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Genotypic and phenotypic variation in carbon metabolism and niche breadth in wild and industrial strains of *Saccharomyces cerevisiae*

By

Dana Ann Opulente

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Dana Opulente

We, the dissertation committee for the above candidate for the
Doctor of Philosophy degree, hereby recommend
acceptance of this dissertation.

Joshua S. Rest, Dissertation Advisor
Associate Professor, Department of Ecology and Evolution

Walter F. Eanes, Chairperson of the Defense
Professor, Department of Ecology and Evolution

Daniel E. Dykhuizen
Distinguished Professor Emeritus, Department of Ecology and Evolution

Dannie Durand
Associate Professor, Carnegie Mellon University

This dissertation is accepted by the Graduate School.

Charles Taber
Dean of the Graduate School

Abstract of the Dissertation

Genotypic and phenotypic variation in carbon metabolism and niche breadth in wild and industrial strains of *Saccharomyces cerevisiae*

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Understanding the evolution of complex traits and the generation of biodiversity are fundamental goals of evolutionary biology. One issue with studying these phenomena is the tractability of large scale experiments. The goal of this dissertation is to use a set of wild and industrial strains of the budding yeast *Saccharomyces cerevisiae* to explore the genotypic and phenotypic variation in carbon metabolism. I first used publicly available data to measure variation in carbon metabolism traits, the ability to use a carbon source, across the genus *Saccharomyces*. Additionally, I assessed whether these traits displayed patterns of coordinated gain and loss and what factors were driving these patterns. Next, I used of wild and industrial strains of *S. cerevisiae* to quantify variation in growth rates among carbon metabolism traits across single carbon environments and multi-dimensional conditions. The use of wild and industrial strains and the use of multi-dimensional conditions provided a level of environmental complexity that cannot be achieved with laboratory strains under single condition perturbations. These data, along with genomic data provided insight into how genotypic variation is translated into phenotypic variation. My results demonstrated significant variation for carbon metabolism among strains and strong non-additive growth rate interactions among multi-dimensional conditions. Furthermore, I found associations between growth rate and gene presence and copy number variation. The niche breadth demonstrated by these strains provided the opportunity to further our understanding of mutational robustness, the ability to maintain function in the presence of genetic perturbations. I mutated a subset of strains used in the previous set of experiments using the mutagen Ethyl methansulfonate and compared relative survivorship and growth rates of ancestral and mutant lines to explore whether mutational robustness varied within a species. I found that strains displayed significant variation in mutational robustness. This is the first example of mutational robustness being measured within a species. Next, I examined whether mutational robustness and niche breadth were correlated and found a positive correlation between them. These results suggest mutational robustness is a by-product of selection for increased niche breadth (environmental robustness).

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I hereby state that permission has been granted by PLOS to reproduce the article "Coevolution trump pleiotropy: carbon assimilation traits are independent of metabolic network structure in budding yeast" (Chapter 1) which I wrote with Joshua Rest (who directed and supervised the research) and was published in PLOS One in January 2013.

Introduction

Understanding the genetic and ecological processes underlying biodiversity is a fundamental goal of evolutionary biology (Wu and Lin 2006, Ehrenreich et al. 2012, Bedhomme et al. 2013, Taylor and Ehrenreich 2014). A major issue with exploring this phenomenon is the tractability of conducting large scale experiments. One way to address questions related to the generation of biodiversity, in a high throughput manner, is to use microbes; large numbers of experiments can be completed in a short time and in controlled settings. Microbes are found in a remarkable range of environments, which can be attributed to their diverse array of metabolic traits (Martini 1993, Barnett and Entian 2005, Liang et al. 2011, Warringer et al. 2011). This diversity can be used to ask questions about the evolution of complex traits, and the generation of phenotypic variation. The goal of this dissertation is to explore phenotypic and genotypic variation for carbon metabolism. I examine the genetic basis of phenotypic variation in the ability to metabolize a carbon source. I assess whether there is a trade-off between metabolic breadth and metabolic efficiency. Finally, I evaluate whether there is a correlation between niche breadth and mutational (genetic) robustness.

The budding yeast, *Saccharomyces cerevisiae,* is in some aspects an under-utilized tool in evolutionary biology. Until recently, most studies of evolution in yeast have been conducted using common laboratory strains, even though it has been shown that these strains have been under selection for laboratory conditions (Varela et al. 2005, Rossignol et al. 2009). These conditions do not represent the environmental complexity which yeast can experience, and therefore can misrepresent how ecological complexity shapes phenotypic diversity among yeast**.** Wild *S. cerevisiae* have been isolated from many environments including, fruit, humans, plants, and soil. Furthermore, yeasts are used in baking, brewing and alcohol production (Liti et al. 2009, Warringer et al. 2011). Within these environments, yeast can experience many different multi-dimensional conditions, including heterogeneous environments which can have various carbon and nitrogen sources available and numerous biotic and abiotic stresses. For example, when growing on grapes, L-proline is an abundant nitrogen source (Huang and Brandriss 2000), fructose and glucose are available and as the grapes begin to decay temperatures will increase. These conditions will simultaneously be experienced by the yeast and therefore all play a role in

shaping fitness. Despite this natural complexity, few studies have examined the effects of these multi-dimensional conditions on fitness (Wei et al. 2012).

Little is known about the evolutionary forces that shape the suite of traits an organism has. Multiple traits could have co-evolved because of patterns of similarity across environments (Saxer et al. 2010). Alternatively, sets of traits could be gained and lost together due to shared genes or pathways (Conner 2002, Wang and Zhang 2009). In chapter 1, I examine the phenotypic diversity of carbon metabolism traits (i.e. the ability to use a carbon source) among 488 strains in the genus *Saccharomyces* and determine whether carbon metabolism traits show patterns of coordinated gain and loss. Additionally, I assess whether these suites of coordinated carbon metabolism traits are associated with adaptation to yeast isolation environments (e.g. fruit, soil, and human), or instead with the presence of particular enzymes or metabolic pathways.

Organisms have varying abilities to maintain homeostasis and survive in the face of environmental change (Wenger et al. 2011, Savory et al. 2014). Genetic variation in metabolism and stress resistance traits are especially pervasive in microorganisms, yet the evolutionary forces and tradeoffs that shape this variation are poorly defined. In chapter 2, I address how genetic variation and trade-offs are associated with phenotypic diversity. I quantify variation in growth rate among 33 wild and industrial strains of *S. cerevisiae* in 14 different carbon sources. I also examine the effects of multiple conditions on fitness for 24 strains across 9 carbon sources and either one of 3 temperatures, 4 nitrogen sources, or 2 osmotic conditions. I examine whether there are trade-offs between growth rate and metabolic breadth among strains. I also quantify interactions among conditions and whether these factors had positive or negative effects on fitness. Among the 33 strains in our collection, 16 strains had sequenced genomes available (Bergström et al. 2014). I use these genomes to assess whether gene content differences, the presence or absence of genes or copy number variation, affect the ability to utilize carbon sources and the efficiency with which those carbon sources are utilized.

Mutational (genetic) robustness, the maintenance of phenotypic stability in the presence of genetic perturbations, is a widespread property of biological systems (Lehner 2010, Lehner and Kaneko 2010). The leading hypothesis for the evolution of mutational robustness is that it is simply a by-product of environmental robustness (Wagner et al. 1997, de Visser et al. 2003), a side-effect of natural selection for molecular network architectures with redundancies that confer

stability in the face of environmental variability (Deutscher et al. 2006, Soyer and Pfeiffer 2010). If this is the case, one expectation is that variation in environmental robustness will correlate with variation in mutational robustness (Wagner et al. 1997, de Visser et al. 2003). In Chapter 2, I quantify naturally occurring variation in mutational robustness, and test the hypothesis that such variation can be explained by differences in environmental robustness, which I quantify using metabolic breadth, i.e., the number of environments in which a given strain can grow. I mutate 19 of the *S. cerevisiae* strains used in chapter 2 using the mutagen Ethyl methanesulfonate (EMS), to compare to the original (ancestral) strain. I use flow cytometry to isolate single cells, in order to evaluate differential survival and growth of mutated descendants relative to the ancestor. In this way I quantify variation mutational robustness for those 19 strains. I use the niche breadth data collected in chapter 2 to quantify correlations between mutation robustness and environmental robustness, increased niche breadth.

Taken together, these experiments not only further our understanding of the genotypic and phenotypic variation within *S. cerevisiae*, but also contribute to our knowledge of fundamental concepts in evolutionary biology. The use of these microbes provides us with the opportunity to study correlations among traits, how genetic variation translates into phenotypic variation. We can also examine whether there are trade-offs between breadth and efficiency. Finally, it provides the opportunity to quantify whether there is variation in mutational robustness within a species, and if mutational robustness is correlated with environmental robustness. A summary table of the strains, phenotypic data, and genomic data used in each section of my dissertation is located in *Table* 1

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Table 1: An overview of all strains/species, phenotypic and genetic data used in each chapter of the dissertation.

Chapter	Yeast	Phenotypic Data	Genetic Data
Chapter 1 Suites of Traits	433 yeast strains from the genus *Saccharomyces*	Qualitative growth data for 45 carbon sources	Enzymes and metabolic pathways present in yeast
Chapter 2 Carbon Growth	33 strains of *Saccharomyces cerevisiae*	Growth rate data on 14 carbon sources	Gene content and copy number variation data for 16 strains of *Saccharomyces cerevisiae*
Chapter 2 Genetic Robustness	19 strains of *Saccharomyces cerevisiae*	Growth rate and survivorship data for approximately 644 mutant per 19 strains and 128 ancestor per 19 strains	The metabolic and protein-protein interaction networks were assembled for 16 strains taking into account both gene content and copy number variation

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Coevolution Trumps Pleiotropy: Carbon Assimilation Traits Are Independent of Metabolic Network Structure in Budding Yeast

Dana A. Opulente[1], Christopher M. Morales[1], Lucas B. Carey[2], Joshua S. Rest[1]*

1 Department of Ecology and Evolution, Stony Brook University, Stony Brook, New York, United States of America, **2** Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot, Israel

Abstract

Phenotypic traits may be gained and lost together because of pleiotropy, the involvement of common genes and networks, or because of simultaneous selection for multiple traits across environments (multiple-trait coevolution). However, the extent to which network pleiotropy versus environmental coevolution shapes shared responses has not been addressed. To test these alternatives, we took advantage of the fact that the genus *Saccharomyces* has variation in habitat usage and diversity in the carbon sources that a given strain can metabolize. We examined patterns of gain and loss in carbon utilization traits across 488 strains of *Saccharomyces* to investigate whether the structure of metabolic pathways or selection pressure from common environments may have caused carbon utilization traits to be gained and lost together. While most carbon sources were gained and lost independently of each other, we found four clusters that exhibit non-random patterns of gain and loss across strains. Contrary to the network pleiotropy hypothesis, we did not find that these patterns are explained by the structure of metabolic pathways or shared enzymes. Consistent with the hypothesis that common environments shape suites of phenotypes, we found that the environment a strain was isolated from partially predicts the carbon sources it can assimilate.

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* E-mail: joshua.rest@stonybrook.edu

Introduction

A goal of evolutionary biology is to understand the selective pressures that shape variation in genomes and phenotypes [1–7]. Little is known about the evolutionary forces that shape the suite of carbon sources that an organism can utilize in metabolism. We propose two hypotheses that shape common utilization and loss: (1) carbon assimilation traits are gained and lost together because sets of carbon sources are common to particular environments, or (2) sets of carbon assimilation traits are gained and lost together because the processing of carbon sources often share common metabolic pathways. The first hypothesis means that multiple traits have coevolved because of patterns of similarity across environments [8], while the latter hypothesis implies that pathway or gene-based pleiotropy drives the coordinated gain and loss of multiple traits [9,10]. The diversity of carbon sources used by *Saccharomyces* provides a unique opportunity to study the patterns of gain and loss in carbon utilization and evaluate how these patterns are related to the structure of the metabolic networks and to each strain's environmental source.

Strains in the genus *Saccharomyces* are found in a range of habitats including soil, plants, fruits, fish, and insects. Correspondingly, *Saccharomyces* strains can utilize a diverse range of carbon sources. Carbon sources metabolized within the genus include simple sugars, polyols, organic and fatty acids, aliphatic alcohols, hydrocarbons, and various heterocyclic and polymeric compounds [11]. However, not all strains can use all of these carbon sources.

We compiled growth data from the CBS-KNAW Fungal Biodiversity Centre for strains in the genus *Saccharomyces* to systematically assess patterns of covariation, gain, and loss in carbon utilization. We find that subsets of carbon traits that are gained and lost together cannot be explained by shared metabolic pathways or shared enzyme use. In contrast, we did find that the environment a strain was isolated from partially predicts the set of carbon sources it may assimilate and metabolize. Together, these results suggest that selection by environmental factors may often trump pleiotropy in shaping covariation in sets of carbon assimilation traits.

Methods

Cataloging carbon utilization phenotypes

Growth phenotypes across multiple carbon sources and strain origin data for 448 strains in the genus *Saccharomyces* were retrieved from CBS-KNAW Fungal Biodiversity Centre [12]. We only considered carbon sources that were tested in at least 200 strains and only strains that were tested for at least 20 carbon sources. Either a normal or weak growth phenotype, as reported in CBS-KNAW, was considered evidence for utilization of a particular carbon source.

Table 1. Summary statistics for the number of carbon sources with normal and weak growth phenotypes across 448 strains of *Saccharomyces*.

Statistic	Normal Growth	Weak Growth	Total Growth	No Growth
Mean	7.04	1.88	8.92	37.83
Median	7	0	8	37
S.D.	2.97	4.31	5.20	5.76

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Of possible growth phenotypes across strains, growth data for 8% of the strains were missing in the dataset. For this missing data, we performed a simple random data imputation to infer the carbon utilization trait.

We tested whether growth phenotypes for a carbon source showed an overrepresentation for weak or strong growth using a χ^2-test. If there was no bias for a specific growth phenotype, we would expect similar numbers of strains displaying either a weak or strong growth phenotype. However, if there was a bias for growth phenotype, the observed data would deviate from similar numbers of weak and strong growth phenotypes.

Carbon source utilization cluster analyses by pathway and enzyme

We assessed whether gains and losses of carbon sources cluster by strain using multiscale bootstrap resampling, with 1000 permutations (R v2.14 package pvclust v1.2–2). We produced a matrix between carbon sources reflecting ability to be utilized by the same strains. Each carbon source was then assigned a cluster and similar clusters were joined together until there was only a single cluster remaining. To assess if these patterns were driven by overlapping metabolic pathways, pathway data for each carbon source was acquired from the Kyoto Encyclopedia of Genes and Genomes (KEGG) v62.0 [13]. Carbon sources were clustered by Ward's method (also with pvclust in R) according to their presence

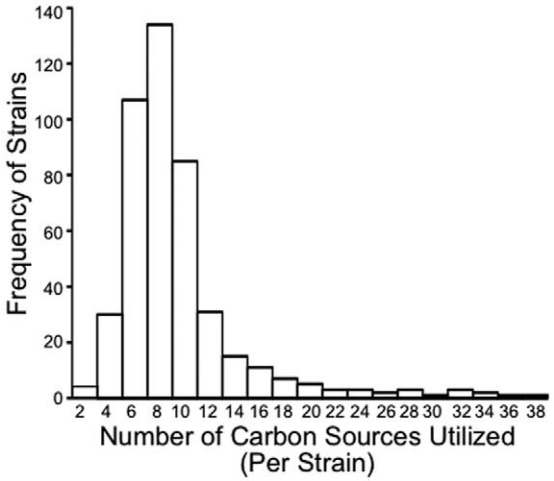

Figure 1. The genus *Saccharomyces* displays variation in the number of carbon sources that each strain can utilize. Growth data was obtained from CBS-KNAW [12].
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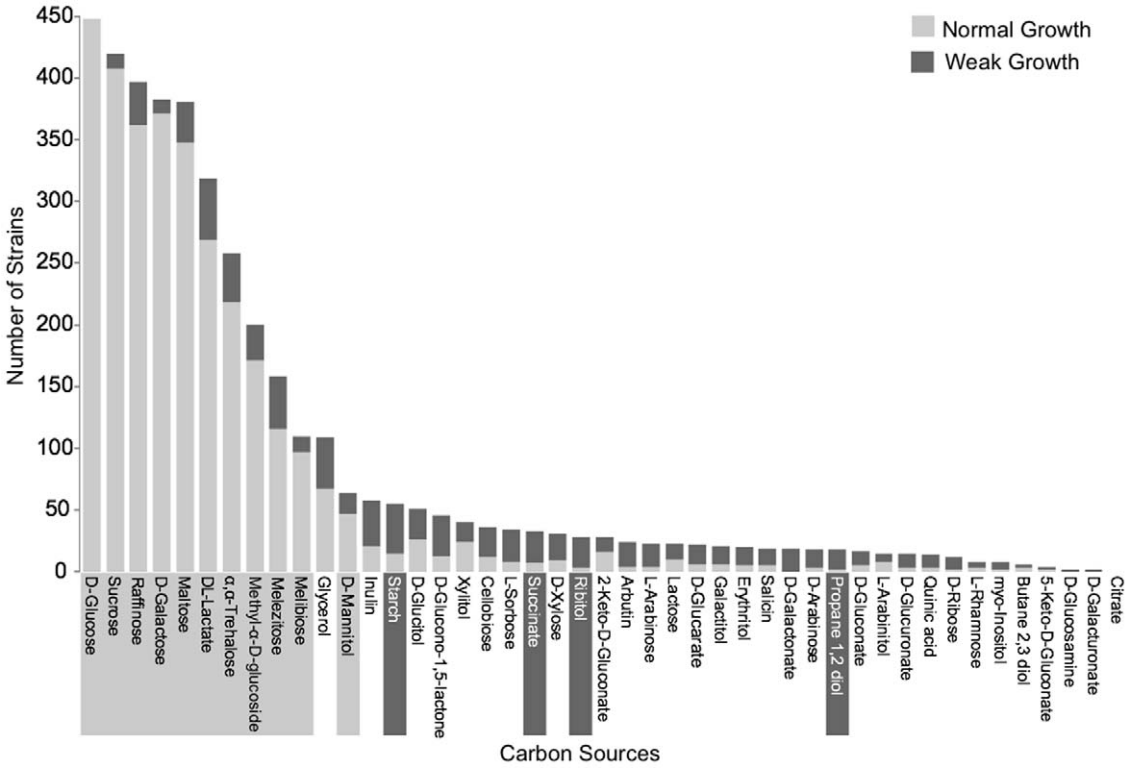

Figure 2. Strains show a bias for weak or normal growth phenotypes for 15 carbon sources. The light and dark grey bars represent weak and normal growth phenotypes, respectively. The light and dark grey boxes surrounding the carbon source names represent carbon sources which display an overrepresentation for a normal or weak growth phenotype, respectively, across all strains (χ^2-test; $p<0.001$).
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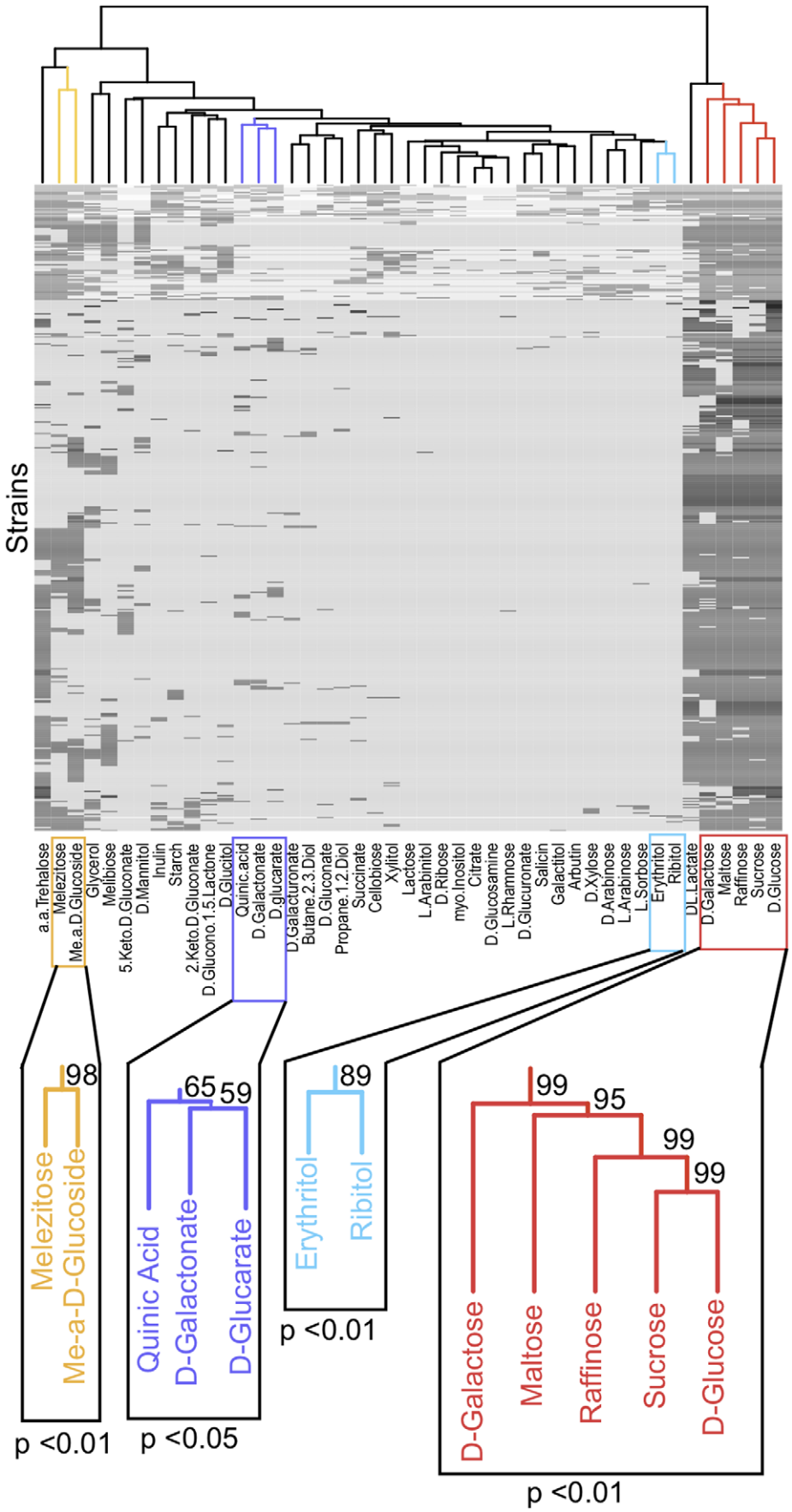

Figure 3. Nonrandom distribution of four clusters of carbon source utilization traits across strains. The heat map shows the ability (black cells) or inability (grey cells) of each strain to utilize each carbon source. Missing data is indicated by white cells. Callout boxes indicate significant clusters of carbon sources according to multiscale bootstrap resampling. P-values and bootstrap support are provided for the significant clusters.
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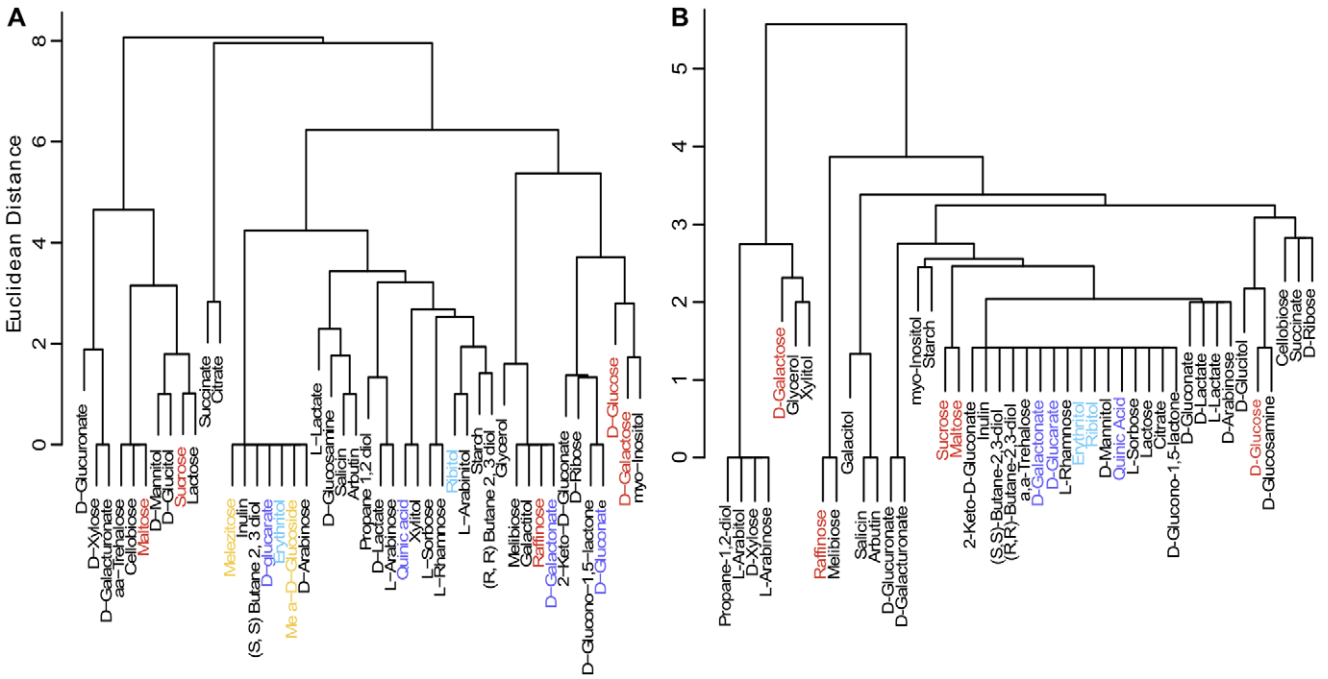

Figure 4. The clustering of carbon sources by (A) their metabolic pathways and (B) enzymes they directly interact with are each different from the clustering of carbon sources by their utilization across strains. The coloring of leaves in **A** and **B** corresponds to carbon sources from significant clusters in Figure 3. The lack of correspondence between these analyses suggests that patterns of gain and loss of carbon utilization traits are not driven by the metabolic pathways in which they are found. Clustering was performed by Ward's method.
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or absence in each metabolic pathway or based on direct interactions with enzymes.

Isolation predicted by carbon sources

We assessed whether carbon source use patterns were driven by a common environment by predicting strain isolations based on carbon source sets. We used a k-nearest neighbor classification ($k = 3$) with a leave-one-out cross validation scheme to determine if carbon source sets could be used to predict strain isolation (MATLAB 2012b).

Results

Carbon source utilization diversity

Carbon utilization is diverse within the genus *Saccharomyces*. On average, strains can grow on approximately 8 carbon sources (*Table 1*); however strains can use a range of 1 to 37 carbon sources (Figure 1).

Saccharomyces strains differ in their growth rate on most carbon sources. In the data analyzed here, strains display either a normal or weak growth phenotype on each carbon source. On average, strains grow normally on 7 carbon sources and grow weakly on an additional 1.88 carbon sources (*Table* 1). All strains grow normally on glucose. To test whether some carbon sources are more likely to result in a slow versus normal growth phenotype, we examined the association between carbon sources and growth rate phenotype. Out of the 45 tested carbon sources, 11 carbon sources are overrepresented for normal growth across strains, relative to a weak growth phenotype (χ^2-test, $p<0.001$, indicated with a light gray boxes in Figure 2). For example, all 488 strains display a normal growth phenotype on glucose, indicating that glucose is overrepresented for the normal growth phenotype ($p = 1.96\times10^{-99}$). This over-representation is expected, as glucose is the preferentially used carbon source of *S. cerevisiae* and other species in the genus [14]. Additional carbon sources which display an overrepresentation for the normal growth phenotype include sucrose ($p = 3.45\times10^{-83}$), D-galactose ($p = 3.68\times10^{-75}$), α,α-trehalose ($p = 1.53\times10^{-28}$), and maltose ($p = 1.38\times10^{-58}$).

In contrast, 4 carbon sources show an overrepresentation for a weak growth phenotype, relative to normal growth phenotype: starch ($p = 7.48\times10^{-4}$), succinate ($p = 9.41\times10^{-4}$), ribitol (3.21×10^{-5}), and propane 1,2 diol ($p = 9.67\times10^{-4}$) (dark gray boxes in Figure 2). For example, of the 55 strains that can use starch, 40 display a weak growth phenotype. This over-representation of weak growth is consistent with previous work showing that while starch can be used by *S. cerevisiae* and other species, they are inefficient at hydrolyzing starch [15,16].

Patterns of gain and loss in carbon utilization

The diversity found for carbon use traits raises the question – is there covariance for gain and loss in carbon utilization? In other words, are strains that have gained or lost the ability to use a particular carbon source more or less likely to have gained or lost the ability to use other carbon sources? There are two mechanisms by which the ability to use particular carbon sources may be gained and lost. First, different environments contain consistently different sets of carbon sources, and strains adapted to alternative environments may be enriched or depleted for respective carbon utilization traits (common environment hypothesis). Second, the metabolism of related carbon sources is achieved by multifunctional enzymes or through alternative steps or configurations of the same metabolic pathways. In these cases, selection for gain or loss of one carbon source may cause concomitant gain or loss of related carbon sources (common network hypothesis).

If carbon source use has been gained and lost in groups, we predict that the distribution of carbon utilization traits will be non-

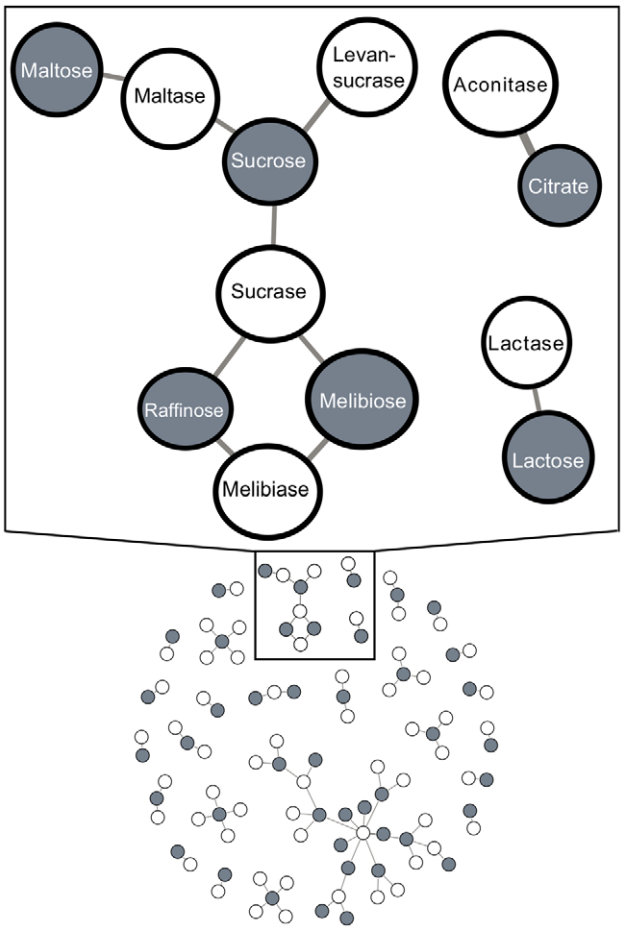

Figure 5. Most enzymes are specialized for catabolism of one or a few carbon sources. White nodes indicate enzymes and gray nodes indicate carbon sources. Edges represent the enzymes that process each carbon source.
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random across diverse *Saccharomyces* strains and species. To test this prediction, we used a multiscale bootstrap analysis to assess whether these carbon utilization traits are distributed non-randomly among strains. Most carbon sources were gained and lost independently of each other. However, we found 4 clusters, involving 2 to 5 carbon sources each, for which gains and losses of carbon sources are significantly associated with each other (Figure 3).

We tested whether common networks are associated with these non-random gains and losses of carbon utilization traits by examining the distribution of carbon gain and loss on the yeast metabolic network. If multiple carbon sources are used in the same pathway, those traits can be gained or lost together through the addition or removal of any node in that pathway. Alternatively, carbon utilization traits may be related only by overlap of just a single enzyme in the pathway [17]. In either of these cases, carbon sources that require the same enzymes will cluster together in carbon utilization patterns. Metabolic network data was collected from KEGG for all carbon sources analyzed in the strain data (i.e. in Figure 3), and clustering of carbon sources by metabolic pathway or shared enzyme was analyzed with hierarchical clustering.

