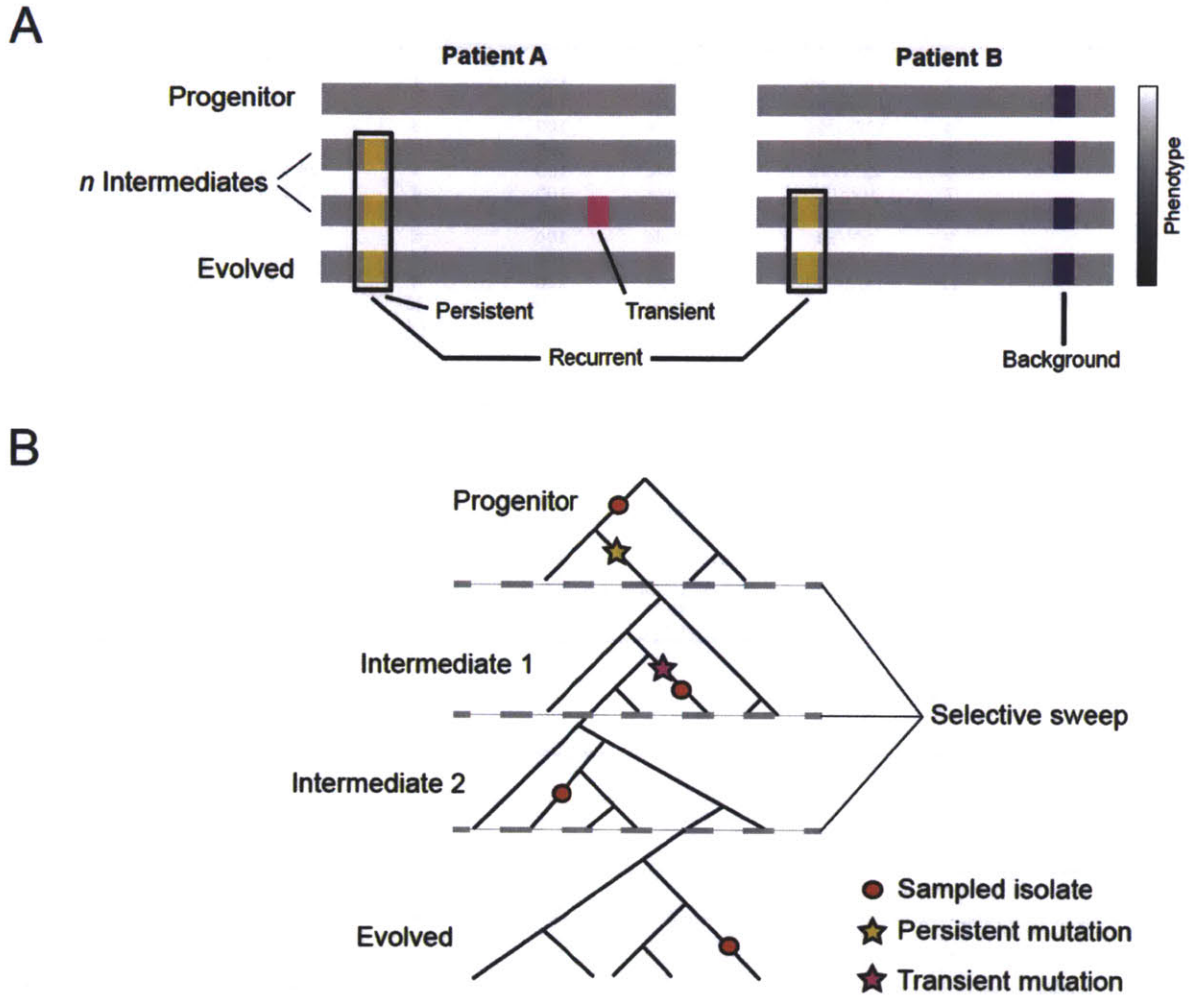
Publication Name	Patient	Strain	Entry Date	Drug Treatment	Dose (mg/day)	E-test MIC (ug/mL)	Depth of Coverage	Reads	Fraction Aligned
White, T.C.	1	1	9/10/90	Fluconazole	100	0.25	19.2192	4,957,416	87.0215%
		2	12/14/90	Fluconazole	100	1	38.7477	9,575,398	95.4372%
		3	12/21/90	Fluconazole	100	4	20.9735	5,379,156	87.8439%
		4	12/31/90	Fluconazole	100	3	25.7020	6,613,910	88.4204%
		5	2/8/91	Fluconazole	100	4	25.5055	6,591,818	88.4265%
		6	2/22/91	Fluconazole	100	4	24.5343	6,347,882	88.1557%
		7	3/25/91	Fluconazole	100	4	30.1535	7,742,300	88.4035%
		8	4/8/91	Fluconazole	100	4	19.5445	5,114,968	85.4924%
		9	6/4/91	Fluconazole	100	4	17.2656	4,642,144	85.1604%
		11	7/15/91	Fluconazole	100	4	20.8076	5,321,510	88.4235%
		12	11/26/91	Fluconazole	200	4	34.0561	8,438,948	95.4677%
		13	12/13/91	Fluconazole	400	32	34.9395	8,593,718	95.1638%
		14	1/28/92	Fluconazole	400	24	20.5015	5,385,134	88.5430%
		15	2/21/92	Clotrimazole	50	24	17.6284	4,679,970	85.7060%
		16	4/1/92	Fluconazole	400	96	17.6442	4,473,684	89.0691%
		17	8/25/92	Fluconazole	800	96	16.3827	4,598,094	81.9933%
		Perea, S. et al.	7	412	2/15/95	Fluconazole	0	0.25	24.2606
2307	11/22/95			Fluconazole	400	0.75	17.8088	4,946,180	84.7707%
Perea, S. et al.	9	1002	4/20/95	Fluconazole	100	0.125	23.7446	5,989,852	93.2972%
		2823	4/6/96	Fluconazole	800		22.9543	5,692,258	92.1211%
		3795	2/26/97	Fluconazole	800	128	15.4739	5,806,668	69.2547%
Perea, S. et al.	14	580	3/13/95	Fluconazole	0	1.5	23.5691	6,419,866	84.7974%
		2440	1/3/96	Fluconazole	800	1.5	27.5816	7,466,482	85.0403%
		2501*	1/4/96	Fluconazole	800	96	22.6987	6,065,350	84.6670%
Perea, S. et al.	15	945	4/14/95	Fluconazole	300	4	17.8029	4,600,706	85.6004%
		1619	7/11/95	Fluconazole	500	64	11.1846	3,969,036	67.7042%
Perea, S. et al.	16	3107	6/5/96	Fluconazole	800	4	20.1296	5,464,854	84.8738%
		3119	6/5/96	Fluconazole	800	96	21.6383	5,725,352	85.2416%
		3120	6/5/96	Fluconazole	800	96	22.1763	5,623,852	92.7914%
		3184	7/1/96	Fluconazole	800		23.6035	5,846,818	91.0434%
		3281	7/16/96	Fluconazole	800		19.4486	5,416,974	83.7257%
Perea, S. et al.	30	5106	1/7/98	Fluconazole	800	0.5	20.8939	5,685,762	83.1623%
		5108	1/7/98	Fluconazole	800	0.75	25.0948	6,601,396	85.1954%
Perea, S. et al.	42	1691	8/3/95	Fluconazole	100		24.1965	6,262,036	87.6899%
		3731	12/27/96	Fluconazole	400	256	22.4400	5,759,330	87.7794%
		3733	12/27/96	Fluconazole	400	256	23.1056	6,167,930	87.2610%
Perea, S. et al.	43	1649	7/19/95	Fluconazole	0	0.125	22.2856	6,177,754	85.2690%
		3034	5/15/96	Fluconazole	400	0.75	19.8168	5,504,546	82.0859%
Perea, S. et al.	59	3917	2/19/97	Fluconazole	800	2	26.6637	6,766,766	88.3911%
		4617	8/28/97	Fluconazole	400	64	16.0395	4,088,796	88.2887%
		4639	9/2/97	Fluconazole	400	128	27.4587	6,922,062	88.8073%
Perea, S. et al.	64	4018	4/2/97	Fluconazole	200		22.8235	6,055,484	85.2527%
		4380	7/14/97	Fluconazole	200		N/A	9,104,318	13.8548%

Not clonally derived from progenitor

\* Isolated on same day from same patient as previously published strain, 2500

**Table 1. Strain history and sequence summary**

Originating lab, clinical history, MIC, and sequence statistics are summarized for each strain. Non-clonal strains are marked in red, and were not phenotyped for resistance. Isolate 2501 was not included in the original publication, but was isolated from the same patient on the same day.



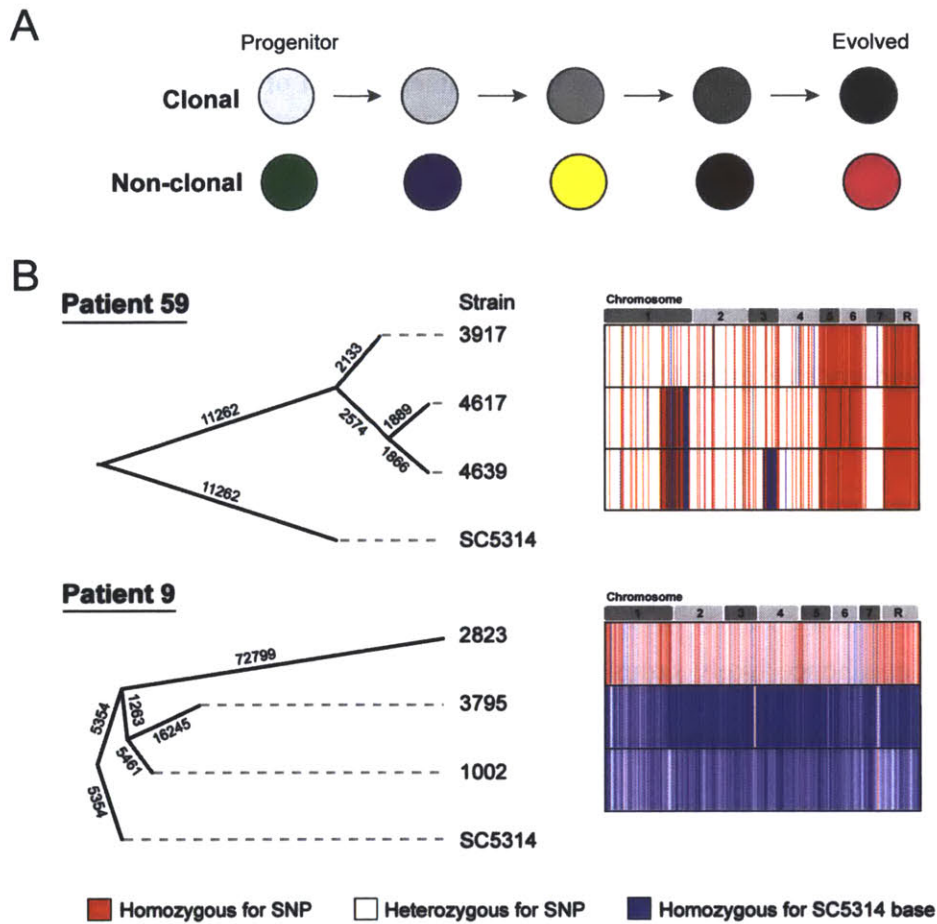
**Figure 1. Persistent and recurrent mutations are likely significant for changing phenotype**  
 A. Mutations that are **persistent (yellow)** are newly acquired compared to the progenitor and retained in all subsequent isolates. Mutations common to all isolates in a series are **background (purple)** and removed from consideration. Mutations that flow in an out of a series are **transient (pink)**, and are removed from consideration. **Recurrence (black boxes)** are considered for functional significance across changing phenotypes (**grayscale, right**).  
 B. Isolates are sampled from a particular patient during different episodes of infection. As a result, each isolate is related to another, though potentially not linearly. As a result, mutations that arise in a particular sample may not be present in a population following a selective sweep (i.e. clonal interference or bottleneck event).



for via selective sweep. (We consider the special case of a mutation only in the endpoint strain as persistent as well, since several of the time courses consist of only 2 or 3 isolates.) *Recurrent* mutations are persistent in more than one series (**Figure 1**, black boxes). We reasoned that recurrent mutations are the most likely to be adaptive, but that some adaptive mutations may be persistent in only one patient. *Transient* mutations (**Figure 1a**, pink) may be the result of evolutionary dead-ends (**Figure 1b**) or could be the result of sequencing errors.

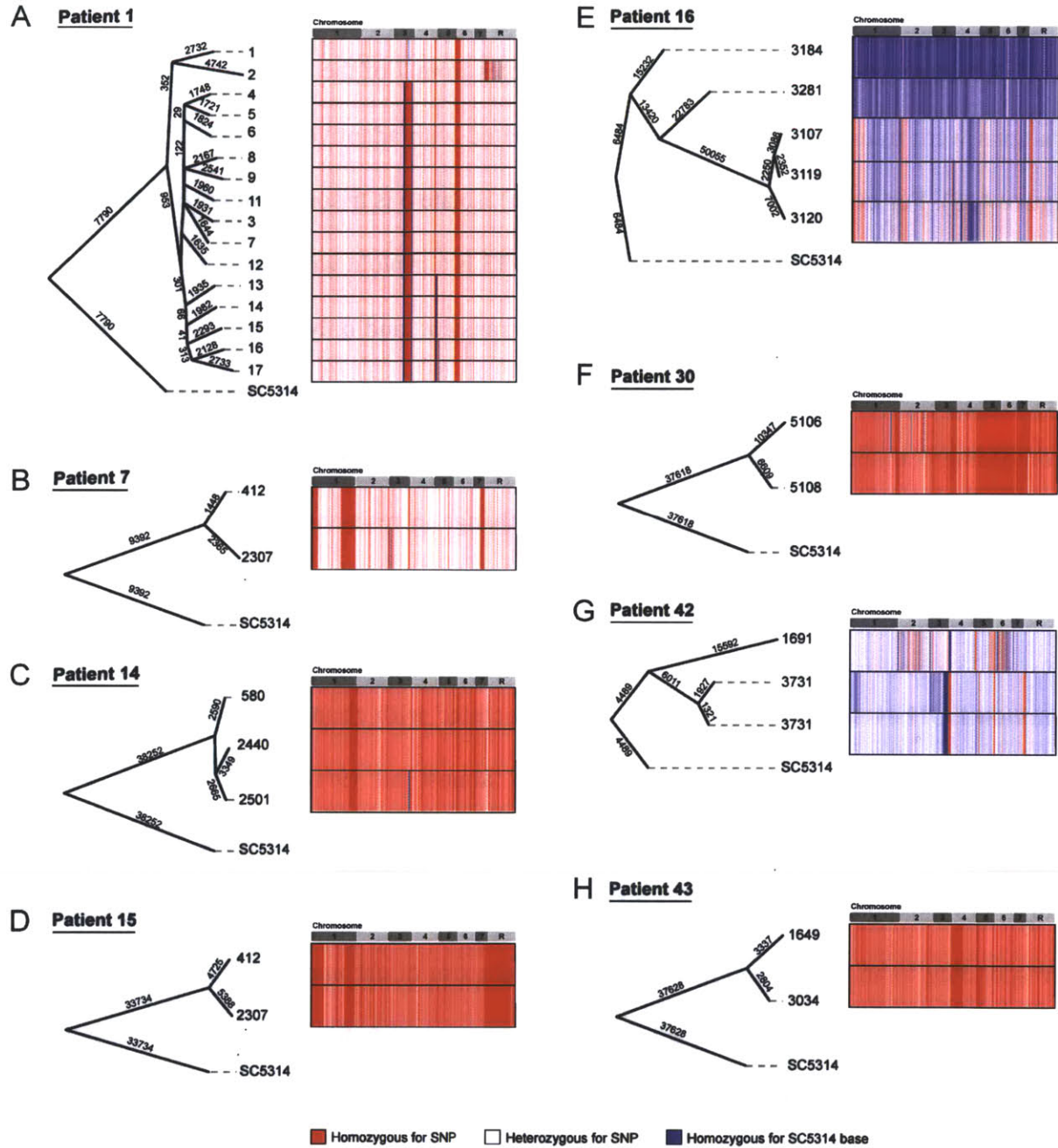
### **Most time courses are clonal**

Analyzing the background SNP mutations, we first determined that most time courses are largely clonal, and hence likely sampled continuous evolutionary trajectories (**Figures 2** and **3**). To distinguish between a clonal trajectory and repeated, independent infections (**Figure 2a**, top and bottom, respectively), we determined the distance between each two strains from their SNP profile, and used neighbor-joining to construct phylogenetic trees, with the reference strain SC5314 as an outgroup (**Methods**, **Figure 2b**, **Figure 3**). All but one (10/11) of the series are predominantly clonal, with an occasional isolate that is not. For example, all 16 strains from Patient 1 are clonal (**Figure 3a**), as are the three strains from Patient 59 (**Figure 2b**). Conversely, only 2 of 3 strains (strains 1002 and 3795) from Patient 9 are clonal, with the other isolate (2823) not related to either of them (**Figure 2b**, **bottom**). In one case (Patient 64) we found that one isolate (4380) was not *Candida albicans*, but likely another *Candida* species. We removed all non-clonal samples from further consideration, and focused in all subsequent analyses on the 22 samples from the 10 patients with at least two clonal isolates.



**Figure 2. SNPs as a method for identifying clonally derived strains.**

There are two models of infection from serial isolation of clinical isolates (a); a clonal model where each isolate is derived from the previous (a, top) and a non-clonal model where consecutive isolates derive from new colonization (a, bottom). An example of a clonal series is patient 59 (b, top); a phylogenetic tree is constructed from a distance matrix based on genotype (b, top left). These data are also visualized via a heterozygosity diagram (b, top right) where each locus contains a SNP from at least one isolate. Each genotype is color-coded; red – homozygous SNP, white – heterozygous SNP, and blue – homozygous for reference. Patient 9 (b, bottom) contains at least one non-clonal isolate, 2823 (distance > than 22,000, b, bottom left). This is confirmed visually by heterozygosity diagram (b, bottom right). Clonal patient series heterozygosity diagrams are of post-filtration SNP calls, non-clonal are of pre-filtration.



### Figure 3. Clonality in patient series.

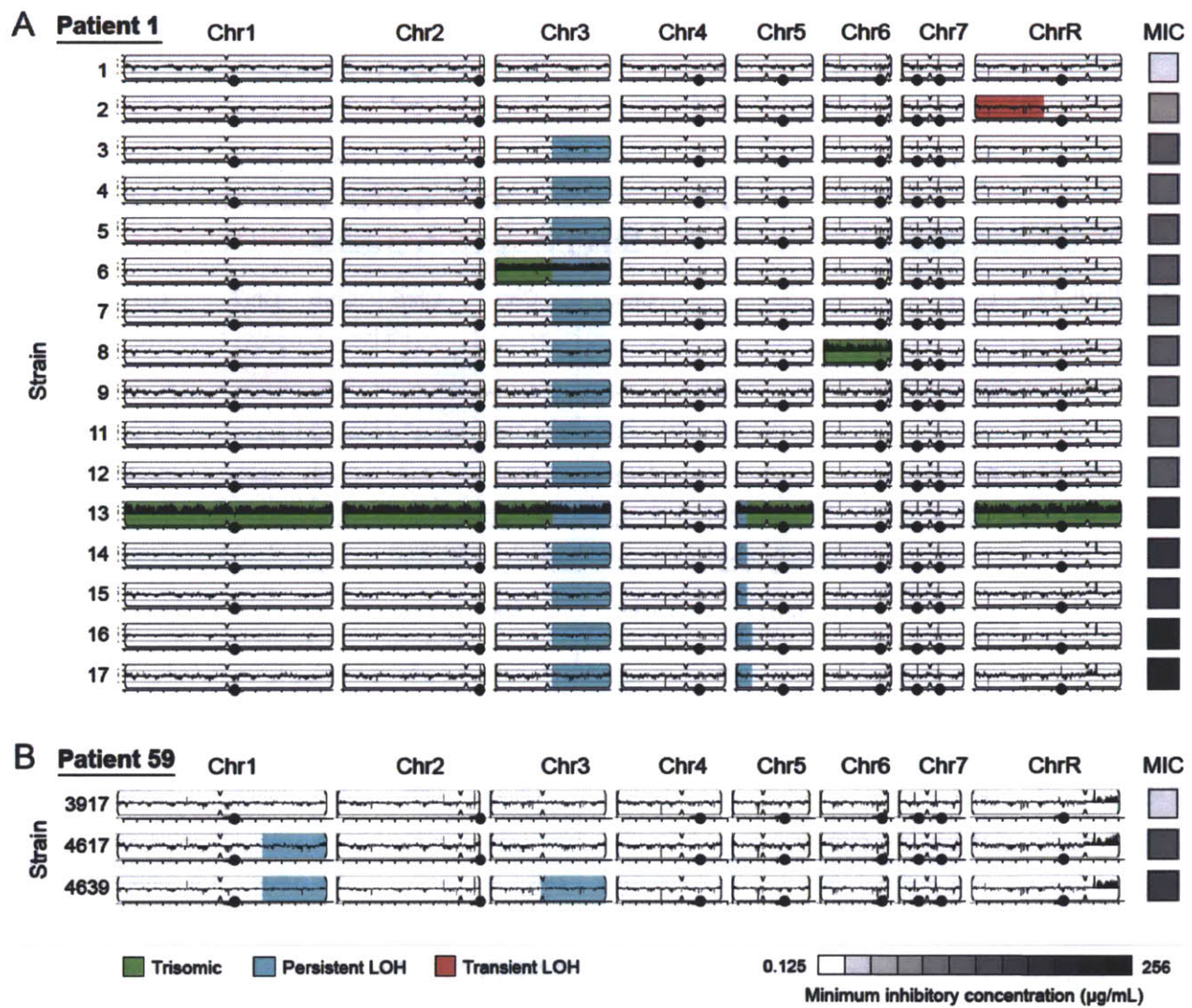
Multi-sample SNP calling (including reference strain SC5314) is used to construct phylogenetic trees via Neighbor-Joining (A-H, left). Patients 16 and 42 (E and G) both contain non-clonal isolates. This effect can be observed visually via heterozygosity diagram (A-H, right), where each locus that contains at least one variant in the series contains a color entry reflecting genotype; a homozygous SNP is red; a heterozygous SNP is white, and a locus homozygous for the reference base is blue. Clonal patient series heterozygosity diagrams are of post-filtration SNP calls, non-clonal are of pre-filtration.

### **Ploidy varies but such variations are not generally adaptive**

While we observed ploidy changes in samples from 7 of the 10 patients (**Methods**), most variations were transient and not generally associated with adaptive changes in drug resistance (**Figure 4, 5**). For example, in Patient 1 (**Figure 4a**) isolate 6 is trisomic for chromosome 3, isolate 8 is trisomic for chromosome 6, and isolate 13 is a triploid with disomies in chromosomes 4, 6, and 7 (**Figure 4a**). All of these changes are transient, and only isolate 13 corresponds to a gain in MIC. Some of the variants do recur (transiently) in other strains, most notably a chromosome 5 trisomy (in patient 1, 15, 16, 30, 42, and 43, **Figures 4a and 5d-h**). However, these changes do not correspond to a consistent change in resistance. Thus, we concluded that most ploidy changes are likely not related to drug resistance in these strains.

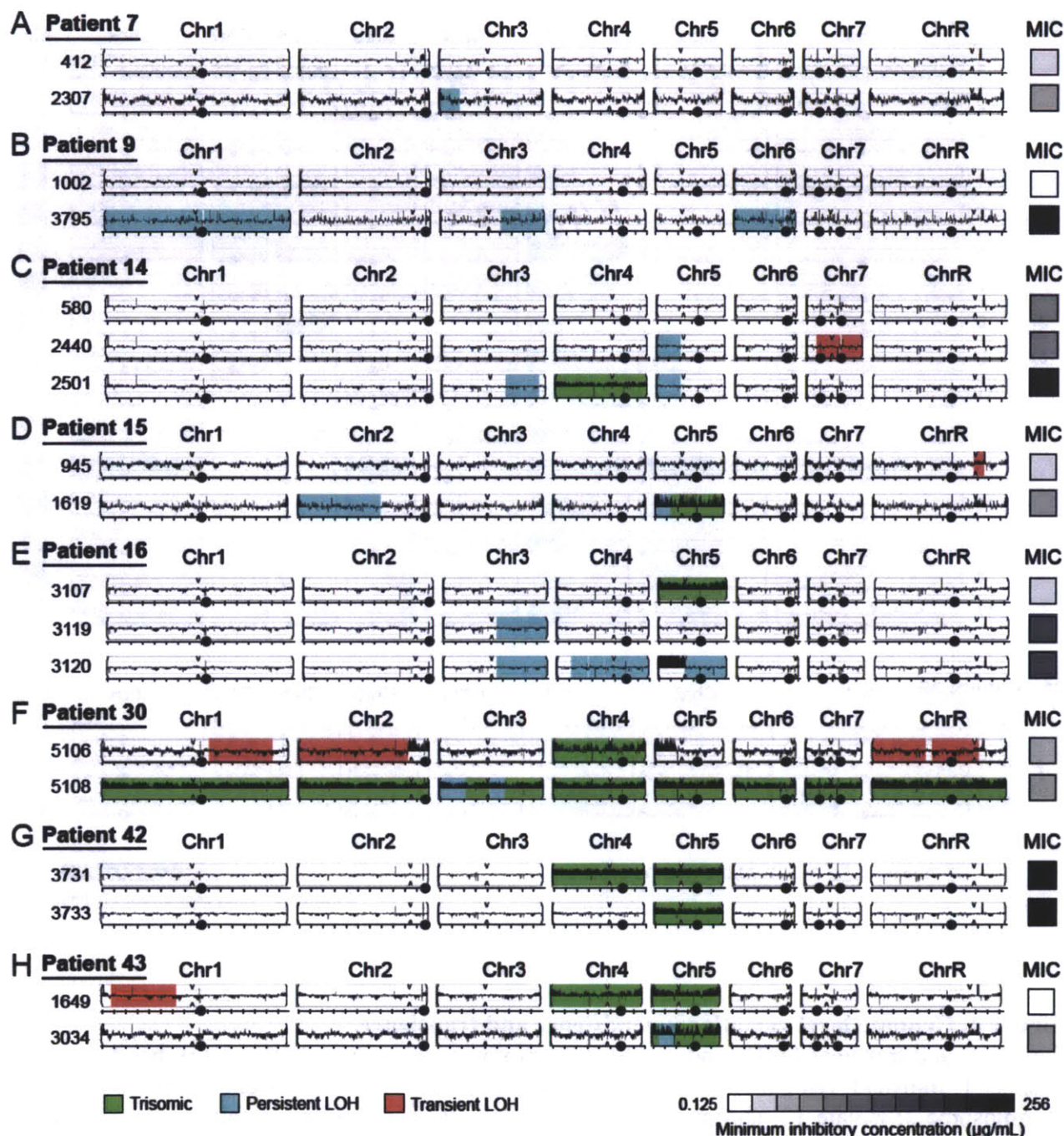
### **Common LOH events that persist generally associated with changes in drug resistance**

Conversely, we found LOH changes in almost all (9/10) series, which are often persistent, recurrent and associated with increased drug resistance (**Figure 4, 5**) and are copy-neutral. For example, there are four LOH events in Patient 1, three of which are persistent and corresponding to an increase in MIC (isolate 3, right arm of chromosome 3; isolate 13, left arm of chromosome 5, and isolate 16, the left arm of chromosome 5, **Figure 4a**). Two of these events also recur in additional time courses, persistently and/or consistent with increase in MIC: an LOH in the right arm of chromosome 3 in Patients 9, 14, 16, 30, and 59 (**Figures 4a,b, and 5b,c**) and an LOH in the left arm of chromosome 5 in Patients 14, 15, 16, and 43 (**Figures 4a, and 5c, h**). In another example, we found a persistent LOH in the right arm of chromosome 1 in Patient 59 (**Figure 4b**) and Patient 9 (**Figure 5b**), corresponding to a change in MIC. (A similar Chr1R LOH in Patient 30 did not however associate with a significant difference in MIC (**Figure 5f**)).



**Figure 4. Genome level variations: persistence and transience**

Persistent and transient LOHs and highlighted trisomies are visible. Patient 1 (a), has four LOH events, 1 transient (isolate 2, chromosome R, red), and three persistent LOHs (isolate 3, chromosome 3; isolate 13, chromosome 5; and isolate 16, chromosome 5, blue). Each of these LOH events co-occurs with an increase in the MIC phenotype (grayscale boxes at right). Some of these changes are recurrent, as Patient 59 (b) shows LOH on the right arm of chromosome 3 as well (isolate 4639, blue). Patient 59 also has a persistent LOH on the right arm of chromosome 1 (isolate 4617, blue). Again, each of these LOH events co-occurs with an increase in MIC. Recurrences of LOH in chromosome 1 (Supplemental Figure 2(b)) and right arm of chromosome 3 (Supplemental Figure 2(b, c, e, f)) are also observed. While many LOH events appear to be persistent, we see ploidy variants (green) in Patient 1, isolates 6, 8 and 13; none of which are persistent.



**Figure 5. Persistent and transient large-scale genome variations**

As in figure 4, the remaining 8 patient series are displayed with transient and persistent LOHs (red and blue, respectively), as well as large trisomies (green). Patients 9, 14, 16 and 30 have persistent LOHs on the right arm of chromosome 3 (b, c, e, f) as did both Patients 1 and 59 (figure 3). Except for patient 30, all of these co-occur with increases in MIC (grayscale, right). LOH also occurs frequently in the left arm of chromosome 5, as well as chromosome 1. We also observe i5L in patients 16, isolate 3120(e), and patient 30, isolate 5106 (f), but neither co-occur with increases in MIC. LOH on chromosome 5 also occurs in high frequency (c, d, h and figure 3a) but this does not always accompany increase in MIC (c).

## **LOH events are accompanied by homozygosity changes in genes that are known players in drug resistance**

The persistence and recurrence of LOH events suggest that they have been positively selected. To identify potential drivers in these regions, we focused on those coding mutations that switched from one homozygous state in the progenitor to a different homozygous state at the LOH, and persisted in this evolved state thereafter. There are 26 such mutations from 7 LOH regions in 7 patients whose progenitor, intermediate(s), and terminal isolate were collected on separate days (**Supplementary Table 2, Table 1**). Some of the mutations encode genes that are key players in drug resistance. For example, there is a non-synonymous homozygous change in the fluconazole drug target ERG11 associated with the formation of the persistent LOH on the left arm of chromosome 5 in Patient 1. In another example, the persistent and recurrent LOH on the right arm of chromosome 3 in Patient 9 is associated with the appearance of a homozygous mutation in MRR1, a regulator of MDR1 expression. Other mutations are in genes not previously related to fluconazole resistance, including telomere function (TEL1 and CAS1), cell wall biosynthesis (CHS4 and ROT2), autophagy (Orf19.6020), and mitochondrial function (orf19.6790, orf19.6979, orf19.6061).

## **Many genes mutate in these in vivo series, some are under selection, but there is also a clear signature of drift**

In addition to the mutations introduced by LOH, 1,915 genes have persistent non-synonymous coding SNP mutations in at least one time course, the vast majority of them (1,805/1,915) corresponding to changes in MIC (**Supplementary Table 3**). 155 of the 1,805

genes have persistent non-synonymous SNPs in 3 or more time courses, and are thus stronger functional candidates (**Supplementary Table 3**). Notably, we cannot fully rule out the possibility that some of the recurrently mutated genes are neutral, since the 155 genes are longer than the other 1,650 persistent genes (mean size:  $2.45 \pm 1.84\text{kb}$  vs.  $1.81 \pm 1.24\text{kb}$ ,  $p < 1.9 \times 10^{-6}$ , t-test).

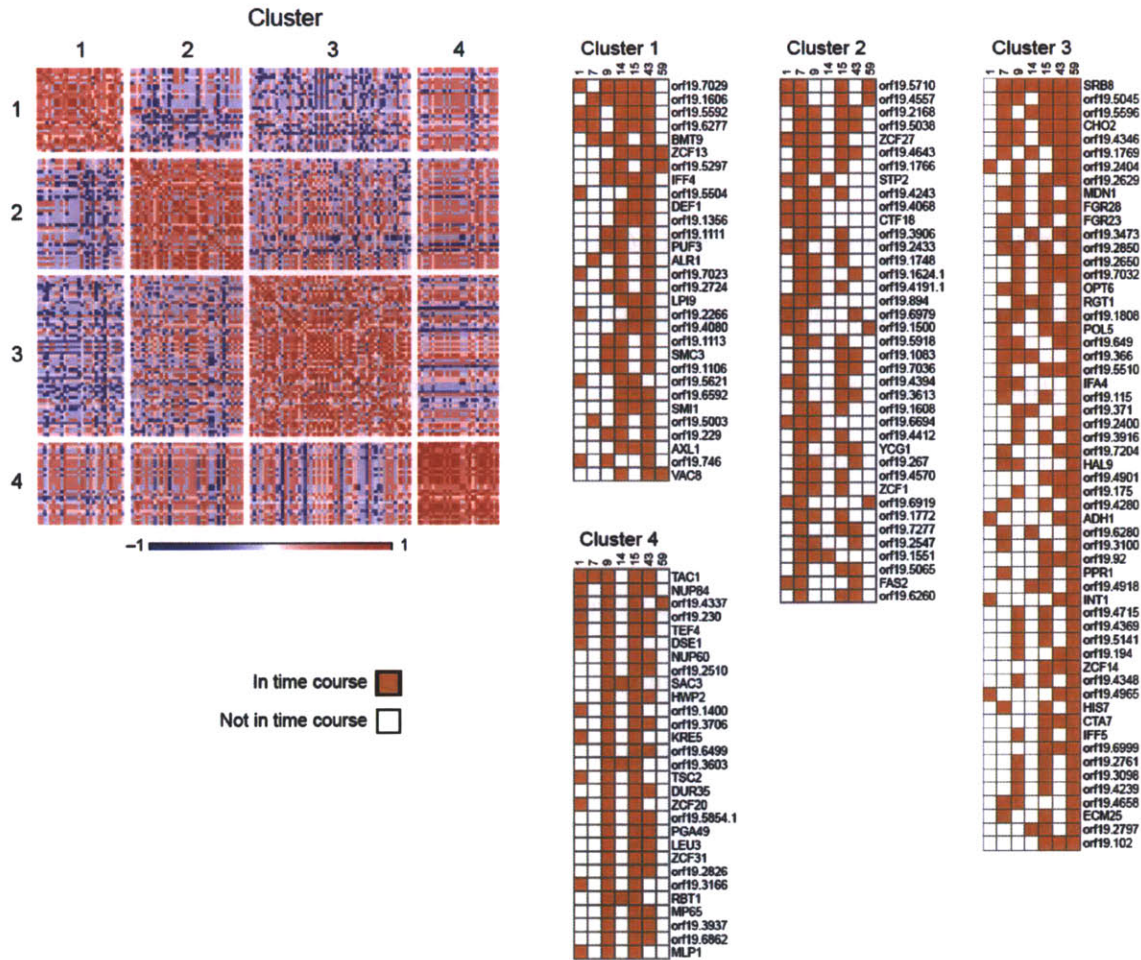
Nevertheless, among these 155 recurrently mutated genes are key genes associated with the drug response (e.g. TAC1, DEF1), filamentous growth (e.g. FGR23 and FGR28), biofilm formation (e.g. SRB8, POL5), and cell wall and adhesion (e.g. IFF4, HWP2, MP65), likely reflecting the complex selective pressure in the human host. Notably, the drug target Erg11 is mutated in 2 time courses in addition to the LOH-coupled event above (**Supplementary Table 2**): a heterozygous point mutation in Patient 59 and a homozygous mutation in Patient 9.

Interestingly, little is known about many of the most recurrently mutated genes. For example, seven of the ten most recurrent genes (mutated in at least 5 of 7 patients) are not well-characterized. These include SRB8, a gene induced early in biofilm formation; orf19.1606, a target of PLC1, an important filamentation factor; and orf19.7029, a putative guanine deaminase, previously implicated in sensitivity to toxic ergosterol analogs[20]. These suggest new genes that may be implicated not only in drug resistance per se, but more broadly in host adaptation during *Candida* infections.

### **Significant co-occurrence of mutated genes associate with filamentation**

The 155 recurrently mutated genes can be partitioned based on the correlation in their occurrence patterns into four ‘co-occurrence clusters’ (**Figure 6**). The correlations we observe are significantly higher than those expected in a null model (KS test,  $P < 2.2 \times 10^{-126}$ , permutation





**Figure 6. Co-occurrence of non-synonymous substitutions coupled to gains in MIC**

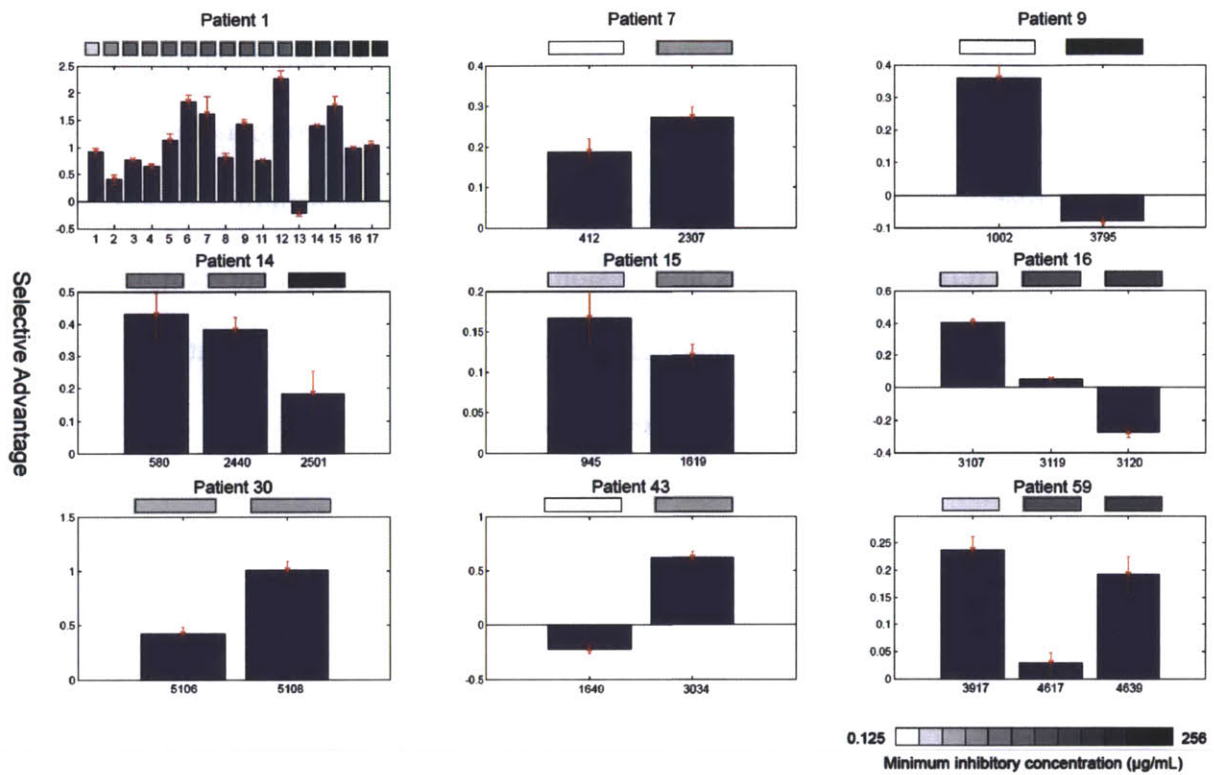
Non-synonymous SNPs, not occurring within a region of LOH, that co-occur with increase in MIC are used to construct a patient-by-gene binary vector (as cluster membership matrices, right). Pearson correlation of each (row) gene vector yields a gene-by-gene correlation matrix, which is then clustered (left). Cluster 4 showed functional enrichment for fungal-type cell wall and cell surface genes ( $P < 0.006$ ,  $P < 0.042$ , respectively; Benjamini-Hochberg corrected) suggesting that selection on fluconazole within the patient is also selecting for cell wall phenotypes.

test). Of the clusters, Cluster 4 is significantly enriched for fungal-type cell wall and cell surface genes ( $p < 0.006$  and  $p < 0.042$ , respectively, Benjamini-Hochberg corrected).

### **Additional phenotypes suggest complex adaptive landscapes**

Since many of the recurrently mutated genes are known to play a role in biofilm formation, filamentation and/or adhesion, we reasoned that some of the mutations might reflect adaptations to the host, possibly independent of the specific selective pressure of the drug. To explore this possibility, we measured four additional phenotypes for each strain (**Methods**) – filamentation, adhesion, and virulence in a worm model of infection (for some strains).

For each phenotype, there are indications of other evolved phenotypes besides drug resistance, either correlated with or independent of change in MIC. **First**, MIC increases are typically accompanied by a decrease in fitness in the absence of drug (patient 1, isolates 2-4, 13, 15 and 16, Patients 9, 14, 15 16, and 59, **Figure 7**), often followed by a subsequent increase in fitness without further changes in MIC (e.g., patient 1, isolates 5-7, **Fig. 7**). This trajectory is consistent with previous observations in bacteria[21] that drug resistance initially confers a fitness cost in the absence of the drug, which is restored by subsequent compensatory mutations. In several cases, the decrease in fitness may stem from concomitant aneuploidies, known to confer proliferative disadvantage[22] (e.g. **Figure 4a**, isolate 13 and **Figure 7**, **Patient 1**, mark). Conversely, loss of trisomies that pre-existed in the progenitor is associated with increase in fitness in Patient 43 (**Figure 5h** and **Figure 7**). **Second**, some fitness increases occur independently of drug selection or ploidy changes (e.g. Patient 1 isolates 12 and 15, Patient 59 isolate 2, Patient 43 isolate 2), and may reflect host adaptations. **Finally**, four of the time courses



**Figure 7. Selective fitness advantage of isolates and their relationship to change in MIC**  
 The selective advantage of each strain (blue) often is often reduced when coincident with increase in MIC (grayscale, above).

showed a consistent increase in filamentation with time (**Supplementary Table 5**), and three show increased adhesion. All are accompanied by an *in vitro* fitness increase (without ploidy changes), and some by a change in MIC.

For example, in Patient 59, there are persistent non-synonymous substitutions in the hyphal genes UEC1 and VAC8 in the intermediate isolate (4617), and mutations in the hyphal genes RSV162, PST1 and OP4 in the terminal isolate (4639), corresponding to the gradual increase in filamentation in these isolates, compared to the progenitor. These phenotypic changes are also reflected by changes in adhesion and with decrease in survival in a *C. elegans* survival assay ( $p < 0.01$ , **Methods**), suggesting a role for these mutations in pathogenesis *in vivo*, independent of drug resistance. We cannot rule out that these changes are independent or in parallel.

## **Discussion**

In conclusion, our genomic sequencing and analysis of *C. albicans* clinical series yields novel insights into the evolution of drug resistance and host adaptation *in vivo*. By comparing ‘consecutive’ strains from one patient, we confidently exclude non-clonal samples, and identify persistent mutations; by comparing mutations between series, we identify recurrent events. Combining these two approaches, and associating mutations with relevant phenotypes, such as MIC, we show that LOH is a common event, that likely sweeps through a population and recurs across populations. Notably, some of the recurrent LOH events we find may have been difficult to detect on SNP arrays, due to the relative paucity of SNPs in those regions in the reference strain, SC5413, itself a clinical isolate. Furthermore, we find a substantial number of persistent mutations that recur between patients and implicate genes from a broad range of processes,

suggesting that some of the observed mutations are likely a result of additional complex selective pressures in the host. Consistently, we show that the strains have evolved additional phenotypes based on fitness, filamentation, adhesion and virulence assays. Finally, our data and, provide a rich resource for other *Candida* researchers and a host of candidates for further functional studies.

## **Materials and Methods**

### **Strains**

Strains were isolated from HIV-infected patients with oropharyngeal candidiasis, as previously described[18, 19]. The patients were not on azole anti-fungal treatment at time of enrollment; subsequent samples were collected during recurrence of infection. The strains and are detailed in **Table 1**.

### **Drug susceptibility**

Minimal inhibitory concentrations (MIC) were determined for each strain using fluconazole E-test strips (0.016–256 µg/ml, Biomérieux) on RPMI 1640-agar plates (Remel). Overnight YPD cultures were diluted in sterile 0.85% NaCl to an OD600 of 0.01 and 250 µL was plated using beads. After a 30-minute pre-incubation, 2-3 E-test strips were applied and plates were incubated at 35°C for 48 hours. The susceptibility endpoint was read at the first growth-inhibition ellipse, and the median value is reported here.

### **Illumina sequencing**

Genomic DNA was prepared from different clinical time courses via a Qiagen Maxiprep kit and sequenced using 76bp paired-end Illumina sequencing[23]. Library preparation included barcoding with an 8 base barcode[24] for 43 samples from 11 patients sequenced in pooled samples. Read sizes after removal of barcodes are 68 bp. All reads were mapped to the SC5314 reference genome (Candida Genome Database, gff downloaded on January 4, 2010) using the BWA alignment tool[25]; the reads were indel-realigned using GATK[26]. Coverage for each

strain is reported in **Table 1**. Coverage was defined as the total number of bases with mapping quality greater than 10 divided by the total number of sites in the nuclear genome.

### **SNP identification and clonality testing**

SNP calling was performed with GATK[26] with the SC5314 alignment used as a reference sequence. After removing non-clonal strains (below), SNP calls were performed again for the remaining clonal isolates in each time course and unreliable SNPs were removed in each time series based on: (1) the RMS of mapping quality (removing SNPs that were 2 standard deviations below the mean); (2) depth of coverage (removing SNPs with coverage that was two standard deviations above the mean); and (3) quality-by-depth (removing SNPs with a QD less than 5).

### **Determination of clonality**

All (unfiltered) multi-sample SNP calls relative to SC5314 were used to construct a distance matrix between every pair of isolates within each time course and between every isolate and SC5314. Two different homozygous genotypes counted as a distance of 1.0, a heterozygous and homozygous genotype as 0.5. We then used neighbor-joining (as implemented in PHYLIP[27]), a bottom-up clustering method, to construct a phylogenetic tree for each time course, and rooted it with SC5314 as an outgroup. We define isolates with a branch distance of greater than 22,000 as non-clonal.

### **Copy-number determination**

For each strain, we calculated a per-locus depth-of-coverage using GATK[26], with a

minimal mapping quality of 10. The number of reads aligning to each 5 kb window across the nuclear genome was calculated and then normalized to the genome median. Each bin was then multiplied to the ploidy for the majority of the genome as determined by FACS assay (below). We then applied a sliding window across each bin, defining a potential CNV if 70% of 10 consecutive bins had a normalized count  $> 2.5x$ . Regional/chromosome copy-number variants (e.g. trisomy) are identified if  $> 15\%$  of the chromosome is identified as having a CNV. Boundaries are confirmed by visual inspection in the Integrative Genome Viewer[28].

### **High-resolution ploidy analysis by flow cytometry**

*C. albicans* were grown to log phase. 200 $\mu$ l of culture was centrifuged in a round bottom microtiter plate and pellets were resuspended in 20 $\mu$ l of 50mM Tris pH8 / 50mM EDTA (50/50 TE). 180 $\mu$ l of 95% ethanol was added and suspensions were stored overnight at 4°C. Cells were centrifuged and pellets washed twice with 200 $\mu$ l of 50/50 TE, then resuspended in 50 $\mu$ l of RNase A at 1mg/ml in 50/50TE and incubated 1 hour at 37°C. Cells were centrifuged and pellets resuspended in 50 $\mu$ l of Proteinase K at 5mg/ml in 50/50 TE for 30 minutes at 37°C. Cells were washed in 50/50 TE and pellets resuspended in 50 $\mu$ l of a 1:85 dilution SYBR Green I (Invitrogen, Carlsbad, CA) in 50/50 TE and incubated overnight in the dark at 4°C. Cells were centrifuged and pellets were resuspended in 700 $\mu$ l 50/50 TE and read on a FACScaliber flow cytometer (BD Biosciences, San Jose, CA). Flow data was fitted with a multi-Gaussian cell cycle model to produce estimates for whole genome ploidy.



## **LOH Determination**

For each time course, we assembled the high quality SNPs (post-filtering, above) from multi-sample calling into the columns of a matrix, ordered by genome position, with the isolates in rows, ordered temporally. The genetic state of each locus in each sample was coded to distinguish loci homozygous for the haploid reference (-1), heterozygous SNPs (0), and homozygous SNPs for the non-reference state (1). We then applied a sliding window method across each chromosome, only looking at sites in which a SNP call was made in at least one isolate. An LOH event was defined as occurring if (1) at least one isolate had a heterozygosity content  $> 40\%$ , and (2) at least one other isolate had a heterozygosity content  $< 5\%$ . Window sizes were of length 500. Boundaries were trimmed such that if a window terminated in a heterozygous site in the isolate for which the LOH occurred, it was trimmed back until it was homozygous. If two 500+ windows were within 7 KB of each, the region was assessed to determine if the event was actually one event and merged if the heterozygous sites in the inter-window space had homozygosed. If two isolates had LOHs that overlapped but did not have precisely identical boundaries, the LOH regions were combined such that the LOH interval for both isolates was the same. All LOH regions were confirmed by visual inspection and are listed in **Supplementary Table 1**.

## **Classification of SNPs**

For each time course, each SNP was classified for its position in the genome (**Supplementary Table 1**). If the SNP fell within an ORF, the reference and altered SNPs were reported. If the SNP fell outside of an ORF, the distance to the closest flanking ORFs was reported, as well as the SNP's orientation with respect to these ORFs. SNP genotypes that are common to all

isolates (including the ‘progenitor’) were classified as background mutations. Genotypes not present in the progenitor or evolved strain, but that occur in one or more intermediate strain were classified as transient. Finally, genotypes that occur after the progenitor, and persist through the terminally evolved time point, are classified as persistent.

### **Analysis of co-occurring mutations**

For co-occurrence analysis we focused only on these that (1) had persistent non-synonymous coding SNPs that did not occur in LOH regions; (2) recurred in three or more time courses (two or more, in the case of filamentation); and (3) where the mutation emerged (became persistent) at the same time as a change in the relevant phenotype (MIC, filamentation, etc). We generated for each such gene a binary patient vector, and created a gene-by-gene Pearson correlation matrix. We used NMF[29] clustering to identify the optimal number of clusters, based on local maximas. We then tested each of the co-occurrence gene clusters for functional enrichment (below). To determine if the degree of co-occurrence would have arisen by chance, we ran 1,000 iterations of one million edge-pair swaps from the original binary matrix, calculating a Pearson correlation matrix for each of the 1,000 iterations. We compared the distribution of Pearson correlations on the real and permuted vectors using a two-sample Kolmogorov-Smirnov (KS) test.

### **Functional enrichment**

We calculated the overlap of each co-occurring cluster with Gene Ontology gene sets (downloaded from [Candida Genome Database](#) on March 22, 2010) and estimated the significance of the overlap using a hypergeometric test as previously described[30]. Nominal, Benjamini-Hochberg adjusted, and Bonferroni adjusted P-values are reported (**Supplementary**

**Table 4).**

### **Competition assay to assess fitness**

We measured the relative fitness of the progenitor and evolved lines in RPMI medium, competing them against a reference strain, expressing ENO1::YFP. Strains stored at -80°C were revived on rich media petri plates and then grown overnight in 3 ml cultures of minimal media in a roller drum at 35 °C. An aliquot of cells in each culture was removed, sonicated in a Branson 450 sonifier, and the concentration of cells was determined using a Cellometer M10 (Nexelocom). The reference strain and experimental competitors were added to fresh RPMI medium in a 1:1 ratio and a final cell concentration of  $1 \times 10^7$  cells/ml. The cultures were grown for 24 hours in a roller drum at 35 °C. Cells were then counted as above, and  $3 \times 10^6$  cells were transferred to fresh RPMI medium grown for 24 hours in a roller drum at 35 °C (transfer cycle 1). This procedure was repeated (transfer cycle 2). This protocol represents 5–10 generations of growth, depending on the strain genotype. The ratio of the two competitors was quantified at the initial and final time points by flow cytometry (Accuri). Three to six independent replicates for each fitness measurement were performed. The selective advantage,  $s$ , or disadvantage of the

evolved population was calculated as  $s = \frac{\ln\left(\frac{E_f}{R_f}\right) - \ln\left(\frac{E_i}{R_i}\right)}{T}$ , where  $E$  and  $R$  are the numbers of evolved and reference cells in the final ( $f$ ) and initial ( $i$ ) populations, and  $T$  is the number of generations that reference cells have proliferated during the competition.

### ***C. elegans* survival assay**

A *C. elegans* survival assay was performed as previously described[31]. Briefly, *E. coli* OP50 and the different *C. albicans* clinical isolates were grown overnight respectively in LB at 37°C and YPD at 30°C. *E. coli* was then centrifuged and resuspended to a final concentration of 200 mg/ml while *C. albicans* isolates were diluted with sterile water to OD<sub>600</sub>=3. Small petri dishes (3.5 cm) containing NGM agar were spotted with a mixture of 10 ml streptomycin (stock solution 50 mg/ml), 2.5 ml of *E. coli*, 0.5 ml of *C. albicans* and 7 ml of sterile water. The plates were incubated overnight at 25°C and 20 young synchronized N2 *C. elegans* adults were transferred on the spotted plates. Synchronous populations of adult worms were obtained by plating eggs on NGM plates seeded with *E. coli* OP50 at 20°C for 2-3 days. In this time frame, the eggs hatch and the larvae reach young adulthood. The survival assay was carried at 20°C and worms were scored daily by gentle prodding with a platinum wire; dead worms were discarded while live ones were transferred to seeded plates grown overnight at 25°C. Worms accidentally killed while transferring or found dead on the edges of the plates were censored. Statistical analysis was performed using SPSS software; survival curves were obtained using the Kaplan-Meier method and p-values by using the log-rank test.

### **Filamentation assay**

Overnight cultures grown in YPD at 30°C were normalized to OD<sub>600</sub>=1 with sterile water and spotted on Spider agar media (1% mannitol, 1% Difco nutrient broth, 0.2% K<sub>2</sub>HPO<sub>4</sub>). Plates were incubated at 37 °C and colonies photographed 3, 7 and 10 days post spotting. As a negative control for filamentation *cph1/cph1 efg1/efg1* [32] double mutant strain was used in this study. Filamentation was scored by observing the edge of each colony and assigning a score out of 7

with 1 corresponding to non-filamentous, 7 corresponding to hyper filamentous, and 2-6 corresponding to intermediate filamentation phenotypes.

### ***In vitro* adhesion assay**

The *In vitro* adhesion assay was performed as previously described for *S. cerevisiae*[33]. Briefly, cultures were grown in Synthetic Complete (SC) media + 0.15% glucose at 30°C overnight. Cells were then centrifuged at maximal speed and resuspended to OD<sub>600</sub>=0.5 in fresh media. 200 ml of each culture were dispensed into 8 wells of a flat bottom 96-well plate and incubated at 37°C for 4 hours. The content of the plate was then decanted and 50 ml of crystal violet added to each well. After 45 minutes of incubation at room temperature, the content of the plate was decanted and the plate was rinsed ten times in DI water by alternate submerging and decanting. 200 ml of 75% methanol was added to each well and absorbance was measured after 30 minutes at OD<sub>590</sub>. An *edt1/edt1* knockout mutant[34] was used as a negative control for adhesion.

### **Supplemental data**

Supplemental tables can be found in Appendix 2.

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## **Chapter 3: Methods for Massively Parallel DNA Sequence Analysis**



## **Introduction**

The recent development of massively parallel sequencing technology has enabled new areas of inquiry never before possible. However, the innovation and progression of massively parallel sequencing comes with new challenges in areas including sequence quality scoring, alignment assembly, as well as variant discovery and annotation[1].

Quality scoring is determined in a chemistry/platform-specific manner (usually in real-time by the sequencer); integration of raw sequence quality affects both alignment and variant detection. Mapping quality scores, a related concept to raw base quality scores, assess how well a read is aligned to a reference genome. This score integrates raw base quality and is also used for variant detection. While these metrics are invaluable for both alignment assembly and variant discovery re-alignment has been shown to be a necessary step for improved variant detection[2]. As many of these tools have been designed to integrate existing human datasets, I demonstrate here how we integrate these approaches for non-human applications.

Aligning short reads to a genome is a non-trivial problem and initially was a bottleneck for analysis[3]. Challenges pertaining to alignment include the large number of reads and the short read size. Not unique to short-read alignment are difficulties with aligning repetitive sequence elements. The most successful approaches are hashing methods, as I describe below. These methods integrate raw base quality scores and provide similar quality scoring describing the read's alignment.

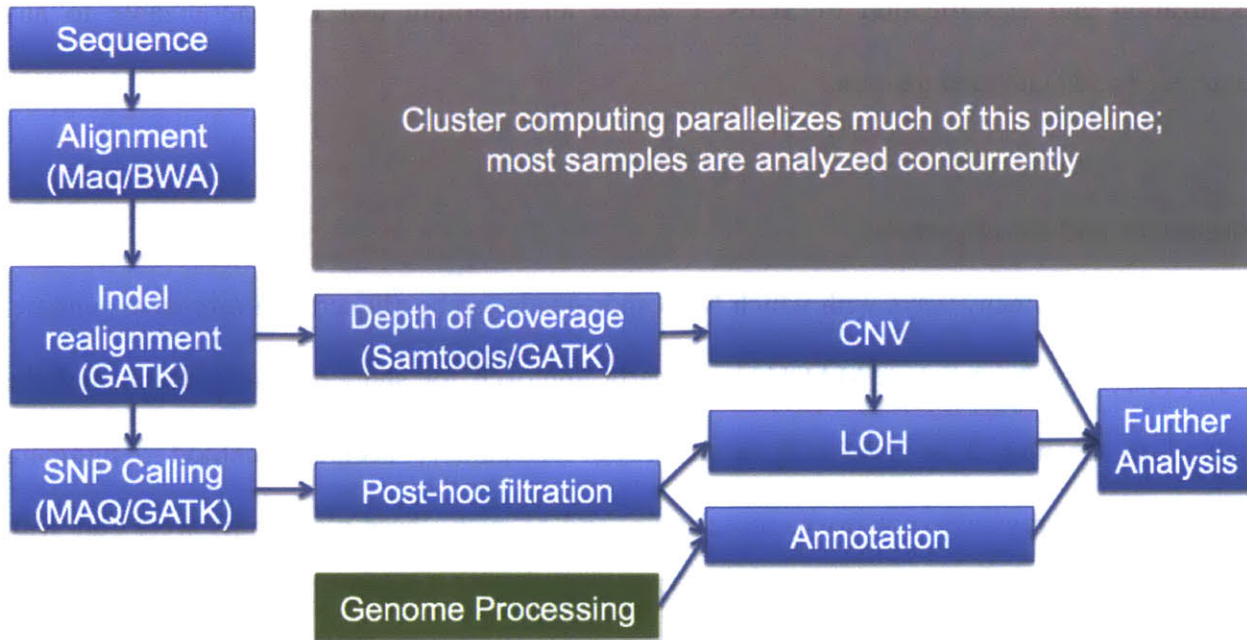
Ultimately, the goal for re-sequencing is to relate newly discovered genomic variants and to characterize them or relate them to phenotype. There are many different types of variants that are of interest; in this chapter I describe how we identify and annotate single nucleotide

polymorphisms (SNPs) and integrate SNP data to identify regions with loss of heterozygosity (LOH). I also describe how we identify large regions with copy-number variations (CNVs).

