1 Yeast growth responses to environmental perturbations are associated with
2 rewiring of large epistatic networks

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Abstract

The phenotypic effects of genetic polymorphisms often depend on the genetic and environmental context. Here, we explore how polymorphic loci in large interaction networks contribute to complex trait variation and in particular how genetic effects and network topologies are influenced by environmental perturbations. This was done by reanalysing a dataset of >4,000 haploid yeast segregants grown on 20 different media. In total, 130 epistatic loci were associated with growth in at least one environment. The across-environment interaction network defined by these loci explained 69 - 100% of the narrow sense heritability in the individual environments. Environmental changes often resulted in network hubs being connected and disconnected from their interactors, leading to changes in additive effects of individual loci, epistatic effects of multi-locus interactions and the total level of genetic variance in growth. The largest variation in genetic effects across environments was found for epistatic loci that were highly connected network hubs in some environments but not in others. In environments where loci were highly connected, the segregating alleles epistatically suppressed or released genetic effects from their interactors. In environments where they were lowly connected, the same alleles made small or no contributions to growth. Hub-loci thus often serve as modulators, influencing the phenotypic effects of environmentally specific sets of interacting effector genes, rather than being effectors themselves. These findings illustrate the importance of the interplay between large genetic interactions networks and the living environment, both for individual phenotypes and population level metrics of genetic variation.

Background

Most biological traits are influenced by the interplay of multiple genes and environmental factors. In most genetic studies, the phenotypic effects of segregating alleles are studied as static features. In reality they are, however, in many cases more likely to be dynamic due to influences by, for example, genotypes at other loci (G-by-G interactions or epistasis), variations in the environment (G-by-E interactions) or both (G-by-G-by-E interactions). Experiments have for many years found epistasis and G-by-E interactions to be abundant in many species¹⁻⁴, and more recently it has also been possible to start exploring the environmental dependence of epistasis (G-by-G-by-E)⁵⁻⁹. For example, it has been shown how both pairwise¹⁰⁻¹⁴ and high-order¹⁵⁻¹⁷ epistatic interactions can be conditional on environment. Consistent with this are results from studies of gene-interaction networks, where abundant rewiring has been detected in response to environmental changes¹⁸⁻²⁰, although the phenotypic consequences of such changes are not yet known. Here, we evaluate the connection between the rewiring of gene-interaction networks, and changes in epistatic effects on complex traits, in response to environmental changes by reanalysing a large yeast dataset to answer the following two questions: *How often are high-order gene interaction networks rewired in response to environmental changes?* and *How does the environmentally induced rewiring of gene interaction networks influence the way that genetic polymorphisms contribute to complex traits?* By addressing these questions, novel insights could be gained on the connection between G-by-G and G-by-E interactions and how important this is for complex trait genetic variation.

Here, we reanalyse a public dataset of 4,390 yeast recombinant offspring (segregants) from a cross between a laboratory strain (BY) and a vineyard strain (RM). Every

segregant was genotyped and phenotyped for growth in 20 environments (media)²¹. Previously, 939 additive QTL and 330 epistatic QTL were mapped when treating growth in these environments as independent traits²¹. In 11 of the 20 growth environments, large gene-interaction networks were identified where polymorphisms at highly connected epistatic network hubs suppressed or released the genetic effects of their interactors¹. Here, a complete interaction network was defined including all loci that contributed epistatically to growth in any of these environments. The rewiring of this epistatic network across the environments, and associated changes in how the interacting loci contributed to growth, were explored. Changes in connectivity of epistatic loci across environments often influenced their effects on growth. When changing the growth environment, network hubs were connected, and disconnected, from their interactions affecting their ability to epistatically suppress and release the genetic effects from radial loci. The interplay between epistasis and G-by-E interactions thus presents a mechanism by which populations can harbour hidden genetic variation in environmentally deactivated interaction networks for future selection response by network rewiring. The potential impact of these findings on the genetic maintenance of trait robustness in individuals and populations, the development of genetic models for quantitative traits as well their implications in areas where this might be of practical importance such as plant breeding and evolution, are discussed.

Results

The yeast intercross population reanalysed here has earlier been analysed treating growth on different media as independent traits. Extensive epistatic interactions were then detected for growth on 19 of the 20 media^{1,21}. Most epistatic QTL interacted with

86 one or two loci, while a few interacted with several loci to form multi-locus radial
87 networks¹. Here, the data was reanalysed using a different approach (Figure 1). First,
88 growth was considered a single complex trait with measurements in different media
89 representing expression of the same phenotype in multiple environments. Differences
90 in the content of the growth media constituted environmental perturbations. Second,
91 the interaction networks mapped in each environment^{1,21} were combined into an
92 across environment interaction network. A schematic example with four loci (A-D) in
93 two environments (1-2) is illustrated in Figure 1A. Thereafter, the rewiring of this
94 complete epistatic network across the environments, and the associated changes in the
95 genetic effects, genetic variance and individual phenotypes were explored (Figure
96 1B). Here, we first present the complete interaction network and summarize its
97 properties. Then, the rewiring of the interaction network across the environments is
98 defined and how this connects to changes in the additive effects of individual loci,
99 epistatic effects of multi-locus interactions and genetic variation of the population
100 were explored. This was done by first using examples for subsets of environments
101 and loci to illustrate principles that are later generalized in analyses of the complete
102 network across all environments.

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105 **Figure 1.** A schematic example of the analytical approach used to study the dynamic
106 genetic architecture of haploid yeast growth in response to environmental
107 perturbations. The circles illustrate loci (A-D) contributing to growth in a particular
108 environment (blue/yellow) or in both environments (red). Lines connecting the circles
109 indicate epistatic interactions between them. The box-plots illustrate the growth of the
110 individuals relative to that in a standard environment (y-axis) with a particular
111 single- or multi-locus genotype (x-axis). **A)** How loci contribute to growth in
112 individual environments has been described in earlier studies of this population¹. **B)**
113 The known loci and interactions were used to define a complete across environment

growth interaction network. The dynamics in the genetic regulation of yeast growth were studied by identifying the rewiring in this network, and associated changes in the genetic effects of individual and combination of alleles, across the studied environments.

Defining an across environment epistatic network of growth loci

The complete across environment growth interaction network included 130 loci that were part of at least one of the 19 epistatic networks detected in the earlier analyses of this population¹ (Figure 1A, Figure S1). Among these 130 loci, 38 (29%) had significant epistatic effects (Figure 2B) and 68 (52%) had significant additive effects (Figure 2C) on growth in multiple environments. The 130 loci were involved in 212 pairwise interactions, with the majority (88%) being unique to one environment, and 12% (27) being active in at least 2 environments (Figure 2D). Together, the 130 loci explained between 69 -100% of the additive genetic variance in growth in the 20 environments (Figure 2E).

Figure 2. Summary of the features of the complete interaction network for yeast growth across the 20 studied environments. **A)** The complete across-environment

*interaction network includes 130 loci contributing epistatically to growth in at least one environment. Each node represents a locus, and its colour shows in how many environments it was involved in significant epistatic interactions. The edges represent significant pairwise interactions between loci, with the number of edges connecting pairs of loci corresponding to the number of times this pair was detected across the 20 environments. **B/C)** Histograms showing the number of environments in which the 130 loci were involved in at least one significant epistatic interaction/ additive effect. **D)** Histogram showing the number environments in which each of the 212 pairwise interactions were significant. **E)** Histogram showing how much of the additive variance for growth in the 20 environments that was explained by the 130 loci in the network.*

The marginal effects of the loci in the network were thus more stable across environments than the interactions and a limited number of loci were highly interactive across many environments. In the following sections, we will explore the consequences of the extensive environmentally dependent rewiring of the epistatic network on growth. First, we use an example of a sub-network involving loci affecting growth across three environments to illustrate the principles and results, before later generalising them in analyses across larger networks and all environments.