In contrast to the common network hypothesis, we find no evidence that the structure of the metabolic network drives patterns of carbon utilization traits. Comparing the sister carbon sources in Figure 3 (carbon source clustered by strain) to the pattern of carbon sources clustered by metabolic pathways (Figure 4A), we find different carbon sources cluster together in the two analyses. The same is true for enzyme overlap: coordination of carbon utilization with enzyme overlap was also not observed (Figure 4B). Some carbon sources are associated with the same enzymes (Figure 5), but the majority of enzymes are specialized for single carbon sources. The dramatic covariation we see for carbon utilization is thus likely associated with gain and loss of specialized enzymes across strains. Such gain and loss may result in different network properties among strains (e.g. degree distribution).

In order to test whether patterns of carbon source gain and loss are associated with common environments, we analyzed whether the carbon source utilization profile of each strain can predict the natural substrate from which each strain was isolated. If strains isolated from similar environments have gained and lost the ability to grow on similar carbon sources, then strain isolation substrates should be predictable based on which carbon sources can be utilized. We were able to predict 30% of strain isolations correctly, whereas using shuffled data as a null hypothesis, strain isolation source could only be predicted 15% of the time (Figure 6). In particular, the predictive value of the carbon utilization profile is well above our background estimates for isolations from dairy products, insects, plants, and water. This suggests that the environmental source of a strain shapes its carbon utilization profile.

Discussion

We hypothesized that carbon utilization clusters in *Saccharomyces* may be the result of two possible mechanisms: (1) pleiotropy due to shared metabolic pathways or overlapping enzymes among carbon sources or (2) multi-trait coevolution due to similarities of carbon sources within environments. We did not find evidence that coordinated gain and loss of carbon source traits is the result of shared pathways or enzymes (clusters in Figure 3 vs. Figures 4A and 4B). In contrast, we found that a strain's set of carbon utilization traits often predicts the substrate from which the strain was originally isolated. This result suggests that a strain's environment determines its ability to use individual carbon sources. One important caveat, however, is that just because a strain was isolated from a particular habitat (e.g. beer or soil) does not mean that it typically grows on that source. Further, isolation of strains from similar sources may sometimes be confounded with shared phylogenetic history. In our data, strains isolated from similar substrates typically came from multiple species, therefore phylogenetic history is likely not a major confounder. This indicates that repeated parallel evolution of similar carbon utilization sets is due to common environmental pressures (e.g., [18]) across multiple strains and species of budding yeast. However, denser environmental sampling and phylogenetic analysis are required to better define the ecology of individual strains and genotypes.

Variation in the number and types of carbon sources available and used by a strain has the potential to affect both gene content and metabolic networks. This is because there are many genes that are likely to be affected by variation in carbon utilization phenotypes. For example, carbon sources are imported by diverse transport proteins [19,20]. It has been demonstrated that there is an enrichment of duplicate genes in *S. cerevisiae* metabolism [4,21–24], supporting the idea that gene copy number changes play an important role in the evolution of diverse metabolism. Ames *et al.*

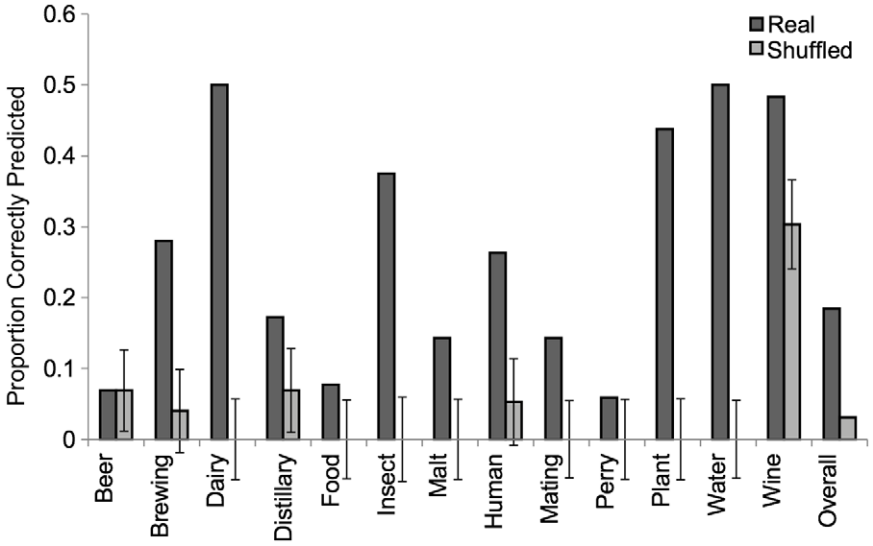

Figure 6. The substrate a strain was isolated from can be predicted based on the set of carbon sources a strain can utilize. Dark gray bars represent the proportion of time that a substrate was correctly predicted. Lighter gray bars represent the background prediction rate and associated confidence intervals based on shuffled data. There was no predictive power for 6 substrates (not shown).
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[10] analyzed variation in gene copy number among 39 strains of *S. cerevisiae* and 28 strains of *S. paradoxus* and found an enrichment of duplicates for genes with catalytic activity and sugar transport. Furthermore, they demonstrated that certain sets of over- and underrepresented duplicates correlate with adaptation to different environments.

Our results provide further support for how network structure can be impacted by the environment, suggesting that a wide metabolic breadth requires larger numbers of nodes, in the form of unique assemblages of specialized enzymes. Such networks will also be more expansive since most carbon sources are not funneled through a single pathway. These two factors suggest that metabolic networks change as a result of variation in metabolic breadth. The recent emphasis on molecular networks has received few rigorous tests about the impact of network structures on evolutionary processes [25,26]. Our results indicate that metabolic network topology may not impose severe constraints on the evolution of carbon utilization phenotypes. Instead, our observation that traits are gained and lost independently of known metabolic network structure suggests that the networks themselves vary and evolve.

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Author Contributions

Conceived and designed the experiments: DO CM LC JR. Performed the experiments: DO. Analyzed the data: DO LC. Contributed reagents/materials/analysis tools: DO CM. Wrote the paper: DO JR.

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Phenotypic and evolutionary consequences of copy number and gene content variation

Chapter 2

Introduction

Gene content variation (GCV) and copy number variation (CNV) contribute to differentiation and adaptive divergence among species (Perry et al. 2008, Paudel et al. 2015) and higher taxonomic levels (Xu et al. 2012)as a result of gene duplication (Ohno 1970) or loss (Cummings et al. 2004). Segmental duplications, for example of Hox (Amores et al. 1998) or Hemoglobin (Hardison 2012) genes are responsible for major transitions in body plan and physiology. GCV and CNV may be substantial even within species, including maize (Swanson-Wagner et al. 2010), cattle (Liu et al. 2010) and humans, some associated with disease (Zhang et al. 2009, Balzola et al. 2010). However, whether GCV and CNV are associated with phenotypic diversity among and within populations, and the consequences of such variation for evolution, are not yet established. In particular, it is unknown whether substantial inter-specific differences in gene content and copy number affect higher-order properties of the metabolic, regulatory, and protein-protein interaction networks. While such networks have often been noted to be highly connected and robust (Barabási and Oltvai 2004), whether such properties vary and evolve, and whether they impart particular properties to individuals, has not been addressed.

In order to study these questions, we chose wild and industrial strains of the budding yeast, *Saccharomyces cerevisiae*. It has previously been reported that isolates differ from one another in DNA copy number in at least 116 genomic regions comprising almost half of the genome, including, for example, in at least five of the alcohol dehydrogenase families (Infante et al. 2003, Conrad and Antonarakis 2007, Sudmant et al. 2011, Conrad et al. 2012, Bergström et al. 2014). Metabolic genes are particularly enriched for duplications and deletions in *S. cerevisiae*, involving perhaps up to half of all metabolic genes, compared to a third of non-metabolic genes (Conant and Wagner 2002, Marland et al. 2004, Kellis et al. 2004, Carreto et al. 2008, Gerlee et al. 2009, Bergström et al. 2014). Consistent with this observation, strains of yeast differ in carbon utilization profiles (Johnston and Carlson 1992). Transport, fermentation and respiration of specific sugars is accomplished by families of genes, for example, *SUC* genes for sucrose and *MAL* genes for maltose, and closely related strains often have different subsets of

genes in each family. Large-scale genomic patterns may play an important role in metabolic diversity; for example, central portions of chromosomes seem to contain core metabolic genes, while genes for peripheral metabolic functions appear to be highly variable because they are located in telomeric regions subject to higher rates of recombination (Argueso et al. 2009).

Here, we measured fitness (growth rate – change in optical density over time) in multiple environments for a panel of diverse yeast strains, both before and after mutagenesis. We assessed these results in light of CNV and GCV, and found complex and nonlinear effects of genetic and phenotypic diversity on fitness across genotypes. We find that phenotypic diversity is also highly correlated with mutational robustness. Most strikingly, higher-order differences in network structure resulting from CNV and GCV partially explain differences among the strains in mutational robustness.

A major axis of genomic variation among diverse populations of yeast is GCV and CNV.

We reanalyzed genomes of 16 wild and industrial strains of *S. cerevisiae* from Bergström et al. (2014) and found that eighteen percent (1195 out of 6610) of genes are variably present across strains (Table 1, Figure 1). These GCV genes are enriched for many processes and functions that are important for interacting with metabolites and other environmental factors including, carbohydrate and sugar metabolism related processes, thiamine metabolic process, and drug transporter activity (Table 2). We also quantified CNV genes (2064 out of 6610) and found enrichment for genes related to carbohydrate and sugar metabolism, and flocculation (for a full list of enrichments see – Table 3). The extensive gene content and copy number variation found among strains, and their associated functions, confirms that a major genomic axis of variation among strains is adaptation for different carbohydrate and sugar metabolism. We therefore next assessed the extent that this genomic diversity is reflected at the phenotypic level.

Extensive natural variation in metabolic breadth and fitness

In order to systematically assess yeast metabolic phenotypes and fitnesses, we grew 33 strains, including the 16 sequenced strains, in synthetic liquid media (0.1g/L NaCL, and ammonium sulfate as a nitrogen source) at 30^{O}C for 96 hours (Table 4, Figure 2). We observed extensive variation in the number and composition of carbon sources that a strain can utilize. Strains can utilize, on average, 8.45 of the 14 carbon sources tested (Figure 3). A subset of these

carbon sources are preferred, able to be used by many strains (e.g. glucose; positive growth in 214/231 assays), while others are non-preferred and used by a few strains (e.g. glycerol, glucitol; positive growth in 65/231 assays) (Figure 4). No strain can metabolize all carbon sources, and some carbon sources are metabolized by only a few strains. For example, only 4 strains can metabolize mannitol, three of which were isolated on or near palm trees. There are 5 strains that utilize 11 carbon sources, three of these strains were isolated from soil and plants (DBVPG 1788, UWOPS03-461.4 and UWOPS05-217.3) and two isolated from humans (YJM 975 and YJM 978, Liti et al. 2009). Four strains metabolize only the 4 carbon sources that all strains can metabolize: fructose, glucose, raffinose, and sucrose. Three of these four strains are brewing related (wine or ginger beer), while the source of the fourth is unknown.

Strains display significant quantitative variation in growth rate (i.e. efficiency); there is an order of magnitude difference in growth rate between preferred and non-preferred carbon sources (Table 4, Figure 5). Furthermore, strains display variation in growth rate within (ANOVA $p<0.001$) and among carbon sources (ANOVA $p<0.001$; Figure 4; Table 5). In addition growth patterns vary significantly among strains (strain x carbon source ANOVA $p<0.001$, Table 5), indicating substantial gene by environment interactions in determining fitness. For example, YJM978 grows moderately fast on galactose but significantly slower on sucrose (Tukey HSD $p<0.001$; Figure 2). In contrast to YJM978, the strain CBS 7765 grows faster on sucrose and slower on galactose (Tukey HSD $p<0.01$).

This substantial quantitative variation in carbon utilization among wild strains is underscored by our discovery of novel carbon sources utilized by *S. cerevisiae.* This species is generally thought to be incapable of utilizing pentoses (Subtil and Boles 2011, 2012), although some recent work has suggested otherwise with important implications for lignocellulosic bioethanol production (e.g. Wenger, Schwartz, and Sherlock 2010a). Previously, two dehydrogenases were isolated from *S. cerevisiae* that can oxidize the methyl pentose sugar D-arabinose (Kim et al. 1998, Amako et al. 2006). As a result of our highly quantitative growth screen, we were able to detect that 8 of our 32 strains inefficiently metabolize D-arabinose, including soil, wine, nectar, and clinical strains (Figure 4). The soil, clinical, nectar, and bili wine strain can also utilize rhamnose, another methyl-pentose sugar, as can a baking strain. This is the first report of rhamnose utilization in *S. cerevisiae.* In addition, we found that 6 of our strains, including the soil, sake, bili wine, fish, and clinical strains, can inefficiently utilize the TCA

cycle intermediate succinate as a sole carbon source, suggesting the existence of an otherwise unknown succinate permease (Kubo et al. 2000, Oyedotun and Lemire 2004).

In order to get an even more expansive measure of phenotypic diversity among yeasts, we tested 21 strains across combinations of environmental variables in a series of multidimensional assays (MDAs), including a range of stress conditions. All MDAs included 10 carbon sources in combination with a second environmental factor: one of 4 nitrogen sources, 3 temperatures or 2 osmotic conditions (Table 4). As expected, we found strong effects of temperature, nitrogen source, and osmotic stress level on growth rate (Figure 6; all ANOVAs $p<0.001$, Table 6A, 6B, 6C).

Metabolic generalist strains are multidimensionally more fit

In our growth assays, we observed a range of growth responses to variation in the environment. For each environmental variable, we identified some strains that can grow over a wide parameter range, and other strains that grow only over a narrow range (e.g. Figure 3 for carbon sources). We consider these environmental parameters to represent slices of niche space, and therefore strains that can grow over a smaller or larger parameter range have narrower and wider niche breadth, respectively.

Whether there are evolutionary and ecological constraints imposed by fitness tradeoffs between wide niche breadth (generalists) and narrow niche breadth (specialists) is a long debated question (Kassen 2002, Butler et al. 2013, Berger et al. 2014). The extensive phenotypic variation in growth of our strains among environments provides us the opportunity to examine evidence for such a tradeoff. We looked for trade-offs between niche breadth and metabolic efficiency, where metabolic efficiency is the average growth rate of a strain across MDA growth environments. We find a positive correlation between MDA niche breadth and efficiency (Figure 7, $R^2 = 0.472$, $p < 0.001$). Thus, rather than a trade-off between niche breadth and efficiency, we find generalists are fitter in both. While it is possible that specialists are specialized for some environment not well-reflected by these in-lab growth assays, specialist strains appear remarkably unfit compared to their generalist cousins. We conclude that drift or lineage-specific loss may have shaped their metabolic capacities, rather than natural selection (Warringer et al. 2011).

Extensive gene content variation underlies niche breadth variation

We next investigated the genomic basis for this dramatic phenotypic variation. We explored the contribution of GCV to metabolic variation among strains, and found that there are 46 unique genes where gene presence is associated with the ability to grow on a carbon source (Table 7). For example, the enzyme alcohol dehydrogenase 2 (ADH2) is associated with the ability to utilize D-arabinose (χ^2, $p<0.005$), and the sugar alcohol glycerol (χ^2, $p<0.005$), as a carbon sources. We also identified 853 GCV genes and 79 CNV genes where gene presence or an increased copy number, respectively, is associated with faster growth rate on a carbon source ($p<0.05$). For example, increased copies of *IMA5* are associated with faster growth on raffinose. *IMA5* is one enzyme responsible for catabolizing raffinose into glucose, fructose, and galactose outside of the cell (Gagiano et al. 2002). Genes where GCVs or CNVs are positively associated with growth are enriched for several carbon metabolism categories (Table 8 & 9). We summarized all genes that are significantly associated with growth and are important for carbon metabolism (Table 10).

We also found 379 genes where presence is negatively associated with growth on a carbon source (Table 7). We also identified 949 GCV genes and 79 CNV genes where gene presence or an increased copy number, respectively, is associated with a slower growth rate on a carbon source ($p < 0.05$). For example, strains with the gene YEL069C, a hexose transporter induced in the presence on non-fermentable carbon source and at low glucose concentrations, generally cannot utilize maltose (χ^2, $p=0.0131$) or succinate (χ^2, $p=0.0367$). For those genes that were negatively associated with growth rate, we did not find GO enrichment for carbohydrate and sugar metabolism (Table 8). This lack of enrichment for genes related to carbohydrate and sugar metabolism among the set of GCV genes associated with slower growth rates on preferred carbon sources suggests that there are no global trade-off s in growth rate among carbon sources. We did find GO enrichment for carbohydrate and sugar metabolism among the set of CNVs where increasing copy number is associated with a slower growth rate (Table 9).

Generalists are mutationally more robust than specialists

Mutational (genetic) robustness, the maintenance of phenotypic stability in the presence of genetic perturbations, is a widespread property of biological systems (Lehner and Kaneko 2010). The leading hypothesis for the evolution of mutational robustness is that it is simply a by-

product of environmental robustness (Wagner et al. 1997, de Visser et al. 2003). If this is the case, one expectation is that variation in environmental robustness will correlate with variation in mutational robustness (Wagner et al. 1997, de Visser et al. 2003). Although this seems to be the case across species (Szöllősi and Derényi 2009), this hypothesis has not been tested within species among naturally occurring genotypes. Here, we sought to quantitate naturally occurring variation in mutational robustness, and to test the hypothesis that such variation can be explained by differences environmental robustness.

We mutated 19 of our *S. cerevisiae* strains using EMS, used flow cytometry to isolate single cells, and evaluated differential survival and growth rate of mutated descendants in two environments. Six out of 19 strains showed significant reduction in survivorship in the glucose environment ($p < 0.05$; Table 11; Figure 8), while 8 of 13 strains showed a significant reduction in survivorship in maltose ($p < 0.05$; Table 11; Figure 8). There was a significant effect of strain in determining the survivorship in both the glucose ($p < 0.005$, Table 12A) and maltose ($p < 0.001$; Table 12B). We also quantified the effect of mutations on growth rate of strains by measuring differences in growth rate distributions between the ancestral and mutant populations for each strain (e.g. BC 187 and CBS 6131, Figure 9), and found significant differences in distributions for 9 strains on glucose and 11 strains on maltose (Figure 10; Table 13).

We found a strong, highly explanatory, and significant positive correlation between relative survivorship of mutated cell lines (mutational robustness) and the number of carbon sources metabolized by the ancestor (environmental robustness) ($p< 0.001$, $R^2 = 0.509$, Figure 11) in the glucose environment. We also found a positive correlation between relative survivorship of mutated cell lines and the absolute number of multidimensional environments in which the ancestor can grow ($p<0.001$, $R^2 = 0.787$, Figure 11) in the glucose environment. We also found a negative correlation between mean growth rate difference and both number of carbon sources metabolized ($p <0.001$, $R^2 = 0.483$, Figure 12) and number of growth environments ($p < 0.01$, $R^2 = 0.458$, Figure 12). In other words, mutations had less of effect as environmental breadth increased. We saw similar, but non-significant, growth trends in the maltose environment, where a smaller number of strains are able to grow. We also quantified additional measures to describe the growth rate distribution including coefficient of variation, skewness and variance (Table 14). We found a positive correlation between the ratio of variation (mutant/ancestor) and both number of carbon environments ($p < 0.05$, $R^2 = 0.225$, Figure 13) and

number of growth environments ($p < 0.001$, $R^2 = 0.509$, Figure 13) on glucose. This suggests that mutations have a broader range of effects on strains with greater environmental breadth however; it does not have an overall negative effect on average growth rate.

These results establish, for the first time, that a large proportion of natural variation in mutational robustness can be explained by naturally segregating variation in environmental robustness phenotypes. Our results suggest that, while the potential for selection to act directly on mutational robustness exists, evolution is more likely driven by evolution of molecular networks in response to nutrient utilization and stress response pathways. It has previously been unclear whether mutational robustness varies among genotypes, whether it evolves, and if so, whether it is subject to natural selection (Freilich et al. 2010). Indeed, experimental evolution of mutational robustness has only been observed in RNA viruses (Montville et al. 2005). Importantly, the variation in genetic robustness among strains we observe here, even if a side effect of environmental robustness, is a phenotype that selection can act upon. Indeed, genetic robustness can promote evolvability through the accumulation of cryptic genetic variation; which can contribute to phenotypic evolution (Masel and Siegal 2009).

Mutational robustness is correlated with network properties

One way that mutational robustness and environmental robustness may be linked is as a result of natural selection for molecular network architectures with redundancies that confer stability in the face of environmental variability (Deutscher et al. 2006, Soyer and Pfeiffer 2010). To test this, we examined whether there are differences in PPI and metabolic network properties among strains that are mutationally sensitive vs. mutationally robust. We reconstructed the yeast protein-protein interaction and metabolic network for all strains where genomic data was available taking into consideration both GCV and CNV, and measured network properties that are hypothesized to be important for mutation robustness (Table 15).

We found a subset of these properties were associated with mutational robustness in both the maltose and glucose environments (Table 16). For example, in the metabolic network, network property closeness, defined as a measure of the average shortest path between a node an all other nodes in a network (Proulx et al. 2005), was positively correlated with mutational robustness in both the glucose ($p = 0.016$, $R^2 = 0.434$; Figure 14) and maltose ($p = 0.038$, $R^2 = 0.331$; Figure 15). Mutations have less of an effect as closeness increases; i.e., as edges between

nodes decreases there is an increase in mutational robustness. We also found a positive correlation between average degree and mutational robustness on glucose ($p = 0.016$, $R^2 = 0.438$; Figure 16). These correlations suggest that as the average connectedness of nodes increases and distance between nodes decreases there is an increase in robustness. This increased connectedness combined with few steps to move between nodes can result in alternative pathways to move from one node to another.

Conclusions

Strains of *S. cerevisiae* display extensive variation in carbon metabolism and environmental breadth and growth rate. A major contributor to this variation in growth rate on different carbon sources, can be attributed to gene content and copy number variation. The association between copy number and gene content variation with higher fitness (faster growth rates) under specific carbon conditions suggests gene content and copy number variation can result in fitness advantages within a species. Furthermore, increasing metabolic breadth among strains is associated with mutational robustness. Both gene content and copy number variation also affect higher-order properties of biological networks. Differences in network structure, of both the protein-protein interaction and metabolic network, across strains are correlated with mutational robustness; suggesting that higher order network properties can buffer against mutational perturbations. Overall, these results show that both the metabolic and protein-protein interaction network can evolve. Furthermore, these results suggest network structure as well as environmental breadth is important for buffering against mutational perturbations.

Methods

Media Preparation

All 97 types of growth media were made from one of four stocks of 2X yeast nitrogen base (ammonium sulfate, glutamate, L-proline, urea), at a final concentration of 5g/L. Each media contained one of 15 possible carbon sources at a final concentration of 20g/L (Table 4). All media was autoclaved, except for those made with urea and L-proline as nitrogen sources, which were filter sterilized due to the formation of precipitates when autoclaved. All media contained 0.1g.L NaCl (Sigma-Aldrich Y0626), except for osmotic stress media, which contained an additional 0.225g/L NaCl.

Strains and Cultures

Strains were obtained from: CBS Fungal Biodiversity Centre and Cubillos et al (2009) (Table 4). Cells were streaked out onto agar plates with Synthetic Defined Media without Tryptophan (SD-Trp, Sunrise Scientific).

Growth Experiments

Four different growth experiments were performed: (1) growth in 15 different carbon sources, (2) full factorial matrix of 10 carbon source environments by 4 different nitrogen sources, (3) a full factorial matrix of 9 carbon sources by 3 temperature conditions, (4) a full factorial matrix of 9 carbon sources by 2 NaCl concentrations (Table 17).

Single colonies of strains were picked using toothpicks and grown for approximately 24 hours in a 96-well plate in SD-Trp at 30°C in a plate shaker (from this point this will be referred to as the template plate). For each replicate of a growth experiment (3-4 replicates/growth experiment), strain location was randomized on a plate. The following day, experimental plates were set-up containing the conditions for the specific growth experiments (Table 17). Environmental conditions for each replicate of a growth experiment were also randomized. The randomization of strains across experiments and environments on a plate ensures no location bias due to the plate reader. A pinner was used to pin the template plate into each of the experimental plates. Plates were covered with a foil seal and placed at 30°C, with the exception of the temperature environments, which were grown at 25°C and 37°C, in a plate shaker for approximately 12 hours. After 12 hours, the optical density of the experimental plates were read every 2 hours for the first 16 hours, and then read every 4 hours for the next 20 hours. Finally, the optical density was read every 8 hours for the next 48 hours.

Growth Analyses

The slope of the growth curve was calculated using the 'grofit' (version 1.1.1, Kamh et al. 2010) package in R (R v2.14). The slope was defined as:

$$\frac{\Delta Optical\ Density}{Time\ (hours)}$$

We then created a linear model to examine variation among slopes across strains on different environments and to look for interactions between environmental conditions.

Genetic Basis of Differential Growth

The genomes of 16 strains of *S. cerevisiae* were aligned to the reference using the mapping pipeline RUM (Grant et al. 2011) using raw sequence reads from Bergstrom et al. (2014). Gene content differences among strains were determined by finding all genes that mapped to the reference, *S288c,* for a strain. A GO enrichment was done on all genes which were variably present across strains using the web-based GO enrichment tool Gorilla (Eden et al. 2007, 2009). All enrichments were calculated with the all genes present in the reference strain used as the background list.

We looked for associations between gene presence/absence and either the ability to grow on a carbon source and growth rate on a carbon source. We used a chi-squared test to look for associations between gene presence/absence and utilization of a carbon source. Genes were sorted into two categories, positive association or negative association with growth. Genes were categorized as positively associated with growth when gene presence was significantly associated ($p < 0.05$) with the ability to grow on a carbon source. Genes were categorized as negatively associated with growth when gene presence was significantly associated ($p < 0.05$) with the inability to grow on a carbon source. We then performed a GO enrichment, using GOrilla, for all genes in either category with all genes that demonstrate gene content variation used as the background set of genes (Eden et al. 2007, 2009). We quantified associations between gene presence/absence and growth rate using a T-test. Genes were again sorted into two categories, positive association or negative association with growth rate. Genes were categorized as positively associated with growth rate when gene presence was significantly associated ($p < 0.05$) with a faster than average growth rate on a carbon source. Genes were categorized as negatively associated with growth when gene presence was significantly associated ($p < 0.05$) with a slower than average growth rate on a carbon source. We then performed a GO enrichment, using GOrilla, for all genes in either category with all genes that demonstrate gene content variation used as the background set of genes (Eden et al. 2007, 2009).

Copy number variation was calculated using the coverage files for each strain. The average coverage of a 500bp window was normalized relative to the chromosome coverage. We used a linear model to associate copy number variants with growth rate for all preferred carbon sources. We used GOrilla to look for enrichments for copy number variants that showed a positive or negative association with growth rate among all carbon sources.

Strains cultures and Mutant Generation

We cultured 19 wild strains of *S. cerevisiae* overnight in 5mls SD-Trp (Supplemental Table S1). After 24 hours of growth we diluted all cultures to the standard optical density (OD) of 0.2. Then we exposed half of each culture to ethyl methanesulfononate (EMS) for one hour (modified protocol from Mable and Otto 2001) to generate mutants. The remaining culture was not treated with a mutagen and was used in experiments as the ancestor.

Measuring cell growth

After mutagenesis, individual mutant and ancestral cells were sorted into 96-well plates using a flow cytometer (FACS Aria). Each plate contained two different environmental conditions, a glucose environment and a maltose environment. After 24 hours of growth, we measured the optical density in a Tecan plate reader every 4 hours for 24 hours followed by measurements every 8 hours for an additional 48 hours.

Quantifying genetic robustness

Cells were deposited into individual wells allowing us to measure two aspects of genetic robustness: survivorship and variation in growth rate. Survivorship was quantified by determining the number of individuals that grew across all wells relative to the number of individuals deposited in the plate. We used a t-test to assess the significance of observed differences in survivorship among ancestors and mutants of each strain. We accessed the significance of differences in survivorship among strains using ANOVA.

We compared the relative survivorship of an ancestral strain to the mutants of that strain. We quantified the slope of a growth curve of individuals using the "grofit" package in R (Kahm et al. 2010) and generated distributions of slopes for both the ancestral and mutant strains. The mutant and ancestral distributions for a strain were compared to quantify a strain's genetic robustness, using the Mann-Whitney-U test. We quantified variation in genetic robustness by comparing the differences in mean slopes between ancestral and mutant distributions. We also quantified additional measures to describe the growth rate distributions – coefficient of variation, variance and skew.

Correlations between environmental and genetic robustness

A linear model was used to measure the correlations between genetic and environmental robustness. We used three proxies for genetic robustness: survivorship of mutants relative to their ancestors, the difference in the mean growth rate for the ancestor and mutant strains, and variance in growth rate distributions (mutant/ancestor). As a substitute for environmental robustness, we used the number of carbon sources a strain is capable of metabolizing and the number of environments in which a strain could grow.

Metabolic and PPI network assembly

To assemble the metabolic networks we used metabolic network information for *S. cerevisiae* from Pathway Tools (v. 13.0, Karp et al. 2009, Caspi et al. 2014). We created an edge list for all enzymes in the metabolic network of *S. cerevisiae* and then incorporated strain specific information, gene content and copy number, to assemble networks for each strain. In the case of copy number, nodes were repeated in the network for the number of copies present within the strain's genome and all edges were maintained for each copy of the node.

To assemble the protein-protein interaction (PPI) network we downloaded interaction data from BioGRID (release 3.1.124; Stark et al. 2006) for *S. cerevisiae*. We created an edge list for all proteins shown to interact using mass spectrometry. We then incorporated strain specific information as previously discussed for the metabolic network assembly to generate a PPI-network for each strain.

Correlations between network properties and genetic robustness

We measured differences in network structure among strains for both the metabolic and PPI-network using the R package, iGraph (Csárdi and Nepusz 2006) by measuring different network properties (Table 15). All properties were calculated using formulas preset in iGraph, with the exception of assortativity. We defined assortativity as the average connectivity of a node's nearest neighbors (Barabási and Oltvai 2004). To calculate assortativity we used the formula:

$$A = \frac{K_1 + K_2 + \cdots + . K_n}{N}$$

where K is the number of edges for each node the node of interest is connected to and N is the total number of nodes.

We used a linear model to assess whether the network properties measured for both the metabolic and PPI network were correlated with our measures of mutational robustness – relative survivorship, mean difference, relative variance, and relative coefficient of variation.

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Table 1: Strains which were aligned to the reference, *S288c*, from Bergstrom et al. (2014)

Strains
SK1
DBVPG 1373
YJM 978
YJM 975
DBVPG 1106
Y12
BC 187
L_1528
L_1374
DBVPG 6044
Y55
DBVPG 1788
DBVPG 6765
YPS 128
UWOPS03-461-4
UWOPS83-787_3

Table 2: Genes that are variably present were enriched for processes and functions related to carbohydrate and sugar transport and metabolism (bold terms).