SNP discovery is at the core of both Chapters 1 and 2, and is an essential goal for re-sequencing. Many methods exist for SNP calling from NGS data, though some are platform specific[4] or are parameterized for a specific organism[5]. An additional challenge is the need for filtration of likely false positives, which can be achieved by PCR validation, a cross-validation method[6], use of contextual statistical annotation, or both. Once a SNP is identified, it can be annotated based on the genomic feature it impacts. SNP identification can also be used to determine the presence of LOH events, which are of particular significance in Chapter 2.

As a function of coverage, CNVs are discernable from DNA NGS data even before reliable SNP calls. Many methods exist to determine boundaries for CNVs, often coupling analysis to structure variants, such as inversions and translocations[7-9]. Other methods focus largely on coverage[10], but because of the repetitive nature of larger genomes, the experimental design sought out by particular studies (e.g. tumor-normal comparisons), or the cost of sufficiently high coverage of large genomes, this approach tends to be less favorable. Given that the genome size of our target genomes spanned from 12-14 megabases, we routinely achieve ~20x coverage. As such, I implement a coverage-based method.

In this chapter, I detail the NGS analytical pipeline (Figure 1) that I developed and used in Chapters 1 and 2. I use existing tools when they are appropriate for a particular task, such as aligners, re-aligners and variant detectors. When tools already exist but are designed for a particular organism, I re-parameterize them, such as for SNP calling in non-human organisms. In cases where few tools exist (or none existed at the initiation of this research), such as rapid



**Figure 1. Overview of analytical pipeline**

An NGS method gives rise to DNA sequence data. The short reads are aligned to a reference genome (via MAQ or BWA). Small indels bias read alignment via local mismatching, so they are removed via local re-alignment. Upon re-alignment, large and small variant detection commences. Then, SNPs are called (MAQ/Samtools as in Chapter 1, or GATK as in Chapter 2) while CNVs and larger structural variations are assessed via multiple methods. SNP calling requires additional filtration for non-haploid organisms. SNPs can be annotated by their changes to resultant proteins, changes in codon frequency, or effects to promoter binding sites. Regions for LOH determination can be rapidly classified.

localization and classification of SNPs, I devise an algorithm that is generalizable to any sequenced and annotated genome.

## **Alignment and Re-alignment**

There are many ways with which NGS short-reads can be aligned to a reference genome. The method in Chapter 1 is MAQ[11], an early approach for short read alignment, and the method in Chapter 2 is BWA[12], a faster but comparably accurate method. Alignment methodology is typically not organism-specific, and as such, these algorithms were run with default parameters.

### ***phred* scores**

*phred* is a standard method to score each base in a read[13, 14], on which early variant detection was predicated. Often referred to as the “quality” score for a base, it is defined as  $Q = -10 \log_{10} P$ , where  $Q$  is the quality score, and  $P$  is the probability of error for that base call. The way this error probability is defined depends on the technological platform from which the sequence data is generated, but in brief, it relates to a signal-to-noise ratio. Even as NGS technology has matured, *phred* scaled quality scores for bases are required for both alignment[11, 12, 15] and variant detection methodologies[2, 5, 16, 17]. For early variant detection, putative hits were assigned a probabilistic score (e.g. via a Bayesian approach) and/or followed up with PCR validation.

### **MAQ**

MAQ[11] maps short DNA sequence reads to a reference genome and identifies short insertions and deletions (*indels*) and SNPs. MAQ assesses each read’s ungapped alignment to the reference genome via a hashing method. Each read will have a mismatch score, defined as

the sum of qualities at mismatching bases. MAQ selects the minimal mismatch score. Because of the errors in base calling from the sequencer itself, mismatched bases with a high quality score penalize an alignment more than those with low base quality. To evaluate the reliability of alignments, MAQ assigns each individual alignment a *phred*-scaled quality (mapping quality) score to determine the probability that the true alignment is not the one found by MAQ. Reads that can be mapped to multiple loci with equally high mapping quality will be assigned at random to any of those loci, but will be assigned a mapping quality of zero. This will allow for subsequent analysis to filter out any contribution from those reads towards genotyping, as their actual location is unknown. We do not discard them outright since those reads may contribute to an estimate of overall copy number of a repetitive sequence.

## **BWA**

The Burrows-Wheeler Aligner, or BWA[12] is based on a Burrows-Wheeler transform[18], which is a “backward search”. This method relies on hashing the genome instead of the reads, as was the process in MAQ. The benefits to this approach are (1) the complexity of read mapping to the genome is a function of the read’s size, not the genome’s size, (2) the algorithm has a relatively small memory footprint and thus (3) the time to complete alignment is greatly improved over other methods. This method performs a gapped alignment for single-end reads. For paired-end reads, gapped alignments are conducted on each mate independently. A read will potentially map to a position if the total number of differences (both mismatches and gaps) is less than a threshold  $k$ . This threshold defaults to having fewer than 4% difference of a read of length  $l$  assuming a 2% uniform base error. For paired-end reads, there is an additional step in alignment: for a given read, good hits are sorted by their chromosomal coordinates and then a linear scan is conducted for the best mapped pairing of both reads. Once mapped, reads

are assigned a mapping quality that integrates mismatching data as described in MAQ, with an added caveat that it is assumed that a true hit can always be found (MAQ does not assume this, and as a result it underestimates mapping quality). BWA does not come with an associated variant caller. For Chapter 2 we use BWA with default parameters for paired-end alignment.

### **Re-alignment**

Because of the degree of divergence between a reference genome and a re-sequenced genome, alignment artifacts are likely to exist. First, small indels may erroneously appear as many mismatching bases, which are then mistaken as SNPs. Additionally, each read is mapped independently, and thus it is not possible to minimize mismatches across an alignment, as that requires insight gleaned from all reads. Furthermore, even when indels are properly identified in the interior of a read during the initial alignment, gap insertion penalties prevent gapped alignment toward the beginning or end of a read. To address these issues, we used the local realignment tool in the GATK package[5], which serves to transform regions with misalignments due to indels into clean reads containing a consensus indel suitable for standard variant discovery approaches. This tool is run in two phases, Realigner Target Creator and Indel Realigner. The Realigner Target Creator can integrate regions with known indels, or it can be run naïvely. In the realignment step, Indel Realigner is used with the intervals specified from the Target Creator. Following local realignment, the GATK Unified Genotyper identifies variations including indels and SNPs[2], and CNV determination can occur independently. In chapter 1 the progenitor and evolved strains are highly related to the reference *Saccharomyces cerevisiae* strain, S288C. Given this relatedness and the strain's haploid chromosome complement, we did not pursue a re-alignment step. However, in Chapter 2, a large degree of heterogeneity is observed between the clinically isolated samples of *C. albicans* and the reference genome SC5314. Thus, in Chapter 2,



we run the Target Creator without specifying known variation and let the algorithm determine suspect intervals before using the Indel Realigner.

## **SNP Calling**

The uncertainty associated with individual bases affects not only alignment, as described above, but also genotyping, and SNP calling in particular[19]. This uncertainty influences all downstream analysis, as alignment and errors in base calling affect the ability to infer genotypes.

MAQ's internal SNP caller produces a consensus genotype inferred from a Bayesian statistical model. Each consensus genotype is associated with a *phred score of the probability of error*. Potential SNPs are detected by comparing the consensus sequence to the reference genome. In Chapter 1, there is no ambiguity regarding the clonality of the progenitor or evolved samples. Thus, SNP filtration consists of identifying strain-specific, coding, non-synonymous SNPs, confirming them via PCR, and upon validation, characterizing them for their contributions phenotypically.

GATK's Unified Genotyper[2] integrates data from one or multiple samples. It uses a Bayesian genotype likelihood model to simultaneously estimate the most likely genotypes and allele frequency in a population of samples. For each locus for which a variant occurs in at least one sample, there is an emitted posterior probability of there being a segregating variant allele. The resulting variant detection is accompanied by a *phred*-scaled confidence value.

## **Clonality Detection**

Clonality determination is made in a time-course dependent manner, in which clinical isolates from a given patient are genotyped together versus a sequenced version of the reference strain, SC5314. A distance matrix is calculated using all varying loci, where a difference in

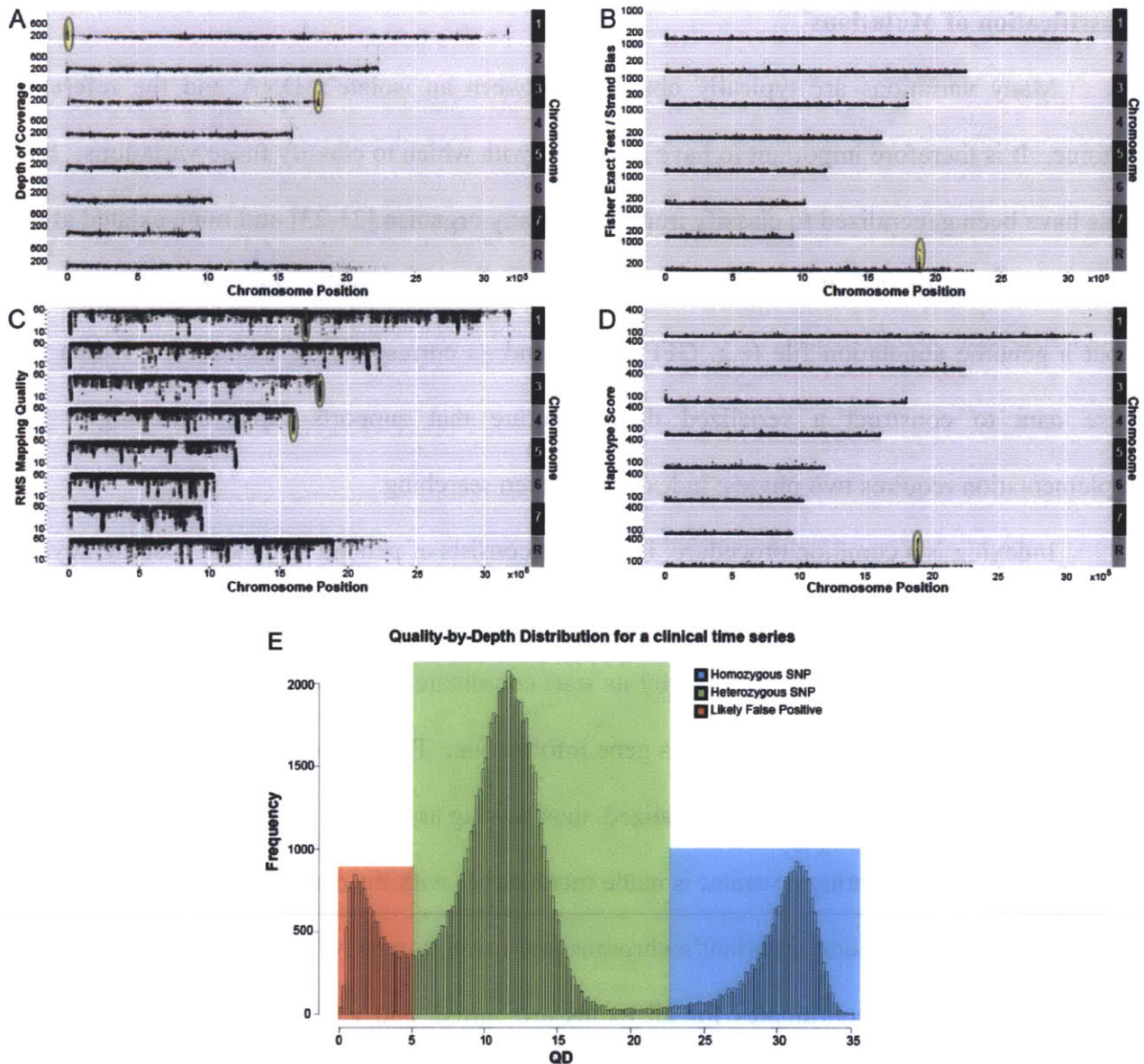
genotype between a homozygous genotype and a heterozygous genotype is scored with a distance of  $\frac{1}{2}$ , and two different homozygous genotypes is scored with a distance of 1. The neighbor-joining method, as implemented in Phylip[20], is applied to each distance matrix for tree construction to determine distance of all time series isolates, with rooting using SC5314 as an outgroup. A distance of 22,000 is defined as being non-clonal.

### **Filtering SNPs**

Upon removal of non-clonal isolates and the reference strain, we re-genotype the time series data using the Unified Genotyper. To reduce the number of false-positives, we rely on contextual annotations provided by GATK:

- QD: quality-by-depth, which is the variant confidence divided by the unfiltered depth,
- MQ: root mean square of the mapping quality of reads across all samples at that locus,
- DP: depth of coverage,
- FS: the *phred*-scaled value of the p-value of a Fisher's Exact Test for strand bias (i.e. a variant is observed only on reads oriented in one direction, and not the reverse complement), and
- HS: the consistency of the site with two, and only two, segregating haplotypes.

In human sequencing, these measures are used for filtration in combination with dbSNP / HapMap data using GATK's Variant Quality Score Recalibrator (VQSR). Because a HapMap dataset is not available in *C. albicans*, we adhere as closely as we can to "best principles" established by the GATK team. For QD, we filter all SNPs with a score less than five. For MQ, we remove all variations with a score less than two standard deviations below the mean. For DP, FS, and HS, we remove all reads with a score two standard deviations above the mean (Figure 2).



**Figure 2: SNPs that are likely to be false positives are filtered from subsequent analysis**

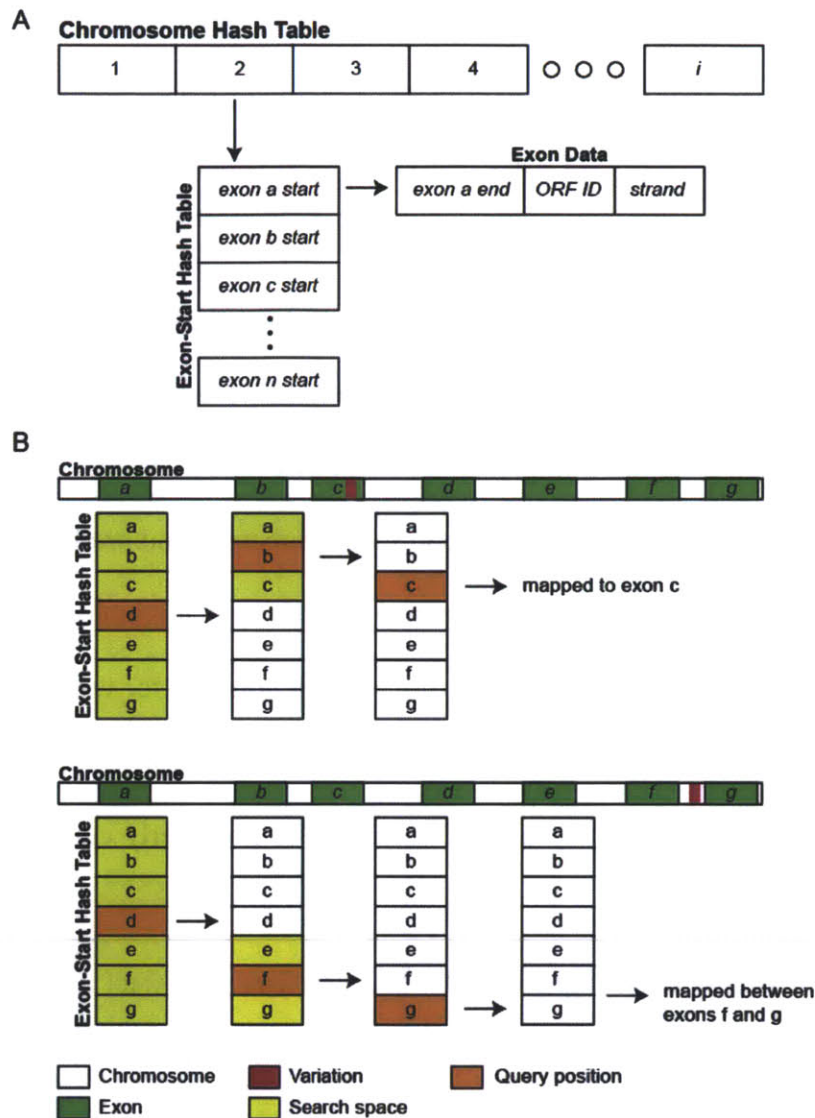
SNP filtration criteria are determined dynamically from the multiple-sample SNP *variant call file* (VCF) files. These data include a quality score as well as many statistical contextual annotations. Because of a lack of HapMap, SNPs are filtered by single parameters: (A)  $DP > \mu_{DP} + 2\sigma_{DP}$ , (B)  $FS > \mu_{FS} + 2\sigma_{FS}$ , (C)  $MQ < \mu_{MQ} - 2\sigma_{MQ}$ , (D)  $HS > \mu_{HS} + 2\sigma_{HS}$  and (E)  $QD < 5$ . Regions highlighted in yellow ovals (A-D) or highlighted in red (E) indicate filtration removed those SNP calls.

## **Classification of Mutations**

Many variations are typically observed between an isolate's DNA and the reference genome. It is therefore important to have a method with which to classify these variations. Few tools have been generalized to classify mutations in any organism[21-23] and none existed at the beginning of this work. I therefore developed a method that is broadly applicable, and takes as input a genome annotation file (e.g. GFF, BED) and its corresponding sequence. I then use these data to construct a serialized data structure that supports rapid searching. My implementation requires two phases: indexing and then searching.

Indexing is a common procedure; in brief, it consists of parsing a file and hashing keys to descriptive information. In this case, an annotation file is parsed for exon data. Each exon is keyed first by its chromosome and then by its start coordinate on the Watson strand (Figure 3a). The second table then maps to the exon's gene information. The nested approach reduces search complexity. Once parsed, the file is serialized, thus serving as a single time investment.

Searching/annotating a variant is made much easier with the described indexing structure. Searching consists of using a variant's chromosome name to retrieve the chromosome-specific hash-table. The start coordinates for all exons are sorted, and a binary search is conducted (figure 3b)[24]. If the variant's coordinate precedes the query exon's start coordinate, the search fails. If the variant's coordinate exceeds the query exon's start coordinate, then the variant's coordinate is compared to the stop coordinate for the exon. If the stop coordinate is greater than the variant's coordinate, then the variant is mapped. If not, the search fails. Each failed search reduces the search space by half until the search converges. If the variant remains unmapped, the nearest two exons and their distances to the variant are reported.



**Figure 3. Design and use of an efficient genome annotation data structure**

(A) A nested-hash table is constructed from parsing a genome-specific annotation file. The first key is the chromosome's name/number and the second is the exon's start coordinate relative to the Watson strand. The second hash entry maps to the exon's end coordinate as well as other descriptive data. Once the structure is populated, it is serialized for subsequent use.

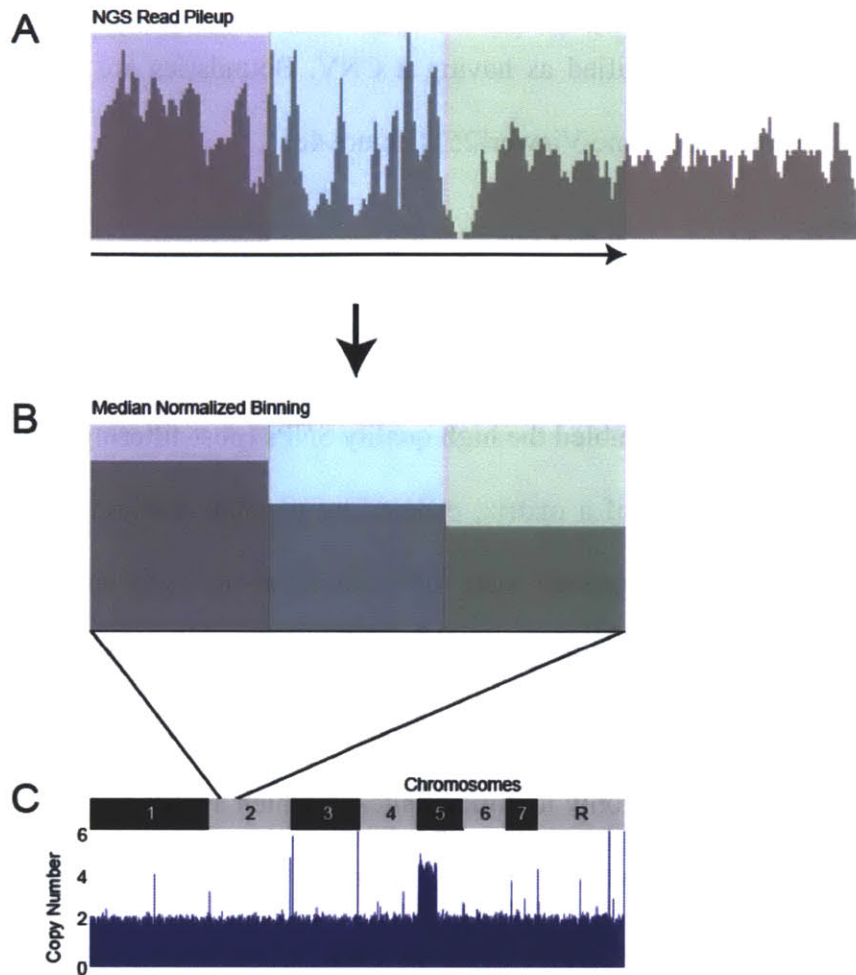
(B) Mapping is determined via a binary search. A variation's chromosome and coordinate (pink) are tested against the nested hash (yellow, with comparison in orange). Failed mapping reduces the search space by half until either mapping the variation within an exon is successful (top), or convergence of search space occurs (bottom), implying that the variation is flanked by exons. Boundary conditions are tested prior to searching.

Downstream analysis is modular and supports many different avenues of investigation. For example, in both Chapters 1 and 2, mutations occurring within an exon allowed for comparison of reference amino acid sequence and variant-adjusted amino acid sequence.

### **Copy-Number Variation**

CNV detection as implemented here occurs in two phases. The first involves depth determination for all loci in the genome. We accomplish this by using a depth-of-coverage walker that is part of the standard implementation of GATK[5]. In brief, this method takes a SAM or BAM file as input, as well as other optional parameters, and produces a per-locus depth readout. I use this method with standard parameters, except minimum mapping quality - a *phred*-scaled metric that assesses the quality of a read alignment - for which I used a parameter of 10, which corresponds to at most a 10% error. This threshold is used because it eliminates any contributions from non-uniquely aligned reads but is not overly conservative (the default setting includes all aligned reads).

The second step is a binning method. The user can pre-select a window size; for this work, a window size of 5kb. The per-locus depth computed in the previous step is then counted for all intervals of the window size across the nuclear genome (Figure 4a). Each window is then normalized to the median count across all windows, and multiplied by the ploidy of the organism (Figure 4b). This number can either be determined in advance through methods such as FACS, or can be left as 1 and corrected as necessary. I then use a sliding window method to go through each normalized bin, defining a potential CNV if 70% of 10 consecutive bins had a normalized count  $> 2.5x$ . Regional/chromosome copy-number variants (e.g. trisomy) are identified if  $>$



**Figure 4. Determination and visualization of copy-number variations**

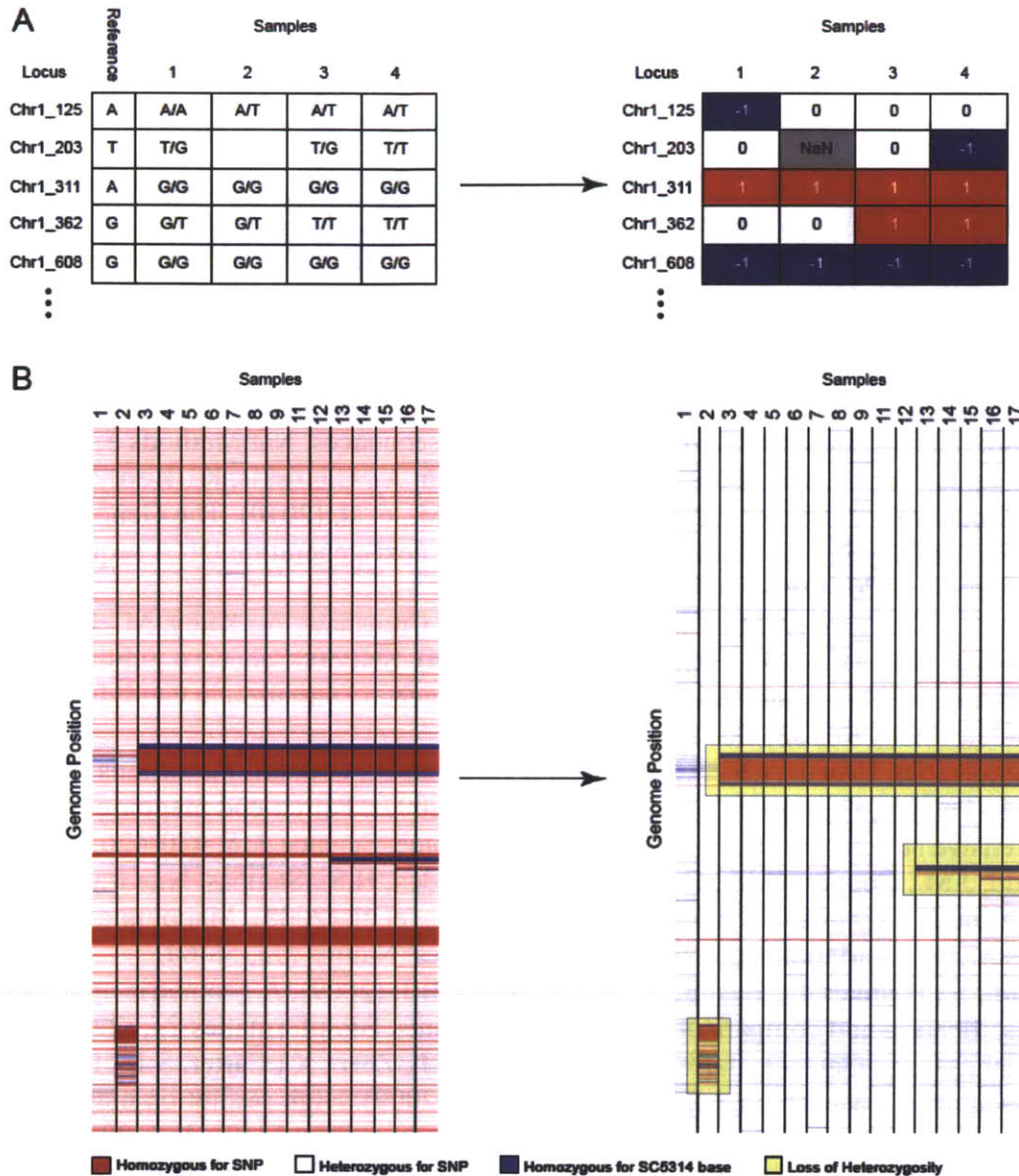
Coverage data is broken in to windows of pre-determined size. (A) Base coverage for each window is determined across the nuclear genome. The median base count across all windows is used to normalize each window(B). If ploidy is known for the strain, each window can be multiplied by the ploidy for stoichiometric representation. Different approaches can be used to determine CNVs. (C) A CNV is shown here in the left arm of chromosome 5, demonstrating the phenomenon of i5L, or an isochromosome in the left arm of chromosome 5.

15% of the chromosome is identified as having a CNV. Boundaries are confirmed by visual inspection in the Integrative Genome Viewer[25] (Figure 4c).

### **Loss-of-Heterozygosity Determination**

For each time course, we assembled the high quality SNPs (post-filtering, above) from multi-sample calling into the columns of a matrix, ordered by genome position, with the isolates in rows, ordered temporally. The genetic state of each locus in each sample was coded to distinguish loci homozygous for the haploid reference (-1), heterozygous SNPs (0), and homozygous SNPs for the non-reference state (1) (Figure 5a). We then applied a sliding window method across each chromosome, only looking at sites in which a SNP call was made in at least one isolate. An LOH event was defined as occurring if (1) at least one isolate had a heterozygosity content  $> 40\%$ , and (2) at least one other isolate had a heterozygosity content  $< 5\%$ . Window sizes were of length 500. Boundaries were trimmed such that if a window terminated in a heterozygous site in the isolate for which the LOH occurred, it was trimmed back until it was homozygous. If two 500+ windows were within 7 KB of each, the region was assessed to determine if the event was actually one event and merged if the heterozygous sites in the inter-window space had homozygosed. If two isolates had LOHs that overlapped but did not have precisely identical boundaries, the LOH regions were combined such that the LOH interval for both isolates was the same. All LOH regions were confirmed by visual inspection (Figure 5b).





**Figure 5. Visualization and identifying LOH**

Genotypes from all positions are mapped relative to a haploid reference genome. Any variation that is observed in any isolate will cause all isolates to be included for genotyping at that locus. All variations are mapped to color space (A). A sliding window approach scans intervals of size 500; if one sample shows greater than 40% heterozygosity, while another shows less than 5%, that window indicates an LOH event. Depicted here is a visual representation of the of a whole genome time series as described (B). White represents a heterozygous genotype, and blue and red represent homozygous genotypes, regions that large changes from white to blue or red demonstrate LOH. Because the sliding window approach is whole genome and agnostic to previously identified variation, the resolution and boundary detection represent significant improvements over other methods, such as SNP arrays. The left panel shows the whole genome, while the right is used highlights LOH discovery in yellow.

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## **Future Directions**

## Overview

In the work presented here, we have used massively parallel sequencing to study *in vivo* and *in vitro* evolutionary trajectories in yeast. In the experimentally evolved strain *S. cerevisiae*, we identified newly arising adaptive alleles from divergent selection and characterized each for its contribution toward evolved fitness. In so doing, we identify patterns of convergent evolution as well as the genetic basis of the first instance of synthetically evolved incipient speciation in yeast. We then applied a similar approach to *in vivo* clinical isolates of *C. albicans*. This approach yielded insights into: (1) the extent of clonality in serial clinical isolates; (2) mitotic recombination as a means of increasing the copy-number of adaptive alleles; (3) the presence/role of genes known to affect drug resistance; and (4) the presence of many previously uncharacterized genes, implicating them in drug resistance acquisition and host adaptation in a clinically significant pathogen. Here, I describe work that has followed the general trend of our research and propose future paths for investigation.

## Mechanism of Speciation

Our work in *S. cerevisiae* identified not only which alleles were newly arising under conditions of strong selection, but also allowed us to characterize the fitness contributions of those alleles. With the evolved alleles identified, we were able to show that ecologically adaptive alleles arising from divergent evolutionary stresses resulted in a DM interaction. However, at the conclusion of our work, there remained several open questions, the most important of which is how the evolved alleles of PMA1 and MKT1 result in reduced fitness.

While our work demonstrated the likely transcriptional effects caused by the mutated MKT1 allele, the exact role of PMA1 remained unclear. The emergence of evolved PMA1

alleles in both sequenced high-salt evolved strains (**S2** and **S6**) initially suggested that those alleles could be constitutively active. Hyperosmotic environments affect membrane potential, and one way to mitigate this stress is via modulating proton pumps. However, given that mutations in PMA1 occurred independently, twice, the likelihood that both would be gain-of-function mutations was less likely. Perreiras *et al.* went on to characterize the mutant PMA1 allele both with and without the evolved MKT1 allele[1] and showed: (1) PMA1 is a loss-of-function mutation and (2) while PMA1 does not alter transcription, the lowered intracellular pH caused by the evolved PMA1 alleles exacerbates the already low expression of hexose transporter genes regulated by MKT1. It is this interaction that delays cell division, thus causing decreased fitness in hybrids that we demonstrated in Chapter 1.

Our work, and the work that has immediately followed, represents a single pathway by which incipient speciation occurs. There are many avenues for further work. In the original work by Dettman *et al.*, there are six strains evolved in high salt conditions (**S1-S6**) and six strains evolved under low glucose, minimal conditions (**M7-M12**)[2]. In that original work, each pairing (**S1XM7**, **S2XM8**, etc.) displayed hybrid inferiority. As a follow up, the rest of the strains in this set should be sequenced. Further, to determine the extent to which hybrid incompatibility is a widespread and recurring phenomenon, it would be of great interest to phenotypically characterize the remaining 30 pairings not tested in the original work (**S1XM8**, **S1XM9**, etc.). With the genomes sequenced and all pairings made and assessed, the degree to which this theme is commonplace would be addressed. Other avenues for consideration may include expanding the different selective conditions and determining how large the mutational landscape can be that can result in DM level interactions. Further, the initial experiment was conducted in diploids[2] but all subsequent characterization has been in haploids. To further test

DM interactions in a system more similar to the yeast's biology, genotyping and phenotyping as done in our work and in follow-up work should be in diploids.

### **Drug Resistance Evolution**

Understanding drug resistance evolution in clinical settings serves two purposes, the first of which is studying a fundamental question in evolutionary biology. The second purpose is relating knowledge of evolution of drug resistance and exploiting it in the clinical setting so as to improve patient outcome. In our work, we note that *C. albicans* acquires resistance to fluconazole through many varied mechanisms. We demonstrate that both commonly known and under-reported mechanisms result in increased levels of resistance. Further, we show a utility in sequencing, both for its ability to uncover all genetic variation for clinical isolates as well as its use in clonality determination. Both are essential to meaningful interpretation of results and, unfortunately, we see that previous work cannot guarantee lineage-relationships, thereby muddling conclusions. The level of detail of this type of work, and its importance to human health, is well recognized, as others are applying similar approaches to different diseases[3-6]. Future work can be divided into four categories: (1) further characterization of known mutations, (2) additional *C. albicans* sequencing, (3) additional clinical time series sequencing in other diseases, and (4) identification of negative selection.

#### **Further characterization of known mutations**

The work presented in Chapter 2 focuses predominantly on persistent, recurrent, non-synonymous substitutions to relate to drug resistance as a primary phenotype. While work has been initiated to characterize these time series isolates with respect to changes in fitness (both with and without drug), virulence, adhesion, and filamentation, with respect to the same set of



genes, our approach does not examine effects caused by to noncoding mutations. Also, we observe changes in genes regulating drug response (e.g. MRR1 and TAC1), suggesting transcriptional re-programming in these time series. Thus, the next avenue for investigation would be to score all persistent, noncoding mutation in promoter regions. By using a PSSM approach and scanning for changes to transcription factor binding site affinity relative to the progenitor genotype, predictions for changes in gene regulation are possible. Already, we have initiated work to profile transcriptional activity in each strain (data not shown). Further profiling, coupled with recurrent changes to promoters or their binding sites, represents a whole new avenue by which to understand the dynamics of *in vivo* drug resistance evolution.

### ***C. albicans* sequencing**

The greatest obstacle we have in generalizing our conclusions from Chapter 2 is power; there are two approaches by which we can improve this. The first approach is additional sequencing of pair-wise sensitive/resistant isolates derived from many individual patients that are clonally related. While this may strengthen our ability to conclude the importance of LOH on the right arm of chromosome 3, it comes at the expense of fine-grain resolution of incremental gains in MIC and which mutations co-occur. Work by Toprak and Veres *et al.* show that incremental gains can often occur by similar mutations occurring *in the same order*[7] in parallel evolving strains. Thus, it seems that a second approach would be of greater benefit – that is, sequencing deep time courses from patients. Given the diversity we observe in clonally derived strains, this approach is of greater priority than many matched pairs for two reasons: (1) The gain in resolution occurring at both a genotype and phenotype level would be valuable to further enhance our understanding of drug resistance progression in this pathogen; and (2) the progression of a phenotype coupled to a dense time series allows for removal of transient

mutations that can arise under a high mutation rate, thus allowing for greater genotype-phenotype association. While the field will benefit from either, it seems that the first priority should be on the acquisition and sequencing of deep, clonally derived time series.

### **Drug resistance acquisition elucidation via clinical series**

While not classically considered within the purview of population genetics, concepts from this field apply to diseases ranging from bacterial infections to cancer. Fundamentally, for example, recurrence in cancer is a disease of drug resistance; sub-clones of an initial tumor are able to escape initial therapy, thus making subsequent treatment with the same chemotherapeutic protocol as the initial treatment undesirable[8]. Already, some are attempting approaches similar to what we have described here[5, 6, 9] to identify recurrent changes in patients and make therapeutic decisions based on sequencing results. This area of research is very fertile and has applications for diseases requiring on-going treatment.

### **Identification of negative selection**

Our work, as well as that of others, focuses on mutated genes that are mutating as being causative of the drug resistant evolved phenotype. Targeting and exploiting the newly mutating genes is a successful strategy[10] but comes with a risk of resistance mutations that will render therapy inert[11]. Unlike diseases such as cancer, however, microbes offer a completely different avenue for treatment; one where evolution of new resistance is less of a problem. In our work, nearly one-third of the genome shows persistent mutations. But this is only generated from *seven* time courses. If we had more data, the next step would be to identify genes under negative selection. Genes that are evolutionarily constrained during drug resistant evolution, especially those lacking human paralogs, are ideal targets for clinical targeting. High-throughput chemical screening of existing agents, or targeted disruption of these genes via novel synthetic

compounds represents an ideal, synergistic treatment scheme for high-risk patients with chronic infections (e.g. HIV patients with recurrent oropharyngeal candidiasis or tuberculosis, etc). While furthering the study of evolutionary mechanisms is important for clinical development, the existence of inexpensive massively parallel sequencing will allow for completely new inroads to treat exogenous causes for disease.

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## **Appendix 1: Chapter 1 Supplemental Tables**

**Table S1. SNPs and Gene-Cluster Size Changes in Haploid Representatives of S2, S6, and M8**

Chromosome	Position, Base, and Amino-Acid Changes	Gene	Notes
<b>S2 Haploid</b>			
7	481971 G-C S-C	<i>PMA1</i>	Main adaptive determinant in high salt
7	646331 C-A M-I	<i>GCD2</i>	No effect on fitness detected
10	456758 C-A P-H	<i>MET3</i>	Confers a no-growth phenotype (auxotrophy) in low glucose
12	560742 C-G	Intergenic region 3' to <i>YLR208W</i> and <i>YLR209C</i>	No effect on fitness detected
14	530695-538465	Expansion, <i>ENA1</i> , <i>ENA2</i> , <i>ENA5</i>	Adaptive determinant in high salt. Synergistic with evolved allele of <i>PMA1</i>
14	543274 A-G D-G	<i>LAP2</i>	No effect on fitness detected
<b>S6 Haploid</b>			
2	464706, G -T, Y-*	<i>CYC8</i>	Adaptive determinant in high salt, synergistic with the S6 evolved allele of <i>PMA1</i>
7	481584 A-C, L-W	<i>PMA1</i>	Adaptive determinant in high salt. Confers slow growth in YPD and low glucose
7	390007, G-A	Noncoding, promoter of <i>YBP2</i>	No effect on fitness detected
11	274875, T-A	Noncoding, promoter of <i>CAB3</i>	No effect on fitness detected
12	470406-486202	Contraction, <i>ASP3-1</i> , <i>ASP3-2</i> , <i>ASP3-3</i> , <i>ASP3-4</i>	No effect on fitness detected
<b>M8 Haploid</b>			
4	1112209 C-A C-F	<i>TIM11</i>	No effect on fitness detected
5	525696 C-G T-I	<i>RPH1</i>	Fitness benefit after the diauxic shift in low glucose, not necessary to reconstitute the full M8 phenotype
7	126872 T-G F-V	<i>MDS3</i>	Fitness benefit before the diauxic shift in low glucose. Evolved allele confers a sporulation deficiency: $10.4\% \pm 0.8$ SE (n=12 measurements) vs. $30.1 \pm 1.0$ SE (n=50)
12	64832 C-T Q-Q	<i>UBI4</i>	No effect on fitness detected
14	467221 A-G D-G	<i>MKT1</i>	Fitness benefit after the diauxic shift in low glucose
15	432852 G-A R-K	<i>SGT1</i>	No effect on fitness detected

Table S2. Comprehensive list of SNPs. In blue, SNP verified by Sanger sequencing. In red, SNP proven false. 0, no SNP detected relative to the reference sequence.

	Progenitor	S2	S6	M8
<b>Total Reads</b>	23405332	18921232	11650340	9917256
<b>Mapped Reads</b>	17287248	10774490	8202201	7304120
<b>Fraction Reads</b>	73.86%	56.94%	70.40%	73.65%
<b>Coverage</b>	51.861744	45.7915825	34.85935425	31.04251

Chromosome	Position	Reference	Prog base	S2 base	S6 base	M8 base
1	3981	A	T	T	T	T
1	3982	T	A	A	A	A
1	5244	G	A	A	A	A
1	27127	T	0	0	C	0
1	27130	C	0	0	G	0
1	36120	C	A	A	A	A
1	36814	A	C	C	C	C
1	40231	C	G	G	G	G
1	41240	A	G	G	G	G
1	41664	T	G	G	G	G
1	41700	C	A	0	A	A
1	41703	C	A	0	A	A
1	46231	C	G	G	G	G
1	46833	G	A	A	A	A
1	47821	T	A	A	A	A
1	47826	C	T	T	T	T
1	48772	T	A	A	A	A
1	49904	C	A	A	A	A
1	50327	C	A	A	A	A
1	55746	A	G	G	G	G
1	55954	A	T	T	T	T
1	62767	A	G	G	G	G
1	70794	C	G	G	G	G
1	70874	A	G	G	G	G
1	96740	G	C	C	C	C
1	97025	A	T	T	T	T
1	97026	T	A	A	A	A
1	97678	C	G	G	G	G
1	97679	C	G	G	G	G
1	98350	C	G	G	G	G
1	98351	G	C	C	C	C
1	99564	T	0	0	0	C
1	99841	A	T	T	T	T
1	100399	G	C	C	C	C
1	110470	C	G	G	G	G
1	110471	G	C	C	C	C
1	113702	C	G	0	G	G

1	113703	G	C	0	C	C
1	120442	C	G	G	G	G
1	134852	T	A	A	A	A
1	134854	G	T	T	T	T
1	152189	C	A	A	A	A
1	152190	A	C	C	C	C
1	167048	G	C	C	C	C
1	167551	G	C	C	C	C
1	167802	C	T	T	T	T
1	172018	A	G	0	0	0
1	172041	A	0	G	0	G
1	172042	G	0	0	0	T
1	172432	C	0	T	0	0
1	172434	G	0	C	0	0
1	174173	G	C	0	C	C
1	174187	C	G	0	G	G
1	174188	G	C	0	C	C
1	175378	T	C	0	C	C
1	178256	G	C	C	C	C
1	178647	T	0	0	C	0
1	179683	T	A	A	A	A
1	179761	C	A	A	A	A
1	193625	A	T	T	T	T
1	199804	T	G	G	G	G
2	11053	T	C	C	C	C
2	11308	A	T	T	T	T
2	11309	A	T	T	T	T
2	11345	A	G	G	G	G
2	11379	A	C	0	C	C
2	13102	C	A	A	A	A
2	13477	G	A	A	A	A
2	13492	A	T	T	T	T
2	13553	G	A	A	A	A
2	13966	C	A	A	A	A
2	13982	G	A	A	A	A
2	15101	T	G	G	G	G
2	15332	G	C	C	C	C
2	15510	G	T	T	T	T
2	15518	A	G	G	G	G
2	15835	T	C	C	C	C
2	16380	C	T	0	T	T
2	16392	A	G	G	G	G
2	17455	A	C	C	C	C
2	23855	C	0	0	A	0
2	23856	C	0	0	A	0
2	23913	C	A	0	A	A
2	30009	C	0	0	T	T



2	36312	T	A	A	A	A
2	36673	A	T	T	T	T
2	38067	C	T	T	T	T
2	38210	A	T	T	T	T
2	38728	C	A	A	A	A
2	38800	C	A	A	A	0
2	38908	G	A	A	A	A
2	38917	C	T	T	T	T
2	38920	C	A	A	A	A
2	42377	C	G	G	G	G
2	45495	T	A	A	A	A
2	48369	A	T	T	T	T
2	55145	A	C	C	C	C
2	59751	T	C	C	C	C
2	68154	T	G	G	G	G
2	68155	G	A	A	A	A
2	73450	C	G	G	G	G
2	75208	A	G	G	G	G
2	89277	G	T	T	T	T
2	92679	C	A	A	A	A
2	95345	G	T	T	T	T
2	113436	G	0	0	0	A
2	114868	G	A	A	A	A
2	114870	A	G	G	G	G
2	201635	G	C	C	C	C
2	210433	A	G	G	G	G
2	220413	A	G	G	G	G
2	220414	G	A	A	A	A
2	237839	G	A	A	A	A
2	237892	G	A	A	A	A
2	238116	G	A	A	A	A
2	238133	G	A	A	A	A
2	241359	G	A	A	A	A
2	241396	G	A	A	A	A
2	245111	T	A	A	A	A
2	250039	T	G	G	G	G
2	250403	C	G	G	G	G
2	254495	G	T	T	T	T
2	254532	C	A	0	0	A
2	254616	T	A	A	A	A
2	315270	C	G	G	G	G
2	315271	G	C	C	C	C
2	323835	C	G	G	G	G
2	323836	G	C	C	C	C
2	370774	C	T	T	T	T
2	374011	T	A	A	A	A
2	375081	C	A	A	A	A

2	375272	T	A	A	A	A
2	376497	A	T	T	T	T
2	385360	C	G	G	G	G
2	385361	G	C	C	C	C
2	388774	T	A	A	A	A
2	388775	T	A	A	A	A
2	392557	C	G	0	G	G
2	392558	G	C	0	C	C
2	392568	C	G	0	G	G
2	392569	G	C	0	C	C
2	426394	C	G	0	G	G
2	426396	G	C	0	C	C
2	432380	T	C	C	C	C
2	433377	C	G	G	G	G
2	433378	G	C	C	C	C
2	437344	A	G	G	G	G
2	439496	T	G	G	G	G
2	447535	C	G	G	G	G
2	447536	G	C	C	C	C
2	456359	C	T	T	T	T
2	464706	G	0	0	T	0
2	488600	T	A	A	A	A
2	488601	C	T	T	T	T
2	513365	A	G	G	G	G
2	514965	A	C	C	C	C
2	514966	C	A	A	A	A
2	527099	A	G	G	G	G
2	547442	A	T	T	T	T
2	625500	T	C	C	C	C
2	627421	T	G	G	G	0
2	627486	A	T	0	T	T
2	627487	T	A	0	A	A
2	631907	G	A	A	A	A
2	631912	G	A	A	A	A
2	631936	G	A	0	0	0
2	631940	C	A	0	A	0
2	631981	A	G	G	G	G
2	633189	T	A	A	A	A
2	634934	C	T	T	T	T
2	635192	A	G	G	G	G
2	635247	A	G	G	G	G
2	635822	C	G	G	G	G
2	636141	A	G	G	G	G
2	636306	A	T	T	T	0
2	636309	A	G	G	G	0
2	636336	G	A	0	A	A
2	636342	G	A	0	A	A

2	738454	C	A	0	A	A
2	739341	A	T	T	T	T
2	740291	C	G	G	G	G
2	740292	G	C	C	C	C
2	743936	G	C	0	C	C
2	743938	C	G	0	G	G
2	754908	T	C	C	C	C
2	774080	C	G	G	G	G
2	774430	C	G	G	G	G
2	780541	C	A	A	A	A
2	781354	G	C	C	C	C
2	786736	C	T	T	T	T
2	786737	T	C	C	C	C
2	793986	A	C	C	C	C
2	793987	C	A	A	A	A
2	796707	A	G	G	G	G
3	101652	A	T	T	T	T
3	101655	T	A	A	A	A
3	143129	T	C	C	C	C
3	148613	C	T	0	0	0
3	152641	G	A	A	A	A
3	162275	A	G	G	G	G
3	162357	T	C	C	C	C
3	162636	T	G	G	G	G
3	162690	G	A	A	A	A
3	163055	T	C	C	C	C
3	250563	A	T	T	T	T
3	275421	A	G	G	G	G
4	24415	C	A	A	A	A
4	27070	C	T	T	T	T
4	30786	G	A	A	A	A
4	108307	T	A	A	A	A
4	119470	G	A	A	A	A
4	119564	T	A	A	A	A
4	121289	G	A	A	A	A
4	130626	T	A	0	A	A
4	132292	T	A	A	A	A
4	277105	C	G	0	G	G
4	277106	G	C	0	C	C
4	369164	T	G	0	0	0
4	392616	A	G	G	G	G
4	396436	G	0	0	0	T
4	396451	T	G	0	G	G
4	396504	C	G	G	G	G
4	864217	A	G	G	G	G
4	1063029	C	A	A	A	A
4	1112209	C	0	0	0	A

4	1176396	T	0	0	C	C
4	1253390	T	C	C	C	C
4	1296177	C	G	G	G	G
4	1400867	C	T	T	T	T
4	1402298	C	T	0	T	T
4	1433703	A	T	0	T	T
4	1457020	C	T	T	T	T
4	1491661	G	A	A	A	A
4	1491667	G	C	C	C	C
4	1516839	T	A	A	0	0
4	1519599	C	G	G	G	G
4	1519663	C	G	G	G	G
4	1524960	A	0	0	G	0
5	9168	G	T	T	T	T
5	18079	A	T	T	T	T
5	48384	T	C	C	C	C
5	108806	C	A	0	0	0
5	154530	T	A	A	A	A
5	232634	C	G	G	G	G
5	278525	C	G	G	G	G
5	278526	G	C	C	C	C
5	305258	G	A	A	A	A
5	305828	A	G	G	G	G
5	305886	A	0	0	0	C
5	305968	T	A	A	A	A
5	308627	C	G	G	G	G
5	308984	G	T	T	T	T
5	309047	G	C	C	C	C
5	352390	A	G	G	G	G
5	434284	C	T	T	T	T
5	502222	T	A	A	A	A
5	517524	T	C	C	C	C
5	525696	C	0	0	0	T
6	4827	T	A	0	A	A
6	48020	A	G	G	G	G
6	58032	G	A	A	A	A
6	58035	G	A	A	A	A
6	66443	C	A	A	A	A
6	83382	G	A	A	A	A
6	95000	A	G	G	G	G
6	95385	C	G	0	G	G
6	95410	T	C	0	C	C
6	118584	G	A	A	A	A
6	173057	C	T	T	T	T
6	191312	T	A	A	A	A
6	191388	G	T	T	T	T
6	219387	A	G	G	G	G

6	236216	C	A	A	A	A
6	241576	A	T	T	T	T
6	248160	A	T	T	T	T
7	89735	G	C	C	C	C
7	89751	T	0	C	0	0
7	95444	A	C	0	0	0
7	98172	G	A	A	A	A
7	125488	T	0	A	0	0
7	125489	C	0	T	0	0
7	125909	C	G	G	G	G
7	125910	G	C	C	C	C
7	126872	T	0	0	0	G
7	203957	C	A	A	A	A
7	230256	C	T	T	T	T
7	275965	C	G	G	G	G
7	276384	A	T	T	T	T
7	303591	A	C	C	C	C
7	384063	C	G	G	G	G
7	384064	G	C	C	C	C
7	384846	C	G	0	G	G
7	384847	G	C	0	C	C
7	386981	C	0	0	0	G
7	386982	G	0	0	0	C
7	390007	G	0	0	A	0
7	397085	C	G	G	G	G
7	397086	G	C	C	C	C
7	397241	A	C	0	C	C
7	413366	G	C	C	C	C
7	413367	C	G	G	G	0
7	481584	A	0	0	C	0
7	481971	G	0	C	0	0
7	598535	C	T	T	T	T
7	607109	T	G	G	G	G
7	610095	A	G	G	G	G
7	622408	A	T	T	T	T
7	630688	C	T	T	T	T
7	646331	C	0	A	0	0
7	783805	A	C	C	C	C
7	796569	A	C	C	C	C
7	796570	C	A	A	A	A
7	948219	A	T	T	T	T
7	999271	C	T	T	T	T
7	999367	A	C	0	C	C
7	1031948	C	A	A	A	A
7	1032373	G	A	A	A	A
7	1033108	C	T	T	T	T
7	1041870	C	T	T	T	T

7	1042083	A	G	G	G	G
7	1042185	A	G	G	G	G
7	1042308	A	G	G	G	G
7	1042313	A	G	G	G	G
7	1042563	G	A	A	A	A
8	62687	G	A	A	A	A
8	212260	C	0	T	0	0
8	217753	G	T	T	T	T
8	240687	G	A	A	A	A
8	417057	G	A	A	A	A
8	445616	C	0	0	0	G
8	445617	A	0	0	0	C
8	496180	G	A	A	A	A
9	203638	A	C	C	C	C
9	318692	T	A	A	A	A
10	76241	T	C	C	C	C
10	81335	T	G	0	G	G
10	81927	A	T	T	T	T
10	84958	G	A	A	A	A
10	89005	C	A	A	A	A
10	90365	A	C	0	C	C
10	96057	G	C	C	C	C
10	97489	C	G	G	G	G
10	99469	C	G	G	G	G
10	99767	G	C	0	C	C
10	99778	G	0	0	C	0
10	99792	A	T	T	T	T
10	99793	A	T	0	T	T
10	102276	C	G	G	G	G
10	102610	A	C	C	C	C
10	102642	A	G	G	G	G
10	102643	A	C	C	C	C
10	113842	G	A	A	A	A
10	123309	T	C	0	C	C
10	123314	T	C	0	C	C
10	129111	T	C	C	C	C
10	171997	C	G	G	G	G
10	171998	G	C	C	C	C
10	179434	C	G	G	G	G
10	179436	G	C	C	C	C
10	204551	G	T	T	0	T
10	204552	T	G	G	G	G
10	205348	C	A	A	A	A
10	414288	C	G	0	G	G
10	414289	G	C	0	C	C
10	421511	G	A	0	A	A
10	456758	C	0	A	0	0

10	625481	G	A	A	A	A
10	627368	C	T	T	T	T
10	627370	T	C	C	C	C
10	627525	C	G	G	G	G
10	627526	C	G	G	G	G
10	629481	T	A	A	A	A
10	664658	G	T	0	T	T
10	670284	T	G	G	G	G
10	676911	G	A	A	A	A
10	687983	A	G	G	G	G
10	708355	T	A	A	A	A
10	708439	A	T	T	T	T
10	709355	C	T	0	T	T
10	713833	C	G	G	G	G
10	715086	G	0	0	0	A
10	716150	A	T	T	T	T
10	716503	C	A	A	A	A
10	717672	C	A	A	A	A
10	717776	G	A	A	A	A
10	722286	G	T	0	T	T
10	724285	T	G	G	G	G
10	724993	G	T	T	T	T
10	727113	C	G	G	G	G
11	7131	C	G	G	G	G
11	7132	G	C	C	C	C
11	69325	T	C	0	C	C
11	69326	G	T	0	T	T
11	189366	C	G	0	0	0
11	192315	A	T	T	T	T
11	192316	T	A	A	A	A
11	197105	C	G	G	G	G
11	197106	G	C	C	C	C
11	199377	A	T	0	0	0
11	199378	T	A	0	A	0
11	242811	T	A	A	A	A
11	253006	A	T	T	T	T
11	253007	T	A	A	A	A
11	274875	T	0	0	A	0
11	316656	C	T	T	T	T
11	335190	C	T	T	T	T
11	357929	T	C	C	C	C
11	393438	C	G	G	G	G
11	393439	G	C	C	C	C
11	453012	T	A	A	A	A
11	457775	C	T	T	T	T
11	463435	G	T	T	T	T
11	463468	G	T	T	T	T

11	479596	C	T	T	T	T
11	509993	C	G	0	G	G
11	509994	G	C	0	C	C
11	610650	C	G	G	G	G
11	618236	G	A	A	A	A
11	618237	A	G	G	G	G
11	666408	T	0	0	G	G
12	12	A	C	0	0	0
12	13	C	A	0	0	0
12	5741	T	C	0	0	C
12	5757	A	T	0	0	T
12	5808	T	0	0	0	C
12	32901	T	0	0	0	G
12	32902	G	A	0	0	A
12	64832	C	0	0	0	T
12	185062	G	A	A	A	A
12	192416	C	T	T	T	T
12	193483	A	C	C	C	C
12	210771	A	T	T	T	T
12	528751	T	A	A	A	A
12	560742	C	0	G	0	0
12	699963	G	A	A	A	A
12	725938	G	A	A	A	A
12	750224	C	T	T	T	T
12	762846	A	T	T	T	T
12	767026	T	C	C	C	C
12	767027	C	T	T	T	T
12	828902	C	T	T	T	T
12	1039433	T	A	A	A	A
13	34473	T	G	G	G	G
13	325904	T	A	A	A	A
13	448332	G	A	0	A	A
13	448333	A	G	0	G	G
13	672128	T	C	C	C	C
13	680935	T	C	0	C	C
13	680939	C	T	0	T	T
13	794225	G	C	0	C	C
13	808976	A	T	T	T	T
13	809197	A	G	G	G	G
13	851734	G	0	A	0	A
13	851740	G	A	A	A	A
13	864682	G	T	T	T	T
13	924339	G	0	0	T	0
14	25775	G	A	A	A	A
14	132573	T	C	0	C	C
14	189081	C	G	0	G	G
14	189082	G	C	0	C	C



14	274732	G	C	C	C	C
14	276356	A	G	0	G	G
14	278945	T	G	G	G	G
14	290429	T	G	G	G	G
14	299120	C	G	G	G	G
14	300950	T	0	0	0	A
14	304165	G	T	T	T	T
14	306231	C	A	A	A	A
14	307728	T	G	G	G	G
14	308753	G	C	C	C	C
14	315278	T	G	G	G	G
14	359024	C	T	T	T	T
14	359342	C	0	0	0	T
14	359347	C	0	0	0	T
14	374744	T	C	C	C	C
14	374768	A	C	C	C	C
14	374810	A	C	C	C	C
14	377889	G	T	T	T	T
14	383566	A	G	G	G	G
14	415073	C	0	T	T	T
14	415090	C	0	T	T	T
14	415098	C	0	T	T	T
14	467221	A	0	0	0	G
14	471769	A	G	G	G	G
14	543274	A	0	G	0	0
14	766523	C	T	T	T	T
15	35765	G	C	C	C	C
15	36013	T	A	A	A	A
15	36056	G	A	A	A	A
15	36119	G	C	C	C	C
15	36149	G	A	A	A	A
15	49829	G	T	T	T	T
15	49912	A	T	0	T	T
15	49919	A	T	0	T	0
15	49922	T	0	A	0	A
15	49941	G	T	T	T	T
15	50001	C	T	T	T	T
15	50009	A	T	T	T	T
15	50011	C	T	T	T	T
15	50069	G	T	T	T	T
15	50081	T	C	C	C	C
15	50430	G	C	C	C	C
15	50431	G	C	C	C	C
15	50767	C	T	T	T	T
15	52199	C	T	T	T	T
15	56036	C	G	G	G	G
15	57699	A	T	T	T	T

15	58601	C	G	G	G	G	G
15	60173	A	G	G	G	G	G
15	60240	C	T	T	T	T	T
15	61985	A	T	T	T	T	T
15	63708	C	T	T	T	T	T
15	64173	G	C	C	C	C	C
15	69084	C	T	T	T	T	T
15	84121	T	C	C	C	C	C
15	186243	A	C	C	C	C	C
15	186978	C	G	G	G	G	G
15	186979	G	C	C	C	C	C
15	190052	C	G	G	G	G	G
15	190053	G	C	C	C	C	C
15	210453	A	C	C	C	C	C
15	210454	C	A	A	A	A	A
15	210486	A	C	C	C	C	C
15	210487	C	A	A	A	A	A
15	259234	A	A	A	A	A	A
15	280393	A	G	G	G	G	G
15	389237	T	G	G	G	G	G
15	432852	G	0	0	0	0	0
15	570495	A	G	G	G	G	G
15	611023	G	T	T	T	T	T
15	611024	C	G	G	G	G	G
15	611036	A	G	G	G	G	G
15	809751	C	T	T	T	T	T
15	874911	C	T	T	T	T	T
15	889947	G	C	C	C	C	C
16	128039	T	G	G	G	G	G
16	191943	C	T	T	T	T	T
16	523639	C	T	T	T	T	T
16	642955	G	A	A	A	A	A
16	642995	C	T	T	T	T	T
16	643579	T	C	C	C	C	C
16	643654	C	A	A	A	A	A
16	727933	G	A	A	A	A	A
16	759398	T	G	G	G	G	G
16	778863	T	A	A	A	A	A
16	890342	T	A	A	A	A	A
17	265	G	A	A	A	A	A
18	20934	T	G	G	G	G	G
18	23283	T	A	A	A	A	A
18	33619	A	0	0	0	0	0
18	39517	G	T	T	T	T	T
18	73136	T	G	G	G	G	G
18	73137	C	T	T	T	T	T
18	82507	T	A	A	A	A	A

**Table S3 (primary data for Figures 1A and 1C): Fitness of segregants from the S2XP cross in high salt and low glucose.** Shown are the genotypes for all relevant alleles (columns “Intergenic” to “MET3”), mating type and fitness in low glucose (20h) and high salt for 48 progeny from an S2XP cross as well as for the haploid progenitor (P) and S2 evolved strain, measured in the same assay. + denotes evolved allele; - denotes ancestral allele.

