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Gene–gene and gene–environment interactions in complex traits in yeast

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Abstract

One of the fundamental questions in biology is how the genotype regulates the phenotype. An increasing number of studies indicate that, in most cases, the effect of a genetic locus on the phenotype is context-dependent, i.e. it is influenced by the genetic background and the environment in which the phenotype is measured. Still, the majority of the studies, in both model organisms and humans, that map the genetic regulation of phenotypic variation in complex traits primarily identify additive loci with independent effects. This does not reflect an absence of the contribution of genetic interactions to phenotypic variation, but instead is a consequence of the technical limitations in mapping gene–gene interactions (GGI) and gene–environment interactions (GEI). Yeast, with its detailed molecular understanding, diverse population genomics and ease of genetic manipulation, is a unique and powerful resource to study the contributions of GGI and GEI in the regulation of phenotypic variation. Here we review studies in yeast that have identified GGI and GEI that regulate phenotypic variation, and discuss the contribution of these findings in explaining missing heritability of complex traits, and how observations from these GGI and GEI studies enhance our understanding of the mechanisms underlying genetic robustness and adaptability that shape the architecture of the genotype–phenotype map.

KEYWORDS

complex traits, cryptic genetic variation, epistasis, gene–environment interaction (GEI), gene–gene interaction (GGI), genetic networks, genetic robustness, higher-order genetic interactions, linkage mapping, missing heritability

1 | INTRODUCTION

Our understanding of the regulation of biological processes has significantly evolved from the one-gene, one-phenotype paradigm, with new studies continuously adding to the current understanding of a complex, polygenic architecture of the relationship between genotype and phenotype (Bloom, Ehrenreich, Loo, & Kruglyak, 2013; Bloom et al., 2015; Fay, 2013; Hou et al., 2016; Liti & Louis, 2012; Märtens, Hallin, Warringer, Liti, & Parts, 2016; Parts, 2014; Taylor & Ehrenreich, 2015). Multiple genes and their products contribute to a phenotype; in turn, a single gene can affect multiple phenotypes. As a result, there exists a highly interconnected network of genes with related molecular functions that contribute to and regulate various cellular processes, resulting in a phenotype.

In the budding yeast, *Saccharomyces cerevisiae*, genome-wide collections of strains with gross genetic perturbations such as deletion, knockdown or overexpression that have been phenotyped in various abiotic and biotic environmental conditions have helped in characterizing the independent functional effects of single genes. These studies show that while only 20% of the genes are essential in rich conditions, 97% of the genes are essential in at least one out of a total of 178 environments (Hillenmeyer et al., 2008). Furthermore, *S. cerevisiae* is the only eukaryotic organism in which genetic interactions have been systematically estimated in a genome-wide manner. The genetic interaction map constructed by comparing the effects of single and double gene deletions in the laboratory strain has determined the network of pairwise genetic interactions that affects yeast growth in rich conditions (Baryshnikova, Costanzo, Myers, Andrews, & Boone, 2013; Costanzo et al., 2010; Costanzo 2016). While these studies have been very significant in uncovering the effects of genetic interactions on growth in rich conditions, they have not demonstrated the effects of genetic interactions in different environments at a global level. Akin to single gene deletions, when genetic interactions for a subset of genes were tested in different environments, their effects emerged

as highly conditional (Gutin, Sadeh, Rahat, Aharoni, & Friedman, 2015; Martin et al., 2015).

Most of the above studies compare the effect of gross perturbations like deletions and have been performed in the laboratory strain S288c, isolated from a fig and cultivated in laboratory conditions for over 100 years (Gu et al., 2005). Comparisons of growth of ecologically and geographically diverse yeast strains across different environments have shown that the laboratory strain has the lowest phenotypic correlation with other strains, making it a phenotypic outlier (Warringer et al., 2011). This indicates that the genetic architecture underlying the same phenotype across diverse natural strains and environments could be very different. Evidentially, genotype–phenotype comparisons in different environments have identified variants within genes that were not identified by deletion, knockdown or overexpression studies in the laboratory strains. Similarly, double deletion studies do not encompass the breadth of genetic interactions that influence the phenotype in natural populations (Gasch, Payseur, & Pool, 2016). Similar discrepancies have been observed in organisms other than yeast, including humans, where different genes were identified to be phenotypically essential in CRISPR-based deletion studies vs. using population genomic variation (Bartha, di Iulio, Venter, & Telenti, 2018). Hence, the deductions regarding the relationship between the genotype and phenotype based solely on a single genetic background (strain) might not necessarily be fully representative of the yeast biology and, more generally, of eukaryotic biology.

There are several advantages to studying different strains, even within a well-studied model system like yeast. Sequencing of natural strains of yeast has revealed significant genetic variation in genomic sequences ranging from 0.3 to 0.8% (Liti, Carter, et al., 2009; Schacherer, Shapiro, Ruderfer, & Kruglyak, 2009; Strope et al., 2015). Bergström et al. (2014) show that 46% of the variants in protein-coding genes are strain specific. Furthermore, phenotypic diversity is even higher than this genomic diversity in budding yeast strains compared with other yeasts (Liti, Warringer, & Blomberg, 2017). Different alleles can have variable effects on the phenotype and even the same allele present in two different genetic backgrounds can have diverse phenotypic consequences (Gasch et al., 2016). This natural diversity in yeast can be exploited to understand the basis of heterogeneity in genotype–phenotype relationships and to gain a deeper understanding of non-linearity in genotype–phenotype associations such as variable expressivity, i.e. when a phenotype is affected to different degrees in individuals carrying the same variant, and incomplete penetrance, i.e. the ability of a variant to affect the phenotype in one individual and not another. Conclusions derived from studying the regulation of complex traits in natural yeast strains have helped expand molecular and functional understanding of diverse genes and pathways (reviewed in Liti & Louis, 2012; Fay, 2013). In this review, we will discuss the understanding of gene–gene (GGI) and gene–environment interactions (GEI) gained by exploring genetic regulation of complex traits in yeast, and implications for our comprehension of the genotype–phenotype map that describes the complex relationship between genes and their phenotypic effects.

GGI and GEI have played a key role in dissecting genes involved in different pathways and other biological processes, but their contribution to phenotypic variation in quantitative traits is less clear (Phillips, 2008). Studies in metazoans have identified very few cases of genetic interactions that affect phenotypic variation in different diseases and traits. Is this because variants (as against large-scale perturbations like gene deletions) have independent effects on the phenotype? Or is the effect of genetic interactions on phenotypic variation too small to be identified using the power of the current study designs? Are new analytical approaches required to determine the role of GGI amongst the genetic variants? GGI mapping studies in yeast have provided insights into these questions and, along with uncovering novel principles of adaptation and evolution in yeast, have contributed to determining the role of these interactions in shaping the genotype–phenotype map. Similarly, while there is a significant appreciation of the importance of environment in influencing the phenotype, it is difficult to untangle the magnitude of environmental influence from other confounding factors such as population history and structure. The insights gained from the high-throughput, systematic studies of yeast populations grown in multiple controlled environments provide a framework to gauge the role of environment in phenotypic variation in a comprehensive manner.