Aspect	Description	P-value	FDR q-value
BP	Transposition, RNA-mediated	4.79E-30	2.18E-26
BP	Transposition	6.20E-29	1.41E-25
BP	Symbiosis, encompassing mutualism through parasitism	8.78E-15	7.99E-12
BP	Viral release from host cell	8.78E-15	9.98E-12
BP	Viral process	8.78E-15	1.33E-11
BP	DNA integration	2.43E-14	1.85E-11
BP	Interspecies interaction between organisms	2.16E-13	1.40E-10
BP	Multi-organism cellular process	6.61E-11	3.76E-08
BP	Multi-organism process	4.42E-10	2.24E-07
BP	**Maltose metabolic process**	**2.66E-09**	**1.21E-06**
BP	RNA-dependent DNA replication	7.01E-07	2.90E-04
BP	DNA biosynthetic process	7.25E-06	2.75E-03
BP	RNA phosphodiester bond hydrolysis, endonucleolytic	2.92E-05	1.02E-02
BP	Disaccharide metabolic process	4.69E-05	1.52E-02
BP	**Carbohydrate transport**	**5.48E-05**	**1.66E-02**
BP	**Monosaccharide transport**	**1.65E-04**	**4.42E-02**
BP	**Disaccharide catabolic process**	**1.85E-04**	**4.44E-02**
BP	Drug transport	1.85E-04	4.68E-02
BP	**Hexose transport**	**1.65E-04**	**4.70E-02**
BP	Cytoplasmic translation	2.41E-04	5.47E-02
BP	Thiamine metabolic process	3.41E-04	7.39E-02
BP	**Oligosaccharide catabolic process**	**3.61E-04**	**7.47E-02**
BP	Thiamine-containing compound metabolic process	6.80E-04	1.34E-01
BP	**Cellular carbohydrate catabolic process**	**7.97E-04**	**1.51E-01**
CC	Retrotransposon nucleocapsid	1.07E-30	9.47E-28
CC	Extracellular region	1.91E-12	8.50E-10
CC	Anchored component of membrane	4.16E-10	1.23E-07
CC	Cell wall	1.14E-07	2.02E-05
CC	External encapsulating structure	1.14E-07	2.53E-05
CC	Fungal-type cell wall	1.88E-07	2.78E-05
CC	Plasma membrane	9.11E-06	1.16E-03
CC	Phosphopyruvate hydratase complex	7.71E-04	8.57E-02
MF	RNA-directed DNA polymerase activity	4.19E-15	9.54E-12
MF	Aspartic-type peptidase activity	4.36E-14	3.31E-11
MF	Aspartic-type endopeptidase activity	4.36E-14	4.96E-11
MF	RNA-DNA hybrid ribonuclease activity	3.27E-11	1.86E-08
MF	DNA-directed DNA polymerase activity	2.63E-10	1.20E-07

Table 2 – continued

Aspect	Description	P-value	FDR q-value
MF	DNA polymerase activity	5.86E-10	2.22E-07
MF	**Carbohydrate transporter activity**	**1.96E-09**	**5.58E-07**
MF	**Carbohydrate transmembrane transporter activity**	**1.96E-09**	**6.38E-07**
MF	**Sugar transmembrane transporter activity**	**1.32E-08**	**3.35E-06**
MF	**Glucose transmembrane transporter activity**	**4.13E-07**	**9.40E-05**
MF	**Hexose transmembrane transporter activity**	**1.19E-06**	**2.26E-04**
MF	**Monosaccharide transmembrane transporter activity**	**1.19E-06**	**2.46E-04**
MF	**Fructose transmembrane transporter activity**	**1.88E-06**	**3.06E-04**
MF	**Mannose transmembrane transporter activity**	**1.88E-06**	**3.30E-04**
MF	Endoribonuclease activity, producing 5'-phosphomonoesters	1.60E-05	2.42E-03
MF	**Alpha-glucosidase activity**	**9.30E-05**	**1.25E-02**
MF	endonuclease activity, active with either RNA or DNA	8.97E-05	1.28E-02
MF	**Beta-fructofuranosidase activity**	**1.28E-04**	**1.46E-02**
MF	**Sucrose alpha-glucosidase activity**	**1.28E-04**	**1.54E-02**
MF	Aryl-alcohol dehydrogenase (NAD+) activity	1.28E-04	1.62E-02
MF	Transcription factor binding transcription factor activity	1.97E-04	2.14E-02
MF	Drug transmembrane transporter activity	3.61E-04	3.57E-02
MF	Drug transporter activity	3.46E-04	3.58E-02
MF	Transcription factor recruiting transcription factor activity	4.74E-04	4.50E-02
MF	Transmembrane transporter activity	5.21E-04	4.74E-02
MF	**Glucoside transmembrane transporter activity**	**7.71E-04**	**6.05E-02**
MF	**Alpha-glucoside transmembrane transporter activity**	**7.71E-04**	**6.27E-02**
MF	Phosphopyruvate hydratase activity	7.71E-04	6.50E-02
MF	**Oligo-1,6-glucosidase activity**	**7.71E-04**	**6.75E-02**

Table 3: Genes that display copy number variation among strains were enriched for processes and functions related to carbohydrate and sugar transport and metabolism (bold terms).

Aspect	Description	P-value	FDR q-value
BP	Transposition, RNA-mediated	1.42E-45	6.55E-42
BP	Transposition	1.12E-42	2.57E-39
BP	Viral process	1.82E-24	2.79E-21
BP	Viral release from host cell	1.82E-24	2.09E-21
BP	Symbiosis, encompassing mutualism through parasitism	1.82E-24	1.67E-21
BP	DNA integration	2.78E-22	2.13E-19
BP	Interspecies interaction between organisms	1.07E-20	7.01E-18
BP	RNA-dependent DNA replication	8.69E-15	4.99E-12
BP	Multi-organism cellular process	2.25E-14	1.15E-11
BP	Multi-organism process	9.89E-13	4.54E-10
BP	DNA biosynthetic process	9.15E-11	3.82E-08
BP	RNA phosphodiester bond hydrolysis, endonucleolytic	1.55E-08	5.92E-06
BP	**Maltose metabolic process**	**2.57E-07**	**9.10E-05**
BP	RNA phosphodiester bond hydrolysis	6.83E-07	2.24E-04
BP	DNA replication	5.93E-06	1.82E-03
BP	Pyrimidine-containing compound metabolic process	3.22E-05	9.24E-03
BP	Nucleic acid phosphodiester bond hydrolysis	6.39E-05	1.73E-02
BP	Pyrimidine-containing compound biosynthetic process	1.85E-04	4.72E-02
BP	Flocculation	5.11E-04	1.24E-01
BP	**Disaccharide metabolic process**	**5.97E-04**	**1.37E-01**
BP	Thiamine-containing compound metabolic process	9.99E-04	2.18E-01
MF	RNA-DNA hybrid ribonuclease activity	2.33E-23	5.31E-20
MF	RNA-directed DNA polymerase activity	3.17E-21	3.61E-18
MF	Aspartic-type endopeptidase activity	6.54E-19	4.96E-16
MF	Aspartic-type peptidase activity	6.54E-19	3.72E-16
MF	Endoribonuclease activity, producing 5'-phosphomonoesters	4.12E-16	1.88E-13
MF	DNA-directed DNA polymerase activity	1.03E-15	3.92E-13
MF	DNA polymerase activity	3.16E-15	1.03E-12
MF	Endonuclease activity, active with either RNA or DNA	3.72E-15	1.06E-12
MF	Endoribonuclease activity	1.63E-12	4.11E-10
MF	Endonuclease activity	3.75E-10	8.54E-08
MF	Ribonuclease activity	6.76E-10	1.40E-07
MF	Endopeptidase activity	2.41E-08	4.57E-06
MF	Nuclease activity	1.77E-07	3.09E-05
MF	Nucleotidyltransferase activity	3.62E-06	5.90E-04
MF	RNA binding	7.44E-05	1.13E-02
MF	Aryl-alcohol dehydrogenase (NAD+) activity	1.44E-04	2.05E-02

Table 3 - continued

Aspect	Description	P-value	FDR q-value
MF	Hydrolase activity, acting on ester bonds	1.92E-04	2.57E-02
MF	Peptidase activity	3.19E-04	4.04E-02
MF	**Sucrose alpha-glucosidase activity**	**5.11E-04**	**6.13E-02**
MF	**Beta-fructofuranosidase activity**	**5.11E-04**	**5.82E-02**
MF	Peptidase activity, acting on L-amino acid peptides	6.82E-04	7.40E-02

Table 4: Experimental growth conditions, strains, and growth rate.
Source: [1]Cubillos et al. (2009) and [2]CBS-KNAW Fungal Biodiversity Centre.
NA = Not Assayed

			Source	1	1	2	2	2	2	2	2	2
			Strain	273614N	BC 187	CBS 1662	CBS 2167	CBS 2246	CBS 4054	CBS 4070	CBS 4416	CBS 6131
Carbon	**Temp**	**Nitrogen**	**NaCl**									
D-Arabinose	30°C	Ammonium	0.1g/L	0.0024	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	30°C	Ammonium	0.1g/L	0.0200	0.0268	0.0494	0.0059	0.0056	0.0000	0.0000	0.0168	0.0439
Fructose	30°C	Ammonium	0.1g/L	0.0491	0.0859	0.0504	0.0225	0.0594	0.0362	0.0520	0.0479	0.0757
Galactose	30°C	Ammonium	0.1g/L	0.0000	0.0833	0.0813	0.0307	0.0157	0.0000	0.0000	0.0679	0.0952
Glucitol	30°C	Ammonium	0.1g/L	0.0060	0.0051	0.0081	0.0000	0.0028	0.0000	0.0000	0.0000	0.0052
Glucose	30°C	Ammonium	0.1g/L	0.0457	0.0749	0.0618	0.0228	0.0642	0.0486	0.0622	0.0642	0.0728
Glycerol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Maltose	30°C	Ammonium	0.1g/L	0.0484	0.0798	0.0661	0.0188	0.0081	0.0000	0.0000	0.0378	0.0696
Mannitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Raffinose	30°C	Ammonium	0.1g/L	0.0684	0.0560	0.0408	0.0211	0.0313	0.0097	0.0111	0.0442	0.0601
Rhamnose	30°C	Ammonium	0.1g/L	0.0013	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005
Succinate	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Sucrose	30°C	Ammonium	0.1g/L	0.0404	0.0701	0.0668	0.0212	0.0662	0.0223	0.0108	0.0560	0.0736
Xylitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	25°C	Ammonium	0.1g/L	NA	0.0231	0.0343	0.0059	0.0052	0.0030	0.0021	0.0124	0.0451
Fructose	25°C	Ammonium	0.1g/L	NA	0.0747	0.0464	0.0338	0.0489	0.0588	0.0649	0.0434	0.0673
Galactose	25°C	Ammonium	0.1g/L	NA	0.0615	0.0733	0.0273	0.0224	0.0000	0.0000	0.0678	0.0890
Glucose	25°C	Ammonium	0.1g/L	NA	0.0625	0.0634	0.0232	0.0568	0.0578	0.0739	0.0530	0.0669
Glycerol	25°C	Ammonium	0.1g/L	NA	0.0668	0.0590	0.0213	0.0000	0.0000	0.0000	0.0393	0.0606
Maltose	25°C	Ammonium	0.1g/L	NA	0.0451	0.0358	0.0177	0.0257	0.0026	0.0063	0.0365	0.0517
Raffinose	25°C	Ammonium	0.1g/L	NA	0.0551	0.0689	0.0267	0.0587	0.0153	0.0212	0.0472	0.0690
Sucrose	25°C	Ammonium	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Xylitol	25°C	Ammonium	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	37°C	Ammonium	0.1g/L	NA	0.0229	0.0248	0.0000	0.0025	0.0000	0.0000	0.0000	0.0000
Fructose	37°C	Ammonium	0.1g/L	NA	0.0772	0.0379	0.0000	0.0527	0.0000	0.0000	0.0000	0.0499
Galactose	37°C	Ammonium	0.1g/L	NA	0.0788	0.0504	0.0000	0.0200	0.0000	0.0000	0.0614	0.0675
Glucose	37°C	Ammonium	0.1g/L	NA	0.0659	0.0479	0.0000	0.0628	0.0000	0.0000	0.0451	0.0440
Glycerol	37°C	Ammonium	0.1g/L	NA	0.0253	0.0413	0.0000	0.0000	0.0000	0.0000	0.0315	0.0436
Maltose	37°C	Ammonium	0.1g/L	NA	0.0404	0.0204	0.0000	0.0275	0.0000	0.0000	0.0142	0.0181
Raffinose	37°C	Ammonium	0.1g/L	NA	0.0676	0.0490	0.0000	0.0614	0.0129	0.0000	0.0392	0.0434
Sucrose	37°C	Ammonium	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 4 - continued

			Source	1	1	2	2	2	2	2	2	2
			Strain	273614N	BC 187	CBS 1662	CBS 2167	CBS 2246	CBS 4054	CBS 4070	CBS 4416	CBS 6131
Carbon	**Temp**	**Nitrogen**	**NaCl**									
Xylitol	37°C	Ammonium	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Arabinose	30°C	Glutamate	0.1g/L	NA	0.0000	0.0000	0.0000	0.0035	0.0000	0.0000	0.0000	0.0000
D-Melezitose	30°C	Glutamate	0.1g/L	NA	0.0057	0.0304	0.0000	0.0073	0.0110	0.0000	0.0000	0.0335
Fructose	30°C	Glutamate	0.1g/L	NA	0.0902	0.0816	0.0275	0.1097	0.0204	0.0361	0.0797	0.1157
Galactose	30°C	Glutamate	0.1g/L	NA	0.0916	0.0673	0.0326	0.0447	0.0000	0.0000	0.0748	0.0916
Glucose	30°C	Glutamate	0.1g/L	NA	0.0597	0.0612	0.0396	0.0788	0.0405	0.0391	0.0656	0.0593
Glycerol	30°C	Glutamate	0.1g/L	NA	0.0000	0.0000	0.0000	0.0046	0.0000	0.0000	0.0000	0.0000
Maltose	30°C	Glutamate	0.1g/L	NA	0.0648	0.0499	0.0310	0.0028	0.0000	0.0000	0.0400	0.0615
Raffinose	30°C	Glutamate	0.1g/L	NA	0.0560	0.0226	0.0238	0.0280	0.0000	0.0115	0.0280	0.0314
Sucrose	30°C	Glutamate	0.1g/L	NA	0.0407	0.0306	0.0283	0.0740	0.0000	0.0061	0.0358	0.0535
Xylitol	30°C	Glutamate	0.1g/L	NA	0.0000	0.0000	0.0000	0.0023	0.0000	0.0000	0.0000	0.0020
D-Arabinose	30°C	L-Proline	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	30°C	L-Proline	0.1g/L	NA	0.0195	0.0331	0.0040	0.0059	0.0075	0.0025	0.0074	0.0265
Fructose	30°C	L-Proline	0.1g/L	NA	0.0445	0.0352	0.0232	0.0418	0.0085	0.0300	0.0516	0.0657
Galactose	30°C	L-Proline	0.1g/L	NA	0.0751	0.0718	0.0300	0.0398	0.0000	0.0000	0.0608	0.0938
Glucose	30°C	L-Proline	0.1g/L	NA	0.0525	0.0320	0.0206	0.0359	0.0083	0.0243	0.0361	0.0673
Glycerol	30°C	L-Proline	0.1g/L	NA	0.0000	0.0000	0.0000	0.0046	0.0000	0.0000	0.0000	0.0000
Maltose	30°C	L-Proline	0.1g/L	NA	0.0848	0.0532	0.0258	0.0057	0.0000	0.0000	0.0447	0.0655
Raffinose	30°C	L-Proline	0.1g/L	NA	0.0440	0.0235	0.0166	0.0300	0.0058	0.0075	0.0334	0.0575
Sucrose	30°C	L-Proline	0.1g/L	NA	0.0000	0.0318	0.0340	0.0586	0.0000	0.0000	0.0699	0.0826
Xylitol	30°C	L-Proline	0.1g/L	NA	0.0000	0.0000	0.0000	0.0011	0.0000	0.0000	0.0000	0.0000
D-Arabinose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	30°C	Urea	0.1g/L	NA	0.0000	0.0746	0.0000	0.0000	0.0000	0.0000	0.0000	0.0401
Fructose	30°C	Urea	0.1g/L	NA	0.0597	0.0606	0.0000	0.0697	0.0000	0.0305	0.0284	0.0668
Galactose	30°C	Urea	0.1g/L	NA	0.0393	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0582
Glucose	30°C	Urea	0.1g/L	NA	0.0217	0.0000	0.0000	0.0188	0.0000	0.0000	0.0000	0.0000
Glycerol	30°C	Urea	0.1g/L	NA	0.0016	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Maltose	30°C	Urea	0.1g/L	NA	0.0440	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0484
Raffinose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Sucrose	30°C	Urea	0.1g/L	NA	0.0099	0.0000	0.0000	0.0277	0.0000	0.0000	0.0000	0.0000
Xylitol	30°C	Urea	0.1g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	30°C	Ammonium	.225g/L	NA	0.0194	0.0137	0.0066	0.0049	0.0033	0.0021	0.0113	0.0160
Fructose	30°C	Ammonium	.225g/L	NA	0.0227	0.0296	0.0225	0.0312	0.0115	0.0158	0.0226	0.0167
Galactose	30°C	Ammonium	.225g/L	NA	0.0247	0.0303	0.0144	0.0121	0.0000	0.0000	0.0324	0.0486
Glucose	30°C	Ammonium	.225g/L	NA	0.0241	0.0225	0.0223	0.0381	0.0170	0.0238	0.0207	0.0115

Table 4 - continued

			Source	1	1	2	2	2	2	2	2	2
			Strain	273614N	BC 187	CBS 1662	CBS 2167	CBS 2246	CBS 4054	CBS 4070	CBS 4416	CBS 6131
Carbon	**Temp**	**Nitrogen**	**NaCl**									
Glycerol	30°C	Ammonium	.225g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Maltose	30°C	Ammonium	.225g/L	NA	0.0132	0.0160	0.0000	0.0000	0.0000	0.0000	0.0086	0.0157
Raffinose	30°C	Ammonium	.225g/L	NA	0.0191	0.0221	0.0105	0.0190	0.0000	0.0070	0.0130	0.0284
Sucrose	30°C	Ammonium	.225g/L	NA	0.0178	0.0286	0.0118	0.0309	0.0088	0.0093	0.0164	0.0094
Xylitol	30°C	Ammonium	.225g/L	NA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

			Source	2	2	2	1	1	1	1	1	1
			Strain	CBS 6872	CBS 7764	CBS 7765	DBVPG 1106	DBVPG 1373	DBVPG 1788	DBVPG 1853	DBVPG 6044	DBVPG 6765
Carbon	**Temp**	**Nitrogen**	**NaCl**									
D-Arabinose	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0144	0.0000	0.0114	0.0067
D-Melezitose	30°C	Ammonium	0.1g/L	0.0000	0.0649	0.0000	0.0064	0.0109	0.0040	0.0089	0.0083	0.0046
Fructose	30°C	Ammonium	0.1g/L	0.0737	0.0640	0.0569	0.0641	0.0223	0.0727	0.0684	0.0600	0.0659
Galactose	30°C	Ammonium	0.1g/L	0.0000	0.0857	0.0350	0.0624	0.0409	0.0889	0.1005	0.0529	0.0601
Glucitol	30°C	Ammonium	0.1g/L	0.0000	0.0074	0.0035	0.0094	0.0040	0.0050	0.0113	0.0069	0.0045
Glucose	30°C	Ammonium	0.1g/L	0.0697	0.0695	0.0595	0.0555	0.0124	0.0823	0.0785	0.0646	0.0700
Glycerol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0022	0.0000	0.0015	0.0000	0.0019	0.0082
Maltose	30°C	Ammonium	0.1g/L	0.0000	0.0578	0.0143	0.0696	0.0246	0.0843	0.0679	0.0000	0.0687
Mannitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0031	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Raffinose	30°C	Ammonium	0.1g/L	0.0057	0.0593	0.0301	0.0310	0.0271	0.0654	0.0706	0.0606	0.0461
Rhamnose	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0046	0.0000
Succinate	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0022	0.0008	0.0014	0.0017	0.0000	0.0000	0.0000
Sucrose	30°C	Ammonium	0.1g/L	0.0249	0.0649	0.0631	0.0603	0.0158	0.0555	0.0716	0.0690	0.0428
Xylitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	25°C	Ammonium	0.1g/L	0.0030	0.0509	0.0046	0.0089	0.0050	NA	0.0061	NA	NA
Fructose	25°C	Ammonium	0.1g/L	0.0498	0.0601	0.0508	0.0568	0.0201	NA	0.0652	NA	NA
Galactose	25°C	Ammonium	0.1g/L	0.0000	0.0792	0.0032	0.0496	0.0000	NA	0.0800	NA	NA
Glucose	25°C	Ammonium	0.1g/L	0.0657	0.0647	0.0567	0.0479	0.0105	NA	0.0692	NA	NA
Glycerol	25°C	Ammonium	0.1g/L	0.0000	0.0525	0.0013	0.0552	0.0357	NA	0.0628	NA	NA
Maltose	25°C	Ammonium	0.1g/L	0.0052	0.0550	0.0257	0.0174	0.0312	NA	0.0494	NA	NA
Raffinose	25°C	Ammonium	0.1g/L	0.0228	0.0581	0.0587	0.0429	0.0337	NA	0.0653	NA	NA
Sucrose	25°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Xylitol	25°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA

Table 4 – continued

			Source	2	2	2	1	1	1	1	1	1
			Strain	CBS 6872	CBS 7764	CBS 7765	DBVPG 1106	DBVPG 1373	DBVPG 1788	DBVPG 1853	DBVPG 6044	DBVPG 6765
Carbon	**Temp**	**Nitrogen**	**NaCl**									
D-Melezitose	37°C	Ammonium	0.1g/L	0.0000	0.0000	0.0028	0.0034	0.0036	NA	0.0065	NA	NA
Fructose	37°C	Ammonium	0.1g/L	0.0000	0.0564	0.0558	0.0526	0.0000	NA	0.0590	NA	NA
Galactose	37°C	Ammonium	0.1g/L	0.0000	0.0621	0.0121	0.0577	0.0448	NA	0.0468	NA	NA
Glucose	37°C	Ammonium	0.1g/L	0.0000	0.0524	0.0619	0.0664	0.0333	NA	0.0633	NA	NA
Glycerol	37°C	Ammonium	0.1g/L	0.0000	0.0445	0.0000	0.0230	0.0227	NA	0.0317	NA	NA
Maltose	37°C	Ammonium	0.1g/L	0.0000	0.0233	0.0285	0.0285	0.0287	NA	0.0172	NA	NA
Raffinose	37°C	Ammonium	0.1g/L	0.0000	0.0522	0.0588	0.0582	0.0408	NA	0.0578	NA	NA
Sucrose	37°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Xylitol	37°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
D-Arabinose	30°C	Glutamate	0.1g/L	0.0000	0.0000	0.0053	0.0028	0.0000	NA	0.0019	NA	NA
D-Melezitose	30°C	Glutamate	0.1g/L	0.0000	0.0317	0.0056	0.0072	0.0068	NA	0.0052	NA	NA
Fructose	30°C	Glutamate	0.1g/L	0.0457	0.1052	0.1004	0.1132	0.0169	NA	0.1161	NA	NA
Galactose	30°C	Glutamate	0.1g/L	0.0000	0.0886	0.0428	0.0881	0.0315	NA	0.1060	NA	NA
Glucose	30°C	Glutamate	0.1g/L	0.0443	0.0710	0.0683	0.0650	0.0483	NA	0.0870	NA	NA
Glycerol	30°C	Glutamate	0.1g/L	0.0000	0.0000	0.0034	0.0075	0.0000	NA	0.0000	NA	NA
Maltose	30°C	Glutamate	0.1g/L	0.0000	0.0591	0.0042	0.0580	0.0400	NA	0.0466	NA	NA
Raffinose	30°C	Glutamate	0.1g/L	0.0000	0.0436	0.0356	0.0000	0.0311	NA	0.0382	NA	NA
Sucrose	30°C	Glutamate	0.1g/L	0.0000	0.0842	0.0745	0.0737	0.0174	NA	0.0669	NA	NA
Xylitol	30°C	Glutamate	0.1g/L	0.0000	0.0000	0.0024	0.0000	0.0000	NA	0.0018	NA	NA
D-Arabinose	30°C	L-Proline	0.1g/L	0.0000	0.0000	0.0012	0.0000	0.0000	NA	0.0000	NA	NA
D-Melezitose	30°C	L-Proline	0.1g/L	0.0076	0.0332	0.0076	0.0059	0.0192	NA	0.0000	NA	NA
Fructose	30°C	L-Proline	0.1g/L	0.0150	0.0726	0.0418	0.0940	0.0552	NA	0.0876	NA	NA
Galactose	30°C	L-Proline	0.1g/L	0.0000	0.0994	0.0424	0.0583	0.0410	NA	0.0909	NA	NA
Glucose	30°C	L-Proline	0.1g/L	0.0107	0.0642	0.0342	0.1110	0.0000	NA	0.0935	NA	NA
Glycerol	30°C	L-Proline	0.1g/L	0.0000	0.0000	0.0031	0.0128	0.0000	NA	0.0000	NA	NA
Maltose	30°C	L-Proline	0.1g/L	0.0000	0.0654	0.0043	0.0751	0.0614	NA	0.0469	NA	NA
Raffinose	30°C	L-Proline	0.1g/L	0.0000	0.0628	0.0317	0.0064	0.0288	NA	0.0451	NA	NA
Sucrose	30°C	L-Proline	0.1g/L	0.0303	0.0817	0.0616	0.0000	0.0000	NA	0.0952	NA	NA
Xylitol	30°C	L-Proline	0.1g/L	0.0009	0.0000	0.0010	0.0000	0.0000	NA	0.0026	NA	NA
D-Arabinose	30°C	Urea	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
D-Melezitose	30°C	Urea	0.1g/L	0.0000	0.0536	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Fructose	30°C	Urea	0.1g/L	0.0000	0.0721	0.0561	0.0667	0.0216	NA	0.0642	NA	NA
Galactose	30°C	Urea	0.1g/L	0.0000	0.0822	0.0000	0.0372	0.0000	NA	0.0561	NA	NA

Table 4 – continued

			Source	2	2	2	1	1	1	1	1	1
			Strain	CBS 6872	CBS 7764	CBS 7765	DBVPG 1106	DBVPG 1373	DBVPG 1788	DBVPG 1853	DBVPG 6044	DBVPG 6765
Carbon	**Temp**	**Nitrogen**	**NaCl**									
Glucose	30°C	Urea	0.1g/L	0.0000	0.0392	0.0198	0.0000	0.0000	NA	0.0269	NA	NA
Glycerol	30°C	Urea	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Maltose	30°C	Urea	0.1g/L	0.0000	0.0778	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Raffinose	30°C	Urea	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Sucrose	30°C	Urea	0.1g/L	0.0000	0.0254	0.0070	0.0052	0.0000	NA	0.0214	NA	NA
Xylitol	30°C	Urea	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
D-Melezitose	30°C	Ammonium	.225g/L	0.0108	0.0188	0.0040	0.0082	0.0105	NA	0.0114	NA	NA
Fructose	30°C	Ammonium	.225g/L	0.0167	0.0307	0.0360	0.0166	0.0165	NA	0.0146	NA	NA
Galactose	30°C	Ammonium	.225g/L	0.0000	0.0361	0.0000	0.0189	0.0204	NA	0.0119	NA	NA
Glucose	30°C	Ammonium	.225g/L	0.0154	0.0380	0.0468	0.0157	0.0141	NA	0.0221	NA	NA
Glycerol	30°C	Ammonium	.225g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA
Maltose	30°C	Ammonium	.225g/L	0.0000	0.0215	0.0000	0.0113	0.0000	NA	0.0134	NA	NA
Raffinose	30°C	Ammonium	.225g/L	0.0084	0.0201	0.0221	0.0230	0.0139	NA	0.0094	NA	NA
Sucrose	30°C	Ammonium	.225g/L	0.0072	0.0199	0.0283	0.0179	0.0113	NA	0.0120	NA	NA
Xylitol	30°C	Ammonium	.225g/L	0.0000	0.0000	0.0000	0.0000	0.0000	NA	0.0000	NA	NA

			Source	1	1	1	1	1	1	1	1	1
			Strain	L_1374	L_1528	NCYC 110	SK1	UWOPS03-461.4	UWOPS05-217.3	UWOPS05-227.2	UWOPS83-787.3	Y12
Carbon	**Temp**	**Nitrogen**	**NaCl**									
D-Arabinose	30°C	Ammonium	0.1g/L	0.0000	0.0062	0.0000	0.0000	0.0000	0.0050	0.0000	0.0000	0.0071
D-Melezitose	30°C	Ammonium	0.1g/L	0.0135	0.0061	0.0000	0.0076	0.0328	0.0256	0.0325	0.0142	0.0408
Fructose	30°C	Ammonium	0.1g/L	0.0660	0.1022	0.0432	0.0420	0.0814	0.0832	0.0672	0.0912	0.0718
Galactose	30°C	Ammonium	0.1g/L	0.0800	0.1039	0.0000	0.0404	0.0776	0.0783	0.0687	0.0940	0.0617
Glucitol	30°C	Ammonium	0.1g/L	0.0036	0.0038	0.0000	0.0019	0.0097	0.0102	0.0111	0.0078	0.0070
Glucose	30°C	Ammonium	0.1g/L	0.0804	0.0896	0.0381	0.0577	0.0653	0.0637	0.0548	0.0768	0.0764
Glycerol	30°C	Ammonium	0.1g/L	0.0057	0.0000	0.0000	0.0000	0.0018	0.0027	0.0000	0.0015	0.0014
Maltose	30°C	Ammonium	0.1g/L	0.0842	0.1091	0.0000	0.0515	0.0338	0.0726	0.0696	0.0000	0.0721
Mannitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0159	0.0191	0.0302	0.0000	0.0000
Raffinose	30°C	Ammonium	0.1g/L	0.0279	0.0257	0.0270	0.0415	0.0695	0.0647	0.0601	0.0328	0.0680
Rhamnose	30°C	Ammonium	0.1g/L	0.0000	0.0017	0.0000	0.0000	0.0012	0.0000	0.0000	0.0000	0.0000

Table 4 – continued

			Source	1	1	1	1	1	1	1	1	1
			Strain	L_1374	L_1528	NCYC 110	SK1	UWOPS03-461.4	UWOPS05-217.3	UWOPS05-227.2	UWOPS83-787.3	Y12
Carbon	**Temp**	**Nitrogen**	**NaCl**									
Succinate	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Sucrose	30°C	Ammonium	0.1g/L	0.0529	0.0533	0.0295	0.0686	0.0645	0.0590	0.0573	0.0624	0.0666
Xylitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0144	0.0000	0.0000	0.0000	0.0000	0.0000
D-Melezitose	25°C	Ammonium	0.1g/L	NA	NA	0.0033	0.0048	NA	NA	0.0334	NA	0.0349
Fructose	25°C	Ammonium	0.1g/L	NA	NA	0.0380	0.0353	NA	NA	0.0624	NA	0.0611
Galactose	25°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0619	NA	0.0402
Glucose	25°C	Ammonium	0.1g/L	NA	NA	0.0349	0.0459	NA	NA	0.0464	NA	0.0622
Glycerol	25°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0373	NA	NA	0.0601	NA	0.0537
Maltose	25°C	Ammonium	0.1g/L	NA	NA	0.0273	0.0380	NA	NA	0.0517	NA	0.0563
Raffinose	25°C	Ammonium	0.1g/L	NA	NA	0.0329	0.0511	NA	NA	0.0465	NA	0.0553
Sucrose	25°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0045	NA	0.0000
Xylitol	25°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
D-Melezitose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0285
Fructose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0778
Galactose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0611
Glucose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0230	NA	0.0742
Glycerol	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0703
Maltose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0136	NA	0.0600
Raffinose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0306	NA	0.0676
Sucrose	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
Xylitol	37°C	Ammonium	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
D-Arabinose	30°C	Glutamate	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0036	NA	0.0031
D-Melezitose	30°C	Glutamate	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0129	NA	0.0065
Fructose	30°C	Glutamate	0.1g/L	NA	NA	0.0461	0.0731	NA	NA	0.0711	NA	0.1187
Galactose	30°C	Glutamate	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0836	NA	0.0936
Glucose	30°C	Glutamate	0.1g/L	NA	NA	0.0493	0.0734	NA	NA	0.0664	NA	0.0801
Glycerol	30°C	Glutamate	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0038
Maltose	30°C	Glutamate	0.1g/L	NA	NA	0.0000	0.0477	NA	NA	0.0688	NA	0.0543
Raffinose	30°C	Glutamate	0.1g/L	NA	NA	0.0461	0.0180	NA	NA	0.0445	NA	0.0531
Sucrose	30°C	Glutamate	0.1g/L	NA	NA	0.0401	0.0540	NA	NA	0.1045	NA	0.0424
Xylitol	30°C	Glutamate	0.1g/L	NA	NA	0.0000	0.0018	NA	NA	0.0000	NA	0.0000
D-Arabinose	30°C	L-Proline	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
D-Melezitose	30°C	L-Proline	0.1g/L	NA	NA	0.0036	0.0000	NA	NA	0.0299	NA	0.0278