Strain No.	MAT	Intergenic	ENA	PMA1-1	LAP2	GCD2	MET3	Low glucose	High salt
sce3243	alpha	-	+	-	-	-	+	0.03	1.01
sce3244	a	-	+	+	-	-	-	0.13	1.67
sce3245	a	+	-	+	+	+	-	0.15	1.1
sce3246	alpha	+	-	-	+	+	+	0.04	0.47
sce3247	alpha	-	-	+	-	-	+	0.03	0.89
sce3248	a	+	-	+	-	+	-	0.14	0.95
sce3249	a	-	+	-	+	+	+	0.03	0.53
sce3250	alpha	+	-	-	+	-	-	0.31	0.54
sce3251	alpha	-	-	+	-	+	-	0.23	0.98
sce3252	a	+	+	-	+	-	+	0.04	0.75
sce3253	a	-	-	+	-	+	-	0.2	1
sce3254	alpha	+	+	-	+	-	+	0.04	0.49
sce3255	alpha	+	-	-	-	+	-	0.27	0.42
sce3256	alpha	-	-	+	+	-	+	0.04	0.92
sce3257	a	+	+	-	+	-	+	0.04	0.38
sce3258	a	-	+	+	-	+	-	0.18	1.47
sce3259	alpha	+	+	-	-	-	+	0.04	0.56
sce3260	alpha	+	-	-	+	-	+	0.04	0.39
sce3261	alpha	+	-	-	+	+	+	0.04	0.49
sce3262	alpha	-	+	+	-	+	+	0.04	1.55
sce3263	alpha	-	-	-	+	+	-	0.32	0.35
sce3264	alpha	+	-	+	-	+	-	0.23	0.87
sce3265	alpha	-	+	-	+	-	-	0.28	0.49
sce3266	alpha	+	+	+	-	+	-	0.22	1.44
sce3267	alpha	-	-	+	+	-	-	0.23	0.88
sce3268	alpha	+	+	-	+	+	-	0.27	0.42
sce3269	a	+	-	-	-	+	-	0.35	0.36
sce3270	a	+	+	-	+	-	+	0.04	0.51
sce3271	a	-	-	+	+	-	+	0.04	1
sce3272	alpha	-	+	+	-	-	-	0.22	1.43
sce3273	a	+	+	-	+	-	-	0.28	0.57
sce3274	alpha	-	-	-	+	-	-	0.32	0.37
sce3275	alpha	-	+	-	-	-	+	0.04	0.52
sce3276	a	-	+	+	-	+	+	0.04	1.56

sce3277	a	-	-	-	-	-	+	0.03	0.35
sce3278	a	+	-	-	+	+	-	0.35	0.36
sce3279	a	-	-	-	+	+	-	0.35	0.35
sce3280	alpha	-	-	+	+	-	+	0.04	0.96
sce3281	alpha	-	-	-	-	+	-	0.25	0.39
sce3282	alpha	+	+	-	+	-	-	0.29	0.52
sce3283	a	-	+	+	-	+	+	0.04	1.74
sce3284	alpha	-	+	-	+	+	-	0.33	0.49
sce3285	alpha	+	+	-	+	-	+	0.04	0.5
sce3286	a	+	+	+	-	-	-	0.27	1.47
sce3287	alpha	-	-	-	+	-	+	0.04	0.45
sce3288	a	+	+	+	+	+	+	0.04	1.52
sce3289	alpha	+	-	-	-	-	+	0.04	0.32
sce3290	alpha	-	+	+	+	-	-	0.3	1.52
P	alpha	-	-	-	-	-	-	0.26	0.41
S2	a	+	+	+	+	+	+	0.04	1.8

**Table S4 (primary data for Figures 2B and 2D): Fitness of segregants from the S6XP cross in high salt.** Shown are the genotypes for all relevant alleles, mating type and fitness in high salt for 48 progeny from an S6XP cross as well as for the haploid progenitor (P) and S6 evolved strain, measured in the same assay. + denotes evolved allele; - denotes ancestral allele.

Strain No.	MAT	PMA1-2	CYC8	ASP	High Salt
sce4198	alpha	-	-	+	0.35
sce4202	a	-	-	+	0.35
sce4187	a	-	-	+	0.36
sce4190	alpha	-	-	-	0.36
sce4209	a	-	-	+	0.4
sce4177	a	-	-	-	0.42
sce4216	a	-	-	+	0.44
sce4212	a	-	-	-	0.45
sce4215	a	-	-	-	0.5
sce4183	alpha	-	-	-	0.52
sce4220	alpha	+	-	+	0.65
sce4200	alpha	+	-	+	0.69
sce4221	a	+	-	-	0.7
sce4203	a	+	-	+	0.71
sce4211	alpha	+	-	+	0.71
sce4194	a	+	-	+	0.73
sce4179	a	+	-	+	0.75
sce4176	a	+	-	+	0.8
sce4196	a	+	-	-	0.8
sce4174	alpha	-	+	-	0.83
sce4180	a	+	-	-	0.83
sce4189	alpha	+	-	+	0.87
sce4199	a	-	+	-	0.88
sce4182	a	+	-	-	0.88
sce4206	a	+	-	-	0.88
sce4188	alpha	-	+	-	0.89
sce4178	alpha	-	+	+	0.9
sce4191	a	-	+	+	0.9
sce4192	a	+	-	-	0.92
sce4204	alpha	-	+	-	0.92
sce4218	alpha	-	+	+	0.92
sce4197	alpha	-	+	-	0.95
sce4195	alpha	-	+	+	1
sce4207	alpha	-	+	+	1
sce4181	alpha	-	+	-	1.05

sce4213	alpha	-	+	-	1.08
sce4219	a	-	+	-	1.1
sce4184	a	-	+	+	1.13
sce4208	alpha	+	+	-	1.3
sce4185	alpha	+	+	+	1.35
sce4210	a	+	+	+	1.38
sce4186	a	+	+	-	1.4
sce4214	alpha	+	+	-	1.45
sce4201	a	+	+	-	1.48
sce4217	alpha		+	+	1.5
sce4193	alpha	+	+	+	1.75
sce4175	alpha	+	+	+	1.9
sce4205	alpha	+	+	-	1.92
S6					1.48
P					0.45

**Table S5 (primary data for Figures 2A and 2B: Fitness of segregants from the M8XP cross in low glucose 20, 24, and 30 h and in high salt. Shown are the genotypes for all relevant alleles, mating type, and fitness in each condition for the 48 progeny from an M8XP cross, as well as for the haploid progenitor (P) and M8 evolved strain, measured in the same assay. + denotes evolved allele; - denotes ancestral allele.**

Strain No.	MAT	RPH1	MDS3	SGT1	MKT1	TIM11	LG 20h	LG 24h	LG 30h	High Salt
Sce3440	a	+	-	+	-	-	0.11	0.57	0.85	0.09
Sce3441	alpha	-	+	-	-	+	0.14	0.53	0.7	0.1
Sce3442	a	-	-	-	+	-	0.04	0.19	0.59	0.04
Sce3443	alpha	+	+	+	+	+	0.05	0.6	0.99	0.07
Sce3444	alpha	-	-	-	+	+	0.04	0.57	1.03	0.04
Sce3445	a	+	+	+	-	-	0.13	0.52	0.75	0.11
Sce3446	alpha	+	-	-	-	+	0.1	0.61	0.87	0.12
Sce3447	a	-	+	+	+	-	0.07	0.4	0.52	0.06
Sce3448	a	-	+	+	+	+	0.13	0.58	0.98	0.06
Sce3449	a	+	-	-	-	-	0.1	0.7	1.03	0.09
Sce3450	alpha	+	+	+	+	-	0.1	0.57	0.84	0.07
Sce3451	alpha	-	-	-	-	+	0.1	0.62	0.85	0.08
Sce3452	alpha	-	+	-	-	-	0.14	0.44	0.54	0.1
Sce3453	a	+	+	+	-	+	0.14	0.64	0.85	0.11
Sce3454	alpha	+	-	-	+	-	0.05	0.61	0.99	0.04
Sce3455	a	-	-	+	+	+	0.06	0.33	0.67	0.05
Sce3456	alpha	+	-	-	+	+	0.05	0.31	0.78	0.04
Sce3457	a	+	+	+	-	-	0.13	0.54	0.84	0.13
Sce3458	alpha	-	+	+	-	+	0.12	0.5	0.63	0.11
Sce3459	a	-	-	-	+	-	0.04	0.39	0.84	0.04
Sce3460	alpha	-	-	-	-	-	0.13	0.65	0.82	0.1
Sce3461	a	+	-	-	+	+	0.07	0.65	0.93	0.06
Sce3463	alpha	-	+	-	-	+	0.16	0.54	0.73	0.11
Sce3464	alpha	+	-	-	+	+	0.13	0.61	0.98	0.06
Sce3465	a	+	+	-	-	-	0.13	0.46	0.53	0.1
Sce3466	alpha	+	+	-	+	-	0.09	0.26	0.42	0.07
Sce3467	a	-	+	+	+	-	0.11	0.56	0.91	0.08
Sce3468	a	-	-	+	+	+	0.09	0.76	1.23	0.06
Sce3469	alpha	+	+	+	-	-	0.16	0.36	0.42	0.1
Sce3470	a	+	-	+	-	-	0.13	0.75	1.01	0.09
Sce3471	a	+	-	+	-	-	0.09	0.73	1	0.09
Sce3472	alpha	+	-	+	-	+	0.1	0.62	0.84	0.09
Sce3473	a	-	+	+	+	+	0.08	0.45	0.56	0.08
Sce3474	a	+	+	-	-	-	0.14	0.52	0.72	0.08
Sce3475	a	+	-	+	-	-	0.1	0.74	0.99	0.09

<b>Sce3476</b>	<b>alpha</b>	-	-	-	-	+	<b>0.11</b>	<b>0.69</b>	<b>0.9</b>	<b>0.08</b>
<b>Sce3477</b>	<b>alpha</b>	+	-	+	-	-	<b>0.12</b>	<b>0.77</b>	<b>1.01</b>	<b>0.08</b>
<b>Sce3478</b>	<b>a</b>	-	+	+	-	-	<b>0.14</b>	<b>0.48</b>	<b>0.61</b>	<b>0.1</b>
<b>Sce3479</b>	<b>a</b>	-	+	-	-	-	<b>0.14</b>	<b>0.44</b>	<b>0.5</b>	<b>0.12</b>
<b>Sce3480</b>	<b>alpha</b>	+	-	+	-	-	<b>0.11</b>	<b>0.61</b>	<b>0.85</b>	<b>0.09</b>
<b>Sce3481</b>	<b>a</b>	-	+	+	+	+	<b>0.07</b>	<b>0.44</b>	<b>0.59</b>	<b>0.09</b>
<b>Sce3482</b>	<b>a</b>	-	+	+	+	-	<b>0.07</b>	<b>0.36</b>	<b>0.44</b>	<b>0.08</b>
<b>Sce3483</b>	<b>a</b>	+	-	-	-	-	<b>0.09</b>	<b>0.69</b>	<b>1.04</b>	<b>0.09</b>
<b>Sce3484</b>	<b>a</b>	-	+	-	-	+	<b>0.14</b>	<b>0.56</b>	<b>0.76</b>	<b>0.12</b>
<b>Sce3485</b>	<b>alpha</b>	+	-	-	-	+	<b>0.11</b>	<b>0.64</b>	<b>0.88</b>	<b>0.1</b>
<b>Sce3486</b>	<b>alpha</b>	+	-	+	+	-	<b>0.09</b>	<b>0.69</b>	<b>1.12</b>	<b>0.07</b>
<b>Sce3487</b>	<b>alpha</b>	+	-	-	+	+	<b>0.08</b>	<b>0.76</b>	<b>1.02</b>	<b>0.05</b>
<b>P</b>	<b>a</b>	-	-	-	-	-	<b>0.09</b>	<b>0.62</b>	<b>0.82</b>	<b>ND</b>
<b>M8</b>	<b>alpha</b>	+	+	+	+	+	<b>0.13</b>	<b>0.78</b>	<b>1.35</b>	<b>ND</b>



**Table S6 (primary data for Supplemental Figures 1A and 1B): Fitness of segregants from the S2XM8 cross in high salt and low glucose (20h).** Shown are the genotypes for all relevant alleles (columns “Intergenic” to “SGT1”), mating type, and fitness in high salt and low glucose (20h) for 96 progeny from an S2XM8 cross, as well as for the haploid progenitor (P), the S2 evolved strain and the M8 evolved strain measured in the same assay. + denotes evolved allele; - denotes ancestral allele.

Strain No.	Mat	Intergenic	PMA1	ENA	MET3	GCD2	LAP2	MDS3	RPH1	TIM11	MKT1	SGT1	LG (20h)	High Salt
sce3343	a	+	+	-	-	+	+	-	-	+	-	+	0.20	0.52
sce3343	a	+	+	-	-	+	+	-	-	+	-	+	0.20	0.52
sce3344	a	+	+	-	-	+	-	+	+	-	+	+	0.10	0.56
sce3345	alpha	-	-	+	+	-	+	+	-	-	-	-	0.01	0.43
sce3346	alpha	-	-	+	+	-	-	-	+	+	+	-	0.01	0.13
sce3347	alpha	-	+	-	-	+	+	-	+	+	-	+	0.17	0.46
sce3348	a	-	-	+	+	-	+	+	+	-	-	-	0.02	0.42
sce3349	alpha	+	+	-	-	+	-	+	-	+	+	+	0.15	0.63
sce3350	a	+	-	+	+	-	-	-	-	-	+	-	0.02	0.19
sce3351	a	-	-	+	+	+	-	+	+	-	+	-	0.02	0.22
sce3352	alpha	+	+	-	-	+	+	-	-	+	-	+	0.18	0.23
sce3353	alpha	-	-	-	+	-	-	+	+	-	+	+	0.02	0.09
sce3354	a	+	+	+	-	-	+	-	-	+	-	-	0.21	0.82
sce3355	alpha	-	-	+	+	-	+	-	-	-	+	-	0.02	0.16
sce3356	a	+	-	-	+	+	-	+	-	+	+	+	0.02	0.28
sce3357	a	-	+	-	-	+	-	-	+	-	-	+	0.16	0.56
sce3358	alpha	+	+	+	-	-	+	+	+	+	-	-	0.25	0.68
sce3359	a	-	-	-	+	+	-	-	+	-	+	-	0.02	0.06
sce3360	alpha	-	+	+	-	+	-	-	+	+	+	+	0.07	0.74
sce3361	a	+	+	+	-	-	+	+	-	-	-	-	0.25	0.87
sce3362	alpha	+	-	-	+	-	+	+	-	+	-	+	0.02	0.14
sce3363	alpha	-	+	+	-	+	-	+	-	+	+	-	0.18	1.19
sce3364	a	+	+	-	-	-	+	+	-	-	-	-	0.16	0.45
sce3365	a	-	-	-	+	-	-	-	+	-	+	+	0.02	0.07
sce3366	alpha	-	-	+	+	+	+	-	+	+	-	+	0.02	0.42
sce3367	alpha	+	-	+	+	-	-	+	+	+	+	+	0.02	0.30
sce3368	alpha	-	+	+	-	+	-	-	-	+	+	-	0.10	0.91
sce3369	a	+	-	-	+	+	+	+	-	-	-	-	0.02	0.20
sce3370	a	-	+	-	-	-	+	-	+	-	-	+	0.15	0.52
sce3371	alpha	-	+	-	-	+	+	+	-	-	-	-	0.20	0.64
sce3372	a	+	+	+	-	-	+	-	+	-	+	+	0.09	0.90
sce3373	alpha	+	-	+	+	-	-	-	-	+	+	+	0.02	0.16
sce3374	a	+	-	-	+	+	-	+	+	+	-	-	0.02	0.17
sce3375	a	-	+	-	+	+	+	-	+	-	-	-	0.02	0.45

sce3376	alpha	-	-	-	+	-	-	-	+	-	+	0.24	0.14
sce3377	alpha	+	-	+	-	-	+	+	+	+	+	0.11	0.18
sce3378	a	-	+	+	+	-	-	+	-	-	+	0.02	1.49
sce3379	alpha	+	-	+	-	-	-	-	+	+	+	0.09	0.14
sce3380	a	+	-	-	-	+	+	+	-	+	-	0.25	0.19
sce3381	a	-	+	+	+	+	-	+	+	-	+	0.02	1.32
sce3382	alpha	-	+	-	+	-	+	-	-	-	+	0.02	0.62
sce3383	alpha	+	+	-	-	-	-	+	-	-	+	0.11	0.60
sce3384	a	-	-	+	+	-	+	-	-	+	-	0.03	0.26
sce3385	alpha	-	+	+	-	+	-	-	+	-	+	0.06	0.85
sce3386	a	+	-	-	+	+	+	+	+	+	-	0.02	0.20
sce3387	a	-	+	-	+	+	+	-	+	+	-	0.02	0.56
sce3388	alpha	-	-	-	-	-	-	+	-	-	+	0.14	0.13
sce3389	alpha	+	+	-	+	-	+	+	-	-	-	0.02	0.79
sce3390	a	+	-	-	-	+	-	-	+	+	+	0.11	0.08
sce3391	alpha	-	-	-	+	+	-	+	-	+	-	0.02	0.20
sce3392	alpha	-	+	-	-	+	+	+	-	+	-	0.18	0.51
sce3393	a	+	+	+	-	-	+	-	+	-	+	0.07	0.76
sce3394	a	+	-	+	+	-	-	-	+	-	+	0.01	0.25
sce3395	a	+	-	+	-	+	+	+	+	-	+	0.05	0.24
sce3396	alpha	-	-	-	-	-	+	-	-	+	-	0.12	0.16
sce3397	alpha	-	+	-	+	-	-	+	-	+	-	0.01	0.58
sce3398	a	+	+	+	+	+	-	-	+	-	+	0.01	0.79
sce3399	alpha	+	+	+	+	+	+	-	+	+	-	0.02	0.96
sce3400	a	-	-	+	-	-	-	+	+	-	-	0.21	0.41
sce3401	a	-	+	-	+	-	+	-	-	+	+	0.02	0.26
sce3402	alpha	+	-	-	-	+	-	+	-	-	+	0.07	0.13
sce3403	alpha	+	+	+	-	+	alpha	-	+	-	+	0.02	1.14
sce3404	a	-	-	-	+	+	+	-	-	-	+	0.01	0.05
sce3405	alpha	+	+	-	-	-	-	-	+	+	-	0.13	0.45
sce3406	a	-	-	+	+	-	+	+	+	-	-	0.01	0.37
sce3407	alpha	-	+	+	+	-	-	+	-	-	+	0.01	1.20
sce3408	alpha	+	-	-	-	-	+	+	+	+	+	0.11	0.10
sce3409	a	-	-	+	-	+	+	-	+	+	-	0.13	0.29
sce3410	a	-	+	-	+	+	-	-	-	-	-	0.02	0.46
sce3411	alpha	+	+	+	-	-	+	+	-	+	+	0.01	1.02
sce3412	a	-	-	-	+	-	+	+	-	-	-	0.01	0.21
sce3414	alpha	-	+	+	-	+	-	-	+	-	+	0.02	0.68
sce3415	a	+	-	+	+	+	-	+	-	-	+	0.01	0.26
sce3416	a	+	-	-	+	-	-	-	-	+	-	0.02	0.12
sce3417	alpha	-	+	-	-	-	+	+	+	-	-	0.12	0.58

sce3418	alpha	-	+	+	-	+	+	-	+	+	+	-	0.07	0.75
sce3419	alpha	+	+	-	+	-	-	-	-	+	+	-	0.01	0.51
sce3420	a	+	+	-	+	+	-	+	-	+	-	-	0.02	0.55
sce3421	a	-	-	-	-	+	+	+	+	-	+	+	0.10	0.15
sce3422	alpha	-	-	+	-	-	+	-	+	-	-	+	0.16	0.34
sce3423	a	+	-	-	-	+	+	+	+	+	-	-	0.30	0.17
sce3424	alpha	-	+	-	+	+	+	+	-	+	-	+	0.02	0.61
sce3425	a	+	-	+	-	-	-	-	+	-	+	-	0.08	0.19
sce3426	alpha	-	+	+	+	-	-	-	-	-	+	+	0.02	0.88
sce3427	alpha	+	-	-	+	+	+	+	-	-	-	-	0.02	0.19
sce3428	a	-	-	+	+	-	-	+	-	+	+	-	0.02	0.44
sce3429	a	+	+	+	-	-	+	-	+	-	-	+	0.16	0.97
sce3430	alpha	-	+	-	-	+	-	-	+	+	+	+	0.05	0.30
sce3431	a	-	+	-	+	-	-	-	+	-	+	+	0.02	0.37
sce3432	alpha	+	-	+	-	-	+	+	-	-	-	-	0.21	0.41
sce3433	a	+	+	-	+	+	-	+	+	+	-	+	0.02	0.73
sce3434	alpha	-	-	-	-	+	+	-	-	+	+	-	0.12	0.42
sce3435	a	+	-	+	+	-	-	+	+	+	+	-	0.02	0.21
sce3436	alpha	+	+	-	-	-	+	+	-	-	-	+	0.19	0.55
sce3437	a	-	+	+	-	+	+	-	+	+	-	+	0.08	1.02
sce3438	alpha	-	-	-	+	+	-	-	-	-	+	-	0.02	0.08
P	a	-	-	-	-	-	-	-	-	-	-	-	0.22	0.18
S2	a	+	+	+	+	+	+	-	-	-	-	-	0.02	0.80
M8	alpha	-	-	-	-	-	-	+	+	+	+	+	0.42	0.16

**Table S6A (primary data for Figure 4A and Figure S2). Fitness of segregants from the S2XM8 cross that harbor the MET3 ancestral allele in low glucose at 20, 24 and 30 hours. Shown are the genotypes for all relevant alleles (columns “MET3” to “TIM11”), mating type, and fitness in low glucose (20, 24, and 30 h) for 48 progeny from an S2XM8 cross that harbor the MET3 ancestral allele, as well as for the haploid progenitor (P), the S2 evolved strain (no growth due to the evolved MET3 allele), and the M8 evolved strain measured in the same assay. + denotes evolved allele; - denotes ancestral allele.**

Strain no.	Mat	MET3	PMA1	ENA	GCD2	genic	LAP2	RPH1	MDS3	MKT1	SGT1	TIM11	LG (20h)	LG (24h)	LG (30)
sce3343	n	-	+	-	+	+	+	-	-	-	+	+	0.20	0.56	0.65
sce3344	n	-	+	-	+	+	-	+	+	+	+	-	0.10	0.03	0.23
sce3347	alpha	-	+	-	+	-	+	+	-	-	+	+	0.17	0.66	0.82
sce3349	alpha	-	+	-	+	+	-	-	+	+	+	+	0.15	0.35	0.43
sce3352	alpha	-	+	-	+	+	+	-	-	-	+	+	0.18	0.65	0.96
sce3354	n	-	+	+	-	+	+	-	-	-	-	+	0.21	0.75	1.14
sce3357	n	-	+	-	+	-	-	+	-	-	+	-	0.16	0.73	1.19
sce3358	alpha	-	+	+	-	+	+	+	+	-	-	+	0.25	0.63	1.00
sce3360	alpha	-	+	+	+	-	-	+	-	+	+	+	0.07	0.67	1.19
sce3361	n	-	+	+	-	+	+	-	+	-	-	-	0.25	0.65	1.03
sce3363	alpha	-	+	+	+	-	-	-	+	+	-	+	0.18	0.66	1.21
sce3364	n	-	+	-	-	+	+	-	+	-	-	-	0.16	0.59	0.89
sce3368	alpha	-	+	+	+	-	-	-	-	+	-	+	0.10	0.28	0.64
sce3370	n	-	+	-	-	-	+	+	-	-	+	-	0.15	0.77	1.22
sce3371	alpha	-	+	-	+	-	+	-	+	-	-	-	0.20	0.57	0.81
sce3372	n	-	+	+	-	+	+	+	-	+	+	-	0.09	0.64	1.17
sce3376	alpha	-	-	-	+	-	-	-	-	-	+	+	0.24	0.64	0.94
sce3377	alpha	-	-	+	-	+	+	+	+	+	+	+	0.11	0.31	0.51
sce3379	alpha	-	-	+	-	+	-	+	-	+	-	+	0.09	0.57	0.89
sce3380	n	-	-	-	+	+	+	-	+	-	+	+	0.25	0.57	0.87
sce3383	alpha	-	+	-	-	+	-	-	+	+	-	-	0.11	0.23	0.47
sce3385	alpha	-	+	+	+	-	-	+	-	+	-	-	0.06	0.24	0.83
sce3388	alpha	-	-	-	-	-	-	-	+	+	+	-	0.14	0.56	0.91
sce3390	n	-	-	-	+	+	-	+	-	+	+	+	0.11	0.84	1.49
sce3392	alpha	-	+	-	+	-	+	-	+	-	-	+	0.18	0.60	0.87
sce3393	n	-	+	+	-	+	+	+	-	+	-	-	0.07	0.70	1.14
sce3395	n	-	-	+	+	+	+	+	+	+	+	-	0.05	0.63	1.18
sce3396	alpha	-	-	-	-	-	+	-	-	-	-	+	0.12	0.69	1.06
sce3400	n	-	-	+	-	-	-	+	+	-	-	-	0.21	0.64	1.01
sce3402	alpha	-	-	-	+	+	-	-	+	+	+	-	0.07	0.59	1.08
sce3403	alpha	-	+	+	+	+	-	-	+	+	+	+	0.02	0.55	0.85
sce3405	alpha	-	+	-	-	+	-	+	-	-	+	+	0.13	0.69	1.06
sce3408	alpha	-	-	-	-	+	+	+	+	+	+	+	0.11	0.65	1.21

sce3409	a	-	-	+	+	-	+	+	-	-	+	+	0.13	0.70	1.13
sce3411	alpha	-	+	+	-	+	+	-	+	+	+	+	0.01	0.09	0.50
sce3414	alpha	-	+	+	+	-	-	+	-	+	+	-	0.02	0.38	0.95
sce3417	alpha	-	+	-	-	-	+	+	+	-	-	-	0.12	0.55	0.68
sce3418	alpha	-	+	+	+	-	+	+	-	+	-	+	0.07	0.27	0.75
sce3421	a	-	-	-	+	-	+	+	+	+	+	-	0.10	0.73	0.84
sce3422	alpha	-	-	+	-	-	+	+	-	-	+	-	0.16	0.94	1.22
sce3423	a	-	-	-	+	+	+	+	+	-	-	+	0.30	0.62	1.03
sce3425	a	-	-	+	-	+	-	+	-	+	-	-	0.08	0.80	1.45
sce3429	a	-	+	+	-	+	+	+	-	-	+	-	0.16	0.76	1.15
sce3430	alpha	-	+	-	+	-	-	+	-	+	+	+	0.05	0.39	0.85
sce3432	alpha	-	-	+	-	+	+	-	+	-	-	-	0.21	0.61	1.03
sce3434	alpha	-	-	-	+	-	+	-	-	+	-	+	0.12	0.73	1.31
sce3436	alpha	-	+	-	-	+	+	-	+	-	+	-	0.19	0.62	1.02
sce3437	a	-	+	+	+	-	+	+	-	-	+	+	0.08	0.75	1.10
P	a	-	-	-	-	-	-	-	-	-	-	-	0.22	0.62	0.92
M8	alpha	-	-	-	-	-	-	+	+	+	+	+	0.42	0.78	1.44
S2	a	+	+	+	+	+	+	-	-	-	-	-	0.02	0.02	0.02

**Table S7 (primary data for Supplemental Figure 1C and 1D): Fitness of segregants from the S6XM8 cross in high salt and low glucose (20h).** Shown are the genotypes for all relevant alleles (columns “CYC8” to “TIM11”), mating type, and fitness in low glucose (20h) and high salt for 96 progeny from an S6XM8 cross as well as for the haploid progenitor (P), the S6 evolved strain and the M8 evolved strain measured in the same assay. + denotes evolved allele; - denotes ancestral allele.

Strain no.	MAT	CYC8	PMA1	ASP3	MDS3	MKT1	RPH1	SGT2	TIM11	LG (20h)	High salt
sce4305	alpha	-	-	-	+	+	-	-	+	0.55	0.46
sce4306	a	+	+	-	-	-	+	+	-	0.02	2.08
sce4307	alpha	-	+	+	-	-	-	+	+	0.05	1.10
sce4308	a	+	-	+	+	+	+	-	-	0.32	1.78
sce4309	a	+	+	-	-	-	-	+	+	0.02	2.37
sce4310	a	-	+	-	-	-	+	+	-	0.05	1.27
sce4311	alpha	-	-	+	+	+	-	-	-	0.52	0.34
sce4312	alpha	+	-	+	+	+	+	-	+	0.35	1.87
sce4313	a	+	+	-	+	+	+	+	-	0.02	2.16
sce4314	alpha	+	-	+	-	-	-	+	-	0.25	1.70
sce4315	a	-	+	+	+	+	-	-	+	0.04	1.03
sce4316	alpha	-	-	-	-	-	+	-	-	0.35	0.56
sce4317	alpha	+	+	+	+	-	+	+	-	0.03	1.96
sce4318	alpha	-	-	-	-	+	+	+	+	0.26	0.38
sce4319	a	-	+	+	+	+	-	-	+	0.04	1.08
sce4320	a	+	-	-	-	-	-	-	-	0.28	1.79
sce4321	alpha	+	+	+	-	-	-	-	+	0.03	2.18
sce4322	alpha	+	-	-	+	+	-	+	+	0.49	1.72
sce4323	a	-	-	-	-	+	+	+	-	0.27	0.44
sce4324	a	-	+	+	+	-	+	-	-	0.08	1.10
sce4325	alpha	+	-	+	+	-	+	+	-	0.45	1.53
sce4326	alpha	+	+	-	-	+	-	+	-	0.01	1.94
sce4327	a	-	-	-	-	-	-	-	+	0.44	0.43
sce4328	a	-	+	+	+	+	+	-	+	0.05	1.00
sce4329	a	-	+	-	+	-	+	+	+	0.09	1.32
sce4330	a	+	+	+	-	-	-	-	+	0.03	2.09
sce4331	alpha	-	-	-	+	+	-	+	-	0.53	0.30
sce4332	alpha	+	-	+	-	+	+	-	-	0.23	1.40
sce4333	a	+	-	-	+	+	+	-	+	0.43	1.31
sce4334	a	+	+	+	+	-	+	+	-	0.04	1.96
sce4335	alpha	-	-	+	-	+	-	-	+	0.27	0.20
sce4336	alpha	-	+	-	-	-	-	+	-	0.06	1.02
sce4337	a	-	+	-	+	+	+	-	-	0.04	0.98

sce4338	a	+	+	+	-	+	-	+	-	0.01	1.74
sce4339	alpha	+	-	+	-	-	-	-	+	0.21	1.28
sce4340	alpha	-	-	-	+	-	+	+	+	0.45	0.42
sce4341	a	-	+	+	+	-	+	+	+	0.08	1.40
sce4342	alpha	+	+	-	+	+	-	+	-	0.03	2.12
sce4343	a	-	-	-	-	+	+	-	+	0.30	0.25
sce4344	alpha	+	-	ND	-	-	-	-	-	0.24	1.11
sce4345	alpha	-	+	+	+	-	-	-	-	0.06	1.12
sce4346	a	+	-	+	-	+	+	+	+	0.18	1.01
sce4347	alpha	-	+	ND	-	+	-	-	+	0.02	0.91
sce4348	a	+	-	-	+	-	+	+	-	0.37	1.27
sce4349	a	-	-	+	+	-	+	-	+	0.45	0.37
sce4350	a	+	+	-	+	-	-	-	+	0.06	2.07
sce4351	alpha	-	+	+	-	+	+	+	-	0.03	0.63
sce4352	alpha	+	-	-	-	+	-	+	-	0.24	1.38
sce4353	alpha	-	-	+	-	+	-	-	-	0.22	0.23
sce4354	a	+	+	+	-	+	-	+	-	0.01	2.16
sce4355	alpha	+	-	+	+	-	+	-	+	0.40	1.32
sce4356	a	-	+	+	+	-	+	+	+	0.07	1.30
sce4357	a	+	+	-	-	+	-	-	+	0.01	2.04
sce4358	alpha	+	+	ND	-	-	+	-	-	0.03	1.91
sce4359	a	-	-	-	+	-	-	+	-	0.51	0.48
sce4360	alpha	-	-	-	+	+	+	+	+	0.54	0.25
sce4361	alpha	-	+	-	-	+	+	-	-	0.03	0.89
sce4362	alpha	+	-	+	-	+	-	-	-	0.17	1.20
sce4363	a	-	-	+	+	-	+	+	-	0.48	0.39
sce4364	a	+	+	-	+	-	-	+	-	0.06	2.12
sce4365	alpha	-	-	+	+	+	+	+	-	0.58	0.25
sce4366	a	-	-	-	-	+	-	+	+	0.30	0.50
sce4367	a	+	+	+	-	-	+	-	+	0.02	1.64
sce4368	alpha	+	+	-	+	-	-	-	-	0.05	2.06
sce4369	a	+	-	-	-	+	-	+	+	0.25	1.34
sce4370	alpha	-	+	+	-	-	-	-	-	0.07	1.10
sce4371	a	-	-	-	+	+	+	+	-	0.53	0.25
sce4372	alpha	+	+	+	+	-	+	-	+	0.05	2.03
sce4373	alpha	+	-	-	-	-	-	-	-	0.26	1.47
sce4374	a	-	+	-	+	+	+	+	-	0.07	1.31
sce4375	alpha	+	+	+	+	-	+	+	+	0.04	2.03
sce4376	a	-	-	+	-	+	-	-	-	0.30	0.23
sce4377	a	-	-	+	+	+	+	+	+	0.49	0.22
sce4378	alpha	-	+	+	-	+	+	-	-	0.01	0.69

sce4379	a	+	-	-	+	-	-	+	-	0.39	1.41
sce4380	alpha	+	+	-	-	-	-	-	+	0.03	2.09
sce4381	alpha	-	+	+	+	+	+	+	+	0.05	1.05
sce4382	alpha	-	-	-	-	-	-	+	-	0.45	0.48
sce4383	a	+	-	-	-	-	+	-	+	0.29	1.33
sce4384	a	+	+	+	+	+	-	-	-	0.02	2.01
sce4385	a	+	-	-	+	-	+	+	-	0.04	0.11
sce4386	a	+	+	+	-	-	+	-	-	0.01	0.30
sce4387	alpha	-	-	-	-	+	-	+	-	0.37	0.27
sce4388	alpha	-	+	+	+	+	-	-	+	0.05	0.96
sce4389	alpha	+	+	+	-	+	+	+	+	0.01	1.97
sce4390	a	+	+	-	+	-	-	+	+	0.07	2.13
sce4391	a	-	-	+	+	-	+	-	-	0.48	0.65
sce4392	alpha	-	-	-	-	+	-	-	-	0.42	0.40
sce4393	a	-	+	-	+	-	-	-	-	0.09	1.64
sce4394	a	-	-	-	+	+	+	+	+	0.54	0.34
sce4395	alpha	+	-	+	-	+	+	+	-	0.18	1.68
sce4396	alpha	+	+	+	-	-	-	-	+	0.04	2.08
sce4397	a	-	-	+	+	+	-	-	+	0.53	0.32
sce4398	alpha	+	+	-	-	+	-	+	+	0.01	2.20
sce4399	a	+	-	+	+	-	+	-	-	0.43	1.63
sce4400	alpha	-	+	-	-	-	+	+	+	0.06	1.20
P	a	-	-	-	-	-	-	-	-	0.37	0.75
M8	alpha	-	-	-	+	+	+	+	+	0.57	ND
S6	a	+	+	+	-	-	-	-	-	ND	1.48



**Table S8. Single-locus P values appear on top line. Pairwise interaction P values appear in the matrix.**

**A. S2XP Offspring in High Salt. P values for single-locus effects and pairwise interactions**

	PMA1	ENA	LAP2	MET3	GCD2
	<10 exp -4	0.008	0.005	0.763	0.418
PMA1		<10 exp -4	0.264	0.742	0.166
ENA			0.005	0.579	0.111
LAP2				0.546	0.423
MET3					0.008
GCD2					

Significant values in red. Near-significant values in blue. 15 comparisons in total. Significance threshold =  $0.05 / 15 = 0.0033$ . The putative ENA - LAP2 interaction is negative, with the evolved allele of LAP2 showing a growth deficit when combined with the ancestral allele of ENA. This interaction does not appear in the S2XM8 cross and was not experimentally tested further here. The evolved alleles of MET3 and GCD2 may be synergistic with one another; note that PMA1, MET3 and GCD2 were the only three-way interaction identified in any of the crosses and environments.

**B. S6XP Offspring in High Salt. P values for single-locus effects and pairwise interactions**

	PMA1	CYC8	ASP
	< 0.002	< 10 exp -4	0.729
PMA1		0.007	0.79
CYC8			0.406
ASP			

Significant values in red. Six comparisons. P-value threshold  $0.05 / 6 = 0.0083$

C. M8XP Offspring in Low Glucose 20h. P values for single-locus effects and pairwise interactions

	MKT1	SGT1	MDS3	RPH1	TIM11
	<10 exp -4	0.748	0.003	0.752	0.491
MKT1		0.109	0.258	0.175	0.69
SGT1			0.013	0.157	0.364
MDS3				0.294	0.921
RPH1					0.269
TIM11					

Significant values in red. 15 comparisons in total. Significance threshold =  $0.05 / 15 = 0.0033$ .

D. M8XP Offspring in Low Glucose 24h. P values for single-locus effects and pairwise interactions

	MKT1	SGT1	MDS3	RPH1	TIM11
	0.037	0.552	0.002	0.015	0.42
MKT1		0.863	0.146	0.665	0.242
SGT1			0.544	0.32	0.108
MDS3				0.138	0.153
RPH1					0.197
TIM11					

Significant values in red. 15 comparisons in total. Significance threshold =  $0.05 / 15 = 0.0033$ .

E. M8XP Offspring in Low Glucose 30h. P values for single-locus effects and pairwise interactions.

	MKT1	SGT1	MDS3	RPH1	TIM11
	0.684	0.862	<10 exp -4	0.021	0.238
MKT1		0.512	0.727	0.924	0.253
SGT1			0.649	0.54	0.263
MDS3				0.747	0.094
RPH1					0.356
TIM11					

Significant values in red. 15 comparisons in total. Significance threshold =  $0.05 / 15 = 0.0033$ .

F. S6XM8 Offspring in Low Glucose. P values for single locus effects and pairwise interactions

	PMA1	CYC8	ASP3	MKT1	SGT1	MDS3	RPH1	TIM11
	<10 exp -4	0.005	0.425	0.206	0.689	0.01	0.51	0.812
PMA1		0.001	0.655	0.401	0.447	<10 exp -4	0.687	0.433
CYC8			0.302	0.651	0.202	0.934	0.317	0.946
ASP3				0.522	0.687	0.477	0.504	0.208
MKT1					0.732	0.409	0.91	0.155
SGT1						0.361	0.734	0.86
MDS3							0.294	0.576
RPH1								0.23
TIM11								

Significant values in red. 36 comparisons in total. P-value threshold =  $0.05 / 36 = 0.0014$ . In green, comparisons not valid because the S6 allele of PMA1 grows very poorly in the low-glucose environment.

G. S6XM8 Offspring in High Salt. P values for single locus effects and pairwise interactions

	PMA1	CYC8	ASP3	MKT1	SGT1	MDS3	RPH1	TIM11
	<10 exp -4	<10 exp -4	0.955	0.008	0.798	0.795	0.163	0.622
PMA1		0.214	0.038	0.87	0.091	0.664	0.129	0.3
CYC8			0.487	0.026	0.572	0.716	0.056	0.413
ASP3				0.956	0.357	0.708	0.072	0.775
MKT1					0.292	0.92	0.514	0.177
SGT1						0.365	0.304	0.202
MDS3							0.916	0.479
RPH1								0.048
TIM11								

Significant values in red. 36 comparisons in total. P-value threshold =  $0.05 / 36 = 0.0014$

H. S2XM8 Offspring in Low Glucose 20h. P values for single-locus effects and pairwise interactions

	PMA1	ENA	LAP2	MET3	GCD2	MKT1	SGT1	MDS3	RPH1
	0.15	0.371	0.003	<10 exp -4	0.789	0.001	0.683	0.547	0.77
PMA1		0.768	0.358	0.453	0.388	0.44	0.533	0.722	0.588
ENA			0.837	0.079	0.199	0.149	0.039	0.983	0.931
LAP2				0.028	0.711	0.584	0.621	0.623	0.985
MET3					0.481	<10 exp -4	0.084	0.133	0.047
GCD2						0.29	0.496	0.601	0.117
MKT1							0.802	0.517	0.796
SGT1								0.07	0.927
MDS3									0.796
RPH1									
TIM11									

Significant values in red. Near-significant values in blue. 55 comparisons in total. P-value threshold = 0.05 / 55 = 0.0009. MET3 comparisons in green not valid as MET3e does not grow in in the low-glucose environment.

I. S2XM8 Offspring in High Salt. P values for single-locus effects and pairwise interactions.

	PMA1	ENA	LAP2	MET3	GCD2	MKT1	SGT1	MDS3	RPH1
	<10 exp -4	<10 exp -4	0.977	0.106	0.877	0.79	0.578	0.524	0.586
PMA1		<10 exp -4	0.052	0.708	0.892	0.0017	0.651	0.245	0.761
ENA			0.538	0.363	0.047	0.183	0.949	0.841	0.136
LAP2				0.801	0.175	0.263	0.391	0.028	0.11
MET3					0.922	0.775	0.511	0.276	0.751
GCD2						0.267	0.656	0.341	0.145
MKT1							0.283	0.198	0.09
SGT1								0.016	0.404
MDS3									0.025
RPH1									
TIM11									

Significant values in red. Near-significant values in blue. 55 comparisons in total. P-value threshold = 0.05 / 55 = 0.0009. 55 comparisons. The putative interaction between PMA1 and MKT1 is slightly positive. P-value threshold = 0.05 / 55 = 0.0009.

J. S2XM8 MET3a Offspring in Low Glucose at 20h. P values for single locus effects and pairwise interactions

	PMA1	ENA	LAP2	GCD2	MKT1	SGT1	MDS3	RPH1	TIM11
	0.466	0.066	0.029	0.525	<10 exp -4	0.094	0.14	0.048	0.595
PMA1		0.752	0.064	0.77	0.78	0.853	0.838	0.784	0.405
ENA			0.93	0.015	0.214	0.195	0.3	0.818	0.264
LAP2				0.437	0.875	0.472	0.837	0.66	0.983
GCD2					0.529	0.975	0.961	0.44	0.081
MKT1						0.615	0.215	0.738	0.615
SGT1							0.001	0.847	0.938
MDS3								0.108	0.7
RPH1									0.415
TIM11									

Significant values in red. 45 comparisons in total. P-value threshold = 0.05 /45 = 0.0011.

K. S2XM8 MET3a Offspring in Low Glucose at 24h. P values for single locus effects and pairwise interactions

	PMA1	ENA	LAP2	GCD2	MKT1	SGT1	MDS3	RPH1	TIM11
	0.029	0.873	0.072	0.307	0.002	0.754	0.046	0.335	0.772
PMA1		0.879	0.102	0.243	0.0149	0.691	0.724	0.973	0.605
ENA			0.565	0.425	0.311	0.997	0.491	0.662	0.093
LAP2				0.445	0.589	0.791	0.939	0.957	0.086
GCD2					0.793	0.409	0.079	0.179	0.101
MKT1						0.474	0.871	0.937	0.939
SGT1							0.047	0.277	0.547
MDS3								0.938	0.909
RPH1									0.938
TIM11									

45 comparisons in total. P-value threshold = 0.05 /45 = 0.0011. Note that the PMA1 - MKT1 interaction in blue falls just short of the significance threshold corrected for multiple comparisons. This interaction was nonetheless selected for further study because it has the lowest P value of any of the 125 valid comparisons between S2 or S6 and M8 SNPs in all crosses and environments.

L. S2XM8 MET3a Offspring in Low Glucose at 30h. P values for single locus effects and pairwise interactions

	PMA1	ENA	LAP2	GCD2	MKT1	SGT1	MDS3	RPH1	TIM11
	0.027	0.252	0.562	0.448	0.326	0.921	0.008	0.111	0.636
PMA1		0.21	0.226	0.236	0.135	0.532	0.994	0.599	0.951
ENA			0.599	0.934	0.576	0.745	0.448	0.81	0.038
LAP2				0.997	0.502	0.95	0.46	0.44	0.346
GCD2					0.517	0.926	0.257	0.625	0.31
MKT1						0.377	0.29	0.77	0.85
SGT1							0.295	0.244	0.316
MDS3								0.39	0.353
RPH1									0.952
TIM11									

45 comparisons in total. P-value threshold =  $0.05 / 45 = 0.0011$ .

## **Appendix 2: Chapter 2 Supplemental Tables**

**Supplementary Table 1. SNP categorization and LOH boundaries.**

A. Shown here are a SNP classifications per time course.

<b>PT1</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
<b>Coding</b>	<b>Synonymous</b>	24547	19085	1979	3483
	<b>Non-synonymous</b>	15481	11955	1095	2431
	<b>Intronic</b>	448	317	50	81
<b>Nonoding</b>	<b>Promoter Potential</b>	20410	14242	1669	4499
	<b>Not promoter</b>	16318	11174	1545	3599

<b>PT7</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
<b>Coding</b>	<b>Synonymous</b>	21028	20148	880	0
	<b>Non-synonymous</b>	13042	12442	600	0
	<b>Intronic</b>	371	363	8	0
<b>Nonoding</b>	<b>Promoter Potential</b>	15632	14584	1048	0
	<b>Not promoter</b>	12527	11707	820	0

<b>PT9</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
<b>Coding</b>	<b>Synonymous</b>	23070	13483	9587	0
	<b>Non-synonymous</b>	14395	8899	5496	0
	<b>Intronic</b>	422	209	213	0
<b>Nonoding</b>	<b>Promoter Potential</b>	19243	11002	8241	0
	<b>Not promoter</b>	14990	8422	6568	0

<b>PT14</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
<b>Coding</b>	<b>Synonymous</b>	33966	31220	1597	1149
	<b>Non-synonymous</b>	21753	19840	1113	800
	<b>Intronic</b>	634	593	22	19
<b>Nonoding</b>	<b>Promoter Potential</b>	29396	26467	1707	1222
	<b>Not promoter</b>	23054	20213	1750	1091

<b>PT15</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
<b>Coding</b>	<b>Synonymous</b>	29961	26151	3810	0
	<b>Non-synonymous</b>	18383	16101	2282	0
	<b>Intronic</b>	596	501	95	0
<b>Nonoding</b>	<b>Promoter Potential</b>	23164	19740	3424	0
	<b>Not promoter</b>	18190	15444	2746	0

<b>PT16</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
<b>Coding</b>	<b>Synonymous</b>	33252	28817	4236	199
	<b>Non-synonymous</b>	21522	18423	2896	203
	<b>Intronic</b>	687	575	105	7
<b>Nonoding</b>	<b>Promoter Potential</b>	29336	24427	4356	553
	<b>Not promoter</b>	23215	18912	3910	393



<b>PT30</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
Coding	Synonymous	31614	23422	8192	0
	Non-synonymous	20214	15054	5160	0
	Intronic	622	432	190	0
Nonoding	Promoter Potential	27312	20166	7146	0
	Not promoter	21301	16488	4813	0

<b>PT42</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
Coding	Synonymous	21533	21013	520	0
	Non-synonymous	13453	13067	386	0
	Intronic	373	352	21	0
Nonoding	Promoter Potential	16415	15814	601	0
	Not promoter	12625	12160	465	0

<b>PT43</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
Coding	Synonymous	33185	31019	2166	0
	Non-synonymous	20781	19432	1349	0
	Intronic	604	534	70	0
Nonoding	Promoter Potential	27015	24783	2232	0
	Not promoter	21072	19207	1865	0

<b>PT59</b>		<b>All</b>	<b>Background</b>	<b>Persistent</b>	<b>Transient</b>
Coding	Synonymous	19278	16285	2806	187
	Non-synonymous	12368	10549	1664	155
	Intronic	374	276	93	5
Nonoding	Promoter Potential	15587	12628	2542	417
	Not promoter	12234	9704	2213	317

B. Shown here are the boundaries coordinates for LOH determination

<b>Time Course</b>									
Patient	Strain	Ca21chr1	Ca21chr2	Ca21chr3	Ca21chr4	Ca21chr5	Ca21chr6	Ca21chr7	Ca21chrR
1	1								
	2								3832-1068234
	3			897974-1795835					
	4			897974-1795835					
	5			897974-1795835					
	6			897974-1795835					
	7			897974-1795835					
	8			897974-1795835					
	9			897974-1795835					

	11			897974-1795835				
	12			897974-1795835				
	13			897974-1795835		8232-170933		
	14			897974-1795835		8232-170933		
	15			897974-1795835		8232-170933		
	16			897974-1795835		8232-170933 171204-245012		
	17			897974-1795835		8232-170933 171204-245012		
7	412							
	2307			1547-351895				
9	1002							
	3795	4543-1686646 1710375-3185786		1029764-1797437			15142-780735 796170-849685 872252-1027763	
14	580							
	2440					24601-419452	168911-553875 590181-941547	
	2501			1090417-1686401		24601-419452		
15	945							1714728-1881053
	1619		3744-456576 481476-1238655 1314147-1416222			4991-266741		
16	3107							
	3119			913796-1798558				
	3120			913796-1798558	250757-545661 557563-833109 833566-1602135	466016-704830 705492-1181271		
30	5106	1839295-2913061	5317-1869518					11797-266628 270449-908781 1017877-1817646
	5108			1851-459269 856580-1124728				
42	3731							
	3733							

43	1649	157253-1302666						
	3034					110956-409423		
59	3917							
	4617	2201226-3180846						
	4639	2201226-3180846		807800-1796049				

**Supplementary Table 2. Drivers of LOH.** Shown are genes with mutations that transition from homozygous genotypes pre-LOH event, to homozygous genotypes of another genotype following its occurrence. A 1 indicates that this type of mutation has occurred in this gene and time course, a 0 indicates that it has not.

ORF	Gene	PT1	PT7	PT9	PT14	PT15	PT43	PT59
orf19.6061	orf19.6061	0	0	1	0	0	0	0
orf19.6020	orf19.6020	0	0	1	0	0	0	0
orf19.6356	orf19.6356	0	0	0	0	0	0	1
orf19.1834	orf19.1834	0	0	0	0	0	0	1
orf19.1135	CAS1	0	0	0	0	0	0	1
orf19.4965	orf19.4965	0	0	0	0	0	0	1
orf19.4905	orf19.4905	0	0	0	0	0	0	1
orf19.1166	CTA3	0	0	1	0	0	0	0
orf19.2296	orf19.2296	0	0	1	0	0	0	0
orf19.2049	orf19.2049	0	0	0	0	1	0	0
orf19.1513	FAB1	0	0	0	0	1	0	0
orf19.193	orf19.193	0	0	0	0	1	0	0
orf19.4498	orf19.4498	0	0	0	0	1	0	0
orf19.1453	SPT5	0	0	0	0	1	0	0
orf19.1684	orf19.1684	0	1	0	0	0	0	0
orf19.6979	orf19.6979	0	0	0	1	0	0	0
orf19.7372	MRR1	0	0	1	0	0	0	0
orf19.7349	CHS4	1	0	0	0	0	0	0
orf19.6790	orf19.6790	0	0	1	0	0	0	0
orf19.974	ROT2	0	0	0	0	1	0	0
orf19.570	IFF8	0	0	0	0	0	1	0
orf19.1934	HST3	0	0	0	0	0	1	0
orf19.1932	CFL4	0	0	0	0	0	1	0
orf19.922	ERG11	1	0	0	0	0	0	0
orf19.5580	TEL1	0	0	1	0	0	0	0
orf19.5742	ALS9	0	0	1	0	0	0	0

**Supplementary Table 3. Recurrent persistent mutations occurring in temporally distinct clinical series.** Shown are mutations that acquire non-synonymous mutations that persist through the series. A 1 indicates a mutation in a given gene and its corresponding time course. A 0 indicates its absence. A 0 indicates no mutations.

