Examining Genetic Background Effects on Canalization in D. melanogaster

Brandon mcintyre & rajat Bhargava

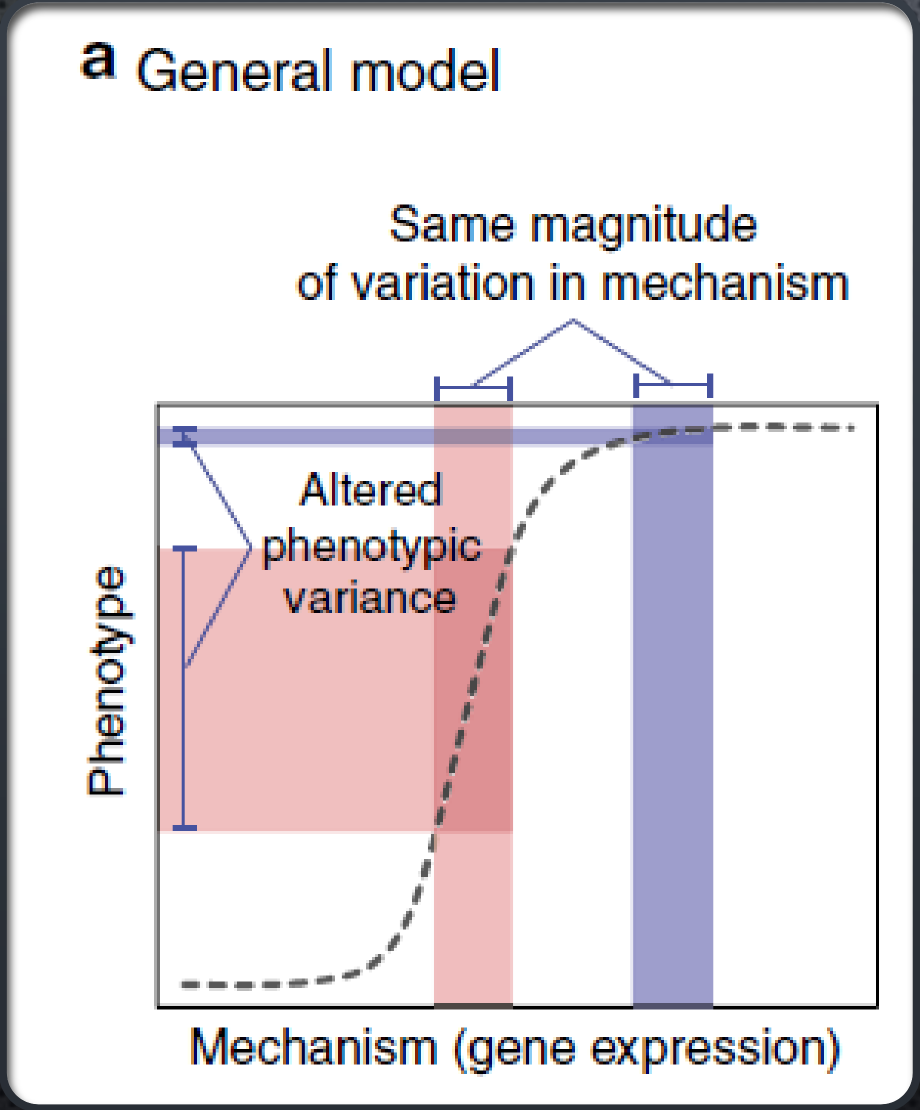
Presentation Outline

- Defining canalization
- Info about data set
- Biological questions
- Between line and within line variation
- are Log transformations appropriate here?
- Modeling & correlation plots