Associations between environmental perturbations, dynamics in the genotype-to-phenotype maps and epistatic network topologies: an example across three environments

The association between changes in the interaction network topology, and the changes of additive effects of individual loci, epistatic effects of multi-locus interactions and phenotypes resulting from particular combinations of alleles across environments, was explored for a 28-locus interaction network defined by connecting the epistatic loci detected for growth in 3 environments. These 3 environments were media where either Indoleacetic acid (IAA) or Formamide had been added, or where the carbon source was changed from Glucose to Raffinose (Figure 3A). Segregant growths were, overall, more similar on the media containing IAA and Formamide than in the medium with Raffinose as carbon source (PCA in Figure 3A; pairwise correlations Figure S2). In total, 6 (4) loci were detected with significant epistatic interactions in 3 (2) environments (Figure 3B). Consistent with the observations for the global network (Figure 2), the number of loci with significant additive effects was larger, with 9 (4) detected in 3 (2) environments (Figure 3C). Out of the 42 total pairwise interactions detected in the 3 environments, overlaps of 1 (9) pairwise interactions were observed for 3 (2) environments. The rewiring of the network associated with changes in the environment thus involved (Figure 3E-G) i) loci that were epistatic in all environments but with changes in the set of loci they interacted with, ii) loci that were epistatic in one environment and disconnected in the other, but that despite this contributed additively to growth or iii) loci that were epistatic in one environment and disconnected in the other, and that due to this no longer contributed to growth.

Environmental changes were thus associated with extensive rewiring of the interaction network. To evaluate the connection between the rewiring and the effects

181 of the loci on growth, a sub-network defined by the locus that was most extensively
182 rewired was explored in more detail (Figure 3E-G). In total, 13 loci in the complete
183 network contributed epistatically to growth in the medium containing IAA. One of
184 these loci interacted with 7 other loci, defining an eight-locus radial growth network.
185 The multi-locus effects of the six strongest loci in this radial network on growth in
186 IAA-containing medium were explored in detail in earlier analyses of this data¹
187 (Figure 3E). Here, we found a significant interaction between the 64 multi-locus
188 genotype classes defined by these loci and the three environments ($P < 2.2 \times 10^{-16}$),
189 suggesting a connection between the wiring of the network and the effects of the loci
190 on growth. The highly connected hub-locus in this network was earlier shown to
191 capacitate the effects on growth from the radial interacting loci¹ (Figure 3H). When
192 the segregants were grown on a medium containing Formamide, the connectivity in
193 this six-locus network changed. Only 3 of the radial loci remained connected to the
194 central hub. Three loci were rewired to interact with other loci, 1 no longer had any
195 effect on growth and a new locus was connected to the hub (Figure 3 E/F). Also the
196 genotype-to-phenotype map for the 6-locus network changed when the segregants
197 were grown in media with Formamide. The main difference was a weaker
198 capacitation effect of the hub-locus (Figure 3 H/I). Even larger differences in wiring,
199 and the genotype-to-phenotype map, were observed when growing the segregants
200 with Raffinose as carbon source. The hub-locus still contributed additively to growth,
201 and was involved in one new epistatic interaction. It had, however, lost the
202 connections to all the interactors contributing to growth on IAA, and two of these no
203 longer contributed to growth. The disconnection of the hub-locus from its original
204 interactors likely explains the loss of phenotypic effect on growth in this medium
205 (Figure 3J). The gradual deactivation of the capacitation (epistatic) effect of the hub-

locus from IAA->Formamide->Raffinose was also consistent with the phenotypic correlations of segregant growths on these media as illustrated in the PCA plot (Figure 3A) and the pairwise correlations of growths in the media (Figure S2). Together these results illustrate the association between the rewiring of the epistatic network and changes in growth effects of the loci involved across environments, i.e. how the connectivity of the hub-locus defines its ability to act as a capacitor of other growth loci.

Figure 3. Illustrations of the relationships between environmental perturbations and contributions by high-order interactions contribute to yeast segregant growth. **A)** A two-dimensional PCA plot illustrating the resemblance in growths of yeast segregants across 20 media. Open squares represent a medium and the filled dots media with added IAA or Formamide or the medium where Raffinose was the carbon source. **B/C)** Histograms showing the number of environments in which the 28 loci had at least one significant epistatic interaction/additive effect. **D)** Histogram showing the number

*environments in which each of the 42 pairwise interactions were significant. **E-G**)*

Illustrations of differences and similarities in types of genetic effects (epistatic,

additive or none) and network connectivity in the epistatic growth network on IAA,

Formamide and Raffinose, containing media, respectively. The hub and radial loci in

the IAA epistatic network studied earlier¹ are highlighted with red/black arrows. The

red lines connects significant pairwise interactions reported in Bloom et al²¹.. The

*grey lines indicate epistatic interaction detected in other media. Panes **H-J**) illustrate*

the genotype-to-phenotype maps for the six most significant loci in the highly

connected epistatic network influencing growth on IAA (more details in Forsberg et

*al¹) on IAA (**H**), Formamide (**I**) and Raffinose (**J**), respectively. They are illustrated*

with boxplots for each the 6-locus genotype. The color of the box indicates the

genotype at the hub QTL (chrVIII: 98,622 bp; green/ gray correspond to BY/ RM

alleles). The x-axis gives the six-locus genotype class, where blue/orange dots

indicate growth-decreasing/increasing alleles at the five radial QTLs (from top to

bottom: chrXIV: 469,224 bp, chrIII: 198,615 bp, chrIV: 998,628 bp, chrXIII: 410,320

bp, chrXII: 645,539 bp).

Extensive network rewiring for loci with variable contributions to growth across environments: effects across all environments

To generalize the findings from the three-environment example above, the connectivity and contribution by all networks to growth across all 20 environments were analysed. The results are described in detail in the sections below.

Rewiring of high-order gene interaction networks in response to environmental changes is common for highly connected loci

246 In total, 13 loci with more than 4 epistatic interactors were detected in at least one of
 247 the 20 environments. The networks defined by these 13 hub loci and their interactors
 248 included 70% (91 of 130) of the loci in the complete network (Figure 2A; Figure S3).
 249 The connectivity of these 13 networks was highly dynamic across the 20
 250 environments, with hubs being fully connected in some environments but completely
 251 disconnected in others (Figure S4A; Figure 4A). Although epistatic network
 252 connectivity changed across environments, it was common that some of the
 253 interactors (0-83%; median 30%) still had significant additive effects in other
 254 environments (Figure 4B; Figure S4 B). The detected epistatic interactions thus
 255 seemed to be more sensitive to environmental perturbations than additive effects
 256 (Figure 4 A/B; Figure S4 A/B). In addition, when the interactions between hub and
 257 radial loci were disconnected from one environment to another, the total contribution
 258 by the whole network to the growth variation decreased (Figure 4C). The rewiring of
 259 the epistatic networks in response to environment changes was thus associated with
 260 their contribution to growth.

261
 262 **Figure 4. Illustrations of the dynamics of the largest mapped epistatic networks,**
 263 **and their contribution to growth variation, across all tested environments. A)**
 264 **Histogram illustrating the changes in connectivity of 13 epistatic networks, with more**
 265 **than 4 interactors, across the 20 environments. For each network, a set of interactors**

was defined to include the radial loci in the most highly connected environment. The percentage of these interactors that were epistatically connected to the hub in each of the remaining 19 environments was calculated (x-axis). The overlap of interactors in the 13 networks across the 20 environments was summarized as the counts of environments with similar percentages of shared interactors (y-axis). **B)** Histogram illustrating the percentage of interactors (defined as in **A** above) that have significant additive effects across the 13 networks and 20 environments. The x-axis shows the percentage of these interactors that have additive effects across the other 19 environments. The y-axis summarizes these percentages across the 13 networks. **C)** In each environment, adjusted r^2 values are calculated for all networks and ranks of these model fits were assigned. The association between the connectivity of the epistatic networks (x-axis; number of loci connected to the hub), and their contributions to the variance in growth (y-axis; rank of adjusted r^2 values) across the 13 networks and 20 environments, is illustrated as box-plots of these ranks grouped by the number of interactors.

Variations in marginal additive effects across environments associated with rewiring of epistatic networks

Significant additive effects on growth in at least one environment were detected for 311 loci in the genome. Although not every locus had significant effects on growth in every environment, these loci did as a group contribute significantly to growth in most environments (Materials and Methods; Table S1). The effects were generally stronger in one or a few of the environments (Figure S5). For example, more than half of the loci were unique to one environment and only 9 loci were associated with growth in more than 10 environments. QTL by environment interactions were thus

291 abundant with 98% (307) loci displaying statistically significant QTL by environment
 292 interaction after multiple testing corrections (Figure 5; Table S2).