**A. Mutations in time courses that are persistent and non-synonymous**

ORF	Gene	PT1	PT7	PT9	PT14	PT15	PT43	PT59	SUM
orf19.736	SRB8	1	1	1	1	1	1	1	7
orf19.2404	orf19.2404	1	0	1	1	0	1	1	5
orf19.4697	MDN1	1	1	1	0	1	0	1	5
orf19.1596	FGR28	0	0	1	1	1	1	1	5
orf19.1616	FGR23	0	1	1	1	1	0	1	5
orf19.5045	orf19.5045	0	1	1	0	1	1	1	5
orf19.3188	TAC1	1	1	1	0	1	1	0	5
orf19.2850	orf19.2850	0	1	1	1	1	0	1	5
orf19.7029	orf19.7029	1	0	1	1	1	1	0	5
orf19.2650	orf19.2650	0	0	1	1	1	1	1	5
orf19.7032	orf19.7032	1	0	1	0	1	1	1	5
orf19.1606	orf19.1606	0	1	1	1	1	1	0	5
orf19.5592	orf19.5592	1	1	0	1	1	1	0	5
orf19.5596	orf19.5596	0	1	0	1	1	1	1	5
orf19.169	CHO2	0	1	1	0	1	1	1	5
orf19.4346	orf19.4346	0	1	1	0	1	1	1	5
orf19.5297	orf19.5297	1	0	1	1	0	1	1	5
orf19.5597	POL5	0	1	0	1	1	1	1	5
orf19.230	orf19.230	1	0	1	1	1	1	0	5
orf19.4658	orf19.4658	1	1	1	1	0	0	1	5
orf19.6277	orf19.6277	1	1	0	1	1	1	0	5
orf19.4958	ECM25	1	1	0	1	1	0	1	5
orf19.1769	orf19.1769	0	1	0	1	0	1	1	4
orf19.2629	orf19.2629	0	0	1	0	1	1	1	4
orf19.1298	NUP84	1	0	1	0	1	1	0	4
orf19.4498	orf19.4498	1	1	0	1	0	1	0	4
orf19.4068	orf19.4068	1	1	1	1	0	0	0	4
orf19.7204	orf19.7204	0	1	0	1	0	1	1	4
orf19.3473	orf19.3473	0	1	0	1	0	1	1	4
orf19.2761	orf19.2761	1	0	1	0	1	0	1	4
orf19.5710	orf19.5710	1	1	0	0	1	0	1	4
orf19.3706	orf19.3706	1	0	1	0	1	1	0	4
orf19.4673	BMT9	0	1	1	1	0	1	0	4
orf19.2647	ZCF14	1	0	0	0	1	1	1	4
orf19.2646	ZCF13	0	0	0	1	1	1	1	4
orf19.4557	orf19.4557	1	1	0	0	1	0	1	4
orf19.4288	CTA7	0	0	0	1	1	1	1	4
orf19.4655	OPT6	0	1	1	0	1	0	1	4
orf19.2747	RGT1	0	0	1	1	1	0	1	4

orf19.7472	IFF4	0	0	1	1	1	1	0	4
orf19.255	ZCF1	0	1	1	1	1	0	0	4
orf19.2168	orf19.2168	0	1	1	0	1	1	0	4
orf19.5038	orf19.5038	0	1	1	0	1	1	0	4
orf19.1808	orf19.1808	0	1	1	0	1	0	1	4
orf19.4337	orf19.4337	1	0	1	0	1	0	1	4
orf19.2652	TEF4	1	0	1	0	1	1	0	4
orf19.4239	orf19.4239	0	0	1	1	1	0	1	4
orf19.649	orf19.649	0	1	1	0	0	1	1	4
orf19.4649	ZCF27	1	1	1	0	1	0	0	4
orf19.4643	orf19.4643	0	1	1	0	1	1	0	4
orf19.5065	orf19.5065	1	1	0	0	1	1	0	4
orf19.366	orf19.366	0	1	1	1	0	0	1	4
orf19.6862	orf19.6862	0	0	1	1	1	1	0	4
orf19.5510	orf19.5510	0	1	0	0	1	1	1	4
orf19.3629	DSE1	1	0	1	0	1	0	0	3
orf19.76	SPB1	1	0	0	0	1	1	0	3
orf19.1768	orf19.1768	0	0	1	1	1	0	0	3
orf19.1766	orf19.1766	0	1	1	0	1	0	0	3
orf19.4510	IFA4	0	1	1	0	0	0	1	3
orf19.4961	STP2	1	1	0	1	0	0	0	3
orf19.115	orf19.115	0	1	0	0	1	0	1	3
orf19.371	orf19.371	0	0	1	1	0	0	1	3
orf19.5504	orf19.5504	1	0	0	0	1	1	0	3
orf19.2400	orf19.2400	0	0	1	0	0	1	1	3
orf19.4245	orf19.4245	0	0	0	1	0	1	1	3
orf19.4243	orf19.4243	0	1	1	0	1	0	0	3
orf19.3239	CTF18	1	1	1	0	0	0	0	3
orf19.3463	orf19.3463	0	0	0	1	1	0	1	3
orf19.3906	orf19.3906	0	1	1	0	1	0	0	3
orf19.2901	NUP60	0	0	1	0	1	1	0	3
orf19.1690	TOS1	0	0	0	1	1	1	0	3
orf19.3910	orf19.3910	0	0	1	1	1	0	0	3
orf19.3916	orf19.3916	0	0	1	0	1	0	1	3
orf19.2433	orf19.2433	1	1	0	0	1	0	0	3
orf19.3190	HAL9	0	1	1	0	0	0	1	3
orf19.4901	orf19.4901	0	0	0	0	1	1	1	3
orf19.1531	orf19.1531	1	1	1	0	0	0	0	3
orf19.1532	SAM37	1	0	1	0	0	1	0	3
orf19.5705	NAM2	1	0	0	0	1	0	1	3
orf19.7561	DEF1	0	0	0	1	1	1	0	3
orf19.175	orf19.175	0	0	1	0	0	1	1	3
orf19.1748	orf19.1748	0	1	1	0	1	0	0	3
orf19.1356	orf19.1356	0	0	0	1	1	1	0	3
orf19.1359	orf19.1359	0	0	1	1	1	0	0	3
orf19.1492	PRP39	1	1	1	0	0	0	0	3
orf19.2510	orf19.2510	0	0	1	0	1	1	0	3

orf19.1111	orf19.1111	0	0	1	1	0	1	0	3
orf19.4280	orf19.4280	0	1	0	0	1	0	1	3
orf19.3997	ADH1	1	0	0	0	0	1	1	3
orf19.1555	SAC3	0	0	1	1	1	0	0	3
orf19.1624.1	orf19.1624.1	0	1	1	0	0	1	0	3
orf19.1795	PUF3	0	0	1	1	0	1	0	3
orf19.4191.1	orf19.4191.1	0	1	1	0	1	0	0	3
orf19.6280	orf19.6280	0	1	0	1	0	0	1	3
orf19.894	orf19.894	1	1	1	0	0	0	0	3
orf19.3380	HWP2	0	0	1	0	1	1	0	3
orf19.3100	orf19.3100	0	1	0	0	1	0	1	3
orf19.92	orf19.92	0	0	0	0	1	1	1	3
orf19.3429	FGR47	0	0	0	1	1	0	1	3
orf19.6979	orf19.6979	1	1	0	0	0	1	0	3
orf19.1500	orf19.1500	1	1	0	0	0	0	1	3
orf19.5918	orf19.5918	0	1	1	0	1	0	0	3
orf19.4459	orf19.4459	1	0	0	0	1	0	1	3
orf19.3986	PPR1	0	1	0	0	1	0	1	3
orf19.1607	ALR1	0	1	0	1	0	1	0	3
orf19.6480	orf19.6480	1	1	0	0	1	0	0	3
orf19.1083	orf19.1083	0	1	0	0	1	1	0	3
orf19.4918	orf19.4918	0	0	0	1	1	0	1	3
orf19.427	orf19.427	1	1	0	0	1	0	0	3
orf19.4257	INT1	1	0	0	0	0	1	1	3
orf19.1400	orf19.1400	1	0	1	0	1	0	0	3
orf19.4715	orf19.4715	0	0	1	0	1	0	1	3
orf19.1662	orf19.1662	0	0	1	1	1	0	0	3
orf19.1096	orf19.1096	1	0	0	0	1	1	0	3
orf19.5976	orf19.5976	1	0	0	1	0	1	0	3
orf19.2182	BLM3	0	0	1	1	1	0	0	3
orf19.7027	orf19.7027	0	0	1	1	0	1	0	3
orf19.7023	orf19.7023	1	0	0	1	0	1	0	3
orf19.2724	orf19.2724	0	0	1	1	0	1	0	3
orf19.6544	LPI9	0	0	0	1	1	1	0	3
orf19.3203	RCY1	1	1	0	0	1	0	0	3
orf19.4369	orf19.4369	0	0	1	0	1	0	1	3
orf19.5141	orf19.5141	0	0	1	0	1	0	1	3
orf19.290	KRE5	1	0	1	0	1	0	0	3
orf19.194	orf19.194	0	0	1	0	0	1	1	3
orf19.6499	orf19.6499	0	0	1	0	1	1	0	3
orf19.1841	orf19.1841	1	1	0	0	0	0	1	3
orf19.2266	orf19.2266	1	0	0	0	1	1	0	3
orf19.6921	orf19.6921	0	0	0	1	1	0	1	3
orf19.7036	orf19.7036	0	1	0	0	1	1	0	3
orf19.4394	orf19.4394	1	1	0	0	1	0	0	3
orf19.4553	orf19.4553	0	1	0	1	1	0	0	3
orf19.3603	orf19.3603	0	0	1	1	1	0	0	3

orf19.4348	orf19.4348	0	0	1	0	1	0	1	3
orf19.4080	orf19.4080	0	0	0	1	1	1	0	3
orf19.1608	orf19.1608	0	1	1	0	1	0	0	3
orf19.1798	TSC2	1	0	1	0	1	0	0	3
orf19.1113	orf19.1113	0	0	1	1	0	1	0	3
orf19.262	SMC3	0	0	1	1	0	1	0	3
orf19.5915	DUR35	0	0	1	0	1	1	0	3
orf19.6694	orf19.6694	1	1	1	0	0	0	0	3
orf19.1296	orf19.1296	0	1	1	1	0	0	0	3
orf19.7194	orf19.7194	0	0	0	1	0	1	1	3
orf19.7193	orf19.7193	1	1	0	1	0	0	0	3
orf19.4965	orf19.4965	1	0	0	0	0	1	1	3
orf19.4064	GPI7	1	0	0	1	1	0	0	3
orf19.4412	orf19.4412	0	1	1	0	1	0	0	3
orf19.1622	YCG1	0	1	0	0	1	1	0	3
orf19.3615	orf19.3615	1	1	1	0	0	0	0	3
orf19.3613	orf19.3613	0	1	0	0	1	1	0	3
orf19.1106	orf19.1106	0	0	1	1	0	1	0	3
orf19.267	orf19.267	0	1	1	0	0	1	0	3
orf19.5505	HIS7	0	1	0	0	1	0	1	3
orf19.4570	orf19.4570	0	1	1	0	1	0	0	3
orf19.4145	ZCF20	1	0	1	0	1	0	0	3
orf19.2879	IFF5	0	0	1	0	1	0	1	3
orf19.5854.1	orf19.5854.1	0	0	1	0	1	1	0	3
orf19.5752	orf19.5752	1	1	0	0	0	0	1	3
orf19.6999	orf19.6999	0	0	0	0	1	1	1	3
orf19.5621	orf19.5621	1	0	0	1	1	0	0	3
orf19.6592	orf19.6592	0	0	0	1	1	1	0	3
orf19.6919	orf19.6919	1	1	0	0	0	0	1	3
orf19.4315	orf19.4315	1	0	1	0	1	0	0	3
orf19.4325	orf19.4325	1	0	1	0	0	1	0	3
orf19.4404	PGA49	0	0	1	0	1	1	0	3
orf19.2907	PGA42	1	0	1	0	1	0	0	3
orf19.4225	LEU3	0	0	1	0	1	1	0	3
orf19.1772	orf19.1772	0	1	1	0	1	0	0	3
orf19.5924	ZCF31	0	0	1	0	1	1	0	3
orf19.7277	orf19.7277	0	1	0	0	1	1	0	3
orf19.3773	CDL1	0	1	1	1	0	0	0	3
orf19.3170	orf19.3170	0	0	1	1	0	1	0	3
orf19.3178	orf19.3178	1	0	1	1	0	0	0	3
orf19.2826	orf19.2826	0	0	1	0	1	1	0	3
orf19.4683	MLP1	1	0	1	0	1	0	0	3
orf19.6294	MYO1	1	0	1	0	1	0	0	3
orf19.5134	orf19.5134	1	0	1	0	0	1	0	3
orf19.5058	SMI1	0	0	0	1	1	1	0	3
orf19.5003	orf19.5003	0	1	0	1	0	1	0	3
orf19.2547	orf19.2547	0	1	1	0	0	1	0	3

orf19.3098	orf19.3098	0	0	1	0	1	0	1	3
orf19.3166	orf19.3166	1	0	1	0	1	0	0	3
orf19.3437	orf19.3437	0	1	0	1	1	0	0	3
orf19.3439	orf19.3439	1	0	0	0	1	0	1	3
orf19.1706	MET18	0	0	0	1	1	1	0	3
orf19.1144	orf19.1144	1	0	0	1	1	0	0	3
orf19.2847.1	orf19.2847.1	0	0	1	1	0	1	0	3
orf19.8	orf19.8	0	0	1	1	0	1	0	3
orf19.229	orf19.229	0	0	1	1	0	1	0	3
orf19.1327	RBT1	0	0	1	1	1	0	0	3
orf19.7342	AXL1	0	0	0	1	1	1	0	3
orf19.2797	orf19.2797	0	0	0	1	1	0	1	3
orf19.1551	orf19.1551	0	1	1	1	0	0	0	3
orf19.1779	MP65	0	0	1	0	1	1	0	3
orf19.4316	orf19.4316	1	0	0	1	1	0	0	3
orf19.102	orf19.102	0	0	0	0	1	1	1	3
orf19.1305	orf19.1305	1	0	1	0	1	0	0	3
orf19.3937	orf19.3937	0	0	1	0	1	1	0	3
orf19.5949	FAS2	1	1	0	0	0	1	0	3
orf19.746	orf19.746	1	0	1	0	0	1	0	3
orf19.745	VAC8	0	0	0	1	0	1	1	3
orf19.6260	orf19.6260	0	1	0	0	1	1	0	3
orf19.6344	RBK1	1	1	0	0	0	1	0	3
orf19.3148	orf19.3148	0	0	1	1	0	1	0	3
orf19.2929	GSC1	1	1	0	0	0	0	0	2
orf19.1541	orf19.1541	1	0	1	0	0	0	0	2
orf19.2383	YKU80	0	0	1	0	0	0	1	2
orf19.4251	ZCF22	0	0	1	0	1	0	0	2
orf19.3213	orf19.3213	0	0	0	1	0	0	1	2
orf19.3216	orf19.3216	0	0	0	0	1	1	0	2
orf19.3214	orf19.3214	0	0	1	1	0	0	0	2
orf19.4339	VPS4	0	1	1	0	0	0	0	2
orf19.2893	orf19.2893	0	0	0	0	1	0	1	2
orf19.400	GCF1	1	0	0	0	0	1	0	2
orf19.757	orf19.757	1	0	0	0	1	0	0	2
orf19.114	orf19.114	0	0	0	0	1	0	1	2
orf19.1299	RPN6	1	0	1	0	0	0	0	2
orf19.2624	orf19.2624	0	1	1	0	0	0	0	2
orf19.5138	IFA21	0	0	1	0	1	0	0	2
orf19.1108	HAM1	0	0	0	0	1	1	0	2
orf19.7343	orf19.7343	0	0	0	1	1	0	0	2
orf19.113	CIP1	0	0	0	0	1	0	1	2
orf19.4248	orf19.4248	1	0	0	1	0	0	0	2
orf19.3267	orf19.3267	0	1	1	0	0	0	0	2
orf19.4066	orf19.4066	0	0	1	0	1	0	0	2
orf19.1684	orf19.1684	0	0	1	0	0	1	0	2
orf19.1681	orf19.1681	0	1	0	0	1	0	0	2



orf19.3601	orf19.3601	0	0	0	0	1	1	0	2
orf19.6420	PGA13	0	0	1	0	0	1	0	2
orf19.301	PGA18	0	0	1	0	1	0	0	2
orf19.5043	orf19.5043	0	0	0	0	1	0	1	2
orf19.1828	BUD16	1	0	0	0	1	0	0	2
orf19.5999	DYN1	0	0	0	0	1	1	0	2
orf19.6494	WHI3	0	0	0	0	1	1	0	2
orf19.1366	orf19.1366	0	0	1	0	1	0	0	2
orf19.1210	orf19.1210	1	1	0	0	0	0	0	2
orf19.922	ERG11	0	0	1	0	0	0	1	2
orf19.2465	POL32	0	1	0	0	1	0	0	2
orf19.2768	AMS1	0	0	1	0	1	0	0	2
orf19.923	THR1	0	0	1	0	0	0	1	2
orf19.787	orf19.787	0	1	0	0	0	0	1	2
orf19.4878	orf19.4878	1	0	0	1	0	0	0	2
orf19.5714	SAP1	1	0	0	0	0	0	1	2
orf19.3694	orf19.3694	1	0	0	1	0	0	0	2
orf19.2505	orf19.2505	0	0	1	0	1	0	0	2
orf19.4232	PTH1	0	0	1	0	1	0	0	2
orf19.4270	orf19.4270	0	1	0	0	1	0	0	2
orf19.6798	SSN6	0	0	0	1	0	1	0	2
orf19.1698	orf19.1698	1	0	0	0	1	0	0	2
orf19.6336	PGA25	0	1	0	0	1	0	0	2
orf19.3470	orf19.3470	0	0	0	0	1	0	1	2
orf19.5729	FGR17	0	0	0	0	1	0	1	2
orf19.124	CIC1	0	1	0	0	1	0	0	2
orf19.1834	orf19.1834	0	0	0	0	1	0	1	2
orf19.5057	orf19.5057	0	1	1	0	0	0	0	2
orf19.5053	orf19.5053	0	0	1	0	1	0	0	2
orf19.5051	orf19.5051	0	0	1	1	0	0	0	2
orf19.5496	AVT1	0	0	0	0	1	1	0	2
orf19.3907	orf19.3907	0	0	0	0	1	0	1	2
orf19.2884	CDC68	0	0	1	0	1	0	0	2
orf19.1509	ROD1	0	0	1	0	0	0	1	2
orf19.3877	orf19.3877	1	0	1	0	0	0	0	2
orf19.3878	orf19.3878	0	0	1	0	0	1	0	2
orf19.7215	orf19.7215	1	0	0	0	0	0	1	2
orf19.792	orf19.792	1	0	0	0	0	0	1	2
orf19.2604	orf19.2604	0	1	0	0	0	0	1	2
orf19.4265	UAP1	0	0	0	0	1	1	0	2
orf19.7369	orf19.7369	1	0	0	0	1	0	0	2
orf19.7366	orf19.7366	0	0	0	0	1	0	1	2
orf19.7365	orf19.7365	0	1	0	0	1	0	0	2
orf19.1033	STR2	1	0	0	1	0	0	0	2
orf19.2516	orf19.2516	0	0	0	1	1	0	0	2
orf19.2515	orf19.2515	0	0	1	1	0	0	0	2
orf19.3648	orf19.3648	0	0	0	0	1	1	0	2

orf19.4752	MSN4	1	1	0	0	0	0	0	2
orf19.4913	orf19.4913	1	1	0	0	0	0	0	2
orf19.7201	SLA2	1	0	1	0	0	0	0	2
orf19.4465	orf19.4465	0	1	0	0	1	0	0	2
orf19.6536	IQG1	1	0	0	0	1	0	0	2
orf19.5302	PGA31	1	0	1	0	0	0	0	2
orf19.4133	orf19.4133	0	1	1	0	0	0	0	2
orf19.4131	orf19.4131	0	0	1	0	1	0	0	2
orf19.4234	orf19.4234	0	0	0	0	1	1	0	2
orf19.5736	ALS5	0	1	1	0	0	0	0	2
orf19.1816	ALS3	0	0	0	0	1	1	0	2
orf19.6424	orf19.6424	0	0	1	1	0	0	0	2
orf19.5046	RAM1	1	0	0	0	1	0	0	2
orf19.1762	OCA1	0	1	0	0	0	1	0	2
orf19.3077	VID21	0	0	1	0	1	0	0	2
orf19.5730	orf19.5730	0	0	0	0	1	0	1	2
orf19.6282	orf19.6282	1	0	1	0	0	0	0	2
orf19.5552	orf19.5552	0	1	0	0	1	0	0	2
orf19.5380	LYS144	0	0	1	0	1	0	0	2
orf19.2457	orf19.2457	1	0	0	0	1	0	0	2
orf19.2452	orf19.2452	1	1	0	0	0	0	0	2
orf19.90	orf19.90	0	0	0	0	0	1	1	2
orf19.2296	orf19.2296	0	0	0	1	1	0	0	2
orf19.2675	orf19.2675	0	0	1	0	1	0	0	2
orf19.6970	orf19.6970	0	0	0	1	0	1	0	2
orf19.6973	orf19.6973	0	0	0	0	1	1	0	2
orf19.1499	CTF1	0	0	0	1	0	0	1	2
orf19.1504	orf19.1504	0	0	1	1	0	0	0	2
orf19.1755	SET2	0	0	0	0	1	1	0	2
orf19.1078	HBR2	1	0	0	0	1	0	0	2
orf19.4921	orf19.4921	0	0	0	1	0	1	0	2
orf19.3254	orf19.3254	0	0	0	1	1	0	0	2
orf19.6317	ADE6	0	0	0	0	1	0	1	2
orf19.4148	orf19.4148	0	0	1	0	1	0	0	2
orf19.4266	SPR28	0	0	0	0	1	1	0	2
orf19.4705	orf19.4705	0	0	1	0	1	0	0	2
orf19.3180	orf19.3180	0	0	1	0	1	0	0	2
orf19.4703	orf19.4703	0	0	1	0	0	1	0	2
orf19.1119	MTR10	0	0	1	0	0	1	0	2
orf19.2775	IDI1	0	0	1	0	1	0	0	2
orf19.1656	orf19.1656	1	0	1	0	0	0	0	2
orf19.5167	IFM1	1	0	0	0	1	0	0	2
orf19.2883	CSO99	0	0	0	1	0	1	0	2
orf19.1240	orf19.1240	0	0	1	0	1	0	0	2
orf19.5725	orf19.5725	1	0	0	0	1	0	0	2
orf19.5728	orf19.5728	0	1	0	0	0	0	1	2
orf19.6573	BEM2	1	0	0	1	0	0	0	2

orf19.1826	MDM34	1	1	0	0	0	0	0	2
orf19.1864	orf19.1864	1	0	0	1	0	0	0	2
orf19.7499	orf19.7499	1	0	0	0	0	0	1	2
orf19.2445	orf19.2445	0	1	0	0	1	0	0	2
orf19.2763	orf19.2763	0	0	1	0	1	0	0	2
orf19.245	DDC1	0	0	0	1	1	0	0	2
orf19.4279	MNN1	0	0	1	0	1	0	0	2
orf19.2881	MNN4	0	0	1	0	1	0	0	2
orf19.7547	orf19.7547	0	0	0	1	0	1	0	2
orf19.3627	orf19.3627	0	0	1	1	0	0	0	2
orf19.3624	orf19.3624	0	0	1	0	1	0	0	2
orf19.3621	orf19.3621	1	0	0	0	0	1	0	2
orf19.2713	orf19.2713	1	0	0	0	1	0	0	2
orf19.5568	VPS51	0	0	0	0	1	0	1	2
orf19.2688	NAN1	0	0	1	0	1	0	0	2
orf19.4627	orf19.4627	1	0	0	0	1	0	0	2
orf19.4405	PPS1	0	0	1	0	0	1	0	2
orf19.2847	orf19.2847	0	1	0	0	0	0	1	2
orf19.4713	orf19.4713	0	0	1	0	1	0	0	2
orf19.130	orf19.130	0	0	0	0	1	1	0	2
orf19.522	orf19.522	0	0	1	0	1	0	0	2
orf19.4640	PWP1	1	0	0	0	0	1	0	2
orf19.1253	PHO4	0	0	1	0	0	0	1	2
orf19.1091	orf19.1091	1	0	0	0	0	1	0	2
orf19.5970	orf19.5970	0	0	0	0	1	1	0	2
orf19.188	orf19.188	0	0	0	1	0	1	0	2
orf19.1893	orf19.1893	1	0	0	0	1	0	0	2
orf19.4829	DOA1	0	0	0	1	1	0	0	2
orf19.1878	orf19.1878	1	0	0	0	1	0	0	2
orf19.2476	orf19.2476	0	1	0	0	1	0	0	2
orf19.2274	orf19.2274	0	0	0	1	0	1	0	2
orf19.243	OXR1	0	0	1	0	1	0	0	2
orf19.6349	RVS162	0	0	0	0	0	1	1	2
orf19.1527	orf19.1527	1	0	1	0	0	0	0	2
orf19.3637	orf19.3637	0	0	1	0	1	0	0	2
orf19.3633	orf19.3633	0	0	1	1	0	0	0	2
orf19.1901	MCM3	1	0	1	0	0	0	0	2
orf19.4366	orf19.4366	0	1	1	0	0	0	0	2
orf19.4764	orf19.4764	0	0	0	0	1	1	0	2
orf19.248	APL5	0	0	0	0	1	1	0	2
orf19.3231	CDC27	0	0	1	1	0	0	0	2
orf19.4284	BUR2	0	0	1	0	1	0	0	2
orf19.5575	orf19.5575	0	0	0	1	0	0	1	2
orf19.1265	orf19.1265	0	0	1	0	1	0	0	2
orf19.1266	orf19.1266	0	0	1	0	1	0	0	2
orf19.5701	orf19.5701	0	0	0	0	1	1	0	2
orf19.5704	orf19.5704	0	0	0	1	1	0	0	2

orf19.6588	NBP2	0	1	0	0	0	0	1	2
orf19.193	orf19.193	0	0	1	0	0	0	1	2
orf19.5569	orf19.5569	1	0	0	0	0	1	0	2
orf19.6492	orf19.6492	0	1	0	0	1	0	0	2
orf19.1849	orf19.1849	1	0	0	0	0	0	1	2
orf19.2399	orf19.2399	0	0	1	1	0	0	0	2
orf19.2265	orf19.2265	1	0	0	0	1	0	0	2
orf19.250	SLC1	1	0	0	0	1	0	0	2
orf19.731	EMP46	0	1	0	0	1	0	0	2
orf19.3829	PHR1	1	0	0	0	1	0	0	2
orf19.1325	ECM38	0	0	1	0	1	0	0	2
orf19.7038	orf19.7038	0	1	0	0	0	1	0	2
orf19.7034	orf19.7034	0	0	0	0	0	1	1	2
orf19.2733	orf19.2733	0	0	1	0	0	0	1	2
orf19.2739	orf19.2739	1	0	1	0	0	0	0	2
orf19.6478	YCF1	1	0	0	0	1	0	0	2
orf19.3735	orf19.3735	0	0	1	0	0	0	1	2
orf19.2137	orf19.2137	0	0	0	0	1	0	1	2
orf19.5653	ATP2	0	0	1	1	0	0	0	2
orf19.3604	orf19.3604	0	0	0	0	1	0	1	2
orf19.3605	PEX17	1	1	0	0	0	0	0	2
orf19.3607	orf19.3607	0	0	0	0	1	1	0	2
orf19.2370	DSL1	0	1	0	0	0	1	0	2
orf19.101	RIM9	0	0	0	1	0	1	0	2
orf19.4771	orf19.4771	0	0	0	0	1	1	0	2
orf19.3443	OYE2	0	1	0	0	1	0	0	2
orf19.4704	ARO1	0	0	1	0	1	0	0	2
orf19.6387	HSP104	0	1	0	0	0	1	0	2
orf19.5177	orf19.5177	1	0	1	0	0	0	0	2
orf19.6126	KGD2	0	0	1	1	0	0	0	2
orf19.1075	orf19.1075	1	0	0	0	1	0	0	2
orf19.718	RRN11	0	1	0	0	1	0	0	2
orf19.6152	orf19.6152	1	0	1	0	0	0	0	2
orf19.276	orf19.276	0	0	1	0	1	0	0	2
orf19.2258	orf19.2258	0	0	0	1	1	0	0	2
orf19.2259	orf19.2259	0	0	1	0	1	0	0	2
orf19.7519	orf19.7519	1	1	0	0	0	0	0	2
orf19.7044	RIM15	0	0	1	1	0	0	0	2
orf19.1345	LIP8	1	0	0	0	1	0	0	2
orf19.2740	orf19.2740	0	0	1	0	1	0	0	2
orf19.3422	FMP27	0	0	0	0	1	0	1	2
orf19.4963	orf19.4963	1	0	0	0	0	1	0	2
orf19.3433	OYE23	0	0	0	0	1	1	0	2
orf19.4414	orf19.4414	1	0	1	0	0	0	0	2
orf19.6977	GPI1	0	1	0	0	1	0	0	2
orf19.3417	ACF2	0	0	0	0	1	0	1	2
orf19.3617	orf19.3617	1	0	0	0	0	0	1	2

orf19.3610	orf19.3610	0	0	0	0	1	1	0	2
orf19.2678	BUB1	0	0	1	0	1	0	0	2
orf19.4349	orf19.4349	0	0	1	0	0	0	1	2
orf19.2819	orf19.2819	0	0	1	0	1	0	0	2
orf19.1275	GAT1	0	0	0	1	1	0	0	2
orf19.4744	orf19.4744	0	1	0	0	1	0	0	2
orf19.4646	UEC1	0	1	0	0	0	0	1	2
orf19.2238	LTE1	0	0	1	0	0	1	0	2
orf19.1611	orf19.1611	1	1	0	0	0	0	0	2
orf19.1610	orf19.1610	0	0	1	0	1	0	0	2
orf19.4184	orf19.4184	0	0	1	0	1	0	0	2
orf19.5328	GCN1	0	0	1	0	1	0	0	2
orf19.4318	MIG1	0	0	1	0	0	0	1	2
orf19.4568	ZCF25	0	0	1	0	1	0	0	2
orf19.5295	orf19.5295	0	0	1	0	1	0	0	2
orf19.2216	PDS5	0	0	1	0	1	0	0	2
orf19.1041	orf19.1041	0	1	0	1	0	0	0	2
orf19.1719	SGA1	0	0	0	1	1	0	0	2
orf19.4416	VPS13	0	0	0	1	1	0	0	2
orf19.6913	GCN2	0	0	1	0	1	0	0	2
orf19.4403	VPS11	0	0	1	0	1	0	0	2
orf19.7071	FGR2	0	0	0	0	1	1	0	2
orf19.6832	orf19.6832	0	0	0	0	0	1	1	2
orf19.1821	orf19.1821	0	0	0	0	1	0	1	2
orf19.265	orf19.265	0	0	1	0	1	0	0	2
orf19.48	orf19.48	0	1	0	0	0	0	1	2
orf19.6586	orf19.6586	0	0	0	1	0	1	0	2
orf19.6580	orf19.6580	0	0	0	0	1	1	0	2
orf19.2787	PRY1	0	1	0	1	0	0	0	2
orf19.6901	orf19.6901	1	0	1	0	0	0	0	2
orf19.864	orf19.864	1	0	1	0	0	0	0	2
orf19.7051	orf19.7051	1	0	0	0	1	0	0	2
orf19.7052	orf19.7052	0	0	1	0	1	0	0	2
orf19.4791	orf19.4791	1	0	0	1	0	0	0	2
orf19.7473	orf19.7473	0	1	1	0	0	0	0	2
orf19.2115	orf19.2115	1	0	1	0	0	0	0	2
orf19.4757	NAR1	0	0	0	1	0	1	0	2
orf19.1166	CTA3	0	0	0	0	1	0	1	2
orf19.4175	TOK1	0	0	1	0	1	0	0	2
orf19.4357	orf19.4357	0	0	0	1	1	0	0	2
orf19.2808	ZCF16	0	0	0	1	1	0	0	2
orf19.139	TRA1	0	1	0	1	0	0	0	2
orf19.1595	orf19.1595	0	1	1	0	0	0	0	2
orf19.4750	orf19.4750	0	0	0	0	1	1	0	2
orf19.1624	orf19.1624	0	0	1	0	1	0	0	2
orf19.5713	YMX6	1	0	0	0	1	0	0	2
orf19.4392	DEM1	0	0	1	1	0	0	0	2

orf19.2534	PIN4	0	1	0	1	0	0	0	2
orf19.2752	ADR1	0	0	0	1	1	0	0	2
orf19.1192	DNA2	0	0	0	0	1	0	1	2
orf19.3969	SFL2	0	0	0	0	1	1	0	2
orf19.4072	IFF6	0	0	0	1	1	0	0	2
orf19.570	IFF8	0	0	1	0	0	0	1	2
orf19.5755	orf19.5755	0	0	0	1	1	0	0	2
orf19.6136	orf19.6136	0	1	1	0	0	0	0	2
orf19.3976	orf19.3976	0	0	0	0	1	0	1	2
orf19.5620	orf19.5620	1	0	0	0	0	1	0	2
orf19.258	orf19.258	0	0	0	0	1	1	0	2
orf19.257	orf19.257	0	0	1	0	1	0	0	2
orf19.251	orf19.251	0	0	0	0	1	1	0	2
orf19.36	orf19.36	0	1	0	1	0	0	0	2
orf19.2231	orf19.2231	0	0	0	1	0	1	0	2
orf19.5934	orf19.5934	0	0	0	0	1	1	0	2
orf19.5935	orf19.5935	0	0	1	1	0	0	0	2
orf19.6918	orf19.6918	0	0	1	1	0	0	0	2
orf19.810	orf19.810	0	0	1	0	0	1	0	2
orf19.929	orf19.929	0	1	1	0	0	0	0	2
orf19.1251	BRN1	0	0	1	0	1	0	0	2
orf19.2165	orf19.2165	0	0	1	0	1	0	0	2
orf19.2169	orf19.2169	1	0	1	0	0	0	0	2
orf19.1456	orf19.1456	0	0	0	1	0	1	0	2
orf19.7001	YCK2	0	0	0	0	1	0	1	2
orf19.3367	orf19.3367	0	0	1	0	1	0	0	2
orf19.2760	orf19.2760	0	0	1	0	1	0	0	2
orf19.3368	orf19.3368	0	0	0	1	1	0	0	2
orf19.2835	orf19.2835	0	0	1	0	0	0	1	2
orf19.5148	CYR1	0	0	1	0	0	0	1	2
orf19.1580	orf19.1580	0	0	1	1	0	0	0	2
orf19.4136	YBL053	0	0	1	0	1	0	0	2
orf19.3803	MNN22	1	0	1	0	0	0	0	2
orf19.1714	PGA44	0	0	1	0	0	0	1	2
orf19.3984	orf19.3984	0	0	0	0	1	0	1	2
orf19.1121	orf19.1121	0	1	1	0	0	0	0	2
orf19.1774	orf19.1774	0	0	1	0	1	0	0	2
orf19.868	ADAEC	0	0	1	1	0	0	0	2
orf19.5748	orf19.5748	1	0	0	0	1	0	0	2
orf19.6690	orf19.6690	0	0	1	1	0	0	0	2
orf19.6698	orf19.6698	0	1	0	0	0	0	1	2
orf19.6453	orf19.6453	0	1	0	0	1	0	0	2
orf19.1338	orf19.1338	1	1	0	0	0	0	0	2
orf19.3965	orf19.3965	0	1	0	0	1	0	0	2
orf19.4167	orf19.4167	0	1	0	0	1	0	0	2
orf19.246	orf19.246	0	0	1	1	0	0	0	2
orf19.719	orf19.719	0	0	1	0	0	0	1	2

orf19.7274	orf19.7274	0	1	0	1	0	0	0	2
orf19.1802	orf19.1802	1	0	1	0	0	0	0	2
orf19.2682	orf19.2682	0	0	1	0	1	0	0	2
orf19.2680	orf19.2680	1	0	1	0	0	0	0	2
orf19.1670	BRO1	0	0	0	0	1	1	0	2
orf19.2175	orf19.2175	0	0	1	0	1	0	0	2
orf19.3793	orf19.3793	0	0	1	0	0	1	0	2
orf19.1680	TFP1	0	1	1	0	0	0	0	2
orf19.4686	orf19.4686	0	0	0	1	0	1	0	2
orf19.4680	orf19.4680	0	0	1	0	1	0	0	2
orf19.4515	orf19.4515	1	0	1	0	0	0	0	2
orf19.2778	orf19.2778	0	0	0	0	1	1	0	2
orf19.2770	orf19.2770	0	1	1	0	0	0	0	2
orf19.3428	orf19.3428	0	0	0	0	1	1	0	2
orf19.4135	PRC2	0	0	1	0	1	0	0	2
orf19.4305.1	orf19.4305.1	0	1	0	0	0	1	0	2
orf19.4209	orf19.4209	0	0	0	0	0	1	1	2
orf19.2915	orf19.2915	0	0	1	0	1	0	0	2
orf19.4870	DBP3	1	0	0	0	1	0	0	2
orf19.1824	PGA50	0	0	0	0	1	0	1	2
orf19.3886	orf19.3886	0	0	0	1	0	1	0	2
orf19.1030	orf19.1030	0	0	0	1	1	0	0	2
orf19.1843	ALG6	0	1	1	0	0	0	0	2
orf19.6687	orf19.6687	1	0	1	0	0	0	0	2
orf19.5648	orf19.5648	0	0	1	0	1	0	0	2
orf19.1326	orf19.1326	0	1	0	0	0	1	0	2
orf19.807	CHS5	1	0	1	0	0	0	0	2
orf19.721	orf19.721	1	0	1	0	0	0	0	2
orf19.1763	IFR1	0	1	1	0	0	0	0	2
orf19.6891	RFC1	1	0	1	0	0	0	0	2
orf19.839	orf19.839	0	0	1	0	0	0	1	2
orf19.831	orf19.831	1	0	1	0	0	0	0	2
orf19.836	orf19.836	1	0	1	0	0	0	0	2
orf19.3592	JEM1	0	0	1	0	0	1	0	2
orf19.2368	orf19.2368	0	0	1	0	0	0	1	2
orf19.3825	RCE1	0	0	1	0	1	0	0	2
orf19.3781	orf19.3781	0	0	1	0	1	0	0	2
orf19.3784	orf19.3784	0	0	1	0	1	0	0	2
orf19.7475	PHO81	0	0	0	0	1	1	0	2
orf19.2791	BBC1	0	1	0	1	0	0	0	2
orf19.2397.3	orf19.2397.3	0	0	1	0	1	0	0	2
orf19.2781	orf19.2781	0	0	0	1	1	0	0	2
orf19.2786	orf19.2786	0	0	0	0	1	1	0	2
orf19.2784	orf19.2784	0	1	0	0	0	1	0	2
orf19.658	GIN1	0	0	0	1	0	1	0	2
orf19.3434	TRY5	0	0	0	0	1	0	1	2
orf19.4707	orf19.4707	1	0	0	0	1	0	0	2

orf19.4761	HST1	0	0	0	1	1	0	0	2
orf19.7030	SSR1	0	0	1	0	1	0	0	2
orf19.3547	orf19.3547	0	0	1	1	0	0	0	2
orf19.1495	orf19.1495	1	0	1	0	0	0	0	2
orf19.4213	FET31	0	0	0	0	1	0	1	2
orf19.4653	orf19.4653	0	0	1	0	1	0	0	2
orf19.4305	orf19.4305	1	0	0	0	1	0	0	2
orf19.1915	MPP10	0	0	1	0	0	0	1	2
orf19.3897	orf19.3897	0	0	1	0	1	0	0	2
orf19.134	orf19.134	0	1	0	0	0	0	1	2
orf19.6143	orf19.6143	0	0	1	0	0	0	1	2
orf19.1314	orf19.1314	0	0	1	0	1	0	0	2
orf19.6476	orf19.6476	0	1	0	0	0	1	0	2
orf19.3945	orf19.3945	0	1	1	0	0	0	0	2
orf19.5300	orf19.5300	0	0	1	0	1	0	0	2
orf19.1839	RPA190	0	1	0	0	1	0	0	2
orf19.3187	ZNC1	0	1	1	0	0	0	0	2
orf19.5491	orf19.5491	0	0	0	0	0	1	1	2
orf19.9	orf19.9	0	0	0	1	0	1	0	2
orf19.5068	IRE1	0	0	0	0	1	0	1	2
orf19.4273	orf19.4273	0	0	0	0	1	1	0	2
orf19.6202	RBT4	0	1	0	0	0	1	0	2
orf19.2372	orf19.2372	0	0	1	0	1	0	0	2
orf19.2681	RBT7	1	0	0	0	1	0	0	2
orf19.4519	SUV3	0	1	1	0	0	0	0	2
orf19.6803	HUT1	0	0	0	1	0	1	0	2
orf19.4766	ARG81	0	1	0	0	1	0	0	2
orf19.2748	ARG83	0	0	0	0	1	1	0	2
orf19.1538	TLG2	0	1	0	1	0	0	0	2
orf19.2307	orf19.2307	0	0	0	1	0	0	1	2
orf19.6313	MNT4	0	0	0	1	0	1	0	2
orf19.1791	orf19.1791	0	0	0	1	1	0	0	2
orf19.1792	orf19.1792	0	0	0	0	1	0	1	2
orf19.1794	orf19.1794	0	1	0	0	1	0	0	2
orf19.1797	orf19.1797	0	1	0	0	0	0	1	2
orf19.3447	orf19.3447	0	0	0	1	1	0	0	2
orf19.1557	orf19.1557	0	0	1	0	0	1	0	2
orf19.5723	POX1	0	1	0	0	0	1	0	2
orf19.6511	LIG1	0	0	1	0	1	0	0	2
orf19.3204	orf19.3204	0	0	1	0	1	0	0	2
orf19.3202	orf19.3202	0	0	1	0	1	0	0	2
orf19.4000	GRF10	1	0	0	0	0	0	1	2
orf19.1177	orf19.1177	0	0	0	1	0	0	1	2
orf19.1771	orf19.1771	0	1	0	1	0	0	0	2
orf19.107	orf19.107	0	0	0	0	1	0	1	2
orf19.1747	KIP2	0	0	0	0	1	1	0	2
orf19.748	orf19.748	0	0	1	0	1	0	0	2



orf19.216	orf19.216	1	0	0	0	1	0	0	2
orf19.215	orf19.215	1	0	1	0	0	0	0	2
orf19.849	orf19.849	1	0	0	0	0	1	0	2
orf19.3840	orf19.3840	0	0	0	1	0	1	0	2
orf19.1943	orf19.1943	0	1	0	0	1	0	0	2
orf19.6566	orf19.6566	0	0	1	0	1	0	0	2
orf19.697	orf19.697	0	0	1	0	0	0	1	2
orf19.6310	orf19.6310	0	0	0	1	1	0	0	2
orf19.6861	orf19.6861	0	0	1	0	1	0	0	2
orf19.6319	orf19.6319	1	1	0	0	0	0	0	2
orf19.5516	orf19.5516	0	0	0	1	1	0	0	2
orf19.1264	CFL2	1	0	1	0	0	0	0	2
orf19.5962	HGT4	0	1	0	0	1	0	0	2
orf19.7131	orf19.7131	1	0	0	1	0	0	0	2
orf19.2415	orf19.2415	0	0	1	0	0	0	1	2
orf19.2418	orf19.2418	0	0	1	0	0	0	1	2
orf19.1620	orf19.1620	0	0	0	0	0	1	0	1
orf19.6831	PRP5	0	1	0	0	0	0	0	1
orf19.4816	orf19.4816	0	1	0	0	0	0	0	1
orf19.3329	orf19.3329	0	0	0	1	0	0	0	1
orf19.7356	orf19.7356	0	0	0	0	1	0	0	1
orf19.7357	orf19.7357	0	0	0	0	1	0	0	1
orf19.7353	orf19.7353	0	0	0	0	1	0	0	1
orf19.4120	LAS1	0	0	1	0	0	0	0	1
orf19.1782	orf19.1782	0	0	0	1	0	0	0	1
orf19.1780	orf19.1780	0	0	0	0	1	0	0	1
orf19.4183	MUC1	0	0	0	0	1	0	0	1
orf19.3458	orf19.3458	1	0	0	0	0	0	0	1
orf19.1789	orf19.1789	0	0	0	0	1	0	0	1
orf19.1547	orf19.1547	1	0	0	0	0	0	0	1
orf19.1546	orf19.1546	0	0	1	0	0	0	0	1
orf19.1548	orf19.1548	0	0	0	0	1	0	0	1
orf19.5491.1	ATP14	0	0	1	0	0	0	0	1
orf19.2170	PHM7	0	0	1	0	0	0	0	1
orf19.4719	CWH41	0	0	1	0	0	0	0	1
orf19.260	SLD1	0	0	1	0	0	0	0	1
orf19.4258	orf19.4258	0	0	0	0	1	0	0	1
orf19.4253	orf19.4253	0	0	0	1	0	0	0	1
orf19.2839	CIRT4B	0	0	0	1	0	0	0	1
orf19.3219	orf19.3219	0	0	0	0	1	0	0	1
orf19.1631	ERG6	0	0	1	0	0	0	0	1
orf19.6026	ERG2	0	1	0	0	0	0	0	1
orf19.4606	ERG8	0	0	1	0	0	0	0	1
orf19.3616	ERG9	1	0	0	0	0	0	0	1
orf19.4078	orf19.4078	0	0	1	0	0	0	0	1
orf19.4678	orf19.4678	1	0	0	0	0	0	0	1
orf19.335	orf19.335	0	0	0	0	1	0	0	1

orf19.4676	orf19.4676	0	0	1	0	0	0	0	1
orf19.4672	orf19.4672	0	0	1	0	0	0	0	1
orf19.1212	orf19.1212	0	0	0	0	0	1	0	1
orf19.4101	orf19.4101	0	0	0	0	1	0	0	1
orf19.4106	orf19.4106	0	0	0	0	1	0	0	1
orf19.1160	orf19.1160	0	1	0	0	0	0	0	1
orf19.367	CNH1	0	0	1	0	0	0	0	1
orf19.2892	orf19.2892	0	0	0	0	1	0	0	1
orf19.2890	orf19.2890	0	0	1	0	0	0	0	1
orf19.2891	orf19.2891	0	0	0	0	1	0	0	1
orf19.593	FGR32	0	0	0	0	0	0	1	1
orf19.2873	TOP2	0	0	1	0	0	0	0	1
orf19.1767	orf19.1767	0	0	0	1	0	0	0	1
orf19.3159	UTP20	0	0	0	0	1	0	0	1
orf19.5031	SSK1	0	1	0	0	0	0	0	1
orf19.4657	orf19.4657	0	0	1	0	0	0	0	1
orf19.1217	orf19.1217	0	0	0	0	1	0	0	1
orf19.5430	BUD21	0	0	0	0	0	0	1	1
orf19.2131	orf19.2131	0	0	0	0	1	0	0	1
orf19.6416	orf19.6416	1	0	0	0	0	0	0	1
orf19.1371	orf19.1371	0	0	1	0	0	0	0	1
orf19.5676	orf19.5676	0	0	0	0	1	0	0	1
orf19.3926	RNY11	0	0	1	0	0	0	0	1
orf19.3929	orf19.3929	0	0	0	0	1	0	0	1
orf19.5561	RAV2	0	0	0	0	1	0	0	1
orf19.5486.1	SMD2	0	0	0	0	1	0	0	1
orf19.390	CDC42	1	0	0	0	0	0	0	1
orf19.2715	RPC53	0	0	1	0	0	0	0	1
orf19.5692	orf19.5692	0	1	0	0	0	0	0	1
orf19.6422	SSY5	0	0	1	0	0	0	0	1
orf19.3480	orf19.3480	0	0	0	0	1	0	0	1
orf19.3859	orf19.3859	1	0	0	0	0	0	0	1
orf19.4853	HCM1	0	0	0	1	0	0	0	1
orf19.1207	orf19.1207	0	0	1	0	0	0	0	1
orf19.3631	STN1	0	0	0	0	0	1	0	1
orf19.5210	orf19.5210	0	0	1	0	0	0	0	1
orf19.5212	orf19.5212	0	0	1	0	0	0	0	1
orf19.1998	orf19.1998	0	0	1	0	0	0	0	1
orf19.816	DCK2	0	0	1	0	0	0	0	1
orf19.6164	orf19.6164	0	0	1	0	0	0	0	1
orf19.1993	orf19.1993	0	0	1	0	0	0	0	1
orf19.1822	UME6	0	0	0	0	0	0	1	1
orf19.1994	orf19.1994	0	0	0	1	0	0	0	1
orf19.1995	orf19.1995	0	0	1	0	0	0	0	1
orf19.690	PLB2	0	0	0	0	1	0	0	1
orf19.376	orf19.376	0	0	0	0	0	0	1	1
orf19.2988	orf19.2988	0	0	0	0	1	0	0	1

orf19.4451	RIA1	0	0	0	0	1	0	0	1
orf19.2081	POM152	0	0	1	0	0	0	0	1
orf19.1618	GFA1	0	0	1	0	0	0	0	1
orf19.4063	GPT1	0	0	0	0	1	0	0	1
orf19.686	orf19.686	0	0	0	0	0	1	0	1
orf19.1311	SPO75	0	0	0	0	1	0	0	1
orf19.6635	orf19.6635	0	0	0	0	1	0	0	1
orf19.7105	FAR1	0	0	1	0	0	0	0	1
orf19.4119	SPO72	0	0	1	0	0	0	0	1
orf19.651	LYP1	0	0	0	0	0	0	1	1
orf19.2537	orf19.2537	0	0	0	0	0	1	0	1
orf19.3054	RPN3	0	0	0	0	1	0	0	1
orf19.2539	orf19.2539	0	0	0	0	0	1	0	1
orf19.3457	SWD3	0	0	0	0	1	0	0	1
orf19.7177	KAP120	0	0	0	0	0	1	0	1
orf19.3139	orf19.3139	0	0	1	0	0	0	0	1
orf19.3135	orf19.3135	0	1	0	0	0	0	0	1
orf19.2401	orf19.2401	0	0	1	0	0	0	0	1
orf19.2532	PRS	0	0	1	0	0	0	0	1
orf19.6742	orf19.6742	1	0	0	0	0	0	0	1
orf19.5507	ENP1	0	0	0	0	0	1	0	1
orf19.4803	orf19.4803	1	0	0	0	0	0	0	1
orf19.3688	orf19.3688	1	0	0	0	0	0	0	1
orf19.3689	orf19.3689	1	0	0	0	0	0	0	1
orf19.1490	MSB2	1	0	0	0	0	0	0	1
orf19.3865	RFX1	0	0	0	1	0	0	0	1
orf19.7345	orf19.7345	0	0	0	1	0	0	0	1
orf19.7344	orf19.7344	0	0	0	0	1	0	0	1
orf19.3048	orf19.3048	0	1	0	0	0	0	0	1
orf19.3715	ASF1	0	0	0	0	0	1	0	1
orf19.1576	orf19.1576	0	0	1	0	0	0	0	1
orf19.1578	orf19.1578	0	0	1	0	0	0	0	1
orf19.5164	ECM39	0	0	1	0	0	0	0	1
orf19.4244	orf19.4244	0	1	0	0	0	0	0	1
orf19.4247	orf19.4247	1	0	0	0	0	0	0	1
orf19.4246	orf19.4246	0	0	1	0	0	0	0	1
orf19.4241	orf19.4241	1	0	0	0	0	0	0	1
orf19.4240	orf19.4240	0	0	0	0	1	0	0	1
orf19.3594	orf19.3594	0	0	0	0	1	0	0	1
orf19.3260	orf19.3260	0	0	0	0	1	0	0	1
orf19.834	orf19.834	0	0	1	0	0	0	0	1
orf19.4062	TRY2	0	0	0	0	1	0	0	1
orf19.1686	orf19.1686	0	0	1	0	0	0	0	1
orf19.707	APG7	0	0	0	1	0	0	0	1
orf19.1685	ZCF7	0	0	0	1	0	0	0	1
orf19.1682	orf19.1682	0	1	0	0	0	0	0	1
orf19.1649	RNA1	0	1	0	0	0	0	0	1

orf19.5674	PGA10	1	0	0	0	0	0	0	1
orf19.2878	PGA15	0	0	1	0	0	0	0	1
orf19.2033	PGA19	1	0	0	0	0	0	0	1
orf19.2018.2	orf19.2018.2	0	0	1	0	0	0	0	1
orf19.7251	WSC4	0	0	0	0	0	1	0	1
orf19.4665	orf19.4665	1	0	0	0	0	0	0	1
orf19.1416	COX11	0	0	1	0	0	0	0	1
orf19.4110	orf19.4110	0	0	0	0	1	0	0	1
orf19.4112	orf19.4112	0	0	1	0	0	0	0	1
orf19.4115	orf19.4115	0	0	0	0	0	1	0	1
orf19.4117	orf19.4117	0	0	0	0	0	0	1	1
orf19.7275	FGR24	0	0	0	1	0	0	0	1
orf19.4268	UTP13	0	1	0	0	0	0	0	1
orf19.4765	PGA6	0	0	0	0	1	0	0	1
orf19.3122.2	orf19.3122.2	0	0	0	0	1	0	0	1
orf19.5041	orf19.5041	0	0	1	0	0	0	0	1
orf19.3555	BUD14	0	1	0	0	0	0	0	1
orf19.1369	orf19.1369	0	0	1	0	0	0	0	1
orf19.4739	MSS116	0	0	0	0	1	0	0	1
orf19.4328	CCC2	0	0	0	0	1	0	0	1
orf19.4848	SKI3	0	0	0	0	1	0	0	1
orf19.353	ULP1	0	0	0	0	1	0	0	1
orf19.1295	VAS1	0	0	0	0	0	1	0	1
orf19.6041	RPO41	0	0	0	0	1	0	0	1
orf19.6247	orf19.6247	0	0	0	0	1	0	0	1
orf19.6244	orf19.6244	0	0	0	0	0	0	1	1
orf19.1215	orf19.1215	0	0	0	0	0	1	0	1
orf19.1214	orf19.1214	0	0	0	0	0	1	0	1
orf19.1961	orf19.1961	0	0	1	0	0	0	0	1
orf19.6240	orf19.6240	0	0	0	0	1	0	0	1
orf19.1219	orf19.1219	0	0	0	0	1	0	0	1
orf19.5221	orf19.5221	1	0	0	0	0	0	0	1
orf19.5223	orf19.5223	1	0	0	0	0	0	0	1
orf19.5224	orf19.5224	1	0	0	0	0	0	0	1
orf19.6248	orf19.6248	0	0	0	0	1	0	0	1
orf19.4033	PRP22	1	0	0	0	0	0	0	1
orf19.1981	orf19.1981	0	0	1	0	0	0	0	1
orf19.1671	UTR2	0	0	0	1	0	0	0	1
orf19.305	orf19.305	0	0	0	0	1	0	0	1
orf19.304	orf19.304	0	0	0	0	1	0	0	1
orf19.7594	orf19.7594	0	0	1	0	0	0	0	1
orf19.2735	SEN2	0	0	1	0	0	0	0	1
orf19.5938	SEN1	0	0	1	0	0	0	0	1
orf19.2320	orf19.2320	0	0	0	0	0	1	0	1
orf19.7203	orf19.7203	0	1	0	0	0	0	0	1
orf19.2325	orf19.2325	0	0	0	1	0	0	0	1
orf19.5145	SSP96	0	0	1	0	0	0	0	1

orf19.6625	orf19.6625	0	0	1	0	0	0	0	1
orf19.2198	FLC3	0	0	0	0	1	0	0	1
orf19.1813	FLC2	0	0	1	0	0	0	0	1
orf19.2517	orf19.2517	0	0	1	0	0	0	0	1
orf19.4867	SWE1	0	0	0	0	0	0	1	1
orf19.2184	orf19.2184	0	0	0	0	1	0	0	1
orf19.3125	orf19.3125	0	0	1	0	0	0	0	1
orf19.3124	orf19.3124	0	0	1	0	0	0	0	1
orf19.3120	orf19.3120	0	0	1	0	0	0	0	1
orf19.2823	RFG1	0	0	0	0	0	1	0	1
orf19.2431	orf19.2431	0	0	0	0	1	0	0	1
orf19.2723	HIT1	0	1	0	0	0	0	0	1
orf19.6928	SAP9	0	0	0	0	0	0	1	1
orf19.5585	SAP5	0	0	0	0	1	0	0	1
orf19.4875	orf19.4875	0	0	0	1	0	0	0	1
orf19.4872	orf19.4872	0	0	0	0	1	0	0	1
orf19.3697	orf19.3697	0	0	0	1	0	0	0	1
orf19.7376	orf19.7376	1	0	0	0	0	0	0	1
orf19.2509	orf19.2509	1	0	0	0	0	0	0	1
orf19.2500	orf19.2500	0	0	0	0	1	0	0	1
orf19.2051	orf19.2051	0	0	1	0	0	0	0	1
orf19.2506	orf19.2506	0	0	0	0	1	0	0	1
orf19.3950	MSM1	0	0	0	0	1	0	0	1
orf19.984	PHO8	1	0	0	0	0	0	0	1
orf19.1648	RAD50	0	0	0	0	1	0	0	1
orf19.4903	orf19.4903	0	0	0	0	1	0	0	1
orf19.4907	orf19.4907	0	0	0	0	1	0	0	1
orf19.4904	orf19.4904	0	0	0	0	1	0	0	1
orf19.4905	orf19.4905	0	0	0	0	0	0	1	1
orf19.4908	orf19.4908	1	0	0	0	0	0	0	1
orf19.3208	DAL52	0	1	0	0	0	0	0	1
orf19.2623	ECM22	0	0	1	0	0	0	0	1
orf19.3586	orf19.3586	0	1	0	0	0	0	0	1
orf19.4473	SPC19	1	0	0	0	0	0	0	1
orf19.4471	orf19.4471	0	0	0	0	0	0	1	1
orf19.3271	orf19.3271	0	0	1	0	0	0	0	1
orf19.3971	orf19.3971	0	0	0	0	1	0	0	1
orf19.4295	orf19.4295	0	0	0	0	0	1	0	1
orf19.939	NAM7	0	0	1	0	0	0	0	1
orf19.35.1	orf19.35.1	0	0	1	0	0	0	0	1
orf19.3675	GAL7	1	0	0	0	0	0	0	1
orf19.4866	CPP1	0	0	0	0	0	0	1	1
orf19.2044	PGA27	0	0	1	0	0	0	0	1
orf19.4615	orf19.4615	0	0	1	0	0	0	0	1
orf19.3477	orf19.3477	0	1	0	0	0	0	0	1
orf19.3476	orf19.3476	0	0	0	0	1	0	0	1
orf19.3093	MSH2	0	0	0	0	1	0	0	1

orf19.4128	orf19.4128	0	0	0	1	0	0	0	1
orf19.559	FGR14	0	0	0	0	1	0	0	1
orf19.3700	TOM70	0	0	0	0	1	0	0	1
orf19.5479	FGR12	0	0	0	0	1	0	0	1
orf19.4067	FGR18	0	0	0	0	1	0	0	1
orf19.5094	BUL1	0	0	0	0	1	0	0	1
orf19.4059	orf19.4059	0	0	0	0	1	0	0	1
orf19.3112	ZRT1	0	0	1	0	0	0	0	1
orf19.1585	ZRT2	0	0	1	0	0	0	0	1
orf19.105	HAL22	0	0	0	0	0	1	0	1
orf19.1439	IPK1	0	0	0	0	1	0	0	1
orf19.1563	ECM3	0	0	1	0	0	0	0	1
orf19.5299	ECM1	0	1	0	0	0	0	0	1
orf19.5052	orf19.5052	0	0	1	0	0	0	0	1
orf19.1089	PEX11	0	0	0	0	1	0	0	1
orf19.1831	orf19.1831	0	0	0	0	1	0	0	1
orf19.7282	PEX13	0	0	0	0	1	0	0	1
orf19.1805	PEX14	0	0	0	0	0	1	0	1
orf19.4635	NIP1	0	0	0	0	1	0	0	1
orf19.610	EFG1	0	0	0	0	0	1	0	1
orf19.1741	DIT1	0	0	1	0	0	0	0	1
orf19.2984	MST1	0	0	0	0	1	0	0	1
orf19.695	RGS2	0	0	0	0	0	0	1	1
orf19.1353	orf19.1353	0	1	0	0	0	0	0	1
orf19.3908	orf19.3908	0	0	1	0	0	0	0	1
orf19.3904	orf19.3904	0	0	0	1	0	0	0	1
orf19.3901	orf19.3901	0	0	0	0	1	0	0	1
orf19.407	GCD6	1	0	0	0	0	0	0	1
orf19.5459	orf19.5459	0	0	1	0	0	0	0	1
orf19.481	GCD1	0	0	0	0	1	0	0	1
orf19.5530	NAB3	0	0	0	0	1	0	0	1
orf19.2560	CDC60	0	0	1	0	0	0	0	1
orf19.775	orf19.775	0	0	0	0	1	0	0	1
orf19.3207	CCN1	0	0	0	0	0	0	1	1
orf19.6507	orf19.6507	0	0	1	0	0	0	0	1
orf19.3876	ZCF19	0	0	0	0	1	0	0	1
orf19.5239	orf19.5239	0	0	0	0	1	0	0	1
orf19.6508	orf19.6508	0	0	1	0	0	0	0	1
orf19.1229	orf19.1229	0	1	0	0	0	0	0	1
orf19.3711	orf19.3711	0	0	1	0	0	0	0	1
orf19.3240	ERG27	0	0	1	0	0	0	0	1
orf19.178	orf19.178	0	0	0	0	0	1	0	1
orf19.177	orf19.177	0	0	0	1	0	0	0	1
orf19.5558	RBF1	0	0	0	1	0	0	0	1
orf19.173	orf19.173	0	0	0	0	0	0	1	1
orf19.1944	GPR1	0	0	0	0	1	0	0	1
orf19.315	orf19.315	0	0	0	0	0	1	0	1

orf19.318	orf19.318	0	0	0	0	1	0	0	1
orf19.7213	orf19.7213	0	0	0	1	0	0	0	1
orf19.2332	orf19.2332	0	0	0	0	1	0	0	1
orf19.6347	orf19.6347	0	0	0	0	1	0	0	1
orf19.6612	orf19.6612	1	0	0	0	0	0	0	1
orf19.6342	orf19.6342	0	0	0	0	1	0	0	1
orf19.3589	SPO11	0	0	0	0	1	0	0	1
orf19.111	CAN2	0	0	0	0	1	0	0	1
orf19.84	CAN3	0	0	0	0	1	0	0	1
orf19.1597	ABG1	1	0	0	0	0	0	0	1
orf19.646	GLN1	0	1	0	0	0	0	0	1
orf19.5759	SNQ2	0	0	0	0	1	0	0	1
orf19.5760	IHD1	0	0	0	0	0	0	1	1
orf19.5074	orf19.5074	0	0	0	0	0	1	0	1
orf19.956	orf19.956	0	0	1	0	0	0	0	1
orf19.3110	orf19.3110	0	0	1	0	0	0	0	1
orf19.2429	orf19.2429	0	0	0	0	1	0	0	1
orf19.7108	orf19.7108	0	0	0	1	0	0	0	1
orf19.7101	orf19.7101	0	0	1	0	0	0	0	1
orf19.6981	orf19.6981	0	0	0	0	0	0	1	1
orf19.6982	orf19.6982	0	0	0	0	0	1	0	1
orf19.6986	orf19.6986	0	0	0	0	0	0	1	1
orf19.5527	orf19.5527	0	0	0	0	1	0	0	1
orf19.918	CDR11	0	0	0	0	1	0	0	1
orf19.2605	orf19.2605	0	0	1	0	0	0	0	1
orf19.458.1	orf19.458.1	0	0	0	0	0	1	0	1
orf19.4688	DAG7	0	0	1	0	0	0	0	1
orf19.4865	orf19.4865	1	0	0	0	0	0	0	1
orf19.4862	orf19.4862	0	0	0	1	0	0	0	1
orf19.7368	orf19.7368	0	0	0	0	0	1	0	1
orf19.2514	orf19.2514	0	0	0	0	0	1	0	1
orf19.3649	orf19.3649	0	0	0	0	1	0	0	1
orf19.1519	orf19.1519	0	0	1	0	0	0	0	1
orf19.3644	orf19.3644	0	0	0	0	1	0	0	1
orf19.3647	SEC8	0	0	0	0	1	0	0	1
orf19.4912	orf19.4912	1	0	0	0	0	0	0	1
orf19.4262	orf19.4262	0	0	0	0	0	1	0	1
orf19.3241	orf19.3241	0	0	1	0	0	0	0	1
orf19.3245	orf19.3245	0	0	1	0	0	0	0	1
orf19.4269	orf19.4269	0	0	0	0	1	0	0	1
orf19.3247	orf19.3247	0	1	0	0	0	0	0	1
orf19.6792	RRD1	0	0	0	0	1	0	0	1
orf19.4286	orf19.4286	0	0	0	0	1	0	0	1
orf19.6967	USO6	0	0	0	0	1	0	0	1
orf19.1427	orf19.1427	0	0	0	0	1	0	0	1
orf19.1428	DUO1	0	0	0	0	0	1	0	1
orf19.2758	PGA38	0	0	0	1	0	0	0	1

