Finding the sources of missing heritability in a yeast cross

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- GWAS studies have been extremely successful in identifying loci associated with many complex traits
- However large proportion of heritable contribution to trait variation is still "missing"



• Is it possible to find the entire "hidden heritability", if we resequence everybody?



- Cross between two yeast strains (S. cerevisae) lab strain and wine strain
- Large panel on yeast segregants were genotyped and phenotyped individually – 1,008 prototrophic haploid segregants were used to estimate heritability and detect underlying loci
- 46 phenotypes, with strong heritable component, were measured

Study design

Spearman correlation coefficients for all pairs of traits

Corgo., Pied Zoocin Neomycin Cathene Menadone YPO. SPC Cathene Menadone YPO. SPC Ed. Befarenine Cathene Damido Merganene Merganene Merganene Merganene Cotel., Chorda Merganene Cotel., Chorda Merganene Cotel., Chorda Merganene Cotel., Chorda Merganene Cotel., Chorda Merganene Cotel., Chorda Merganene Cathene Cotel., Chorda Mercal Cathene Cat	
Paraquat 19 28 8 15 5 3 -7 0 -9 -13 8 12 0 9 9 -4 -2 -7 -3 1 -5 -2 -3 -5 2 8 18 15 12 20 14 -2 -6 5 7 0 1 1 10 5 4 -7 -1 -7 2	 ``
Congo_fied 34 2 -6 11 4 4 5 9 9 15 18 5 15 21 1 3 6 2 -2 -22-16-18-2 -7 3 18 21 27 31 1 -10-9 -9 -1 -12-15-17-2 -10-5 -2 -6 -10-15	
Zeocin 20 5 18 21 6 15 1 15 2 0 8 25 26 7 -8 0 5 16-12 0 -19-9 -3 -7 18 23 15 27 4 -1 -20-16 -1 -19-20-19 -2 -6 -8 -1 -4 -8 -13	
Neomycin 13 10 23 20 10-20-17-2-12-8 6 -20 10 -4 1 7 18 -1 8 2 0 -2 -4 2 18 1 2 3 -3-11-4 -1 -4-12-13-2 -9 -7 5 2 4 -1	
Ceptadin 16 15 16 -5 7 -1-11 1 -16-3-29-2 15-11-1 10 9 7 20 2 10 24 9 26 27 14 22 14 7 10 -1 13 19 17 12 15 14 10 4 4 3	-0.8
Caffeine 42 27 11 18 16 2 -1-11 9 -9 12 -2-16-1 -1 -6 12 -1 -2 14 4 6 29 17 13 15 11 1 -8-10-7 -4 -4 -5 2 0 14 1 -5-19	
Menadione 12 -8 5 7 -3-2034 4 15-12 0 4 -1 -8 3 -7 -23 1 -5-1027 -7 -4 9 -9-20-27-20-18-22-25-17-18-24 14 0 -4-22	
YPD 37C 14 -6 -4 5 -9 42 13 3 11 -9 -5 2 -10 -9 -4 -1 -19 4 -10 -18 20 -15 -15 9 -11 -32 -34 -48 -20 -35 -37 -36 -38 -40 10 -2 -15 -33	
E6_Berbarnine 24 24 21 1 -2 16 6 8 7 1 2 -10 -4 0 -6 -2 -2 -15 -2 -2 -9 -7 6 -1 -6 -18 -13 -17 -19 -14 -14 -17 -14 3 1 -1 -4	-0.6
Cycloheamide 30 3 1 0 -2 -7 -3 6 -5 5 -19 -2 -6 2 11 4 14 7 7 24 16 15 9 16 3 -7 2 7 13 0 9 8 8 1 6 -3	
Damoe 5 7 25 15 25 12 10 3 2 4 7 -6-2-5 0 0 14 5 7 3 3 9 4 3 19 5 6 2 11 6 11 16 7 3 1	
Manganese_suffate 5 0 19 3 -6 -2 8 -7 -16 -1 -15 -7 4 -10 -1 6 -1 -6 -5 -6 -5 -6 -5 -13 -8 -4 -16 -20 -13 -12 -12 9 11 4 -1	
Hankamyon -3 3 11 -5 6 7 -3 -13 -9 -7 1 5 7 5 10 7 12 12 4 0 3 1 4 1 7 6 12 10 8 1 3 -1 8	0.4