2 | GENE–GENE INTERACTIONS

Unlike molecular and biophysical interactions, genetic interactions are not limited to specific biomolecules like mRNA, proteins or metabolites. Within an organism, a genetic interaction regulating a phenotype can be mediated at any molecular level. This is one reason why systematic genetic networks tend to be denser than biophysical networks (Costanzo et al., 2010, 2016). However, genetic interactions identified by such synthetic perturbations within laboratory strains vs. those identified between naturally occurring variants uncover different aspects of the genotype–phenotype map.

Quantitative trait loci (QTL) are the genetic loci that contribute to phenotypic variation between genetically divergent strains (Figure 1A). QTL are identified by performing linkage mapping on the segregants generated by crossing two strains, phenotyping them and performing genotype–phenotype comparisons (reviewed in Mackay, Stone, & Ayroles, 2009). The comprehensibility of mapping is determined by the amount of heritability explained by the loci identified, i.e. the proportion of phenotypic variance attributable to genetic variance. Broad sense heritability refers to all genetic contributions to the phenotypic variance whereas narrow sense heritability refers to additive genetic contributions to the phenotypic variance. A QTL is additive if its effect on the phenotype is independent of variation at other loci. On the other hand, phenotypic variation will be the result of a genetic interaction if variants in two loci contribute non-additively to the phenotype. Missing heritability, i.e. the inability of loci identified through mapping to explain the variance in the phenotype, has been a long-standing problem in population and quantitative genetics (Eichler et al., 2010). One leading cause of missing heritability in genome-wide studies is the differential contribution of rare and common variants. It is possible that, instead of a few common variants, a large number of rare variants that are often not captured by genome-wide association studies contribute to phenotypic differences (Zuk et al., 2014). On the other hand, common variants could indeed be the major contributors to phenotypic variation (Golan, Lander, & Rosset, 2014) but can be incompletely penetrant, i.e. affect the phenotype in only a subset of individuals that carry them, or have variable expressivity, i.e. affect the phenotype to different degrees in

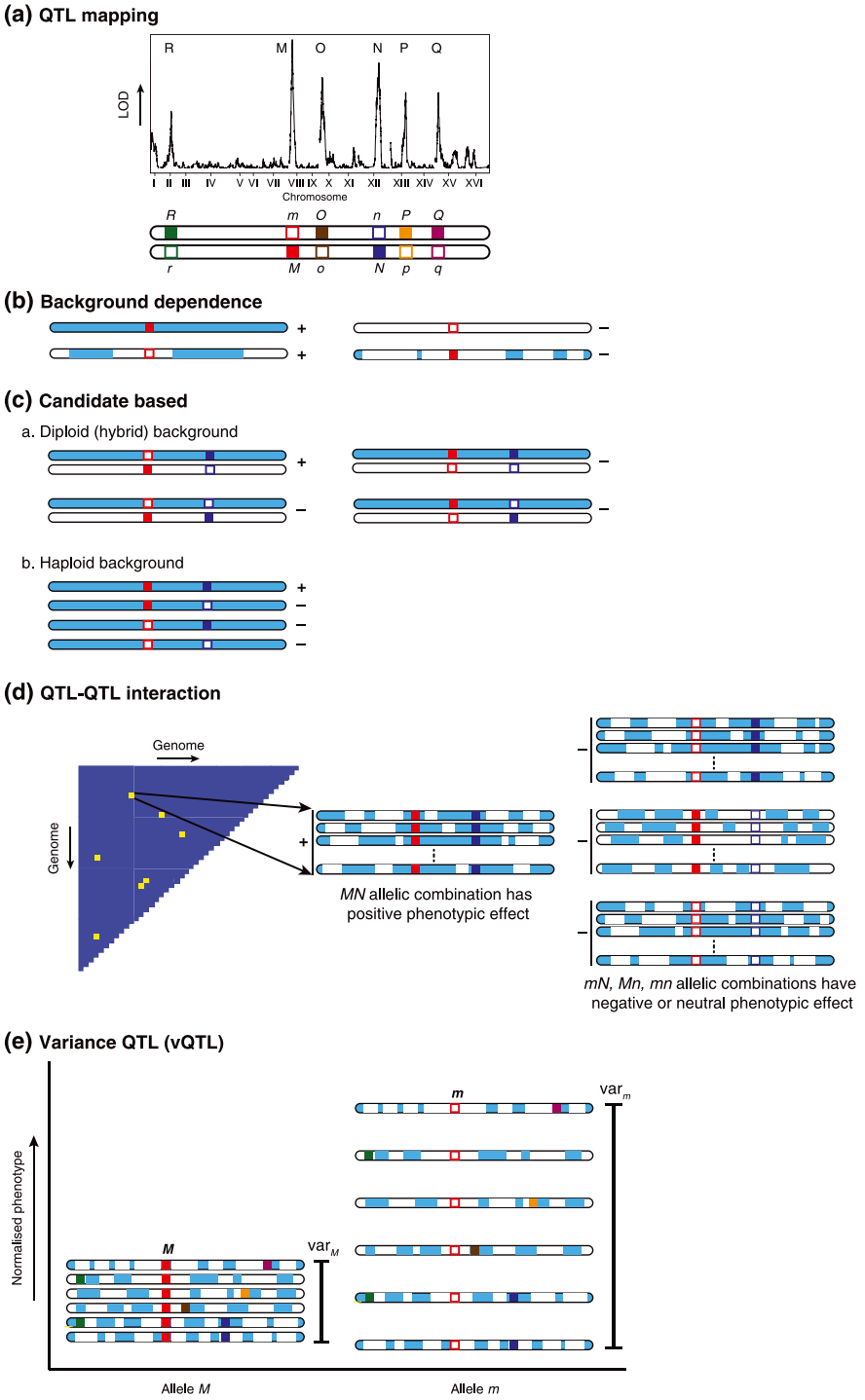

FIGURE 1 Gene–gene interactions (GGI). (A) Quantitative trait loci (QTL) mapping in a segregating biparental population identify additive loci (denoted as M-R on the genome). Closed box denotes positive allele (*M-R*) while open box is either a negative or neutral allele (*m-r*). (B) The effect of a locus is dependent on the genetic background of the strain it is present in. The locus M can have both positive or neutral effect on the phenotype depending on the genetic background. Additionally, either of the alleles of the locus M (*M* or *m*) can show a positive effect on the phenotype depending on the genetic background. (C) Candidate based approaches – gene–gene interaction can be detected in (a) diploid or (b) haploid background. Only one of the allelic combinations (*MN*) has the positive effect on the phenotype, while other combinations (*Mn*, *mN*, *mn*) have negative or no effect. (D) Genome-wide interaction mapping identifies the effect of all QTL–QTL combinations on the phenotype. The heatmap depicts all variants present in the segregating population on the *x*- and *y*-axes. Blue colour on the heatmap indicates that the effect of the two corresponding QTL is additive, whereas yellow indicates that it is interactive. The zoomed-out figure shows the distribution of alleles across segregants that is used to identify QTL–QTL interactions. In this case, loci M and N interact to affect the phenotype. All segregants containing allelic combination *MN* have a higher growth than the rest of the allelic combinations (*Mn*, *mN*, *mn*). (E) Variance QTL is a mapping technique that identifies loci with differential effects on the population variance. In presence of the *M* allele, the phenotypic effects of the other loci are suppressed in the segregating populations. However, these loci show their effects in the presence of the *m* allele, resulting in an increased phenotypic variance of the population. This can also be interpreted as differential regulation of cryptic genetic variation, where it is buffered by *M* allele and released by the *m* allele [Colour figure can be viewed at wileyonlinelibrary.com]

different individuals. This differential penetrance can be a result of genetic background dependence (GGI) or environmental influence on the effect of the loci (GEI; Zuk, Hechter, Sunyaev, & Lander, 2012). Mapping these interactions will be key to explaining the missing heritability, estimating the contribution of rare and common variants, and understanding incomplete penetrance and variable expressivity.