orf19.2608	ADH5	0	1	0	0	0	0	0	1
orf19.271	ADH4	0	0	0	0	1	0	0	1
orf19.7521	REP1	0	0	1	0	0	0	0	1
orf19.3923	PGA37	0	0	1	0	0	0	0	1
orf19.4607	orf19.4607	0	0	1	0	0	0	0	1
orf19.3481	orf19.3481	0	1	0	0	0	0	0	1
orf19.669	PRM1	0	0	0	0	1	0	0	1
orf19.1405	PHO13	0	0	1	0	0	0	0	1
orf19.4132	orf19.4132	0	1	0	0	0	0	0	1
orf19.4737	TPO3	0	0	0	1	0	0	0	1
orf19.7148	TPO2	0	0	0	1	0	0	0	1
orf19.1736	orf19.1736	0	0	1	0	0	0	0	1
orf19.1734	orf19.1734	0	0	1	0	0	0	0	1
orf19.1730	orf19.1730	0	0	0	0	1	0	0	1
orf19.4162	MLH1	0	0	1	0	0	0	0	1
orf19.6396	orf19.6396	0	0	0	0	0	1	0	1
orf19.5742	ALS9	0	0	0	0	1	0	0	1
orf19.2209	YVC1	0	0	1	0	0	0	0	1
orf19.3113	orf19.3113	0	0	0	0	0	1	0	1
orf19.1378	SUP35	0	0	1	0	0	0	0	1
orf19.2585	orf19.2585	0	0	1	0	0	0	0	1
orf19.1646	orf19.1646	0	0	0	1	0	0	0	1
orf19.2241	PST1	0	0	0	0	0	0	1	1
orf19.1270	FRE3	0	0	1	0	0	0	0	1
orf19.3529	ABP2	1	0	0	0	0	0	0	1
orf19.5902	RAS2	0	0	1	0	0	0	0	1
orf19.1349	orf19.1349	0	0	0	1	0	0	0	1
orf19.1348	orf19.1348	0	0	1	0	0	0	0	1
orf19.5426	orf19.5426	1	0	0	0	0	0	0	1
orf19.3924	orf19.3924	0	0	0	0	1	0	0	1
orf19.540	orf19.540	0	0	0	0	1	0	0	1
orf19.1236	orf19.1236	0	0	1	0	0	0	0	1
orf19.3809	BAS1	0	0	1	0	0	0	0	1
orf19.149	orf19.149	0	0	0	1	0	0	0	1
orf19.6283	orf19.6283	1	0	0	0	0	0	0	1
orf19.899	orf19.899	0	0	1	0	0	0	0	1
orf19.6284	orf19.6284	0	0	0	1	0	0	0	1
orf19.323	orf19.323	0	0	0	0	1	0	0	1
orf19.6863	VPH1	0	0	1	0	0	0	0	1
orf19.3255	TEN1	0	1	0	0	0	0	0	1
orf19.2504	BMS1	0	0	1	0	0	0	0	1
orf19.4975	HYR1	0	0	0	1	0	0	0	1
orf19.3608	orf19.3608	0	0	0	0	0	1	0	1
orf19.6357	orf19.6357	0	0	0	0	1	0	0	1
orf19.6356	orf19.6356	0	0	0	0	0	1	0	1
orf19.6602	orf19.6602	0	0	0	0	1	0	0	1
orf19.5884	orf19.5884	0	0	0	0	1	0	0	1



orf19.5555	orf19.5555	0	0	0	1	0	0	0	1
orf19.6199	orf19.6199	0	1	0	0	0	0	0	1
orf19.57	PSF2	0	0	0	0	1	0	0	1
orf19.1321	HWP1	0	0	0	0	1	0	0	1
orf19.2649	PCL1	1	0	0	0	0	0	0	1
orf19.4012	PCL5	0	0	0	0	1	0	0	1
orf19.7489	orf19.7489	0	0	1	0	0	0	0	1
orf19.1367	MTW1	0	0	0	0	0	1	0	1
orf19.3107	orf19.3107	0	0	0	0	1	0	0	1
orf19.3105	orf19.3105	0	0	1	0	0	0	0	1
orf19.2458	orf19.2458	0	0	0	0	1	0	0	1
orf19.2455	orf19.2455	1	0	0	0	0	0	0	1
orf19.896	CHK1	0	0	1	0	0	0	0	1
orf19.3109	orf19.3109	0	0	0	1	0	0	0	1
orf19.4255	ECM331	0	0	1	0	0	0	0	1
orf19.95	orf19.95	1	0	0	0	0	0	0	1
orf19.2671	orf19.2671	0	0	1	0	0	0	0	1
orf19.7392	orf19.7392	0	0	0	0	1	0	0	1
orf19.7002	orf19.7002	1	0	0	0	0	0	0	1
orf19.7007	orf19.7007	0	0	0	0	1	0	0	1
orf19.2070	orf19.2070	0	0	1	0	0	0	0	1
orf19.7553	orf19.7553	1	0	0	0	0	0	0	1
orf19.3494	CTF5	0	1	0	0	0	0	0	1
orf19.1505	orf19.1505	0	1	0	0	0	0	0	1
orf19.3764	GSG1	0	0	0	0	1	0	0	1
orf19.6053	CIS2	0	0	0	0	1	0	0	1
orf19.7037	YAE1	0	0	0	0	0	1	0	1
orf19.5911	CMK1	0	0	1	0	0	0	0	1
orf19.4928	SEC2	0	0	0	0	1	0	0	1
orf19.3250	orf19.3250	0	0	1	0	0	0	0	1
orf19.4654	orf19.4654	0	0	0	0	1	0	0	1
orf19.4307	orf19.4307	0	0	0	0	1	0	0	1
orf19.1430	orf19.1430	0	0	0	0	1	0	0	1
orf19.1433	orf19.1433	0	0	0	0	1	0	0	1
orf19.1434	orf19.1434	0	0	1	0	0	0	0	1
orf19.1438	orf19.1438	0	0	1	0	0	0	0	1
orf19.3742	orf19.3742	0	0	0	0	0	0	1	1
orf19.4639	orf19.4639	1	0	0	0	0	0	0	1
orf19.4637	orf19.4637	0	0	0	0	1	0	0	1
orf19.2842	GZF3	0	0	0	0	0	1	0	1
orf19.1202	orf19.1202	0	0	0	0	1	0	0	1
orf19.4142	orf19.4142	0	0	1	0	0	0	0	1
orf19.4149	orf19.4149	0	1	0	0	0	0	0	1
orf19.2852	orf19.2852	0	1	0	0	0	0	0	1
orf19.2853	orf19.2853	0	0	1	0	0	0	0	1
orf19.2857	orf19.2857	0	0	0	0	1	0	0	1
orf19.728	TSC11	0	1	0	0	0	0	0	1

orf19.6255	orf19.6255	0	0	0	0	1	0	0	1
orf19.1720	orf19.1720	0	0	0	0	0	1	0	1
orf19.4308	HSL1	0	0	0	0	1	0	0	1
orf19.4701	orf19.4701	0	1	0	0	0	0	0	1
orf19.4702	orf19.4702	0	0	1	0	0	0	0	1
orf19.3199	PIKA	0	0	0	0	1	0	0	1
orf19.2919	MPH1	0	0	1	0	0	0	0	1
orf19.5605	orf19.5605	0	0	0	0	0	1	0	1
orf19.3774.1	orf19.3774.1	0	0	0	0	1	0	0	1
orf19.1115	GUK1	0	0	0	0	1	0	0	1
orf19.1453	SPT5	0	0	0	1	0	0	0	1
orf19.557	orf19.557	0	0	0	0	0	0	1	1
orf19.1260	LEA1	0	0	0	0	1	0	0	1
orf19.6569	orf19.6569	0	0	0	0	1	0	0	1
orf19.3815	orf19.3815	0	0	0	0	0	0	1	1
orf19.854	UGA11	0	0	0	1	0	0	0	1
orf19.1086	orf19.1086	0	0	0	1	0	0	0	1
orf19.1087	orf19.1087	0	0	0	0	1	0	0	1
orf19.154	orf19.154	0	0	0	1	0	0	0	1
orf19.5720	orf19.5720	0	1	0	0	0	0	0	1
orf19.5724	orf19.5724	0	0	0	0	0	1	0	1
orf19.5095	orf19.5095	0	0	0	1	0	0	0	1
orf19.2771	BEM3	0	0	0	0	0	1	0	1
orf19.5821	orf19.5821	0	0	0	0	0	1	0	1
orf19.5940	ZCF32	0	1	0	0	0	0	0	1
orf19.5124	RBR3	1	0	0	0	0	0	0	1
orf19.6360	orf19.6360	0	0	0	1	0	0	0	1
orf19.6366	orf19.6366	0	0	1	0	0	0	0	1
orf19.5894	orf19.5894	0	0	0	0	1	0	0	1
orf19.3895	CHT2	0	0	1	0	0	0	0	1
orf19.1515	CHT4	0	0	1	0	0	0	0	1
orf19.5543	orf19.5543	0	1	0	0	0	0	0	1
orf19.6168	orf19.6168	0	0	1	0	0	0	0	1
orf19.4548	MAK32	0	1	0	0	0	0	0	1
orf19.6382	orf19.6382	1	0	0	0	0	0	0	1
orf19.1863	orf19.1863	1	0	0	0	0	0	0	1
orf19.7494	orf19.7494	0	0	1	0	0	0	0	1
orf19.7497	orf19.7497	1	0	0	0	0	0	0	1
orf19.7490	orf19.7490	0	0	0	0	1	0	0	1
orf19.2449	orf19.2449	0	0	0	0	1	0	0	1
orf19.2440	orf19.2440	0	0	0	0	1	0	0	1
orf19.2442	orf19.2442	0	0	0	0	0	0	1	1
orf19.6705	orf19.6705	0	1	0	0	0	0	0	1
orf19.6703	orf19.6703	0	0	1	0	0	0	0	1
orf19.1860.1	orf19.1860.1	0	0	1	0	0	0	0	1
orf19.2285	orf19.2285	0	0	1	0	0	0	0	1
orf19.81	orf19.81	0	0	0	0	0	1	0	1

orf19.3962	HAS1	0	0	0	0	0	0	1	1
orf19.2664	orf19.2664	0	0	0	0	1	0	0	1
orf19.2540	SAS3	0	0	0	1	0	0	0	1
orf19.6953	IRS4	0	0	0	0	1	0	0	1
orf19.1002	orf19.1002	0	0	0	0	1	0	0	1
orf19.7011	orf19.7011	0	0	1	0	0	0	0	1
orf19.7012	orf19.7012	0	0	1	0	0	0	0	1
orf19.7545	orf19.7545	0	0	1	0	0	0	0	1
orf19.6017	orf19.6017	0	0	0	0	1	0	0	1
orf19.1005	orf19.1005	0	0	0	0	1	0	0	1
orf19.4932	orf19.4932	1	0	0	0	0	0	0	1
orf19.4936	orf19.4936	1	0	0	0	0	0	0	1
orf19.6637	orf19.6637	0	0	0	0	1	0	0	1
orf19.3713	orf19.3713	0	0	1	0	0	0	0	1
orf19.55	orf19.55	1	0	0	0	0	0	0	1
orf19.3618	YWP1	1	0	0	0	0	0	0	1
orf19.3719	orf19.3719	0	0	1	0	0	0	0	1
orf19.2717	SAS10	0	0	0	0	1	0	0	1
orf19.3539	orf19.3539	0	0	0	1	0	0	0	1
orf19.1047	ERB1	0	0	0	1	0	0	0	1
orf19.1404	orf19.1404	0	0	0	0	1	0	0	1
orf19.4626	orf19.4626	0	0	0	0	1	0	0	1
orf19.4622	orf19.4622	0	0	1	0	0	0	0	1
orf19.4621	orf19.4621	0	0	1	0	0	0	0	1
orf19.4153	orf19.4153	0	1	0	0	0	0	0	1
orf19.568	SPE2	0	0	0	0	0	0	1	1
orf19.5977	CEM1	0	0	0	0	1	0	0	1
orf19.6032	SPE1	0	0	0	0	1	0	0	1
orf19.1718	ZCF8	0	0	0	0	1	0	0	1
orf19.1717	orf19.1717	0	0	0	1	0	0	0	1
orf19.4815	YTM1	0	0	0	1	0	0	0	1
orf19.7175	HLJ1	0	0	0	0	0	0	1	1
orf19.1664	orf19.1664	0	0	0	0	0	1	0	1
orf19.1667	orf19.1667	0	0	0	0	1	0	0	1
orf19.132	orf19.132	0	0	0	0	0	0	1	1
orf19.5782	orf19.5782	0	0	1	0	0	0	0	1
orf19.5391	orf19.5391	0	0	0	0	1	0	0	1
orf19.131	orf19.131	0	0	0	0	1	0	0	1
orf19.641	orf19.641	0	0	0	0	0	1	0	1
orf19.1317	OSH3	0	0	0	0	1	0	0	1
orf19.5156	orf19.5156	0	0	1	0	0	0	0	1
orf19.7115	SAC7	0	0	0	0	0	0	1	1
orf19.3474	IPL1	0	0	0	0	0	0	1	1
orf19.5544	SAC6	0	0	0	0	1	0	0	1
orf19.768	SYG1	0	0	0	0	1	0	0	1
orf19.1926	SEF2	1	0	0	0	0	0	0	1
orf19.520	orf19.520	0	0	0	0	0	0	1	1

orf19.3828	orf19.3828	0	0	0	1	0	0	0	1
orf19.2324	UBA4	0	0	0	0	1	0	0	1
orf19.1258	orf19.1258	0	0	1	0	0	0	0	1
orf19.3276	PWP2	0	0	1	0	0	0	0	1
orf19.3827	orf19.3827	0	0	1	0	0	0	0	1
orf19.5861.1	orf19.5861.1	0	0	0	0	1	0	0	1
orf19.7512	orf19.7512	0	0	1	0	0	0	0	1
orf19.5580	TEL1	0	0	0	0	0	1	0	1
orf19.635	orf19.635	0	0	0	0	1	0	0	1
orf19.634	orf19.634	0	0	0	1	0	0	0	1
orf19.3966	CRH12	0	0	0	0	0	1	0	1
orf19.2706	CRH11	0	0	1	0	0	0	0	1
orf19.184	orf19.184	0	0	0	0	0	0	1	1
orf19.182	orf19.182	0	1	0	0	0	0	0	1
orf19.1897	orf19.1897	0	0	0	0	0	1	0	1
orf19.5579	orf19.5579	0	1	0	0	0	0	0	1
orf19.1890	orf19.1890	0	0	1	0	0	0	0	1
orf19.5573	orf19.5573	1	0	0	0	0	0	0	1
orf19.5574	orf19.5574	0	0	0	0	0	1	0	1
orf19.1383	orf19.1383	0	0	0	0	1	0	0	1
orf19.1381	orf19.1381	0	0	0	0	1	0	0	1
orf19.3826	orf19.3826	0	0	1	0	0	0	0	1
orf19.4002	DUN1	0	0	0	0	1	0	0	1
orf19.1876	orf19.1876	0	0	0	0	1	0	0	1
orf19.1693	CAS4	0	0	1	0	0	0	0	1
orf19.985	orf19.985	0	1	0	0	0	0	0	1
orf19.3940	orf19.3940	0	0	0	0	0	1	0	1
orf19.450	orf19.450	1	0	0	0	0	0	0	1
orf19.980	orf19.980	0	1	0	0	0	0	0	1
orf19.4772	SSU81	0	0	0	1	0	0	0	1
orf19.2478	orf19.2478	0	1	0	0	0	0	0	1
orf19.7159	orf19.7159	0	0	0	1	0	0	0	1
orf19.5076.1	orf19.5076.1	0	0	0	0	1	0	0	1
orf19.2278	orf19.2278	0	0	0	0	1	0	0	1
orf19.866	RAD32	0	0	1	0	0	0	0	1
orf19.1638	orf19.1638	0	0	0	0	1	0	0	1
orf19.6952	orf19.6952	0	0	0	0	1	0	0	1
orf19.3010	orf19.3010	1	0	0	0	0	0	0	1
orf19.7232	IRR1	0	0	0	0	1	0	0	1
orf19.7024	orf19.7024	0	0	0	0	1	0	0	1
orf19.6008	orf19.6008	0	1	0	0	0	0	0	1
orf19.2010	orf19.2010	0	1	0	0	0	0	0	1
orf19.6003	orf19.6003	0	0	0	0	1	0	0	1
orf19.2728	orf19.2728	0	0	0	0	1	0	0	1
orf19.2725	orf19.2725	0	0	0	0	0	1	0	1
orf19.979	FAS1	0	0	1	0	0	0	0	1
orf19.3639	orf19.3639	1	0	0	0	0	0	0	1

orf19.2721	orf19.2721	0	0	0	0	1	0	0	1
orf19.1529	orf19.1529	0	0	0	0	0	1	0	1
orf19.1528	orf19.1528	1	0	0	0	0	0	0	1
orf19.4354	MCM2	0	0	0	0	0	1	0	1
orf19.4946	orf19.4946	0	0	0	0	1	0	0	1
orf19.4942	orf19.4942	0	0	0	0	1	0	0	1
orf19.3704	orf19.3704	0	0	0	0	1	0	0	1
orf19.2653	orf19.2653	0	0	0	0	1	0	0	1
orf19.1412	orf19.1412	0	0	0	0	1	0	0	1
orf19.1411	orf19.1411	0	0	0	0	1	0	0	1
orf19.3522	orf19.3522	0	0	1	0	0	0	0	1
orf19.1414	orf19.1414	0	0	0	0	1	0	0	1
orf19.4894	orf19.4894	0	0	0	0	1	0	0	1
orf19.4896	orf19.4896	0	0	0	0	1	0	0	1
orf19.4893	orf19.4893	0	0	0	0	1	0	0	1
orf19.4365	orf19.4365	0	0	0	0	0	0	1	1
orf19.7359	CRZ1	1	0	0	0	0	0	0	1
orf19.2356	CRZ2	0	0	0	0	0	0	1	1
orf19.1605	PMS1	0	0	1	0	0	0	0	1
orf19.2509.1	orf19.2509.1	0	0	0	0	1	0	0	1
orf19.4094	orf19.4094	0	0	1	0	0	0	0	1
orf19.4767	ZCF28	0	0	0	0	0	1	0	1
orf19.4097	orf19.4097	0	0	0	0	1	0	0	1
orf19.4760	orf19.4760	0	0	0	0	1	0	0	1
orf19.4768	orf19.4768	0	0	0	0	1	0	0	1
orf19.6345	RPG1A	0	0	0	0	0	1	0	1
orf19.2364	MIS11	1	0	0	0	0	0	0	1
orf19.1676	orf19.1676	0	0	0	1	0	0	0	1
orf19.6214	ATC1	0	0	0	0	1	0	0	1
orf19.1914	FAV3	0	0	0	1	0	0	0	1
orf19.1679	orf19.1679	0	1	0	0	0	0	0	1
orf19.1678	orf19.1678	1	0	0	0	0	0	0	1
orf19.4169	orf19.4169	0	0	1	0	0	0	0	1
orf19.4160	orf19.4160	0	0	1	0	0	0	0	1
orf19.4164	orf19.4164	0	0	1	0	0	0	0	1
orf19.4166	ZCF21	0	0	1	0	0	0	0	1
orf19.2783	PIR32	0	1	0	0	0	0	0	1
orf19.5381	orf19.5381	0	0	0	0	1	0	0	1
orf19.5367	RDH54	0	0	1	0	0	0	0	1
orf19.4645	BEM1	0	0	0	0	1	0	0	1
orf19.533	orf19.533	0	0	1	0	0	0	0	1
orf19.2825	orf19.2825	0	0	0	0	0	0	1	1
orf19.1268	orf19.1268	0	0	1	0	0	0	0	1
orf19.3833	orf19.3833	0	1	0	0	0	0	0	1
orf19.3831	orf19.3831	0	0	0	0	1	0	0	1
orf19.1066	GIG1	0	0	0	0	1	0	0	1
orf19.5702	orf19.5702	0	0	0	0	1	0	0	1

orf19.1386	orf19.1386	0	0	0	0	1	0	0	1
orf19.5963	orf19.5963	0	0	0	0	1	0	0	1
orf19.144	SNU114	0	1	0	0	0	0	0	1
orf19.2711.1	orf19.2711.1	1	0	0	0	0	0	0	1
orf19.5965	orf19.5965	0	0	0	0	1	0	0	1
orf19.3666	orf19.3666	0	1	0	0	0	0	0	1
orf19.199	orf19.199	0	0	0	0	1	0	0	1
orf19.5255	PXA2	0	0	0	1	0	0	0	1
orf19.860	BMT8	0	1	0	0	0	0	0	1
orf19.1203	SRO77	0	0	0	0	1	0	0	1
orf19.1367.1	orf19.1367.1	0	0	1	0	0	0	0	1
orf19.3282	BMT3	0	0	1	0	0	0	0	1
orf19.5566	orf19.5566	1	0	0	0	0	0	0	1
orf19.5602	BMT6	0	0	0	0	1	0	0	1
orf19.5612	BMT4	0	0	0	0	1	0	0	1
orf19.6147	orf19.6147	0	0	0	0	1	0	0	1
orf19.6493	orf19.6493	0	0	0	0	1	0	0	1
orf19.6491	orf19.6491	0	0	1	0	0	0	0	1
orf19.4585	TFG1	0	0	1	0	0	0	0	1
orf19.5365	orf19.5365	0	0	0	0	1	0	0	1
orf19.5500	MAK16	0	0	0	0	1	0	0	1
orf19.2619	PHO113	0	1	0	0	0	0	0	1
orf19.3727	PHO112	0	0	1	0	0	0	0	1
orf19.1844	orf19.1844	0	0	0	0	1	0	0	1
orf19.996	orf19.996	0	0	0	0	1	0	0	1
orf19.445	orf19.445	1	0	0	0	0	0	0	1
orf19.5097	CAT8	0	0	0	0	1	0	0	1
orf19.5343	ASH1	0	0	0	0	1	0	0	1
orf19.448	orf19.448	0	0	0	1	0	0	0	1
orf19.2261	orf19.2261	0	0	1	0	0	0	0	1
orf19.2260	orf19.2260	0	0	0	0	1	0	0	1
orf19.2263	orf19.2263	0	0	0	0	0	0	1	1
orf19.69	orf19.69	0	0	0	0	1	0	0	1
orf19.1286	orf19.1286	0	1	0	0	0	0	0	1
orf19.1287	orf19.1287	0	0	0	0	1	0	0	1
orf19.1285	orf19.1285	0	0	0	0	1	0	0	1
orf19.801	TBF1	0	0	1	0	0	0	0	1
orf19.1945	AUR1	0	0	0	0	1	0	0	1
orf19.1743	ACS1	0	0	1	0	0	0	0	1
orf19.5672	MEP2	0	0	1	0	0	0	0	1
orf19.377	PHR3	0	0	0	0	1	0	0	1
orf19.2000	orf19.2000	0	0	0	1	0	0	0	1
orf19.2002	orf19.2002	0	1	0	0	0	0	0	1
orf19.2736	HFL2	0	0	1	0	0	0	0	1
orf19.4746	JIP5	0	0	0	0	1	0	0	1
orf19.3010.1	ECM33	0	0	0	0	1	0	0	1
orf19.4955	orf19.4955	0	0	0	0	0	1	0	1

orf19.4951	orf19.4951	0	0	0	0	1	0	0	1
orf19.3252	DAL81	0	0	1	0	0	0	0	1
orf19.6309	MSS11	0	0	0	0	0	0	1	1
orf19.3285	orf19.3285	0	0	1	0	0	0	0	1
orf19.2651	CAM1-1	0	0	0	0	1	0	0	1
orf19.3281	orf19.3281	0	0	0	0	1	0	0	1
orf19.3775	SSK2	0	0	1	0	0	0	0	1
orf19.3553	RPF2	0	0	1	0	0	0	0	1
orf19.4420	orf19.4420	0	0	1	0	0	0	0	1
orf19.7452	orf19.7452	0	0	0	0	0	1	0	1
orf19.3593	RPT6	0	0	1	0	0	0	0	1
orf19.5440	RPT2	0	0	0	0	0	0	1	1
orf19.7529	EPL1	1	0	0	0	0	0	0	1
orf19.3512	orf19.3512	0	0	1	0	0	0	0	1
orf19.4261	TIF5	0	0	0	0	0	1	0	1
orf19.4395	orf19.4395	0	0	0	0	1	0	0	1
orf19.7624	orf19.7624	0	0	0	0	1	0	0	1
orf19.4391	orf19.4391	0	0	0	1	0	0	0	1
orf19.3423	TIF3	0	0	0	0	1	0	0	1
orf19.4399	orf19.4399	0	0	0	0	1	0	0	1
orf19.4398	orf19.4398	0	0	1	0	0	0	0	1
orf19.4883	orf19.4883	0	0	0	0	1	0	0	1
orf19.7158	orf19.7158	1	0	0	0	0	0	0	1
orf19.4880	orf19.4880	0	0	0	0	0	1	0	1
orf19.1279	CDS1	0	0	0	0	1	0	0	1
orf19.3600	orf19.3600	1	0	0	0	0	0	0	1
orf19.3356	ESP1	0	1	0	0	0	0	0	1
orf19.2868	orf19.2868	0	0	1	0	0	0	0	1
orf19.2863	orf19.2863	0	0	0	1	0	0	0	1
orf19.4372	orf19.4372	0	0	0	0	1	0	0	1
orf19.2867	orf19.2867	0	0	0	0	1	0	0	1
orf19.723	BCR1	0	0	1	0	0	0	0	1
orf19.4088	orf19.4088	0	1	0	0	0	0	0	1
orf19.4081	orf19.4081	0	0	1	0	0	0	0	1
orf19.2335	orf19.2335	0	0	0	0	1	0	0	1
orf19.2616	UGT51C1	0	0	0	0	1	0	0	1
orf19.4341	orf19.4341	0	1	0	0	0	0	0	1
orf19.1604	orf19.1604	0	0	1	0	0	0	0	1
orf19.1600	orf19.1600	0	0	0	0	1	0	0	1
orf19.1609	orf19.1609	0	0	0	0	1	0	0	1
orf19.4174	orf19.4174	0	0	1	0	0	0	0	1
orf19.4172	orf19.4172	0	0	1	0	0	0	0	1
orf19.4171	orf19.4171	0	0	1	0	0	0	0	1
orf19.4274	PUT1	0	0	0	0	1	0	0	1
orf19.2552	orf19.2552	0	0	0	0	0	0	1	1
orf19.5498	EFH1	0	0	0	0	1	0	0	1
orf19.1084	CDC39	0	0	0	0	0	1	0	1

orf19.3623	SMC2	0	0	1	0	0	0	0	1
orf19.1116	orf19.1116	0	0	1	0	0	0	0	1
orf19.5531	CDC37	0	0	0	0	0	1	0	1
orf19.6556	orf19.6556	0	0	0	0	1	0	0	1
orf19.1272	orf19.1272	0	0	0	0	1	0	0	1
orf19.1059	HHF1	0	0	0	1	0	0	0	1
orf19.3468	ALG11	0	0	0	0	1	0	0	1
orf19.4890	CLA4	0	0	0	1	0	0	0	1
orf19.6559	orf19.6559	1	0	0	0	0	0	0	1
orf19.6558	orf19.6558	1	0	0	0	0	0	0	1
orf19.10	ALK8	0	0	1	0	0	0	0	1
orf19.612	orf19.612	0	0	0	0	1	0	0	1
orf19.6673	HEX1	0	0	0	0	1	0	0	1
orf19.1343	orf19.1343	0	0	0	0	1	0	0	1
orf19.6031	VPS27	1	0	0	0	0	0	0	1
orf19.6670	CAC2	0	0	0	0	1	0	0	1
orf19.6005	HGT5	0	0	0	0	1	0	0	1
orf19.3668	HGT2	0	0	0	0	1	0	0	1
orf19.291	orf19.291	1	0	0	0	0	0	0	1
orf19.5601	orf19.5601	0	0	0	0	1	0	0	1
orf19.5358	orf19.5358	0	0	0	0	1	0	0	1
orf19.2135	TSM1	0	0	0	1	0	0	0	1
orf19.6482	orf19.6482	0	0	0	0	0	1	0	1
orf19.6488	orf19.6488	0	0	1	0	0	0	0	1
orf19.5353	orf19.5353	1	0	0	0	0	0	0	1
orf19.470	orf19.470	0	0	1	0	0	0	0	1
orf19.477	orf19.477	0	0	1	0	0	0	0	1
orf19.1613	ILV2	0	0	1	0	0	0	0	1
orf19.3461	orf19.3461	0	0	0	0	0	1	0	1
orf19.5771	PBP2	0	0	1	0	0	0	0	1
orf19.6739	orf19.6739	0	0	0	0	1	0	0	1
orf19.696	STE2	0	0	0	1	0	0	0	1
orf19.2257	orf19.2257	0	0	1	0	0	0	0	1
orf19.6481	YPS7	0	0	1	0	0	0	0	1
orf19.2252	orf19.2252	0	0	0	0	1	0	0	1
orf19.51	orf19.51	0	0	0	1	0	0	0	1
orf19.5506	PLC1	0	0	0	1	0	0	0	1
orf19.6934	orf19.6934	0	0	1	0	0	0	0	1
orf19.2038	orf19.2038	0	0	1	0	0	0	0	1
orf19.879	orf19.879	0	0	1	0	0	0	0	1
orf19.7511	orf19.7511	0	0	1	0	0	0	0	1
orf19.7043	orf19.7043	0	0	0	0	1	0	0	1
orf19.871	orf19.871	0	0	0	1	0	0	0	1
orf19.6022	orf19.6022	0	1	0	0	0	0	0	1
orf19.6018	LRO1	0	0	0	0	1	0	0	1
orf19.5926	ARG11	0	0	0	0	1	0	0	1
orf19.6027	orf19.6027	0	1	0	0	0	0	0	1



orf19.2133	LIP4	0	0	0	1	0	0	0	1
orf19.6025	orf19.6025	0	0	0	1	0	0	0	1
orf19.6024	orf19.6024	0	1	0	0	0	0	0	1
orf19.5172	LIP9	0	0	0	0	0	0	1	1
orf19.2746	orf19.2746	0	0	1	0	0	0	0	1
orf19.4966	orf19.4966	0	0	0	0	1	0	0	1
orf19.3680	SEP7	0	1	0	0	0	0	0	1
orf19.3728	orf19.3728	0	0	1	0	0	0	0	1
orf19.4415	orf19.4415	0	0	1	0	0	0	0	1
orf19.3722	orf19.3722	0	0	1	0	0	0	0	1
orf19.3726	orf19.3726	0	0	1	0	0	0	0	1
orf19.6496	TRS33	0	0	0	0	1	0	0	1
orf19.484	MRPL40	0	0	0	0	1	0	0	1
orf19.7468	orf19.7468	0	0	0	0	1	0	0	1
orf19.2106	orf19.2106	1	0	0	0	0	0	0	1
orf19.7460	orf19.7460	0	0	1	0	0	0	0	1
orf19.2488	FAL1	0	0	0	0	1	0	0	1
orf19.7463	orf19.7463	0	0	1	0	0	0	0	1
orf19.5919	MEA1	0	0	0	0	0	0	1	1
orf19.3501	orf19.3501	0	0	0	0	1	0	0	1
orf19.1479	orf19.1479	0	1	0	0	0	0	0	1
orf19.1476	orf19.1476	0	0	1	0	0	0	0	1
orf19.1525	orf19.1525	0	0	0	0	0	1	0	1
orf19.6533	MSK1	0	0	0	0	0	1	0	1
orf19.2818	orf19.2818	0	0	1	0	0	0	0	1
orf19.4747	HEM14	0	1	0	0	0	0	0	1
orf19.4347	orf19.4347	1	0	0	0	0	0	0	1
orf19.4340	orf19.4340	1	0	0	0	0	0	0	1
orf19.434	PRD1	0	0	0	0	1	0	0	1
orf19.4748	orf19.4748	1	0	0	0	0	0	0	1
orf19.647.3	orf19.647.3	0	0	0	0	1	0	0	1
orf19.4741	orf19.4741	0	0	0	0	1	0	0	1
orf19.4981	orf19.4981	0	0	0	0	1	0	0	1
orf19.1757	orf19.1757	0	0	1	0	0	0	0	1
orf19.2922	orf19.2922	0	0	1	0	0	0	0	1
orf19.2921	orf19.2921	0	0	1	0	0	0	0	1
orf19.2928	orf19.2928	1	0	0	0	0	0	0	1
orf19.1617	orf19.1617	0	0	0	0	1	0	0	1
orf19.1619	orf19.1619	0	0	0	0	1	0	0	1
orf19.4182	orf19.4182	0	0	1	0	0	0	0	1
orf19.4187	orf19.4187	0	0	1	0	0	0	0	1
orf19.4185	orf19.4185	0	0	1	0	0	0	0	1
orf19.4189	orf19.4189	0	0	0	0	1	0	0	1
orf19.1753	PUS7	0	0	0	0	1	0	0	1
orf19.4682	HGT17	0	0	0	0	1	0	0	1
orf19.6141	HGT16	0	0	0	1	0	0	0	1
orf19.1358	GCN4	0	0	0	0	1	0	0	1

orf19.4533	orf19.4533	0	0	0	0	1	0	0	1
orf19.579	FOL1	0	0	1	0	0	0	0	1
orf19.4482	IFI3	1	0	0	0	0	0	0	1
orf19.4573	ZCF26	0	0	0	0	1	0	0	1
orf19.511	orf19.511	0	0	1	0	0	0	0	1
orf19.512	orf19.512	0	0	0	0	0	0	1	1
orf19.3954	orf19.3954	0	0	0	0	0	1	0	1
orf19.3628	RSP5	0	0	1	0	0	0	0	1
orf19.3374	ECE1	0	0	1	0	0	0	0	1
orf19.3337	orf19.3337	0	0	0	0	1	0	0	1
orf19.1045	orf19.1045	0	0	0	1	0	0	0	1
orf19.5083	DRG1	0	0	0	0	1	0	0	1
orf19.5765	orf19.5765	0	0	0	1	0	0	0	1
orf19.5767	orf19.5767	0	0	0	0	1	0	0	1
orf19.761	TCO89	1	0	0	0	0	0	0	1
orf19.609	orf19.609	0	1	0	0	0	0	0	1
orf19.6985	TEA1	0	1	0	0	0	0	0	1
orf19.604	orf19.604	0	0	0	1	0	0	0	1
orf19.852	SAP98	0	0	1	0	0	0	0	1
orf19.7442	orf19.7442	0	0	0	0	0	1	0	1
orf19.3122	ARR3	0	0	0	0	1	0	0	1
orf19.391	UPC2	1	0	0	0	0	0	0	1
orf19.7499.1	orf19.7499.1	0	0	0	0	1	0	0	1
orf19.5587	orf19.5587	0	0	0	0	1	0	0	1
orf19.5586	orf19.5586	0	0	0	0	0	1	0	1
orf19.5589	orf19.5589	0	0	0	0	1	0	0	1
orf19.505	SRV2	0	0	0	0	1	0	0	1
orf19.5617	orf19.5617	0	0	0	0	1	0	0	1
orf19.3298	CCH1	0	0	0	0	1	0	0	1
orf19.3894	orf19.3894	1	0	0	0	0	0	0	1
orf19.1827	orf19.1827	0	0	0	0	1	0	0	1
orf19.5362	PSO2	0	0	0	1	0	0	0	1
orf19.1823	orf19.1823	0	0	0	0	0	0	1	1
orf19.5830	orf19.5830	0	0	1	0	0	0	0	1
orf19.467	orf19.467	0	0	0	1	0	0	0	1
orf19.261	orf19.261	0	0	0	0	1	0	0	1
orf19.2247	orf19.2247	0	0	0	1	0	0	0	1
orf19.2246	orf19.2246	0	0	0	0	1	0	0	1
orf19.6230	orf19.6230	0	0	0	0	1	0	0	1
orf19.6585	orf19.6585	1	0	0	0	0	0	0	1
orf19.6587	orf19.6587	0	1	0	0	0	0	0	1
orf19.6583	orf19.6583	0	0	0	1	0	0	0	1
orf19.6909	orf19.6909	0	1	0	0	0	0	0	1
orf19.4969	KEM1	0	0	0	0	1	0	0	1
orf19.5548	LYS14	0	0	0	0	1	0	0	1
orf19.7057	orf19.7057	0	0	0	0	1	0	0	1
orf19.2024	orf19.2024	0	0	0	0	0	1	0	1

orf19.3050	AGE1	0	0	0	0	1	0	0	1
orf19.3630	RRP8	0	1	0	0	0	0	0	1
orf19.4976	orf19.4976	0	0	0	1	0	0	0	1
orf19.2834	RPD3	0	0	0	0	0	1	0	1
orf19.4407	orf19.4407	0	0	0	0	1	0	0	1
orf19.3758	orf19.3758	0	1	0	0	0	0	0	1
orf19.2110	orf19.2110	0	0	1	0	0	0	0	1
orf19.3196	orf19.3196	0	1	0	0	0	0	0	1
orf19.6550	orf19.6550	0	0	0	0	1	0	0	1
orf19.3573	PEX6	0	0	0	0	0	1	0	1
orf19.3409	SEC12	0	0	0	0	1	0	0	1
orf19.4571	orf19.4571	0	0	1	0	0	0	0	1
orf19.3102	CTA6	1	0	0	0	0	0	0	1
orf19.3376	orf19.3376	0	0	0	0	1	0	0	1
orf19.3371	JAB1	0	0	1	0	0	0	0	1
orf19.3373	orf19.3373	0	0	1	0	0	0	0	1
orf19.2805	PEX8	0	1	0	0	0	0	0	1
orf19.2804	orf19.2804	0	0	1	0	0	0	0	1
orf19.451	SOK1	1	0	0	0	0	0	0	1
orf19.3405	ZCF18	0	0	0	0	1	0	0	1
orf19.3818	GOA1	0	0	0	0	1	0	0	1
orf19.1592	orf19.1592	0	0	0	0	0	1	0	1
orf19.4756	orf19.4756	0	0	0	0	0	1	0	1
orf19.4751	orf19.4751	0	0	0	1	0	0	0	1
orf19.4998	ROB1	1	0	0	0	0	0	0	1
orf19.2236	FHL1	0	0	0	0	0	0	1	1
orf19.3227	FTH2	0	0	0	0	0	1	0	1
orf19.4995	orf19.4995	0	0	0	0	0	1	0	1
orf19.2930	orf19.2930	0	1	0	0	0	0	0	1
orf19.7074	orf19.7074	0	1	0	0	0	0	0	1
orf19.5121	OPT5	0	0	0	0	1	0	0	1
orf19.2938	orf19.2938	0	0	0	0	1	0	0	1
orf19.3506	DBR1	0	0	0	0	1	0	0	1
orf19.1626	orf19.1626	0	0	1	0	0	0	0	1
orf19.4195	orf19.4195	0	0	0	0	0	0	1	1
orf19.3990	orf19.3990	0	0	0	0	0	1	0	1
orf19.7173	orf19.7173	0	0	0	1	0	0	0	1
orf19.808	orf19.808	0	0	1	0	0	0	0	1
orf19.7271	orf19.7271	0	0	0	1	0	0	0	1
orf19.5291	orf19.5291	0	0	0	0	0	1	0	1
orf19.4048	DES1	0	1	0	0	0	0	0	1
orf19.4808	NUP188	0	0	0	1	0	0	0	1
orf19.1363	orf19.1363	0	0	0	0	1	0	0	1
orf19.4361	IFF3	0	0	0	1	0	0	0	1
orf19.5634	FRP1	0	0	1	0	0	0	0	1
orf19.6522	orf19.6522	0	0	0	0	1	0	0	1
orf19.2654	RMS1	0	0	0	0	0	1	0	1

orf19.3557	GPI19	0	0	0	1	0	0	0	1
orf19.1050	orf19.1050	1	0	0	0	0	0	0	1
orf19.832	GPI13	0	0	1	0	0	0	0	1
orf19.5026	orf19.5026	0	1	0	0	0	0	0	1
orf19.5757	orf19.5757	0	0	0	0	0	0	1	1
orf19.1804	orf19.1804	0	0	0	0	0	1	0	1
orf19.1902	NOC4	0	0	0	0	0	1	0	1
orf19.2579	orf19.2579	0	0	1	0	0	0	0	1
orf19.992	LKH1	0	0	0	0	1	0	0	1
orf19.676	orf19.676	0	0	0	0	0	1	0	1
orf19.6138	orf19.6138	0	0	1	0	0	0	0	1
orf19.3973	orf19.3973	0	1	0	0	0	0	0	1
orf19.5626	orf19.5626	0	0	0	1	0	0	0	1
orf19.5628	orf19.5628	0	0	0	1	0	0	0	1
orf19.1032	SKO1	0	0	0	1	0	0	0	1
orf19.2361	SPT10	0	0	1	0	0	0	0	1
orf19.5808	orf19.5808	0	0	1	0	0	0	0	1
orf19.494	orf19.494	0	0	0	0	0	1	0	1
orf19.3150	GRE2	0	0	1	0	0	0	0	1
orf19.499	orf19.499	0	0	1	0	0	0	0	1
orf19.702	orf19.702	0	0	0	0	1	0	0	1
orf19.254	orf19.254	0	0	1	0	0	0	0	1
orf19.35	orf19.35	0	0	1	0	0	0	0	1
orf19.7564	DPB2	0	0	0	0	1	0	0	1
orf19.5930	orf19.5930	0	0	0	0	1	0	0	1
orf19.5931	ARV1	0	0	0	0	0	1	0	1
orf19.5932	orf19.5932	0	0	0	0	1	0	0	1
orf19.3599	TIF4631	0	0	0	1	0	0	0	1
orf19.4610	orf19.4610	0	0	0	0	1	0	0	1
orf19.6912	orf19.6912	0	0	1	0	0	0	0	1
orf19.2582	orf19.2582	0	0	0	0	0	0	1	1
orf19.7063	orf19.7063	0	0	1	0	0	0	0	1
orf19.7067	orf19.7067	0	0	0	0	1	0	0	1
orf19.7088	orf19.7088	1	0	0	0	0	0	0	1
orf19.5484	SER1	0	0	0	0	1	0	0	1
orf19.2563	orf19.2563	0	0	1	0	0	0	0	1
orf19.210	orf19.210	0	0	0	0	1	0	0	1
orf19.7086	orf19.7086	0	0	0	0	1	0	0	1
orf19.3823	ZDS1	0	0	0	0	1	0	0	1
orf19.5640	PEX5	0	0	1	0	0	0	0	1
orf19.925	orf19.925	0	0	1	0	0	0	0	1
orf19.2005	REG1	0	0	1	0	0	0	0	1
orf19.5001	CUP2	0	0	0	1	0	0	0	1
orf19.59	RE11	1	0	0	0	0	0	0	1
orf19.1450	orf19.1450	1	0	0	0	0	0	0	1
orf19.4222	SST2	0	0	0	0	1	0	0	1
orf19.3152	AMO2	0	0	1	0	0	0	0	1

orf19.4690	orf19.4690	0	0	1	0	0	0	0	1
orf19.4691	orf19.4691	0	0	0	0	1	0	0	1
orf19.4508	orf19.4508	0	0	1	0	0	0	0	1
orf19.4509	orf19.4509	0	0	1	0	0	0	0	1
orf19.4502	orf19.4502	0	0	1	0	0	0	0	1
orf19.3364	orf19.3364	0	0	1	0	0	0	0	1
orf19.5243	TRP3	1	0	0	0	0	0	0	1
orf19.4326	orf19.4326	0	1	0	0	0	0	0	1
orf19.940	BUD2	0	0	1	0	0	0	0	1
orf19.2838	orf19.2838	0	0	0	0	0	0	1	1
orf19.4299	MSW1	0	0	0	0	1	0	0	1
orf19.4592	HSX11	1	0	0	0	0	0	0	1
orf19.5758	SAL6	0	0	0	0	0	0	1	1
orf19.20	RTS1	0	0	0	0	1	0	0	1
orf19.5170	ENA21	0	0	0	0	1	0	0	1
orf19.4214	orf19.4214	0	0	0	0	0	0	1	1
orf19.24	RTA2	0	0	1	0	0	0	0	1
orf19.2012	NOT3	0	0	1	0	0	0	0	1
orf19.6011	SIN3	0	0	0	0	1	0	0	1
orf19.5897	orf19.5897	0	0	0	0	1	0	0	1
orf19.3734	GEF2	0	0	1	0	0	0	0	1
orf19.2903	AGO1	0	0	1	0	0	0	0	1
orf19.1634	orf19.1634	0	0	1	0	0	0	0	1
orf19.2908	orf19.2908	0	0	0	0	1	0	0	1
orf19.1632	orf19.1632	0	0	1	0	0	0	0	1
orf19.2998	TSR2	1	0	0	0	0	0	0	1
orf19.6321	PGA48	0	0	0	0	0	0	1	1
orf19.4851	TFA1	0	0	0	1	0	0	0	1
orf19.3638	PGA46	0	0	0	0	1	0	0	1
orf19.2906	PGA41	0	0	0	0	1	0	0	1
orf19.2910	PGA43	0	0	0	0	1	0	0	1
orf19.3765	RAX2	0	0	0	0	0	1	0	1
orf19.3980	orf19.3980	0	0	0	0	1	0	0	1
orf19.2917.1	orf19.2917.1	0	0	1	0	0	0	0	1
orf19.234	PHA2	1	0	0	0	0	0	0	1
orf19.5005	OSM2	0	0	0	0	1	0	0	1
orf19.1123	orf19.1123	0	0	0	0	0	1	0	1
orf19.4784	CRP1	0	0	0	0	1	0	0	1
orf19.231	APL2	0	0	1	0	0	0	0	1
orf19.272	FAA21	0	0	0	0	1	0	0	1
orf19.5288	IFE2	0	0	0	0	0	0	1	1
orf19.769	IFE1	1	0	0	0	0	0	0	1
orf19.1026	orf19.1026	1	0	0	0	0	0	0	1
orf19.5747	orf19.5747	0	0	0	0	1	0	0	1
orf19.5035	orf19.5035	1	0	0	0	0	0	0	1
orf19.5034	orf19.5034	0	1	0	0	0	0	0	1
orf19.5037	HRQ2	0	0	0	0	1	0	0	1

orf19.1891	APR1	1	0	0	0	0	0	0	1
orf19.5162	BCK1	0	0	0	0	1	0	0	1
orf19.4924	orf19.4924	0	0	0	0	0	1	0	1
orf19.666	orf19.666	0	0	0	0	1	0	0	1
orf19.1413	YFH1	0	0	0	0	1	0	0	1
orf19.6691	orf19.6691	0	0	0	0	0	1	0	1
orf19.6693	orf19.6693	0	0	1	0	0	0	0	1
orf19.2507	ARP9	0	0	1	0	0	0	0	1
orf19.5623	ARP4	0	0	0	0	1	0	0	1
orf19.2641	ARP1	0	0	0	0	1	0	0	1
orf19.6450	orf19.6450	1	0	0	0	0	0	0	1
orf19.6456	orf19.6456	0	0	0	0	0	1	0	1
orf19.6457	orf19.6457	0	0	0	0	1	0	0	1
orf19.5322	orf19.5322	1	0	0	0	0	0	0	1
orf19.2154	HXK1	1	0	0	0	0	0	0	1
orf19.4242	CST20	1	0	0	0	0	0	0	1
orf19.5817	orf19.5817	0	0	1	0	0	0	0	1
orf19.302	orf19.302	0	0	0	0	1	0	0	1
orf19.1324	RAD2	0	0	1	0	0	0	0	1
orf19.5061	ADE5,7	0	0	0	0	1	0	0	1
orf19.4275	RAD9	0	0	0	0	1	0	0	1
orf19.2228	orf19.2228	0	0	0	0	0	0	1	1
orf19.29	orf19.29	0	0	1	0	0	0	0	1
orf19.2227	orf19.2227	0	0	1	0	0	0	0	1
orf19.22	orf19.22	0	0	0	0	1	0	0	1
orf19.21	orf19.21	0	0	0	0	1	0	0	1
orf19.1935	orf19.1935	0	0	1	0	0	0	0	1
orf19.1933	orf19.1933	0	0	0	0	1	0	0	1
orf19.5253	orf19.5253	0	0	0	0	0	1	0	1
orf19.5921	orf19.5921	0	0	0	0	1	0	0	1
orf19.645.1	VMA13	0	0	0	0	1	0	0	1
orf19.740	HAP41	0	0	0	1	0	0	0	1
orf19.6033	CMP1	0	0	0	0	0	0	1	1
orf19.804	orf19.804	0	0	0	0	0	0	1	1
orf19.805	orf19.805	0	0	0	1	0	0	0	1
orf19.7073	orf19.7073	0	0	0	0	1	0	0	1
orf19.7079	orf19.7079	0	0	1	0	0	0	0	1
orf19.6679	orf19.6679	0	0	0	1	0	0	0	1
orf19.2138	ILS1	0	0	0	1	0	0	0	1
orf19.6852	orf19.6852	0	0	0	0	1	0	0	1
orf19.3086	orf19.3086	0	0	1	0	0	0	0	1
orf19.3083	orf19.3083	0	0	0	0	0	0	1	1
orf19.3080	orf19.3080	0	0	1	0	0	0	0	1
orf19.7095	orf19.7095	0	0	0	0	1	0	0	1
orf19.2574	orf19.2574	0	0	1	0	0	0	0	1
orf19.7096	orf19.7096	0	1	0	0	0	0	0	1
orf19.2832	INN1	0	0	0	0	0	1	0	1

orf19.3777	orf19.3777	0	0	0	0	0	1	0	1
orf19.937	orf19.937	0	0	0	0	0	0	1	1
orf19.2684	orf19.2684	0	0	0	1	0	0	0	1
orf19.3177	orf19.3177	0	0	0	0	1	0	0	1
orf19.3175	orf19.3175	1	0	0	0	0	0	0	1
orf19.3211	RCF3	0	0	0	0	1	0	0	1
orf19.3798	orf19.3798	0	0	1	0	0	0	0	1
orf19.3796	DCR1	0	0	0	0	1	0	0	1
orf19.3797	orf19.3797	0	0	0	0	1	0	0	1
orf19.2365	POL2	0	0	1	0	0	0	0	1
orf19.4511	orf19.4511	0	0	1	0	0	0	0	1
orf19.6628	orf19.6628	0	0	0	0	1	0	0	1
orf19.2779	orf19.2779	0	0	0	0	0	1	0	1
orf19.22.1	orf19.22.1	0	0	0	0	1	0	0	1
orf19.7300	orf19.7300	0	0	0	0	1	0	0	1
orf19.2471	GIM5	1	0	0	0	0	0	0	1
orf19.7083	DCC1	0	0	0	0	1	0	0	1
orf19.56	ARG2	0	0	0	0	1	0	0	1
orf19.2827	orf19.2827	0	1	0	0	0	0	0	1
orf19.2822	orf19.2822	0	0	0	0	0	0	1	1
orf19.4332	orf19.4332	0	0	0	0	0	1	0	1
orf19.5776	TOM1	0	0	0	0	0	1	0	1
orf19.2828	orf19.2828	0	0	0	0	1	0	0	1
orf19.2474	PRC3	0	0	0	0	1	0	0	1
orf19.1401	EAP1	0	0	0	1	0	0	0	1
orf19.87	GPX1	0	0	0	0	1	0	0	1
orf19.4203	orf19.4203	0	0	0	0	0	0	1	1
orf19.5630	APA2	0	0	0	0	1	0	0	1
orf19.3552	orf19.3552	0	0	1	0	0	0	0	1
orf19.4028	orf19.4028	0	0	0	0	1	0	0	1
orf19.913.2	orf19.913.2	0	0	0	0	0	1	0	1
orf19.2917	orf19.2917	0	0	0	0	0	1	0	1
orf19.2914	orf19.2914	0	0	1	0	0	0	0	1
orf19.1661	DBP5	0	0	0	0	1	0	0	1
orf19.5015	MYO2	0	0	0	1	0	0	0	1
orf19.738	MYO5	0	0	1	0	0	0	0	1
orf19.4077	MIT1	0	0	0	1	0	0	0	1
orf19.2767	PGA59	0	0	0	0	0	0	1	1
orf19.2685	PGA54	0	0	1	0	0	0	0	1
orf19.5191	FGR6-1	0	0	0	0	0	0	1	1
orf19.5137	orf19.5137	0	0	0	1	0	0	0	1
orf19.5139	orf19.5139	1	0	0	0	0	0	0	1
orf19.100	orf19.100	0	0	0	0	1	0	0	1
orf19.3228	orf19.3228	0	0	1	0	0	0	0	1
orf19.5595	SHE3	0	0	0	0	0	0	1	1
orf19.3699	TEP1	0	0	0	0	1	0	0	1
orf19.7059	orf19.7059	0	0	0	0	1	0	0	1

orf19.5009	orf19.5009	0	0	0	0	1	0	0	1
orf19.1223	DBF2	0	0	1	0	0	0	0	1
orf19.653	orf19.653	0	1	0	0	0	0	0	1
orf19.120	orf19.120	0	1	0	0	0	0	0	1
orf19.1659	ALG8	0	0	0	0	0	1	0	1
orf19.1990	SNX4	1	0	0	0	0	0	0	1
orf19.1221	ALG2	0	0	0	0	0	1	0	1
orf19.4410	ALG1	0	0	0	0	1	0	0	1
orf19.2187	ALG7	0	0	1	0	0	0	0	1
orf19.1238	TUB4	0	0	1	0	0	0	0	1
orf19.2215	GLE1	0	0	0	0	0	0	1	1
orf19.1323	orf19.1323	0	0	0	0	1	0	0	1
orf19.6114	orf19.6114	0	0	1	0	0	0	0	1
orf19.4015	CAG1	0	0	0	0	1	0	0	1
orf19.5644	orf19.5644	1	0	0	0	0	0	0	1
orf19.6119	orf19.6119	0	0	1	0	0	0	0	1
orf19.5488	orf19.5488	0	0	0	0	1	0	0	1
orf19.5489	orf19.5489	0	0	0	0	1	0	0	1
orf19.3071	MIH1	1	0	0	0	0	0	0	1
orf19.5155	CHS6	0	0	1	0	0	0	0	1
orf19.5865	orf19.5865	0	0	1	0	0	0	0	1
orf19.5869	orf19.5869	0	0	1	0	0	0	0	1
orf19.4322	DAP2	0	0	0	0	1	0	0	1
orf19.1836	APN2	0	0	0	0	1	0	0	1
orf19.239	orf19.239	1	0	0	0	0	0	0	1
orf19.2210	orf19.2210	0	0	1	0	0	0	0	1
orf19.4054	CTA24	0	0	0	0	0	1	0	1
orf19.2213	orf19.2213	1	0	0	0	0	0	0	1
orf19.4608	PDC12	0	0	0	1	0	0	0	1
orf19.5269	orf19.5269	0	0	0	0	1	0	0	1
orf19.5262	orf19.5262	0	0	0	0	1	0	0	1
orf19.4630	CPA1	0	0	0	0	1	0	0	1
orf19.6686	ENP2	0	0	0	0	0	0	1	1
orf19.349	orf19.349	0	0	0	0	1	0	0	1
orf19.341	orf19.341	0	0	0	0	1	0	0	1
orf19.346	orf19.346	0	1	0	0	0	0	0	1
orf19.797	BAT21	0	0	0	1	0	0	0	1
orf19.6065	orf19.6065	0	0	0	0	1	0	0	1
orf19.2367	orf19.2367	0	1	0	0	0	0	0	1
orf19.2362	orf19.2362	0	0	0	0	1	0	0	1
orf19.5050	MTO1	0	0	1	0	0	0	0	1
orf19.1814	orf19.1814	0	0	1	0	0	0	0	1
orf19.3091	orf19.3091	0	0	1	0	0	0	0	1
orf19.2549	orf19.2549	0	0	0	0	0	1	0	1
orf19.6014	RRS1	0	0	0	0	1	0	0	1
orf19.4884	WOR1	1	0	0	0	0	0	0	1
orf19.1789.1	LYS1	0	0	0	1	0	0	0	1



orf19.3762	orf19.3762	1	0	0	0	0	0	0	1
orf19.2143	orf19.2143	0	0	0	1	0	0	0	1
orf19.3163	orf19.3163	1	0	0	0	0	0	0	1
orf19.1445	ESC4	1	0	0	0	0	0	0	1
orf19.3780	orf19.3780	0	0	0	0	1	0	0	1
orf19.3783	orf19.3783	0	0	1	0	0	0	0	1
orf19.3787	orf19.3787	0	0	0	0	0	1	0	1
orf19.2454	PHO87	1	0	0	0	0	0	0	1
orf19.4520	orf19.4520	0	1	0	0	0	0	0	1
orf19.4521	orf19.4521	0	0	1	0	0	0	0	1
orf19.4834	orf19.4834	0	0	0	0	1	0	0	1
orf19.4529	orf19.4529	0	0	0	0	1	0	0	1
orf19.2991	HOL1	0	0	0	0	1	0	0	1
orf19.3304	orf19.3304	0	1	0	0	0	0	0	1
orf19.3431	orf19.3431	0	0	0	0	1	0	0	1
orf19.3430	orf19.3430	0	1	0	0	0	0	0	1
orf19.3635	orf19.3635	1	0	0	0	0	0	0	1
orf19.2580	HST2	1	0	0	0	0	0	0	1
orf19.4789	orf19.4789	1	0	0	0	0	0	0	1
orf19.5526	SEC20	0	0	0	0	0	0	1	1
orf19.4732	SEC24	0	0	0	0	1	0	0	1
orf19.3545	orf19.3545	0	0	1	0	0	0	0	1
orf19.3543	orf19.3543	0	0	0	1	0	0	0	1
orf19.2968	orf19.2968	0	0	0	0	1	0	0	1
orf19.4014	orf19.4014	1	0	0	0	0	0	0	1
orf19.2963	orf19.2963	0	1	0	0	0	0	0	1
orf19.6512	EXO70	0	0	1	0	0	0	0	1
orf19.4013	orf19.4013	0	0	0	0	1	0	0	1
orf19.581	orf19.581	0	0	1	0	0	0	0	1
orf19.1491	orf19.1491	0	0	1	0	0	0	0	1
orf19.6796	orf19.6796	1	0	0	0	0	0	0	1
orf19.1497	ZCF6	0	0	1	0	0	0	0	1
orf19.943	FET33	0	0	1	0	0	0	0	1
orf19.4656	orf19.4656	1	0	0	0	0	0	0	1
orf19.4306	orf19.4306	0	0	0	0	1	0	0	1
orf19.4076	MET10	0	0	0	0	0	1	0	1
orf19.2863.1	orf19.2863.1	0	0	0	1	0	0	0	1
orf19.4679	AGP2	0	0	1	0	0	0	0	1
orf19.6243	VPS34	0	0	0	0	1	0	0	1
orf19.156	FGR51	0	0	1	0	0	0	0	1
orf19.1143	orf19.1143	0	0	0	0	1	0	0	1
orf19.5163	SFI1	0	0	1	0	0	0	0	1
orf19.795	VPS36	0	0	1	0	0	0	0	1
orf19.7574	orf19.7574	0	0	0	0	1	0	0	1
orf19.4755	KEX2	0	0	0	0	1	0	0	1
orf19.4934	OP4	0	0	0	0	0	0	1	1
orf19.6266	orf19.6266	0	0	0	1	0	0	0	1