293
 294 **Figure 5.** The variations in additive effects on segregant growth and their
 295 associations with network connectivity. A) 311 loci had significant additive genetic
 296 effects on growth in at least one of the 20 environments. The estimated additive effects
 297 (y-axis) for each locus (x-axis) in the 20 studied environments are illustrated using
 298 dots in different colours. The loci (represented by the most significant SNPs) are
 299 sorted from left to right by the variance of the estimated additive effects across the
 300 environments. All additive effects estimates were obtained by fitting all 311 loci
 301 jointly in a linear model. The 4 loci without significant genotype by environment

interactions are indicated with black arrows below the x-axis. Out of the 13 highly connected loci (interacting with more than 4 other loci), 11 had significant additive effects in at least one environment¹ and they are highlighted with red arrows on the top. **B)** An illustration of the relationship between the maximum number of epistatic interactions (x-axis) and the variance in their estimated additive effects across the 20 media. Each blue dot represents a locus with a significant additive effect. The red dashed line is the regression line (P value = 7.1×10^{-39}).

All 11 QTL that were highly connected (> 4 epistatic interactors) in at least one environment displayed large variations in the marginal additive effects across the environments (Figure 5A; P -value = 6.1×10^{-8} ; Wilcoxon rank sum test). As the network wiring of these loci also changed much between environments, we hypothesised that the additive effects in the different environments were associated with changes in the number of G-by-G interactions of the locus. To test this, we estimated the correlation between the variations in the number of epistatic interactors and variance in the additive effects across the 20 environments. This correlation was highly significant (Figure 5B; P value = 7.1×10^{-39} ; linear regression), suggesting that the variation in additive effects of polymorphisms across the 20 environments was connected to the rewirings in the epistatic network.

Variation in the non-additive genetic variance contributed by loci across 20 environments is correlated with the rewiring of the epistatic network

As reported earlier²¹, there were considerable variation in both the phenotypic and genetic variation in growth (Figure S6A), as well as broad sense ($0.11 < H^2 < 0.88$; median 0.64) and narrow sense ($0.09 < h^2 < 0.70$; median 0.43) heritability between

environments (Figure S6B). The contributions from the epistatic network rewiring to the differences in the non-additive genetic variances between the environments were evaluated across all traits and loci. A significant positive correlation ($P\text{-value} = 5.6 \times 10^{-31}$; regression; Figure 6) was detected between the differences in the levels of non-additive genetic variance ($H^2_{\text{env1}} - H^2_{\text{env2}}$) and differences in the number of total epistatic connections. This highlights the general importance of G-by-G-by-E interactions for growth in this population, as well as the contributions by the high-order network connectivity for the non-additive variance in particular.

Figure 6. Illustration of the relationship between the network wiring and amount of non-additive genetic variance explained by the epistatic network across the growth environments. A significant correlation ($P\text{-value} = 5.6 \times 10^{-31}$ from regression) was detected between the pairwise differences in the number of epistatic interactions (x-axis) and the non-additive variances ($H^2_{\text{env1}} - H^2_{\text{env2}}$; y-axis) for the loci in the complete interaction network across the 20 environments.

Discussion

Yeast has, for many years, facilitated studies on the genetic basis of complex traits. Large haploid segregant populations can be generated, where alleles segregate at

intermediate allele frequencies. Earlier work using such populations have shown their value in, for example, dissecting the genetic basis of gene expression²² and understanding the sources of the “missing heritability”²³. By generating very large populations, and high-throughput phenotyping the segregants in replicates across many environments, such populations have also facilitated studies on more complex genetic mechanisms including genotype by environment interactions¹⁻⁴, how high-order interactions contribute to complex trait variation and prediction²¹ and the conditional effects of epistatic interactions on environmental factors^{7,9,19}. Here, we reanalysed a very large, publically available haploid segregant yeast dataset where one complex trait – colony size – had been measured across many environments. In this way, we could reveal that the gene-interaction networks contributing to growth, and their associated high dimensional genotype to phenotype maps, were highly dynamic across growth environments. Further, we also illustrated the importance of these dynamics for the differences in trait expression of individual segregants, and genetic variance expressed in the population, across the evaluated environments.

The effects of genotype-by-environment interactions on yeast growth

The studied dataset did not allow direct estimation of the contribution by systematic environmental (i.e. growth medium) effects on the phenotypes as the available growth measurements were pre-normalised against growth in a control medium²¹. However, estimates of the contributions by direct genetic (G) and genotype-by-environment (G-by-E) effects showed that direct genetic effects only contributed about 1/3 as much to the variance in growth compared to contributions by G-by-E. Consistent with the large contributions from G-by-E, we found large differences in the genetic architecture of growth (defined as associated loci and their genetic effects) across

environments. The wiring into interaction networks, as well as marginal additive effects, of many growth loci were highly environmentally specific. Likely as a consequence of this, the phenotype changed across environments with the rewiring of the genetic growth network. The same polymorphisms thus contributed to growth in different ways across the environments, regardless of whether their effects were quantified via marginal additive effects or variance explained by the complete network. In the following sections we discuss these findings in more detail as well as their implications for the mapping, and understanding the evolution of complex traits.

High environmental specificity for both additive and epistatic genetic effects

Most of the detected loci, regardless of whether they were originally mapped via their additive effects or epistatic interactions, only contributed to growth in one or a few environments. This in itself indicates extensive G-by-E interactions for growth in this population. However, loci mapped by their additive effects replicated to a greater extent across environments than loci mapped via their epistatic effects. Epistatic loci were thus, often highly environmentally specific suggesting a connection between G-by-G and G-by-E in this population. This is consistent with previous analysis on a similar yeast cross, where cryptic genetic variation is released under rare allelic combinations in specific environmental conditions⁹. Here, this G-by-G-by-E was quantified by evaluating the rewiring of the interaction network across environments, and its importance for growth was studied by measuring the associated changes in the allelic effects on growth. The low overlap of epistatic interactions across environments (Figure 2, Figure S1) illustrates the dynamics in the interaction network in response to environmental perturbations. The epistatic network is almost always rewired between the environments, likely in response to the different stressors in the

media. This illustrates the role of G-by-G-by-E interactions for yeast growth where the environmentally induced rewiring influences the genetic effects of individual and combinations of loci, altering the level of genetic variance of the population in the environments. Such dynamic variations in the allelic effects on growth across environments is thus likely important in many studies of complex traits, for example when aiming to understand the processes allowing individuals and populations respond to changes in the surrounding environments.

Environmental specificity of high-order interaction effects facilitates buffering of genetic effects in populations

Capacitating epistasis, defined as interactions where major loci in epistatic networks that can hide/release the genetic variance of other interactors, in radial multi-locus networks has earlier been identified as an important mechanism by which polymorphisms in one or a few hub-loci can buffer a significant amount of genetic variation from its interacting loci^{1,3}. Here, it was shown that the topology of the interaction networks, as well as the capacitation effects of the hub-loci, generally were environment specific: the capacitors released the large phenotypic effects of its interactors in some environments, whereas they were often disconnected from them in others. Together with previous findings where yeast growth plasticity was found to be regulated by environment-specific multi-QTL interaction⁷, G-by-G-by-E interactions are thus likely to be a buffering mechanism allowing populations to accumulate cryptic genetic variation in a wide range of environments, for later release in response to environmental perturbations facilitating large and rapid responses.

Network capacitation influences individual robustness to environmental perturbations

Our results suggest that the interplay between network interactions and environmental factors are important also for individual robustness. Individuals with more non-capacitation hub alleles perform better, on an average (Figure S7), and tend to show less variability across environments. This might be of relevance to, for example, plant breeding where one of the key challenges is to minimise the impact of genotype by environment interactions on production. Interactions in large gene interaction networks, buffered by environmental factors, might thus be an important driver of observed G-by-E interactions in populations. Targeted breeding for particular alleles at central network hubs might provide routes to genotypes that are either robust performers when challenged by environmental changes or high performers in more defined environments. In addition, G-by-G-by-E might provides multiple routes for populations and individuals to adapt to environmental changes. With the presence of environmentally independent additive effects, it is likely that alleles can be accumulated to intermediate frequencies in populations with small or no fitness costs in many environments. Upon rapid environmental change, the G-by-G-by-E interactions studied here can suppress or release large amounts of selectable genetic variation at a considerably higher rate²⁴⁻²⁶, facilitating more rapid and larger selection responses beyond predictions obtained based on the levels of additive variance, or heritabilities, in the populations.