2.1 | Approaches to mapping gene–gene (QTL–QTL) interactions

The ability to map GGI depends on the sample size and population structure of the segregants being tested, phenotypes considered, mapping techniques used and the statistical comparisons performed. Here we enumerate the studies that either provide indirect insights or have been specifically undertaken to understand the extent of GGI in populations (also see the Box).

2.1.1 | Indirect evidence for gene–gene interactions from background dependence

Without directly estimating GGI, the studies discussed below provide indirect evidence that supports an influential role of genetic interactions in phenotypic variation by demonstrating background dependence of allelic effects (Figure 1B). Sinha, Nicholson, Steinmetz, and McCusker (2006) showed that each of the three alleles of *MKT1*,

Box: Gene–gene interactions (GGI) and additive vs. interactive genetic architecture

A fundamental characteristic of adaptation and evolution, and hence complex traits is GGI or epistasis (Hansen, 2013; Hemani, Knott, & Haley, 2013). While originally associated with suppression of the phenotype of one gene by another gene (as defined by Bateson), the definition of epistasis in association with complex traits in an allelic context, as coined by Fisher, refers to any statistical deviation from the additive combination of two loci in their effects on a phenotype (Carlborg & Haley, 2004; Phillips, 2008). Essentially, it means that two genes interact to regulate variation in the phenotype if their allelic combinations show a phenotype that deviates from the sum of their independent effects (additive effects). This deviation can either be synergistic, i.e. the allelic combination can perform better than the sum of their independent effects, resulting in positive epistasis, or suppressive, i.e. the allelic combination performs worse than expected, resulting in negative epistasis (Mackay, 2014). To map such genetic interactions, the population is divided based on two genetic loci (into four categories in case of a haploid population and nine in case of a diploid) instead of one (Mackay, 2014; Phillips, 2008). These allelic combinations are then multiple-tested against a null additive model of their effect on the phenotype. While such mapping allows identification of genetic interactions regulating the phenotype, they are severely limited by the population size as the same population is now divided into a greater number of groups compared with single quantitative trait loci (QTL) mapping. Simply put, to identify interacting loci with the same accuracy and power as single loci, the sample sizes required increase exponentially by the power of 2 (from n to n^2). A central contradiction in the regulation of the genotype–phenotype map is that, while a highly interactive genetic network is emerging from systems-level molecular studies, in both model organisms and humans, the majority of the phenotypic variation in both Mendelian and complex traits is still explained by additive loci. A comparison of different types of GGI studies in yeast uncover the reasons that might underlie this apparent paradox.

1. Most loci that show interactions often have independent effects (Bhatia et al., 2014; Bloom et al., 2013; Cubillos et al., 2011), indicating that genetic interactions tend to modify the effects of loci. Even in a scenario where major allele frequency equals the minor allele frequency and the population is in a Hardy–Weinberg equilibrium, only one-quarter of the population would carry both the loci.
2. Comparison of interaction studies performed in different biparental populations has shown that most of the GGI tend to be strain specific (Cubillos et al., 2011, 2013), indicating that these, often small-effect, interactions are background dependent. This explains why genome-wide association studies, with multiple parent populations with varying allele-frequencies, fail to identify these GGI.
3. Furthermore, studies reveal that background dependence of the effect of loci can be explained, at least partially, by the higher-order interactions between multiple loci (Taylor & Ehrenreich, 2014; Yadav et al., 2016a). This may underlie the inability of two-locus scans to identify interactions, and the small effect of two-locus interactions in cases where they are identified.

These insights from yeast genetics and genomics advocate for a change in approaches for mapping genetic interactions and epistasis. These results further imply that, while genetic interactions might not, on average, have high effect sizes, they will play a key role in predicting the effect of a genetic variant in different backgrounds. Together, they would help explain the missing heritability in complex traits and understand the incomplete penetrance of genetic loci.

RHO2 and *END3* had differential effects on high-temperature growth when present in genetically divergent strains, including laboratory, clinical and vineyard isolates. If a dominant large-effect single QTL has a negative epistatic effect on many small-effect QTL, i.e. it masks the phenotype of these minor effect QTL, then eliminating this large-effect QTL uncovers the effects of these small-effect QTL (Demogines, Smith, Kruglyak, & Alani, 2008; Sinha et al., 2008; Yang et al., 2013). However, systematic mapping of GGI is still required to discriminate between the following two possibilities. The first is a case of bona fide genetic interaction where the influence of a small-effect locus is epistatically masked by the large-effect locus. The second is a technical artefact of the dynamic range of detection methods where the influence of small-effect locus is too small to be detected when a large-effect locus is present. This genetic background dependence has been observed in other studies using multiple crossing techniques (Cubillos et al., 2011; Cubillos et al., 2013; Ehrenreich et al., 2012; Parts et al., 2011; Sinha et al., 2008; Torabi & Kruglyak, 2011; Yang et al., 2013).

The genetic basis for this background dependence was identified in specific cases. In a round robin cross among 12 strains, the loci that regulated variation in growth in sodium chloride and caffeine were influenced by the mating-type locus of the strains (Treusch, Albert, Bloom, Kotenko, & Kruglyak, 2015). In another example, for variation in sporulation efficiency in a segregating population derived from oak (YPS606) and wine (BC187) yeast strains, *RME1* interacted with *IME1* and *RSF1* (Gerke, Lorenz, & Cohen, 2009), whereas in S288c- and SK1-derived populations, *RME1* interacted with *MKT1* and *TAO3* (Deutschbauer & Davis, 2005).

2.1.2 | Candidate approach to mapping gene–gene (QTN–QTN) interactions

The most successful examples of gene–gene interactions, resolved at the genetic level, have been dissected using candidate approaches, i.e. non-systematic approaches that target specific genes (Figure 1C). The basic and most common unit of genetic variation in populations is single nucleotide polymorphism (SNP) and the nucleotide change

underlying a QTL is called a Quantitative Trait Nucleotide (QTN). A few studies in yeast have investigated GGI, or more precisely, SNP–SNP (QTN–QTN) interactions between causal genes affecting quantitative traits. Sporulation efficiency variation in yeast was mapped to precisely three nucleotides in *RME1(ins-308A)*, *MKT1(D30G)* and *TAO3(E1493Q)* between SK1 and S288c (Deutschbauer & Davis, 2005). For all of these, the QTN from the SK1 background conferred higher sporulation efficiency. These polymorphisms showed a strict additive model at 24 h sporulation, i.e. the phenotypic effect of QTN–QTN interaction was equivalent to the sum of their single phenotypic effects and a potential epistatic relationship at 48 h. In another study, the causal genes for variation in sporulation efficiency in YPS606 and BC187 segregants identified genetic interactions among QTN *IME1(L325M)*, *IME1(A-548G)* and *RSF1(D181G)* (Gerke et al., 2009). For high-temperature growth, QTN *MKT1(D30G)*, *END3(S258N)* and *RHO2(3′UTR polymorphisms)* showed both additive and epistatic interactions (Sinha et al., 2006). The phenotypic effect of QTN in *MKT1* and *RHO2*, as well as *MKT1* and *END3*, was found to be additive. In contrast, the genetic interaction between *END3* and *RHO2* was negatively epistatic, i.e. the combined phenotypic effect of the QTN of both the genes was less than the sum of their single effects.