orf19.3746	IFC1	0	0	1	0	0	0	0	1
orf19.3749	IFC3	0	0	0	0	0	0	1	1
orf19.1524	SPR3	0	0	1	0	0	0	0	1
orf19.5019	orf19.5019	1	0	0	0	0	0	0	1
orf19.5959	NOP14	0	0	0	0	1	0	0	1
orf19.1008	orf19.1008	0	0	1	0	0	0	0	1
orf19.1009	orf19.1009	0	0	0	1	0	0	0	1
orf19.3370	DOT4	0	0	1	0	0	0	0	1
orf19.5557	MNN4-4	0	0	0	0	0	1	0	1
orf19.5783	orf19.5783	0	0	1	0	0	0	0	1
orf19.133	orf19.133	0	0	0	0	0	0	1	1
orf19.77.1	orf19.77.1	0	1	0	0	0	0	0	1
orf19.5780	orf19.5780	1	0	0	0	0	0	0	1
orf19.137	orf19.137	0	0	0	0	1	0	0	1
orf19.643	orf19.643	0	0	1	0	0	0	0	1
orf19.1942	SGE1	0	0	0	0	0	0	1	1
orf19.6477	orf19.6477	0	0	0	0	1	0	0	1
orf19.1310	orf19.1310	0	0	0	0	1	0	0	1
orf19.5306	orf19.5306	0	0	1	0	0	0	0	1
orf19.5499	orf19.5499	0	0	0	0	1	0	0	1
orf19.5495	orf19.5495	0	0	0	0	1	0	0	1
orf19.4082	DDR48	0	0	1	0	0	0	0	1
orf19.3756	CHR1	0	1	0	0	0	0	0	1
orf19.5879	orf19.5879	0	0	1	0	0	0	0	1
orf19.1633	UTP4	0	0	0	0	1	0	0	1
orf19.6789	orf19.6789	0	0	0	0	1	0	0	1
orf19.6786	orf19.6786	0	0	0	0	1	0	0	1
orf19.1958	orf19.1958	0	1	0	0	0	0	0	1
orf19.6275	orf19.6275	0	0	0	0	1	0	0	1
orf19.5270	orf19.5270	0	0	0	0	1	0	0	1
orf19.5274	orf19.5274	0	0	0	1	0	0	0	1
orf19.1290	XKS1	0	0	1	0	0	0	0	1
orf19.2911	SEC3	0	0	0	0	0	1	0	1
orf19.1842	orf19.1842	0	0	0	0	0	1	0	1
orf19.352	orf19.352	0	0	0	0	1	0	0	1
orf19.2598	VMA4	0	0	0	0	1	0	0	1
orf19.6307	orf19.6307	0	0	1	0	0	0	0	1
orf19.6305	orf19.6305	0	0	1	0	0	0	0	1
orf19.6654	orf19.6654	0	0	0	0	0	1	0	1
orf19.6308	orf19.6308	0	0	0	0	0	0	1	1
orf19.4773	AOX2	1	0	0	0	0	0	0	1
orf19.5244	MCD4	1	0	0	0	0	0	0	1
orf19.2558	orf19.2558	0	1	0	0	0	0	0	1
orf19.1333	SNG3	0	0	0	0	1	0	0	1
orf19.6899	orf19.6899	0	0	0	0	1	0	0	1
orf19.1756	GPD1	0	0	0	0	1	0	0	1
orf19.6893	orf19.6893	0	0	1	0	0	0	0	1

orf19.6897	orf19.6897	0	0	1	0	0	0	0	1
orf19.5292	AXL2	0	0	0	0	1	0	0	1
orf19.915	orf19.915	0	0	0	1	0	0	0	1
orf19.3156	orf19.3156	0	0	1	0	0	0	0	1
orf19.6249	HAK1	0	0	0	0	1	0	0	1
orf19.4820	orf19.4820	0	0	0	0	1	0	0	1
orf19.4825	orf19.4825	0	0	0	0	1	0	0	1
orf19.4532	orf19.4532	1	0	0	0	0	0	0	1
orf19.3269	GSL2	0	0	0	1	0	0	0	1
orf19.2495	GSL1	0	0	0	1	0	0	0	1
orf19.2795	orf19.2795	1	0	0	0	0	0	0	1
orf19.4785	PTC1	0	0	0	0	0	1	0	1
orf19.2538	PTC2	0	0	0	0	0	1	0	1
orf19.3705	PTC6	0	0	0	1	0	0	0	1
orf19.3446	orf19.3446	0	0	0	0	1	0	0	1
orf19.1796	orf19.1796	0	0	0	0	1	0	0	1
orf19.1799	GAP5	0	0	1	0	0	0	0	1
orf19.3449	orf19.3449	0	0	0	1	0	0	0	1
orf19.94	orf19.94	0	0	0	0	1	0	0	1
orf19.4799	orf19.4799	1	0	0	0	0	0	0	1
orf19.4220	orf19.4220	0	0	1	0	0	0	0	1
orf19.6972	SMI1B	0	0	0	0	0	1	0	1
orf19.4001	orf19.4001	0	0	0	0	1	0	0	1
orf19.2977	orf19.2977	0	0	0	1	0	0	0	1
orf19.2971	orf19.2971	0	0	0	0	1	0	0	1
orf19.3404	orf19.3404	0	0	0	0	1	0	0	1
orf19.4099	ECM17	0	0	0	0	1	0	0	1
orf19.5844	orf19.5844	0	0	0	1	0	0	0	1
orf19.1782.1	orf19.1782.1	0	0	0	0	1	0	0	1
orf19.4788	ARG5,6	1	0	0	0	0	0	0	1
orf19.4642	orf19.4642	0	0	1	0	0	0	0	1
orf19.4310	orf19.4310	1	0	0	0	0	0	0	1
orf19.6140	FRE30	1	0	0	0	0	0	0	1
orf19.5059	GCS1	0	0	0	0	1	0	0	1
orf19.2615	MDL1	0	0	0	0	1	0	0	1
orf19.1778	orf19.1778	0	0	1	0	0	0	0	1
orf19.5967	FGR44	0	1	0	0	0	0	0	1
orf19.4769	IPT1	0	0	0	0	1	0	0	1
orf19.1777	orf19.1777	0	0	1	0	0	0	0	1
orf19.3209	FGR42	1	0	0	0	0	0	0	1
orf19.6534.2	orf19.6534.2	0	0	0	0	1	0	0	1
orf19.1968.1	orf19.1968.1	0	0	0	0	0	0	1	1
orf19.5066	orf19.5066	0	0	0	0	1	0	0	1
orf19.3770	ARG8	0	0	1	0	0	0	0	1
orf19.1683	PPH21	0	1	0	0	0	0	0	1
orf19.5610	ARG3	1	0	0	0	0	0	0	1
orf19.6877	PNG2	0	1	0	0	0	0	0	1

orf19.652	orf19.652	0	0	1	0	0	0	0	1
orf19.6469	orf19.6469	0	0	0	0	1	0	0	1
orf19.1303	orf19.1303	0	0	1	0	0	0	0	1
orf19.1302	orf19.1302	0	0	0	0	1	0	0	1
orf19.1300	orf19.1300	0	0	0	0	1	0	0	1
orf19.1306	orf19.1306	0	0	0	0	1	0	0	1
orf19.3264	CCE1	0	0	1	0	0	0	0	1
orf19.4952	orf19.4952	0	0	0	0	0	1	0	1
orf19.5465	orf19.5465	0	0	0	0	0	1	0	1
orf19.4899	GCA1	0	0	0	1	0	0	0	1
orf19.999	GCA2	0	0	0	0	1	0	0	1
orf19.5688	orf19.5688	0	0	0	0	0	1	0	1
orf19.217	orf19.217	0	0	1	0	0	0	0	1
orf19.6797	orf19.6797	0	0	0	1	0	0	0	1
orf19.580	orf19.580	0	0	1	0	0	0	0	1
orf19.587	orf19.587	0	0	1	0	0	0	0	1
orf19.6790	orf19.6790	0	0	0	0	1	0	0	1
orf19.6269	orf19.6269	0	0	0	0	1	0	0	1
orf19.3841	orf19.3841	0	0	0	1	0	0	0	1
orf19.5203	orf19.5203	0	0	0	0	1	0	0	1
orf19.3140	orf19.3140	0	0	1	0	0	0	0	1
orf19.17	SCP1	0	0	1	0	0	0	0	1
orf19.2099	orf19.2099	1	0	0	0	0	0	0	1
orf19.2090	orf19.2090	0	0	1	0	0	0	0	1
orf19.2091	orf19.2091	0	0	1	0	0	0	0	1
orf19.5958	CDR2	0	0	0	1	0	0	0	1
orf19.7223	orf19.7223	0	1	0	0	0	0	0	1
orf19.7539.1	orf19.7539.1	0	0	1	0	0	0	0	1
orf19.5518	orf19.5518	1	0	0	0	0	0	0	1
orf19.6864	orf19.6864	0	0	1	0	0	0	0	1
orf19.6316	orf19.6316	0	0	0	0	0	0	1	1
orf19.6869	orf19.6869	0	0	1	0	0	0	0	1
orf19.5515	orf19.5515	1	0	0	0	0	0	0	1
orf19.5607	orf19.5607	1	0	0	0	0	0	0	1
orf19.2528	orf19.2528	0	0	0	1	0	0	0	1
orf19.3000	ORC1	0	0	0	0	1	0	0	1
orf19.6888	orf19.6888	0	0	1	0	0	0	0	1
orf19.1932	CFL4	0	0	1	0	0	0	0	1
orf19.1263	CFL1	0	0	1	0	0	0	0	1
orf19.5011	KAR9	1	0	0	0	0	0	0	1
orf19.6449	orf19.6449	0	0	0	0	0	1	0	1
orf19.7130	orf19.7130	1	0	0	0	0	0	0	1
orf19.1246	orf19.1246	0	0	1	0	0	0		0

B. Shown are mutations that are persistent, non-synonymous, and coupled to an increase in MIC.

ORF	Gene	PT1	PT7	PT9	PT14	PT15	PT43	PT59	SUM
orf19.736	SRB8	0	1	1	1	1	1	1	6
orf19.5045	orf19.5045	0	1	1	0	1	1	1	5
orf19.3188	TAC1	1	1	1	0	1	1	0	5
orf19.7029	orf19.7029	1	0	1	1	1	1	0	5
orf19.1606	orf19.1606	0	1	1	1	1	1	0	5
orf19.5592	orf19.5592	1	1	0	1	1	1	0	5
orf19.5596	orf19.5596	0	1	0	1	1	1	1	5
orf19.169	CHO2	0	1	1	0	1	1	1	5
orf19.4346	orf19.4346	0	1	1	0	1	1	1	5
orf19.6277	orf19.6277	1	1	0	1	1	1	0	5
orf19.1769	orf19.1769	0	1	0	1	0	1	1	4
orf19.2404	orf19.2404	1	0	1	0	0	1	1	4
orf19.2629	orf19.2629	0	0	1	0	1	1	1	4
orf19.1298	NUP84	1	0	1	0	1	1	0	4
orf19.4697	MDN1	0	1	1	0	1	0	1	4
orf19.1596	FGR28	0	0	1	0	1	1	1	4
orf19.1616	FGR23	0	1	1	0	1	0	1	4
orf19.3473	orf19.3473	0	1	0	1	0	1	1	4
orf19.2850	orf19.2850	0	1	1	0	1	0	1	4
orf19.5710	orf19.5710	1	1	0	0	1	0	1	4
orf19.2650	orf19.2650	0	0	1	0	1	1	1	4
orf19.4673	BMT9	0	1	1	1	0	1	0	4
orf19.7032	orf19.7032	0	0	1	0	1	1	1	4
orf19.2646	ZCF13	0	0	0	1	1	1	1	4
orf19.4557	orf19.4557	1	1	0	0	1	0	1	4
orf19.5297	orf19.5297	0	0	1	1	0	1	1	4
orf19.4655	OPT6	0	1	1	0	1	0	1	4
orf19.2747	RGT1	0	0	1	1	1	0	1	4
orf19.7472	IFF4	0	0	1	1	1	1	0	4
orf19.2168	orf19.2168	0	1	1	0	1	1	0	4
orf19.5038	orf19.5038	0	1	1	0	1	1	0	4
orf19.1808	orf19.1808	0	1	1	0	1	0	1	4
orf19.5597	POL5	0	1	0	0	1	1	1	4
orf19.4337	orf19.4337	1	0	1	0	1	0	1	4
orf19.230	orf19.230	1	0	1	0	1	1	0	4
orf19.2652	TEF4	1	0	1	0	1	1	0	4
orf19.649	orf19.649	0	1	1	0	0	1	1	4
orf19.4649	ZCF27	1	1	1	0	1	0	0	4
orf19.4643	orf19.4643	0	1	1	0	1	1	0	4
orf19.366	orf19.366	0	1	1	1	0	0	1	4
orf19.5510	orf19.5510	0	1	0	0	1	1	1	4
orf19.3629	DSE1	1	0	1	0	1	0	0	3
orf19.1766	orf19.1766	0	1	1	0	1	0	0	3
orf19.4510	IFA4	0	1	1	0	0	0	1	3

orf19.4961	STP2	1	1	0	1	0	0	0	3
orf19.115	orf19.115	0	1	0	0	1	0	1	3
orf19.371	orf19.371	0	0	1	1	0	0	1	3
orf19.5504	orf19.5504	1	0	0	0	1	1	0	3
orf19.2400	orf19.2400	0	0	1	0	0	1	1	3
orf19.4243	orf19.4243	0	1	1	0	1	0	0	3
orf19.4068	orf19.4068	1	1	1	0	0	0	0	3
orf19.3239	CTF18	1	1	1	0	0	0	0	3
orf19.3906	orf19.3906	0	1	1	0	1	0	0	3
orf19.2901	NUP60	0	0	1	0	1	1	0	3
orf19.3916	orf19.3916	0	0	1	0	1	0	1	3
orf19.7204	orf19.7204	0	1	0	0	0	1	1	3
orf19.2433	orf19.2433	1	1	0	0	1	0	0	3
orf19.3190	HAL9	0	1	1	0	0	0	1	3
orf19.4901	orf19.4901	0	0	0	0	1	1	1	3
orf19.7561	DEF1	0	0	0	1	1	1	0	3
orf19.175	orf19.175	0	0	1	0	0	1	1	3
orf19.1748	orf19.1748	0	1	1	0	1	0	0	3
orf19.1356	orf19.1356	0	0	0	1	1	1	0	3
orf19.2510	orf19.2510	0	0	1	0	1	1	0	3
orf19.1111	orf19.1111	0	0	1	1	0	1	0	3
orf19.4280	orf19.4280	0	1	0	0	1	0	1	3
orf19.3997	ADH1	1	0	0	0	0	1	1	3
orf19.1555	SAC3	0	0	1	1	1	0	0	3
orf19.1624.1	orf19.1624.1	0	1	1	0	0	1	0	3
orf19.1795	PUF3	0	0	1	1	0	1	0	3
orf19.4191.1	orf19.4191.1	0	1	1	0	1	0	0	3
orf19.6280	orf19.6280	0	1	0	1	0	0	1	3
orf19.894	orf19.894	1	1	1	0	0	0	0	3
orf19.3380	HWP2	0	0	1	0	1	1	0	3
orf19.3100	orf19.3100	0	1	0	0	1	0	1	3
orf19.92	orf19.92	0	0	0	0	1	1	1	3
orf19.6979	orf19.6979	1	1	0	0	0	1	0	3
orf19.1500	orf19.1500	1	1	0	0	0	0	1	3
orf19.5918	orf19.5918	0	1	1	0	1	0	0	3
orf19.3986	PPR1	0	1	0	0	1	0	1	3
orf19.1607	ALR1	0	1	0	1	0	1	0	3
orf19.1083	orf19.1083	0	1	0	0	1	1	0	3
orf19.4918	orf19.4918	0	0	0	1	1	0	1	3
orf19.4257	INT1	1	0	0	0	0	1	1	3
orf19.1400	orf19.1400	1	0	1	0	1	0	0	3
orf19.4715	orf19.4715	0	0	1	0	1	0	1	3
orf19.7023	orf19.7023	1	0	0	1	0	1	0	3
orf19.2724	orf19.2724	0	0	1	1	0	1	0	3
orf19.3706	orf19.3706	0	0	1	0	1	1	0	3
orf19.6544	LPI9	0	0	0	1	1	1	0	3
orf19.4369	orf19.4369	0	0	1	0	1	0	1	3

orf19.5141	orf19.5141	0	0	1	0	1	0	1	3
orf19.290	KRE5	1	0	1	0	1	0	0	3
orf19.194	orf19.194	0	0	1	0	0	1	1	3
orf19.6499	orf19.6499	0	0	1	0	1	1	0	3
orf19.2266	orf19.2266	1	0	0	0	1	1	0	3
orf19.7036	orf19.7036	0	1	0	0	1	1	0	3
orf19.2647	ZCF14	0	0	0	0	1	1	1	3
orf19.4394	orf19.4394	1	1	0	0	1	0	0	3
orf19.3613	orf19.3613	0	1	0	0	1	1	0	3
orf19.3603	orf19.3603	0	0	1	1	1	0	0	3
orf19.4348	orf19.4348	0	0	1	0	1	0	1	3
orf19.4080	orf19.4080	0	0	0	1	1	1	0	3
orf19.1608	orf19.1608	0	1	1	0	1	0	0	3
orf19.1798	TSC2	1	0	1	0	1	0	0	3
orf19.1113	orf19.1113	0	0	1	1	0	1	0	3
orf19.262	SMC3	0	0	1	1	0	1	0	3
orf19.5915	DUR35	0	0	1	0	1	1	0	3
orf19.6694	orf19.6694	1	1	1	0	0	0	0	3
orf19.4965	orf19.4965	1	0	0	0	0	1	1	3
orf19.4412	orf19.4412	0	1	1	0	1	0	0	3
orf19.1622	YCG1	0	1	0	0	1	1	0	3
orf19.1106	orf19.1106	0	0	1	1	0	1	0	3
orf19.267	orf19.267	0	1	1	0	0	1	0	3
orf19.5505	HIS7	0	1	0	0	1	0	1	3
orf19.4570	orf19.4570	0	1	1	0	1	0	0	3
orf19.4288	CTA7	0	0	0	0	1	1	1	3
orf19.4145	ZCF20	1	0	1	0	1	0	0	3
orf19.2879	IFF5	0	0	1	0	1	0	1	3
orf19.5854.1	orf19.5854.1	0	0	1	0	1	1	0	3
orf19.6999	orf19.6999	0	0	0	0	1	1	1	3
orf19.5621	orf19.5621	1	0	0	1	1	0	0	3
orf19.255	ZCF1	0	1	1	0	1	0	0	3
orf19.6592	orf19.6592	0	0	0	1	1	1	0	3
orf19.6919	orf19.6919	1	1	0	0	0	0	1	3
orf19.2761	orf19.2761	0	0	1	0	1	0	1	3
orf19.4404	PGA49	0	0	1	0	1	1	0	3
orf19.4225	LEU3	0	0	1	0	1	1	0	3
orf19.1772	orf19.1772	0	1	1	0	1	0	0	3
orf19.5924	ZCF31	0	0	1	0	1	1	0	3
orf19.7277	orf19.7277	0	1	0	0	1	1	0	3
orf19.2826	orf19.2826	0	0	1	0	1	1	0	3
orf19.5058	SMI1	0	0	0	1	1	1	0	3
orf19.5003	orf19.5003	0	1	0	1	0	1	0	3
orf19.2547	orf19.2547	0	1	1	0	0	1	0	3
orf19.3098	orf19.3098	0	0	1	0	1	0	1	3
orf19.3166	orf19.3166	1	0	1	0	1	0	0	3
orf19.4239	orf19.4239	0	0	1	0	1	0	1	3

orf19.4658	orf19.4658	0	1	1	0	0	0	1	3
orf19.229	orf19.229	0	0	1	1	0	1	0	3
orf19.1327	RBT1	0	0	1	1	1	0	0	3
orf19.4958	ECM25	0	1	0	0	1	0	1	3
orf19.7342	AXL1	0	0	0	1	1	1	0	3
orf19.2797	orf19.2797	0	0	0	1	1	0	1	3
orf19.1551	orf19.1551	0	1	1	1	0	0	0	3
orf19.1779	MP65	0	0	1	0	1	1	0	3
orf19.5065	orf19.5065	0	1	0	0	1	1	0	3
orf19.102	orf19.102	0	0	0	0	1	1	1	3
orf19.3937	orf19.3937	0	0	1	0	1	1	0	3
orf19.5949	FAS2	1	1	0	0	0	1	0	3
orf19.746	orf19.746	1	0	1	0	0	1	0	3
orf19.745	VAC8	0	0	0	1	0	1	1	3
orf19.6260	orf19.6260	0	1	0	0	1	1	0	3
orf19.6862	orf19.6862	0	0	1	0	1	1	0	3
orf19.4683	MLP1	1	0	1	0	1	0	0	3
orf19.2929	GSC1	1	1	0	0	0	0	0	2
orf19.2383	YKU80	0	0	1	0	0	0	1	2
orf19.4251	ZCF22	0	0	1	0	1	0	0	2
orf19.3216	orf19.3216	0	0	0	0	1	1	0	2
orf19.3214	orf19.3214	0	0	1	1	0	0	0	2
orf19.4339	VPS4	0	1	1	0	0	0	0	2
orf19.76	SPB1	0	0	0	0	1	1	0	2
orf19.1768	orf19.1768	0	0	1	0	1	0	0	2
orf19.2893	orf19.2893	0	0	0	0	1	0	1	2
orf19.114	orf19.114	0	0	0	0	1	0	1	2
orf19.2624	orf19.2624	0	1	1	0	0	0	0	2
orf19.5138	IFA21	0	0	1	0	1	0	0	2
orf19.1108	HAM1	0	0	0	0	1	1	0	2
orf19.113	CIP1	0	0	0	0	1	0	1	2
orf19.4498	orf19.4498	0	1	0	0	0	1	0	2
orf19.4248	orf19.4248	1	0	0	1	0	0	0	2
orf19.4245	orf19.4245	0	0	0	0	0	1	1	2
orf19.3267	orf19.3267	0	1	1	0	0	0	0	2
orf19.4066	orf19.4066	0	0	1	0	1	0	0	2
orf19.1684	orf19.1684	0	0	1	0	0	1	0	2
orf19.1681	orf19.1681	0	1	0	0	1	0	0	2
orf19.3601	orf19.3601	0	0	0	0	1	1	0	2
orf19.6420	PGA13	0	0	1	0	0	1	0	2
orf19.301	PGA18	0	0	1	0	1	0	0	2
orf19.3463	orf19.3463	0	0	0	0	1	0	1	2
orf19.5043	orf19.5043	0	0	0	0	1	0	1	2
orf19.1828	BUD16	1	0	0	0	1	0	0	2
orf19.5999	DYN1	0	0	0	0	1	1	0	2
orf19.3910	orf19.3910	0	0	1	0	1	0	0	2
orf19.1366	orf19.1366	0	0	1	0	1	0	0	2



orf19.1210	orf19.1210	1	1	0	0	0	0	0	2
orf19.922	ERG11	0	0	1	0	0	0	1	2
orf19.2768	AMS1	0	0	1	0	1	0	0	2
orf19.923	THR1	0	0	1	0	0	0	1	2
orf19.787	orf19.787	0	1	0	0	0	0	1	2
orf19.5714	SAP1	1	0	0	0	0	0	1	2
orf19.2505	orf19.2505	0	0	1	0	1	0	0	2
orf19.4232	PTH1	0	0	1	0	1	0	0	2
orf19.4270	orf19.4270	0	1	0	0	1	0	0	2
orf19.1698	orf19.1698	1	0	0	0	1	0	0	2
orf19.1531	orf19.1531	0	1	1	0	0	0	0	2
orf19.1532	SAM37	0	0	1	0	0	1	0	2
orf19.5705	NAM2	0	0	0	0	1	0	1	2
orf19.6336	PGA25	0	1	0	0	1	0	0	2
orf19.3470	orf19.3470	0	0	0	0	1	0	1	2
orf19.5729	FGR17	0	0	0	0	1	0	1	2
orf19.124	CIC1	0	1	0	0	1	0	0	2
orf19.1834	orf19.1834	0	0	0	0	1	0	1	2
orf19.5057	orf19.5057	0	1	1	0	0	0	0	2
orf19.5053	orf19.5053	0	0	1	0	1	0	0	2
orf19.5051	orf19.5051	0	0	1	1	0	0	0	2
orf19.5496	AVT1	0	0	0	0	1	1	0	2
orf19.3907	orf19.3907	0	0	0	0	1	0	1	2
orf19.1359	orf19.1359	0	0	1	0	1	0	0	2
orf19.2884	CDC68	0	0	1	0	1	0	0	2
orf19.1509	ROD1	0	0	1	0	0	0	1	2
orf19.3878	orf19.3878	0	0	1	0	0	1	0	2
orf19.1492	PRP39	0	1	1	0	0	0	0	2
orf19.7215	orf19.7215	1	0	0	0	0	0	1	2
orf19.2604	orf19.2604	0	1	0	0	0	0	1	2
orf19.4265	UAP1	0	0	0	0	1	1	0	2
orf19.7369	orf19.7369	1	0	0	0	1	0	0	2
orf19.7366	orf19.7366	0	0	0	0	1	0	1	2
orf19.7365	orf19.7365	0	1	0	0	1	0	0	2
orf19.2516	orf19.2516	0	0	0	1	1	0	0	2
orf19.3648	orf19.3648	0	0	0	0	1	1	0	2
orf19.4465	orf19.4465	0	1	0	0	1	0	0	2
orf19.6536	IQG1	1	0	0	0	1	0	0	2
orf19.4133	orf19.4133	0	1	1	0	0	0	0	2
orf19.4131	orf19.4131	0	0	1	0	1	0	0	2
orf19.4234	orf19.4234	0	0	0	0	1	1	0	2
orf19.5736	ALS5	0	1	1	0	0	0	0	2
orf19.1816	ALS3	0	0	0	0	1	1	0	2
orf19.6424	orf19.6424	0	0	1	1	0	0	0	2
orf19.1762	OCA1	0	1	0	0	0	1	0	2
orf19.3077	VID21	0	0	1	0	1	0	0	2
orf19.5730	orf19.5730	0	0	0	0	1	0	1	2

orf19.5552	orf19.5552	0	1	0	0	1	0	0	2
orf19.5380	LYS144	0	0	1	0	1	0	0	2
orf19.2457	orf19.2457	1	0	0	0	1	0	0	2
orf19.2452	orf19.2452	1	1	0	0	0	0	0	2
orf19.90	orf19.90	0	0	0	0	0	1	1	2
orf19.2296	orf19.2296	0	0	0	1	1	0	0	2
orf19.2675	orf19.2675	0	0	1	0	1	0	0	2
orf19.6973	orf19.6973	0	0	0	0	1	1	0	2
orf19.1755	SET2	0	0	0	0	1	1	0	2
orf19.4459	orf19.4459	0	0	0	0	1	0	1	2
orf19.6317	ADE6	0	0	0	0	1	0	1	2
orf19.4148	orf19.4148	0	0	1	0	1	0	0	2
orf19.4266	SPR28	0	0	0	0	1	1	0	2
orf19.4705	orf19.4705	0	0	1	0	1	0	0	2
orf19.3180	orf19.3180	0	0	1	0	1	0	0	2
orf19.4703	orf19.4703	0	0	1	0	0	1	0	2
orf19.1119	MTR10	0	0	1	0	0	1	0	2
orf19.2775	IDI1	0	0	1	0	1	0	0	2
orf19.1656	orf19.1656	1	0	1	0	0	0	0	2
orf19.6480	orf19.6480	0	1	0	0	1	0	0	2
orf19.5167	IFM1	1	0	0	0	1	0	0	2
orf19.1240	orf19.1240	0	0	1	0	1	0	0	2
orf19.5728	orf19.5728	0	1	0	0	0	0	1	2
orf19.6573	BEM2	1	0	0	1	0	0	0	2
orf19.7499	orf19.7499	1	0	0	0	0	0	1	2
orf19.427	orf19.427	0	1	0	0	1	0	0	2
orf19.2445	orf19.2445	0	1	0	0	1	0	0	2
orf19.6494	WHI3	0	0	0	0	1	1	0	2
orf19.2763	orf19.2763	0	0	1	0	1	0	0	2
orf19.245	DDC1	0	0	0	1	1	0	0	2
orf19.4279	MNN1	0	0	1	0	1	0	0	2
orf19.2881	MNN4	0	0	1	0	1	0	0	2
orf19.7547	orf19.7547	0	0	0	1	0	1	0	2
orf19.3627	orf19.3627	0	0	1	1	0	0	0	2
orf19.3624	orf19.3624	0	0	1	0	1	0	0	2
orf19.3621	orf19.3621	1	0	0	0	0	1	0	2
orf19.5568	VPS51	0	0	0	0	1	0	1	2
orf19.2688	NAN1	0	0	1	0	1	0	0	2
orf19.4627	orf19.4627	1	0	0	0	1	0	0	2
orf19.4405	PPS1	0	0	1	0	0	1	0	2
orf19.2847	orf19.2847	0	1	0	0	0	0	1	2
orf19.4713	orf19.4713	0	0	1	0	1	0	0	2
orf19.1662	orf19.1662	0	0	1	0	1	0	0	2
orf19.130	orf19.130	0	0	0	0	1	1	0	2
orf19.522	orf19.522	0	0	1	0	1	0	0	2
orf19.4640	PWP1	1	0	0	0	0	1	0	2
orf19.1253	PHO4	0	0	1	0	0	0	1	2

orf19.1096	orf19.1096	0	0	0	0	1	1	0	2
orf19.1091	orf19.1091	1	0	0	0	0	1	0	2
orf19.5976	orf19.5976	0	0	0	1	0	1	0	2
orf19.5970	orf19.5970	0	0	0	0	1	1	0	2
orf19.2182	BLM3	0	0	1	0	1	0	0	2
orf19.188	orf19.188	0	0	0	1	0	1	0	2
orf19.1893	orf19.1893	1	0	0	0	1	0	0	2
orf19.1878	orf19.1878	1	0	0	0	1	0	0	2
orf19.2274	orf19.2274	0	0	0	1	0	1	0	2
orf19.243	OXR1	0	0	1	0	1	0	0	2
orf19.6349	RVS162	0	0	0	0	0	1	1	2
orf19.7027	orf19.7027	0	0	1	0	0	1	0	2
orf19.1527	orf19.1527	1	0	1	0	0	0	0	2
orf19.3637	orf19.3637	0	0	1	0	1	0	0	2
orf19.3633	orf19.3633	0	0	1	1	0	0	0	2
orf19.3203	RCY1	0	1	0	0	1	0	0	2
orf19.4366	orf19.4366	0	1	1	0	0	0	0	2
orf19.4764	orf19.4764	0	0	0	0	1	1	0	2
orf19.248	APL5	0	0	0	0	1	1	0	2
orf19.4284	BUR2	0	0	1	0	1	0	0	2
orf19.1265	orf19.1265	0	0	1	0	1	0	0	2
orf19.1266	orf19.1266	0	0	1	0	1	0	0	2
orf19.5701	orf19.5701	0	0	0	0	1	1	0	2
orf19.5704	orf19.5704	0	0	0	1	1	0	0	2
orf19.6588	NBP2	0	1	0	0	0	0	1	2
orf19.193	orf19.193	0	0	1	0	0	0	1	2
orf19.6492	orf19.6492	0	1	0	0	1	0	0	2
orf19.1849	orf19.1849	1	0	0	0	0	0	1	2
orf19.2399	orf19.2399	0	0	1	1	0	0	0	2
orf19.1841	orf19.1841	0	1	0	0	0	0	1	2
orf19.2265	orf19.2265	1	0	0	0	1	0	0	2
orf19.731	EMP46	0	1	0	0	1	0	0	2
orf19.6921	orf19.6921	0	0	0	0	1	0	1	2
orf19.3829	PHR1	1	0	0	0	1	0	0	2
orf19.1325	ECM38	0	0	1	0	1	0	0	2
orf19.7038	orf19.7038	0	1	0	0	0	1	0	2
orf19.7034	orf19.7034	0	0	0	0	0	1	1	2
orf19.2733	orf19.2733	0	0	1	0	0	0	1	2
orf19.6478	YCF1	1	0	0	0	1	0	0	2
orf19.3735	orf19.3735	0	0	1	0	0	0	1	2
orf19.2137	orf19.2137	0	0	0	0	1	0	1	2
orf19.2476	orf19.2476	0	1	0	0	1	0	0	2
orf19.4553	orf19.4553	0	1	0	0	1	0	0	2
orf19.3604	orf19.3604	0	0	0	0	1	0	1	2
orf19.3607	orf19.3607	0	0	0	0	1	1	0	2
orf19.2370	DSL1	0	1	0	0	0	1	0	2
orf19.101	RIM9	0	0	0	1	0	1	0	2

orf19.4771	orf19.4771	0	0	0	0	1	1	0	2
orf19.3443	OYE2	0	1	0	0	1	0	0	2
orf19.4704	ARO1	0	0	1	0	1	0	0	2
orf19.6387	HSP104	0	1	0	0	0	1	0	2
orf19.5177	orf19.5177	1	0	1	0	0	0	0	2
orf19.1075	orf19.1075	1	0	0	0	1	0	0	2
orf19.718	RRN11	0	1	0	0	1	0	0	2
orf19.6152	orf19.6152	1	0	1	0	0	0	0	2
orf19.276	orf19.276	0	0	1	0	1	0	0	2
orf19.2258	orf19.2258	0	0	0	1	1	0	0	2
orf19.2259	orf19.2259	0	0	1	0	1	0	0	2
orf19.1296	orf19.1296	0	1	1	0	0	0	0	2
orf19.7194	orf19.7194	0	0	0	0	0	1	1	2
orf19.7519	orf19.7519	1	1	0	0	0	0	0	2
orf19.7044	RIM15	0	0	1	1	0	0	0	2
orf19.1345	LIP8	1	0	0	0	1	0	0	2
orf19.2740	orf19.2740	0	0	1	0	1	0	0	2
orf19.3422	FMP27	0	0	0	0	1	0	1	2
orf19.4963	orf19.4963	1	0	0	0	0	1	0	2
orf19.3433	OYE23	0	0	0	0	1	1	0	2
orf19.4414	orf19.4414	1	0	1	0	0	0	0	2
orf19.6977	GPI1	0	1	0	0	1	0	0	2
orf19.3417	ACF2	0	0	0	0	1	0	1	2
orf19.3617	orf19.3617	1	0	0	0	0	0	1	2
orf19.3615	orf19.3615	0	1	1	0	0	0	0	2
orf19.3610	orf19.3610	0	0	0	0	1	1	0	2
orf19.2678	BUB1	0	0	1	0	1	0	0	2
orf19.4349	orf19.4349	0	0	1	0	0	0	1	2
orf19.2819	orf19.2819	0	0	1	0	1	0	0	2
orf19.4744	orf19.4744	0	1	0	0	1	0	0	2
orf19.4646	UEC1	0	1	0	0	0	0	1	2
orf19.1690	TOS1	0	0	0	0	1	1	0	2
orf19.2238	LTE1	0	0	1	0	0	1	0	2
orf19.1610	orf19.1610	0	0	1	0	1	0	0	2
orf19.4184	orf19.4184	0	0	1	0	1	0	0	2
orf19.5328	GCN1	0	0	1	0	1	0	0	2
orf19.4318	MIG1	0	0	1	0	0	0	1	2
orf19.4568	ZCF25	0	0	1	0	1	0	0	2
orf19.5295	orf19.5295	0	0	1	0	1	0	0	2
orf19.2216	PDS5	0	0	1	0	1	0	0	2
orf19.1041	orf19.1041	0	1	0	1	0	0	0	2
orf19.1719	SGA1	0	0	0	1	1	0	0	2
orf19.6913	GCN2	0	0	1	0	1	0	0	2
orf19.4403	VPS11	0	0	1	0	1	0	0	2
orf19.7071	FGR2	0	0	0	0	1	1	0	2
orf19.6832	orf19.6832	0	0	0	0	0	1	1	2
orf19.1821	orf19.1821	0	0	0	0	1	0	1	2

orf19.265	orf19.265	0	0	1	0	1	0	0	2
orf19.48	orf19.48	0	1	0	0	0	0	1	2
orf19.6580	orf19.6580	0	0	0	0	1	1	0	2
orf19.6901	orf19.6901	1	0	1	0	0	0	0	2
orf19.7051	orf19.7051	1	0	0	0	1	0	0	2
orf19.7052	orf19.7052	0	0	1	0	1	0	0	2
orf19.5723	POX1	0	1	0	0	0	1	0	2
orf19.7473	orf19.7473	0	1	1	0	0	0	0	2
orf19.1166	CTA3	0	0	0	0	1	0	1	2
orf19.4175	TOK1	0	0	1	0	1	0	0	2
orf19.1595	orf19.1595	0	1	1	0	0	0	0	2
orf19.4750	orf19.4750	0	0	0	0	1	1	0	2
orf19.1624	orf19.1624	0	0	1	0	1	0	0	2
orf19.5713	YMX6	1	0	0	0	1	0	0	2
orf19.4392	DEM1	0	0	1	1	0	0	0	2
orf19.2752	ADR1	0	0	0	1	1	0	0	2
orf19.1192	DNA2	0	0	0	0	1	0	1	2
orf19.3969	SFL2	0	0	0	0	1	1	0	2
orf19.570	IFF8	0	0	1	0	0	0	1	2
orf19.5752	orf19.5752	0	1	0	0	0	0	1	2
orf19.6136	orf19.6136	0	1	1	0	0	0	0	2
orf19.3976	orf19.3976	0	0	0	0	1	0	1	2
orf19.5620	orf19.5620	1	0	0	0	0	1	0	2
orf19.258	orf19.258	0	0	0	0	1	1	0	2
orf19.257	orf19.257	0	0	1	0	1	0	0	2
orf19.251	orf19.251	0	0	0	0	1	1	0	2
orf19.36	orf19.36	0	1	0	1	0	0	0	2
orf19.5934	orf19.5934	0	0	0	0	1	1	0	2
orf19.5935	orf19.5935	0	0	1	1	0	0	0	2
orf19.6918	orf19.6918	0	0	1	1	0	0	0	2
orf19.810	orf19.810	0	0	1	0	0	1	0	2
orf19.4315	orf19.4315	0	0	1	0	1	0	0	2
orf19.929	orf19.929	0	1	1	0	0	0	0	2
orf19.1251	BRN1	0	0	1	0	1	0	0	2
orf19.2165	orf19.2165	0	0	1	0	1	0	0	2
orf19.1456	orf19.1456	0	0	0	1	0	1	0	2
orf19.7001	YCK2	0	0	0	0	1	0	1	2
orf19.3367	orf19.3367	0	0	1	0	1	0	0	2
orf19.2760	orf19.2760	0	0	1	0	1	0	0	2
orf19.3368	orf19.3368	0	0	0	1	1	0	0	2
orf19.4325	orf19.4325	0	0	1	0	0	1	0	2
orf19.2835	orf19.2835	0	0	1	0	0	0	1	2
orf19.5148	CYR1	0	0	1	0	0	0	1	2
orf19.4136	YBL053	0	0	1	0	1	0	0	2
orf19.3803	MNN22	1	0	1	0	0	0	0	2
orf19.1714	PGA44	0	0	1	0	0	0	1	2
orf19.2907	PGA42	0	0	1	0	1	0	0	2

orf19.3984	orf19.3984	0	0	0	0	1	0	1	2
orf19.1121	orf19.1121	0	1	1	0	0	0	0	2
orf19.3429	FGR47	0	0	0	0	1	0	1	2
orf19.1774	orf19.1774	0	0	1	0	1	0	0	2
orf19.868	ADAEC	0	0	1	1	0	0	0	2
orf19.6690	orf19.6690	0	0	1	1	0	0	0	2
orf19.6698	orf19.6698	0	1	0	0	0	0	1	2
orf19.6453	orf19.6453	0	1	0	0	1	0	0	2
orf19.1338	orf19.1338	1	1	0	0	0	0	0	2
orf19.3965	orf19.3965	0	1	0	0	1	0	0	2
orf19.4167	orf19.4167	0	1	0	0	1	0	0	2
orf19.2465	POL32	0	1	0	0	1	0	0	2
orf19.246	orf19.246	0	0	1	1	0	0	0	2
orf19.719	orf19.719	0	0	1	0	0	0	1	2
orf19.7274	orf19.7274	0	1	0	1	0	0	0	2
orf19.3773	CDL1	0	1	1	0	0	0	0	2
orf19.2682	orf19.2682	0	0	1	0	1	0	0	2
orf19.2680	orf19.2680	1	0	1	0	0	0	0	2
orf19.1670	BRO1	0	0	0	0	1	1	0	2
orf19.2175	orf19.2175	0	0	1	0	1	0	0	2
orf19.3170	orf19.3170	0	0	1	0	0	1	0	2
orf19.3793	orf19.3793	0	0	1	0	0	1	0	2
orf19.1680	TFP1	0	1	1	0	0	0	0	2
orf19.4680	orf19.4680	0	0	1	0	1	0	0	2
orf19.4515	orf19.4515	1	0	1	0	0	0	0	2
orf19.2778	orf19.2778	0	0	0	0	1	1	0	2
orf19.2770	orf19.2770	0	1	1	0	0	0	0	2
orf19.3428	orf19.3428	0	0	0	0	1	1	0	2
orf19.4135	PRC2	0	0	1	0	1	0	0	2
orf19.4305.1	orf19.4305.1	0	1	0	0	0	1	0	2
orf19.4209	orf19.4209	0	0	0	0	0	1	1	2
orf19.2915	orf19.2915	0	0	1	0	1	0	0	2
orf19.6294	MYO1	0	0	1	0	1	0	0	2
orf19.1824	PGA50	0	0	0	0	1	0	1	2
orf19.5134	orf19.5134	0	0	1	0	0	1	0	2
orf19.1843	ALG6	0	1	1	0	0	0	0	2
orf19.5648	orf19.5648	0	0	1	0	1	0	0	2
orf19.1326	orf19.1326	0	1	0	0	0	1	0	2
orf19.721	orf19.721	1	0	1	0	0	0	0	2
orf19.1763	IFR1	0	1	1	0	0	0	0	2
orf19.6891	RFC1	1	0	1	0	0	0	0	2
orf19.839	orf19.839	0	0	1	0	0	0	1	2
orf19.836	orf19.836	1	0	1	0	0	0	0	2
orf19.3592	JEM1	0	0	1	0	0	1	0	2
orf19.2368	orf19.2368	0	0	1	0	0	0	1	2
orf19.3825	RCE1	0	0	1	0	1	0	0	2
orf19.3781	orf19.3781	0	0	1	0	1	0	0	2

orf19.3784	orf19.3784	0	0	1	0	1	0	0	2
orf19.7475	PHO81	0	0	0	0	1	1	0	2
orf19.2397.3	orf19.2397.3	0	0	1	0	1	0	0	2
orf19.2781	orf19.2781	0	0	0	1	1	0	0	2
orf19.2786	orf19.2786	0	0	0	0	1	1	0	2
orf19.2784	orf19.2784	0	1	0	0	0	1	0	2
orf19.3437	orf19.3437	0	1	0	0	1	0	0	2
orf19.3434	TRY5	0	0	0	0	1	0	1	2
orf19.3439	orf19.3439	0	0	0	0	1	0	1	2
orf19.4707	orf19.4707	1	0	0	0	1	0	0	2
orf19.7030	SSR1	0	0	1	0	1	0	0	2
orf19.1495	orf19.1495	1	0	1	0	0	0	0	2
orf19.4213	FET31	0	0	0	0	1	0	1	2
orf19.4653	orf19.4653	0	0	1	0	1	0	0	2
orf19.1915	MPP10	0	0	1	0	0	0	1	2
orf19.1706	MET18	0	0	0	0	1	1	0	2
orf19.1144	orf19.1144	0	0	0	1	1	0	0	2
orf19.3897	orf19.3897	0	0	1	0	1	0	0	2
orf19.134	orf19.134	0	1	0	0	0	0	1	2
orf19.6143	orf19.6143	0	0	1	0	0	0	1	2
orf19.2847.1	orf19.2847.1	0	0	1	0	0	1	0	2
orf19.1314	orf19.1314	0	0	1	0	1	0	0	2
orf19.6476	orf19.6476	0	1	0	0	0	1	0	2
orf19.3945	orf19.3945	0	1	1	0	0	0	0	2
orf19.5300	orf19.5300	0	0	1	0	1	0	0	2
orf19.1839	RPA190	0	1	0	0	1	0	0	2
orf19.3187	ZNC1	0	1	1	0	0	0	0	2
orf19.5491	orf19.5491	0	0	0	0	0	1	1	2
orf19.8	orf19.8	0	0	1	0	0	1	0	2
orf19.9	orf19.9	0	0	0	1	0	1	0	2
orf19.5068	IRE1	0	0	0	0	1	0	1	2
orf19.4273	orf19.4273	0	0	0	0	1	1	0	2
orf19.6202	RBT4	0	1	0	0	0	1	0	2
orf19.2372	orf19.2372	0	0	1	0	1	0	0	2
orf19.4519	SUV3	0	1	1	0	0	0	0	2
orf19.4766	ARG81	0	1	0	0	1	0	0	2
orf19.2748	ARG83	0	0	0	0	1	1	0	2
orf19.1538	TLG2	0	1	0	1	0	0	0	2
orf19.3447	orf19.3447	0	0	0	1	1	0	0	2
orf19.1792	orf19.1792	0	0	0	0	1	0	1	2
orf19.1794	orf19.1794	0	1	0	0	1	0	0	2
orf19.1797	orf19.1797	0	1	0	0	0	0	1	2
orf19.1557	orf19.1557	0	0	1	0	0	1	0	2
orf19.6511	LIG1	0	0	1	0	1	0	0	2
orf19.3204	orf19.3204	0	0	1	0	1	0	0	2
orf19.3202	orf19.3202	0	0	1	0	1	0	0	2
orf19.1177	orf19.1177	0	0	0	1	0	0	1	2

orf19.107	orf19.107	0	0	0	0	1	0	1	2
orf19.1747	KIP2	0	0	0	0	1	1	0	2
orf19.1305	orf19.1305	0	0	1	0	1	0	0	2
orf19.748	orf19.748	0	0	1	0	1	0	0	2
orf19.216	orf19.216	1	0	0	0	1	0	0	2
orf19.215	orf19.215	1	0	1	0	0	0	0	2
orf19.849	orf19.849	1	0	0	0	0	1	0	2
orf19.3840	orf19.3840	0	0	0	1	0	1	0	2
orf19.1943	orf19.1943	0	1	0	0	1	0	0	2
orf19.6344	RBK1	0	1	0	0	0	1	0	2
orf19.6566	orf19.6566	0	0	1	0	1	0	0	2
orf19.697	orf19.697	0	0	1	0	0	0	1	2
orf19.6310	orf19.6310	0	0	0	1	1	0	0	2
orf19.6861	orf19.6861	0	0	1	0	1	0	0	2
orf19.6319	orf19.6319	1	1	0	0	0	0	0	2
orf19.1264	CFL2	1	0	1	0	0	0	0	2
orf19.5962	HGT4	0	1	0	0	1	0	0	2
orf19.3148	orf19.3148	0	0	1	0	0	1	0	2
orf19.2415	orf19.2415	0	0	1	0	0	0	1	2
orf19.2418	orf19.2418	0	0	1	0	0	0	1	2
orf19.1620	orf19.1620	0	0	0	0	0	1	0	1
orf19.6831	PRP5	0	1	0	0	0	0	0	1
orf19.4816	orf19.4816	0	1	0	0	0	0	0	1
orf19.3329	orf19.3329	0	0	0	1	0	0	0	1
orf19.7356	orf19.7356	0	0	0	0	1	0	0	1
orf19.7357	orf19.7357	0	0	0	0	1	0	0	1
orf19.7353	orf19.7353	0	0	0	0	1	0	0	1
orf19.4120	LAS1	0	0	1	0	0	0	0	1
orf19.1780	orf19.1780	0	0	0	0	1	0	0	1
orf19.4183	MUC1	0	0	0	0	1	0	0	1
orf19.3458	orf19.3458	1	0	0	0	0	0	0	1
orf19.1789	orf19.1789	0	0	0	0	1	0	0	1
orf19.1541	orf19.1541	0	0	1	0	0	0	0	1
orf19.1546	orf19.1546	0	0	1	0	0	0	0	1
orf19.1548	orf19.1548	0	0	0	0	1	0	0	1
orf19.5491.1	ATP14	0	0	1	0	0	0	0	1
orf19.2170	PHM7	0	0	1	0	0	0	0	1
orf19.4719	CWH41	0	0	1	0	0	0	0	1
orf19.260	SLD1	0	0	1	0	0	0	0	1
orf19.4258	orf19.4258	0	0	0	0	1	0	0	1
orf19.3213	orf19.3213	0	0	0	0	0	0	1	1
orf19.2839	CIRT4B	0	0	0	1	0	0	0	1
orf19.3219	orf19.3219	0	0	0	0	1	0	0	1
orf19.1631	ERG6	0	0	1	0	0	0	0	1
orf19.6026	ERG2	0	1	0	0	0	0	0	1
orf19.4606	ERG8	0	0	1	0	0	0	0	1
orf19.3616	ERG9	1	0	0	0	0	0	0	1



orf19.4078	orf19.4078	0	0	1	0	0	0	0	1
orf19.335	orf19.335	0	0	0	0	1	0	0	1
orf19.4676	orf19.4676	0	0	1	0	0	0	0	1
orf19.4672	orf19.4672	0	0	1	0	0	0	0	1
orf19.1212	orf19.1212	0	0	0	0	0	1	0	1
orf19.4101	orf19.4101	0	0	0	0	1	0	0	1
orf19.4106	orf19.4106	0	0	0	0	1	0	0	1
orf19.1160	orf19.1160	0	1	0	0	0	0	0	1
orf19.367	CNH1	0	0	1	0	0	0	0	1
orf19.2892	orf19.2892	0	0	0	0	1	0	0	1
orf19.2890	orf19.2890	0	0	1	0	0	0	0	1
orf19.2891	orf19.2891	0	0	0	0	1	0	0	1
orf19.593	FGR32	0	0	0	0	0	0	1	1
orf19.2873	TOP2	0	0	1	0	0	0	0	1
orf19.1767	orf19.1767	0	0	0	1	0	0	0	1
orf19.3159	UTP20	0	0	0	0	1	0	0	1
orf19.5031	SSK1	0	1	0	0	0	0	0	1
orf19.5074	orf19.5074	0	0	0	0	0	1	0	1
orf19.5430	BUD21	0	0	0	0	0	0	1	1
orf19.2131	orf19.2131	0	0	0	0	1	0	0	1
orf19.1371	orf19.1371	0	0	1	0	0	0	0	1
orf19.5676	orf19.5676	0	0	0	0	1	0	0	1
orf19.3926	RNY11	0	0	1	0	0	0	0	1
orf19.3929	orf19.3929	0	0	0	0	1	0	0	1
orf19.5561	RAV2	0	0	0	0	1	0	0	1
orf19.400	GCF1	0	0	0	0	0	1	0	1
orf19.5486.1	SMD2	0	0	0	0	1	0	0	1
orf19.390	CDC42	1	0	0	0	0	0	0	1
orf19.2715	RPC53	0	0	1	0	0	0	0	1
orf19.757	orf19.757	0	0	0	0	1	0	0	1
orf19.5692	orf19.5692	0	1	0	0	0	0	0	1
orf19.6422	SSY5	0	0	1	0	0	0	0	1
orf19.3480	orf19.3480	0	0	0	0	1	0	0	1
orf19.3859	orf19.3859	1	0	0	0	0	0	0	1
orf19.1207	orf19.1207	0	0	1	0	0	0	0	1
orf19.3631	STN1	0	0	0	0	0	1	0	1
orf19.5210	orf19.5210	0	0	1	0	0	0	0	1
orf19.5212	orf19.5212	0	0	1	0	0	0	0	1
orf19.1998	orf19.1998	0	0	1	0	0	0	0	1
orf19.816	DCK2	0	0	1	0	0	0	0	1
orf19.6164	orf19.6164	0	0	1	0	0	0	0	1
orf19.1993	orf19.1993	0	0	1	0	0	0	0	1
orf19.1822	UME6	0	0	0	0	0	0	1	1
orf19.1995	orf19.1995	0	0	1	0	0	0	0	1
orf19.690	PLB2	0	0	0	0	1	0	0	1
orf19.376	orf19.376	0	0	0	0	0	0	1	1
orf19.2988	orf19.2988	0	0	0	0	1	0	0	1

orf19.4451	RIA1	0	0	0	0	1	0	0	1
orf19.2081	POM152	0	0	1	0	0	0	0	1
orf19.1618	GFA1	0	0	1	0	0	0	0	1
orf19.4063	GPT1	0	0	0	0	1	0	0	1
orf19.686	orf19.686	0	0	0	0	0	1	0	1
orf19.1311	SPO75	0	0	0	0	1	0	0	1
orf19.6635	orf19.6635	0	0	0	0	1	0	0	1
orf19.7105	FAR1	0	0	1	0	0	0	0	1
orf19.4119	SPO72	0	0	1	0	0	0	0	1
orf19.651	LYP1	0	0	0	0	0	0	1	1
orf19.2537	orf19.2537	0	0	0	0	0	1	0	1
orf19.3054	RPN3	0	0	0	0	1	0	0	1
orf19.1299	RPN6	0	0	1	0	0	0	0	1
orf19.2539	orf19.2539	0	0	0	0	0	1	0	1
orf19.3457	SWD3	0	0	0	0	1	0	0	1
orf19.7177	KAP120	0	0	0	0	0	1	0	1
orf19.3139	orf19.3139	0	0	1	0	0	0	0	1
orf19.3135	orf19.3135	0	1	0	0	0	0	0	1
orf19.2401	orf19.2401	0	0	1	0	0	0	0	1
orf19.2532	PRS	0	0	1	0	0	0	0	1
orf19.6742	orf19.6742	1	0	0	0	0	0	0	1
orf19.5507	ENP1	0	0	0	0	0	1	0	1
orf19.3688	orf19.3688	1	0	0	0	0	0	0	1
orf19.3689	orf19.3689	1	0	0	0	0	0	0	1
orf19.7344	orf19.7344	0	0	0	0	1	0	0	1
orf19.7343	orf19.7343	0	0	0	0	1	0	0	1
orf19.3048	orf19.3048	0	1	0	0	0	0	0	1
orf19.3715	ASF1	0	0	0	0	0	1	0	1
orf19.1576	orf19.1576	0	0	1	0	0	0	0	1
orf19.1578	orf19.1578	0	0	1	0	0	0	0	1
orf19.5164	ECM39	0	0	1	0	0	0	0	1
orf19.4244	orf19.4244	0	1	0	0	0	0	0	1
orf19.4247	orf19.4247	1	0	0	0	0	0	0	1
orf19.4246	orf19.4246	0	0	1	0	0	0	0	1
orf19.4241	orf19.4241	1	0	0	0	0	0	0	1
orf19.4240	orf19.4240	0	0	0	0	1	0	0	1
orf19.3594	orf19.3594	0	0	0	0	1	0	0	1
orf19.3260	orf19.3260	0	0	0	0	1	0	0	1
orf19.834	orf19.834	0	0	1	0	0	0	0	1
orf19.4062	TRY2	0	0	0	0	1	0	0	1
orf19.1686	orf19.1686	0	0	1	0	0	0	0	1
orf19.2616	UGT51C1	0	0	0	0	1	0	0	1
orf19.1685	ZCF7	0	0	0	1	0	0	0	1
orf19.1682	orf19.1682	0	1	0	0	0	0	0	1
orf19.1649	RNA1	0	1	0	0	0	0	0	1
orf19.5674	PGA10	1	0	0	0	0	0	0	1
orf19.2878	PGA15	0	0	1	0	0	0	0	1

orf19.2018.2	orf19.2018.2	0	0	1	0	0	0	0	1
orf19.7251	WSC4	0	0	0	0	0	1	0	1
orf19.4665	orf19.4665	1	0	0	0	0	0	0	1
orf19.1416	COX11	0	0	1	0	0	0	0	1
orf19.4110	orf19.4110	0	0	0	0	1	0	0	1
orf19.4112	orf19.4112	0	0	1	0	0	0	0	1
orf19.4115	orf19.4115	0	0	0	0	0	1	0	1
orf19.4117	orf19.4117	0	0	0	0	0	0	1	1
orf19.1757	orf19.1757	0	0	1	0	0	0	0	1
orf19.4268	UTP13	0	1	0	0	0	0	0	1
orf19.4765	PGA6	0	0	0	0	1	0	0	1
orf19.3122.2	orf19.3122.2	0	0	0	0	1	0	0	1
orf19.5041	orf19.5041	0	0	1	0	0	0	0	1
orf19.3555	BUD14	0	1	0	0	0	0	0	1
orf19.3962	HAS1	0	0	0	0	0	0	1	1
orf19.1369	orf19.1369	0	0	1	0	0	0	0	1
orf19.4739	MSS116	0	0	0	0	1	0	0	1
orf19.4328	CCC2	0	0	0	0	1	0	0	1
orf19.4848	SKI3	0	0	0	0	1	0	0	1
orf19.353	ULP1	0	0	0	0	1	0	0	1
orf19.1295	VAS1	0	0	0	0	0	1	0	1
orf19.6041	RPO41	0	0	0	0	1	0	0	1
orf19.6247	orf19.6247	0	0	0	0	1	0	0	1
orf19.6244	orf19.6244	0	0	0	0	0	0	1	1
orf19.1215	orf19.1215	0	0	0	0	0	1	0	1
orf19.1214	orf19.1214	0	0	0	0	0	1	0	1
orf19.1217	orf19.1217	0	0	0	0	1	0	0	1
orf19.6240	orf19.6240	0	0	0	0	1	0	0	1
orf19.1219	orf19.1219	0	0	0	0	1	0	0	1
orf19.5221	orf19.5221	1	0	0	0	0	0	0	1
orf19.5223	orf19.5223	1	0	0	0	0	0	0	1
orf19.6248	orf19.6248	0	0	0	0	1	0	0	1
orf19.4033	PRP22	1	0	0	0	0	0	0	1
orf19.1981	orf19.1981	0	0	1	0	0	0	0	1
orf19.305	orf19.305	0	0	0	0	1	0	0	1
orf19.304	orf19.304	0	0	0	0	1	0	0	1
orf19.7594	orf19.7594	0	0	1	0	0	0	0	1
orf19.302	orf19.302	0	0	0	0	1	0	0	1
orf19.2735	SEN2	0	0	1	0	0	0	0	1
orf19.5938	SEN1	0	0	1	0	0	0	0	1
orf19.2320	orf19.2320	0	0	0	0	0	1	0	1
orf19.7203	orf19.7203	0	1	0	0	0	0	0	1
orf19.5145	SSP96	0	0	1	0	0	0	0	1
orf19.6625	orf19.6625	0	0	1	0	0	0	0	1
orf19.2198	FLC3	0	0	0	0	1	0	0	1
orf19.1813	FLC2	0	0	1	0	0	0	0	1
orf19.4867	SWE1	0	0	0	0	0	0	1	1