Connections to available knowledge

Our reanalyses of experimental data show that G-by-G-by-E interactions were generally important for the variation in growth across environments. This extends and

connects earlier results from numerous studies in multiple species illustrating the importance of G-by-G and G-by-E for complex trait variation¹⁻⁷. For example, many yeast genes are known to be nonessential in one genetic background, but essential in another, with the essential genes often being highly connected hubs in interaction networks¹⁹. Similar mechanisms have been studied also in bacteria where, for example, evaluations of the effects of 18 randomly selected mutations in *E.coli* in two environments and five genetic backgrounds illustrate that all of them have genetic background dependent effect on phenotypic plasticity¹³. Capacitation is also a well known mechanisms studied in detail in several species, including the heat shock protein *HSP90*^{27,28} in *Arabidopsis thaliana* and *EGFR* in *Drosophila melanogaster*²⁹. Studying the connection between G-by-G and G-by-E requires large and powerful populations. Yeast is a model where such data can be generated and using large segregating experimental populations, single trait G-by-G-by-E interactions have been dissected in detail¹⁹. Our work connects and generalises these earlier findings from multiple species, populations and traits. We show how the network topology, and its underlying interactions, are likely central for the expression of complex phenotypes in individuals, and also how these effects are captured by quantitative genetics models¹. Further we also illustrate how dynamic genetic effects are in response to environmental perturbations and the likely central role of genetic interactions in general and capacitating epistasis in particular for this. Despite the experimental and analytical challenges, these results highlight the importance of considering not only G-by-G and G-by-E, but also their mutual dependence on one another, when interpreting the results from complex trait genetic studies aiming to understand complex trait variation and evolution.

Hypothetical molecular mechanisms underlying the observed effects

A number of the mapped hub-QTL harbour candidate genes with known biological functions, including *GPA1*³⁰, *HAPI*^{31–33}, *KRE33*³⁴, *MKT1*³⁵ and *IRA2*³⁶ (Figure S3). Although they are obvious positional, further work is required to validate the functional candidate genes, in particular if and how they might contribute to the dynamic changes across environments. Not only because earlier work focussed on marginal genetic effects, rather than network effects, but also as the studies were performed in the environments where the effects were most prominent. Some earlier findings, however, allows us to present hypotheses about ways that they might contribute to the effects discovered here. For example, several hub-QTL were also epistatic hubs for expression QTLs²² where interactions between *HAPI* - *KRE33* and between *HAPI* - *MKT1* contributed to variations in the expression levels of many genes²². These studies were, however, performed in a single environment and expression QTL are known to often be environmentally dependent^{37,38}. Further studies of transcriptomic and metabolic data across multiple environments would therefore be a possible route to explore whether changes in the topology of the genetic networks around these loci across environments results in associated changes also at transcriptomic and metabolic levels.

Potential implications for modelling of quantitative traits

The studies of this yeast population here, and earlier¹, illustrate that the most highly connected loci in the interaction networks (the hubs) often serve as modulators. They have little, or no, individual effects but rather influence the phenotype by releasing the effects of environmentally specific sets of interacting effector genes. This is an opposite scenario to that assumed in the recently proposed Omnigenetic model for

quantitative traits³⁹, where it is postulated that the highly connected loci in the networks are effectors that are modulated by many other genes. One consequence of this is that results from association studies where loci are detected based on their marginal additive effects need to be interpreted with caution. This is because it might be incorrect to assume that such effects suggest that the locus has a direct (effector) influence on the trait or disease, while it in fact could be entirely a composite effect of contributions by multiple other effector loci. Another potential modelling challenge highlighted here is the potentially large influence by epistasis by environment interactions. We find that they might not only influence the variation in quantitative traits by modulating the effects of individual genes, but also in defining which sets of interactors that are under genetic control by capacitor loci. Further theoretical, and empirical, work is needed to explore the potential implications of these findings for modelling of quantitative trait variation from molecular data in, for example, genome-wide association studies and studies on the basis for, maintenance of and utilization of genetic variation in short- and long-term adaptations to natural and artificial selection.

Conclusions

In summary, we show that epistatic network rewiring is a common response to environmental perturbations. The dynamics in the network topology across environments were connected to changes in allelic effects of individual loci, epistatic effects of multi-locus interactions and the genetic variance contributed by these on the population level. These findings illustrated how G-by-G-by-E interactions influences both individual phenotypes and population level genetic variation. Our results provide novel insights on the fundamental mechanisms contributing to variation in complex traits with practical implications to, in particular, fields where the genetic mechanisms

facilitating responses to variations in the environment are central, including evolutionary biology and breeding.

Methods

Downloaded data for the BY x RM haploid segregant yeast population

A detailed description of the generation of the BY × RM strains, as well as the genotyping, phenotyping, quality control of genotypes, filtering and normalization of growth measurements is available in Bloom *et al*²¹. All the data analysed here was downloaded from the supplements of that paper. The previously detected additive and epistatic QTLs, as well as their connectivity into within-environment interaction networks, are available in the supplementary information of Forsberg *et al*¹.

Estimating the contributions by genotype and genotype-by-environment interactions to the phenotypic variance

The phenotypic variance was partitioned into contributions from genotype (G), genotype-by-environment (G-by-E) and residual (environmental; E) effects by fitting model (1) to the data:

$$\bar{y}_{ij} = \mu + id_i + E_j + id_i * E_j + e \quad (1)$$

$\bar{y}_{ij}$ is the mean growth for the replicates of individual i in environment j ($j = 1..n$; n is the number of growth conditions); id_i is the individual segregant (genotype) coded as a factor and E_j is a dummy variable representing the growth condition (environment). $id_i * E_j$ is the interaction (G-by-E) between a particular segregant (genotype) and growth condition (environment). Since the available data was normalised against a control medium, there was (as expected) no significant contribution by E . The relative

contributions to the total growth (phenotypic) variance from G and G-by-E were estimated by their respective sum of squares (Sum of Square for id is calculated as $\sum_1^p (id_i - \bar{id})^2$ and Sum of Square for the interaction $id * E$ is calculated as $\sum_1^p (id_i * E_j - \bar{id}_i * \bar{E}_j)^2$)

Defining a set of independently associated additive growth loci

A set of across-environment growth loci was defined. First, QTLs detected in the earlier environment-separate analyses with peak associations within 20kb and in pairwise $r^2 > 0.9$ were selected. Second, all the loci selected in step 1 were subjected to a multi-locus polygenic association analysis^{40,41} to identify a final set of statistically independent loci (FDR < 0.05) with additive effects on growth in each tested environment²¹. Alternative definitions ranging from physical distance < 20 kb and $r^2 > 0.6$ to physical distance < 10 kb and $r^2 > 0.9$ were evaluated and found to result in very similar results in practice (result not shown).

Across environment evaluation of the additive growth loci

Several growth loci in the final set defined above only had significant individual associations in one growth environment. To test if they, as a group, contributed to the polygenic inheritance of growth also in other environments we compared the fit of the following models to the data (models 2 and 3) using a likelihood ratio test.

$$\bar{Y} = X_1\beta_1 + e \quad (2)$$

$$\bar{Y} = X_1\beta_1 + X_2\beta_2 + e \quad (3)$$

Here, $\bar{Y}$ is a vector of the average growth of each segregant (genotype) in a particular environment and e is the normally distributed residual. The joint contributions by the individually significant/non-significant loci in a specific environment was modelled in

$X_1\beta_1/X_2\beta_2$, respectively. X_1 includes a column vector of 1's for the population mean and column vectors with the genotype of each significantly associated SNP in the environment with the two homozygous genotypes coded as 0/2, respectively. X_2 includes column vectors with genotypes of all loci in the set defined above that was not individually significant in the tested environment. β_1/β_2 are vectors including the estimated additive effects for the two sets of loci. A likelihood ratio test was used to compare the fit of the two models using the *lrtest* function in R package *lmtest*⁴².