The main advantage of studying GGI at such high resolution is that the phenotypic effect is assigned very specifically to a polymorphism without the ambiguity of any other variant confounding the result. Since these effects are tested in homozygous diploid or haploid backgrounds, heterogeneity of the background (heterozygosity) and mode of inheritance (dominance vs. recessive) do not confound the estimation of genetic interactions. However, mapping QTN–QTN interactions is time consuming as it first involves mapping the causal loci and then identifying causal nucleotide within those loci. Moreover, the above approach will have to be substantially modified if multiple causal QTN within a QTL affect the phenotype. For example, multiple polymorphisms within *IRA2* contribute to its additive effect (Cubillos et al., 2013; Smith & Kruglyak, 2008), and all or a select few of these polymorphisms could be involved in the multiple genetic interactions of the locus (Yadav, Radhakrishnan, Bhanot, & Sinha, 2015). Subject to the power of the study and the size of the locus, the majority of the loci identified by mapping contain several genes with multiple coding and non-coding SNPs. It is possible that one or more of these coding SNPs may be causal, and while the synonymous SNPs will not change the protein sequence, owing to differences in codon biases, these SNPs can affect other processes like translational efficiency. Most importantly, owing to the limitation of designing strains for specific nucleotide variations, this approach cannot yet be applied genome-wide. Despite the tedium of mapping QTN and thereafter estimating the effects of combinations of these QTN, it is important to map QTN–QTN interactions. Apart from understanding the genetic and molecular changes that alter the phenotype, mapping QTN and QTN–QTN interactions plays a crucial role in answering several long-standing questions regarding the architecture of complex traits. Fine-mapping the QTN and comparing their effects with that of the entire locus will help in understanding the contribution of each variant to the phenotype. Estimating allele frequency of a QTN, identified in a biparental population, across diverse yeast strains can determine whether causal alleles tend to be rare (Sinha et al., 2006) or common (Muller, Lucas, Georgianna, & McCusker, 2011). Common causal variants would provide an opportunity to study the effects of variants across diverse genetic backgrounds and dissect the genetic interactions that underlie variable penetrance and hence missing heritability.

For cases where it is not possible to fine-map each locus to a nucleotide level, an alternative is studying RHA–RHA interaction. Reciprocal hemizygosity analysis, RHA, is a fine-mapping tool to compare the effects of two alleles in a hybrid genetic background. These alleles can be of varying sizes, i.e. restricted to the size of the gene (Steinmetz et al., 2002) or larger genomic regions (Singh & Sinha, 2014; Yang et al., 2013). RHA has been a very successful in identifying causal alleles that contribute to a phenotype. Since it was first introduced by Steinmetz et al. (2002), it has been extensively used to map phenotypic differences precisely to an allele (Ambroset et al., 2011; Ben-Ari et al., 2006; Cubillos et al., 2011, 2013; Gagneur et al., 2013; Hou et al., 2016; Kim & Fay, 2009; Kim, Huh, Riles, Reyes, & Fay, 2012; Lewis, Broman, Will, & Gasch, 2014; Liti, Haricharan, et al., 2009; Lorenz & Cohen, 2014; Maurer et al., 2016; Parts et al., 2011; Romano, et al., 2010; Salinas et al., 2016; Singh & Sinha, 2014; Sinha et al., 2006; Sinha et al., 2008; Swinnen et al., 2012; Wilkening et al., 2014; Yang et al., 2013). Unlike other fine mapping techniques such as backcrossing and generation of recombinant inbred lines, RHA is a one-step technique to fine map the causal genes within a large locus. Furthermore, RHA has been successfully employed to map genes and alleles between interacting loci (Sinha et al., 2006; Yang et al., 2013) and to study their phenotypic effects across homogeneous backgrounds. Finally, RHA–RHA can identify genetic interactions between loci in linkage disequilibrium that are difficult to dissect in recombinant populations. In case of high-temperature growth, RHA–RHA was used to identify an epistatic interaction between *RHO2* and *END3* alleles that are in linkage disequilibrium (Sinha et al., 2006). Despite having a better performing *END3* allele, the laboratory strain grows poorly compared with the clinical isolate at high temperatures. RHA–RHA interactions revealed that this is because of a negative epistatic interaction between the laboratory strain alleles of *END3* and *RHO2*, where the *RHO2* allele masks the high-temperature growth phenotype of *END3*.

Despite the success of RHA, its application to study even targeted RHA–RHA interactions are still contingent upon mapping and dissecting QTL–QTL interactions to a gene level. Additionally, the candidate-based targeted approaches to map interactions are limited to loci with large effect sizes. Finally, since these interactions are tested in a uniform background, any contribution of the genetic background to these interactions is levelled, thereby limiting the estimation of their potential effect size.

2.1.3 | QTL–QTL interactions

The comprehensive approach to identifying the full extent of pairwise GGI within two parental strains is to test all possible pairs of polymorphisms between the strains for potential genetic interaction, i.e. whole genome by whole genome interaction analysis (Figure 1D). A biparental haploid population is divided into four groups (compared with just

two for single QTL mapping) based on the biallelic combinations of the genotype of the segregants. To perform QTL–QTL analysis for *n* number of variants, the total number of unique paired combinations to be tested is given by the binomial coefficient *C*(*n*,2), which is a substantially larger than the *n* combination required for single QTL mapping. Therefore, while this is a comprehensive approach to identify genetic interactions, the ability to perform a genome-wide QTL–QTL screen is limited by the size of the population (also see the Box). This limitation was demonstrated by a study that conducted mapping for single and interacting loci in multiparental populations, identifying 82 single loci but only one QTL–QTL interaction (Cubillos et al., 2011).

Studies with large sample sizes that have identified multiple QTL–QTL interactions (Bloom et al., 2013, 2015; Hallin et al., 2016) show that QTL–QTL interactions explain a very small amount of phenotypic variance compared with the additive loci. Bloom et al. (2015) identified 797 single additive QTL and 205 QTL–QTL interactions in a biparental population of 4000 recombinants grown in 20 environments, with QTL–QTL interactions explaining an average of 9.2% phenotypic variance compared with 43.3% explained by the additive loci. A similar trend is observed in other populations, where QTL–QTL interactions explained 1–15% overall phenotypic variance, with an average of 7%, within one environment for a phenotype (Hallin et al., 2016). In addition, most of the loci participating in epistatic interactions often have an independent effect. Of the 19 QTL–QTL interactions identified in segregants from a cross between BY and YJM789 (clinical isolate) grown in different carbon sources, 11 interactions involved at least one significant additive QTL (Bhatia et al., 2014), while the remaining eight interactions had low effect size on average. Similarly, in the majority (92%) of the QTL–QTL interaction pairs, at least one locus was a significant additive QTL (Bloom et al., 2015). Together, these studies indicate that, while genetic interactions are common among QTL, their contribution to phenotypic variation, as judged by these techniques, is limited.