orf19.2184	orf19.2184	0	0	0	0	1	0	0	1
orf19.3125	orf19.3125	0	0	1	0	0	0	0	1
orf19.3124	orf19.3124	0	0	1	0	0	0	0	1
orf19.3120	orf19.3120	0	0	1	0	0	0	0	1
orf19.2823	RFG1	0	0	0	0	0	1	0	1
orf19.2431	orf19.2431	0	0	0	0	1	0	0	1
orf19.2723	HIT1	0	1	0	0	0	0	0	1
orf19.6928	SAP9	0	0	0	0	0	0	1	1
orf19.5585	SAP5	0	0	0	0	1	0	0	1
orf19.4875	orf19.4875	0	0	0	1	0	0	0	1
orf19.4872	orf19.4872	0	0	0	0	1	0	0	1
orf19.3697	orf19.3697	0	0	0	1	0	0	0	1
orf19.3694	orf19.3694	0	0	0	1	0	0	0	1
orf19.7376	orf19.7376	1	0	0	0	0	0	0	1
orf19.2509	orf19.2509	1	0	0	0	0	0	0	1
orf19.2500	orf19.2500	0	0	0	0	1	0	0	1
orf19.2051	orf19.2051	0	0	1	0	0	0	0	1
orf19.2506	orf19.2506	0	0	0	0	1	0	0	1
orf19.3950	MSM1	0	0	0	0	1	0	0	1
orf19.984	PHO8	1	0	0	0	0	0	0	1
orf19.1648	RAD50	0	0	0	0	1	0	0	1
orf19.4903	orf19.4903	0	0	0	0	1	0	0	1
orf19.6798	SSN6	0	0	0	0	0	1	0	1
orf19.4907	orf19.4907	0	0	0	0	1	0	0	1
orf19.4904	orf19.4904	0	0	0	0	1	0	0	1
orf19.4905	orf19.4905	0	0	0	0	0	0	1	1
orf19.3208	DAL52	0	1	0	0	0	0	0	1
orf19.2623	ECM22	0	0	1	0	0	0	0	1
orf19.3586	orf19.3586	0	1	0	0	0	0	0	1
orf19.4471	orf19.4471	0	0	0	0	0	0	1	1
orf19.3271	orf19.3271	0	0	1	0	0	0	0	1
orf19.3971	orf19.3971	0	0	0	0	1	0	0	1
orf19.4295	orf19.4295	0	0	0	0	0	1	0	1
orf19.939	NAM7	0	0	1	0	0	0	0	1
orf19.35.1	orf19.35.1	0	0	1	0	0	0	0	1
orf19.3675	GAL7	1	0	0	0	0	0	0	1
orf19.4866	CPP1	0	0	0	0	0	0	1	1
orf19.2044	PGA27	0	0	1	0	0	0	0	1
orf19.4615	orf19.4615	0	0	1	0	0	0	0	1
orf19.3477	orf19.3477	0	1	0	0	0	0	0	1
orf19.3476	orf19.3476	0	0	0	0	1	0	0	1
orf19.3093	MSH2	0	0	0	0	1	0	0	1
orf19.559	FGR14	0	0	0	0	1	0	0	1
orf19.3700	TOM70	0	0	0	0	1	0	0	1
orf19.5479	FGR12	0	0	0	0	1	0	0	1
orf19.4067	FGR18	0	0	0	0	1	0	0	1
orf19.5094	BUL1	0	0	0	0	1	0	0	1

orf19.4059	orf19.4059	0	0	0	0	1	0	0	1
orf19.3112	ZRT1	0	0	1	0	0	0	0	1
orf19.1585	ZRT2	0	0	1	0	0	0	0	1
orf19.105	HAL22	0	0	0	0	0	1	0	1
orf19.1439	IPK1	0	0	0	0	1	0	0	1
orf19.1563	ECM3	0	0	1	0	0	0	0	1
orf19.5299	ECM1	0	1	0	0	0	0	0	1
orf19.5052	orf19.5052	0	0	1	0	0	0	0	1
orf19.1089	PEX11	0	0	0	0	1	0	0	1
orf19.1831	orf19.1831	0	0	0	0	1	0	0	1
orf19.7282	PEX13	0	0	0	0	1	0	0	1
orf19.1805	PEX14	0	0	0	0	0	1	0	1
orf19.4635	NIP1	0	0	0	0	1	0	0	1
orf19.610	EFG1	0	0	0	0	0	1	0	1
orf19.1741	DIT1	0	0	1	0	0	0	0	1
orf19.2984	MST1	0	0	0	0	1	0	0	1
orf19.695	RGS2	0	0	0	0	0	0	1	1
orf19.1353	orf19.1353	0	1	0	0	0	0	0	1
orf19.3908	orf19.3908	0	0	1	0	0	0	0	1
orf19.3901	orf19.3901	0	0	0	0	1	0	0	1
orf19.407	GCD6	1	0	0	0	0	0	0	1
orf19.5459	orf19.5459	0	0	1	0	0	0	0	1
orf19.481	GCD1	0	0	0	0	1	0	0	1
orf19.5530	NAB3	0	0	0	0	1	0	0	1
orf19.2560	CDC60	0	0	1	0	0	0	0	1
orf19.775	orf19.775	0	0	0	0	1	0	0	1
orf19.3207	CCN1	0	0	0	0	0	0	1	1
orf19.6507	orf19.6507	0	0	1	0	0	0	0	1
orf19.3877	orf19.3877	0	0	1	0	0	0	0	1
orf19.3876	ZCF19	0	0	0	0	1	0	0	1
orf19.5239	orf19.5239	0	0	0	0	1	0	0	1
orf19.6508	orf19.6508	0	0	1	0	0	0	0	1
orf19.1229	orf19.1229	0	1	0	0	0	0	0	1
orf19.3240	ERG27	0	0	1	0	0	0	0	1
orf19.178	orf19.178	0	0	0	0	0	1	0	1
orf19.5558	RBF1	0	0	0	1	0	0	0	1
orf19.173	orf19.173	0	0	0	0	0	0	1	1
orf19.1944	GPR1	0	0	0	0	1	0	0	1
orf19.315	orf19.315	0	0	0	0	0	1	0	1
orf19.318	orf19.318	0	0	0	0	1	0	0	1
orf19.2332	orf19.2332	0	0	0	0	1	0	0	1
orf19.6347	orf19.6347	0	0	0	0	1	0	0	1
orf19.6612	orf19.6612	1	0	0	0	0	0	0	1
orf19.6342	orf19.6342	0	0	0	0	1	0	0	1
orf19.3589	SPO11	0	0	0	0	1	0	0	1
orf19.111	CAN2	0	0	0	0	1	0	0	1
orf19.84	CAN3	0	0	0	0	1	0	0	1

orf19.646	GLN1	0	1	0	0	0	0	0	1
orf19.5759	SNQ2	0	0	0	0	1	0	0	1
orf19.5760	IHD1	0	0	0	0	0	0	1	1
orf19.956	orf19.956	0	0	1	0	0	0	0	1
orf19.3110	orf19.3110	0	0	1	0	0	0	0	1
orf19.2429	orf19.2429	0	0	0	0	1	0	0	1
orf19.3113	orf19.3113	0	0	0	0	0	1	0	1
orf19.792	orf19.792	0	0	0	0	0	0	1	1
orf19.7101	orf19.7101	0	0	1	0	0	0	0	1
orf19.6981	orf19.6981	0	0	0	0	0	0	1	1
orf19.6982	orf19.6982	0	0	0	0	0	1	0	1
orf19.6986	orf19.6986	0	0	0	0	0	0	1	1
orf19.5527	orf19.5527	0	0	0	0	1	0	0	1
orf19.918	CDR11	0	0	0	0	1	0	0	1
orf19.2605	orf19.2605	0	0	1	0	0	0	0	1
orf19.458.1	orf19.458.1	0	0	0	0	0	1	0	1
orf19.4688	DAG7	0	0	1	0	0	0	0	1
orf19.4865	orf19.4865	1	0	0	0	0	0	0	1
orf19.4862	orf19.4862	0	0	0	1	0	0	0	1
orf19.7368	orf19.7368	0	0	0	0	0	1	0	1
orf19.2517	orf19.2517	0	0	1	0	0	0	0	1
orf19.2515	orf19.2515	0	0	1	0	0	0	0	1
orf19.2514	orf19.2514	0	0	0	0	0	1	0	1
orf19.3649	orf19.3649	0	0	0	0	1	0	0	1
orf19.4752	MSN4	0	1	0	0	0	0	0	1
orf19.1519	orf19.1519	0	0	1	0	0	0	0	1
orf19.3644	orf19.3644	0	0	0	0	1	0	0	1
orf19.3647	SEC8	0	0	0	0	1	0	0	1
orf19.4913	orf19.4913	0	1	0	0	0	0	0	1
orf19.4912	orf19.4912	1	0	0	0	0	0	0	1
orf19.4262	orf19.4262	0	0	0	0	0	1	0	1
orf19.3241	orf19.3241	0	0	1	0	0	0	0	1
orf19.7201	SLA2	0	0	1	0	0	0	0	1
orf19.3245	orf19.3245	0	0	1	0	0	0	0	1
orf19.4269	orf19.4269	0	0	0	0	1	0	0	1
orf19.3247	orf19.3247	0	1	0	0	0	0	0	1
orf19.6792	RRD1	0	0	0	0	1	0	0	1
orf19.4286	orf19.4286	0	0	0	0	1	0	0	1
orf19.6967	USO6	0	0	0	0	1	0	0	1
orf19.1427	orf19.1427	0	0	0	0	1	0	0	1
orf19.1428	DUO1	0	0	0	0	0	1	0	1
orf19.2608	ADH5	0	1	0	0	0	0	0	1
orf19.271	ADH4	0	0	0	0	1	0	0	1
orf19.5302	PGA31	0	0	1	0	0	0	0	1
orf19.7521	REP1	0	0	1	0	0	0	0	1
orf19.3923	PGA37	0	0	1	0	0	0	0	1
orf19.4607	orf19.4607	0	0	1	0	0	0	0	1

orf19.3481	orf19.3481	0	1	0	0	0	0	0	1
orf19.669	PRM1	0	0	0	0	1	0	0	1
orf19.1405	PHO13	0	0	1	0	0	0	0	1
orf19.4132	orf19.4132	0	1	0	0	0	0	0	1
orf19.4737	TPO3	0	0	0	1	0	0	0	1
orf19.1736	orf19.1736	0	0	1	0	0	0	0	1
orf19.1734	orf19.1734	0	0	1	0	0	0	0	1
orf19.1730	orf19.1730	0	0	0	0	1	0	0	1
orf19.4162	MLH1	0	0	1	0	0	0	0	1
orf19.6396	orf19.6396	0	0	0	0	0	1	0	1
orf19.5742	ALS9	0	0	0	0	1	0	0	1
orf19.2209	YVC1	0	0	1	0	0	0	0	1
orf19.1378	SUP35	0	0	1	0	0	0	0	1
orf19.2585	orf19.2585	0	0	1	0	0	0	0	1
orf19.2241	PST1	0	0	0	0	0	0	1	1
orf19.1270	FRE3	0	0	1	0	0	0	0	1
orf19.3529	ABP2	1	0	0	0	0	0	0	1
orf19.5902	RAS2	0	0	1	0	0	0	0	1
orf19.1348	orf19.1348	0	0	1	0	0	0	0	1
orf19.3924	orf19.3924	0	0	0	0	1	0	0	1
orf19.5046	RAM1	0	0	0	0	1	0	0	1
orf19.540	orf19.540	0	0	0	0	1	0	0	1
orf19.1236	orf19.1236	0	0	1	0	0	0	0	1
orf19.3809	BAS1	0	0	1	0	0	0	0	1
orf19.149	orf19.149	0	0	0	1	0	0	0	1
orf19.6283	orf19.6283	1	0	0	0	0	0	0	1
orf19.6282	orf19.6282	0	0	1	0	0	0	0	1
orf19.899	orf19.899	0	0	1	0	0	0	0	1
orf19.6284	orf19.6284	0	0	0	1	0	0	0	1
orf19.323	orf19.323	0	0	0	0	1	0	0	1
orf19.6863	VPH1	0	0	1	0	0	0	0	1
orf19.3255	TEN1	0	1	0	0	0	0	0	1
orf19.2504	BMS1	0	0	1	0	0	0	0	1
orf19.3608	orf19.3608	0	0	0	0	0	1	0	1
orf19.6357	orf19.6357	0	0	0	0	1	0	0	1
orf19.6356	orf19.6356	0	0	0	0	0	1	0	1
orf19.6602	orf19.6602	0	0	0	0	1	0	0	1
orf19.5884	orf19.5884	0	0	0	0	1	0	0	1
orf19.5555	orf19.5555	0	0	0	1	0	0	0	1
orf19.6199	orf19.6199	0	1	0	0	0	0	0	1
orf19.57	PSF2	0	0	0	0	1	0	0	1
orf19.1321	HWP1	0	0	0	0	1	0	0	1
orf19.4012	PCL5	0	0	0	0	1	0	0	1
orf19.7489	orf19.7489	0	0	1	0	0	0	0	1
orf19.1367	MTW1	0	0	0	0	0	1	0	1
orf19.3107	orf19.3107	0	0	0	0	1	0	0	1
orf19.3105	orf19.3105	0	0	1	0	0	0	0	1

orf19.2458	orf19.2458	0	0	0	0	1	0	0	1
orf19.2455	orf19.2455	1	0	0	0	0	0	0	1
orf19.896	CHK1	0	0	1	0	0	0	0	1
orf19.3109	orf19.3109	0	0	0	1	0	0	0	1
orf19.4255	ECM331	0	0	1	0	0	0	0	1
orf19.2671	orf19.2671	0	0	1	0	0	0	0	1
orf19.6970	orf19.6970	0	0	0	0	0	1	0	1
orf19.7392	orf19.7392	0	0	0	0	1	0	0	1
orf19.7002	orf19.7002	1	0	0	0	0	0	0	1
orf19.7007	orf19.7007	0	0	0	0	1	0	0	1
orf19.2070	orf19.2070	0	0	1	0	0	0	0	1
orf19.7553	orf19.7553	1	0	0	0	0	0	0	1
orf19.3494	CTF5	0	1	0	0	0	0	0	1
orf19.1499	CTF1	0	0	0	0	0	0	1	1
orf19.1505	orf19.1505	0	1	0	0	0	0	0	1
orf19.1504	orf19.1504	0	0	1	0	0	0	0	1
orf19.3764	GSG1	0	0	0	0	1	0	0	1
orf19.6053	CIS2	0	0	0	0	1	0	0	1
orf19.7037	YAE1	0	0	0	0	0	1	0	1
orf19.5911	CMK1	0	0	1	0	0	0	0	1
orf19.1078	HBR2	0	0	0	0	1	0	0	1
orf19.4921	orf19.4921	0	0	0	0	0	1	0	1
orf19.3254	orf19.3254	0	0	0	0	1	0	0	1
orf19.4928	SEC2	0	0	0	0	1	0	0	1
orf19.3250	orf19.3250	0	0	1	0	0	0	0	1
orf19.4654	orf19.4654	0	0	0	0	1	0	0	1
orf19.1430	orf19.1430	0	0	0	0	1	0	0	1
orf19.1433	orf19.1433	0	0	0	0	1	0	0	1
orf19.1434	orf19.1434	0	0	1	0	0	0	0	1
orf19.1438	orf19.1438	0	0	1	0	0	0	0	1
orf19.3742	orf19.3742	0	0	0	0	0	0	1	1
orf19.4639	orf19.4639	1	0	0	0	0	0	0	1
orf19.4637	orf19.4637	0	0	0	0	1	0	0	1
orf19.2842	GZF3	0	0	0	0	0	1	0	1
orf19.1202	orf19.1202	0	0	0	0	1	0	0	1
orf19.4142	orf19.4142	0	0	1	0	0	0	0	1
orf19.4149	orf19.4149	0	1	0	0	0	0	0	1
orf19.2852	orf19.2852	0	1	0	0	0	0	0	1
orf19.2853	orf19.2853	0	0	1	0	0	0	0	1
orf19.2857	orf19.2857	0	0	0	0	1	0	0	1
orf19.728	TSC11	0	1	0	0	0	0	0	1
orf19.6255	orf19.6255	0	0	0	0	1	0	0	1
orf19.1720	orf19.1720	0	0	0	0	0	1	0	1
orf19.4308	HSL1	0	0	0	0	1	0	0	1
orf19.4701	orf19.4701	0	1	0	0	0	0	0	1
orf19.4702	orf19.4702	0	0	1	0	0	0	0	1
orf19.3199	PIKA	0	0	0	0	1	0	0	1



orf19.2919	MPH1	0	0	1	0	0	0	0	1
orf19.5605	orf19.5605	0	0	0	0	0	1	0	1
orf19.3774.1	orf19.3774.1	0	0	0	0	1	0	0	1
orf19.1115	GUK1	0	0	0	0	1	0	0	1
orf19.1453	SPT5	0	0	0	1	0	0	0	1
orf19.557	orf19.557	0	0	0	0	0	0	1	1
orf19.2883	CSO99	0	0	0	0	0	1	0	1
orf19.1260	LEA1	0	0	0	0	1	0	0	1
orf19.6569	orf19.6569	0	0	0	0	1	0	0	1
orf19.1246	orf19.1246	0	0	1	0	0	0	0	1
orf19.3815	orf19.3815	0	0	0	0	0	0	1	1
orf19.854	UGA11	0	0	0	1	0	0	0	1
orf19.1087	orf19.1087	0	0	0	0	1	0	0	1
orf19.5720	orf19.5720	0	1	0	0	0	0	0	1
orf19.5725	orf19.5725	0	0	0	0	1	0	0	1
orf19.5724	orf19.5724	0	0	0	0	0	1	0	1
orf19.2771	BEM3	0	0	0	0	0	1	0	1
orf19.5821	orf19.5821	0	0	0	0	0	1	0	1
orf19.5940	ZCF32	0	1	0	0	0	0	0	1
orf19.6366	orf19.6366	0	0	1	0	0	0	0	1
orf19.1826	MDM34	0	1	0	0	0	0	0	1
orf19.5894	orf19.5894	0	0	0	0	1	0	0	1
orf19.3895	CHT2	0	0	1	0	0	0	0	1
orf19.1515	CHT4	0	0	1	0	0	0	0	1
orf19.5543	orf19.5543	0	1	0	0	0	0	0	1
orf19.6168	orf19.6168	0	0	1	0	0	0	0	1
orf19.4548	MAK32	0	1	0	0	0	0	0	1
orf19.6382	orf19.6382	1	0	0	0	0	0	0	1
orf19.1863	orf19.1863	1	0	0	0	0	0	0	1
orf19.1864	orf19.1864	1	0	0	0	0	0	0	1
orf19.7494	orf19.7494	0	0	1	0	0	0	0	1
orf19.7497	orf19.7497	1	0	0	0	0	0	0	1
orf19.7490	orf19.7490	0	0	0	0	1	0	0	1
orf19.2449	orf19.2449	0	0	0	0	1	0	0	1
orf19.2440	orf19.2440	0	0	0	0	1	0	0	1
orf19.2442	orf19.2442	0	0	0	0	0	0	1	1
orf19.6705	orf19.6705	0	1	0	0	0	0	0	1
orf19.6703	orf19.6703	0	0	1	0	0	0	0	1
orf19.1860.1	orf19.1860.1	0	0	1	0	0	0	0	1
orf19.2285	orf19.2285	0	0	1	0	0	0	0	1
orf19.81	orf19.81	0	0	0	0	0	1	0	1
orf19.2664	orf19.2664	0	0	0	0	1	0	0	1
orf19.2540	SAS3	0	0	0	1	0	0	0	1
orf19.6953	IRS4	0	0	0	0	1	0	0	1
orf19.1002	orf19.1002	0	0	0	0	1	0	0	1
orf19.7011	orf19.7011	0	0	1	0	0	0	0	1
orf19.7012	orf19.7012	0	0	1	0	0	0	0	1

orf19.7545	orf19.7545	0	0	1	0	0	0	0	1
orf19.6017	orf19.6017	0	0	0	0	1	0	0	1
orf19.1005	orf19.1005	0	0	0	0	1	0	0	1
orf19.2713	orf19.2713	0	0	0	0	1	0	0	1
orf19.4936	orf19.4936	1	0	0	0	0	0	0	1
orf19.6637	orf19.6637	0	0	0	0	1	0	0	1
orf19.3713	orf19.3713	0	0	1	0	0	0	0	1
orf19.3711	orf19.3711	0	0	1	0	0	0	0	1
orf19.3618	YWP1	1	0	0	0	0	0	0	1
orf19.3719	orf19.3719	0	0	1	0	0	0	0	1
orf19.2717	SAS10	0	0	0	0	1	0	0	1
orf19.3539	orf19.3539	0	0	0	1	0	0	0	1
orf19.1047	ERB1	0	0	0	1	0	0	0	1
orf19.1404	orf19.1404	0	0	0	0	1	0	0	1
orf19.4626	orf19.4626	0	0	0	0	1	0	0	1
orf19.4622	orf19.4622	0	0	1	0	0	0	0	1
orf19.4621	orf19.4621	0	0	1	0	0	0	0	1
orf19.4153	orf19.4153	0	1	0	0	0	0	0	1
orf19.568	SPE2	0	0	0	0	0	0	1	1
orf19.5977	CEM1	0	0	0	0	1	0	0	1
orf19.6032	SPE1	0	0	0	0	1	0	0	1
orf19.1718	ZCF8	0	0	0	0	1	0	0	1
orf19.1791	orf19.1791	0	0	0	0	1	0	0	1
orf19.7175	HLJ1	0	0	0	0	0	0	1	1
orf19.1580	orf19.1580	0	0	1	0	0	0	0	1
orf19.1664	orf19.1664	0	0	0	0	0	1	0	1
orf19.1667	orf19.1667	0	0	0	0	1	0	0	1
orf19.132	orf19.132	0	0	0	0	0	0	1	1
orf19.5782	orf19.5782	0	0	1	0	0	0	0	1
orf19.5391	orf19.5391	0	0	0	0	1	0	0	1
orf19.131	orf19.131	0	0	0	0	1	0	0	1
orf19.641	orf19.641	0	0	0	0	0	1	0	1
orf19.1317	OSH3	0	0	0	0	1	0	0	1
orf19.5156	orf19.5156	0	0	1	0	0	0	0	1
orf19.7115	SAC7	0	0	0	0	0	0	1	1
orf19.3474	IPL1	0	0	0	0	0	0	1	1
orf19.5544	SAC6	0	0	0	0	1	0	0	1
orf19.768	SYG1	0	0	0	0	1	0	0	1
orf19.1926	SEF2	1	0	0	0	0	0	0	1
orf19.520	orf19.520	0	0	0	0	0	0	1	1
orf19.3828	orf19.3828	0	0	0	1	0	0	0	1
orf19.2324	UBA4	0	0	0	0	1	0	0	1
orf19.1258	orf19.1258	0	0	1	0	0	0	0	1
orf19.3276	PWP2	0	0	1	0	0	0	0	1
orf19.3827	orf19.3827	0	0	1	0	0	0	0	1
orf19.5861.1	orf19.5861.1	0	0	0	0	1	0	0	1
orf19.7512	orf19.7512	0	0	1	0	0	0	0	1

orf19.5580	TEL1	0	0	0	0	0	1	0	1
orf19.4305	orf19.4305	0	0	0	0	1	0	0	1
orf19.635	orf19.635	0	0	0	0	1	0	0	1
orf19.3966	CRH12	0	0	0	0	0	1	0	1
orf19.2706	CRH11	0	0	1	0	0	0	0	1
orf19.184	orf19.184	0	0	0	0	0	0	1	1
orf19.182	orf19.182	0	1	0	0	0	0	0	1
orf19.1897	orf19.1897	0	0	0	0	0	1	0	1
orf19.5579	orf19.5579	0	1	0	0	0	0	0	1
orf19.1890	orf19.1890	0	0	1	0	0	0	0	1
orf19.5573	orf19.5573	1	0	0	0	0	0	0	1
orf19.5574	orf19.5574	0	0	0	0	0	1	0	1
orf19.5575	orf19.5575	0	0	0	0	0	0	1	1
orf19.1383	orf19.1383	0	0	0	0	1	0	0	1
orf19.1381	orf19.1381	0	0	0	0	1	0	0	1
orf19.3826	orf19.3826	0	0	1	0	0	0	0	1
orf19.4002	DUN1	0	0	0	0	1	0	0	1
orf19.1876	orf19.1876	0	0	0	0	1	0	0	1
orf19.1693	CAS4	0	0	1	0	0	0	0	1
orf19.985	orf19.985	0	1	0	0	0	0	0	1
orf19.3940	orf19.3940	0	0	0	0	0	1	0	1
orf19.980	orf19.980	0	1	0	0	0	0	0	1
orf19.7624	orf19.7624	0	0	0	0	1	0	0	1
orf19.2478	orf19.2478	0	1	0	0	0	0	0	1
orf19.5076.1	orf19.5076.1	0	0	0	0	1	0	0	1
orf19.2278	orf19.2278	0	0	0	0	1	0	0	1
orf19.866	RAD32	0	0	1	0	0	0	0	1
orf19.1638	orf19.1638	0	0	0	0	1	0	0	1
orf19.6952	orf19.6952	0	0	0	0	1	0	0	1
orf19.3010	orf19.3010	1	0	0	0	0	0	0	1
orf19.7232	IRR1	0	0	0	0	1	0	0	1
orf19.7024	orf19.7024	0	0	0	0	1	0	0	1
orf19.6008	orf19.6008	0	1	0	0	0	0	0	1
orf19.2010	orf19.2010	0	1	0	0	0	0	0	1
orf19.6003	orf19.6003	0	0	0	0	1	0	0	1
orf19.2728	orf19.2728	0	0	0	0	1	0	0	1
orf19.2725	orf19.2725	0	0	0	0	0	1	0	1
orf19.979	FAS1	0	0	1	0	0	0	0	1
orf19.4747	HEM14	0	1	0	0	0	0	0	1
orf19.2721	orf19.2721	0	0	0	0	1	0	0	1
orf19.1529	orf19.1529	0	0	0	0	0	1	0	1
orf19.1901	MCM3	0	0	1	0	0	0	0	1
orf19.4354	MCM2	0	0	0	0	0	1	0	1
orf19.4946	orf19.4946	0	0	0	0	1	0	0	1
orf19.4942	orf19.4942	0	0	0	0	1	0	0	1
orf19.3704	orf19.3704	0	0	0	0	1	0	0	1
orf19.2653	orf19.2653	0	0	0	0	1	0	0	1

orf19.1412	orf19.1412	0	0	0	0	1	0	0	1
orf19.1411	orf19.1411	0	0	0	0	1	0	0	1
orf19.3522	orf19.3522	0	0	1	0	0	0	0	1
orf19.1414	orf19.1414	0	0	0	0	1	0	0	1
orf19.4894	orf19.4894	0	0	0	0	1	0	0	1
orf19.4896	orf19.4896	0	0	0	0	1	0	0	1
orf19.4893	orf19.4893	0	0	0	0	1	0	0	1
orf19.4365	orf19.4365	0	0	0	0	0	0	1	1
orf19.7359	CRZ1	1	0	0	0	0	0	0	1
orf19.2356	CRZ2	0	0	0	0	0	0	1	1
orf19.1605	PMS1	0	0	1	0	0	0	0	1
orf19.2509.1	orf19.2509.1	0	0	0	0	1	0	0	1
orf19.4094	orf19.4094	0	0	1	0	0	0	0	1
orf19.4767	ZCF28	0	0	0	0	0	1	0	1
orf19.4097	orf19.4097	0	0	0	0	1	0	0	1
orf19.4760	orf19.4760	0	0	0	0	1	0	0	1
orf19.4768	orf19.4768	0	0	0	0	1	0	0	1
orf19.6345	RPG1A	0	0	0	0	0	1	0	1
orf19.2364	MIS11	1	0	0	0	0	0	0	1
orf19.6214	ATC1	0	0	0	0	1	0	0	1
orf19.231	APL2	0	0	1	0	0	0	0	1
orf19.1679	orf19.1679	0	1	0	0	0	0	0	1
orf19.4169	orf19.4169	0	0	1	0	0	0	0	1
orf19.484	MRPL40	0	0	0	0	1	0	0	1
orf19.4160	orf19.4160	0	0	1	0	0	0	0	1
orf19.4164	orf19.4164	0	0	1	0	0	0	0	1
orf19.4166	ZCF21	0	0	1	0	0	0	0	1
orf19.2783	PIR32	0	1	0	0	0	0	0	1
orf19.5381	orf19.5381	0	0	0	0	1	0	0	1
orf19.3231	CDC27	0	0	1	0	0	0	0	1
orf19.5367	RDH54	0	0	1	0	0	0	0	1
orf19.4645	BEM1	0	0	0	0	1	0	0	1
orf19.533	orf19.533	0	0	1	0	0	0	0	1
orf19.2825	orf19.2825	0	0	0	0	0	0	1	1
orf19.4829	DOA1	0	0	0	0	1	0	0	1
orf19.1268	orf19.1268	0	0	1	0	0	0	0	1
orf19.3833	orf19.3833	0	1	0	0	0	0	0	1
orf19.3831	orf19.3831	0	0	0	0	1	0	0	1
orf19.1066	GIG1	0	0	0	0	1	0	0	1
orf19.5702	orf19.5702	0	0	0	0	1	0	0	1
orf19.1386	orf19.1386	0	0	0	0	1	0	0	1
orf19.5963	orf19.5963	0	0	0	0	1	0	0	1
orf19.144	SNU114	0	1	0	0	0	0	0	1
orf19.2711.1	orf19.2711.1	1	0	0	0	0	0	0	1
orf19.5965	orf19.5965	0	0	0	0	1	0	0	1
orf19.3666	orf19.3666	0	1	0	0	0	0	0	1
orf19.199	orf19.199	0	0	0	0	1	0	0	1

orf19.5255	PXA2	0	0	0	1	0	0	0	1
orf19.860	BMT8	0	1	0	0	0	0	0	1
orf19.1203	SRO77	0	0	0	0	1	0	0	1
orf19.5569	orf19.5569	0	0	0	0	0	1	0	1
orf19.1367.1	orf19.1367.1	0	0	1	0	0	0	0	1
orf19.3282	BMT3	0	0	1	0	0	0	0	1
orf19.5566	orf19.5566	1	0	0	0	0	0	0	1
orf19.5602	BMT6	0	0	0	0	1	0	0	1
orf19.5612	BMT4	0	0	0	0	1	0	0	1
orf19.6147	orf19.6147	0	0	0	0	1	0	0	1
orf19.6493	orf19.6493	0	0	0	0	1	0	0	1
orf19.6491	orf19.6491	0	0	1	0	0	0	0	1
orf19.4585	TFG1	0	0	1	0	0	0	0	1
orf19.5365	orf19.5365	0	0	0	0	1	0	0	1
orf19.5500	MAK16	0	0	0	0	1	0	0	1
orf19.2619	PHO113	0	1	0	0	0	0	0	1
orf19.3727	PHO112	0	0	1	0	0	0	0	1
orf19.1844	orf19.1844	0	0	0	0	1	0	0	1
orf19.996	orf19.996	0	0	0	0	1	0	0	1
orf19.445	orf19.445	1	0	0	0	0	0	0	1
orf19.5097	CAT8	0	0	0	0	1	0	0	1
orf19.5343	ASH1	0	0	0	0	1	0	0	1
orf19.448	orf19.448	0	0	0	1	0	0	0	1
orf19.2261	orf19.2261	0	0	1	0	0	0	0	1
orf19.2260	orf19.2260	0	0	0	0	1	0	0	1
orf19.2263	orf19.2263	0	0	0	0	0	0	1	1
orf19.69	orf19.69	0	0	0	0	1	0	0	1
orf19.1286	orf19.1286	0	1	0	0	0	0	0	1
orf19.1287	orf19.1287	0	0	0	0	1	0	0	1
orf19.1285	orf19.1285	0	0	0	0	1	0	0	1
orf19.801	TBF1	0	0	1	0	0	0	0	1
orf19.1945	AUR1	0	0	0	0	1	0	0	1
orf19.250	SLC1	0	0	0	0	1	0	0	1
orf19.1743	ACS1	0	0	1	0	0	0	0	1
orf19.5672	MEP2	0	0	1	0	0	0	0	1
orf19.377	PHR3	0	0	0	0	1	0	0	1
orf19.2002	orf19.2002	0	1	0	0	0	0	0	1
orf19.2736	HFL2	0	0	1	0	0	0	0	1
orf19.2739	orf19.2739	0	0	1	0	0	0	0	1
orf19.4746	JIP5	0	0	0	0	1	0	0	1
orf19.3010.1	ECM33	0	0	0	0	1	0	0	1
orf19.4955	orf19.4955	0	0	0	0	0	1	0	1
orf19.4951	orf19.4951	0	0	0	0	1	0	0	1
orf19.3252	DAL81	0	0	1	0	0	0	0	1
orf19.6309	MSS11	0	0	0	0	0	0	1	1
orf19.3285	orf19.3285	0	0	1	0	0	0	0	1
orf19.2651	CAM1-1	0	0	0	0	1	0	0	1

orf19.3281	orf19.3281	0	0	0	0	1	0	0	1
orf19.3775	SSK2	0	0	1	0	0	0	0	1
orf19.3553	RPF2	0	0	1	0	0	0	0	1
orf19.4420	orf19.4420	0	0	1	0	0	0	0	1
orf19.7452	orf19.7452	0	0	0	0	0	1	0	1
orf19.3593	RPT6	0	0	1	0	0	0	0	1
orf19.5440	RPT2	0	0	0	0	0	0	1	1
orf19.7529	EPL1	1	0	0	0	0	0	0	1
orf19.5653	ATP2	0	0	1	0	0	0	0	1
orf19.3512	orf19.3512	0	0	1	0	0	0	0	1
orf19.4261	TIF5	0	0	0	0	0	1	0	1
orf19.4395	orf19.4395	0	0	0	0	1	0	0	1
orf19.4391	orf19.4391	0	0	0	1	0	0	0	1
orf19.4399	orf19.4399	0	0	0	0	1	0	0	1
orf19.4398	orf19.4398	0	0	1	0	0	0	0	1
orf19.4883	orf19.4883	0	0	0	0	1	0	0	1
orf19.4880	orf19.4880	0	0	0	0	0	1	0	1
orf19.1279	CDS1	0	0	0	0	1	0	0	1
orf19.3356	ESP1	0	1	0	0	0	0	0	1
orf19.3605	PEX17	0	1	0	0	0	0	0	1
orf19.2868	orf19.2868	0	0	1	0	0	0	0	1
orf19.4372	orf19.4372	0	0	0	0	1	0	0	1
orf19.2867	orf19.2867	0	0	0	0	1	0	0	1
orf19.723	BCR1	0	0	1	0	0	0	0	1
orf19.4088	orf19.4088	0	1	0	0	0	0	0	1
orf19.4081	orf19.4081	0	0	1	0	0	0	0	1
orf19.2335	orf19.2335	0	0	0	0	1	0	0	1
orf19.707	APG7	0	0	0	1	0	0	0	1
orf19.1275	GAT1	0	0	0	0	1	0	0	1
orf19.1604	orf19.1604	0	0	1	0	0	0	0	1
orf19.1600	orf19.1600	0	0	0	0	1	0	0	1
orf19.1609	orf19.1609	0	0	0	0	1	0	0	1
orf19.4174	orf19.4174	0	0	1	0	0	0	0	1
orf19.4172	orf19.4172	0	0	1	0	0	0	0	1
orf19.4171	orf19.4171	0	0	1	0	0	0	0	1
orf19.4274	PUT1	0	0	0	0	1	0	0	1
orf19.2552	orf19.2552	0	0	0	0	0	0	1	1
orf19.5498	EFH1	0	0	0	0	1	0	0	1
orf19.1084	CDC39	0	0	0	0	0	1	0	1
orf19.3623	SMC2	0	0	1	0	0	0	0	1
orf19.1116	orf19.1116	0	0	1	0	0	0	0	1
orf19.5531	CDC37	0	0	0	0	0	1	0	1
orf19.6556	orf19.6556	0	0	0	0	1	0	0	1
orf19.6126	KGD2	0	0	1	0	0	0	0	1
orf19.1272	orf19.1272	0	0	0	0	1	0	0	1
orf19.1059	HHF1	0	0	0	1	0	0	0	1
orf19.3468	ALG11	0	0	0	0	1	0	0	1

orf19.6559	orf19.6559	1	0	0	0	0	0	0	1
orf19.6558	orf19.6558	1	0	0	0	0	0	0	1
orf19.10	ALK8	0	0	1	0	0	0	0	1
orf19.612	orf19.612	0	0	0	0	1	0	0	1
orf19.6673	HEX1	0	0	0	0	1	0	0	1
orf19.1343	orf19.1343	0	0	0	0	1	0	0	1
orf19.6031	VPS27	1	0	0	0	0	0	0	1
orf19.6670	CAC2	0	0	0	0	1	0	0	1
orf19.6005	HGT5	0	0	0	0	1	0	0	1
orf19.3668	HGT2	0	0	0	0	1	0	0	1
orf19.291	orf19.291	1	0	0	0	0	0	0	1
orf19.5601	orf19.5601	0	0	0	0	1	0	0	1
orf19.5358	orf19.5358	0	0	0	0	1	0	0	1
orf19.2135	TSM1	0	0	0	1	0	0	0	1
orf19.6482	orf19.6482	0	0	0	0	0	1	0	1
orf19.6488	orf19.6488	0	0	1	0	0	0	0	1
orf19.5353	orf19.5353	1	0	0	0	0	0	0	1
orf19.470	orf19.470	0	0	1	0	0	0	0	1
orf19.477	orf19.477	0	0	1	0	0	0	0	1
orf19.1613	ILV2	0	0	1	0	0	0	0	1
orf19.3461	orf19.3461	0	0	0	0	0	1	0	1
orf19.5771	PBP2	0	0	1	0	0	0	0	1
orf19.6739	orf19.6739	0	0	0	0	1	0	0	1
orf19.2257	orf19.2257	0	0	1	0	0	0	0	1
orf19.6481	YPS7	0	0	1	0	0	0	0	1
orf19.2252	orf19.2252	0	0	0	0	1	0	0	1
orf19.51	orf19.51	0	0	0	1	0	0	0	1
orf19.7193	orf19.7193	0	1	0	0	0	0	0	1
orf19.6934	orf19.6934	0	0	1	0	0	0	0	1
orf19.2038	orf19.2038	0	0	1	0	0	0	0	1
orf19.879	orf19.879	0	0	1	0	0	0	0	1
orf19.7511	orf19.7511	0	0	1	0	0	0	0	1
orf19.7043	orf19.7043	0	0	0	0	1	0	0	1
orf19.6022	orf19.6022	0	1	0	0	0	0	0	1
orf19.6018	LRO1	0	0	0	0	1	0	0	1
orf19.5926	ARG11	0	0	0	0	1	0	0	1
orf19.6027	orf19.6027	0	1	0	0	0	0	0	1
orf19.2133	LIP4	0	0	0	1	0	0	0	1
orf19.6025	orf19.6025	0	0	0	1	0	0	0	1
orf19.6024	orf19.6024	0	1	0	0	0	0	0	1
orf19.5172	LIP9	0	0	0	0	0	0	1	1
orf19.2746	orf19.2746	0	0	1	0	0	0	0	1
orf19.4966	orf19.4966	0	0	0	0	1	0	0	1
orf19.3680	SEP7	0	1	0	0	0	0	0	1
orf19.4064	GPI7	0	0	0	0	1	0	0	1
orf19.3728	orf19.3728	0	0	1	0	0	0	0	1
orf19.4415	orf19.4415	0	0	1	0	0	0	0	1

orf19.3722	orf19.3722	0	0	1	0	0	0	0	1
orf19.3726	orf19.3726	0	0	1	0	0	0	0	1
orf19.6496	TRS33	0	0	0	0	1	0	0	1
orf19.1836	APN2	0	0	0	0	1	0	0	1
orf19.7468	orf19.7468	0	0	0	0	1	0	0	1
orf19.2106	orf19.2106	1	0	0	0	0	0	0	1
orf19.7460	orf19.7460	0	0	1	0	0	0	0	1
orf19.2488	FAL1	0	0	0	0	1	0	0	1
orf19.7463	orf19.7463	0	0	1	0	0	0	0	1
orf19.5919	MEA1	0	0	0	0	0	0	1	1
orf19.3501	orf19.3501	0	0	0	0	1	0	0	1
orf19.1479	orf19.1479	0	1	0	0	0	0	0	1
orf19.1476	orf19.1476	0	0	1	0	0	0	0	1
orf19.1525	orf19.1525	0	0	0	0	0	1	0	1
orf19.6533	MSK1	0	0	0	0	0	1	0	1
orf19.3423	TIF3	0	0	0	0	1	0	0	1
orf19.2818	orf19.2818	0	0	1	0	0	0	0	1
orf19.4347	orf19.4347	1	0	0	0	0	0	0	1
orf19.4340	orf19.4340	1	0	0	0	0	0	0	1
orf19.4341	orf19.4341	0	1	0	0	0	0	0	1
orf19.434	PRD1	0	0	0	0	1	0	0	1
orf19.647.3	orf19.647.3	0	0	0	0	1	0	0	1
orf19.4741	orf19.4741	0	0	0	0	1	0	0	1
orf19.4981	orf19.4981	0	0	0	0	1	0	0	1
orf19.2922	orf19.2922	0	0	1	0	0	0	0	1
orf19.2921	orf19.2921	0	0	1	0	0	0	0	1
orf19.1617	orf19.1617	0	0	0	0	1	0	0	1
orf19.1611	orf19.1611	0	1	0	0	0	0	0	1
orf19.1619	orf19.1619	0	0	0	0	1	0	0	1
orf19.4182	orf19.4182	0	0	1	0	0	0	0	1
orf19.4187	orf19.4187	0	0	1	0	0	0	0	1
orf19.4185	orf19.4185	0	0	1	0	0	0	0	1
orf19.4189	orf19.4189	0	0	0	0	1	0	0	1
orf19.1753	PUS7	0	0	0	0	1	0	0	1
orf19.4682	HGT17	0	0	0	0	1	0	0	1
orf19.1358	GCN4	0	0	0	0	1	0	0	1
orf19.4533	orf19.4533	0	0	0	0	1	0	0	1
orf19.579	FOL1	0	0	1	0	0	0	0	1
orf19.4482	IFI3	1	0	0	0	0	0	0	1
orf19.4573	ZCF26	0	0	0	0	1	0	0	1
orf19.511	orf19.511	0	0	1	0	0	0	0	1
orf19.512	orf19.512	0	0	0	0	0	0	1	1
orf19.3954	orf19.3954	0	0	0	0	0	1	0	1
orf19.3628	RSP5	0	0	1	0	0	0	0	1
orf19.3374	ECE1	0	0	1	0	0	0	0	1
orf19.3337	orf19.3337	0	0	0	0	1	0	0	1
orf19.5083	DRG1	0	0	0	0	1	0	0	1



orf19.5767	orf19.5767	0	0	0	0	1	0	0	1
orf19.761	TCO89	1	0	0	0	0	0	0	1
orf19.609	orf19.609	0	1	0	0	0	0	0	1
orf19.6985	TEA1	0	1	0	0	0	0	0	1
orf19.852	SAP98	0	0	1	0	0	0	0	1
orf19.7442	orf19.7442	0	0	0	0	0	1	0	1
orf19.3122	ARR3	0	0	0	0	1	0	0	1
orf19.391	UPC2	1	0	0	0	0	0	0	1
orf19.7499.1	orf19.7499.1	0	0	0	0	1	0	0	1
orf19.5587	orf19.5587	0	0	0	0	1	0	0	1
orf19.5586	orf19.5586	0	0	0	0	0	1	0	1
orf19.5589	orf19.5589	0	0	0	0	1	0	0	1
orf19.4416	VPS13	0	0	0	0	1	0	0	1
orf19.505	SRV2	0	0	0	0	1	0	0	1
orf19.5617	orf19.5617	0	0	0	0	1	0	0	1
orf19.3298	CCH1	0	0	0	0	1	0	0	1
orf19.1827	orf19.1827	0	0	0	0	1	0	0	1
orf19.1823	orf19.1823	0	0	0	0	0	0	1	1
orf19.5830	orf19.5830	0	0	1	0	0	0	0	1
orf19.261	orf19.261	0	0	0	0	1	0	0	1
orf19.2247	orf19.2247	0	0	0	1	0	0	0	1
orf19.2246	orf19.2246	0	0	0	0	1	0	0	1
orf19.6230	orf19.6230	0	0	0	0	1	0	0	1
orf19.6585	orf19.6585	1	0	0	0	0	0	0	1
orf19.6586	orf19.6586	0	0	0	0	0	1	0	1
orf19.6587	orf19.6587	0	1	0	0	0	0	0	1
orf19.7083	DCC1	0	0	0	0	1	0	0	1
orf19.6909	orf19.6909	0	1	0	0	0	0	0	1
orf19.2787	PRY1	0	1	0	0	0	0	0	1
orf19.4969	KEM1	0	0	0	0	1	0	0	1
orf19.864	orf19.864	0	0	1	0	0	0	0	1
orf19.5548	LYS14	0	0	0	0	1	0	0	1
orf19.7057	orf19.7057	0	0	0	0	1	0	0	1
orf19.2024	orf19.2024	0	0	0	0	0	1	0	1
orf19.3050	AGE1	0	0	0	0	1	0	0	1
orf19.3630	RRP8	0	1	0	0	0	0	0	1
orf19.2834	RPD3	0	0	0	0	0	1	0	1
orf19.4407	orf19.4407	0	0	0	0	1	0	0	1
orf19.3758	orf19.3758	0	1	0	0	0	0	0	1
orf19.2110	orf19.2110	0	0	1	0	0	0	0	1
orf19.2115	orf19.2115	0	0	1	0	0	0	0	1
orf19.3196	orf19.3196	0	1	0	0	0	0	0	1
orf19.6550	orf19.6550	0	0	0	0	1	0	0	1
orf19.3573	PEX6	0	0	0	0	0	1	0	1
orf19.3409	SEC12	0	0	0	0	1	0	0	1
orf19.4757	NAR1	0	0	0	0	0	1	0	1
orf19.4571	orf19.4571	0	0	1	0	0	0	0	1

orf19.3102	CTA6	1	0	0	0	0	0	0	1
orf19.3376	orf19.3376	0	0	0	0	1	0	0	1
orf19.3371	JAB1	0	0	1	0	0	0	0	1
orf19.3373	orf19.3373	0	0	1	0	0	0	0	1
orf19.4357	orf19.4357	0	0	0	0	1	0	0	1
orf19.5897	orf19.5897	0	0	0	0	1	0	0	1
orf19.2805	PEX8	0	1	0	0	0	0	0	1
orf19.2804	orf19.2804	0	0	1	0	0	0	0	1
orf19.451	SOK1	1	0	0	0	0	0	0	1
orf19.3405	ZCF18	0	0	0	0	1	0	0	1
orf19.139	TRA1	0	1	0	0	0	0	0	1
orf19.3818	GOA1	0	0	0	0	1	0	0	1
orf19.1592	orf19.1592	0	0	0	0	0	1	0	1
orf19.4756	orf19.4756	0	0	0	0	0	1	0	1
orf19.4751	orf19.4751	0	0	0	1	0	0	0	1
orf19.4998	ROB1	1	0	0	0	0	0	0	1
orf19.2236	FHL1	0	0	0	0	0	0	1	1
orf19.3227	FTH2	0	0	0	0	0	1	0	1
orf19.4995	orf19.4995	0	0	0	0	0	1	0	1
orf19.2930	orf19.2930	0	1	0	0	0	0	0	1
orf19.5121	OPT5	0	0	0	0	1	0	0	1
orf19.2938	orf19.2938	0	0	0	0	1	0	0	1
orf19.3506	DBR1	0	0	0	0	1	0	0	1
orf19.1626	orf19.1626	0	0	1	0	0	0	0	1
orf19.4195	orf19.4195	0	0	0	0	0	0	1	1
orf19.3990	orf19.3990	0	0	0	0	0	1	0	1
orf19.7173	orf19.7173	0	0	0	1	0	0	0	1
orf19.808	orf19.808	0	0	1	0	0	0	0	1
orf19.2534	PIN4	0	1	0	0	0	0	0	1
orf19.87	GPX1	0	0	0	0	1	0	0	1
orf19.5291	orf19.5291	0	0	0	0	0	1	0	1
orf19.4048	DES1	0	1	0	0	0	0	0	1
orf19.1363	orf19.1363	0	0	0	0	1	0	0	1
orf19.4072	IFF6	0	0	0	0	1	0	0	1
orf19.4361	IFF3	0	0	0	1	0	0	0	1
orf19.5634	FRP1	0	0	1	0	0	0	0	1
orf19.6522	orf19.6522	0	0	0	0	1	0	0	1
orf19.2654	RMS1	0	0	0	0	0	1	0	1
orf19.3557	GPI19	0	0	0	1	0	0	0	1
orf19.1050	orf19.1050	1	0	0	0	0	0	0	1
orf19.832	GPI13	0	0	1	0	0	0	0	1
orf19.5026	orf19.5026	0	1	0	0	0	0	0	1
orf19.5755	orf19.5755	0	0	0	0	1	0	0	1
orf19.5757	orf19.5757	0	0	0	0	0	0	1	1
orf19.1804	orf19.1804	0	0	0	0	0	1	0	1
orf19.1902	NOC4	0	0	0	0	0	1	0	1
orf19.2579	orf19.2579	0	0	1	0	0	0	0	1

orf19.992	LKH1	0	0	0	0	1	0	0	1
orf19.676	orf19.676	0	0	0	0	0	1	0	1
orf19.6138	orf19.6138	0	0	1	0	0	0	0	1
orf19.3973	orf19.3973	0	1	0	0	0	0	0	1
orf19.1032	SKO1	0	0	0	1	0	0	0	1
orf19.2361	SPT10	0	0	1	0	0	0	0	1
orf19.5808	orf19.5808	0	0	1	0	0	0	0	1
orf19.494	orf19.494	0	0	0	0	0	1	0	1
orf19.3150	GRE2	0	0	1	0	0	0	0	1
orf19.499	orf19.499	0	0	1	0	0	0	0	1
orf19.702	orf19.702	0	0	0	0	1	0	0	1
orf19.254	orf19.254	0	0	1	0	0	0	0	1
orf19.35	orf19.35	0	0	1	0	0	0	0	1
orf19.2231	orf19.2231	0	0	0	0	0	1	0	1
orf19.7564	DPB2	0	0	0	0	1	0	0	1
orf19.5930	orf19.5930	0	0	0	0	1	0	0	1
orf19.5931	ARV1	0	0	0	0	0	1	0	1
orf19.5932	orf19.5932	0	0	0	0	1	0	0	1
orf19.4610	orf19.4610	0	0	0	0	1	0	0	1
orf19.6912	orf19.6912	0	0	1	0	0	0	0	1
orf19.2582	orf19.2582	0	0	0	0	0	0	1	1
orf19.7063	orf19.7063	0	0	1	0	0	0	0	1
orf19.7067	orf19.7067	0	0	0	0	1	0	0	1
orf19.7088	orf19.7088	1	0	0	0	0	0	0	1
orf19.5484	SER1	0	0	0	0	1	0	0	1
orf19.2563	orf19.2563	0	0	1	0	0	0	0	1
orf19.210	orf19.210	0	0	0	0	1	0	0	1
orf19.7086	orf19.7086	0	0	0	0	1	0	0	1
orf19.3823	ZDS1	0	0	0	0	1	0	0	1
orf19.5640	PEX5	0	0	1	0	0	0	0	1
orf19.925	orf19.925	0	0	1	0	0	0	0	1
orf19.2005	REG1	0	0	1	0	0	0	0	1
orf19.5001	CUP2	0	0	0	1	0	0	0	1
orf19.2169	orf19.2169	0	0	1	0	0	0	0	1
orf19.59	REI1	1	0	0	0	0	0	0	1
orf19.1450	orf19.1450	1	0	0	0	0	0	0	1
orf19.4222	SST2	0	0	0	0	1	0	0	1
orf19.3152	AMO2	0	0	1	0	0	0	0	1
orf19.4690	orf19.4690	0	0	1	0	0	0	0	1
orf19.4691	orf19.4691	0	0	0	0	1	0	0	1
orf19.4508	orf19.4508	0	0	1	0	0	0	0	1
orf19.4509	orf19.4509	0	0	1	0	0	0	0	1
orf19.4502	orf19.4502	0	0	1	0	0	0	0	1
orf19.3364	orf19.3364	0	0	1	0	0	0	0	1
orf19.4326	orf19.4326	0	1	0	0	0	0	0	1
orf19.940	BUD2	0	0	1	0	0	0	0	1
orf19.2838	orf19.2838	0	0	0	0	0	0	1	1

orf19.4299	MSW1	0	0	0	0	1	0	0	1
orf19.4592	HSX11	1	0	0	0	0	0	0	1
orf19.5758	SAL6	0	0	0	0	0	0	1	1
orf19.1961	orf19.1961	0	0	1	0	0	0	0	1
orf19.20	RTS1	0	0	0	0	1	0	0	1
orf19.5170	ENA21	0	0	0	0	1	0	0	1
orf19.4214	orf19.4214	0	0	0	0	0	0	1	1
orf19.24	RTA2	0	0	1	0	0	0	0	1
orf19.2012	NOT3	0	0	1	0	0	0	0	1
orf19.6011	SIN3	0	0	0	0	1	0	0	1
orf19.3734	GEF2	0	0	1	0	0	0	0	1
orf19.2903	AGO1	0	0	1	0	0	0	0	1
orf19.1634	orf19.1634	0	0	1	0	0	0	0	1
orf19.2908	orf19.2908	0	0	0	0	1	0	0	1
orf19.1632	orf19.1632	0	0	1	0	0	0	0	1
orf19.2998	TSR2	1	0	0	0	0	0	0	1
orf19.6321	PGA48	0	0	0	0	0	0	1	1
orf19.3638	PGA46	0	0	0	0	1	0	0	1
orf19.2906	PGA41	0	0	0	0	1	0	0	1
orf19.2910	PGA43	0	0	0	0	1	0	0	1
orf19.3765	RAX2	0	0	0	0	0	1	0	1
orf19.3980	orf19.3980	0	0	0	0	1	0	0	1
orf19.2917.1	orf19.2917.1	0	0	1	0	0	0	0	1
orf19.5005	OSM2	0	0	0	0	1	0	0	1
orf19.1123	orf19.1123	0	0	0	0	0	1	0	1
orf19.4784	CRP1	0	0	0	0	1	0	0	1
orf19.272	FAA21	0	0	0	0	1	0	0	1
orf19.5288	IFE2	0	0	0	0	0	0	1	1
orf19.1026	orf19.1026	1	0	0	0	0	0	0	1
orf19.5747	orf19.5747	0	0	0	0	1	0	0	1
orf19.5034	orf19.5034	0	1	0	0	0	0	0	1
orf19.5037	HRQ2	0	0	0	0	1	0	0	1
orf19.5748	orf19.5748	0	0	0	0	1	0	0	1
orf19.1891	APR1	1	0	0	0	0	0	0	1
orf19.5162	BCK1	0	0	0	0	1	0	0	1
orf19.4924	orf19.4924	0	0	0	0	0	1	0	1
orf19.666	orf19.666	0	0	0	0	1	0	0	1
orf19.1413	YFH1	0	0	0	0	1	0	0	1
orf19.6691	orf19.6691	0	0	0	0	0	1	0	1
orf19.6693	orf19.6693	0	0	1	0	0	0	0	1
orf19.2507	ARP9	0	0	1	0	0	0	0	1
orf19.5623	ARP4	0	0	0	0	1	0	0	1
orf19.2641	ARP1	0	0	0	0	1	0	0	1
orf19.6456	orf19.6456	0	0	0	0	0	1	0	1
orf19.6457	orf19.6457	0	0	0	0	1	0	0	1
orf19.5322	orf19.5322	1	0	0	0	0	0	0	1
orf19.2154	HXK1	1	0	0	0	0	0	0	1

orf19.5817	orf19.5817	0	0	1	0	0	0	0	1
orf19.1324	RAD2	0	0	1	0	0	0	0	1
orf19.5061	ADE5,7	0	0	0	0	1	0	0	1
orf19.4275	RAD9	0	0	0	0	1	0	0	1
orf19.2228	orf19.2228	0	0	0	0	0	0	1	1
orf19.29	orf19.29	0	0	1	0	0	0	0	1
orf19.2227	orf19.2227	0	0	1	0	0	0	0	1
orf19.22	orf19.22	0	0	0	0	1	0	0	1
orf19.21	orf19.21	0	0	0	0	1	0	0	1
orf19.1935	orf19.1935	0	0	1	0	0	0	0	1
orf19.1933	orf19.1933	0	0	0	0	1	0	0	1
orf19.5253	orf19.5253	0	0	0	0	0	1	0	1
orf19.5921	orf19.5921	0	0	0	0	1	0	0	1
orf19.645.1	VMA13	0	0	0	0	1	0	0	1
orf19.6033	CMP1	0	0	0	0	0	0	1	1
orf19.804	orf19.804	0	0	0	0	0	0	1	1
orf19.7074	orf19.7074	0	1	0	0	0	0	0	1
orf19.7073	orf19.7073	0	0	0	0	1	0	0	1
orf19.7079	orf19.7079	0	0	1	0	0	0	0	1
orf19.6679	orf19.6679	0	0	0	1	0	0	0	1
orf19.2138	ILS1	0	0	0	1	0	0	0	1
orf19.1802	orf19.1802	0	0	1	0	0	0	0	1
orf19.6852	orf19.6852	0	0	0	0	1	0	0	1
orf19.3086	orf19.3086	0	0	1	0	0	0	0	1
orf19.3083	orf19.3083	0	0	0	0	0	0	1	1
orf19.3080	orf19.3080	0	0	1	0	0	0	0	1
orf19.7095	orf19.7095	0	0	0	0	1	0	0	1
orf19.2574	orf19.2574	0	0	1	0	0	0	0	1
orf19.7096	orf19.7096	0	1	0	0	0	0	0	1
orf19.2832	INN1	0	0	0	0	0	1	0	1
orf19.3777	orf19.3777	0	0	0	0	0	1	0	1
orf19.937	orf19.937	0	0	0	0	0	0	1	1
orf19.2684	orf19.2684	0	0	0	1	0	0	0	1
orf19.3177	orf19.3177	0	0	0	0	1	0	0	1
orf19.3175	orf19.3175	1	0	0	0	0	0	0	1
orf19.3178	orf19.3178	0	0	1	0	0	0	0	1
orf19.3211	RCF3	0	0	0	0	1	0	0	1
orf19.3798	orf19.3798	0	0	1	0	0	0	0	1
orf19.3796	DCR1	0	0	0	0	1	0	0	1
orf19.3797	orf19.3797	0	0	0	0	1	0	0	1
orf19.4686	orf19.4686	0	0	0	0	0	1	0	1
orf19.2365	POL2	0	0	1	0	0	0	0	1
orf19.4511	orf19.4511	0	0	1	0	0	0	0	1
orf19.6628	orf19.6628	0	0	0	0	1	0	0	1
orf19.2779	orf19.2779	0	0	0	0	0	1	0	1
orf19.22.1	orf19.22.1	0	0	0	0	1	0	0	1
orf19.7300	orf19.7300	0	0	0	0	1	0	0	1