Detect individual loci involved in genotype by environment interactions

All growth loci defined in the polygenic analysis were evaluated for genotype by environment interactions. This by fitting the following two models to the data:

$$y_{ijk} = u + E_j + a_1b_1 + a_2b_2 + \dots a_nb_n + e \quad (4)$$

$$y_{ijk} = u + E_j + a_1b_1 + a_2b_2 + \dots a_nb_n + E_ja_xB_x + e \quad (5)$$

In both models, y_{ijk} is the growth of replicate k for segregant i in environment j ($j = 1..20$ environments; $k = 1..n_{ij}$; n_{ij} is the number of replicates for individual i in environment j); a_x is the indicator regression variable for the genotype of QTL x coded as 0 and 2 for the homozygous minor and major alleles; b_x are the corresponding estimated additive effects; u is the population mean and E_j is the effect of environment j ($j = 1..20$) on growth. Model 5 also includes an interaction term $E_ja_xB_x$ between one of the QTL and the environment. Model 5 was fitted for each QTL one at a time to test for its interaction with the 20 growth environments. The significance of each QTL by environment interaction was evaluated using a likelihood ratio test between models 4 and 5. Polygenicity was accounted for by the simultaneous fitting of all mapped loci in the two models. The analyses were performed using custom R scripts⁴³.

595

596 ***Estimating the additive effects of QTL in different growth environments***

597 A linear model (model 6) was used to estimate the additive effects of all the additive
598 loci selected in the polygenic analysis in each tested environment.

599 $\bar{Y} = X\beta + e$ (6)

600 Here, $\bar{Y}$ is the average growth of the replicates for each segregant (genotype) in each
601 tested condition. e is the normally distributed residual. X includes a column vector of
602 1's for the population mean and additional column vectors with the indicator
603 regression variables for all the SNPs included in the model (coded as 0/2 for the two
604 homozygous genotypes, respectively). β is a column vector with the corresponding
605 additive effects. This model was fitted for each environment independently to obtain
606 estimates of the additive effects for each locus in each environment.

607

608 ***Construction of an across-environment epistatic interaction network***

609 A complete across-environment epistatic growth interaction network was constructed
610 from the environment specific networks reported in Forsberg *et al*¹. First, the
611 environment specific networks inferred for each growth environment were extracted
612 from the results of Forsberg *et al*¹. Second, we evaluated whether any of the pairwise
613 interactions detected for a specific environment made significant contribution to
614 growth at the remaining environments under a more lenient significant threshold only
615 correcting for the total number of pairwise interactions detected across all
616 environments. This was performed using a likelihood ratio test between models with
617 and without the pairwise interaction for a particular pair of epistatic loci as described
618 in detail by Bloom *et al*²¹. Then, the across-environment network was constructed by
619 connecting the loci display pairwise interaction in any of the 20 environments using

*igraph*⁴⁴ as described in Forsberg *et al*¹. These analyses were performed using custom scripts implemented in R⁴³ [will be made available upon publication or by request during review]. The raw data from which these were constructed are available as supplement 5 in Bloom *et al*²¹; The analysis scripts/results from these earlier analyses are available at <https://github.com/simfor/yeast-epistasis-paper> and are described in detail by Forsberg *et al*¹).

Evaluation of the G-by-G-by-E interaction for a six-locus interaction network

The effects of a six locus interaction network, originally detected and explored for growth in IAA containing growth medium in Forsberg *et al*¹, were here evaluated across multiple environments. This analysis was performed to explore the association between the rewiring of the epistatic genetic network and its contribution to growth in the different environments. To quantify the effects of G-by-G-by-E interactions, models 4 and 5 were fitted to the data with a_x ($x = n = 1$) used as the indicator variable for each of the 64-genotype classes defined by the genotypes at the 6 loci. All other parameters, and the likelihood ratio test used to obtain the P-values for comparing the models, were the same as described above.

List of abbreviation

G-by-G interaction: Genotype by Genotype interaction
G-by-E interaction: Genotype by Environment interaction
G-by-G-by-E interaction: Genotype by Genotype by Environment interaction

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Additional files

All supplementary figures and tables are available in Additional file1

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ÖC and YZ initiated the study and designed the project; YZ performed the data analyses; ÖC and YZ summarised the results and wrote the manuscript. Both authors read and approved the final manuscript.

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780

Supplementary information for “Yeast growth responses to environmental perturbations are associated with rewiring of large epistatic networks” by Yanjun Zan and Örjan Carlborg

Figure S1. Joint epistatic network constructed by connecting shared loci from 20 epistatic networks detected for each media/environment. Each dot in this plot is a loci and the colour of the dot describes if the loci is detected with epistatic interaction for the current media with yes being blue or red (connected with more than 4 other loci) and no being grey. The pairwise interactions between loci are indicated by connected edges. The number of edges connecting two loci describes the number of times it is detected across 20 medias, and the detected connection for current media is highlighted with red (detected in Bloom et al.), blue (our study) and grey (other medias).

Figure S2. Illustration of the phenotype resemblance and change of phenotypic/genetic variance under different growth condition. A). 3-dimentional PCA plot of the yeast growth measured as the radial of colony on 20 different mediums. These mediums were made by adding small-chemical molelues to mimic different enviroments¹¹. B). Pairwise Spearman rank correlation among growth measured on these 20 mediums. Numbers in the cell are 100 times the Spearman correlation, and environments were sorted based on their order after hierarchical cluster.

Figure S3. Illustration of the connectivity of the 13 hubs. 13 hubs connected with more than 4 loci in at least 1 environment is highlighted in red, loci epistatically interact with these hubs in at least one environment are labeled in yellow.

Figure S4. Rewiring of the 13 epistatic networks across 20 environments. *A)* Proportion of epistatically connected loci for a specific environment. Each row of the heatmap represents a network with the hub alleles and candidate genes marked to the left and each column represents an environment. The environments are sorted based on their order after hierarchical cluster. *B)* Histogram of the proportion of deactivated loci, including these either remained either as additive loci or rewired to other loci.

Figure S5. Pairwise overlap of loci detected with additive effects. Numbers on the diagonal is the number of additive loci detected for a particular environment, and numbers in the cell are the number of overlap additive loci. Phenotype were sorted based on their order after hierarchical cluster.

Figure S6 Change of genetic variance and broad/narrow sense heritability. A). The phenotypic variance, genetic variance and additive variance for growth under 20 midums. Genetic variance and additive variance was estimated as the product of phentypic variance and broad- and narrow-sense heritability (panel B) reported in Bloom et al¹.

Figure S7. Relationship between the mean growth rank across 20 environments and the number of non-compacitated alleles. X-axis is the number of non-compacitated alleles across 13 hubs detected in our study, and y-axis is the mean growth rank obtained by first ranking the growth measurements across 20 environments and then taking the arithmetic mean.

Table S1. Summary of the P values from likelihood ratio test comparing a full model with all 311 growth QTL detected for all environments and a reduced model with QTL only detected for focal environments

Environment	Number of QTL ¹	P values ²	Significance ³
CobaltChloride	35	3.44e-04	Yes
CopperSulfate	29	8.44e-04	Yes
Diamide	73	2.27e-04	Yes
E6-Berbamine	60	1.30e-03	Yes
Ethanol	30	4.35e-05	Yes
Formamide	51	4.64e-03	No
Hydroxyurea	13	4.03e-04	Yes
IndolaceticAcid	18	2.56e-04	Yes
Lactate	63	2.89e-03	No
Lactose	44	1.06e-03	Yes
MagnesiumChloride	29	4.80e-04	Yes
ManganeseSulfate	54	8.38e-05	Yes
Menadione	57	1.09e-02	No
Neomycin	54	1.96e-11	Yes
Raffinose	46	1.06e-05	Yes
Trehalose	58	5.71e-03	No
Xylose	32	1.58e-09	Yes
YNB	53	1.06e-04	Yes
YPD	41	1.04e-04	Yes
Zeocin	66	3.43e-06	Yes

¹Number of QTL: The number of additive QTL detected at focal environment

²P values from likelihood ratio test testing whether these loci, not individually associated with focal environments made significant contribution to growth as a group