2.1.4 | Higher-order genetic interactions

Much like single QTL, background dependence of the phenotypic effects of QTL–QTL interactions indicates that other variants interact with these two-locus interactions, suggesting the presence of higher-order genetic interactions (Deutschbauer & Davis, 2005; Gerke et al., 2009; Sinha et al., 2006; Yang et al., 2013). In a study testing high-temperature growth, it was observed that genetic interaction between the causal alleles *MKT1* and *NCS2* depended on the genetic background in which the combination was present (Sinha et al., 2008). The interaction was only observed when the genetic background was YJM421/S288c (50% YJM421 background) but not in the backcross hybrid backgrounds (25% YJM421 background). Similarly, the genetic interaction between *MKT1–RHO2* was observed only in the YJM145/S288c background (Sinha et al., 2006) but was absent in YJM421/S288c (Sinha et al., 2008). The same phenotype in segregants of MUCL28177 and S288c identified *PRP42-SMD2* interaction that was background specific (Yang et al., 2013). Higher-order genetic interactions involving alleles of *END3*, *TRR1*, *IRA2*, *FLO8* and *MSS11* were mapped for colony morphology in backcross progeny of a cross between BY4716 and 322134S strains (Taylor & Ehrenreich, 2014). The prevalence of higher-order interactions in genetic architecture could be a potential reason for the inability to identify large-effect two-locus interactions in genetic crosses (Taylor & Ehrenreich, 2015). The inability of single-locus and QTL–QTL interactions to entirely explain the phenotypic variance suggests that higher-order epistatic interactions may underlie phenotypic variation.

The ability of the already underpowered QTL–QTL analysis is further limited when mapping for higher-order interactions such as three-locus interactions, making it difficult to identify statistically significant interactions (Bloom et al., 2015). A study that estimated the contribution of three-loci interactions showed that they explained a very small percentage of phenotypic variance (average 1.7%; Hallin et al., 2016). Further, in another study, the higher-order epistatic interactions were unique to each environment (Bhatia et al., 2014). However, these studies indicate that these higher-order interactions may underlie the phenotypic heterogeneity of a population containing the same allele and hence explain the pervasive incomplete penetrance observed in both model organisms and humans.

While a relatively larger number of segregants (1000–4000) can identify QTL–QTL interactions (Bloom et al., 2015), the interacting loci often have large interval sizes, which is due to small effect sizes of these interactions and limited recombination events within the population. Hence, while population studies in yeast have the power to identify genetic interactions at a locus level and estimate their contribution to phenotypic variation, more work needs to be done to identify the genes contributing to, and the mechanisms underlying, these genetic interactions.

2.1.5 | Genome-wide association studies

Candidate-based, targeted and multilocus interaction approaches described above cover more genetic diversity than SGA, but are still limited to genetic variation present in only two parental strains. Moreover, as segregants are synthesized by crossing two natural strains in approaches based on linkage mapping, an equal weighting is given to all segregating polymorphisms without accounting for their adaptive or evolutionary significance.

An alternate to linkage mapping is genome-wide association studies (GWAS), where multiple natural strains with diverse evolutionary histories and genetic backgrounds with varying allele frequencies are used to identify the loci contributing to phenotypic variation (Mackay et al., 2009). The main advantage of this approach is that the strains are studied in their natural genetic state (not synthetically generated recombinants), which allows understanding of the role of genetic interactions in shaping adaptation. A few GWAS (Connelly & Akey, 2012; Diao & Chen, 2012; Tomar et al., 2013) have been performed in yeast using a collection of wild SGRP strains (Liti, Carter, et al., 2009). However, the currently available small number of natural yeast strains with whole genome sequences significantly limits the application of this approach to even single locus mapping, making genome-wide scans for genetic interactions practically impossible.

In addition, natural yeast strains have a strong population structure, i.e. genetic stratification within populations that arises because of non-random mating and genetic drift (Connelly & Akey, 2012; Diao

& Chen, 2012). This impacts all genotype–phenotype analysis and thereby further complicates the ability to perform GWAS in yeast and identify additive and interacting loci (Bergström et al., 2014; Connelly & Akey, 2012; Diao & Chen, 2012; Liti, Carter, et al., 2009; Tomar et al., 2013). As a result, while it is possible to detect *cis*-acting QTL in these GWA studies, identification of *trans*-acting QTL is often confounded by population structure. These limitations can be overcome by increasing the number of yeast strains with the help of undertakings such as the ongoing 1000 yeast genomes project (http://1002genomes.u-strasbg.fr). However, whether these strains would be enough to circumvent the complexity of such strong population structure remains to be seen.

3 | GENE–ENVIRONMENT INTERACTIONS

A GEI occurs when the effect of a gene or a locus depends on the environment in which the phenotype is measured. Phenotypes show a diverse range of environment dependence, with Mendelian phenotypes often being less susceptible to the environment than complex traits. GEI mapping can uncover the dependence and vulnerability of the phenotype to different environments, as well as explain the missing heritability of a population phenotyped in heterogeneous environments. However, accurate, unbiased GEI mapping is often hindered by the inability to test the same population in different environments in both humans and model organisms. As a result, it is often difficult to uncouple the contribution of genetic and environmental influences on the phenotypic differences.

Yeast is highly sensitive to the environment, and the ability to test the same population in various environments provides a platform to study the full extent of GEI (Bhatia et al., 2014; Gagneur et al., 2013; Gerke, Lorenz, Ramnarine, & Cohen, 2010; Granek & Magwene, 2010; Matsui & Ehrenreich, 2016; Smith & Kruglyak, 2008). As exemplified by the yeast deletion collection, a strain containing a deletion of a single gene can have varied growth phenotypes in different environments (Hillenmeyer et al., 2008). Furthermore, the same gene deletion in the strains with different evolutionary histories can have variable effects within and across environments (Singh & Sinha, 2014; Sinha et al., 2006; Wilkening et al., 2014). Studies in yeast have contributed to a deeper understanding of both the extent and the nature of GEI. Mapping GEI in the yeast strains isolated from a variety of ecological niches provides a platform to identify alleles that aid adaptation to these diverse conditions as well as to study the pleiotropic effects of such alleles in novel environments (Liti, 2015; Liti, Carter, et al., 2009; Warringer et al., 2011).