Table 4 – continued

			Source	1	1	1	1	1	1	1	1	1
			Strain	L_1374	L_1528	NCYC 110	SK1	UWOPS03-461.4	UWOPS05-217.3	UWOPS05-227.2	UWOPS83-787.3	Y12
Carbon	**Temp**	**Nitrogen**	**NaCl**									
Fructose	30°C	L-Proline	0.1g/L	NA	NA	0.0305	0.0410	NA	NA	0.0915	NA	0.0811
Galactose	30°C	L-Proline	0.1g/L	NA	NA	0.0000	0.0042	NA	NA	0.0804	NA	0.0835
Glucose	30°C	L-Proline	0.1g/L	NA	NA	0.0259	0.0000	NA	NA	0.1083	NA	0.0965
Glycerol	30°C	L-Proline	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0049	NA	0.0022
Maltose	30°C	L-Proline	0.1g/L	NA	NA	0.0000	0.0248	NA	NA	0.0738	NA	0.0644
Raffinose	30°C	L-Proline	0.1g/L	NA	NA	0.0289	0.0249	NA	NA	0.0492	NA	0.0727
Sucrose	30°C	L-Proline	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
Xylitol	30°C	L-Proline	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0037
D-Arabinose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
D-Melezitose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
Fructose	30°C	Urea	0.1g/L	NA	NA	0.0475	0.0000	NA	NA	0.0594	NA	0.0000
Galactose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0390	NA	0.0000
Glucose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0413	NA	0.0000
Glycerol	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0018	NA	0.0010
Maltose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0403	NA	0.0000
Raffinose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0196
Sucrose	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0372	NA	0.0252
Xylitol	30°C	Urea	0.1g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
D-Melezitose	30°C	Ammonium	.225g/L	NA	NA	0.0055	0.0092	NA	NA	0.0038	NA	0.0219
Fructose	30°C	Ammonium	.225g/L	NA	NA	0.0075	0.0237	NA	NA	0.0113	NA	0.0514
Galactose	30°C	Ammonium	.225g/L	NA	NA	0.0000	0.0138	NA	NA	0.0078	NA	0.0263
Glucose	30°C	Ammonium	.225g/L	NA	NA	0.0074	0.0216	NA	NA	0.0075	NA	0.0566
Glycerol	30°C	Ammonium	.225g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000
Maltose	30°C	Ammonium	.225g/L	NA	NA	0.0000	0.0000	NA	NA	0.0067	NA	0.0282
Raffinose	30°C	Ammonium	.225g/L	NA	NA	0.0041	0.0127	NA	NA	0.0115	NA	0.0272
Sucrose	30°C	Ammonium	.225g/L	NA	NA	0.0087	0.0190	NA	NA	0.0083	NA	0.0420
Xylitol	30°C	Ammonium	.225g/L	NA	NA	0.0000	0.0000	NA	NA	0.0000	NA	0.0000

Table 4 – continued

			Source	1	1	1	1	1	1
			Strain	Y55	YJM 975	YJM 978	YJM 981	YPS 128	YPS 606
Carbon	**Temp**	**Nitrogen**	**NaCl**						
D-Arabinose	30°C	Ammonium	0.1g/L	0.0000	0.0063	0.0000	0.0000	0.0000	0.0000
D-Melezitose	30°C	Ammonium	0.1g/L	0.0187	0.0087	0.0063	0.0122	0.0355	0.0382
Fructose	30°C	Ammonium	0.1g/L	0.0680	0.0703	0.0728	0.0661	0.0829	0.0579
Galactose	30°C	Ammonium	0.1g/L	0.0827	0.0734	0.0751	0.0637	0.0889	0.0491
Glucitol	30°C	Ammonium	0.1g/L	0.0086	0.0053	0.0094	0.0075	0.0112	0.0113
Glucose	30°C	Ammonium	0.1g/L	0.0644	0.0689	0.0728	0.0703	0.0623	0.0466
Glycerol	30°C	Ammonium	0.1g/L	0.0000	0.0223	0.0159	0.0000	0.0000	0.0022
Maltose	30°C	Ammonium	0.1g/L	0.0806	0.0758	0.0553	0.0706	0.0000	0.0134
Mannitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Raffinose	30°C	Ammonium	0.1g/L	0.0736	0.0373	0.0201	0.0159	0.0468	0.0456
Rhamnose	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Succinate	30°C	Ammonium	0.1g/L	0.0000	0.0016	0.0039	0.0000	0.0000	0.0000
Sucrose	30°C	Ammonium	0.1g/L	0.0623	0.0627	0.0369	0.0405	0.0540	0.0535
Xylitol	30°C	Ammonium	0.1g/L	0.0000	0.0000	0.0065	0.0000	0.0000	0.0000
D-Melezitose	25°C	Ammonium	0.1g/L	NA	0.0095	0.0082	NA	NA	0.0404
Fructose	25°C	Ammonium	0.1g/L	NA	0.0653	0.0691	NA	NA	0.0558
Galactose	25°C	Ammonium	0.1g/L	NA	0.0592	0.0606	NA	NA	0.0425
Glucose	25°C	Ammonium	0.1g/L	NA	0.0579	0.0649	NA	NA	0.0336
Glycerol	25°C	Ammonium	0.1g/L	NA	0.0647	0.0513	NA	NA	0.0000
Maltose	25°C	Ammonium	0.1g/L	NA	0.0404	0.0184	NA	NA	0.0373
Raffinose	25°C	Ammonium	0.1g/L	NA	0.0508	0.0323	NA	NA	0.0390
Sucrose	25°C	Ammonium	0.1g/L	NA	0.0067	0.0000	NA	NA	0.0000
Xylitol	25°C	Ammonium	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
D-Melezitose	37°C	Ammonium	0.1g/L	NA	0.0039	0.0021	NA	NA	0.0129
Fructose	37°C	Ammonium	0.1g/L	NA	0.0681	0.0746	NA	NA	0.0541
Galactose	37°C	Ammonium	0.1g/L	NA	0.0268	0.0353	NA	NA	0.0511
Glucose	37°C	Ammonium	0.1g/L	NA	0.0680	0.0708	NA	NA	0.0479
Glycerol	37°C	Ammonium	0.1g/L	NA	0.0394	0.0360	NA	NA	0.0000
Maltose	37°C	Ammonium	0.1g/L	NA	0.0246	0.0005	NA	NA	0.0476
Raffinose	37°C	Ammonium	0.1g/L	NA	0.0565	0.0336	NA	NA	0.0521
Sucrose	37°C	Ammonium	0.1g/L	NA	0.0066	0.0051	NA	NA	0.0000
Xylitol	37°C	Ammonium	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
D-Arabinose	30°C	Glutamate	0.1g/L	NA	0.0032	0.0037	NA	NA	0.0030
D-Melezitose	30°C	Glutamate	0.1g/L	NA	0.0060	0.0108	NA	NA	0.0292
Fructose	30°C	Glutamate	0.1g/L	NA	0.0882	0.1044	NA	NA	0.1151

Table 4 – continued

			Source	1	1	1	1	1	1
			Strain	Y55	YJM 975	YJM 978	YJM 981	YPS 128	YPS 606
Carbon	**Temp**	**Nitrogen**	**NaCl**						
Galactose	30°C	Glutamate	0.1g/L	NA	0.0847	0.0757	NA	NA	0.0968
Glucose	30°C	Glutamate	0.1g/L	NA	0.0700	0.0603	NA	NA	0.0714
Glycerol	30°C	Glutamate	0.1g/L	NA	0.0089	0.0081	NA	NA	0.0045
Maltose	30°C	Glutamate	0.1g/L	NA	0.0539	0.0268	NA	NA	0.0029
Raffinose	30°C	Glutamate	0.1g/L	NA	0.0299	0.0000	NA	NA	0.0428
Sucrose	30°C	Glutamate	0.1g/L	NA	0.0527	0.0027	NA	NA	0.0766
Xylitol	30°C	Glutamate	0.1g/L	NA	0.0024	0.0022	NA	NA	0.0000
D-Arabinose	30°C	L-Proline	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
D-Melezitose	30°C	L-Proline	0.1g/L	NA	0.0059	0.0164	NA	NA	0.0318
Fructose	30°C	L-Proline	0.1g/L	NA	0.0705	0.0864	NA	NA	0.0869
Galactose	30°C	L-Proline	0.1g/L	NA	0.0753	0.0667	NA	NA	0.0903
Glucose	30°C	L-Proline	0.1g/L	NA	0.0759	0.1031	NA	NA	0.1091
Glycerol	30°C	L-Proline	0.1g/L	NA	0.0129	0.0099	NA	NA	0.0054
Maltose	30°C	L-Proline	0.1g/L	NA	0.0683	0.0486	NA	NA	0.0054
Raffinose	30°C	L-Proline	0.1g/L	NA	0.0504	0.0023	NA	NA	0.0380
Sucrose	30°C	L-Proline	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
Xylitol	30°C	L-Proline	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
D-Arabinose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
D-Melezitose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
Fructose	30°C	Urea	0.1g/L	NA	0.0538	0.0430	NA	NA	0.1007
Galactose	30°C	Urea	0.1g/L	NA	0.0201	0.0000	NA	NA	0.0238
Glucose	30°C	Urea	0.1g/L	NA	0.0139	0.0000	NA	NA	0.0403
Glycerol	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
Maltose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
Raffinose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
Sucrose	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0204
Xylitol	30°C	Urea	0.1g/L	NA	0.0000	0.0000	NA	NA	0.0000
D-Melezitose	30°C	Ammonium	.225g/L	NA	0.0195	0.0049	NA	NA	0.0079
Fructose	30°C	Ammonium	.225g/L	NA	0.0267	0.0294	NA	NA	0.0106
Galactose	30°C	Ammonium	.225g/L	NA	0.0215	0.0273	NA	NA	0.0130
Glucose	30°C	Ammonium	.225g/L	NA	0.0258	0.0283	NA	NA	0.0080
Glycerol	30°C	Ammonium	.225g/L	NA	0.0032	0.0019	NA	NA	0.0000
Maltose	30°C	Ammonium	.225g/L	NA	0.0195	0.0133	NA	NA	0.0000
Raffinose	30°C	Ammonium	.225g/L	NA	0.0239	0.0133	NA	NA	0.0066
Sucrose	30°C	Ammonium	.225g/L	NA	0.0231	0.0104	NA	NA	0.0052
Xylitol	30°C	Ammonium	.225g/L	NA	0.0000	0.0000	NA	NA	0.0000

Table 5: Results of ANOVA tests for significance of effects contributing to differences in growth rates for different strains and carbon sources

Factor	Df	F-Value	P-value
Strain	32	88.52	$2.0X10^{-16}$
Carbon	13	1045	$2.0X10^{-16}$
Preferred[1]	1	671.9	$2.0X10^{-16}$
Strain:Carbon	416	11.02	$2.0X10^{-16}$

[1] From planned comparisons

Table 6: Results of ANOVA tests for significance of effects contributing to differences in growth rates. Factors tested are: A) different strains, carbon sources, and temperatures, B) different strains, carbon sources, and nitrogen sources, and C) different strains, carbon sources, and sodium chloride concentrations.

A)

Factor	Df	F-Value	P-value
Strain	20	212.738	$2.0X10^{-16}$
Carbon	7	738.957	$2.0X10^{-16}$
Temperature	2	358.104	$2.0X10^{-16}$
Strain:Carbon	140	19.422	$2.0X10^{-16}$
Strain:Temperature	40	9.105	$2.0X10^{-16}$
Carbon:Temperature	14	9.48	$2.0X10^{-16}$
Strain:Carbon:Temp	280	2.492	$2.0X10^{-16}$

B)

Factor	Df	F-Value	P-value
Strain	20	196.398	$2.0X10^{-16}$
Carbon	9	1275.065	$2.0X10^{-16}$
Nitrogen	3	503.741	$2.0X10^{-16}$
Strain:Carbon	180	23.884	$2.0X10^{-16}$
Strain:Nitrogen	60	7.475	$2.0X10^{-16}$
Carbon:Nitrogen	27	44.716	$2.0X10^{-16}$
Strain:Carbon:Nitrogen	540	3	$2.0X10^{-16}$

C)

Factor	Df	F-Value	P-value
Strain	20	123.744	$2.0X10^{-16}$
Carbon	7	461.811	$2.0X10^{-16}$
Osmotic	1	1389.796	$2.0X10^{-16}$
Strain:Carbon	140	12.61	$2.0X10^{-16}$
Strain:Osmotic	20	16.117	$2.0X10^{-16}$
Carbon:Osmotic	7	46.889	$2.0X10^{-16}$
Strain:Carbon:Osmotic	140	2.408	$7.63X10^{-16}$

Table 7: A table of genes which show a significant association ($p < 0.05$) between the presence of that gene and the utilization of a non-preferred carbon source. A negative association represents genes, that when present in a strain, were less likely able to grow on the carbon source. A positive association represents genes, that when present in a strain, were more likley able to grow on the carbon source.

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
D-Arabinose	Negative	YBR115C	3	0	3	10	6.154	0.013
D-Arabinose	Negative	YER011W	3	0	3	10	6.154	0.013
D-Arabinose	Negative	YNL333W	1	3	5	7	4.267	0.039
D-Arabinose	Positive	YMR303C	5	8	1	2	6.112	0.013
D-Arabinose	Positive	YBR272C	6	5	0	5	4.364	0.037
D-Arabinose	Positive	YIR023W	5	7	1	3	4.267	0.039
D-Arabinose	Positive	YOL105C	5	7	1	3	4.267	0.039
Glycerol	Negative	YIL176C	2	0	8	6	9.600	0.002
Glycerol	Negative	YJL223C	2	0	8	6	9.600	0.002
Glycerol	Negative	YDR316W-A	1	2	9	4	5.605	0.018
Glycerol	Negative	YER159C-A	1	2	9	4	5.605	0.018
Glycerol	Negative	YGR161C-C	1	2	9	4	5.605	0.018
Glycerol	Negative	YJL222W-B	1	2	9	4	5.605	0.018
Glycerol	Negative	YML045W-A	1	2	9	4	5.605	0.018
Glycerol	Negative	YMR051C	1	2	9	4	5.605	0.018
Glycerol	Negative	YPR158W-A	1	2	9	4	5.605	0.018
Glycerol	Negative	YML109W	5	0	5	6	4.364	0.0374
Glycerol	Negative	YAR033W	3	1	7	5	4.267	0.039
Glycerol	Negative	YHR218W	3	1	7	5	4.267	0.039
Glycerol	Positive	YMR303C	7	6	3	0	7.467	0.006
Glycerol	Positive	YLR349W	10	3	0	3	6.154	0.013
Glycerol	Positive	YIL011W	9	4	1	2	5.605	0.018
Mannitol	Negative	YAL003W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YAL022C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YAL026C-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YAL053W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBL047C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBL073W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBR037C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBR067C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBR147W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YCL028W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YCR020C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YCR031C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDL005C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDL040C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDL075W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDR077W	0	0	1	15	16.000	6.33E-05

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Mannitol	Negative	YAL003W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YAL022C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YAL026C-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YAL053W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBL047C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBL073W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBR037C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBR067C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBR147W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YCL028W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YCR020C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YCR031C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDL005C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDL040C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDL075W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDR077W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDR099W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDR186C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YDR423C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YEL033W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YER133W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YFL054C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YFL055W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YFR029W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YGL034C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YGL089C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YGL258W-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YGR121W-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YHL001W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YHL019C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YHL027W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YHR010W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YIL068W-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YIR018C-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YKL088W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YKL219W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YKR012C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YKR013W	0	0	1	15	16.000	6.33E-05

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Mannitol	Negative	YLR048W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YLR078C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YLR095C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YLR122C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YLR223C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YLR437C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YMR320W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YNL294C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YNL298W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YNL339C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YOR041C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YOR199W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YOR267C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YPR123C	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YPR140W	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YPR159C-A	0	0	1	15	16.000	6.33E-05
Mannitol	Negative	YBL027W	0	1	1	14	7.467	0.006
Mannitol	Negative	YBR178W	0	1	1	14	7.467	0.006
Mannitol	Negative	YCR089W	0	1	1	14	7.467	0.006
Mannitol	Negative	YDL034W	0	1	1	14	7.467	0.006
Mannitol	Negative	YDL223C	0	1	1	14	7.467	0.006
Mannitol	Negative	YDR322C-A	0	1	1	14	7.467	0.006
Mannitol	Negative	YHR199C-A	0	1	1	14	7.467	0.006
Mannitol	Negative	YLR286C	0	1	1	14	7.467	0.006
Mannitol	Negative	YLR342W	0	1	1	14	7.467	0.006
Mannitol	Negative	YMR008C	0	1	1	14	7.467	0.006
Mannitol	Negative	YNL143C	0	1	1	14	7.467	0.006
Mannitol	Negative	YNL249C	0	1	1	14	7.467	0.006
Mannitol	Negative	YNL269W	0	1	1	14	7.467	0.006
Mannitol	Negative	YNL339W-B	0	1	1	14	7.467	0.006
Mannitol	Negative	YOL011W	0	1	1	14	7.467	0.006
Mannitol	Negative	YOR373W	0	1	1	14	7.467	0.006
Mannitol	Negative	YPR042C	0	1	1	14	7.467	0.006
Mannitol	Negative	YAL035W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YCR041W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YCR106W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YCR107W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YDL080C	0	2	1	13	4.622	0.0312

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Mannitol	Negative	YDL182W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YFL002W-B	0	2	1	13	4.622	0.0312
Mannitol	Negative	YGL260W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YHR021C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YHR173C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YJL123C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YKL066W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YLL066C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YLL066W-A	0	2	1	13	4.622	0.0312
Mannitol	Negative	YLL067W-A	0	2	1	13	4.622	0.0312
Mannitol	Negative	YMR245W	0	2	1	13	4.622	0.0312
Mannitol	Negative	YNL240C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YNL260C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YOR178C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YOR387C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YPR022C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YPR199C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YPR200C	0	2	1	13	4.622	0.0312
Mannitol	Negative	YPR201W	0	2	1	13	4.622	0.0312
Mannitol	Positive	YER046W-A	1	15	0	0	16.000	6.33E-05
Mannitol	Positive	YKL224C	1	14	0	1	7.467	0.006
Mannitol	Positive	YER189W	1	13	0	2	4.622	0.0312
Mannitol	Positive	YIR042C	1	13	0	2	4.622	0.0312
Rhamnose	Negative	YNL249C	1	0	2	13	9.905	0.002
Rhamnose	Negative	YCR041W	1	1	2	12	5.566	0.018
Rhamnose	Negative	YDL080C	1	1	2	12	5.566	0.018
Rhamnose	Negative	YFL002W-B	1	1	2	12	5.566	0.018
Rhamnose	Negative	YGL260W	1	1	2	12	5.566	0.018
Rhamnose	Negative	YHR021C	1	1	2	12	5.566	0.018
Rhamnose	Negative	YLL066C	1	1	2	12	5.566	0.018
Rhamnose	Negative	YLL066W-A	1	1	2	12	5.566	0.018
Rhamnose	Negative	YLL067W-A	1	1	2	12	5.566	0.018
Rhamnose	Negative	YOL159C-A	1	1	2	12	5.566	0.018
Rhamnose	Negative	YOR178C	1	1	2	12	5.566	0.018
Rhamnose	Negative	YOR387C	1	1	2	12	5.566	0.018
Rhamnose	Negative	YPR022C	1	1	2	12	5.566	0.018
Rhamnose	Negative	YAL003W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YAL022C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YAL026C-A	2	0	1	13	4.622	0.031

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Rhamnose	Negative	YAL031W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YAL053W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YAR064W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBL047C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBL073W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBL100W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBL113W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBR037C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBR067C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBR147W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YBR298C-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YCL028W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YCR020C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YCR031C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YCR052W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YCR096C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDL005C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDL040C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDL075W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR077W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR095C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR099W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR186C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR365W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR373W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YDR423C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YEL033W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YEL077W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YER133W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YFL054C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YFL055W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YFR029W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL034C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL089C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL118C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL150C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL227W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL258W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGL261C	2	0	1	13	4.622	0.031

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Rhamnose	Negative	YGR027W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YGR121W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHL001W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHL019C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHL027W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR010W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR118C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR154W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR213W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR213W-B	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR214W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YHR219C-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YIL018W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YIL058W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YIL068W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YIR018C-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YJR031C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YKL088W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YKL219W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YKR012C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YKR013W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YKR045C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLL043W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR003C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR048W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR078C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR095C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR122C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR223C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR415C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YLR437C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YML034W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YMR046W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YMR097C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YMR119W-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YMR277W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YMR292W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YMR320W	2	0	1	13	4.622	0.031

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Rhamnose	Negative	YNL284C-A	2	0	1	13	4.622	0.031
Rhamnose	Negative	YNL294C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YNL298W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YNL337W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YNL339C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YNR070W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOL004W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOR008C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOR041C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOR199W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOR255W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOR267C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YOR392W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YPL249C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YPL282C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YPR123C	2	0	1	13	4.622	0.031
Rhamnose	Negative	YPR140W	2	0	1	13	4.622	0.031
Rhamnose	Negative	YPR159C-A	2	0	1	13	4.622	0.031
Rhamnose	Positive	YCR038C	3	10	0	3	6.154	0.013
Rhamnose	Positive	YKL109W	2	12	1	1	5.565	0.018
Rhamnose	Positive	YAL068W-A	3	9	0	4	4.747	0.029
Rhamnose	Positive	YKL030W	3	9	0	4	4.747	0.029
Rhamnose	Positive	YNL065W	3	9	0	4	4.747	0.029
Rhamnose	Positive	YER046W-A	1	13	2	0	4.622	0.032
Rhamnose	Positive	YJR161C	1	13	2	0	4.622	0.032
Succinate	Negative	YKL097C	1	0	4	11	11.733	0.0006
Succinate	Negative	YGR294W	2	0	3	11	8.123	0.004
Succinate	Negative	YJL019W	2	0	3	11	8.123	0.004
Succinate	Negative	YDR500C	1	1	4	10	8.045	0.005
Succinate	Negative	YIL060W	1	1	4	10	8.045	0.005
Succinate	Negative	YLR260W	1	1	4	10	8.045	0.005
Succinate	Negative	YCL042W	0	3	5	8	7.273	0.007
Succinate	Negative	YHR141C	0	3	5	8	7.273	0.007
Succinate	Negative	YHR143W	0	3	5	8	7.273	0.007
Succinate	Negative	YIL119C	0	3	5	8	7.273	0.007
Succinate	Negative	YJL220W	0	3	5	8	7.273	0.007
Succinate	Negative	YOL155W-A	0	3	5	8	7.273	0.007
Succinate	Negative	YOR113W	0	3	5	8	7.273	0.007

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Succinate	Negative	YAL067W-A	0	4	5	7	5.657	0.017
Succinate	Negative	YAL068W-A	0	4	5	7	5.657	0.017
Succinate	Negative	YBL017C	0	4	5	7	5.657	0.017
Succinate	Negative	YFL051C	0	4	5	7	5.657	0.017
Succinate	Negative	YFL060C	0	4	5	7	5.657	0.017
Succinate	Negative	YFR026C	0	4	5	7	5.657	0.017
Succinate	Negative	YGR291C	0	4	5	7	5.657	0.017
Succinate	Negative	YGR293C	0	4	5	7	5.657	0.017
Succinate	Negative	YIL059C	0	4	5	7	5.657	0.017
Succinate	Negative	YIL171W-A	0	4	5	7	5.657	0.017
Succinate	Negative	YIR039C	0	4	5	7	5.657	0.017
Succinate	Negative	YIR040C	0	4	5	7	5.657	0.017
Succinate	Negative	YJL158C	0	4	5	7	5.657	0.017
Succinate	Negative	YJR015W	0	4	5	7	5.657	0.017
Succinate	Negative	YLR255C	0	4	5	7	5.657	0.017
Succinate	Negative	YLR287C-A	0	4	5	7	5.657	0.017
Succinate	Negative	YML056C	0	4	5	7	5.657	0.017
Succinate	Negative	YNL065W	0	4	5	7	5.657	0.017
Succinate	Negative	YNL205C	0	4	5	7	5.657	0.017
Succinate	Negative	YOR096W	0	4	5	7	5.657	0.017
Succinate	Negative	YOR183W	0	4	5	7	5.657	0.017
Succinate	Negative	YBR030W	1	2	4	9	5.605	0.018
Succinate	Negative	YBR108W	1	2	4	9	5.605	0.018
Succinate	Negative	YIL159W	1	2	4	9	5.605	0.018
Succinate	Negative	YBR142W	3	0	2	11	5.029	0.025
Succinate	Negative	YBR219C	3	0	2	11	5.029	0.025
Succinate	Negative	YDL211C	3	0	2	11	5.029	0.025
Succinate	Negative	YDR215C	3	0	2	11	5.029	0.025
Succinate	Negative	YFL010W-A	3	0	2	11	5.029	0.025
Succinate	Negative	YGL057C	3	0	2	11	5.029	0.025
Succinate	Negative	YGR068C	3	0	2	11	5.029	0.025
Succinate	Negative	YGR153W	3	0	2	11	5.029	0.025
Succinate	Negative	YHL035C	3	0	2	11	5.029	0.025
Succinate	Negative	YJL042W	3	0	2	11	5.029	0.025
Succinate	Negative	YJR152W	3	0	2	11	5.029	0.025
Succinate	Negative	YLL010C	3	0	2	11	5.029	0.025
Succinate	Negative	YLR279W	3	0	2	11	5.029	0.025
Succinate	Negative	YML084W	3	0	2	11	5.029	0.025

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Succinate	Negative	YNL325C	3	0	2	11	5.029	0.025
Succinate	Negative	YOL086C	3	0	2	11	5.029	0.025
Succinate	Negative	YOL134C	3	0	2	11	5.029	0.025
Succinate	Negative	YOL144W	3	0	2	11	5.029	0.025
Succinate	Negative	YOR305W	3	0	2	11	5.029	0.025
Succinate	Negative	YPR185W	3	0	2	11	5.029	0.025
Succinate	Negative	YAL068C	2	1	3	10	4.752	0.029
Succinate	Negative	YFL059W	2	1	3	10	4.752	0.029
Succinate	Negative	YGR001C	2	1	3	10	4.752	0.029
Succinate	Negative	YJR023C	2	1	3	10	4.752	0.029
Succinate	Negative	YJR090C	2	1	3	10	4.752	0.029
Succinate	Negative	YKR047W	2	1	3	10	4.752	0.029
Succinate	Negative	YKR057W	2	1	3	10	4.752	0.029
Succinate	Negative	YLR232W	2	1	3	10	4.752	0.029
Succinate	Negative	YAL064W-B	0	5	5	6	4.364	0.037
Succinate	Negative	YAL065C	0	5	5	6	4.364	0.037
Succinate	Negative	YEL069C	0	5	5	6	4.364	0.037
Succinate	Negative	YER187W	0	5	5	6	4.364	0.037
Succinate	Negative	YFR016C	0	5	5	6	4.364	0.037
Succinate	Negative	YGR189C	0	5	5	6	4.364	0.037
Succinate	Negative	YHL048C-A	0	5	5	6	4.364	0.037
Succinate	Negative	YJL218W	0	5	5	6	4.364	0.037
Succinate	Negative	YLR055C	0	5	5	6	4.364	0.037
Succinate	Negative	YLR412C-A	0	5	5	6	4.364	0.037
Succinate	Negative	YNL331C	0	5	5	6	4.364	0.037
Succinate	Negative	YGR233C	1	3	4	8	3.883	0.049
Succinate	Negative	YJL214W	1	3	4	8	3.883	0.049
Succinate	Negative	YLR205C	1	3	4	8	3.883	0.049
Succinate	Positive	YDR210W-A	4	11	1	0	11.733	0.0006
Succinate	Positive	YBR302C	4	10	1	1	8.045	0.005
Succinate	Positive	YML132W	4	10	1	1	8.045	0.005
Succinate	Positive	YCR108C	5	7	0	4	5.657	0.017
Succinate	Positive	YDR012W	5	7	0	4	5.657	0.017
Succinate	Positive	YDR036C	5	7	0	4	5.657	0.017
Succinate	Positive	YDR037W	5	7	0	4	5.657	0.017
Succinate	Positive	YHR007C-A	5	7	0	4	5.657	0.017
Succinate	Positive	YLR114C	5	7	0	4	5.657	0.017
Succinate	Positive	YLR467W	5	7	0	4	5.657	0.017

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Succinate	Positive	YML125C	5	7	0	4	5.657	0.017
Succinate	Positive	YAR027W	5	6	0	5	4.364	0.037
Succinate	Positive	YBR112C	5	6	0	5	4.364	0.037
Succinate	Positive	YDL243C	5	6	0	5	4.364	0.037
Succinate	Positive	YDR170W-A	5	6	0	5	4.364	0.037
Succinate	Positive	YDR192C	5	6	0	5	4.364	0.037
Succinate	Positive	YHR044C	5	6	0	5	4.364	0.037
Succinate	Positive	YKL054C	5	6	0	5	4.364	0.037
Succinate	Positive	YLR237W	5	6	0	5	4.364	0.037
Succinate	Positive	YMR048W	5	6	0	5	4.364	0.037
Succinate	Positive	YOR396W	5	6	0	5	4.364	0.037
Succinate	Positive	YPL277C	5	6	0	5	4.364	0.037
Succinate	Positive	YDL037C	4	8	1	3	3.883	0.049
Xylitol	Negative	YGR014W	0	1	2	13	9.905	0.002
Xylitol	Negative	YHR095W	0	1	2	13	9.905	0.002
Xylitol	Negative	YKL068W	0	1	2	13	9.905	0.002
Xylitol	Negative	YOR013W	0	1	2	13	9.905	0.002
Xylitol	Negative	YAL013W	1	0	1	14	7.467	0.006
Xylitol	Negative	YBL052C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBL092W	1	0	1	14	7.467	0.006
Xylitol	Negative	YBL097W	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR008C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR023C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR040W	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR061C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR065C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR097W	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR111W-A	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR121C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR146W	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR218C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR247C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR261C	1	0	1	14	7.467	0.006
Xylitol	Negative	YBR270C	1	0	1	14	7.467	0.006
Xylitol	Negative	YCL025C	1	0	1	14	7.467	0.006
Xylitol	Negative	YCR061W	1	0	1	14	7.467	0.006
Xylitol	Negative	YCR086W	1	0	1	14	7.467	0.006
Xylitol	Negative	YCR093W	1	0	1	14	7.467	0.006

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Xylitol	Negative	YDL247W-A	1	0	1	14	7.467	0.006
Xylitol	Negative	YDR135C	1	0	1	14	7.467	0.006
Xylitol	Negative	YDR157W	1	0	1	14	7.467	0.006
Xylitol	Negative	YDR227W	1	0	1	14	7.467	0.006
Xylitol	Negative	YDR293C	1	0	1	14	7.467	0.006
Xylitol	Negative	YDR507C	1	0	1	14	7.467	0.006
Xylitol	Negative	YEL055C	1	0	1	14	7.467	0.006
Xylitol	Negative	YER101C	1	0	1	14	7.467	0.006
Xylitol	Negative	YER119C-A	1	0	1	14	7.467	0.006
Xylitol	Negative	YFL020C	1	0	1	14	7.467	0.006
Xylitol	Negative	YFR019W	1	0	1	14	7.467	0.006
Xylitol	Negative	YFR032C	1	0	1	14	7.467	0.006
Xylitol	Negative	YGL022W	1	0	1	14	7.467	0.006
Xylitol	Negative	YGL104C	1	0	1	14	7.467	0.006
Xylitol	Negative	YGL251C	1	0	1	14	7.467	0.006
Xylitol	Negative	YGR066C	1	0	1	14	7.467	0.006
Xylitol	Negative	YGR175C	1	0	1	14	7.467	0.006
Xylitol	Negative	YHR165C	1	0	1	14	7.467	0.006
Xylitol	Negative	YHR174W	1	0	1	14	7.467	0.006
Xylitol	Negative	YHR200W	1	0	1	14	7.467	0.006
Xylitol	Negative	YIL003W	1	0	1	14	7.467	0.006
Xylitol	Negative	YIL007C	1	0	1	14	7.467	0.006
Xylitol	Negative	YIL032C	1	0	1	14	7.467	0.006
Xylitol	Negative	YIL106W	1	0	1	14	7.467	0.006
Xylitol	Negative	YIL112W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJL005W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJL098W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJL202C	1	0	1	14	7.467	0.006
Xylitol	Negative	YJR002W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJR040W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJR053W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJR078W	1	0	1	14	7.467	0.006
Xylitol	Negative	YJR150C	1	0	1	14	7.467	0.006
Xylitol	Negative	YJR155W	1	0	1	14	7.467	0.006
Xylitol	Negative	YKL018W	1	0	1	14	7.467	0.006
Xylitol	Negative	YKL022C	1	0	1	14	7.467	0.006
Xylitol	Negative	YKL039W	1	0	1	14	7.467	0.006
Xylitol	Negative	YKL089W	1	0	1	14	7.467	0.006

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Xylitol	Negative	YKL103C	1	0	1	14	7.467	0.006
Xylitol	Negative	YKL162C	1	0	1	14	7.467	0.006
Xylitol	Negative	YKR050W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLL015W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLL031C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR006C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR022C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR052W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR056W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR081W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR120C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR121C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR138W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR172C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR190W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR192C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR213C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR236C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR239C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR264W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR280C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR317W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR401C	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR403W	1	0	1	14	7.467	0.006
Xylitol	Negative	YLR439W	1	0	1	14	7.467	0.006
Xylitol	Negative	YML049C	1	0	1	14	7.467	0.006
Xylitol	Negative	YML074C	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR009W	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR014W	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR040W	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR088C	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR166C	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR225C	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR254C	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR304W	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR307W	1	0	1	14	7.467	0.006
Xylitol	Negative	YMR316C-B	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL035C	1	0	1	14	7.467	0.006

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Xylitol	Negative	YNL046W	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL058C	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL078W	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL122C	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL138W-A	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL167C	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL192W	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL210W	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL309W	1	0	1	14	7.467	0.006
Xylitol	Negative	YNL316C	1	0	1	14	7.467	0.006
Xylitol	Negative	YNR053C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL033W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL056W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL059W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL085C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL116W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL141W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOL148C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR006C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR010C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR040W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR062C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR072W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR072W-A	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR083W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR098C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR156C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR161W-B	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR181W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR202W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR244W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR246C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR284W	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR348C	1	0	1	14	7.467	0.006
Xylitol	Negative	YOR377W	1	0	1	14	7.467	0.006
Xylitol	Negative	YPL223C	1	0	1	14	7.467	0.006
Xylitol	Negative	YPL229W	1	0	1	14	7.467	0.006
Xylitol	Negative	YPR112C	1	0	1	14	7.467	0.006
Xylitol	Negative	YFL031W	0	2	2	12	6.857	0.009

Table 7 – continued

Carbon	Association	Gene	BothYes	BothNo	GrowYes GeneNo	GrowNo GeneYes	Chi-Square	p-Value
Xylitol	Negative	YBR272C	0	3	2	11	5.029	0.025
Xylitol	Negative	YDL191W	0	3	2	11	5.029	0.025
Xylitol	Negative	YGR107W	0	3	2	11	5.029	0.025
Xylitol	Negative	YLR296W	0	3	2	11	5.029	0.025
Xylitol	Negative	YPL190C	0	3	2	11	5.029	0.025
Xylitol	Positive	YAR010C	1	14	1	0	7.467	0.006
Xylitol	Positive	YDR210C-D	1	14	1	0	7.467	0.006
Xylitol	Positive	YFL067W	1	14	1	0	7.467	0.006
Xylitol	Positive	YLR256W-A	1	14	1	0	7.467	0.006
Xylitol	Positive	YOL103W-A	1	14	1	0	7.467	0.006
Xylitol	Positive	YPR137C-A	1	14	1	0	7.467	0.006
Xylitol	Positive	YPR158W-B	1	14	1	0	7.467	0.006

Table 8: GO enrichment of gene presence/absence significantly associated with variation in growth rate on carbon sources. Faster growth rates due to the presence are indicated with the word "positive"; while slower growth rates are represented by the word "negative".