³Significance: whether the p value reach multiple testing

Table S2. Summary of the QTL by E analysis for 311 growth QTL

SNP Name	Chromosome	Position	P_vlaue	GxE ¹
193500_chrl_193500_C_T	1	193500	3.88e-242	Yes
4348634_chrvII_609644_T_C	7	609644	3.62e-84	Yes
6164100_chrX_331639_C_T	10	331639	9.88e-12	Yes
3089307_chrv_197352_T_C	5	197352	5.32e-58	Yes
8347770_chrXIII_24565_A_G	13	24565	0.00e+00	Yes
6493214_chrX_660753_C_T	10	660753	6.16e-127	Yes
7894865_chrXII_649837_A_G	12	649837	0.00e+00	Yes
10107829_chrXV_75860_A_G	15	75860	5.95e-300	Yes
4111213_chrvII_372223_T_G	7	372223	1.28e-73	Yes
9734886_chrXIV_487250_G_C	14	487250	0.00e+00	Yes
10590922_chrXV_558953_G_A	15	558953	8.92e-140	Yes
3175379_chrv_283424_T_C	5	283424	8.24e-68	Yes
1139178_chrIII_95776_T_C	3	95776	2.42e-49	Yes
9238100_chrXIII_914895_A_T	13	914895	3.13e-54	Yes
10973374_chrXV_941405_C_T	15	941405	5.77e-19	Yes
7815060_chrXII_570032_G_A	12	570032	1.48e-232	Yes
4951944_chrvIII_122014_T_C	8	122014	0.00e+00	Yes
10233761_chrXV_201792_T_C	15	201792	0.00e+00	Yes
40866_chrl_40866_T_C	1	40866	5.18e-154	Yes
3661374_chrvI_192545_C_T	6	192545	2.64e-08	Yes
7614510_chrXII_369482_A_G	12	369482	1.74e-59	Yes
10875861_chrXV_843892_A_G	15	843892	2.28e-30	Yes
7379379_chrXII_134351_T_C	12	134351	2.76e-43	Yes
1255174_chrIII_211772_G_A	3	211772	6.91e-31	Yes
796888_chrII_566670_T_A	2	566670	7.23e-88	Yes
9790206_chrXIV_542570_G_A	14	542570	3.72e-235	Yes
8372793_chrXIII_49588_C_T	13	49588	0.00e+00	Yes
10465962_chrXV_433993_C_T	15	433993	1.90e-127	Yes
8434826_chrXIII_111621_T_C	13	111621	0.00e+00	Yes
2308435_chrIV_948413_A_G	4	948413	6.39e-101	Yes
421432_chrII_191214_G_A	2	191214	3.44e-23	Yes
5892760_chrX_60299_C_T	10	60299	6.23e-89	Yes
10170631_chrXV_138662_A_G	15	138662	0.00e+00	Yes
11644024_chrXVI_520764_G_A	16	520764	7.39e-102	Yes
5572582_chrIX_180009_T_A	9	180009	6.19e-38	Yes
10196253_chrXV_164284_T_A	15	164284	0.00e+00	Yes
5441452_chrIX_48879_C_T	9	48879	3.59e-25	Yes
7193645_chrXI_615433_T_C	11	615433	2.10e-62	Yes
1974760_chrIV_614738_A_C	4	614738	4.04e-36	Yes
5040640_chrVIII_210710_A_T	8	210710	4.06e-122	Yes
3918900_chrvII_179910_G_A	7	179910	0.00e+00	Yes
4590187_chrvII_851197_T_G	7	851197	2.32e-70	Yes
9624126_chrXIV_376490_A_G	14	376490	0.00e+00	Yes
11615614_chrXVI_492354_C_T	16	492354	2.61e-118	Yes

9142223_chrXIII_819018_C_T	13	819018	1.20e-40	Yes
774352_chrII_544134_G_A	2	544134	7.47e-111	Yes
623487_chrII_393269_T_C	2	393269	3.42e-96	Yes
3866036_chrVII_127046_A_G	7	127046	0.00e+00	Yes
3153148_chrV_261193_A_T	5	261193	1.46e-52	Yes
2834907_chrIV_1474885_A_G	4	1474885	2.89e-07	Yes
8560038_chrXIII_236833_C_T	13	236833	0.00e+00	Yes
10067884_chrXV_35915_T_C	15	35915	2.00e-93	Yes
1295281_chrIII_251879_C_T	3	251879	1.58e-16	Yes
9711190_chrXIV_463554_A_T	14	463554	0.00e+00	Yes
5011062_chrVIII_181132_A_G	8	181132	2.17e-105	Yes
5531209_chrIX_138636_T_A	9	138636	3.78e-57	Yes
8231374_chrXII_986346_G_A	12	986346	1.01e-08	Yes
5581492_chrIX_188919_A_T	9	188919	6.04e-51	Yes
5666111_chrIX_273538_G_A	9	273538	1.22e-78	Yes
11498533_chrXVI_375273_C_T	16	375273	2.23e-146	Yes
3701448_chrVI_232619_G_A	6	232619	2.39e-07	Yes
487143_chrII_256925_T_C	2	256925	5.88e-45	Yes
4945907_chrVIII_115977_A_T	8	115977	0.00e+00	Yes
684479_chrII_454261_G_A	2	454261	1.52e-133	Yes
1118075_chrIII_74673_A_G	3	74673	3.48e-33	Yes
4537389_chrVII_798399_T_C	7	798399	1.36e-56	Yes
8587605_chrXIII_264400_A_G	13	264400	0.00e+00	Yes
10280547_chrXV_248578_G_A	15	248578	9.41e-211	Yes
3936455_chrVII_197465_A_G	7	197465	0.00e+00	Yes
10653941_chrXV_621972_A_G	15	621972	8.37e-84	Yes
4216167_chrVII_477177_C_G	7	477177	1.23e-119	Yes
9750134_chrXIV_502498_C_T	14	502498	0.00e+00	Yes
10688536_chrXV_656567_G_A	15	656567	2.85e-58	Yes
884725_chrII_654507_T_C	2	654507	1.19e-47	Yes
4139152_chrVII_400162_T_C	7	400162	4.15e-76	Yes
5290246_chrVIII_460316_T_C	8	460316	4.70e-30	Yes
6787397_chrXI_209185_T_A	11	209185	2.78e-44	Yes
5653342_chrIX_260769_T_C	9	260769	3.51e-125	Yes
5430557_chrIX_37984_T_G	9	37984	8.27e-23	Yes
9385314_chrXIV_137678_C_T	14	137678	5.60e-33	Yes
7534566_chrXII_289538_G_A	12	289538	8.28e-32	Yes
3823704_chrVII_84714_T_A	7	84714	2.53e-164	Yes
8073782_chrXII_828754_T_C	12	828754	6.92e-76	Yes
4994073_chrVIII_164143_G_A	8	164143	1.73e-109	Yes
10442033_chrXV_410064_A_G	15	410064	5.13e-175	Yes
7298297_chrXII_53269_C_T	12	53269	3.91e-09	Yes
7693396_chrXII_448368_A_G	12	448368	9.07e-33	Yes
10134640_chrXV_102671_A_T	15	102671	0.00e+00	Yes
8736983_chrXIII_413778_C_T	13	413778	2.67e-76	Yes
6354106_chrX_521645_T_G	10	521645	1.04e-101	Yes