3.1 | Approaches to mapping gene–environment interactions

3.1.1 | Indirect evidence

Similar to GGI, indirect evidence for the abundance for GEI comes from studies that have mapped loci independently in various environments (Bloom et al., 2013, 2015; Hallin et al., 2016; Perlstein et al., 2006; Perlstein, Ruderfer, Roberts, Schreiber, & Kruglyak, 2007; Smith & Kruglyak, 2008; Steinmetz et al., 2002). These studies indicated that the large effect loci showed two categories of response – they can either be highly environment specific, e.g. a *MAL13* variant renders the laboratory strain incapable of utilizing maltose, but has no effect on other carbon sources (Bloom et al., 2013), and a *RAD5* variant has an effect only in genotoxic environments (Demogines et al., 2008), or they can have an effect on the phenotype in multiple conditions, such as variation in stress response genes like *IRA2* or *MKT1* that have effects across multiple environments (Fay, 2013). Many factors can contribute to an apparent difference in the effect of a locus across two environments, including overall phenotypic variation in the environments and effect of other loci. Hence, a two-way environmental comparison is necessary to get an accurate estimate of the abundance and directionality of GEI (Figure 2).

3.1.2 | Gene–environment interaction mapping

The direct approach to mapping GEI of a locus is to study its effects across two environments using the environment as a covariate, i.e. a variable that can influence the phenotype (Figure 2), and estimate the effect of the locus after normalizing for phenotypic variation in the two environments (Broman, Wu, Sen, & Churchill, 2003). Since this approach allows for a genome-wide scan for GEI, loci can be identified independent of their effects in individual environments. This reveals a large number of small effect loci with GEI that would not be identified in independent QTL mapping. GEI have been identified for both biparental (Bhatia et al., 2014; Smith & Kruglyak, 2008; Yadav et al., 2015) and multiparental yeast populations (Cubillos et al., 2011, 2013). Moreover, many small-effect loci that are not detected in single environment mapping are identified when their effects are compared across environments (Bhatia et al., 2014; Yadav et al., 2015). Such systematic GEI shows that the majority of the loci, independent of their effect size, show an interaction with the environment.

Based on the relative effects on the phenotype across two environments, GEI exhibited by a locus can be classified into three categories: environment specific, scale and antagonistic effects (Figure 2B). It is important to note that it is statistically challenging to distinguish between the effect of small effect environment-specific or scale effects, and there is a danger of over-interpreting the environmental specificity for small effect loci or underestimating the environmental dependence in case of large effect loci.

3.2 | Insights from GEI mapping

GEI mapping in yeast provides a unique platform to study the independent effect of variants, accumulated in strains over the course of evolution, across multiple pairs of environments and to determine their relative effects on the phenotype. It is a tool to study the genetic regulation of the response to different environments. In his *Genetical Theory of Adaptation*, Fisher proposed that it is highly unlikely that a genetic variant will confer a beneficial effect on all phenotypes in multiple environments (Fisher, 1930; Levins, 1968). Most of these variants will be neutral across several environments and some can even show trade-off across two or more environments, i.e. have advantageous effects in one and detrimental effects in another, thereby restricting

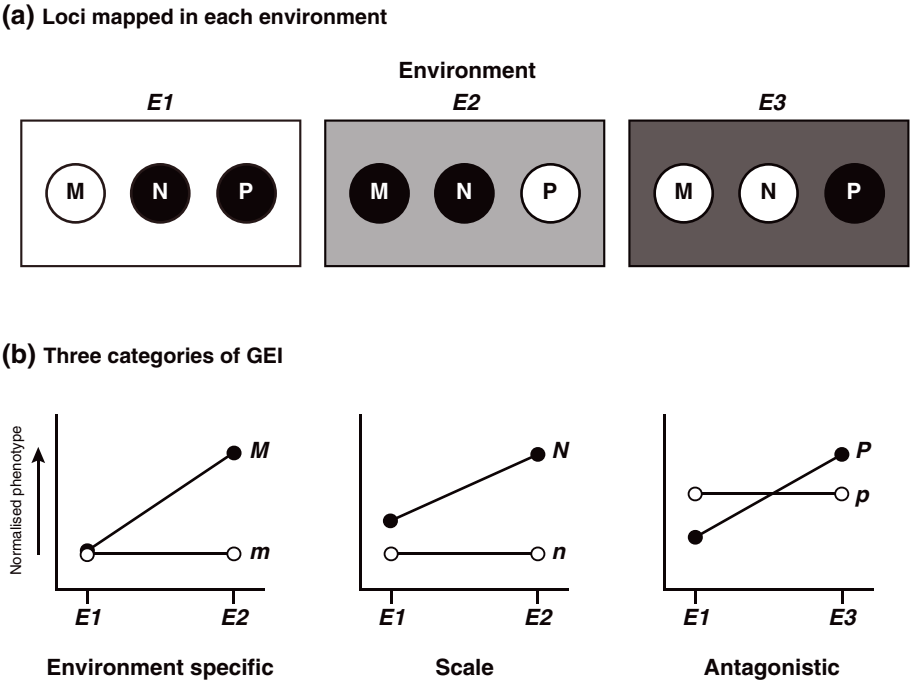

FIGURE 2 Gene–environment interactions (GEI). (A) *E1*, *E2* and *E3* are three different environments and the circles depict three loci that affect the phenotype in these environments. A white circle indicates that the locus has no effect, whereas a black circle indicates that the alleles of the locus have different effects on the phenotype. Loci N and P have an effect in *E1*, M and N in *E2* and P in *E3*. (B) Reaction norm diagrams, which describe the pattern of phenotypic expression of a single genotype in two or more environments, depicting the three categories of GEI shown by loci M, N and P in *E1*, *E2* and *E3*

1. Environment-specific or conditionally neutral – in this case, the alleles show a phenotypic difference in one environment but no effect in the other, i.e. the slopes of the reaction norms of the two alleles are divergent from a point, across an environmental pair. Locus M shows environment-specific GEI as it has no effect in *E1* but allele *M* performs better than allele *m* in *E2*.
2. Scale – in this case, a locus shows an effect on both environments, with the alleles showing a difference in the same direction in the two environments, but with varying magnitudes, i.e. the reaction norm slopes are divergent but now with a significant difference between the allelic effects in both environments. Locus N shows scale GEI as it has an effect in the same direction in both *E1* and *E2* with allele *N* performing better than allele *n*, but the magnitude of this allelic difference in larger in *E2* than in *E1*.
3. Antagonistic – this is the most special class of GEI in which alleles show opposing effects in the two environments, i.e. the slopes of the two alleles intersect with each other. Locus P shows antagonistic GEI as it has an effect in both *E1* and *E3*, but while allele *p* performs better in *E1*, allele *P* performs better in *E3*.

[Colour figure can be viewed at wileyonlinelibrary.com]

adaptation (Hill, O'Meara, & Cowen, 2015; Magwene Granek, et al., 2011; Wenger et al., 2011; Zakrzewska et al., 2011). Comparing the abundance and effect of loci showing GEI has provided empirical evidence for these predictions.

3.2.1 | Effect size of GEI

Loci regulating complex traits tend to show a range of effect sizes of GEI with a few loci showing a large effect and the majority of the loci showing small-effect GEI (Bhatia et al., 2014; Yadav et al., 2015). A variant in the *MAL13* gene that affects growth in only maltose and not any other carbon source is an intuitive example of a large-effect locus showing GEI. Most large-effect GEI are already identified by independent mapping studies and the power of GEI mapping lies in the identification of small-effect loci that contribute to environmental dependence and cumulatively increase the amount of variance explained in each environment. In addition, these small-effect loci that show GEI can be the primary contributors to phenotypic plasticity, i.e. the ability of individuals to show diverse phenotypes across multiple environments (plasticity QTL; Yadav, Dhole, & Sinha, 2016b).