orf19.2471	GIM5	1	0	0	0	0	0	0	1
orf19.56	ARG2	0	0	0	0	1	0	0	1
orf19.2827	orf19.2827	0	1	0	0	0	0	0	1
orf19.2822	orf19.2822	0	0	0	0	0	0	1	1
orf19.4332	orf19.4332	0	0	0	0	0	1	0	1
orf19.5776	TOM1	0	0	0	0	0	1	0	1
orf19.2828	orf19.2828	0	0	0	0	1	0	0	1
orf19.2474	PRC3	0	0	0	0	1	0	0	1
orf19.4203	orf19.4203	0	0	0	0	0	0	1	1
orf19.5630	APA2	0	0	0	0	1	0	0	1
orf19.3552	orf19.3552	0	0	1	0	0	0	0	1
orf19.4028	orf19.4028	0	0	0	0	1	0	0	1
orf19.913.2	orf19.913.2	0	0	0	0	0	1	0	1
orf19.2917	orf19.2917	0	0	0	0	0	1	0	1
orf19.2914	orf19.2914	0	0	1	0	0	0	0	1
orf19.4870	DBP3	0	0	0	0	1	0	0	1
orf19.1661	DBP5	0	0	0	0	1	0	0	1
orf19.738	MYO5	0	0	1	0	0	0	0	1
orf19.2767	PGA59	0	0	0	0	0	0	1	1
orf19.2685	PGA54	0	0	1	0	0	0	0	1
orf19.5191	FGR6-1	0	0	0	0	0	0	1	1
orf19.5137	orf19.5137	0	0	0	1	0	0	0	1
orf19.5139	orf19.5139	1	0	0	0	0	0	0	1
orf19.100	orf19.100	0	0	0	0	1	0	0	1
orf19.3228	orf19.3228	0	0	1	0	0	0	0	1
orf19.5595	SHE3	0	0	0	0	0	0	1	1
orf19.3699	TEP1	0	0	0	0	1	0	0	1
orf19.3886	orf19.3886	0	0	0	0	0	1	0	1
orf19.7059	orf19.7059	0	0	0	0	1	0	0	1
orf19.1030	orf19.1030	0	0	0	0	1	0	0	1
orf19.5009	orf19.5009	0	0	0	0	1	0	0	1
orf19.1223	DBF2	0	0	1	0	0	0	0	1
orf19.653	orf19.653	0	1	0	0	0	0	0	1
orf19.120	orf19.120	0	1	0	0	0	0	0	1
orf19.1659	ALG8	0	0	0	0	0	1	0	1
orf19.1221	ALG2	0	0	0	0	0	1	0	1
orf19.4410	ALG1	0	0	0	0	1	0	0	1
orf19.2187	ALG7	0	0	1	0	0	0	0	1
orf19.6687	orf19.6687	0	0	1	0	0	0	0	1
orf19.1238	TUB4	0	0	1	0	0	0	0	1
orf19.2215	GLE1	0	0	0	0	0	0	1	1
orf19.1323	orf19.1323	0	0	0	0	1	0	0	1
orf19.6114	orf19.6114	0	0	1	0	0	0	0	1
orf19.4015	CAG1	0	0	0	0	1	0	0	1
orf19.5644	orf19.5644	1	0	0	0	0	0	0	1
orf19.6119	orf19.6119	0	0	1	0	0	0	0	1
orf19.5488	orf19.5488	0	0	0	0	1	0	0	1

orf19.5489	orf19.5489	0	0	0	0	1	0	0	1
orf19.807	CHS5	0	0	1	0	0	0	0	1
orf19.5155	CHS6	0	0	1	0	0	0	0	1
orf19.5865	orf19.5865	0	0	1	0	0	0	0	1
orf19.5869	orf19.5869	0	0	1	0	0	0	0	1
orf19.4322	DAP2	0	0	0	0	1	0	0	1
orf19.2210	orf19.2210	0	0	1	0	0	0	0	1
orf19.4054	CTA24	0	0	0	0	0	1	0	1
orf19.2213	orf19.2213	1	0	0	0	0	0	0	1
orf19.5269	orf19.5269	0	0	0	0	1	0	0	1
orf19.5262	orf19.5262	0	0	0	0	1	0	0	1
orf19.4630	CPA1	0	0	0	0	1	0	0	1
orf19.6686	ENP2	0	0	0	0	0	0	1	1
orf19.349	orf19.349	0	0	0	0	1	0	0	1
orf19.341	orf19.341	0	0	0	0	1	0	0	1
orf19.831	orf19.831	0	0	1	0	0	0	0	1
orf19.346	orf19.346	0	1	0	0	0	0	0	1
orf19.797	BAT21	0	0	0	1	0	0	0	1
orf19.6065	orf19.6065	0	0	0	0	1	0	0	1
orf19.2367	orf19.2367	0	1	0	0	0	0	0	1
orf19.2362	orf19.2362	0	0	0	0	1	0	0	1
orf19.5050	MTO1	0	0	1	0	0	0	0	1
orf19.1814	orf19.1814	0	0	1	0	0	0	0	1
orf19.3091	orf19.3091	0	0	1	0	0	0	0	1
orf19.2549	orf19.2549	0	0	0	0	0	1	0	1
orf19.6014	RRS1	0	0	0	0	1	0	0	1
orf19.4884	WOR1	1	0	0	0	0	0	0	1
orf19.2143	orf19.2143	0	0	0	1	0	0	0	1
orf19.1445	ESC4	1	0	0	0	0	0	0	1
orf19.3780	orf19.3780	0	0	0	0	1	0	0	1
orf19.3783	orf19.3783	0	0	1	0	0	0	0	1
orf19.3787	orf19.3787	0	0	0	0	0	1	0	1
orf19.2454	PHO87	1	0	0	0	0	0	0	1
orf19.2791	BBC1	0	1	0	0	0	0	0	1
orf19.4520	orf19.4520	0	1	0	0	0	0	0	1
orf19.4521	orf19.4521	0	0	1	0	0	0	0	1
orf19.4834	orf19.4834	0	0	0	0	1	0	0	1
orf19.4529	orf19.4529	0	0	0	0	1	0	0	1
orf19.2991	HOL1	0	0	0	0	1	0	0	1
orf19.3304	orf19.3304	0	1	0	0	0	0	0	1
orf19.658	GIN1	0	0	0	0	0	1	0	1
orf19.3431	orf19.3431	0	0	0	0	1	0	0	1
orf19.3430	orf19.3430	0	1	0	0	0	0	0	1
orf19.2580	HST2	1	0	0	0	0	0	0	1
orf19.4761	HST1	0	0	0	0	1	0	0	1
orf19.4789	orf19.4789	1	0	0	0	0	0	0	1
orf19.5526	SEC20	0	0	0	0	0	0	1	1

orf19.4732	SEC24	0	0	0	0	1	0	0	1
orf19.3547	orf19.3547	0	0	1	0	0	0	0	1
orf19.3545	orf19.3545	0	0	1	0	0	0	0	1
orf19.3543	orf19.3543	0	0	0	1	0	0	0	1
orf19.2968	orf19.2968	0	0	0	0	1	0	0	1
orf19.4014	orf19.4014	1	0	0	0	0	0	0	1
orf19.2963	orf19.2963	0	1	0	0	0	0	0	1
orf19.6512	EXO70	0	0	1	0	0	0	0	1
orf19.4013	orf19.4013	0	0	0	0	1	0	0	1
orf19.1491	orf19.1491	0	0	1	0	0	0	0	1
orf19.6796	orf19.6796	1	0	0	0	0	0	0	1
orf19.1497	ZCF6	0	0	1	0	0	0	0	1
orf19.943	FET33	0	0	1	0	0	0	0	1
orf19.4656	orf19.4656	1	0	0	0	0	0	0	1
orf19.4657	orf19.4657	0	0	1	0	0	0	0	1
orf19.4306	orf19.4306	0	0	0	0	1	0	0	1
orf19.4076	MET10	0	0	0	0	0	1	0	1
orf19.4679	AGP2	0	0	1	0	0	0	0	1
orf19.6243	VPS34	0	0	0	0	1	0	0	1
orf19.156	FGR51	0	0	1	0	0	0	0	1
orf19.1143	orf19.1143	0	0	0	0	1	0	0	1
orf19.5163	SF11	0	0	1	0	0	0	0	1
orf19.795	VPS36	0	0	1	0	0	0	0	1
orf19.7574	orf19.7574	0	0	0	0	1	0	0	1
orf19.4755	KEX2	0	0	0	0	1	0	0	1
orf19.4934	OP4	0	0	0	0	0	0	1	1
orf19.3746	IFC1	0	0	1	0	0	0	0	1
orf19.3749	IFC3	0	0	0	0	0	0	1	1
orf19.1524	SPR3	0	0	1	0	0	0	0	1
orf19.5019	orf19.5019	1	0	0	0	0	0	0	1
orf19.5959	NOP14	0	0	0	0	1	0	0	1
orf19.1008	orf19.1008	0	0	1	0	0	0	0	1
orf19.1009	orf19.1009	0	0	0	1	0	0	0	1
orf19.3370	DOT4	0	0	1	0	0	0	0	1
orf19.5557	MNN4-4	0	0	0	0	0	1	0	1
orf19.5783	orf19.5783	0	0	1	0	0	0	0	1
orf19.133	orf19.133	0	0	0	0	0	0	1	1
orf19.77.1	orf19.77.1	0	1	0	0	0	0	0	1
orf19.5780	orf19.5780	1	0	0	0	0	0	0	1
orf19.137	orf19.137	0	0	0	0	1	0	0	1
orf19.643	orf19.643	0	0	1	0	0	0	0	1
orf19.1942	SGE1	0	0	0	0	0	0	1	1
orf19.6477	orf19.6477	0	0	0	0	1	0	0	1
orf19.1310	orf19.1310	0	0	0	0	1	0	0	1
orf19.5306	orf19.5306	0	0	1	0	0	0	0	1
orf19.5499	orf19.5499	0	0	0	0	1	0	0	1
orf19.5495	orf19.5495	0	0	0	0	1	0	0	1



orf19.4082	DDR48	0	0	1	0	0	0	0	1
orf19.3756	CHR1	0	1	0	0	0	0	0	1
orf19.5879	orf19.5879	0	0	1	0	0	0	0	1
orf19.6789	orf19.6789	0	0	0	0	1	0	0	1
orf19.6786	orf19.6786	0	0	0	0	1	0	0	1
orf19.1958	orf19.1958	0	1	0	0	0	0	0	1
orf19.6275	orf19.6275	0	0	0	0	1	0	0	1
orf19.5270	orf19.5270	0	0	0	0	1	0	0	1
orf19.1290	XKS1	0	0	1	0	0	0	0	1
orf19.2911	SEC3	0	0	0	0	0	1	0	1
orf19.1842	orf19.1842	0	0	0	0	0	1	0	1
orf19.352	orf19.352	0	0	0	0	1	0	0	1
orf19.2681	RBT7	0	0	0	0	1	0	0	1
orf19.2598	VMA4	0	0	0	0	1	0	0	1
orf19.6307	orf19.6307	0	0	1	0	0	0	0	1
orf19.6305	orf19.6305	0	0	1	0	0	0	0	1
orf19.6654	orf19.6654	0	0	0	0	0	1	0	1
orf19.6308	orf19.6308	0	0	0	0	0	0	1	1
orf19.4773	AOX2	1	0	0	0	0	0	0	1
orf19.6803	HUT1	0	0	0	0	0	1	0	1
orf19.2558	orf19.2558	0	1	0	0	0	0	0	1
orf19.1333	SNG3	0	0	0	0	1	0	0	1
orf19.6899	orf19.6899	0	0	0	0	1	0	0	1
orf19.1756	GPD1	0	0	0	0	1	0	0	1
orf19.6893	orf19.6893	0	0	1	0	0	0	0	1
orf19.6897	orf19.6897	0	0	1	0	0	0	0	1
orf19.5292	AXL2	0	0	0	0	1	0	0	1
orf19.915	orf19.915	0	0	0	1	0	0	0	1
orf19.3156	orf19.3156	0	0	1	0	0	0	0	1
orf19.6249	HAK1	0	0	0	0	1	0	0	1
orf19.4820	orf19.4820	0	0	0	0	1	0	0	1
orf19.4825	orf19.4825	0	0	0	0	1	0	0	1
orf19.4532	orf19.4532	1	0	0	0	0	0	0	1
orf19.3269	GSL2	0	0	0	1	0	0	0	1
orf19.2495	GSL1	0	0	0	1	0	0	0	1
orf19.2795	orf19.2795	1	0	0	0	0	0	0	1
orf19.2307	orf19.2307	0	0	0	0	0	0	1	1
orf19.4785	PTC1	0	0	0	0	0	1	0	1
orf19.2538	PTC2	0	0	0	0	0	1	0	1
orf19.6313	MNT4	0	0	0	0	0	1	0	1
orf19.3446	orf19.3446	0	0	0	0	1	0	0	1
orf19.1796	orf19.1796	0	0	0	0	1	0	0	1
orf19.1799	GAP5	0	0	1	0	0	0	0	1
orf19.3449	orf19.3449	0	0	0	1	0	0	0	1
orf19.94	orf19.94	0	0	0	0	1	0	0	1
orf19.4799	orf19.4799	1	0	0	0	0	0	0	1
orf19.4791	orf19.4791	1	0	0	0	0	0	0	1

orf19.2808	ZCF16	0	0	0	0	1	0	0	1
orf19.4220	orf19.4220	0	0	1	0	0	0	0	1
orf19.6972	SMI1B	0	0	0	0	0	1	0	1
orf19.4001	orf19.4001	0	0	0	0	1	0	0	1
orf19.4000	GRF10	0	0	0	0	0	0	1	1
orf19.2977	orf19.2977	0	0	0	1	0	0	0	1
orf19.2971	orf19.2971	0	0	0	0	1	0	0	1
orf19.3404	orf19.3404	0	0	0	0	1	0	0	1
orf19.4099	ECM17	0	0	0	0	1	0	0	1
orf19.1782.1	orf19.1782.1	0	0	0	0	1	0	0	1
orf19.4788	ARG5,6	1	0	0	0	0	0	0	1
orf19.4316	orf19.4316	0	0	0	0	1	0	0	1
orf19.4642	orf19.4642	0	0	1	0	0	0	0	1
orf19.5059	GCS1	0	0	0	0	1	0	0	1
orf19.2615	MDL1	0	0	0	0	1	0	0	1
orf19.1778	orf19.1778	0	0	1	0	0	0	0	1
orf19.5967	FGR44	0	1	0	0	0	0	0	1
orf19.4769	IPT1	0	0	0	0	1	0	0	1
orf19.1771	orf19.1771	0	1	0	0	0	0	0	1
orf19.1777	orf19.1777	0	0	1	0	0	0	0	1
orf19.3209	FGR42	1	0	0	0	0	0	0	1
orf19.6534.2	orf19.6534.2	0	0	0	0	1	0	0	1
orf19.1968.1	orf19.1968.1	0	0	0	0	0	0	1	1
orf19.5066	orf19.5066	0	0	0	0	1	0	0	1
orf19.3770	ARG8	0	0	1	0	0	0	0	1
orf19.1683	PPH21	0	1	0	0	0	0	0	1
orf19.5610	ARG3	1	0	0	0	0	0	0	1
orf19.6877	PNG2	0	1	0	0	0	0	0	1
orf19.652	orf19.652	0	0	1	0	0	0	0	1
orf19.6469	orf19.6469	0	0	0	0	1	0	0	1
orf19.1303	orf19.1303	0	0	1	0	0	0	0	1
orf19.1302	orf19.1302	0	0	0	0	1	0	0	1
orf19.1300	orf19.1300	0	0	0	0	1	0	0	1
orf19.1306	orf19.1306	0	0	0	0	1	0	0	1
orf19.3264	CCE1	0	0	1	0	0	0	0	1
orf19.4952	orf19.4952	0	0	0	0	0	1	0	1
orf19.5465	orf19.5465	0	0	0	0	0	1	0	1
orf19.4899	GCA1	0	0	0	1	0	0	0	1
orf19.999	GCA2	0	0	0	0	1	0	0	1
orf19.5688	orf19.5688	0	0	0	0	0	1	0	1
orf19.217	orf19.217	0	0	1	0	0	0	0	1
orf19.581	orf19.581	0	0	1	0	0	0	0	1
orf19.580	orf19.580	0	0	1	0	0	0	0	1
orf19.587	orf19.587	0	0	1	0	0	0	0	1
orf19.6790	orf19.6790	0	0	0	0	1	0	0	1
orf19.6269	orf19.6269	0	0	0	0	1	0	0	1
orf19.5203	orf19.5203	0	0	0	0	1	0	0	1

orf19.1633	UTP4	0	0	0	0	1	0	0	1
orf19.17	SCP1	0	0	1	0	0	0	0	1
orf19.2099	orf19.2099	1	0	0	0	0	0	0	1
orf19.2090	orf19.2090	0	0	1	0	0	0	0	1
orf19.2091	orf19.2091	0	0	1	0	0	0	0	1
orf19.5958	CDR2	0	0	0	1	0	0	0	1
orf19.7223	orf19.7223	0	1	0	0	0	0	0	1
orf19.7539.1	orf19.7539.1	0	0	1	0	0	0	0	1
orf19.5518	orf19.5518	1	0	0	0	0	0	0	1
orf19.6864	orf19.6864	0	0	1	0	0	0	0	1
orf19.6316	orf19.6316	0	0	0	0	0	0	1	1
orf19.5516	orf19.5516	0	0	0	0	1	0	0	1
orf19.6869	orf19.6869	0	0	1	0	0	0	0	1
orf19.3000	ORC1	0	0	0	0	1	0	0	1
orf19.6888	orf19.6888	0	0	1	0	0	0	0	1
orf19.1932	CFL4	0	0	1	0	0	0	0	1
orf19.1263	CFL1	0	0	1	0	0	0	0	1
orf19.3140	orf19.3140	0	0	1	0	0	0	0	1
orf19.6449	orf19.6449	0	0	0	0	0	1	0	1
orf19.7130	orf19.7130	1	0	0	0	0	0	0	1
orf19.7131	orf19.7131	1	0	0	0	0	0	0	1
orf19.4307	orf19.4307	0	0	0	0	1	0	0	1

**Supplementary Table 4. Clustered recurrent, persistently mutated genes and their enrichments.**

A. Shown are persistently mutated genes that are recurrent in three or more time courses.

ORF	GENE	Cluster	PT1	PT7	PT9	PT14	PT15	PT43	PT59
orf19.5592	orf19.5592	1	1	1	0	1	1	1	0
orf19.5596	orf19.5596	1	0	1	0	1	1	1	1
orf19.5597	POL5	1	0	1	0	1	1	1	1
orf19.6277	orf19.6277	1	1	1	0	1	1	1	0
orf19.1769	orf19.1769	1	0	1	0	1	0	1	1
orf19.7204	orf19.7204	1	0	1	0	1	0	1	1
orf19.3473	orf19.3473	1	0	1	0	1	0	1	1
orf19.2646	ZCF13	1	0	0	0	1	1	1	1
orf19.4288	CTA7	1	0	0	0	1	1	1	1
orf19.4245	orf19.4245	1	0	0	0	1	0	1	1
orf19.1690	TOS1	1	0	0	0	1	1	1	0
orf19.7561	DEF1	1	0	0	0	1	1	1	0
orf19.1356	orf19.1356	1	0	0	0	1	1	1	0
orf19.1607	ALR1	1	0	1	0	1	0	1	0
orf19.6544	LPI9	1	0	0	0	1	1	1	0
orf19.4553	orf19.4553	1	0	1	0	1	1	0	0
orf19.4080	orf19.4080	1	0	0	0	1	1	1	0
orf19.7194	orf19.7194	1	0	0	0	1	0	1	1
orf19.4064	GPI7	1	1	0	0	1	1	0	0
orf19.5621	orf19.5621	1	1	0	0	1	1	0	0
orf19.6592	orf19.6592	1	0	0	0	1	1	1	0
orf19.5058	SMI1	1	0	0	0	1	1	1	0
orf19.5003	orf19.5003	1	0	1	0	1	0	1	0
orf19.3437	orf19.3437	1	0	1	0	1	1	0	0
orf19.1706	MET18	1	0	0	0	1	1	1	0
orf19.1144	orf19.1144	1	1	0	0	1	1	0	0
orf19.7342	AXL1	1	0	0	0	1	1	1	0
orf19.4316	orf19.4316	1	1	0	0	1	1	0	0
orf19.745	VAC8	1	0	0	0	1	0	1	1
orf19.5045	orf19.5045	2	0	1	1	0	1	1	1
orf19.169	CHO2	2	0	1	1	0	1	1	1
orf19.4346	orf19.4346	2	0	1	1	0	1	1	1
orf19.2168	orf19.2168	2	0	1	1	0	1	1	0
orf19.5038	orf19.5038	2	0	1	1	0	1	1	0
orf19.649	orf19.649	2	0	1	1	0	0	1	1
orf19.4643	orf19.4643	2	0	1	1	0	1	1	0
orf19.1766	orf19.1766	2	0	1	1	0	1	0	0
orf19.4243	orf19.4243	2	0	1	1	0	1	0	0
orf19.3906	orf19.3906	2	0	1	1	0	1	0	0
orf19.2901	NUP60	2	0	0	1	0	1	1	0
orf19.1748	orf19.1748	2	0	1	1	0	1	0	0

orf19.2510	orf19.2510	2	0	0	1	0	1	1	0
orf19.1624.1	orf19.1624.1	2	0	1	1	0	0	1	0
orf19.4191.1	orf19.4191.1	2	0	1	1	0	1	0	0
orf19.3380	HWP2	2	0	0	1	0	1	1	0
orf19.5918	orf19.5918	2	0	1	1	0	1	0	0
orf19.1083	orf19.1083	2	0	1	0	0	1	1	0
orf19.6499	orf19.6499	2	0	0	1	0	1	1	0
orf19.7036	orf19.7036	2	0	1	0	0	1	1	0
orf19.1608	orf19.1608	2	0	1	1	0	1	0	0
orf19.5915	DUR35	2	0	0	1	0	1	1	0
orf19.4412	orf19.4412	2	0	1	1	0	1	0	0
orf19.1622	YCG1	2	0	1	0	0	1	1	0
orf19.3613	orf19.3613	2	0	1	0	0	1	1	0
orf19.267	orf19.267	2	0	1	1	0	0	1	0
orf19.4570	orf19.4570	2	0	1	1	0	1	0	0
orf19.5854.1	orf19.5854.1	2	0	0	1	0	1	1	0
orf19.4404	PGA49	2	0	0	1	0	1	1	0
orf19.4225	LEU3	2	0	0	1	0	1	1	0
orf19.1772	orf19.1772	2	0	1	1	0	1	0	0
orf19.5924	ZCF31	2	0	0	1	0	1	1	0
orf19.7277	orf19.7277	2	0	1	0	0	1	1	0
orf19.2826	orf19.2826	2	0	0	1	0	1	1	0
orf19.2547	orf19.2547	2	0	1	1	0	0	1	0
orf19.1779	MP65	2	0	0	1	0	1	1	0
orf19.3937	orf19.3937	2	0	0	1	0	1	1	0
orf19.6260	orf19.6260	2	0	1	0	0	1	1	0
orf19.1616	FGR23	3	0	1	1	1	1	0	1
orf19.2850	orf19.2850	3	0	1	1	1	1	0	1
orf19.2629	orf19.2629	3	0	0	1	0	1	1	1
orf19.4655	OPT6	3	0	1	1	0	1	0	1
orf19.2747	RGT1	3	0	0	1	1	1	0	1
orf19.255	ZCF1	3	0	1	1	1	1	0	0
orf19.1808	orf19.1808	3	0	1	1	0	1	0	1
orf19.4239	orf19.4239	3	0	0	1	1	1	0	1
orf19.366	orf19.366	3	0	1	1	1	0	0	1
orf19.5510	orf19.5510	3	0	1	0	0	1	1	1
orf19.4510	IFA4	3	0	1	1	0	0	0	1
orf19.115	orf19.115	3	0	1	0	0	1	0	1
orf19.371	orf19.371	3	0	0	1	1	0	0	1
orf19.3463	orf19.3463	3	0	0	0	1	1	0	1
orf19.3916	orf19.3916	3	0	0	1	0	1	0	1
orf19.3190	HAL9	3	0	1	1	0	0	0	1
orf19.4901	orf19.4901	3	0	0	0	0	1	1	1
orf19.4280	orf19.4280	3	0	1	0	0	1	0	1
orf19.6280	orf19.6280	3	0	1	0	1	0	0	1
orf19.3100	orf19.3100	3	0	1	0	0	1	0	1
orf19.92	orf19.92	3	0	0	0	0	1	1	1

orf19.3429	FGR47	3	0	0	0	1	1	0	1
orf19.3986	PPR1	3	0	1	0	0	1	0	1
orf19.4918	orf19.4918	3	0	0	0	1	1	0	1
orf19.4715	orf19.4715	3	0	0	1	0	1	0	1
orf19.4369	orf19.4369	3	0	0	1	0	1	0	1
orf19.5141	orf19.5141	3	0	0	1	0	1	0	1
orf19.6921	orf19.6921	3	0	0	0	1	1	0	1
orf19.4348	orf19.4348	3	0	0	1	0	1	0	1
orf19.1296	orf19.1296	3	0	1	1	1	0	0	0
orf19.5505	HIS7	3	0	1	0	0	1	0	1
orf19.2879	IFF5	3	0	0	1	0	1	0	1
orf19.6999	orf19.6999	3	0	0	0	0	1	1	1
orf19.3773	CDL1	3	0	1	1	1	0	0	0
orf19.3098	orf19.3098	3	0	0	1	0	1	0	1
orf19.2797	orf19.2797	3	0	0	0	1	1	0	1
orf19.1551	orf19.1551	3	0	1	1	1	0	0	0
orf19.102	orf19.102	3	0	0	0	0	1	1	1
orf19.4697	MDN1	4	1	1	1	0	1	0	1
orf19.4658	orf19.4658	4	1	1	1	1	0	0	1
orf19.4958	ECM25	4	1	1	0	1	1	0	1
orf19.4498	orf19.4498	4	1	1	0	1	0	1	0
orf19.4068	orf19.4068	4	1	1	1	1	0	0	0
orf19.5710	orf19.5710	4	1	1	0	0	1	0	1
orf19.2647	ZCF14	4	1	0	0	0	1	1	1
orf19.4557	orf19.4557	4	1	1	0	0	1	0	1
orf19.4649	ZCF27	4	1	1	1	0	1	0	0
orf19.5065	orf19.5065	4	1	1	0	0	1	1	0
orf19.4961	STP2	4	1	1	0	1	0	0	0
orf19.3239	CTF18	4	1	1	1	0	0	0	0
orf19.2433	orf19.2433	4	1	1	0	0	1	0	0
orf19.1531	orf19.1531	4	1	1	1	0	0	0	0
orf19.5705	NAM2	4	1	0	0	0	1	0	1
orf19.1492	PRP39	4	1	1	1	0	0	0	0
orf19.3997	ADH1	4	1	0	0	0	0	1	1
orf19.894	orf19.894	4	1	1	1	0	0	0	0
orf19.6979	orf19.6979	4	1	1	0	0	0	1	0
orf19.1500	orf19.1500	4	1	1	0	0	0	0	1
orf19.4459	orf19.4459	4	1	0	0	0	1	0	1
orf19.6480	orf19.6480	4	1	1	0	0	1	0	0
orf19.427	orf19.427	4	1	1	0	0	1	0	0
orf19.4257	INT1	4	1	0	0	0	0	1	1
orf19.3203	RCY1	4	1	1	0	0	1	0	0
orf19.1841	orf19.1841	4	1	1	0	0	0	0	1
orf19.4394	orf19.4394	4	1	1	0	0	1	0	0
orf19.6694	orf19.6694	4	1	1	1	0	0	0	0
orf19.7193	orf19.7193	4	1	1	0	1	0	0	0
orf19.4965	orf19.4965	4	1	0	0	0	0	1	1

orf19.3615	orf19.3615	4	1	1	1	0	0	0	0
orf19.5752	orf19.5752	4	1	1	0	0	0	0	1
orf19.6919	orf19.6919	4	1	1	0	0	0	0	1
orf19.3439	orf19.3439	4	1	0	0	0	1	0	1
orf19.5949	FAS2	4	1	1	0	0	0	1	0
orf19.6344	RBK1	4	1	1	0	0	0	1	0
orf19.3188	TAC1	5	1	1	1	0	1	1	0
orf19.7032	orf19.7032	5	1	0	1	0	1	1	1
orf19.1298	NUP84	5	1	0	1	0	1	1	0
orf19.2761	orf19.2761	5	1	0	1	0	1	0	1
orf19.3706	orf19.3706	5	1	0	1	0	1	1	0
orf19.4337	orf19.4337	5	1	0	1	0	1	0	1
orf19.2652	TEF4	5	1	0	1	0	1	1	0
orf19.3629	DSE1	5	1	0	1	0	1	0	0
orf19.76	SPB1	5	1	0	0	0	1	1	0
orf19.5504	orf19.5504	5	1	0	0	0	1	1	0
orf19.1532	SAM37	5	1	0	1	0	0	1	0
orf19.1400	orf19.1400	5	1	0	1	0	1	0	0
orf19.1096	orf19.1096	5	1	0	0	0	1	1	0
orf19.290	KRE5	5	1	0	1	0	1	0	0
orf19.2266	orf19.2266	5	1	0	0	0	1	1	0
orf19.1798	TSC2	5	1	0	1	0	1	0	0
orf19.4145	ZCF20	5	1	0	1	0	1	0	0
orf19.4315	orf19.4315	5	1	0	1	0	1	0	0
orf19.4325	orf19.4325	5	1	0	1	0	0	1	0
orf19.2907	PGA42	5	1	0	1	0	1	0	0
orf19.4683	MLP1	5	1	0	1	0	1	0	0
orf19.6294	MYO1	5	1	0	1	0	1	0	0
orf19.5134	orf19.5134	5	1	0	1	0	0	1	0
orf19.3166	orf19.3166	5	1	0	1	0	1	0	0
orf19.1305	orf19.1305	5	1	0	1	0	1	0	0
orf19.746	orf19.746	5	1	0	1	0	0	1	0
orf19.2404	orf19.2404	6	1	0	1	1	0	1	1
orf19.1596	FGR28	6	0	0	1	1	1	1	1
orf19.7029	orf19.7029	6	1	0	1	1	1	1	0
orf19.2650	orf19.2650	6	0	0	1	1	1	1	1
orf19.1606	orf19.1606	6	0	1	1	1	1	1	0
orf19.5297	orf19.5297	6	1	0	1	1	0	1	1
orf19.230	orf19.230	6	1	0	1	1	1	1	0
orf19.4673	BMT9	6	0	1	1	1	0	1	0
orf19.7472	IFF4	6	0	0	1	1	1	1	0
orf19.6862	orf19.6862	6	0	0	1	1	1	1	0
orf19.2400	orf19.2400	6	0	0	1	0	0	1	1
orf19.175	orf19.175	6	0	0	1	0	0	1	1
orf19.1111	orf19.1111	6	0	0	1	1	0	1	0
orf19.1795	PUF3	6	0	0	1	1	0	1	0
orf19.5976	orf19.5976	6	1	0	0	1	0	1	0

orf19.7027	orf19.7027	6	0	0	1	1	0	1	0
orf19.7023	orf19.7023	6	1	0	0	1	0	1	0
orf19.2724	orf19.2724	6	0	0	1	1	0	1	0
orf19.194	orf19.194	6	0	0	1	0	0	1	1
orf19.1113	orf19.1113	6	0	0	1	1	0	1	0
orf19.262	SMC3	6	0	0	1	1	0	1	0
orf19.1106	orf19.1106	6	0	0	1	1	0	1	0
orf19.3170	orf19.3170	6	0	0	1	1	0	1	0
orf19.3178	orf19.3178	6	1	0	1	1	0	0	0
orf19.2847.1	orf19.2847.1	6	0	0	1	1	0	1	0
orf19.8	orf19.8	6	0	0	1	1	0	1	0
orf19.229	orf19.229	6	0	0	1	1	0	1	0
orf19.3148	orf19.3148	6	0	0	1	1	0	1	0
orf19.1768	orf19.1768	7	0	0	1	1	1	0	0
orf19.3910	orf19.3910	7	0	0	1	1	1	0	0
orf19.1359	orf19.1359	7	0	0	1	1	1	0	0
orf19.1555	SAC3	7	0	0	1	1	1	0	0
orf19.1662	orf19.1662	7	0	0	1	1	1	0	0
orf19.2182	BLM3	7	0	0	1	1	1	0	0
orf19.3603	orf19.3603	7	0	0	1	1	1	0	0
orf19.1327	RBT1	7	0	0	1	1	1	0	0
orf19.736	SRB8	0	1	1	1	1	1	1	1

B. Shown are the GO enrichments for each cluster, as well as each gene. Benjamini-Hochberg correction and Bonferroni correction are supplied in combination with the nominal P-value.

Cluster 1								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0179	GO:0005515 - protein binding	6250	121	29	3	0.125	0.125
2	0.3453	GO:0005634 - nucleus	6250	640	29	4	0.800	2.417
3	0.3662	GO:0005739 - mitochondrion	6250	464	29	3	0.800	2.563
4	0.5442	GO:0005575 - cellular component	6250	2120	29	10	0.800	3.810
5	0.6748	GO:0003674 - molecular function	6250	2743	29	12	0.800	4.724
6	0.6964	GO:0005737 - cytoplasm	6250	753	29	3	0.800	4.875
7	0.8003	GO:0008150 - biological process	6250	2080	29	8	0.800	5.602

Cluster 2								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0494	GO:0008150 - biological process	6250	2080	38	18	0.177	0.297
2	0.0589	GO:0005575 - cellular component	6250	2120	38	18	0.177	0.354
3	0.1180	GO:0009986 - cell surface	6250	198	38	3	0.236	0.708



4	0.1772	GO:0003674 - molecular function	6250	2743	38	20	0.266	1.063
5	0.4899	GO:0005737 - cytoplasm	6250	753	38	5	0.555	2.940
6	0.5552	GO:0005634 - nucleus	6250	640	38	4	0.555	3.331

Cluster 3								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0129	GO:0003674 - molecular function	6250	2743	38	24	0.064	0.064
2	0.0292	GO:0005575 - cellular component	6250	2120	38	19	0.073	0.146
3	0.1620	GO:0008150 - biological process	6250	2080	38	16	0.270	0.810
4	0.2234	GO:0030447 - filamentous growth	6250	269	38	3	0.279	1.117
5	0.5436	GO:0005739 - mitochondrion	6250	464	38	3	0.544	2.718

Cluster 4								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0150	GO:0005739 - mitochondrion	6250	464	36	7	0.120	0.120
2	0.0318	GO:0005515 - protein binding	6250	121	36	3	0.127	0.254
3	0.0744	GO:0003700 - transcription factor activity	6250	171	36	3	0.199	0.596
4	0.1813	GO:0003674 - molecular function	6250	2743	36	19	0.363	1.451
5	0.2905	GO:0008150 - biological process	6250	2080	36	14	0.408	2.324
6	0.3064	GO:0005634 - nucleus	6250	640	36	5	0.408	2.451
7	0.4409	GO:0005737 - cytoplasm	6250	753	36	5	0.452	3.528
8	0.4521	GO:0005575 - cellular component	6250	2120	36	13	0.452	3.616

Cluster 5								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.2179	GO:0008150 - biological process	6250	2080	26	11	0.506	0.872
2	0.3311	GO:0003674 - molecular function	6250	2743	26	13	0.506	1.325
3	0.3812	GO:0005575 - cellular component	6250	2120	26	10	0.506	1.525
4	0.5063	GO:0005634 - nucleus	6250	640	26	3	0.506	2.025

Cluster 6								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0545	GO:0003674 - molecular function	6250	2743	28	17	0.218	0.218
2	0.1889	GO:0008150 - biological process	6250	2080	28	12	0.279	0.756

		biological_process						
3	0.2095	GO:0005575 - cellular_component	6250	2120	28	12	0.279	0.838
4	0.6729	GO:0005737 - cytoplasm	6250	753	28	3	0.673	2.692
<b>Cluster 7</b>								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0873	GO:0008150 - biological_process	6250	2080	8	5	0.262	0.349
2	0.2394	GO:0003674 - molecular_function	6250	2743	8	5	0.359	0.958
3	0.5462	GO:0005575 - cellular_component	6250	2120	8	3	0.546	2.185
<b>Unclusterd</b>								
rank	p	GO	N	K	n	k	BHP	Bonferroni

<b>All Clusters</b>								
rank	p	GO	N	K	n	k	BHP	Bonferroni
1	0.0006	GO:0003704 - specific RNA polymerase II transcription factor activity	6250	45	204	7	<b>0.023</b>	0.023
2	0.0022	GO:0003674 - molecular_function	6250	2743	204	110	<b>0.024</b>	0.087
3	0.0022	GO:0005654 - nucleoplasm	6250	29	204	5	<b>0.024</b>	0.088
4	0.0024	GO:0007120 - axial cellular bud site selection	6250	18	204	4	<b>0.024</b>	0.094
5	0.0100	GO:0008150 - biological_process	6250	2080	204	84	0.077	0.399
6	0.0115	GO:0005575 - cellular_component	6250	2120	204	85	0.077	0.460
7	0.0138	GO:0000747 - conjugation with cellular fusion	6250	29	204	4	0.079	0.552
8	0.0166	GO:0000142 - cellular bud neck contractile ring	6250	17	204	3	0.083	0.665
9	0.0259	GO:0007064 - mitotic sister chromatid cohesion	6250	20	204	3	0.115	1.037
10	0.0368	GO:0009277 - fungal-type cell wall	6250	96	204	7	0.147	1.470
11	0.0505	GO:0005198 - structural molecule activity	6250	43	204	4	0.180	2.020
12	0.0580	GO:0006406 - mRNA export from nucleus	6250	45	204	4	0.180	2.321
13	0.0585	GO:0009986 - cell surface	6250	198	204	11	0.180	2.342
14	0.0730	GO:0005643 - nuclear pore	6250	30	204	3	0.209	2.919
15	0.0839	GO:0030446 - hyphal cell wall	6250	51	204	4	0.224	3.357

16	0.0999	GO:0005515 - protein binding	6250	121	204	7	0.250	3.998
17	0.1314	GO:0045944 - positive regulation of transcription from RNA polymerase II promoter	6250	60	204	4	0.309	5.258
18	0.1493	GO:0006364 - rRNA processing	6250	63	204	4	0.332	5.973
19	0.1745	GO:0009060 - aerobic respiration	6250	67	204	4	0.367	6.980
20	0.2316	GO:0016563 - transcription activator activity	6250	51	204	3	0.463	9.263
21	0.2627	GO:0030447 - filamentous growth	6250	269	204	11	0.480	10.506
22	0.2669	GO:0043565 - sequence-specific DNA binding	6250	55	204	3	0.480	10.674
23	0.2758	GO:0005576 - extracellular region	6250	56	204	3	0.480	11.032
24	0.3247	GO:0003700 - transcription factor activity	6250	171	204	7	0.541	12.986
25	0.3388	GO:0000324 - fungal-type vacuole	6250	63	204	3	0.542	13.553
26	0.4108	GO:0009405 - pathogenesis	6250	187	204	7	0.632	16.431
27	0.4318	GO:0005634 - nucleus	6250	640	204	22	0.639	17.272
28	0.4474	GO:0005739 - mitochondrion	6250	464	204	16	0.639	17.896
29	0.4962	GO:0005935 - cellular bud neck	6250	81	204	3	0.684	19.847
30	0.5446	GO:0031505 - fungal-type cell wall organization	6250	87	204	3	0.700	21.784
31	0.5482	GO:0006355 - regulation of transcription, DNA-dependent	6250	119	204	4	0.700	21.928
32	0.5601	GO:0005759 - mitochondrial matrix	6250	89	204	3	0.700	22.405
33	0.6774	GO:0030448 - hyphal growth	6250	174	204	5	0.798	27.094
34	0.7027	GO:0005625 - soluble fraction	6250	110	204	3	0.798	28.109
35	0.7152	GO:0005783 - endoplasmic reticulum	6250	182	204	5	0.798	28.607
36	0.7182	GO:0005730 - nucleolus	6250	148	204	4	0.798	28.729
37	0.7969	GO:0042493 - response to drug	6250	343	204	9	0.862	31.876
38	0.8585	GO:0016020 - membrane	6250	145	204	3	0.891	34.340
39	0.8683	GO:0005737 - cytoplasm	6250	753	204	20	0.891	34.730
40	0.9983	GO:0005886 - plasma membrane	6250	416	204	5	0.998	39.932

C. Shown are persistently mutated genes that are recurrent in three or more time courses that co-occur with increases to MIC. Clustering was determined via NMF of the Pearson correlations of each row-vector.

ORF	Genes	Cluster	PT1	PT7	PT9	PT14	PT15	PT43	PT59
orf19.7029	orf19.7029	1	1	0	1	1	1	1	0
orf19.1606	orf19.1606	1	0	1	1	1	1	1	0
orf19.5592	orf19.5592	1	1	1	0	1	1	1	0
orf19.6277	orf19.6277	1	1	1	0	1	1	1	0
orf19.4673	BMT9	1	0	1	1	1	0	1	0
orf19.2646	ZCF13	1	0	0	0	1	1	1	1
orf19.5297	orf19.5297	1	0	0	1	1	0	1	1
orf19.7472	IFF4	1	0	0	1	1	1	1	0
orf19.5504	orf19.5504	1	1	0	0	0	1	1	0
orf19.7561	DEF1	1	0	0	0	1	1	1	0
orf19.1356	orf19.1356	1	0	0	0	1	1	1	0
orf19.1111	orf19.1111	1	0	0	1	1	0	1	0
orf19.1795	PUF3	1	0	0	1	1	0	1	0
orf19.1607	ALR1	1	0	1	0	1	0	1	0
orf19.7023	orf19.7023	1	1	0	0	1	0	1	0
orf19.2724	orf19.2724	1	0	0	1	1	0	1	0
orf19.6544	LPI9	1	0	0	0	1	1	1	0
orf19.2266	orf19.2266	1	1	0	0	0	1	1	0
orf19.4080	orf19.4080	1	0	0	0	1	1	1	0
orf19.1113	orf19.1113	1	0	0	1	1	0	1	0
orf19.262	SMC3	1	0	0	1	1	0	1	0
orf19.1106	orf19.1106	1	0	0	1	1	0	1	0
orf19.5621	orf19.5621	1	1	0	0	1	1	0	0
orf19.6592	orf19.6592	1	0	0	0	1	1	1	0
orf19.5058	SMI1	1	0	0	0	1	1	1	0
orf19.5003	orf19.5003	1	0	1	0	1	0	1	0
orf19.229	orf19.229	1	0	0	1	1	0	1	0
orf19.7342	AXL1	1	0	0	0	1	1	1	0
orf19.746	orf19.746	1	1	0	1	0	0	1	0
orf19.745	VAC8	1	0	0	0	1	0	1	1
orf19.5710	orf19.5710	2	1	1	0	0	1	0	1
orf19.4557	orf19.4557	2	1	1	0	0	1	0	1
orf19.2168	orf19.2168	2	0	1	1	0	1	1	0
orf19.5038	orf19.5038	2	0	1	1	0	1	1	0
orf19.4649	ZCF27	2	1	1	1	0	1	0	0
orf19.4643	orf19.4643	2	0	1	1	0	1	1	0
orf19.1766	orf19.1766	2	0	1	1	0	1	0	0
orf19.4961	STP2	2	1	1	0	1	0	0	0
orf19.4243	orf19.4243	2	0	1	1	0	1	0	0
orf19.4068	orf19.4068	2	1	1	1	0	0	0	0
orf19.3239	CTF18	2	1	1	1	0	0	0	0
orf19.3906	orf19.3906	2	0	1	1	0	1	0	0

orf19.2433	orf19.2433	2	1	1	0	0	1	0	0
orf19.1748	orf19.1748	2	0	1	1	0	1	0	0
orf19.1624.1	orf19.1624.1	2	0	1	1	0	0	1	0
orf19.4191.1	orf19.4191.1	2	0	1	1	0	1	0	0
orf19.894	orf19.894	2	1	1	1	0	0	0	0
orf19.6979	orf19.6979	2	1	1	0	0	0	1	0
orf19.1500	orf19.1500	2	1	1	0	0	0	0	1
orf19.5918	orf19.5918	2	0	1	1	0	1	0	0
orf19.1083	orf19.1083	2	0	1	0	0	1	1	0
orf19.7036	orf19.7036	2	0	1	0	0	1	1	0
orf19.4394	orf19.4394	2	1	1	0	0	1	0	0
orf19.3613	orf19.3613	2	0	1	0	0	1	1	0
orf19.1608	orf19.1608	2	0	1	1	0	1	0	0
orf19.6694	orf19.6694	2	1	1	1	0	0	0	0
orf19.4412	orf19.4412	2	0	1	1	0	1	0	0
orf19.1622	YCG1	2	0	1	0	0	1	1	0
orf19.267	orf19.267	2	0	1	1	0	0	1	0
orf19.4570	orf19.4570	2	0	1	1	0	1	0	0
orf19.255	ZCF1	2	0	1	1	0	1	0	0
orf19.6919	orf19.6919	2	1	1	0	0	0	0	1
orf19.1772	orf19.1772	2	0	1	1	0	1	0	0
orf19.7277	orf19.7277	2	0	1	0	0	1	1	0
orf19.2547	orf19.2547	2	0	1	1	0	0	1	0
orf19.1551	orf19.1551	2	0	1	1	1	0	0	0
orf19.5065	orf19.5065	2	0	1	0	0	1	1	0
orf19.5949	FAS2	2	1	1	0	0	0	1	0
orf19.6260	orf19.6260	2	0	1	0	0	1	1	0
orf19.736	SRB8	3	0	1	1	1	1	1	1
orf19.5045	orf19.5045	3	0	1	1	0	1	1	1
orf19.5596	orf19.5596	3	0	1	0	1	1	1	1
orf19.169	CHO2	3	0	1	1	0	1	1	1
orf19.4346	orf19.4346	3	0	1	1	0	1	1	1
orf19.1769	orf19.1769	3	0	1	0	1	0	1	1
orf19.2404	orf19.2404	3	1	0	1	0	0	1	1
orf19.2629	orf19.2629	3	0	0	1	0	1	1	1
orf19.4697	MDN1	3	0	1	1	0	1	0	1
orf19.1596	FGR28	3	0	0	1	0	1	1	1
orf19.1616	FGR23	3	0	1	1	0	1	0	1
orf19.3473	orf19.3473	3	0	1	0	1	0	1	1
orf19.2850	orf19.2850	3	0	1	1	0	1	0	1
orf19.2650	orf19.2650	3	0	0	1	0	1	1	1
orf19.7032	orf19.7032	3	0	0	1	0	1	1	1
orf19.4655	OPT6	3	0	1	1	0	1	0	1
orf19.2747	RGT1	3	0	0	1	1	1	0	1
orf19.1808	orf19.1808	3	0	1	1	0	1	0	1
orf19.5597	POL5	3	0	1	0	0	1	1	1
orf19.649	orf19.649	3	0	1	1	0	0	1	1

orf19.366	orf19.366	3	0	1	1	1	0	0	1
orf19.5510	orf19.5510	3	0	1	0	0	1	1	1
orf19.4510	IFA4	3	0	1	1	0	0	0	1
orf19.115	orf19.115	3	0	1	0	0	1	0	1
orf19.371	orf19.371	3	0	0	1	1	0	0	1
orf19.2400	orf19.2400	3	0	0	1	0	0	1	1
orf19.3916	orf19.3916	3	0	0	1	0	1	0	1
orf19.7204	orf19.7204	3	0	1	0	0	0	1	1
orf19.3190	HAL9	3	0	1	1	0	0	0	1
orf19.4901	orf19.4901	3	0	0	0	0	1	1	1
orf19.175	orf19.175	3	0	0	1	0	0	1	1
orf19.4280	orf19.4280	3	0	1	0	0	1	0	1
orf19.3997	ADH1	3	1	0	0	0	0	1	1
orf19.6280	orf19.6280	3	0	1	0	1	0	0	1
orf19.3100	orf19.3100	3	0	1	0	0	1	0	1
orf19.92	orf19.92	3	0	0	0	0	1	1	1
orf19.3986	PPR1	3	0	1	0	0	1	0	1
orf19.4918	orf19.4918	3	0	0	0	1	1	0	1
orf19.4257	INT1	3	1	0	0	0	0	1	1
orf19.4715	orf19.4715	3	0	0	1	0	1	0	1
orf19.4369	orf19.4369	3	0	0	1	0	1	0	1
orf19.5141	orf19.5141	3	0	0	1	0	1	0	1
orf19.194	orf19.194	3	0	0	1	0	0	1	1
orf19.2647	ZCF14	3	0	0	0	0	1	1	1
orf19.4348	orf19.4348	3	0	0	1	0	1	0	1
orf19.4965	orf19.4965	3	1	0	0	0	0	1	1
orf19.5505	HIS7	3	0	1	0	0	1	0	1
orf19.4288	CTA7	3	0	0	0	0	1	1	1
orf19.2879	IFF5	3	0	0	1	0	1	0	1
orf19.6999	orf19.6999	3	0	0	0	0	1	1	1
orf19.2761	orf19.2761	3	0	0	1	0	1	0	1
orf19.3098	orf19.3098	3	0	0	1	0	1	0	1
orf19.4239	orf19.4239	3	0	0	1	0	1	0	1
orf19.4658	orf19.4658	3	0	1	1	0	0	0	1
orf19.4958	ECM25	3	0	1	0	0	1	0	1
orf19.2797	orf19.2797	3	0	0	0	1	1	0	1
orf19.102	orf19.102	3	0	0	0	0	1	1	1
orf19.3188	TAC1	4	1	1	1	0	1	1	0
orf19.1298	NUP84	4	1	0	1	0	1	1	0
orf19.4337	orf19.4337	4	1	0	1	0	1	0	1
orf19.230	orf19.230	4	1	0	1	0	1	1	0
orf19.2652	TEF4	4	1	0	1	0	1	1	0
orf19.3629	DSE1	4	1	0	1	0	1	0	0
orf19.2901	NUP60	4	0	0	1	0	1	1	0
orf19.2510	orf19.2510	4	0	0	1	0	1	1	0
orf19.1555	SAC3	4	0	0	1	1	1	0	0
orf19.3380	HWP2	4	0	0	1	0	1	1	0

orf19.1400	orf19.1400	4	1	0	1	0	1	0	0
orf19.3706	orf19.3706	4	0	0	1	0	1	1	0
orf19.290	KRE5	4	1	0	1	0	1	0	0
orf19.6499	orf19.6499	4	0	0	1	0	1	1	0
orf19.3603	orf19.3603	4	0	0	1	1	1	0	0
orf19.1798	TSC2	4	1	0	1	0	1	0	0
orf19.5915	DUR35	4	0	0	1	0	1	1	0
orf19.4145	ZCF20	4	1	0	1	0	1	0	0
orf19.5854.1	orf19.5854.1	4	0	0	1	0	1	1	0
orf19.4404	PGA49	4	0	0	1	0	1	1	0
orf19.4225	LEU3	4	0	0	1	0	1	1	0
orf19.5924	ZCF31	4	0	0	1	0	1	1	0
orf19.2826	orf19.2826	4	0	0	1	0	1	1	0
orf19.3166	orf19.3166	4	1	0	1	0	1	0	0
orf19.1327	RBT1	4	0	0	1	1	1	0	0
orf19.1779	MP65	4	0	0	1	0	1	1	0
orf19.3937	orf19.3937	4	0	0	1	0	1	1	0
orf19.6862	orf19.6862	4	0	0	1	0	1	1	0
orf19.4683	MLP1	4	1	0	1	0	1	0	0

D. Shown are the GO enrichments for each cluster for the MIC-coupled persistent recurrent mutation list. Benjamini-Hochberg corrected and Bonferroni corrected p-values are supplied in combination with the nominal P-value.

Cluster 1									
rank	p	GO	N	K	n	k	BHP	Bonferonni	
1	0.164	GO:0008150 - biological process	6250	2080	30	13	0.324	0.819	
2	0.188	GO:0005634 - nucleus	6250	640	30	5	0.324	0.938	
3	0.194	GO:0003674 - molecular function	6250	2743	30	16	0.324	0.972	
4	0.299	GO:0005575 - cellular component	6250	2120	30	12	0.374	1.497	
5	0.387	GO:0005739 - mitochondrion	6250	464	30	3	0.387	1.935	

Cluster 2									
rank	p	GO	N	K	n	k	BHP	Bonferonni	
1	0.001	GO:0008150 - biological process	6250	2080	39	23	0.005	0.005	
2	0.008	GO:0005575 - cellular component	6250	2120	39	21	0.024	0.048	
3	0.020	GO:0003674 - molecular function	6250	2743	39	24	0.039	0.118	
4	0.328	GO:0005739 - mitochondrion	6250	464	39	4	0.492	1.969	
5	0.514	GO:0005737 - cytoplasm	6250	753	39	5	0.576	3.083	
6	0.576	GO:0005634 - nucleus	6250	640	39	4	0.576	3.458	

Cluster 3									
rank	p	GO	N	K	n	k	BHP	Bonferonni	
1	0.078	GO:0005625 - soluble fraction	6250	110	57	3	0.292	0.941	
2	0.094	GO:0006355 - regulation of transcription, DNA-dependent	6250	119	57	3	0.292	1.128	
3	0.097	GO:0030447 - filamentous growth	6250	269	57	5	0.292	1.167	

4	0.106	GO:0009986 - cell surface	6250	198	57	4	0.292	1.267
5	0.122	GO:0005575 - cellular component	6250	2120	57	24	0.292	1.461
6	0.204	GO:0003700 - transcription factor activity	6250	171	57	3	0.408	2.449
7	0.252	GO:0003674 - molecular function	6250	2743	57	28	0.432	3.023
8	0.328	GO:0008150 - biological process	6250	2080	57	21	0.493	3.941
9	0.620	GO:0005739 - mitochondrion	6250	464	57	4	0.827	7.442
10	0.741	GO:0005886 - plasma membrane	6250	416	57	3	0.849	8.897
11	0.833	GO:0005737 - cytoplasm	6250	753	57	5	0.849	9.999
12	0.849	GO:0005634 - nucleus	6250	640	57	4	0.849	10.193

Cluster 4								
rank	p	GO	N	K	n	k	BHP	Bonferonni
1	0.001	<b>GO:0009277 - fungal-type cell wall</b>	<b>6250</b>	<b>96</b>	<b>29</b>	<b>4</b>	<b>0.006</b>	<b>0.009</b>
2	0.001	<b>GO:0006406 - mRNA export from nucleus</b>	<b>6250</b>	<b>45</b>	<b>29</b>	<b>3</b>	<b>0.006</b>	<b>0.011</b>
3	0.012	<b>GO:0009986 - cell surface</b>	<b>6250</b>	<b>198</b>	<b>29</b>	<b>4</b>	<b>0.042</b>	<b>0.125</b>
4	0.054	GO:0009405 - pathogenesis	6250	187	29	3	0.136	0.545
5	0.072	GO:0042493 - response to drug	6250	343	29	4	0.143	0.717
6	0.170	GO:0005634 - nucleus	6250	640	29	5	0.283	1.695
7	0.469	GO:0005737 - cytoplasm	6250	753	29	4	0.670	4.690
8	0.675	GO:0003674 - molecular function	6250	2743	29	12	0.843	6.748
9	0.984	GO:0008150 - biological process	6250	2080	29	5	0.996	9.839
10	0.996	GO:0005575 - cellular component	6250	2120	29	4	0.996	9.963

All Genes								
rank	p	GO	N	K	n	k	BHP	Bonferonni
1	0.000	<b>GO:0003704 - specific RNA polymerase II transcription factor activity</b>	<b>6250</b>	<b>45</b>	<b>155</b>	<b>7</b>	<b>0.004</b>	<b>0.004</b>
2	0.009	GO:0007120 - axial cellular bud site selection	6250	18	155	3	0.141	0.316
3	0.013	GO:0007064 - mitotic sister chromatid cohesion	6250	20	155	3	0.141	0.425
4	0.021	GO:0005198 - structural molecule activity	6250	43	155	4	0.141	0.721
5	0.025	GO:0006406 - mRNA export from nucleus	6250	45	155	4	0.141	0.838
6	0.030	GO:0003674 - molecular function	6250	2743	155	80	0.141	1.033
7	0.031	GO:0009277 - fungal-type cell wall	6250	96	155	6	0.141	1.069
8	0.034	GO:0005654 - nucleoplasm	6250	29	155	3	0.141	1.160
9	0.037	GO:0005643 - nuclear pore	6250	30	155	3	0.141	1.266
10	0.045	GO:0008150 - biological process	6250	2080	155	62	0.153	1.527
11	0.057	GO:0009986 - cell surface	6250	198	155	9	0.172	1.938
12	0.061	GO:0045944 - positive regulation of transcription from RNA polymerase II promoter	6250	60	155	4	0.172	2.070
13	0.079	GO:0005515 - protein binding	6250	121	155	6	0.199	2.703



14	0.084	GO:0009060 - aerobic respiration	6250	67	155	4	0.199	2.857
15	0.088	GO:0005575 - cellular component	6250	2120	155	61	0.199	2.983
16	0.132	GO:0030446 - hyphal cell wall	6250	51	155	3	0.264	4.489
17	0.132	GO:0016563 - transcription activator activity	6250	51	155	3	0.264	4.489
18	0.155	GO:0043565 - sequence-specific DNA binding	6250	55	155	3	0.293	5.278
19	0.205	GO:0006364 - rRNA processing	6250	63	155	3	0.367	6.968
20	0.223	GO:0030447 - filamentous growth	6250	269	155	9	0.380	7.593
21	0.250	GO:0003700 - transcription factor activity	6250	171	155	6	0.405	8.504
22	0.319	GO:0009405 - pathogenesis	6250	187	155	6	0.461	10.842
23	0.321	GO:0005634 - nucleus	6250	640	155	18	0.461	10.926
24	0.326	GO:0005935 - cellular bud neck	6250	81	155	3	0.461	11.073
25	0.342	GO:0006355 - regulation of transcription, DNA-dependent	6250	119	155	4	0.462	11.612
26	0.365	GO:0005739 - mitochondrion	6250	464	155	13	0.462	12.402
27	0.367	GO:0031505 - fungal-type cell wall organization	6250	87	155	3	0.462	12.467
28	0.473	GO:0005783 - endoplasmic reticulum	6250	182	155	5	0.574	16.085
29	0.517	GO:0005625 - soluble fraction	6250	110	155	3	0.606	17.577
30	0.623	GO:0042493 - response to drug	6250	343	155	8	0.693	21.188
31	0.632	GO:0030448 - hyphal growth	6250	174	155	4	0.693	21.482
32	0.703	GO:0016020 - membrane	6250	145	155	3	0.747	23.915
33	0.783	GO:0005737 - cytoplasm	6250	753	155	16	0.807	26.619
34	0.981	GO:0005886 - plasma membrane	6250	416	155	5	0.981	33.338

**Supplementary Table 5. Filamentation summary of each strain.** Shown are the strain IDs and their filamentation intensity as described in the methods section of Chapter 2.

Strain	Filamentation
1	0
2	1
3	1
4	1
5	2
6	0
7	3
8	2
9	1
11	2
12	5
13	0
14	3
15	1
16	0
17	2
412	1
2307	2
1002	5
3795	6
580	3
2440	3
2501	4
945	0
1619	0
3107	0
3119	0
5106	0
5108	0
1649	0
3034	0
3917	0
4617	6
4639	7