Assoc.	Aspect	Description	P-value	FDR q-value
Positive	BP	Transposition, RNA-mediated	2.50E-18	1.14E-14
Positive	BP	Transposition	3.99E-17	9.08E-14
Positive	**BP**	**Maltose metabolic process**	**7.01E-09**	**1.06E-05**
Positive	BP	Interspecies interaction between organisms	9.49E-06	1.08E-02
Positive	BP	Viral process	1.24E-05	1.13E-02
Positive	BP	Viral release from host cell	1.24E-05	9.40E-03
Positive	BP	Symbiosis, encompassing mutualism through parasitism	1.24E-05	8.06E-03
Positive	**BP**	**Carbohydrate transport**	**1.64E-05**	**9.36E-03**
Positive	BP	Multi-organism cellular process	2.75E-05	1.39E-02
Positive	BP	DNA integration	4.15E-05	1.89E-02
Positive	BP	Multi-organism process	9.19E-05	3.80E-02
Positive	**BP**	**Disaccharide metabolic process**	**2.56E-04**	**9.73E-02**
Positive	**BP**	**Hexose transport**	**2.78E-04**	**9.74E-02**
Positive	**BP**	**Monosaccharide transport**	**2.78E-04**	**9.04E-02**
Positive	**MF**	**Carbohydrate transmembrane transporter activity**	**4.26E-08**	**9.72E-05**
Positive	**MF**	**Carbohydrate transporter activity**	**4.26E-08**	**4.86E-05**
Positive	**MF**	**Sugar transmembrane transporter activity**	**4.27E-08**	**3.25E-05**
Positive	MF	RNA-directed DNA polymerase activity	1.07E-06	6.08E-04
Positive	**MF**	**Glucose transmembrane transporter activity**	**2.86E-06**	**1.30E-03**
Positive	**MF**	**Monosaccharide transmembrane transporter activity**	**6.18E-06**	**2.35E-03**
Positive	**MF**	**Hexose transmembrane transporter activity**	**6.18E-06**	**2.01E-03**
Positive	MF	Aspartic-type endopeptidase activity	8.02E-06	2.29E-03
Positive	MF	Aspartic-type peptidase activity	8.02E-06	2.04E-03
Positive	MF	DNA-directed DNA polymerase activity	8.36E-06	1.91E-03
Positive	MF	DNA polymerase activity	1.25E-05	2.59E-03
Positive	**MF**	**Mannose transmembrane transporter activity**	**1.48E-05**	**2.82E-03**
Positive	**MF**	**Fructose transmembrane transporter activity**	**1.48E-05**	**2.61E-03**
Positive	MF	RNA-DNA hybrid ribonuclease activity	1.15E-04	1.88E-02
Positive	**MF**	**Alpha-glucosidase activity**	**2.00E-04**	**3.04E-02**
Positive	**MF**	**Oligo-1,6-glucosidase activity**	**2.23E-04**	**3.18E-02**
Positive	MF	phosphopyruvate hydratase activity	2.23E-04	3.00E-02
Positive	**MF**	**Alpha-glucoside transmembrane transporter activity**	**2.23E-04**	**2.83E-02**
Positive	**MF**	**Glucoside transmembrane transporter activity**	**2.23E-04**	**2.68E-02**
Positive	CC	Retrotransposon nucleocapsid	1.19E-18	1.06E-15
Positive	CC	Extracellular region	1.92E-07	8.52E-05
Positive	CC	Anchored component of membrane	2.05E-07	6.08E-05

Table 8 – continued

Assoc.	Aspect	Description	P-value	FDR q-value
Positive	CC	External encapsulating structure	3.58E-07	7.96E-05
Positive	CC	Cell wall	3.58E-07	6.37E-05
Positive	CC	Fungal-type cell wall	9.44E-07	1.40E-04
Positive	CC	Plasma membrane	6.72E-05	8.54E-03
Positive	CC	Phosphopyruvate hydratase complex	2.23E-04	2.48E-02
Negative	BP	Transposition, RNA-mediated	1.40E-19	6.39E-16
Negative	BP	Transposition	3.33E-19	7.58E-16
Negative	BP	DNA integration	1.87E-06	2.84E-03
Negative	BP	Interspecies interaction between organisms	3.82E-06	4.35E-03
Negative	BP	Viral process	3.99E-06	3.64E-03
Negative	BP	Viral release from host cell	3.99E-06	3.03E-03
Negative	BP	Symbiosis, encompassing mutualism through parasitism	3.99E-06	2.60E-03
Negative	BP	Multi-organism cellular process	7.96E-06	4.53E-03
Negative	BP	Multi-organism process	1.01E-05	5.12E-03
Negative	BP	Thiamine metabolic process	8.47E-05	3.86E-02
Negative	BP	Cytoplasmic translation	1.08E-04	4.47E-02
Negative	BP	Thiamine-containing compound metabolic process	1.74E-04	6.60E-02
Negative	BP	Thiamine-containing compound biosynthetic process	3.86E-04	1.35E-01
Negative	BP	Thiamine biosynthetic process	3.86E-04	1.25E-01
Negative	MF	Aspartic-type endopeptidase activity	8.73E-08	1.99E-04
Negative	MF	Aspartic-type peptidase activity	8.73E-08	9.96E-05
Negative	MF	RNA-directed DNA polymerase activity	4.08E-07	3.11E-04
Negative	MF	DNA-directed DNA polymerase activity	7.10E-06	4.05E-03
Negative	MF	DNA polymerase activity	1.09E-05	4.99E-03
Negative	MF	RNA-DNA hybrid ribonuclease activity	5.22E-05	1.99E-02
Negative	MF	Transcription factor recruiting transcription factor activity	2.21E-04	7.22E-02
Negative	MF	Transcription factor binding transcription factor activity	7.86E-04	2.24E-01
Negative	MF	Aryl-alcohol dehydrogenase (NAD+) activity	8.08E-04	2.05E-01
Negative	CC	Retrotransposon nucleocapsid	6.04E-20	5.37E-17
Negative	CC	Extracellular region	1.31E-08	5.83E-06
Negative	CC	Anchored component of membrane	8.98E-08	2.66E-05
Negative	CC	External encapsulating structure	1.52E-06	3.38E-04
Negative	CC	Cell wall	1.52E-06	2.71E-04
Negative	CC	Fungal-type cell wall	3.39E-06	5.02E-04
Negative	CC	Plasma membrane	2.76E-04	3.51E-02

Table 9: GO enrichment among copy number variants which show a positive and negative association with growth rate among carbon sources. The bold terms represent GO terms related to carbon catabolism and transport.

Assoc.	Aspect	Description	P-value	FDR q-value
Positive	BP	Transposition, RNA-mediated	2.12E-43	6.70E-40
Positive	BP	Transposition	6.95E-43	1.10E-39
Positive	BP	RNA-dependent DNA replication	1.34E-20	1.41E-17
Positive	BP	DNA integration	1.70E-19	1.34E-16
Positive	BP	Symbiosis, encompassing mutualism through parasitism	1.03E-18	3.62E-16
Positive	BP	Interspecies interaction between organisms	1.03E-18	4.07E-16
Positive	BP	Viral release from host cell	1.03E-18	4.65E-16
Positive	BP	Multi-organism cellular process	7.97E-19	5.03E-16
Positive	BP	Viral process	1.03E-18	5.43E-16
Positive	BP	Multi-organism process	4.34E-18	1.37E-15
Positive	BP	DNA biosynthetic process	2.31E-17	6.61E-15
Positive	BP	DNA replication	4.10E-14	9.94E-12
Positive	BP	RNA phosphodiester bond hydrolysis, endonucleolytic	3.98E-14	1.04E-11
Positive	BP	DNA recombination	1.14E-12	2.57E-10
Positive	BP	RNA phosphodiester bond hydrolysis	2.21E-12	4.64E-10
Positive	BP	Proteolysis	2.16E-09	4.25E-07
Positive	BP	Nucleic acid phosphodiester bond hydrolysis	2.52E-09	4.68E-07
Positive	BP	Single-organism cellular process	3.69E-06	6.46E-04
Positive	BP	Single-organism process	1.34E-05	2.22E-03
Positive	BP	DNA metabolic process	8.34E-05	1.31E-02
Positive	**BP**	**Monosaccharide transport**	**3.05E-04**	**4.37E-02**
Positive	**BP**	**Hexose transport**	**3.05E-04**	**4.57E-02**
Positive	BP	Thiamine-containing compound metabolic process	6.78E-04	9.29E-02
Positive	CC	Retrotransposon nucleocapsid	2.12E-43	1.41E-40
Positive	CC	Nuclear part	1.78E-10	5.90E-08
Positive	MF	RNA-directed DNA polymerase activity	4.41E-21	5.59E-18
Positive	MF	DNA-directed DNA polymerase activity	2.88E-19	1.22E-16
Positive	MF	DNA polymerase activity	2.88E-19	1.82E-16
Positive	MF	Aspartic-type peptidase activity	1.38E-18	2.91E-16
Positive	MF	Aspartic-type endopeptidase activity	1.38E-18	3.49E-16
Positive	MF	RNA-DNA hybrid ribonuclease activity	1.38E-18	4.36E-16
Positive	MF	Peptidase activity	4.23E-18	7.66E-16
Positive	MF	Endoribonuclease activity, producing 5'-phosphomonoesters	5.49E-17	8.69E-15
Positive	MF	RNA binding	7.05E-17	8.94E-15
Positive	MF	Peptidase activity, acting on L-amino acid peptides	6.39E-17	9.00E-15
Positive	MF	Ribonuclease activity	1.09E-16	1.25E-14

Table 9 – continued

Assoc.	Aspect	Description	P-value	FDR q-value
Positive	MF	Endoribonuclease activity	2.83E-16	2.99E-14
Positive	MF	Nucleotidyltransferase activity	3.83E-16	3.74E-14
Positive	MF	Endonuclease activity, active with RNA and DNA	6.17E-16	5.58E-14
Positive	MF	Endonuclease activity	6.69E-15	5.65E-13
Positive	MF	Endopeptidase activity	1.08E-14	8.56E-13
Positive	MF	Nuclease activity	1.20E-14	8.97E-13
Positive	MF	Hydrolase activity, acting on ester bonds	2.19E-09	1.54E-07
Positive	MF	Nucleic acid binding	8.69E-09	5.79E-07
Positive	MF	Transferase activity, transferring phosphorus-containing groups	8.04E-08	5.09E-06
Positive	MF	DNA binding	6.56E-06	3.96E-04
Positive	MF	Cation binding	1.05E-04	6.05E-03
Positive	MF	Hydrolase activity	2.33E-04	1.28E-02
Positive	**MF**	**Glucose transmembrane transporter activity**	**3.05E-04**	**1.33E-02**
Positive	**MF**	**Fructose transmembrane transporter activity**	**3.05E-04**	**1.38E-02**
Positive	**MF**	**Hexose transmembrane transporter activity**	**3.05E-04**	**1.43E-02**
Positive	**MF**	**Monosaccharide transmembrane transporter activity**	**3.05E-04**	**1.48E-02**
Positive	**MF**	**Mannose transmembrane transporter activity**	**3.05E-04**	**1.54E-02**
Positive	**MF**	**Oligo-1,6-glucosidase activity**	**3.03E-04**	**1.60E-02**
Positive	MF	Heterocyclic compound binding	5.43E-04	2.29E-02
Positive	MF	Organic cyclic compound binding	5.87E-04	2.40E-02
Positive	MF	Metal ion binding	7.61E-04	3.01E-02
Negative	BP	Sodium ion transmembrane transport	4.51E-04	1.00E+00
Negative	CC	Plasma membrane	1.18E-05	7.85E-03
Negative	MF	Sodium ion transmembrane transporter activity	4.51E-04	1.14E-01
Negative	**MF**	**Carbohydrate transporter activity**	**3.39E-04**	**1.43E-01**
Negative	MF	Sodium-exporting ATPase activity, phosphorylative mech.	4.51E-04	1.43E-01
Negative	**MF**	**Sugar transmembrane transporter activity**	**1.19E-04**	**1.51E-01**
Negative	MF	Aryl-alcohol dehydrogenase (NAD+) activity	9.91E-04	1.79E-01
Negative	MF	Oxidoreductase activity	9.29E-04	1.96E-01
Negative	**MF**	**Carbohydrate transmembrane transporter activity**	**3.39E-04**	**2.15E-01**

Table 10: Genes related to carbon metabolism.Gene presence and copy numbers associated with growth or growth rate are indicated with a 1 (positive) or -1 (negative). The number of strains possessing each gene is indicated under the strain column.

Substrate Info					CNV Growth Association							
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Sucrose**	**Raffinose**	**D-Melezitose**	**Glucitol**	**Galactose**
General Nitrogen catabolism	YKR039W	GAP1	16	Klasson et al. 1999	0	0	0	0	0	0	0	0
	YNL229C	URE2	16	ter Schure et al. 1998, Grundmann et al. 2001	0	0	0	0	0	0	0	0
	YER040W	GLN3	16		0	0	0	0	0	0	0	0
	YFR029W	PTR3	15	Klasson et al. 1999, Forsberg et al. 2001	0	0	0	0	0	0	0	0
	YDR160W	SSY1	16		0	0	0	0	0	0	0	0
	YJL156C	SSY5	16		0	0	0	0	0	0	0	0
Ammonium	YOR375C	GDH1	16	DeLuna et al. 2001	0	0	0	0	0	0	0	0
	YAL062W	GDH3	16		0	0	0	0	0	0	0	0
	YPR035W	GLN1	16	ter Schure et al. 1998, Grundmann et al. 2001	0	0	0	0	0	0	0	0
	YDL171C	GLT1	16		0	0	0	0	0	0	0	0
	YNL142W	MEP2	16	Marini et al. 1994, Lorenz and Heitman 1998, Grundmann et al. 2001	0	0	0	0	0	0	0	0
	YGR121C	MEP1	16		0	0	0	0	0	0	0	0
	YPR138C	MEP3	16		0	0	0	0	0	0	0	0
General Carbon Metabolism Genes	YOL051W	GAL11	6	Choi et al. 2008	0	0	0	0	0	0	0	0
	YER133W	GLC7	15	Neigeborn et al. 1987	0	0	0	0	0	0	0	0
	YJR090C	GRR1	12	Vallier et al. 1991, Flick and Johnston 1991	0	0	0	0	0	0	0	0
	YDR028C	HEX2	16	Niederacher and Entian 1991, Barnett and Entian 2005, Entian and Barnett 1992	0	0	0	0	0	0	0	0
	YGL035C	MIG1	16	Carlson 1998	0	0	0	0	0	0	0	0
	YLR071C	RGR1	15	Sakai et al. 1990	0	0	0	0	0	0	0	0
	YBR112C	SSN6	10	Chujo et al. 2014	0	0	0	0	0	0	0	0
	YCR084C	TUP1	16	Chujo et al. 2014	0	0	0	0	0	0	0	0
D-Arabinose	YBR149W	ARA1	16	Kim et al. 1998	0	0	0	0	0	0	0	0
	YMR041C	ARA2	16	Kim et al. 1998	0	0	0	0	0	0	0	0
	YJR096W	YJR096w	16	Träff et al. 2002	0	0	0	0	0	0	0	0
	YDR368W	YPR1	16	Träff et al. 2002, Masuda et al. 2008	0	0	0	0	0	0	0	0
D-Melezitose	NA	MAL64	NA	Gibson et al. 1997	0	0	0	0	0	0	0	0
Galactose	YBR021W	FUR4	16	Traven et al. 2006	0	0	0	0	0	0	0	0
	YBR020W	GAL1	16		0	0	0	0	0	0	0	0
	YBR019C	GAL10	16		0	0	0	0	0	0	0	0
	YOL051W	GAL11	6	Choi et al. 2008	0	0	0	0	0	0	0	0
	YLR081W	GAL2	15	Traven et al. 2006	0	0	0	0	0	0	0	0
Galactose	YDR009W	GAL3	16	Bhat and Murthy 2001, Timson et al. 2002, Traven et al. 2006	0	0	0	0	0	0	0	0
	YPL248C	GAL4	13		0	0	0	0	0	0	0	0
	YBR018C	GAL7	16	Traven et al. 2006	0	0	0	0	0	0	0	0
	YML051W	GAL80	16	Bhat and Murthy 2001, Timson et al. 2002, Traven et al. 2006	0	0	0	0	0	0	0	0
	YER027C	GAL83	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0	0
	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0	0
	YJL217W	REE1	3	Choi et al. 2008	0	0	0	0	0	1	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0	0
	YBR289W	SNF5	11		0	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					CNV Growth Association							
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Sucrose**	**Raffinose**	**D-Melezitose**	**Glucitol**	**Galactose**
Glucitol/Sorbitol and Xylitol	YJR159W	SOR1	5	Sarthy et al. 1994, Wenger et al. 2010	0	0	0	0	0	0	0	0
Glucitol/Sorbitol and Xylitol	YDL246C	SOR2	5		0	0	0	0	0	0	0	0
Glucose	YCL040W	GLK1	16	Rodriguez et al. 2001	0	0	0	0	0	0	0	0
Glucose and Fructose	YFR053C	HXK1	16		0	0	0	0	0	0	0	0
	YGL253W	HXK2	16	Bisson and Fraenkel 1983, Winde et al. 1996, Rodriguez et al. 2001	0	0	0	0	0	0	0	0
	YDL194W	SNF3	16	Vallier and Carlson 1991, Dietvorst et al. 2010	0	0	0	0	0	0	0	0
Glutamate	YPL265W	DIP5	16	Klasson et al. 1999	0	0	0	0	0	0	0	0
	YDL215C	GDH2	16	Miller and Magasanik 1990, DeLuna et al. 2001	0	0	0	0	0	0	0	0
	YNL142W	MEP2	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0	0
	YGL084C	GUP1	16	Holst et al. 2000	0	0	0	0	0	0	0	0
	YPL189W	GUP2	16		0	0	0	0	0	0	0	0
	YHL032C	GUT1	16	Sprague and Cronan 1977, Albertyn et al. 1994	0	0	0	0	0	0	0	0
	YIL155C	GUT2	16		0	0	0	0	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0	0
	YBR289W	SNF5	11		0	0	0	0	0	0	0	0
	YDR536W	STL1	16	Ferreira et al. 2005	0	0	0	0	0	0	0	0
Maltose, Galactose and Glycerol	YER027C	GAL83	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					CNV Growth Association							
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Sucrose**	**Raffinose**	**D-Melezitose**	**Glucitol**	**Galactose**
Maltose	YGR287C	IMA1	8	Teste et al. 2010	0	0	0	0	0	0	-1	0
	YJL216C	IMA5	3	Daran-Lapujade et al. 2004, Teste et al. 2010	0	0	0	1	1	1	0	0
	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0	0
	YGR292W	MAL12	NA	Needleman et al. 1984, Naumov et al. 1994	0	0	0	0	0	0	0	0
	YGR288W	MAL13	8		0	0	0	0	0	0	0	0
	NA	MAL2x	NA		0	0	0	0	0	0	0	0
	YBR298C	MAL31	11		0	0	1	0	0	0	0	0
	YBR299W	MAL32	8		0	0	0	0	0	-1	-1	0
	YBR297W	MAL33	9		1	1	0	1	0	0	0	0
	NA	MAL4x	NA		0	0	0	0	0	0	0	0
	NA	MAL6x	NA		0	0	0	0	0	0	0	0
	NA	MALx1	NA		0	0	0	0	0	0	0	0
	NA	MALx2	NA		0	0	0	0	0	0	0	0
	NA	MALx3	NA		0	0	0	0	0	0	0	0
	YIR002C	MPH1	16	Dietvorst et al. 2005	0	0	0	0	0	0	0	0
	YDL247W	MPH2	5		0	0	0	0	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0	0
	YGL115W	SNF4	16	Schüller 2003	0	0	0	0	0	0	0	0
	YBR289W	SNF5	11	Abrams et al. 1986	0	0	0	0	0	0	0	0
Mannitol	YBR112C	SSN6	10	Chujo et al. 2014	0	0	0	0	0	0	0	0
	YEL070W	DSF1	4		0	0	0	0	1	1	0	0
Mannitol	YNR073C	YNR073C	9	Quain and Boulton 1987, Chujo et al. 2014	0	0	0	0	0	0	-1	0
	YCR084C	TUP1	16	Chujo et al. 2014	0	0	0	0	0	0	0	0
Proline	YGR121C	MEP1	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0	0
	YEL062W	NPR2	16	Rousselet et al. 1995	0	0	0	0	0	0	0	0
	YLR142W	PUT1	16	Huang and Brandriss 2000	0	0	0	0	0	0	0	0
	YHR037W	PUT2	16		0	0	0	0	0	0	0	0
	YKL015W	PUT3	16		0	0	0	0	0	0	0	0
	YOR348C	PUT4	15	Rousselet et al. 1995	0	0	0	0	0	0	0	0
Galactose, Maltose and Raffinose	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0	0
Maltose, Galactose, Raffinose, and Galactose	YDR422C	SIP1	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0	0
Maltose, Galactose, and Glycerol	YGL208W	SIP2	16		0	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					CNV Growth Association							
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Sucrose**	**Raffinose**	**D-Melezitose**	**Glucitol**	**Galactose**
Sucrose, Raffinose and Galactose	YDR477W	SNF1	16	Carlson et al. 1981a, b, Neigeborn and Carlson 1984, Abrams et al. 1986, Celenza et al. 1989, Vallier and Carlson 1991, Tu et al. 1993, Sanz 2003, Schüller 2003, Dietvorst et al. 2010	0	0	0	0	0	0	0	0
	YOR290C	SNF2	16		0	0	0	0	0	0	0	0
	YGL115W	SNF4	16		0	0	0	0	0	0	0	0
	YBR289W	SNF5	11		0	0	0	0	0	0	0	0
	YHL025W	SNF6	16		0	0	0	0	0	0	0	0
	YLR025W	SNF7	16		0	0	0	0	0	0	0	0
	YPL002C	SNF8	16		0	0	0	0	0	0	0	0
		SNF9	NA		0	0	0	0	0	0	0	0
		SNF10	NA		0	0	0	0	0	0	0	0
	YDR073W	SNF11	11		0	0	0	0	0	0	0	0
	YOL051W	GAL11	6		0	0	0	0	0	0	0	0
	NA	SUCx	NA	Gascón et al. 1968, Carlson et al. 1981a, b	0	0	0	0	0	0	0	0
Raffinose	YDR422C	SIP1	16	Vallier and Carlson 1991	0	0	0	0	0	0	0	0
	YOL116W	MSN1	15		0	0	0	0	0	0	0	0
Rhamnose	NA	NA	NA	NA	0	0	0	0	0	0	0	0
Succinate	YDR178W	SDH4	16	Oyedotun and Lemire 2004	0	0	0	0	0	0	0	0
	YJL045W	SHD1b	16	Kubo et al. 2000	0	0	0	0	0	0	0	0
	YKL141W	SDH3	16	Oyedotun and Lemire 2004	0	0	0	0	0	0	0	0
	YKL148C	SHD1	16		0	0	0	0	0	0	0	0
	YLL041C	SDH2	16		0	0	0	0	0	0	0	0
Sucrose	YJL216C	IMA5	3	Naumoff and Naumov 2010, Deng et al. 2014	0	0	0	1	1	1	0	0
	YGR287C	IMA1	8	Deng 2014, Deng et al. 2014	0	0	0	0	0	0	-1	0
	YIL172C	IMA3	4		0	0	0	1	1	0	0	0
	YOL157C	IMA2	3		0	0	0	1	0	0	0	0
Carbon Transporters	YGR289C	AGT1/MAL11	5	Needleman et al. 1984, Naumov et al. 1994, Daran-Lapujade et al. 2004, Salema-Oom et al. 2005	0	0	0	0	0	0	0	0
	NA	HXTx	NA	Wieczorke et al. 1999	0	0	0	0	0	0	0	0
	YDL247W	MPH2	5		0	0	0	0	0	0	0	0
	YGR289C	MALx1	5		0	0	0	0	0	0	0	0
	YJR160C	MPH3	6		0	0	0	0	0	0	0	0
	YLR081W	GAL2	15		0	0	0	0	0	0	0	0
	YKL038W	RGT1	16	Lakshmanan et al. 2003	0	0	0	0	0	0	0	0
	YOR047C	STD1	16		0	0	0	0	0	0	0	0
	YDR277C	MTH1	16		0	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					CNV Growth Association							
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Sucrose**	**Raffinose**	**D-Melezitose**	**Glucitol**	**Galactose**
Urea	YBR208C	DUR1,2	16	Cooper and Sumrada 1975, Cooper et al. 1980	0	0	0	0	0	0	0	0
	YEL062W	NPR2	16	Rousselet et al. 1995	0	0	0	0	0	0	0	0
Urea	YGR121C	MEP1	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0	0
	YIR023W	UGA35	8	Vissers et al. 1990	0	0	0	0	0	0	0	0
	YHL016C	DUR3	16	ElBerry et al. 1993	0	0	0	0	0	0	0	0
Xylitol	NA	XDH1	NA	Wenger et al. 2010	0	0	0	0	0	0	0	0
	YLR070C	XYL2	16		0	0	0	0	0	0	0	0

Substrate Info					GCD Growth Rate Assoc.						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Galactose**	**Sucrose**	**Raffinose**	**D-Melezitose**
General Nitrogen catabolism	YKR039W	GAP1	16	Klasson et al. 1999	0	0	0	0	0	0	0
	YNL229C	URE2	16	ter Schure et al. 1998, Grundmann et al. 2001	0	0	0	0	0	0	0
	YER040W	GLN3	16		0	0	0	0	0	0	0
	YFR029W	PTR3	15	Klasson et al. 1999, Forsberg et al. 2001	0	-1	0	-1	0	-1	-1
	YDR160W	SSY1	16		0	0	0	0	0	0	0
	YJL156C	SSY5	16		0	0	0	0	0	0	0
Ammonium	YOR375C	GDH1	16	DeLuna et al. 2001	0	0	0	0	0	0	0
	YAL062W	GDH3	16		0	0	0	0	0	0	0
	YPR035W	GLN1	16	ter Schure et al. 1998, Grundmann et al. 2001	0	0	0	0	0	0	0
	YDL171C	GLT1	16		0	0	0	0	0	0	0
	YNL142W	MEP2	16	Marini et al. 1994, Lorenz and Heitman 1998, Grundmann et al. 2001	0	0	0	0	0	0	0
	YGR121C	MEP1	16		0	0	0	0	0	0	0
	YPR138C	MEP3	16		0	0	0	0	0	0	0
General Carbon Metabolism Genes	YOL051W	GAL11	6	Choi et al. 2008	-1	0	-1	0	0	0	1
	YER133W	GLC7	15	Neigeborn et al. 1987	0	-1	0	-1	0	-1	-1

Table 10 – continued

Substrate Info					GCD Growth Rate Assoc.						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Galactose**	**Sucrose**	**Raffinose**	**D-Melezitose**
General Carbon Metabolism Genes	YJR090C	GRR1	12	Vallier et al. 1991, Flick and Johnston 1991	-1	0	-1	-1	0	1	1
	YDR028C	HEX2	16	Niederacher and Entian 1991, Barnett and Entian 2005, Entian and Barnett 1992	0	0	0	0	0	0	0
	YGL035C	MIG1	16	Carlson 1998	0	0	0	0	0	0	0
	YLR071C	RGR1	15	Sakai et al. 1990	-1	-1	-1	-1	0	-1	-1
	YBR112C	SSN6	10	Chujo et al. 2014	0	0	0	1	-1	-1	-1
	YCR084C	TUP1	16	Chujo et al. 2014	0	0	0	0	0	0	0
D-Arabinose	YBR149W	ARA1	16	Kim et al. 1998	0	0	0	0	0	0	0
	YMR041C	ARA2	16	Kim et al. 1998	0	0	0	0	0	0	0
	YJR096W	YJR096w	16	Träff et al. 2002	0	0	0	0	0	0	0
	YDR368W	YPR1	16	Träff et al. 2002, Masuda et al. 2008	0	0	0	0	0	0	0
D-Melezitose	NA	MAL64	NA	Gibson et al. 1997	0	0	0	0	0	0	0
Galactose	YBR021W	FUR4	16	Traven et al. 2006	0	0	0	0	0	0	0
	YBR020W	GAL1	16		0	0	0	0	0	0	0
	YBR019C	GAL10	16		0	0	0	0	0	0	0
	YOL051W	GAL11	6	Choi et al. 2008	-1	0	-1	0	0	0	1
	YLR081W	GAL2	15	Traven et al. 2006	-1	0	0	0	1	1	1
	YDR009W	GAL3	16	Bhat and Murthy 2001, Timson et al. 2002, Traven et al. 2006	0	0	0	0	0	0	0
	YPL248C	GAL4	13		0	1	0	1	0	-1	-1
	YBR018C	GAL7	16	Traven et al. 2006	0	0	0	0	0	0	0
	YML051W	GAL80	16	Bhat and Murthy 2001, Timson et al. 2002, Traven et al. 2006	0	0	0	0	0	0	0
	YER027C	GAL83	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0
	YJL217W	REE1	3	Choi et al. 2008	1	1	0	0	0	1	1
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0
	YBR289W	SNF5	11		-1	0	-1	0	-1	-1	-1
Glucitol/Sorbitol and Xylitol	YJR159W	SOR1	5	Sarthy et al. 1994, Wenger et al. 2010	-1	-1	0	-1	0	0	1
Glucitol/Sorbitol and Xylitol	YDL246C	SOR2	5		-1	-1	0	-1	0	0	1
Glucose	YCL040W	GLK1	16	Rodriguez et al. 2001	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					GCD Growth Rate Assoc.						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Galactose**	**Sucrose**	**Raffinose**	**D-Melezitose**
Glucose	YCL040W	GLK1	16	Rodriguez et al. 2001	0	0	0	0	0	0	0
Glucose and Fructose	YFR053C	HXK1	16		0	0	0	0	0	0	0
	YGL253W	HXK2	16	Bisson and Fraenkel 1983, Winde et al. 1996, Rodriguez et al. 2001	0	0	0	0	0	0	0
	YDL194W	SNF3	16	Vallier and Carlson 1991, Dietvorst et al. 2010	0	0	0	0	0	0	0
Glutamate	YPL265W	DIP5	16	Klasson et al. 1999	0	0	0	0	0	0	0
	YDL215C	GDH2	16	Miller and Magasanik 1990, DeLuna et al. 2001	0	0	0	0	0	0	0
	YNL142W	MEP2	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0
	YGL084C	GUP1	16	Holst et al. 2000	0	0	0	0	0	0	0
	YPL189W	GUP2	16		0	0	0	0	0	0	0
	YHL032C	GUT1	16	Sprague and Cronan 1977, Albertyn et al. 1994	0	0	0	0	0	0	0
	YIL155C	GUT2	16		0	0	0	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0
	YBR289W	SNF5	11		-1	0	-1	0	-1	-1	-1
	YDR536W	STL1	16	Ferreira et al. 2005	0	0	0	0	0	0	0
Maltose, Galactose and Glycerol	YER027C	GAL83	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
Maltose	YGR287C	IMA1	8	Teste et al. 2010	1	0	0	0	0	1	0
	YJL216C	IMA5	3	Daran-Lapujade et al. 2004, Teste et al. 2010	1	1	0	0	0	1	1
	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0
	YGR292W	MAL12	NA	Needleman et al. 1984, Naumov et al. 1994	0	0	0	0	0	0	0
	YGR288W	MAL13	8		1	1	0	1	0	1	1
	NA	MAL2x	NA		0	0	0	0	0	0	0
	YBR298C	MAL31	11		0	0	1	0	0	0	0
	YBR299W	MAL32	8		-1	-1	0	-1	0	-1	-1
	YBR297W	MAL33	9		0	1	1	0	0	-1	-1
	NA	MAL4x	NA		0	0	0	0	0	0	0
	NA	MAL6x	NA		0	0	0	0	0	0	0
	NA	MALx1	NA		0	0	0	0	0	0	0
	NA	MALx2	NA		0	0	0	0	0	0	0
	NA	MALx3	NA		0	0	0	0	0	0	0
	YIR002C	MPH1	16	Dietvorst et al. 2005	0	0	0	0	0	0	0
	YDL247W	MPH2	5		0	0	1	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0
	YGL115W	SNF4	16	Schüller 2003	0	0	0	0	0	0	0
	YBR289W	SNF5	11	Abrams et al. 1986	-1	0	-1	0	-1	-1	-1
Mannitol	YBR112C	SSN6	10	Chujo et al. 2014	0	0	0	1	-1	-1	-1
	YEL070W	DSF1	4		0	0	-1	0	0	1	1
	YNR073C	YNR073C	9	Quain and Boulton 1987, Chujo et al. 2014	-1	-1	0	0	-1	-1	-1
	YCR084C	TUP1	16	Chujo et al. 2014	0	0	0	0	0	0	0