3.2.2 | Trade-offs in adaptation and evolution

A trade-off, i.e. when a locus has opposing effects across a pair of environments with one allele performing better in one environment and the other allele in the other, is the most extreme and perhaps the most interesting example of GEI (Figure 2B).

A study that mapped GEI in a biparental segregating population phenotyped for growth in 12 environments showed that a large proportion (~40%) of the loci show trade-off across at least one pair of environments (Wei & Zhang, 2017; Yadav et al., 2015). Moreover, loci tend to show trade-off across different types of stresses, i.e. stresses that elicit different global cellular responses and pathways, e.g. across rich conditions and oxidative stresses. However, the trade-off was also observed across stresses that invoke similar systematic cellular and molecular responses (Gasch et al., 2001; Gasch et al., 2000). For

example, in two different oxidative stresses, one-third of the loci showing GEI were found to show trade-off across paraquat and hydroxyurea (Yadav et al., 2015). Additionally, various laboratory evolution studies have shown that indeed evolution for a particular phenotype results in fixation of alleles that show trade-off in other environments, e.g. carbon-limited environments (Wenger et al., 2011).

A trade-off can occur when an allele with a positive or neutral effect under a selection pressure shows negative effects on the phenotype in an environment that is not under selection. Therefore, a high abundance of trade-off does not imply that variants with opposing effects across different environments are selected during the course of evolution. All trade-off does not necessarily result in antagonistic pleiotropy, which specifically implies long-term selection of alleles with opposite effects on different phenotypes or environments (Hedrick, 1999). While it is difficult to distinguish between trade-off and antagonistic pleiotropy using only linkage mapping analysis, comparing fixation patterns of alleles in diverse yeast populations or strains can help decipher the phenotypic implications of a locus. A recently acquired allele or an allele present in the same phylogenetic branch that shows opposite effects across environments is more likely to be an example of trade-off with a possibility of being lost under opposing selection. In contrast, multiple alleles with beneficial effects in different environments can be maintained in divergent strains, i.e. show signatures of balancing selection (Turelli & Barton, 2004). While abundant trade-off has been identified in yeast GEI studies, only a few loci have a large effect with characteristics of antagonistic pleiotropy (Hughes & Leips, 2016; Qian, Ma, Xiao, Wang, & Zhang, 2012; Smith & Kruglyak, 2008; Yadav et al., 2015). We would like to state that these are deductions since it is not possible to accurately estimate the evolutionary importance of effect size of an allele based on phenotypic measurements in a laboratory condition.

One of the molecular pathways whose genes have frequently shown antagonistic pleiotropy is the Ras/PKA pathway (Granek, Kayıkçı, & Magwene, 2011). A negative regulator of this pathway, *IRA2*, showed trade-off across diverse nutritional and oxidative stresses (Yadav et al., 2015). Laboratory yeast evolution studies in limiting glucose conditions showed that most adaptive haploid strains were enriched for Ras/PKA pathway genes, including *IRA2* (Venkataram et al., 2016). Additionally, *IRA2* and several other Ras/PKA pathway genes showed balancing selection in isolates of both *S. cerevisiae* and *S. paradoxus*, indicating that multiple genes in the pathway contribute to the phenotypic diversity of these strains in natural populations. This antagonistic pleiotropy can be mitigated by GGI within the parental strains, thus maintaining conditionally damaging alleles within a strain (Ono, Gerstein, & Otto, 2017; Yadav et al., 2015). Pleiotropy can result from the same or different molecular functions of the same locus. Even though the same loci are identified in different environments, the genetic interactions tend to be highly environment-specific, indicating differential effects of these loci on various biological processes.

3.2.3 | Case studies of environmentally driven selection

It is intuitive that GEI can actively influence genetic variation by facilitating selection of loci that provide a fitness advantage in specific environment(s). The high phenotypic diversity of budding yeast strains is inferred to be the result of domestication of budding yeast for various purposes and its occupation of environmental niches more diverse than other yeast strains such as *S. paradoxus* (Liti, Carter, et al., 2009). This enhanced phenotypic diversity of *S. cerevisiae* strains provides an opportunity to study the interplay between environment and genetic variation.

Interestingly, despite being isolated from unique environmental conditions, at a genome-wide level, yeast strains do not cluster based on their ecological niches but their geographical history, suggesting that it is largely an outcome of genetic drift (Liti, Carter, et al., 2009; Wenger et al., 2011). This is akin to what is observed in other organisms including humans, where genetic history, rather than the environment, influences the overall population structure (The 1000 Genomes Project Consortium, 2012; The 1000 Genomes Project Consortium, 2015). However, broad signatures of environmental influence have been detected by GEI analysis for specific strains and phenotypes. In a comparison of the genomes of clinical and non-clinical isolates, certain alleles that may provide a pathogenic potential were more frequent in clinical vs. non-clinical strains, independent of their geographical origin (Muller & McCusker, 2009; Strope et al., 2015).

Allelic bias is observed when an allele is beneficial in one environment but detrimental in another, which results in maintenance of two or more alleles of a gene in the population. Adaptive loss of aquaporins in subgroups of natural yeast strains resulting in a difference in freeze–thaw tolerance indicates a signature of balancing selection (Will et al., 2010), i.e. maintenance of multiple alleles of a gene in a population. Although aquaporins are necessary for surviving freeze–thaw, they are disadvantageous in high-sugar substrates found in natural environments of most yeast strains. As a result, functional aquaporins have been lost at least six times in the history of these yeast strains. Similarly, among the yeast strains, signatures of balancing selection were identified in *IRA2*, as one allele was beneficial in various oxidative and genotoxic stresses and the other allele was fitter in rich carbon source conditions (Yadav et al., 2015). In a set of 12 biophysically interacting high-temperature growth genes, alleles from a clinical strain were advantageous over alleles from the laboratory strain when grown at high temperature on solid medium. However, these allelic effects were reversed when the growth medium was changed to liquid with the laboratory alleles being more advantageous, thereby revealing novel complexities underlying GEI (Fraser et al., 2012).

GEI can also influence the accumulation of mutations at a shorter timescale. In the laboratory strain S288c, *MKT1*, a gene important for growth in various stresses (Dimitrov, Brem, Kruglyak, & Gottschling, 2009; Lewis et al., 2014; Smith & Kruglyak, 2008), has a functionally null mutation, while all the wild-type strains carry the functional allele (Liti, Carter, et al., 2009; Strope et al., 2015). A more striking example of environmentally driven selection is of the *GAL* genes where different yeast strains have independently lost the ability to utilize galactose owing to mutations in various genes of the GAL system (Warringer et al., 2011). The laboratory strain has a point mutation in *GAL2*, the West African strains have several large mutations in *GAL2* and *GAL4* genes, and the mosaic strains have mutations in *GAL3* (Liti, Carter, et al., 2009).