11541717_chrXVI_418457_T_C	16	418457	1.49e-100	Yes
1641349_chrIV_281327_T_C	4	281327	1.82e-38	Yes
2717811_chrIV_1357789_T_G	4	1357789	8.57e-27	Yes
8654539_chrXIII_331334_A_G	13	331334	1.25e-276	Yes
7110331_chrXI_532119_G_A	11	532119	1.94e-37	Yes
1902084_chrIV_542062_T_C	4	542062	3.40e-35	Yes
2630055_chrIV_1270033_C_T	4	1270033	2.43e-12	Yes
9512173_chrXIV_264537_A_G	14	264537	9.43e-173	Yes
4299073_chrVII_560083_G_A	7	560083	2.07e-109	Yes
10615684_chrXV_583715_A_G	15	583715	8.44e-112	Yes
2509052_chrIV_1149030_T_C	4	1149030	9.65e-56	Yes
33147_chrl_33147_G_T	1	33147	7.86e-130	Yes
10858985_chrXV_827016_A_T	15	827016	5.50e-23	Yes
9184667_chrXIII_861462_G_A	13	861462	4.51e-55	Yes
8664927_chrXIII_341722_T_C	13	341722	1.87e-227	Yes
3599017_chrVI_130188_C_T	6	130188	4.33e-27	Yes
4397128_chrVII_658138_T_C	7	658138	7.50e-22	Yes
7767974_chrXII_522946_A_G	12	522946	1.75e-58	Yes
6887963_chrXI_309751_T_G	11	309751	8.70e-34	Yes
6970318_chrXI_392106_C_T	11	392106	9.65e-51	Yes
10798650_chrXV_766681_G_A	15	766681	6.53e-07	Yes
1291951_chrIII_248549_C_T	3	248549	5.10e-14	Yes
5492996_chrIX_100423_T_C	9	100423	3.32e-59	Yes
4161376_chrVII_422386_C_T	7	422386	4.99e-78	Yes
6340986_chrX_508525_G_A	10	508525	5.98e-95	Yes
3560948_chrVI_92119_A_G	6	92119	4.45e-18	Yes
9084976_chrXIII_761771_C_T	13	761771	8.68e-42	Yes
8260775_chrXII_1015747_G_A	12	1015747	3.57e-03	No
114652_chrl_114652_C_T	1	114652	4.26e-28	Yes
9897446_chrXIV_649810_A_G	14	649810	2.91e-117	Yes
11330697_chrXVI_207437_T_A	16	207437	6.98e-89	Yes
1782092_chrIV_422070_C_T	4	422070	4.34e-43	Yes
5881260_chrX_48799_G_A	10	48799	1.34e-63	Yes
665194_chrII_434976_G_T	2	434976	2.63e-121	Yes
1089964_chrIII_46562_T_A	3	46562	1.28e-09	Yes
11936407_chrXVI_813147_T_C	16	813147	2.05e-06	Yes
1422346_chrIV_62324_G_C	4	62324	8.79e-21	Yes
5202635_chrVIII_372705_C_A	8	372705	2.88e-21	Yes
4251340_chrVII_512350_A_T	7	512350	3.59e-119	Yes
6225749_chrX_393288_T_C	10	393288	2.10e-33	Yes
3676508_chrVI_207679_A_C	6	207679	1.17e-08	Yes
964804_chrII_734586_C_T	2	734586	2.19e-16	Yes
8178548_chrXII_933520_G_T	12	933520	8.70e-27	Yes
7356451_chrXII_111423_A_G	12	111423	4.21e-37	Yes
5634465_chrIX_241892_A_G	9	241892	5.25e-71	Yes
3418667_chrV_526712_A_T	5	526712	5.71e-11	Yes

9024358_chrXIII_701153_G_C	13	701153	2.16e-136	Yes
3301125_chrV_409170_T_C	5	409170	3.23e-39	Yes
7349496_chrXII_104468_A_T	12	104468	6.43e-31	Yes
9961304_chrXIV_713668_T_C	14	713668	2.39e-18	Yes
7504079_chrXII_259051_C_T	12	259051	8.74e-20	Yes
2424307_chrIV_1064285_G_A	4	1064285	1.02e-35	Yes
1521242_chrIV_161220_A_G	4	161220	1.47e-15	Yes
8060554_chrXII_815526_A_G	12	815526	2.58e-87	Yes
10341838_chrXV_309869_T_C	15	309869	4.74e-183	Yes
3266770_chrV_374815_G_A	5	374815	7.68e-46	Yes
3534631_chrVI_65802_T_G	6	65802	2.53e-13	Yes
5348875_chrVIII_518945_A_G	8	518945	7.82e-35	Yes
1220483_chrIII_177081_G_C	3	177081	3.16e-50	Yes
9195907_chrXIII_872702_T_C	13	872702	1.49e-58	Yes
10493762_chrXV_461793_G_A	15	461793	1.01e-54	Yes
6806359_chrXI_228147_C_A	11	228147	4.47e-38	Yes
1309673_chrIII_266271_G_A	3	266271	1.96e-12	Yes
1999059_chrIV_639037_G_T	4	639037	3.86e-22	Yes
6937354_chrXI_359142_T_C	11	359142	8.99e-46	Yes
8733525_chrXIII_410320_T_C	13	410320	5.42e-97	Yes
4684968_chrVII_945978_C_T	7	945978	9.19e-32	Yes
8474614_chrXIII_151409_T_C	13	151409	4.72e-292	Yes
5945399_chrX_112938_T_A	10	112938	8.11e-240	Yes
1240708_chrIII_197306_T_C	3	197306	1.24e-51	Yes
2561643_chrIV_1201621_C_T	4	1201621	1.15e-37	Yes
5271763_chrVIII_441833_A_G	8	441833	2.29e-35	Yes
2358650_chrIV_998628_A_T	4	998628	2.95e-126	Yes
3396166_chrV_504211_A_C	5	504211	1.04e-13	Yes
3342341_chrV_450386_C_T	5	450386	3.57e-31	Yes
6713295_chrXI_135083_A_G	11	135083	1.98e-52	Yes
10976399_chrXV_944430_T_C	15	944430	2.90e-16	Yes
6625055_chrXI_46843_C_T	11	46843	2.90e-43	Yes
8966073_chrXIII_642868_G_A	13	642868	1.94e-86	Yes
3103942_chrV_211987_C_G	5	211987	5.70e-50	Yes
4039180_chrVII_300190_G_A	7	300190	4.64e-87	Yes
7473402_chrXII_228374_G_C	12	228374	1.83e-07	Yes
3545271_chrVI_76442_G_A	6	76442	4.56e-15	Yes
7807333_chrXII_562305_C_G	12	562305	1.11e-170	Yes
11055361_chrXV_1023392_T_G	15	1023392	2.33e-07	Yes
1757949_chrIV_397927_G_A	4	397927	1.64e-51	Yes
11517118_chrXVI_393858_A_G	16	393858	1.75e-128	Yes
5558748_chrIX_166175_C_T	9	166175	3.30e-42	Yes
1171626_chrIII_128224_T_C	3	128224	1.42e-48	Yes
11578735_chrXVI_455475_T_A	16	455475	7.08e-94	Yes
1202358_chrIII_158956_T_C	3	158956	1.51e-47	Yes
2074955_chrIV_714933_T_C	4	714933	9.69e-25	Yes

7330660_chrXII_85632_T_G	12	85632	5.07e-13	Yes
4023350_chrVII_284360_A_G	7	284360	2.19e-101	Yes
9185900_chrXIII_862695_C_T	13	862695	6.24e-57	Yes
1107706_chrIII_64304_C_T	3	64304	4.07e-16	Yes
1581197_chrIV_221175_G_A	4	221175	7.77e-32	Yes
6611885_chrXI_33673_G_A	11	33673	7.92e-23	Yes
8623529_chrXIII_300324_G_C	13	300324	0.00e+00	Yes
10414113_chrXV_382144_C_T	15	382144	1.53e-205	Yes
5928463_chrX_96002_G_T	10	96002	6.04e-193	Yes
3567664_chrVI_98835_T_A	6	98835	3.90e-21	Yes
2440545_chrIV_1080523_C_T	4	1080523	2.28e-36	Yes
7996016_chrXII_750988_C_T	12	750988	2.41e-253	Yes
6848038_chrXI_269826_A_G	11	269826	1.64e-24	Yes
760082_chrII_529864_G_A	2	529864	1.22e-114	Yes
925586_chrII_695368_T_C	2	695368	6.30e-24	Yes
6594950_chrXI_16738_T_C	11	16738	6.50e-15	Yes
5678919_chrIX_286346_G_A	9	286346	1.79e-66	Yes
9435376_chrXIV_187740_T_C	14	187740	3.24e-68	Yes
11739349_chrXVI_616089_G_A	16	616089	6.69e-20	Yes
3161012_chrV_269057_A_G	5	269057	4.73e-60	Yes
9167252_chrXIII_844047_C_T	13	844047	1.99e-49	Yes
10551485_chrXV_519516_C_G	15	519516	3.83e-75	Yes
5093312_chrVIII_263382_T_C	8	263382	1.59e-31	Yes
138823_chrI_138823_A_G	1	138823	1.04e-44	Yes
7921913_chrXII_676885_G_A	12	676885	0.00e+00	Yes
5303814_chrVIII_473884_A_G	8	473884	1.45e-26	Yes
3885183_chrVII_146193_A_G	7	146193	0.00e+00	Yes
9462469_chrXIV_214833_G_A	14	214833	8.34e-103	Yes
2413305_chrIV_1053283_G_A	4	1053283	3.12e-42	Yes
935324_chrII_705106_A_T	2	705106	5.91e-25	Yes
11020152_chrXV_988183_G_A	15	988183	8.40e-13	Yes
6324127_chrX_491666_G_A	10	491666	5.22e-81	Yes
2248498_chrIV_888476_T_C	4	888476	4.55e-43	Yes
6997404_chrXI_419192_A_G	11	419192	3.12e-41	Yes
6751527_chrXI_173315_G_C	11	173315	1.69e-42	Yes
9536458_chrXIV_288822_C_T	14	288822	3.39e-202	Yes
8151459_chrXII_906431_T_C	12	906431	4.57e-25	Yes
8493990_chrXIII_170785_T_A	13	170785	7.79e-260	Yes
1342500_chrIII_299098_C_T	3	299098	2.00e-07	Yes
8847982_chrXIII_524777_C_A	13	524777	3.13e-25	Yes
5979363_chrX_146902_A_G	10	146902	1.49e-155	Yes
10988277_chrXV_956308_G_T	15	956308	7.30e-15	Yes
11217478_chrXVI_94218_T_C	16	94218	2.74e-20	Yes
6379661_chrX_547200_C_T	10	547200	3.97e-105	Yes
3520086_chrVI_51257_A_G	6	51257	8.69e-10	Yes
10864545_chrXV_832576_G_A	15	832576	1.18e-28	Yes