Table 10 - continued

Substrate Info					GCD Growth Rate Assoc.						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Galactose**	**Sucrose**	**Raffinose**	**D-Melezitose**
Proline	YGR121C	MEP1	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0
	YEL062W	NPR2	16	Rousselet et al. 1995	0	0	0	0	0	0	0
	YLR142W	PUT1	16	Huang and Brandriss 2000	0	0	0	0	0	0	0
	YHR037W	PUT2	16		0	0	0	0	0	0	0
	YKL015W	PUT3	16		0	0	0	0	0	0	0
	YOR348C	PUT4	15	Rousselet et al. 1995	-1	0	0	0	1	1	1
Galactose, Maltose and Raffinose	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0
Maltose, Galactose, Raffinose, and Galactose	YDR422C	SIP1	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
Maltose, Galactose, and Glycerol	YGL208W	SIP2	16		0	0	0	0	0	0	0
Sucrose, Raffinose and Galactose	YDR477W	SNF1	16	Carlson et al. 1981a, b, Neigeborn and Carlson 1984, Abrams et al. 1986, Celenza et al. 1989, Vallier and Carlson 1991, Tu et al. 1993, Sanz 2003, Schüller 2003, Dietvorst et al. 2010	0	0	0	0	0	0	0
	YOR290C	SNF2	16		0	0	0	0	0	0	0
	YGL115W	SNF4	16		0	0	0	0	0	0	0
	YBR289W	SNF5	11		-1	0	-1	0	-1	-1	-1
	YHL025W	SNF6	16		0	0	0	0	0	0	0
	YLR025W	SNF7	16		0	0	0	0	0	0	0
	YPL002C	SNF8	16		0	0	0	0	0	0	0
		SNF9	NA		0	0	0	0	0	0	0
		SNF10	NA		0	0	0	0	0	0	0
	YDR073W	SNF11	11		1	0	0	0	0	0	0
	YOL051W	GAL11	6		-1	0	-1	0	0	0	1
	NA	SUCx	NA	Gascón et al. 1968, Carlson et al. 1981a, b	0	0	0	0	0	0	0
	YER027C	GAL83	16	Yang et al. 1994, Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
Raffinose	YDR422C	SIP1	16	Vallier and Carlson 1991	0	0	0	0	0	0	0
	YOL116W	MSN1	15		-1	0	0	0	1	1	1
Rhamnose	NA	NA	NA	NA	0	0	0	0	0	0	0
Succinate	YDR178W	SDH4	16	Oyedotun and Lemire 2004	0	0	0	0	0	0	0
	YJL045W	SHD1b	16	Kubo et al. 2000	0	0	0	0	0	0	0
	YKL141W	SDH3	16	Oyedotun and Lemire 2004	0	0	0	0	0	0	0
	YKL148C	SHD1	16		0	0	0	0	0	0	0
	YLL041C	SDH2	16		0	0	0	0	0	0	0
Sucrose	YJL216C	IMA5	3	Naumoff and Naumov 2010, Deng et al. 2014	1	1	0	0	0	1	1
	YGR287C	IMA1	8	Deng 2014, Deng et al. 2014	1	0	0	0	0	1	0
	YIL172C	IMA3	4		1	0	1	0	1	1	1
	YOL157C	IMA2	3		0	1	-1	1	0	0	0

Table 10 – continued

Substrate Info					GCD Growth Rate Assoc.						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**Glucose**	**Fructose**	**Maltose**	**Galactose**	**Sucrose**	**Raffinose**	**D-Melezitose**
Carbon Transporters	YGR289C	AGT1/MAL11	5	Needleman et al. 1984, Naumov et al. 1994, Daran-Lapujade et al. 2004, Salema-Oom et al. 2005	1	1	0	0	0	1	1
	NA	HXTx	NA	Wieczorke et al. 1999	0	0	0	0	0	0	0
	YDL247W	MPH2	5		0	0	1	0	0	0	0
	YGR289C	MALx1	5		1	1	0	0	0	1	1
	YJR160C	MPH3	6		1	1	1	0	0	1	1
	YLR081W	GAL2	15		-1	0	0	0	1	1	1
	YKL038W	RGT1	16	Lakshmanan et al. 2003	0	0	0	0	0	0	0
	YOR047C	STD1	16		0	0	0	0	0	0	0
	YDR277C	MTH1	16		0	0	0	0	0	0	0
Urea	YBR208C	DUR1,2	16	Cooper and Sumrada 1975, Cooper et al. 1980	0	0	0	0	0	0	0
	YEL062W	NPR2	16	Rousselet et al. 1995	0	0	0	0	0	0	0
	YGR121C	MEP1	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0
	YIR023W	UGA35	8	Vissers et al. 1990	1	1	1	0	0	0	0
	YHL016C	DUR3	16	ElBerry et al. 1993	0	0	0	0	0	0	0
Xylitol	NA	XDH1	NA	Wenger et al. 2010	0	0	0	0	0	0	0
	YLR070C	XYL2	16		0	0	0	0	0	0	0

Substrate Info					GCD Utilization Association						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**D-Arabinose**	**Glucitol**	**Glycerol**	**Mannitol**	**Rhamnose**	**Succinate**	**Xylitol**
General Nitrogen catabolism	YKR039W	GAP1	16	Klasson et al. 1999	0	0	0	0	0	0	0
	YNL229C	URE2	16	ter Schure et al. 1998, Grundmann et al. 2001	0	0	0	0	0	0	0
	YER040W	GLN3	16		0	0	0	0	0	0	0
	YFR029W	PTR3	15	Klasson et al. 1999, Forsberg et al. 2001	0	0	0	-1	-1	0	0
	YDR160W	SSY1	16		0	0	0	0	0	0	0
	YJL156C	SSY5	16		0	0	0	0	0	0	0
Ammonium	YOR375C	GDH1	16	DeLuna et al. 2001	0	0	0	0	0	0	0
	YAL062W	GDH3	16		0	0	0	0	0	0	0
	YPR035W	GLN1	16	ter Schure et al. 1998, Grundmann et al. 2001	0	0	0	0	0	0	0
	YDL171C	GLT1	16		0	0	0	0	0	0	0
	YNL142W	MEP2	16	Marini et al. 1994, Lorenz and Heitman 1998, Grundmann et al. 2001	0	0	0	0	0	0	0
	YGR121C	MEP1	16		0	0	0	0	0	0	0
	YPR138C	MEP3	16		0	0	0	0	0	0	0
General Carbon Metabolism Genes	YOL051W	GAL11	6	Choi et al. 2008	0	0	0	0	0	0	0
	YER133W	GLC7	15	Neigeborn et al. 1987	0	0	0	-1	-1	0	0
	YJR090C	GRR1	12	Vallier et al. 1991, Flick and Johnston 1991	0	0	0	0	0	-1	0
	YDR028C	HEX2	16	Niederacher and Entian 1991, Barnett and Entian 2005, Entian and Barnett 1992	0	0	0	0	0	0	0
	YGL035C	MIG1	16	Carlson 1998	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					GCD Utilization Association						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**D-Arabinose**	**Glucitol**	**Glycerol**	**Mannitol**	**Rhamnose**	**Succinate**	**Xylitol**
General Carbon Metabolism Genes	YLR071C	RGR1	15	Sakai et al. 1990	0	0	0	0	0	0	0
	YBR112C	SSN6	10	Chujo et al. 2014	0	0	0	0	0	1	0
	YCR084C	TUP1	16	Chujo et al. 2014	0	0	0	0	0	0	0
D-Arabinose	YBR149W	ARA1	16	Kim et al. 1998	0	0	0	0	0	0	0
	YMR041C	ARA2	16	Kim et al. 1998	0	0	0	0	0	0	0
	YJR096W	YJR096w	16	Träff et al. 2002	0	0	0	0	0	0	0
	YDR368W	YPR1	16	Träff et al. 2002, Masuda et al. 2008	0	0	0	0	0	0	0
D-Melezitose	NA	MAL64	NA	Gibson et al. 1997	0	0	0	0	0	0	0
Galactose	YBR021W	FUR4	16	Traven et al. 2006	0	0	0	0	0	0	0
	YBR020W	GAL1	16		0	0	0	0	0	0	0
	YBR019C	GAL10	16		0	0	0	0	0	0	0
	YOL051W	GAL11	6	Choi et al. 2008	0	0	0	0	0	0	0
	YLR081W	GAL2	15	Traven et al. 2006	0	0	0	0	0	0	-1
	YDR009W	GAL3	16	Bhat and Murthy 2001, Timson et al. 2002, Traven et al. 2006	0	0	0	0	0	0	0
	YPL248C	GAL4	13		0	0	0	0	0	0	0
	YBR018C	GAL7	16	Traven et al. 2006	0	0	0	0	0	0	0
	YML051W	GAL80	16	Bhat and Murthy 2001, Timson et al. 2002, Traven et al. 2006	0	0	0	0	0	0	0
	YER027C	GAL83	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0
	YJL217W	REE1	3	Choi et al. 2008	0	0	0	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0
	YBR289W	SNF5	11		0	0	0	0	0	0	0
Glucitol/Sorbitol and Xylitol	YJR159W	SOR1	5	Sarthy et al. 1994, Wenger et al. 2010	0	0	0	0	0	0	0
Glucitol/Sorbitol and Xylitol	YDL246C	SOR2	5		0	0	0	0	0	0	0
Glucose	YCL040W	GLK1	16	Rodriguez et al. 2001	0	0	0	0	0	0	0
Glucose and Fructose	YFR053C	HXK1	16		0	0	0	0	0	0	0
	YGL253W	HXK2	16	Bisson and Fraenkel 1983, Winde et al. 1996, Rodriguez et al. 2001	0	0	0	0	0	0	0
	YDL194W	SNF3	16	Vallier and Carlson 1991, Dietvorst et al. 2010	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					GCD Utilization Association						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**D-Arabinose**	**Glucitol**	**Glycerol**	**Mannitol**	**Rhamnose**	**Succinate**	**Xylitol**
Glutamate	YPL265W	DIP5	16	Klasson et al. 1999	0	0	0	0	0	0	0
	YDL215C	GDH2	16	Miller and Magasanik 1990, DeLuna et al. 2001	0	0	0	0	0	0	0
	YNL142W	MEP2	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0
	YGL084C	GUP1	16	Holst et al. 2000	0	0	0	0	0	0	0
	YPL189W	GUP2	16		0	0	0	0	0	0	0
	YHL032C	GUT1	16	Sprague and Cronan 1977, Albertyn et al. 1994	0	0	0	0	0	0	0
	YIL155C	GUT2	16		0	0	0	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0
	YBR289W	SNF5	11		0	0	0	0	0	0	0
	YDR536W	STL1	16	Ferreira et al. 2005	0	0	0	0	0	0	0
Maltose, Galactose and Glycerol	YER027C	GAL83	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
Maltose	YGR287C	IMA1	8	Teste et al. 2010	0	0	0	0	0	0	0
	YJL216C	IMA5	3	Daran-Lapujade et al. 2004, Teste et al. 2010	0	0	0	0	0	0	0
	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0
	YGR292W	MAL12	NA	Needleman et al. 1984, Naumov et al. 1994	0	0	0	0	0	0	0
	YGR288W	MAL13	8		0	0	0	0	0	0	0
	NA	MAL2x	NA		0	0	0	0	0	0	0
	YBR298C	MAL31	11		0	0	0	0	0	0	0
	YBR299W	MAL32	8		0	0	0	0	0	0	0
	YBR297W	MAL33	9		0	0	0	0	0	0	0
	NA	MAL4x	NA		0	0	0	0	0	0	0
	NA	MAL6x	NA		0	0	0	0	0	0	0
	NA	MALx1	NA		0	0	0	0	0	0	0
	NA	MALx2	NA		0	0	0	0	0	0	0
	NA	MALx3	NA		0	0	0	0	0	0	0
	YIR002C	MPH1	16	Dietvorst et al. 2005	0	0	0	0	0	0	0
	YDL247W	MPH2	5		0	0	0	0	0	0	0
	YOR290C	SNF2	16	Abrams et al. 1986	0	0	0	0	0	0	0
	YGL115W	SNF4	16	Schüller 2003	0	0	0	0	0	0	0
	YBR289W	SNF5	11	Abrams et al. 1986	0	0	0	0	0	0	0
Mannitol	YBR112C	SSN6	10	Chujo et al. 2014	0	0	0	0	0	1	0
	YEL070W	DSF1	4		0	0	0	0	0	0	0
	YNR073C	YNR073C	9	Quain and Boulton 1987, Chujo et al. 2014	0	0	0	0	0	0	0
	YCR084C	TUP1	16	Chujo et al. 2014	0	0	0	0	0	0	0
Proline	YGR121C	MEP1	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0
	YEL062W	NPR2	16	Rousselet et al. 1995	0	0	0	0	0	0	0
	YLR142W	PUT1	16	Huang and Brandriss 2000	0	0	0	0	0	0	0
	YHR037W	PUT2	16		0	0	0	0	0	0	0
	YKL015W	PUT3	16		0	0	0	0	0	0	0
	YOR348C	PUT4	15	Rousselet et al. 1995	0	0	0	0	0	0	-1
Galactose, Maltose and Raffinose	YIL154C	IMP2'	16	Lodi et al. 1995	0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					GCD Utilization Association						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**D-Arabinose**	**Glucitol**	**Glycerol**	**Mannitol**	**Rhamnose**	**Succinate**	**Xylitol**
Maltose, Galactose, Raffinose, and Galactose	YDR422C	SIP1	16	Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
Maltose, Galactose, and Glycerol	YGL208W	SIP2	16		0	0	0	0	0	0	0
Sucrose, Raffinose and Galactose	YDR477W	SNF1	16	Carlson et al. 1981a, b, Neigeborn and Carlson 1984, Abrams et al. 1986, Celenza et al. 1989, Vallier and Carlson 1991, Tu et al. 1993, Sanz 2003, Schüller 2003, Dietvorst et al. 2010	0	0	0	0	0	0	0
	YOR290C	SNF2	16		0	0	0	0	0	0	0
	YGL115W	SNF4	16		0	0	0	0	0	0	0
	YBR289W	SNF5	11		0	0	0	0	0	0	0
	YHL025W	SNF6	16		0	0	0	0	0	0	0
	YLR025W	SNF7	16		0	0	0	0	0	0	0
	YPL002C	SNF8	16		0	0	0	0	0	0	0
		SNF9	NA		0	0	0	0	0	0	0
		SNF10	NA		0	0	0	0	0	0	0
	YDR073W	SNF11	11		0	0	0	0	0	0	0
	YOL051W	GAL11	6		0	0	0	0	0	0	0
	NA	SUCx	NA	Gascón et al. 1968, Carlson et al. 1981a, b	0	0	0	0	0	0	0
	YER027C	GAL83	16	Yang et al. 1994, Schüller 2003, Choi et al. 2008	0	0	0	0	0	0	0
Raffinose	YDR422C	SIP1	16	Vallier and Carlson 1991	0	0	0	0	0	0	0
	YOL116W	MSN1	15		0	0	0	0	0	0	-1
Rhamnose	NA	NA	NA	NA	0	0	0	0	0	0	0
Succinate	YDR178W	SDH4	16	Oyedotun and Lemire 2004	0	0	0	0	0	0	0
	YJL045W	SHD1b	16	Kubo et al. 2000	0	0	0	0	0	0	0
	YKL141W	SDH3	16	Oyedotun and Lemire 2004	0	0	0	0	0	0	0
	YKL148C	SHD1	16		0	0	0	0	0	0	0
	YLL041C	SDH2	16		0	0	0	0	0	0	0
Sucrose	YJL216C	IMA5	3	Naumoff and Naumov 2010, Deng et al. 2014	0	0	0	0	0	0	0
	YGR287C	IMA1	8	Deng 2014, Deng et al. 2014	0	0	0	0	0	0	0
	YIL172C	IMA3	4		0	0	0	0	0	0	0
	YOL157C	IMA2	3		0	0	0	0	0	0	0
Carbon Transporters	YGR289C	AGT1/MAL11	5	Needleman et al. 1984, Naumov et al. 1994, Daran-Lapujade et al. 2004, Salema-Oom et al. 2005	0	0	0	0	0	0	0
	NA	HXTx	NA	Wieczorke et al. 1999	0	0	0	0	0	0	0
	YDL247W	MPH2	5		0	0	0	0	0	0	0
	YGR289C	MALx1	5		0	0	0	0	0	0	0
	YJR160C	MPH3	6		0	0	0	0	0	0	0
	YLR081W	GAL2	15		0	0	0	0	0	0	-1
	YKL038W	RGT1	16	Lakshmanan et al. 2003	0	0	0	0	0	0	0
	YOR047C	STD1	16		0	0	0	0	0	0	0
	YDR277C	MTH1	16		0	0	0	0	0	0	0

Table 10 – continued

Substrate Info					GCD Utilization Association						
Substrate	**Systematic**	**Gene**	**Strain**	**Citation**	**D-Arabinose**	**Glucitol**	**Glycerol**	**Mannitol**	**Rhamnose**	**Succinate**	**Xylitol**
Urea	YBR208C	DUR1,2	16	Cooper and Sumrada 1975, Cooper et al. 1980	0	0	0	0	0	0	0
	YEL062W	NPR2	16	Rousselet et al. 1995	0	0	0	0	0	0	0
	YGR121C	MEP1	16	Marini et al. 1994, Lorenz and Heitman 1998	0	0	0	0	0	0	0
	YIR023W	UGA35	8	Vissers et al. 1990	1	0	0	0	0	0	0
	YHL016C	DUR3	16	ElBerry et al. 1993	0	0	0	0	0	0	0
Xylitol	NA	XDH1	NA	Wenger et al. 2010	0	0	0	0	0	0	0
	YLR070C	XYL2	16		0	0	0	0	0	0	0

Table 11: T-test for absolute survivorship of mutant and ancestoral strains on glucose and maltose. The asterisk represents signficant ($p < 0.05$) differences in survivorship between mutant and ancestors for a strain.

Carbon	Strain	P-Value	
Glucose	DBVPG 6044	$1.47X10^{-16}$	*
Glucose	CBS 4054	$3.09X10^{-07}$	*
Glucose	CBS 6872	$4.64X10^{-07}$	*
Glucose	CBS 4070	0.0002	*
Glucose	UWOPS03_461_4	0.017	*
Glucose	SK1	0.024	*
Glucose	Y12	0.068	
Glucose	NCYC 110	0.128	
Glucose	DBVPG 1788	0.156	
Glucose	YJM 981	0.156	
Glucose	Y55	0.176	
Glucose	DBVPG 1106	0.323	
Glucose	DBVPG 6765	0.561	
Glucose	YJM 978	0.585	
Glucose	L_1374	0.610	
Glucose	YJM 975	0.614	
Glucose	CBS 7764	0.624	
Glucose	CBS 6131	0.844	
Glucose	BC187	0.898	
Maltose	UWOPS03_461_4	$3.12X10^{-07}$	*
Maltose	YJM 978	0.0002	*
Maltose	YJM 975	0.0002	*
Maltose	NCYC 110	0.00054	*
Maltose	L_1374	0.012	*
Maltose	Y12	0.034	*
Maltose	SK1	0.038	*
Maltose	DBVPG 6765	0.045	*
Maltose	Y55	0.102	
Maltose	YJM 981	0.123	
Maltose	DBVPG 1106	0.183	
Maltose	CBS 7764	0.300	
Maltose	BC187	0.424	
Maltose	CBS 6131	0.593	
Maltose	CBS 4054	NA[1]	
Maltose	CBS 4070	NA[1]	
Maltose	CBS 6872	NA[1]	
Maltose	DBVPG 1788	NA[1]	
Maltose	DBVPG 6044	NA[1]	

[1]*Strains were not able to metabolize Maltose*

Table 12: ANOVA of absolute survivorship across strain in A) glucose environment and B) maltose environment.

A)

Factor	Df	F value	P value
Strain	18	267.638	$<2.0 \times 10^{-16}$
Type	1	29.317	6.38×10^{-8}
Strain:Type	18	2.325	0.0012

B)

Factor	Df	F value	P value
Strain	18	188.168	$<2.0 \times 10^{-16}$
Type	1	48.313	4.01×10^{-12}
Strain:Type	18	3.286	3.03×10^{-6}

Table 13: Mann-Whitney-U test to determine significant differences between the growth rate distributions of ancestral and mutatant strains. Significant p-values ($p < 0.05$) are denoted with an asterisk.

Carbon	Strain	Statistic	P-Value	
Glucose	DBVPG 6044	892	$1.19X10^{-05}$	*
Glucose	CBS 6872	1582	0.001	*
Glucose	L_1374	5041	0.003	*
Glucose	CBS 4070	1392	0.006	*
Glucose	UWOPS03_461_4	5124	0.009	*
Glucose	YJM 981	7526	0.016	*
Glucose	NCYC 110	973	0.033	*
Glucose	BC187	4381	0.035	*
Glucose	CBS 4054	869	0.036	*
Glucose	Y12	7617	0.078	
Glucose	DBVPG 1106	3111	0.090	
Glucose	CBS 6131	2114	0.100	
Glucose	YJM 975	5550	0.148	
Glucose	CBS 7764	2290	0.250	
Glucose	DBVPG 1788	1466	0.388	
Glucose	SK1	3115	0.436	
Glucose	DBVPG 6765	4956	0.558	
Glucose	YJM 978	6499	0.656	
Glucose	Y55	3367	0.946	
Maltose	Y55	4623	$2.06X10^{-08}$	*
Maltose	L_1374	7847	$1.90X10^{-07}$	*
Maltose	YJM 981	5807	$5.70X10^{-07}$	*
Maltose	DBVPG 6765	6360	$5.41X10^{-06}$	*
Maltose	BC187	7058	$7.39X10^{-05}$	*
Maltose	UWOPS03_461_4	860	0.0004	*
Maltose	DBVPG 1106	3481	0.0007	*
Maltose	Y12	5866	0.003	*
Maltose	SK1	2505	0.003	*
Maltose	YJM 978	2908	0.006	*
Maltose	NCYC 110	1121	0.034	*
Maltose	YJM 975	5857	0.098	
Maltose	CBS 6131	1559	0.293	
Maltose	CBS 7764	1265	0.363	
Maltose	DBVPG 6044[1]	NA	NA[1]	
Maltose	CBS 4070	NA	NA[1]	
Maltose	DBVPG 1788	NA	NA[1]	
Maltose	CBS 4054	NA	NA[1]	
Maltose	CBS 6872	NA	NA[1]	

[1]*Strains were not able to metabolize Maltose*

Table 14: Summary table of all measures calculated to describe the growth rate distributions for both the mutants (M) and ancestors (A) of a strain in both glucose and maltose media.

Media	Strain	Type	Mean Difference	Skew	Coefficient of Variation
Glucose	BC187	A	0.0013	0.472	0.205
		M		-1.114	0.303
Glucose	CBS 4054	A	-0.0122	1.017	1.555
		M		2.395	1.355
Glucose	CBS 4070	A	-0.0041	1.256	1.265
		M		3.354	2.714
Glucose	CBS 6131	A	-0.0063	-0.967	0.373
		M		0.518	0.629
Glucose	CBS 6872	A	-0.0141	0.679	1.167
		M		2.884	2.247
Glucose	CBS 7764	A	-0.0041	-1.234	0.402
		M		-0.355	0.507
Glucose	DBVPG 1106	A	0.0032	-1.006	0.208
		M		-0.159	0.457
Glucose	DBVPG 1788	A	0.0026	0.818	1.063
		M		-0.013	0.913
Glucose	DBVPG 6044	A	-0.0319	-0.482	0.661
		M		4.974	3.777
Glucose	DBVPG 6765	A	0.0021	4.766	0.598
		M		3.415	0.659
Glucose	L_1374	A	0.0028	1.726	0.530
		M		-0.649	0.366
Glucose	NCYC 110	A	-0.0142	0.216	0.864
		M		1.242	1.495
Glucose	SK1	A	0.0035	0.141	0.515
		M		0.224	0.581
Glucose	UWOPS03-461_4	A	-0.0071	0.793	0.406
		M		1.505	0.716
Glucose	Y12	A	-0.0034	-0.249	0.175
		M		-0.064	0.361
Glucose	Y55	A	-0.0032	0.594	0.528
		M		-0.214	0.454
Glucose	YJM 975	A	0.0083	-0.539	0.215
		M		2.679	0.548
Glucose	YJM 978	A	-0.0013	-0.610	0.224
		M		0.762	0.477
Glucose	YJM 981	A	-0.0061	-2.791	0.186
		M		-0.309	0.420

Table 14 – continued

Media	Strain	Type	Mean Difference	Skew	Coefficient of Variation
Maltose	BC187	A	-0.0070	-0.818	0.308
		M		3.011	0.524
Maltose	CBS 4054	A	0.0001	1.490	0.998
		M		2.382	1.252
Maltose	CBS 4070	A	0.0002	2.084	1.423
		M		3.500	1.554
Maltose	CBS 6131	A	-0.0082	-0.446	0.603
		M		-0.221	0.733
Maltose	CBS 6872	A	0.0001	1.291	0.836
		M		2.600	1.103
Maltose	CBS 7764	A	-0.0069	0.142	0.957
		M		0.160	0.925
Maltose	DBVPG 1106	A	-0.0167	1.920	0.637
		M		-0.372	0.507
Maltose	DBVPG 1788	A	0.0002	1.572	1.445
		M		3.931	1.810
Maltose	DBVPG 6044	A	0.0004	1.744	1.310
		M		4.730	1.702
Maltose	DBVPG 6765	A	-0.0111	-1.286	0.408
		M		-0.581	0.556
Maltose	L_1374	A	-0.0128	0.769	0.423
		M		-0.473	0.486
Maltose	NCYC 110	A	-0.0159	0.819	1.322
		M		3.841	3.036
Maltose	SK1	A	-0.0112	0.285	0.623
		M		1.010	0.898
Maltose	UWOPS03-461_4	A	-0.0200	0.182	0.620
		M		0.765	1.190
Maltose	Y12	A	-0.0062	-0.728	0.429
		M		0.189	0.611
Maltose	Y55	A	-0.0205	0.268	0.455
		M		0.795	0.812
Maltose	YJM 975	A	-0.0033	-0.389	0.364
		M		0.577	0.472
Maltose	YJM 978	A	-0.0109	-0.875	0.428
		M		0.264	0.870
Maltose	YJM 981	A	-0.0067	-1.304	0.350
		M		1.954	0.605

Table 15: Network properties measured for both the metabolic and PPI network.

Network Properties	Definition
Closeness	Average shortest path between a node and all other nodes in a network
Assortativity	Average connectivity of neighboring nodes
Betweenness (nodes)	Frequency with which a node is located on the shortest path between all other nodes
Betweenness (edges)	Frequency with which an edge is located on the shortest path between all other nodes
Degree	Number of nodes a specific node interacts with
Eccentricity (radius)	Shortest path distance between a specific node and the furthest node in a graph
Shortest Path	Measure of the smallest number of steps between two nodes

Table 16: Metabolic and PPI network properties are correlated with measures of mutational robustness. A linear model was used to determine which network properties were associated with the different measures of mutational robustness. All network properties that were signficantly associated ($p < 0.05$) with mutational robustness are included in the table.

Data	Measure	Network	Network Property	Statisic	P-Value	R^2
Glucose	Mean Diff	Metabolic	Betweenness (edge)	-3.20	0.0109	0.4793
Glucose	Mean Diff	Metabolic	Degree	2.96	0.0159	0.4376
Glucose	Mean Diff	Metabolic	Closeness	2.94	0.0164	0.4337
Glucose	Mean Diff	Metabolic	Betweenness	-2.27	0.0495	0.293
Glucose	Mean Diff	PPI	Betweenness	-2.86	0.0211	0.4439
Maltose	Mean Diff	Metabolic	Betweenness (edge)	-2.46	0.036	0.3363
Maltose	Mean Diff	Metabolic	Closeness	2.44	0.0375	0.3308
Maltose	Survivorship	Metabolic	Betweenness	-2.41	0.0422	0.3492
Maltose	Coeff Ratio	Metabolic	Betweenness (edge)	2.94	0.0166	0.4323
Maltose	Coeff Ratio	Metabolic	Betweenness	2.86	0.0188	0.418
Maltose	Coeff Ratio	Metabolic	Degree	-2.83	0.0196	0.4126
Maltose	Coeff Ratio	Metabolic	Shortest Path	2.54	0.0317	0.3527
Maltose	Coeff Ratio	Metabolic	Eccentricity	2.31	0.0463	0.3022

Table 17: Plate set-up design for carbon metabolism experiments and interacting environment experiments. Carbon metabolism experiments: Each number represents an individual strain's location on a plate. Light gray boxes represent wells that contain a carbon source media, dark gray wells represent negative control wells that contain that same carbon source media but no yeast, and black wells are a positive control which contains SD-Trp and an individual yeast strain. Interacting environment experiments: Experimental plate set-up for growth nitrogen, temperature and osmotic growth experiments. Each number represents an individual strain (24 in total) and each color represents a different carbon source on the plate.