4 | INFERRING THE ROLE OF GENE–GENE AND GENE–ENVIRONMENT INTERACTIONS IN SHAPING THE GENOTYPE–PHENOTYPE MAP

The architecture of the genotype–phenotype map confers robustness to genetic and environmental perturbations while facilitating the fixation of variants beneficial in specific selection pressures (Siegal & Leu, 2014). While it is one of the fundamental long-standing questions in biology, understanding of the mechanisms underlying robustness has been difficult to deduce at both genetic and molecular levels. This is because of the technical limitations of measuring robustness in higher organisms, large sample sizes required to simultaneously measure the effect of multiple variants and complexity of the genomic architecture and population structure. GGI and GEI mapping studies, by refining the model of genotype–phenotype map, shine a light upon the mechanisms of robustness and evolvability, and the balance between the two (also see the Box).

The turning point in the theory of molecular evolution was uncovering of evidence that showed that the majority of the variants may not have an effect on the phenotype (ENCODE Project Consortium, 2012; Siegal & Leu, 2014). This could happen if the variants are indeed inconsequential to the phenotype or if their phenotypic consequences are buffered by other mechanisms (Siegal, 2013). It has been postulated that the majority of the genes within an organism contribute to this buffering, although empirical evidence exists for only a couple of cases (Siegal & Masel, 2012). Interactions of a variant with other loci as well as the environment, i.e. GGI and GEI, can play a key role in buffering the phenotypic consequences of the variant (Siegal & Leu, 2014).

With each replication event, new genetic variants are introduced that are then meiotically segregated in the population. While these variants arise independently, their influence on the phenotype is a combined outcome of the genetic and environmental background in which the variant is present. Also, since different populations experience disparate selective forces, and thus follow divergent evolutionary trajectories, fixation of a variant is dependent on the genetic background, i.e. the other genetic variants in a population (Gibson & Dworkin, 2004; Masel & Siegal, 2009; Masel & Trotter, 2010; McGuigan & Sgrò, 2009; Paaby & Rockman, 2014). As a result, often deleterious alleles are maintained in populations because their effects are suppressed in certain genetic backgrounds. This suppression or genetic buffering results in incomplete penetrance of the deleterious alleles. Even though most striking with respect to deleterious mutations, this heterogeneity of the phenotype is observed for variants with both positive and negative effects. While the effect of a variant is determined by the other variants present in linkage, generating mapping populations by crossing two strains delinks these linkages that can lead to a revelation of the individual variant effects (Liti & Louis, 2012).

One such phenomenon contributing to genetic buffering is the regulation of cryptic genetic variation, which refers to genetic variants that show their effects only in certain genetic backgrounds or environments and are phenotypically neutral in others (Gibson & Dworkin, 2004; Gibson & Reed, 2008; Masel & Trotter, 2010; Paaby & Rockman, 2014). Genetic buffering can be understood as a special manifestation of GGI and GEI, where the effects of not just a single locus, but a large number of variants depend on specific genetic backgrounds and environments. GGI and GEI mapping can be used to identify global modulators of genetic buffering (Paaby & Rockman, 2014; Schell, Mullis, & Ehrenreich, 2016).

Novel mapping strategies have identified variance QTL (vQTL) that regulate the phenotypic variance instead of only the overall mean, i.e. they govern the phenotypic manifestation of other genetic variants present in the individuals (Fraser & Schadt, 2010; Rönnegård & Valdar, 2011, 2012). While these genetic variants are able to manifest phenotypically in the presence of one allele of the vQTL, they are buffered in the presence of the other allele (Figure 1E). Many conventional additive loci with a strong effect on the population mean also have differential effects on the phenotypic variance (McGuigan & Sgrò, 2009; Yadav, Dhole, & Sinha, 2016a). Additionally, multiple vQTL interact with each other to regulate this phenotypic manifestation of other variants, in an environment-specific manner (Yadav et al., 2016a), suggesting that differential regulation of genetic buffering could be a potential contributor to other central phenomena such as GEI. For instance, the abundance of small-effect GEI can be explained by differential buffering of these variants across two environments. These loci could potentially be the global regulators of genetic buffering.

This influence of differential buffering on GEI indicates that in order to gain a comprehensive understanding of effects of loci across environments, it is not sufficient to focus on either a single or multiple environments independently (Bloom et al., 2013, 2015; Perlstein et al., 2007). This is demonstrated by a study that attempts to map loci regulating the plasticity of yeast growth across multiple environments (Yadav et al., 2016b). Plasticity refers to the ability of a genotype to show diverse phenotypes in different environments, which facilitates adaptation and helps populations escape extinctions in novel environments, thereby driving evolution. While some loci that affect plasticity are also pleiotropic, others have a significant effect on phenotypic plasticity without being significant in any environment independently (Yadav et al., 2016b). These results indicate that to understand the molecular basis of adaptation it is important to study multiple strains and many environments together and not in isolation.

5 | FUTURE DIRECTIONS

The study of complex traits in yeast, especially GGI and GEI, has provided insights into complex features of the genotype–phenotype map, which would have been difficult in other systems, for example, multilocus interactions, plasticity QTL and background dependence, and consequently the molecular mechanisms of adaptation and evolution. However, the field of complex traits in yeast is surprisingly lacking in gene-level resolution of the loci involved in GGI and GEI. This hinders identification of biological mechanisms contributing to or affected by such interactions. One of the underlying causes for this lack of gene-level resolution is the primary use of linkage mapping in identifying these loci, which identifies large haplotypes containing multiple genes. A single or multiple variants in same or different genes can contribute to the effect of the causal locus (Steinmetz et al., 2002). This lack of resolution often hampers the accuracy of identification and mechanistic understanding of GGI and GEI. A

perceived antagonistic GEI could be a result of independent, opposite effects of two variants present in the physical linkage, such that they are identified within the same locus. One of the future challenges in the study of complex traits in yeast is attaining a gene and variant level resolution of GGI and GEI, which is of utmost priority to understand the mechanistic basis of these interactions. Variant level resolution can be achieved by fine mapping, increasing the number of segregants used for linkage mapping or performing GWAS using a large number of yeast strains.

Studies in yeast have challenged the notion of complex vs. Mendelian traits and demonstrated a strong population and environment dependence of such categorization, i.e. the mode of inheritance of a trait depends on the population and the environment in which the phenotype is measured. Gene and variant level resolution of the loci identified for different traits in yeast will shed light upon the relative contribution of coding and regulatory variants in regulation of different traits. A highly simplified conclusion from over 15 years of mapping of human traits and diseases is that Mendelian diseases are caused by coding variants, whereas complex traits highly susceptible to the effect of the environment and the background are primarily regulated by non-coding variants (Hindorff et al., 2009). Even though yeast, for the most part, lacks enhancers, it contains highly specialized promoters, non-coding variants within which contribute to phenotypic variation (Salinas et al., 2016). GGI and GEI are believed to be rampant in both complex and many Mendelian traits in humans to different degrees, resulting in variable expressivity and incomplete penetrance. However, the loci contributing to this phenotypic heterogeneity are difficult to identify because of low power to map GGI and GEI in human traits. Studies in yeast have demonstrated the power of the model organism to identify a range of GGI and GEI. The next steps in the field would be to integrate the effects of these interactions on phenotype with effects on different biomolecules such as mRNA, protein and metabolites to understand the molecular mechanisms underlying GGI and GEI.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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