10244782_chrXV_212813_T_C	15	212813	2.15e-316	Yes
6646084_chrXI_67872_C_G	11	67872	6.25e-70	Yes
7011842_chrXI_433630_T_C	11	433630	3.12e-31	Yes
5515513_chrIX_122940_A_T	9	122940	1.84e-55	Yes
9901193_chrXIV_653557_C_T	14	653557	3.50e-89	Yes
8836630_chrXIII_513425_A_T	13	513425	1.38e-16	Yes
4726124_chrVII_987134_T_A	7	987134	2.34e-22	Yes
188190_chrl_188190_T_C	1	188190	3.19e-130	Yes
1598848_chrIV_238826_G_T	4	238826	3.91e-32	Yes
4581196_chrVII_842206_T_C	7	842206	8.72e-82	Yes
6256867_chrX_424406_A_T	10	424406	2.78e-41	Yes
1861689_chrIV_501667_A_C	4	501667	5.74e-29	Yes
5968656_chrX_136195_G_A	10	136195	8.97e-212	Yes
6280789_chrX_448328_C_T	10	448328	2.54e-41	Yes
602948_chrII_372730_G_A	2	372730	1.32e-88	Yes
2419116_chrIV_1059094_C_T	4	1059094	4.86e-42	Yes
6452525_chrX_620064_T_C	10	620064	2.52e-84	Yes
1414245_chrIV_54223_C_T	4	54223	4.54e-27	Yes
9300295_chrXIV_52659_G_T	14	52659	2.60e-03	No
9773211_chrXIV_525575_T_C	14	525575	0.00e+00	Yes
6945298_chrXI_367086_A_T	11	367086	8.70e-51	Yes
6136044_chrX_303583_C_T	10	303583	1.96e-08	Yes
10262035_chrXV_230066_C_T	15	230066	4.31e-263	Yes
8293957_chrXII_1048929_G_T	12	1048929	5.47e-02	No
4070183_chrVII_331193_A_G	7	331193	1.46e-59	Yes
3847228_chrVII_108238_G_C	7	108238	2.46e-262	Yes
1728757_chrIV_368735_G_A	4	368735	3.65e-49	Yes
1989747_chrIV_629725_G_A	4	629725	2.30e-26	Yes
2221279_chrIV_861257_A_G	4	861257	2.41e-33	Yes
1606765_chrIV_246743_G_C	4	246743	2.81e-35	Yes
3252364_chrV_360409_C_A	5	360409	2.41e-47	Yes
11014104_chrXV_982135_A_T	15	982135	1.46e-13	Yes
1467219_chrIV_107197_G_T	4	107197	5.23e-13	Yes
9795044_chrXIV_547408_G_A	14	547408	3.81e-222	Yes
8084909_chrXII_839881_G_A	12	839881	7.77e-50	Yes
5214936_chrVIII_385006_G_A	8	385006	2.08e-24	Yes
3965142_chrVII_226152_C_T	7	226152	0.00e+00	Yes
11174690_chrXVI_51430_C_T	16	51430	8.16e-18	Yes
8212296_chrXII_967268_A_G	12	967268	2.20e-12	Yes
6297026_chrX_464565_C_A	10	464565	6.08e-47	Yes
4878229_chrVIII_48299_T_C	8	48299	2.41e-97	Yes
5455388_chrIX_62815_A_G	9	62815	3.39e-35	Yes
3037458_chrV_145503_A_G	5	145503	4.44e-33	Yes
2693492_chrIV_1333470_C_T	4	1333470	3.48e-17	Yes
3968793_chrVII_229803_G_A	7	229803	4.98e-318	Yes
8933051_chrXIII_609846_C_T	13	609846	7.40e-69	Yes

707172_chrII_476954_C_T	2	476954	2.94e-135	Yes
173222_chrI_173222_A_C	1	173222	8.53e-73	Yes
7820825_chrXII_575797_G_T	12	575797	9.97e-252	Yes
6402295_chrX_569834_C_T	10	569834	3.88e-84	Yes
939170_chrII_708952_T_C	2	708952	7.15e-24	Yes
6085025_chrX_252564_T_C	10	252564	8.19e-31	Yes
4794687_chrVII_1055697_A_G	7	1055697	9.89e-05	Yes
7205226_chrXI_627014_C_T	11	627014	1.41e-59	Yes
11695724_chrXVI_572464_T_A	16	572464	4.51e-47	Yes
3716953_chrVI_248124_C_T	6	248124	7.87e-06	Yes
2819033_chrIV_1459011_C_T	4	1459011	2.19e-07	Yes
1941203_chrIV_581181_T_C	4	581181	8.43e-28	Yes
337341_chrII_107123_A_T	2	107123	1.62e-04	No
4572794_chrVII_833804_C_A	7	833804	2.43e-71	Yes
8040064_chrXII_795036_C_A	12	795036	5.11e-112	Yes
5689026_chrIX_296453_T_A	9	296453	4.06e-53	Yes
450642_chrII_220424_A_C	2	220424	3.39e-34	Yes
9008894_chrXIII_685689_T_C	13	685689	8.82e-119	Yes
8661636_chrXIII_338431_A_G	13	338431	7.00e-253	Yes
60384_chrI_60384_C_T	1	60384	1.01e-122	Yes
8519173_chrXIII_195968_G_A	13	195968	4.96e-289	Yes
3227559_chrV_335604_T_C	5	335604	1.10e-40	Yes
6301141_chrX_468680_G_A	10	468680	1.07e-55	Yes
11027149_chrXV_995180_A_G	15	995180	5.09e-09	Yes
5050085_chrVIII_220155_T_C	8	220155	1.27e-99	Yes
6036897_chrX_204436_C_A	10	204436	1.10e-48	Yes
1393233_chrIV_33211_A_G	4	33211	1.86e-25	Yes
1694415_chrIV_334393_T_C	4	334393	4.63e-41	Yes
4913863_chrVIII_83933_G_A	8	83933	5.06e-313	Yes
3633940_chrVI_165111_A_G	6	165111	1.07e-16	Yes
1441607_chrIV_81585_T_C	4	81585	2.08e-14	Yes
130776_chrI_130776_C_G	1	130776	3.76e-37	Yes
11204417_chrXVI_81157_G_A	16	81157	4.19e-19	Yes
281133_chrII_50915_C_T	2	50915	1.25e-05	Yes
8951620_chrXIII_628415_G_A	13	628415	1.25e-87	Yes
7528822_chrXII_283794_C_T	12	283794	2.80e-35	Yes
2767557_chrIV_1407535_A_G	4	1407535	4.30e-22	Yes

¹G x E: whether the p value reaches multiple testing threshold