Plate set-up for carbon metabolism experiments

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
A	1	9	17	25	33	1	1	9	17	25	33	1
B	2	10	18	26	34	10	2	10	18	26	34	10
C	3	11	19	27	35	24	3	11	19	27	35	24
D	4	12	20	28	BL	20	4	12	20	28	BL	20
E	5	13	21	29	BL	32	5	13	21	29	BL	32
F	6	14	22	30	BL	35	6	14	22	30	BL	35
G	7	15	23	31	BL	6	7	15	23	31	BL	6
H	8	16	24	32	BL	14	8	16	24	32	BL	14
	Carbon Source A					SD	Carbon Source B					SD

Plate set -up for interacting environments experiments

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
A	1	9	17	1	9	17	1	9	17	1	9	17
B	2	10	18	2	10	18	2	10	18	2	10	18
C	3	11	19	3	11	19	3	11	19	3	11	19
D	4	12	20	4	12	20	4	12	20	4	12	20
E	5	13	21	5	13	21	5	13	21	5	13	21
F	6	14	22	6	14	22	6	14	22	6	14	22
G	7	15	23	7	15	23	7	15	23	7	15	23
H	8	16	24	8	16	24	8	16	24	8	16	24
	Carbon Source A			Carbon Source B			Carbon Source C			Carbon Source D		

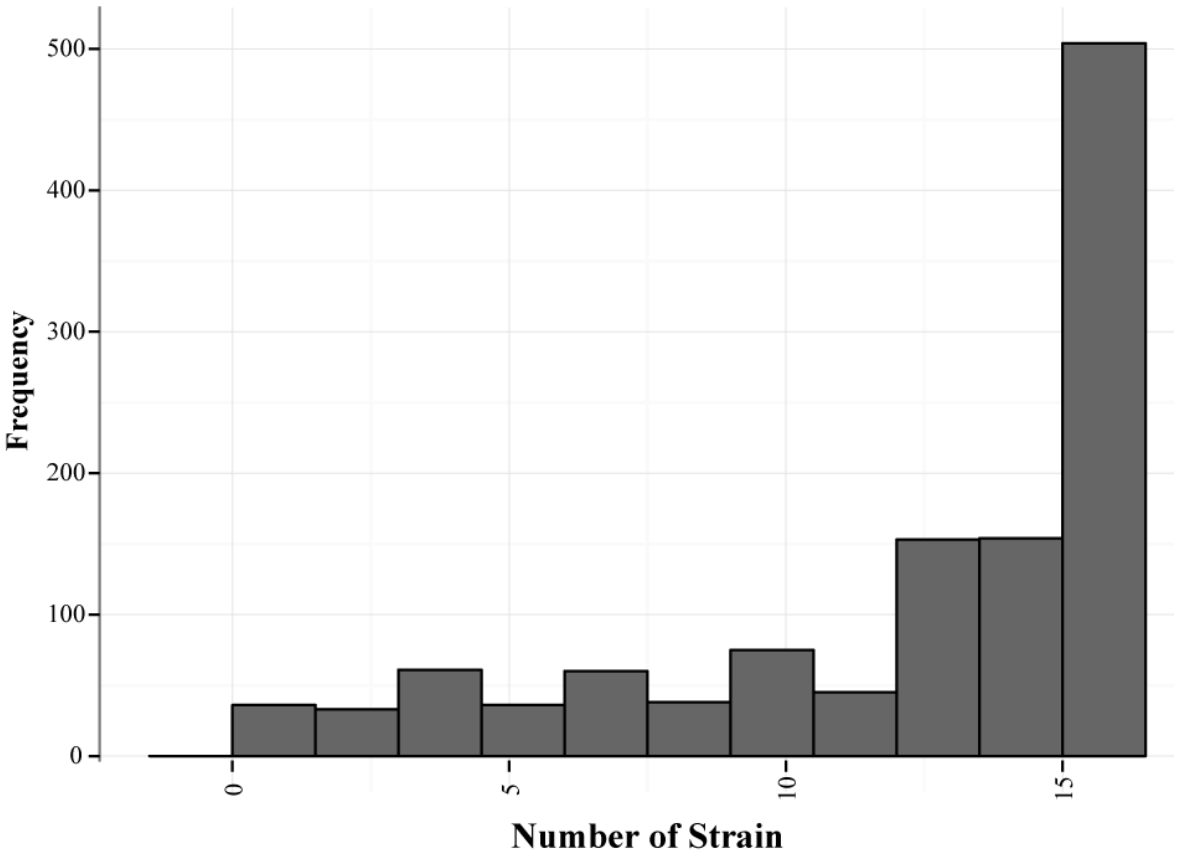

Figure 1: Eighteen percent (1195 of 6800) of genes in the reference are variably present across wild strains. We quantified the number of strains which had each gene found in the reference.

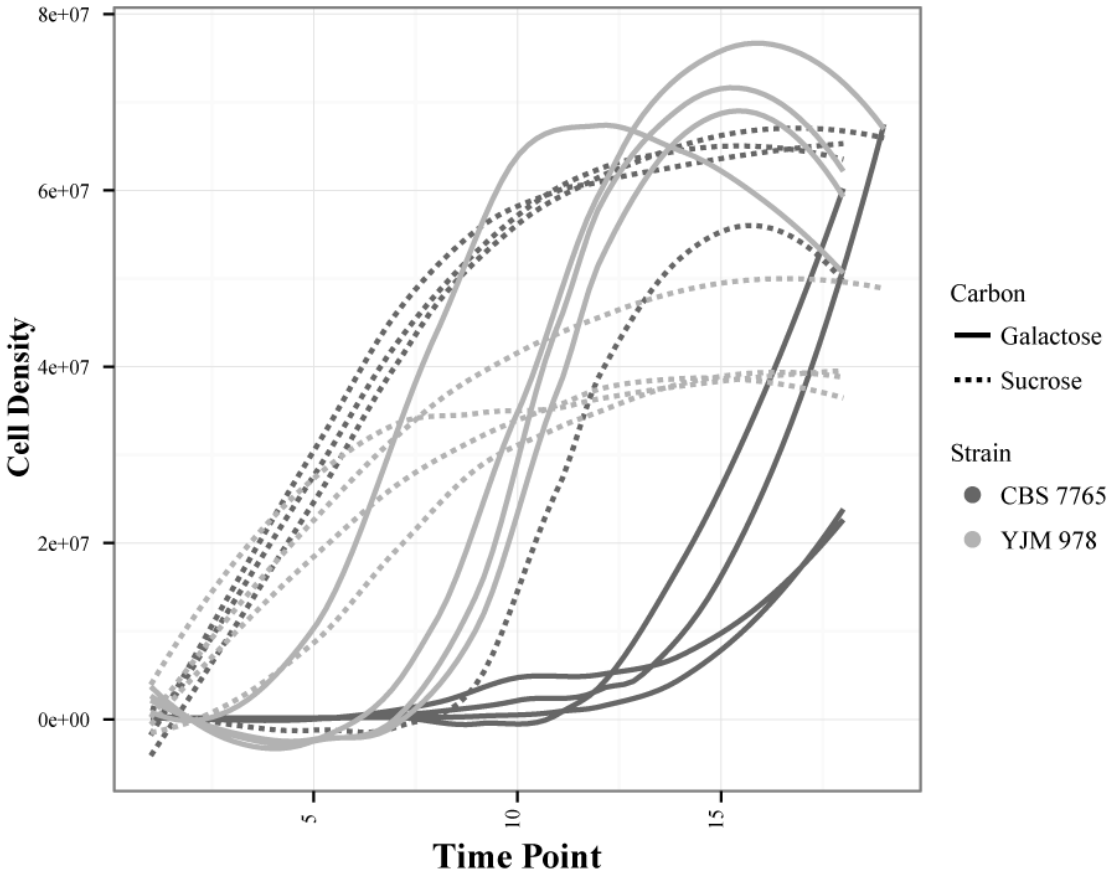

Figure 2: Strain of *S. cerevisiae* display significant variation in metabolism within a carbon source (p-value = $2X10^{-16}$). A) Example growth curve replicates for two strains, YJM 978 (light gray) and CBS 7765 (dark gray), grown in two different carbon environments, galactose (solid line) and sucrose (dotted line).

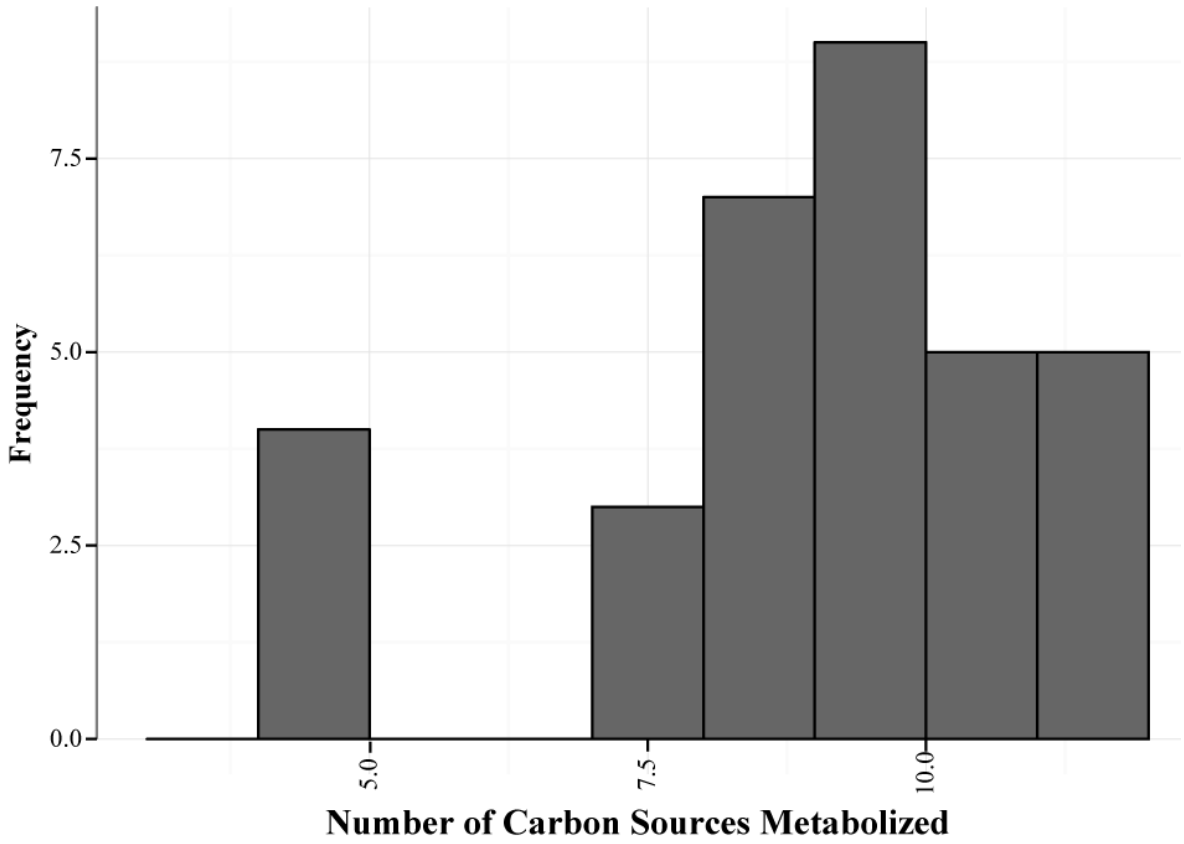

Figure 3: *S. cerevisiae* strains display variation in the number of carbon sources that each strain can metabolize. On average, a strain can metabolize 8.45 carbon sources. However, the metabolic breadth ranges from 4 to 11 carbon sources.

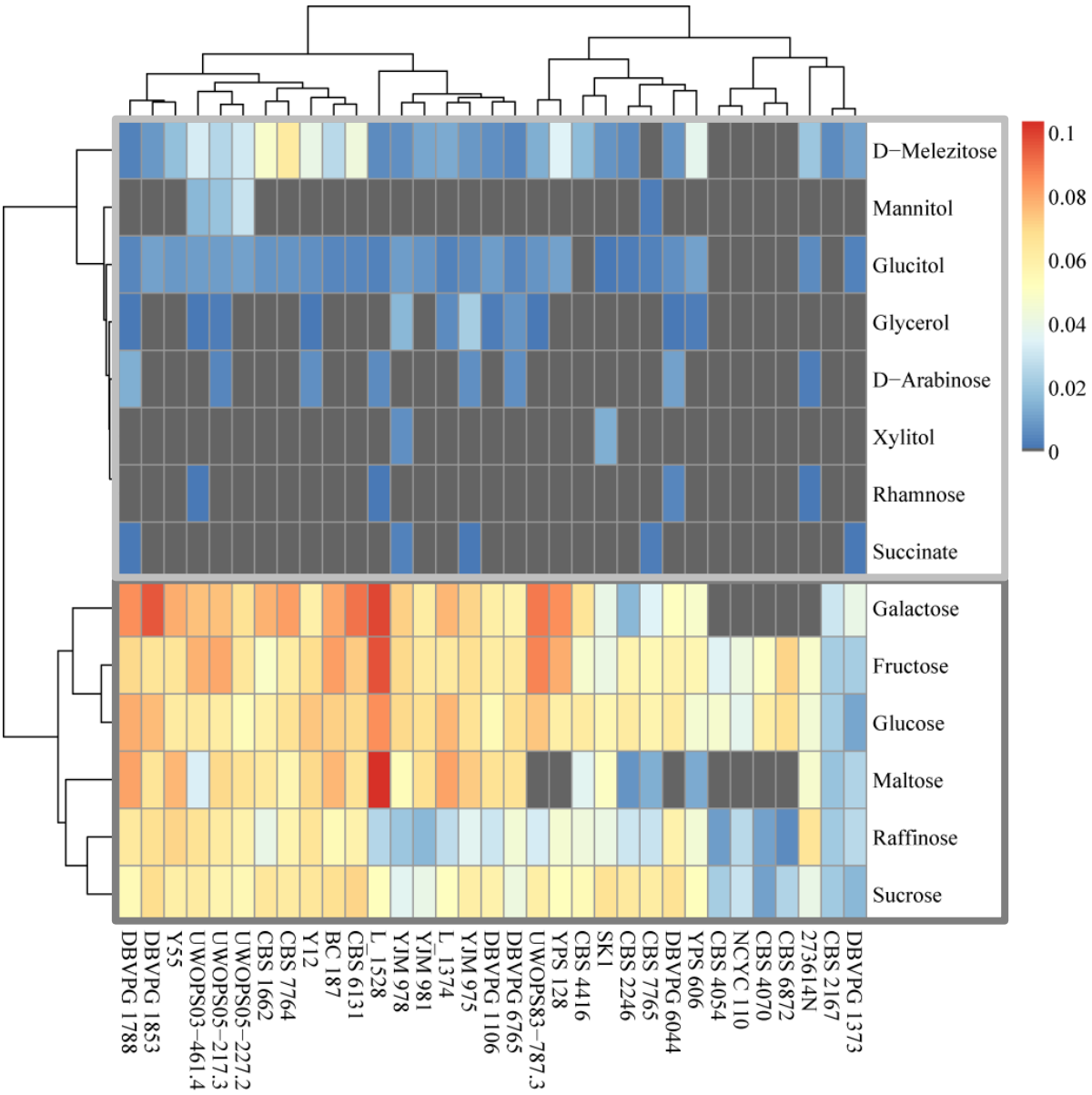

Figure 4: Strains of *S. cerevisiae* perceive to classes of carbon source, preferred, carbon sources most strains can utilize (denoted by dark gray box) and not preferred, carbon sources few strains can utilize (denoted by light gray box). Furthermore, Strains display significant variation in growth rate across carbon environments. The heatmap displays strain growth on carbon sources. The inability to grow on a carbon source is represented with a gray bar.

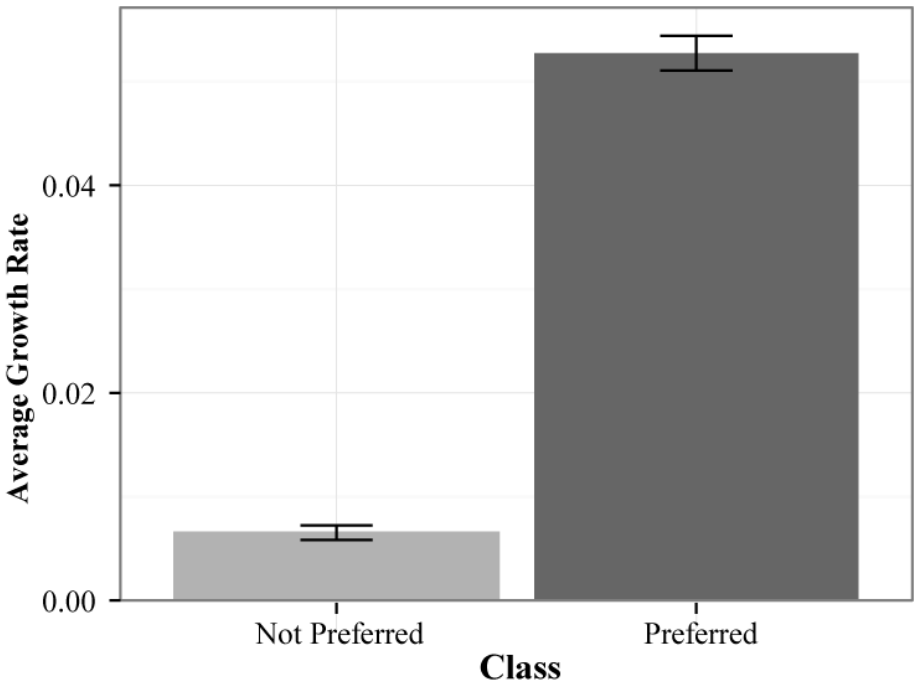

Figure 5: The average growth rate of a strain on a preferred carbon source (dark gray) is an order of magnitude higher than on a non-preferred carbon source (light gray).

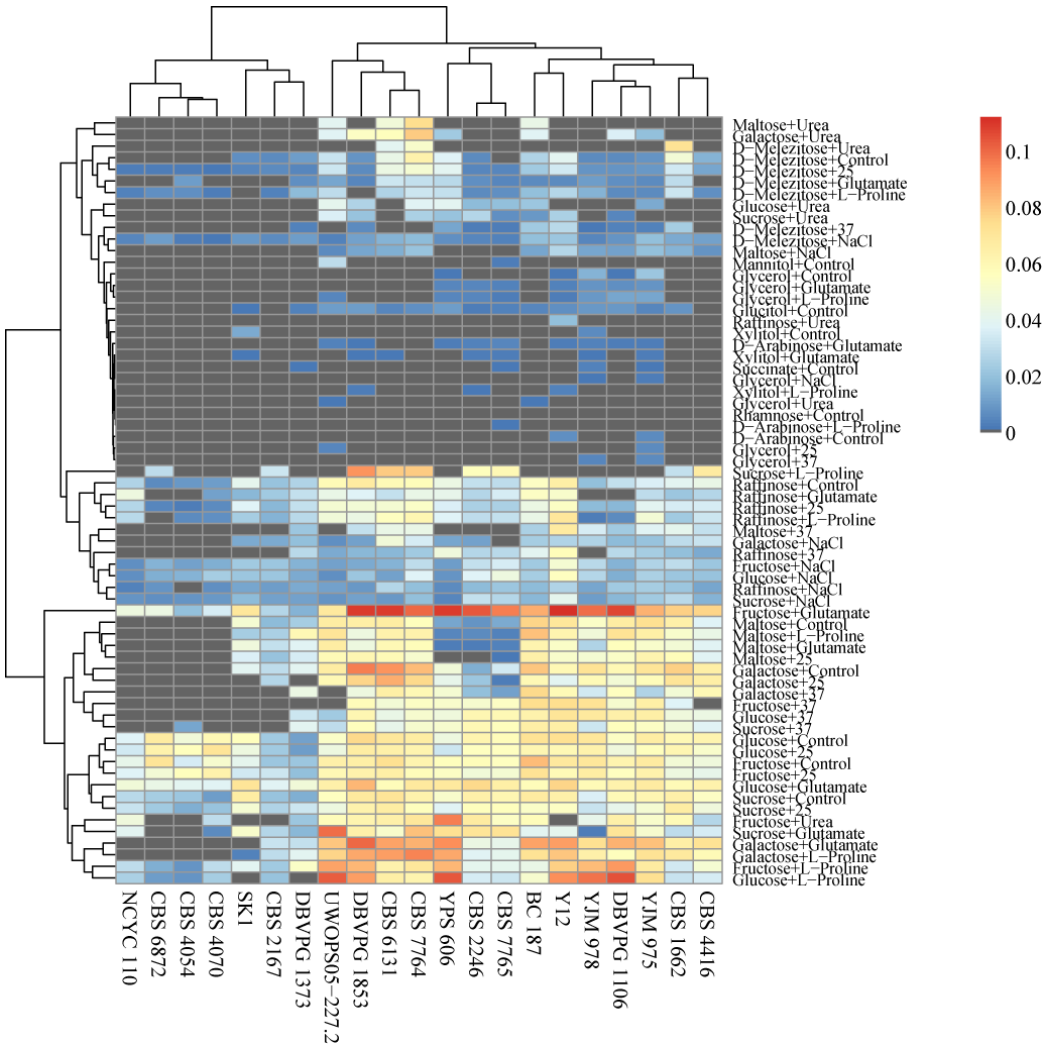

Figure 6: Strains display significant variation in growth rate across growth environments and show significant interactions among conditions. The heatmap displays strain growth in across carbon sources. The inability to grow in an environment is represented by gray.

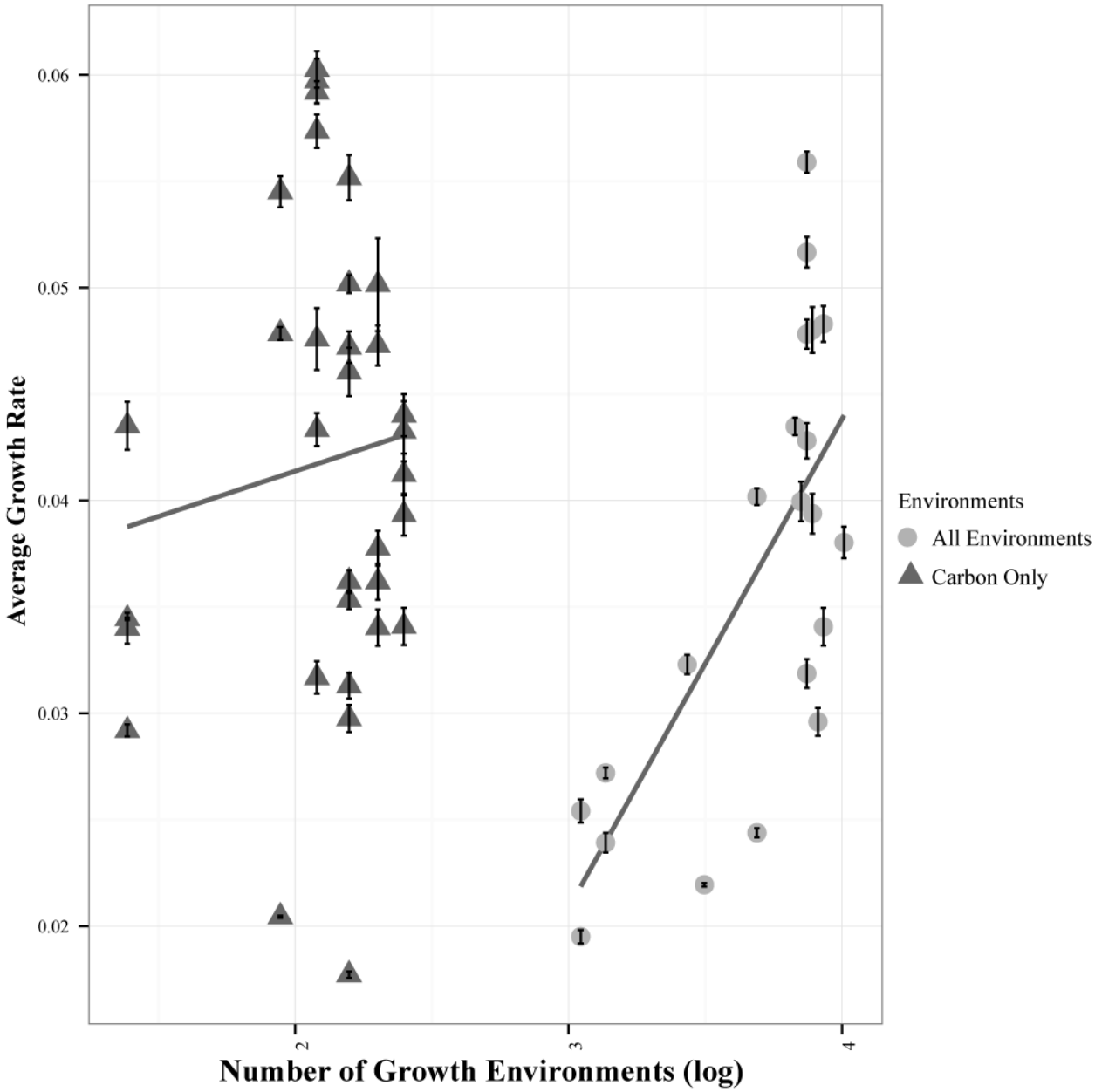

Figure 7: There is a positive correlation between average growth rate and environmental breadth (light gray) (r^2 = 0. 4735, p-value = 0.00034). The correlation between average growth rate versus carbon breadth (dark gray) was not significant.

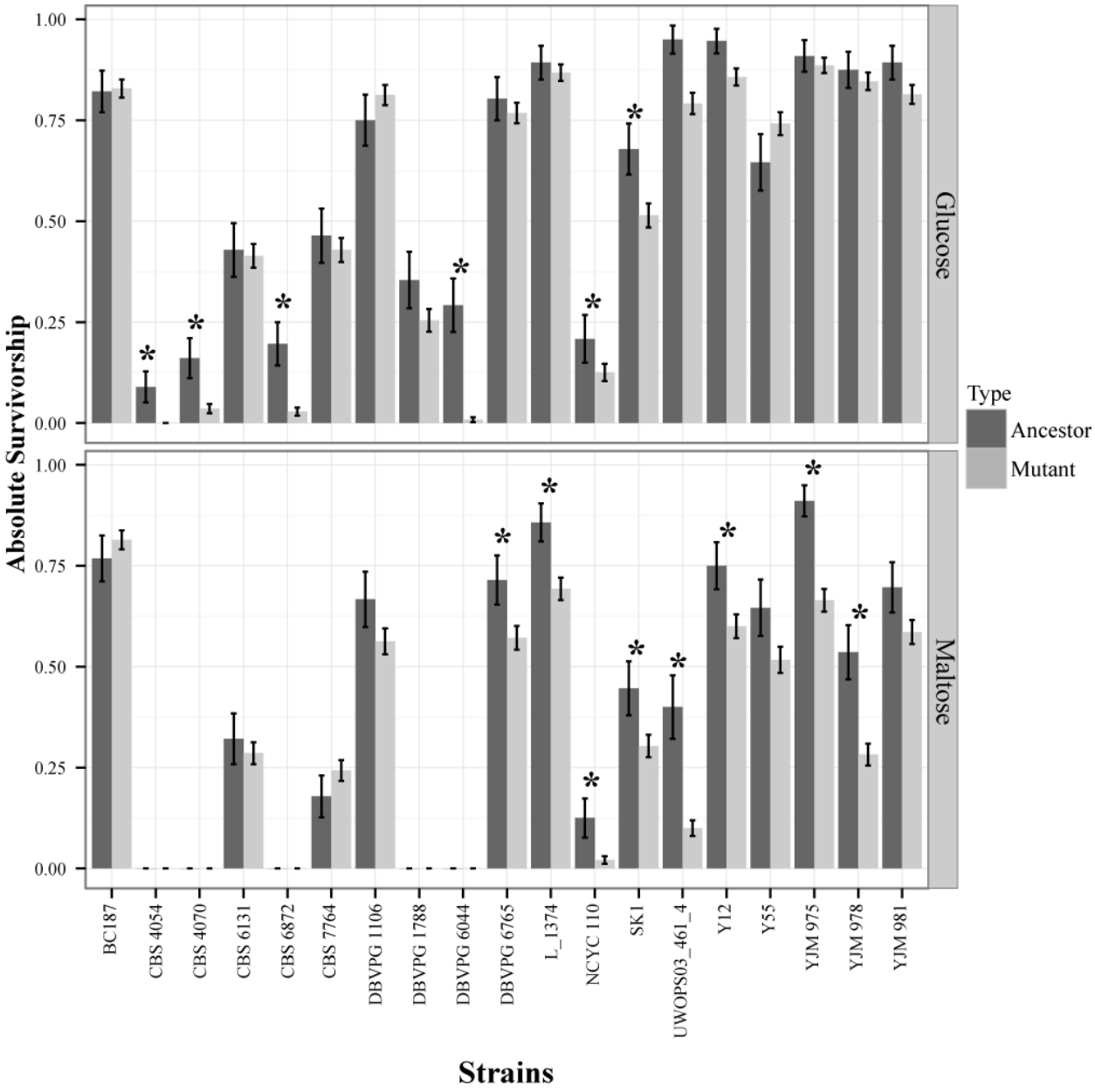

Figure 8: Strains show variation in survivorship among strains. We calculated the survivorship of strains for both the ancestor (dark gray) and mutant (light gray). Significance of the observed differences between the ancestors and mutants of a strain was assessed using a T-test. An asterisk is used to denote strains where there is a significant difference in survivorship between ancestor and mutants.

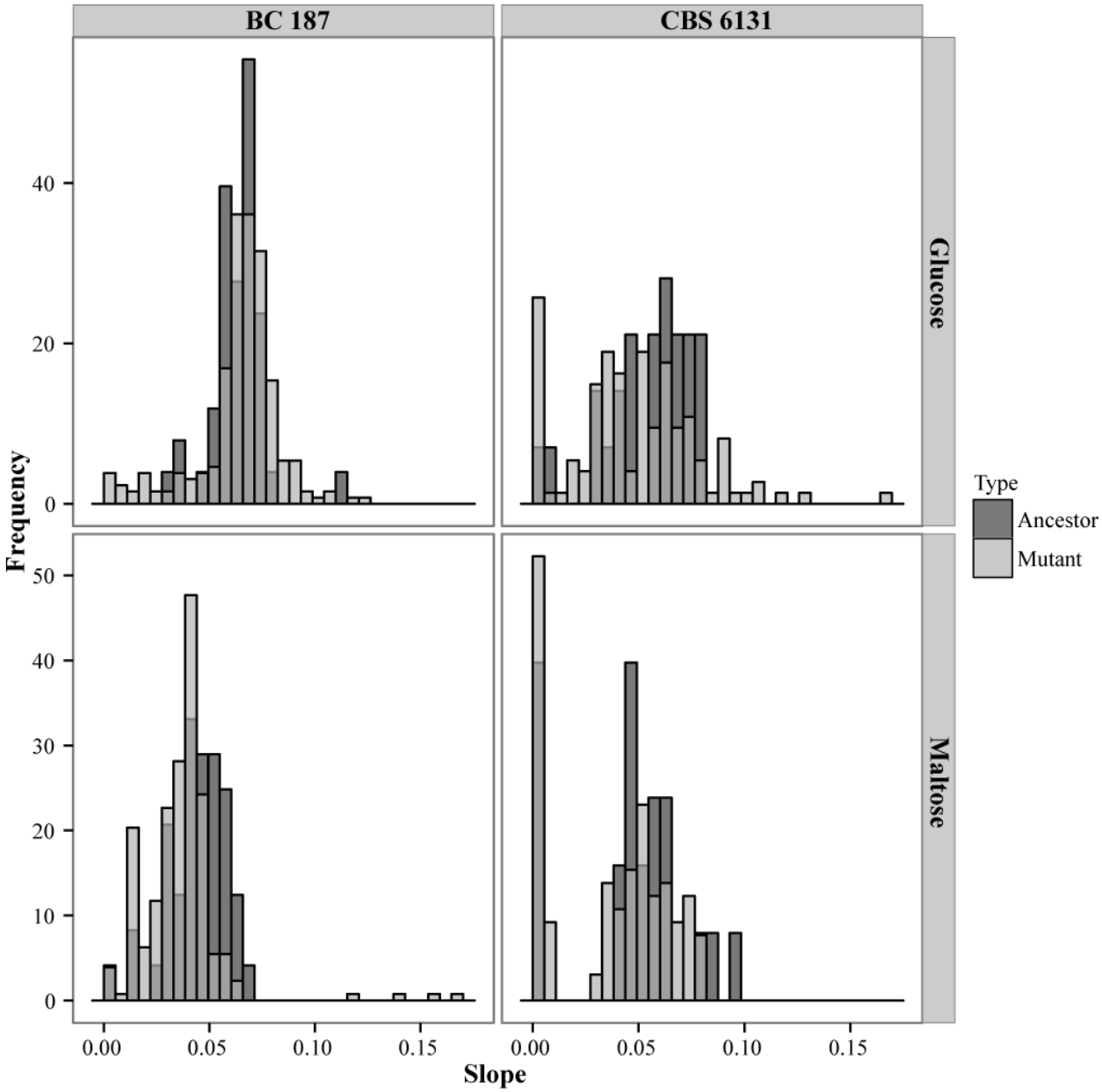

Figure 9: Overlapping distributions of growth rates for ancestral (dark gray) and mutant (light gray) for the strains BC 187 and CBS 6131 on both glucose and maltose.