moundations (Add 19 12 1 12 9 -113 7 8 -9 -3 -4 -1 18 -15 -5 10 -7 6 23 23 36 13 16 15 22 21 20 -4 -7 5 22	-0.4
MOO - 1 - 2 - 4 - 2 -	-0.2
Cobalt Chloride 1a 91 7 1 0 13 10 8 4 1 8 10 3 16 10 17 5 50 50 40 7 3 3 10	
Concer 37 17 4 4 17 1 4 3 4 17 1 3 4 16 15 20 10 26 26 26 27 18 27 18 10 15 7 19	
Libium Chicrole 15 8 4 3 6 3 -11 6 10 22 34 14 23 21 16 21 11 15 13 8 13 0 8	- 0
YNR ph3 27 11 21 17 15 14 11 12 23 17 16 15 22 26 24 17 21 19 5 18 13 18	
YNDph8 8 5 13 8 22 23 5 16 22 14 5 14 15 14 10 10 16 0 16 5 10	
Mallose 18 12 17 23 14 23 18 11 9 6 21 22 24 17 20 21 7 7 4 6	
Calcium_Chloride 27 24 44 24 30 23 20 31 29 34 41 39 38 40 38 28 19 12 23	
VPD:4C 35 41 55 24 23 19 27 36 27 32 29 47 38 42 10 6 9 27	-0.2
4-Hydroxybenzaldehyde 51 49 29 19 9 3 9 30 12 6 24 16 16 36 26 6 11	
SDS 57 35 26 18 25 17 25 36 31 39 34 41 18 11 6 15	
YPD:15C 20 13 23 17 15 17 18 20 32 23 29 7 9 6 14	
Galactose 42 21 26 20 25 39 43 42 36 40 24 10 9 19	-0.4
Mannose 29 34 29 38 44 37 40 32 40 21 14 3 18	
6-Azaaracii 33 31 32 34 36 30 35 33 17 26 19 31	
Magnesium_Chloride 36 37 49 48 42 49 44 12 5 13 32	
Ethanol 45 50 44 57 48 53 21 16 14 43	-0.6
Raffwore 51 48 50 51 48 35 31 14 35	
Lactate 82 73 74 80 13 7 20 37	
Lactose 65 67 72 8 3 20 35	
Xylose 25 m 20 12 19 41	
Service 16 5 16 32	-0.8
1000000 15 / 15 00	
E-Basedera a	
3-Hadrocytome	1

- proportion of phenotypic variance attributable to genetic variance
- Broad-sense heritability: all the genetic contributions to a population's phenotypic variance including **additive**, dominant, and **epistatic** (multi-genic interactions), GxE

$$H^2 = \frac{Var(G)}{Var(P)}$$

• Narrow-sense heritability: additive effects only $h^2 = \frac{Var(A)}{Var(P)}$





Heritability of 46 yeast traits

Most additive heritability is explained by detected QTL





QTL detection for a complex trait (E6 berbamine)



Prediction of segregant trait values from QTL phenotypes



Cumulative phenotypic variance explained

Non-additive genetic variance explained by QTL-QTL interactions



- Up to 54% of genetic variations in GxG
- QTLxQTL interactions only describe small part of that variability most of it remains elusive
- Statistical power is lower for detecting interactions
- Interaction effects are expected to be smaller
- There might be high number of interactions with more than 2 loci

Genetic interactions



QTL effect sizes across all traits

- It is possible to find all the "hidden heritability" if the sample size is large enough as most of the genetic variance comes from many loci with small (but not infinitesimal) effects
- Gene-gene interactions play important role for some phenotypes (up to 50%) and two-locus interactions explain only minority of this contribution

Conclusions

References