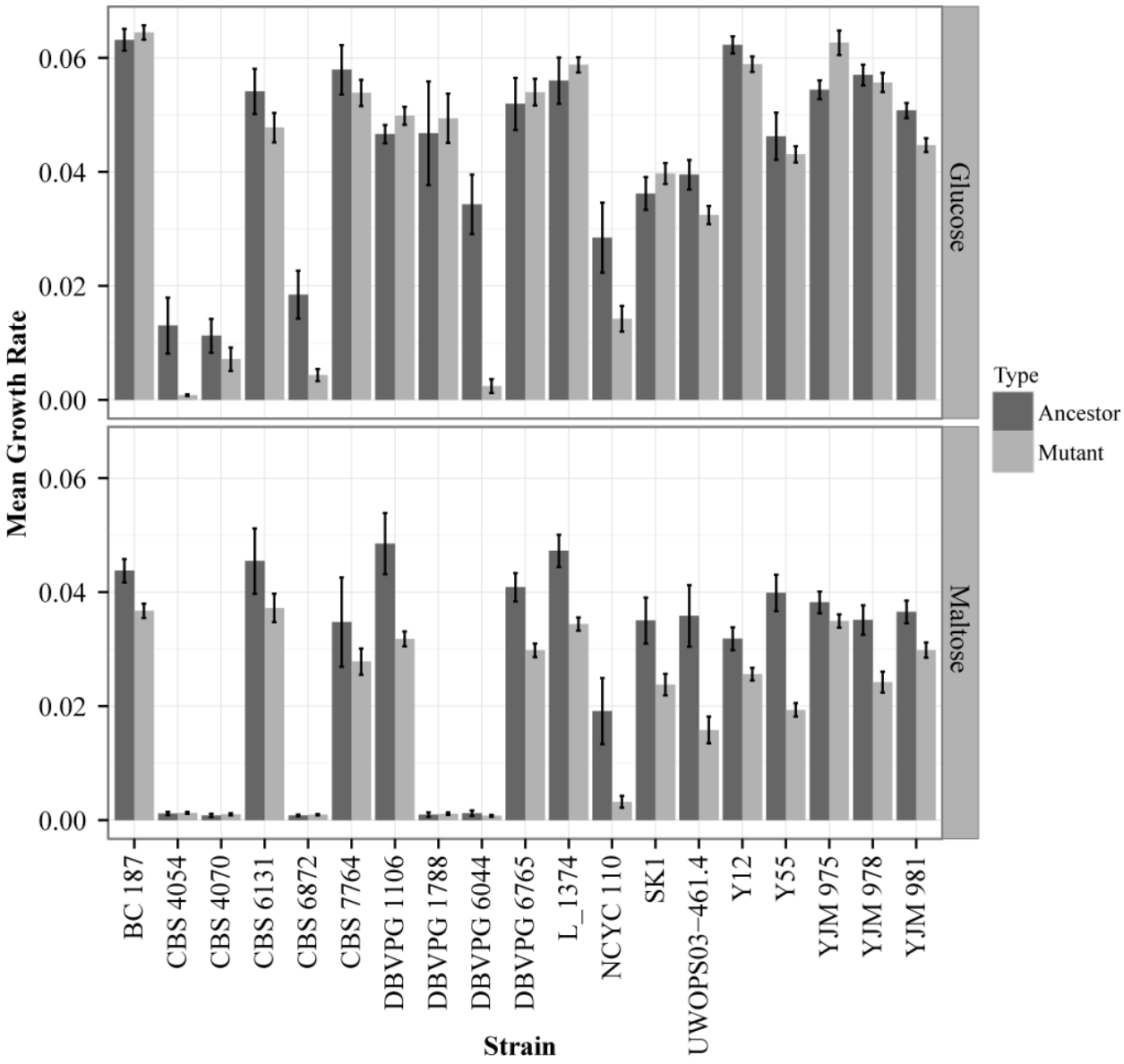

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Figure 10: Mean growth rates among ancestral (dark gray) and mutant (light gray) strains.

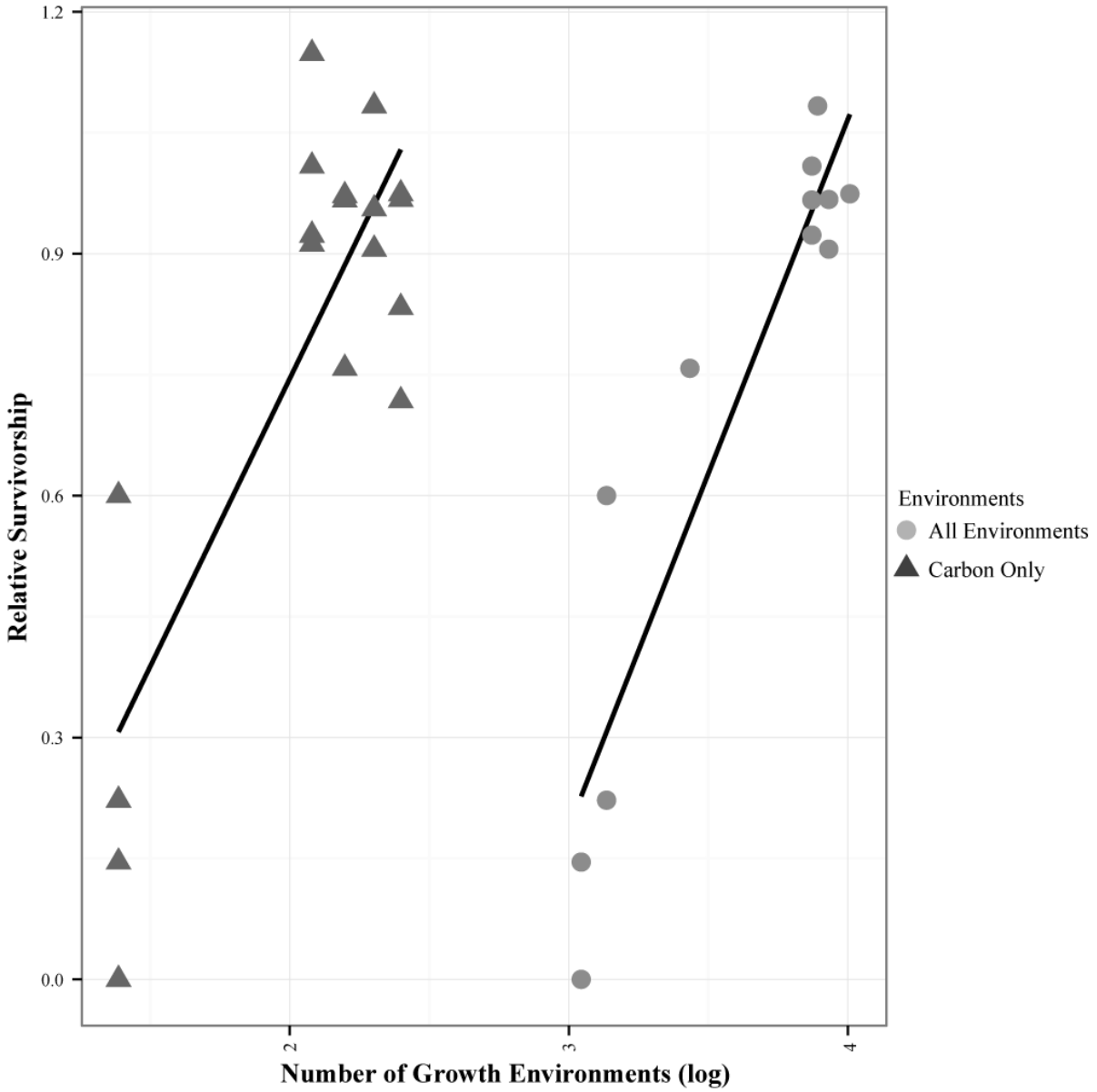

Figure 11: There is a positive correlation between genetic and environmental robustness for survivorship. In the glucose environment, we found a positive correlation between relative survivorship (mutant/ancestor) and the number of carbon sources metabolized by a strain (dark gray triangles, $p = 1.66 \times 10^{-4}$, $R^2 = 0.573$) and a positive correlation (light gray circles, $p = 5.11 \times 10^{-5}$, $R^2 = 0.801$) between the relative survivorship and number of number of environments a strain can grow in.

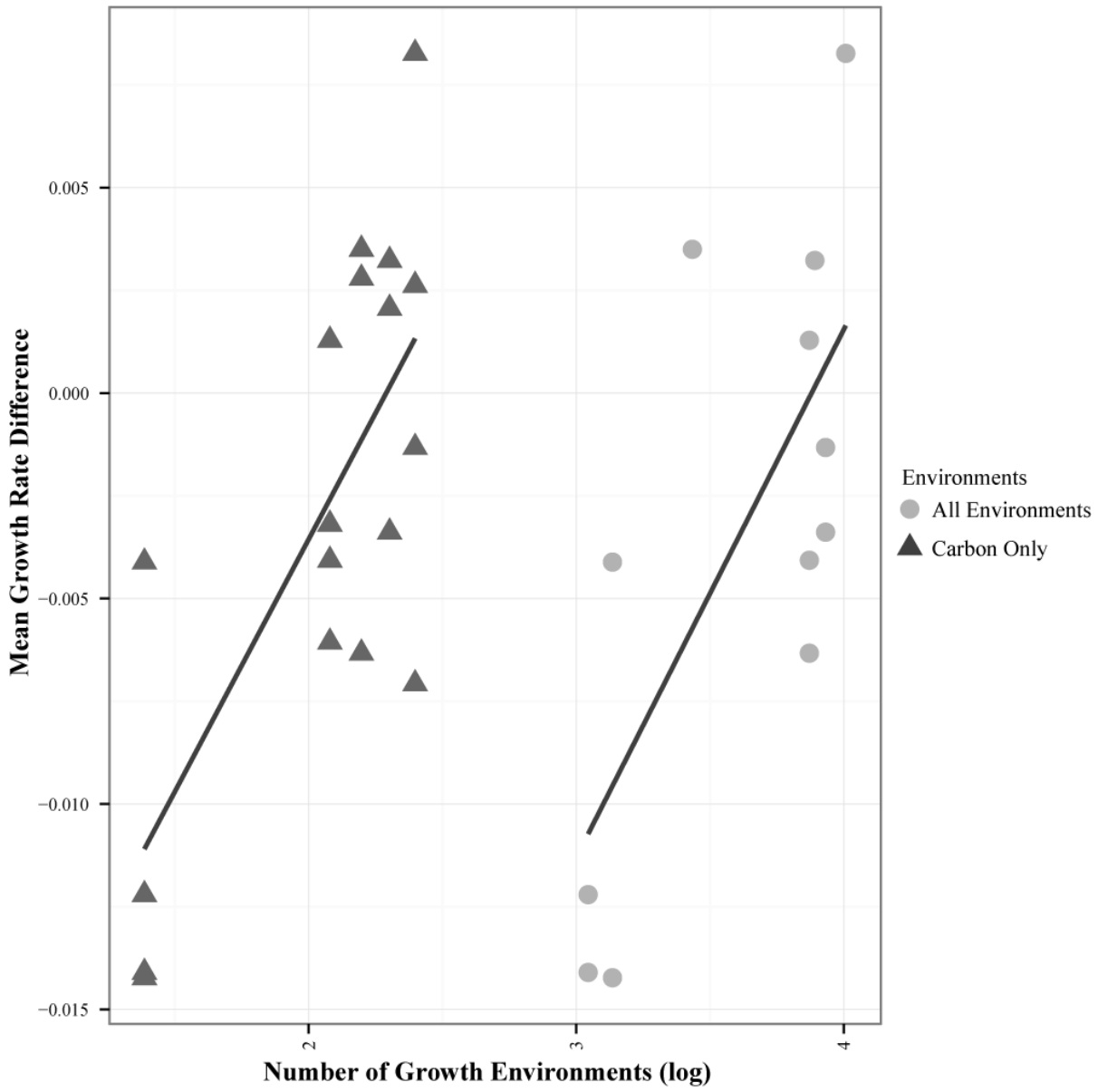

Figure 12: There is a positive correlation between genetic and environmental robustness for growth rate. In the glucose environment, we found a positive correlation between the difference in mean growth rate and carbon breadth (dark gray triangles, $p = 6.13 \times 10^{-4}$, $r^2 = 0.501$) and a positive correlation between the difference in mean growth rate and total environmental breadth (light gray circles, $p = 0.01$, $r^2 = 0.438$).

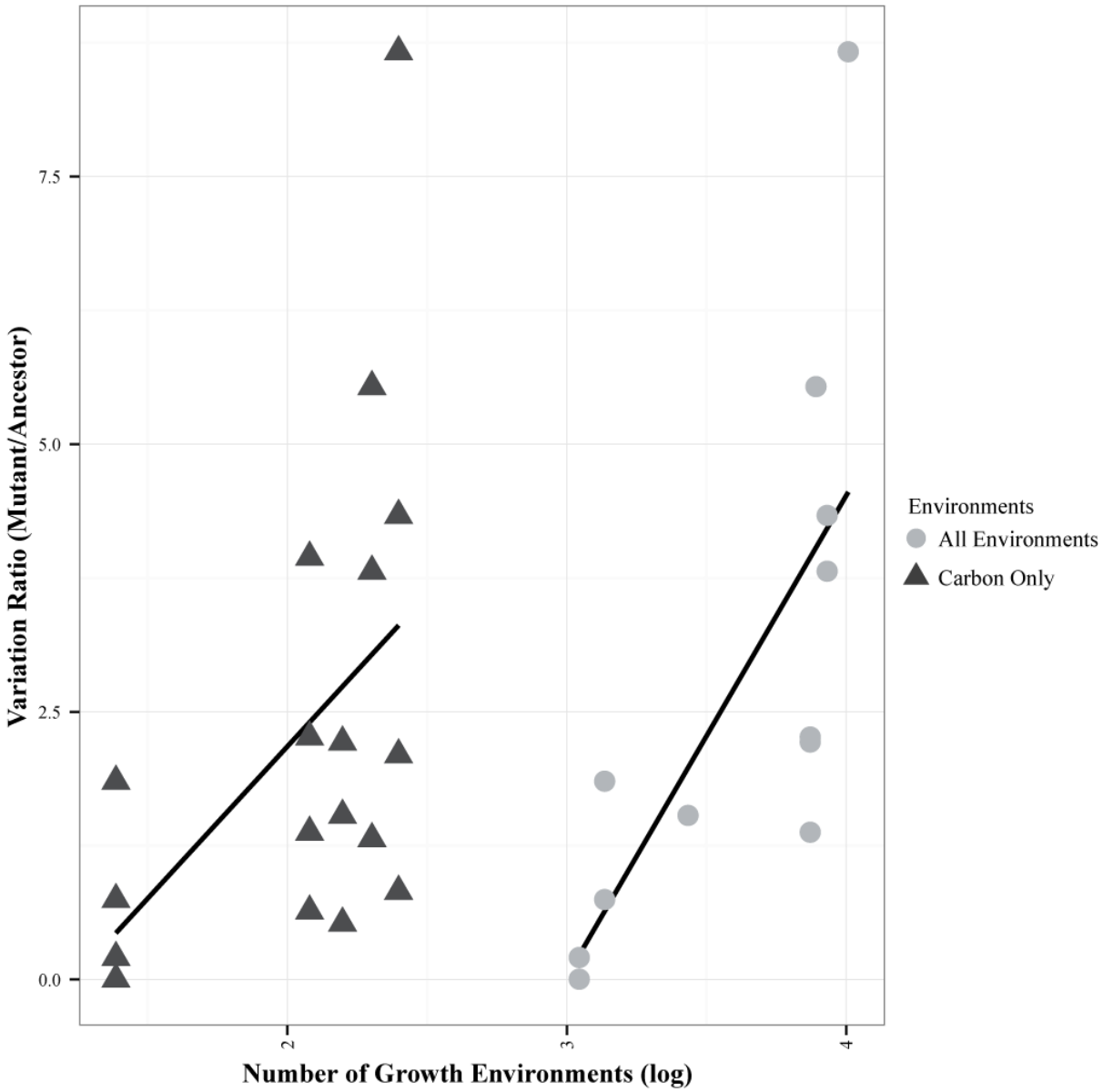

Figure 13: There is a positive correlation between genetic and environmental robustness for variation in growth rate distributions. In the glucose environment, we found a positive correlation between the ratio of the variance of the growth rate distributions (mutant/ancestor) and the number of carbon sources metabolized by a strain ($p = 0.027$, $R^2 = 0.225$) and a positive correlation ($p = 0.006$, $R^2 = 0.509$) between the relative survivorship and number of number of environments a strain can grow in.

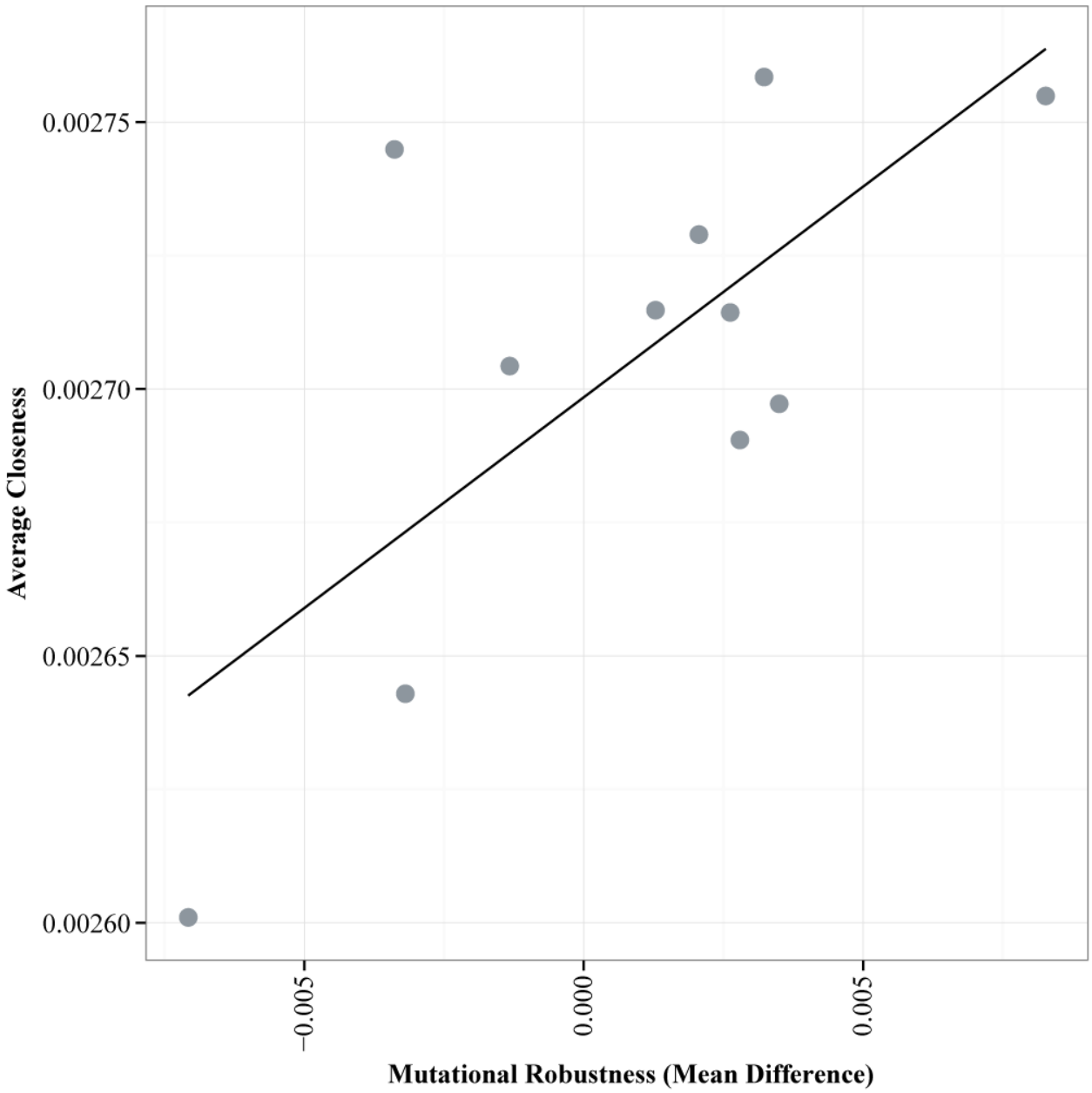

Figure 14: There is a correlation between network closeness and mutational robustness for mean growth rate differences. In the glucose environment, we found a positive correlation ($p = 0.0164$, $r^2 = 0.434$) between the difference in mean growth rate and closeness in the metabolic network.

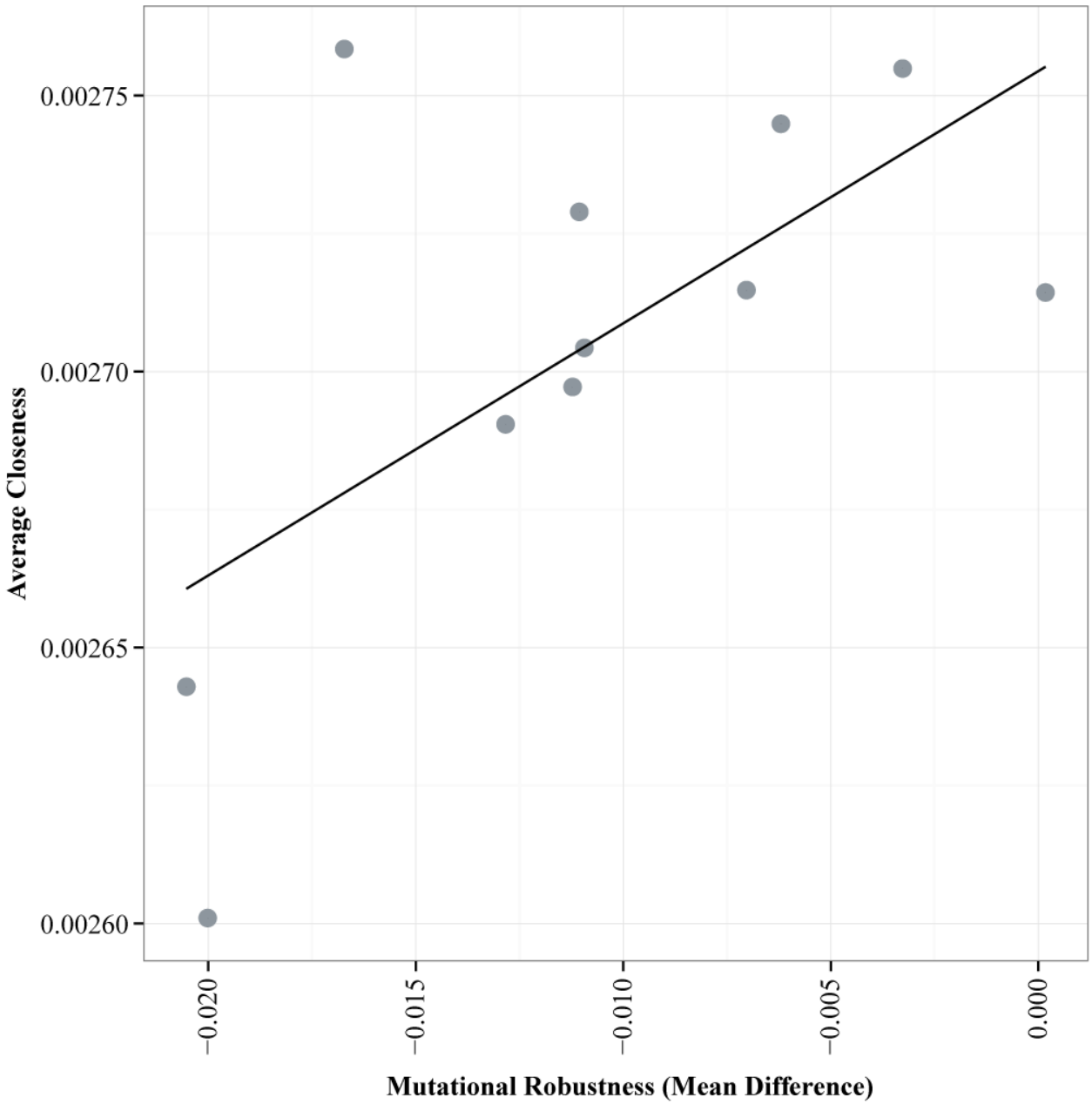

Figure 15: There is a correlation between network closeness and mutational robustness for mean growth rate differences. In the maltose environment, we found a positive correlation ($p = 0.0375$, $r^2 = 0.331$) between the difference in mean growth rate and closeness in the metabolic network.

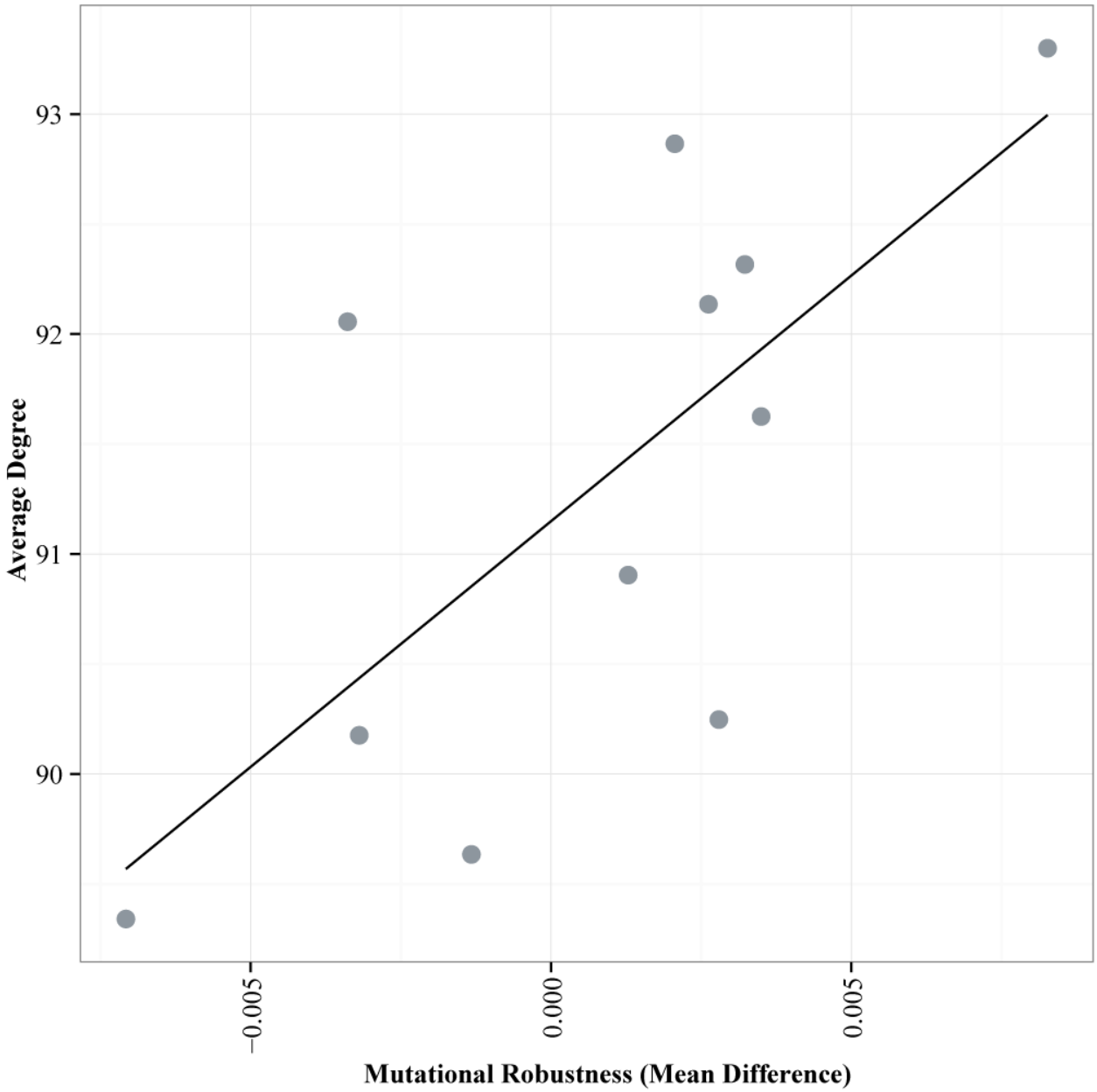

Figure 16: There is a correlation between network degree and mutational robustness for mean growth rate differences. In the glucose environment, we found a positive correlation ($p = 0.0159$, $r^2 = 0.438$) between the difference in mean growth rate and degree in the metabolic network.

Conclusions

The use of wild and industrial yeast presents an excellent opportunity to examine the processes that shape phenotypic diversity. The availability of genomic data coupled with the tractability to implement large scale experiments allows us to explore the genetic basis of traits (Scannell et al. 2011). In chapter 1, we demonstrated that many carbon metabolism traits are gained and lost independently of each other. However, the sets of traits which were gained and lost together appear to be due to adaptation to specific environmental conditions. Our findings suggest that the evolution of carbon metabolism traits is not heavily constrained by metabolic network structure.

In chapter 2, we found strains displayed variation in metabolic breadth; more striking than this was the extensive variation in growth rate among strains. Increased growth rate was associated with the presence of genes related to carbohydrate metabolism and transport. Growth variation was also associated with the presence of copy number variants. We also found that some strains could metabolize a set of non-preferred carbon sources. These carbon sources were associated with the presence of certain genes. However, we did not see an association between copy number variation and growth on non-preferred carbon sources. Aside from detecting significant variation in carbon metabolism among strains, we also detected interactions between strain, carbon source, and a panel of additional environmental factors. These interactions suggest additional environmental factors can shape the evolution of a seemingly independent trait; this can be through cross talk between pathways or pleiotropic genes (Conner 2002, Wang and Zhang 2009). We also demonstrated a lack of trade-off between metabolic breadth and growth rate among strains. In contrast, we found that carbon generalists on average grew faster in all environments relative to specialist strains.

Mutational robustness is a widespread property of biological systems (Lehner 2010). However, the principles and mechanisms which govern this stability in the face of random mutation are poorly understood (Hartman et al. 2001). This study is the first to demonstrate variation in mutational robustness within a species. We also found that this variation is positively correlated with niche breadth, providing support for the hypothesis that mutational robustness is simply a by-product of environmental robustness (Wagner et al. 1997, de Visser et al. 2003).

Given the considerable fitness advantage that yeast environmental generalists hold in growth rate (chapter 2) and survivorship across multiple environmental dimensions of carbon,

nitrogen, stress (chapter 2), and in mutagenic insult (chapter 2), it may seem perplexing that specialists exist at all. However, there are two reasonable explanations: one invoking adaptation and one invoking more neutral or ratchet type processes. The adaptationist explanation is simply that these strains are specialized and have higher fitness in some untested set of environmental conditions, fairly different than the standard laboratory growth conditions on which our growth environments are based (Varela et al. 2005, Rossignol et al. 2009). The neutral explanation is that genes that are not used in an environment are quickly lost through drift due to substantial bottlenecks; and that over the long run the result is generally maladaptive for the strains. More likely, some combination of selection and drift are responsible for this result. This is consistent with the recent observation that trait variation is better predicted by population history than by its environment (Warringer et al. 2011).

There are many additional experiments which can be done to elucidate the evolution of complex traits. One avenue to explore is to quantify which genes are associated with growth in interacting environmental conditions. Additionally, analyzing the levels of gene expression within carbon and multi-dimensional environments can assess the role regulation plays in the variation we detected, as well as detect the contribution of genes that vary in expression pattern, but not in copy number. Alternatively, one could further examine the evolution of mutational robustness by examining the most narrowly specialized strains. We can better address this question with the genomes of specialist strains; however they are currently not available. These genomes would allow us to determine whether there are certain genomic features which make generalists more mutationally robust than specialists. Are there redundant enzymes which buffer the effects of mutations? Finally, all mutated individuals were frozen for future use; therefore it is possible to sequence the genomes of these mutated strains. The genomes can provide insight on whether certain types of mutations affect generalists or specialists more, as well as, whether mutations of certain genes have a more detrimental effect; for example, do mutations of known network hubs effect generalist and specialist strains equally (Masel and Siegal 2009, Soyer and Pfeiffer 2010)?

What is for certain is that the extreme diversity in phenotypes and fitnesses, multidimentionally and mutationally, suggests that the microbial world and microbial ecology is much more complex and fine-grained than we might have imagined. Perhaps the biggest

challenge, and opportunity, is understanding how these individual genetic entities interact with each other and alter the fitness of their neighbors, and thus of themselves.

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