  -rank-reduced model

  -Markov chain monte carlo generalized linear mixed model (MCMCglmm)
- Next steps

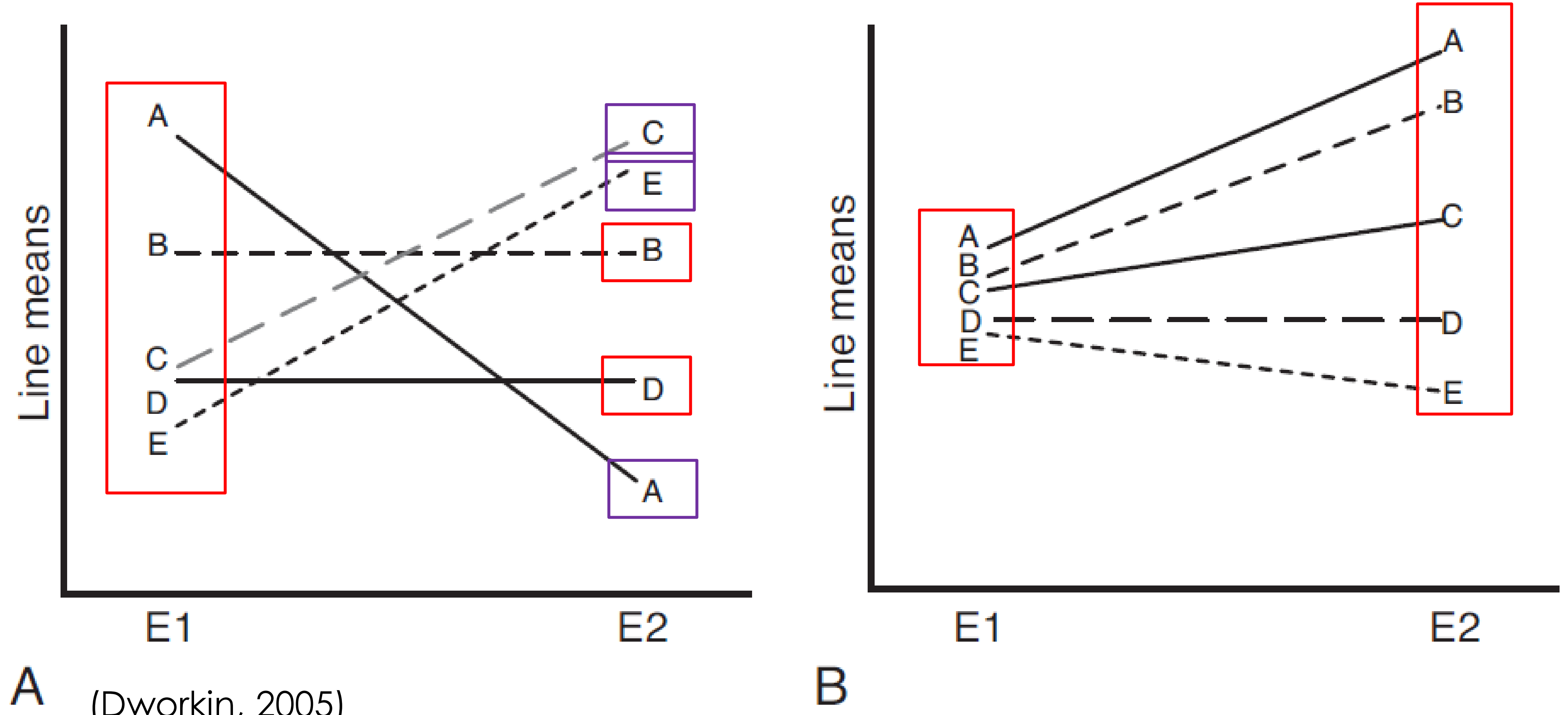
Defining Canalization



- Canalization: a process where the phenotypic variance of a trait is reduced when faced with a given perturbation.
- Characterized by non-linear sigmoidal relationship between gene activity and phenotypic effect
- No agreement on what defines variability for canalization
- Two main definitions
  1) Reaction norm of the mean (between line variation)
  2) Variation approach (within line variation)

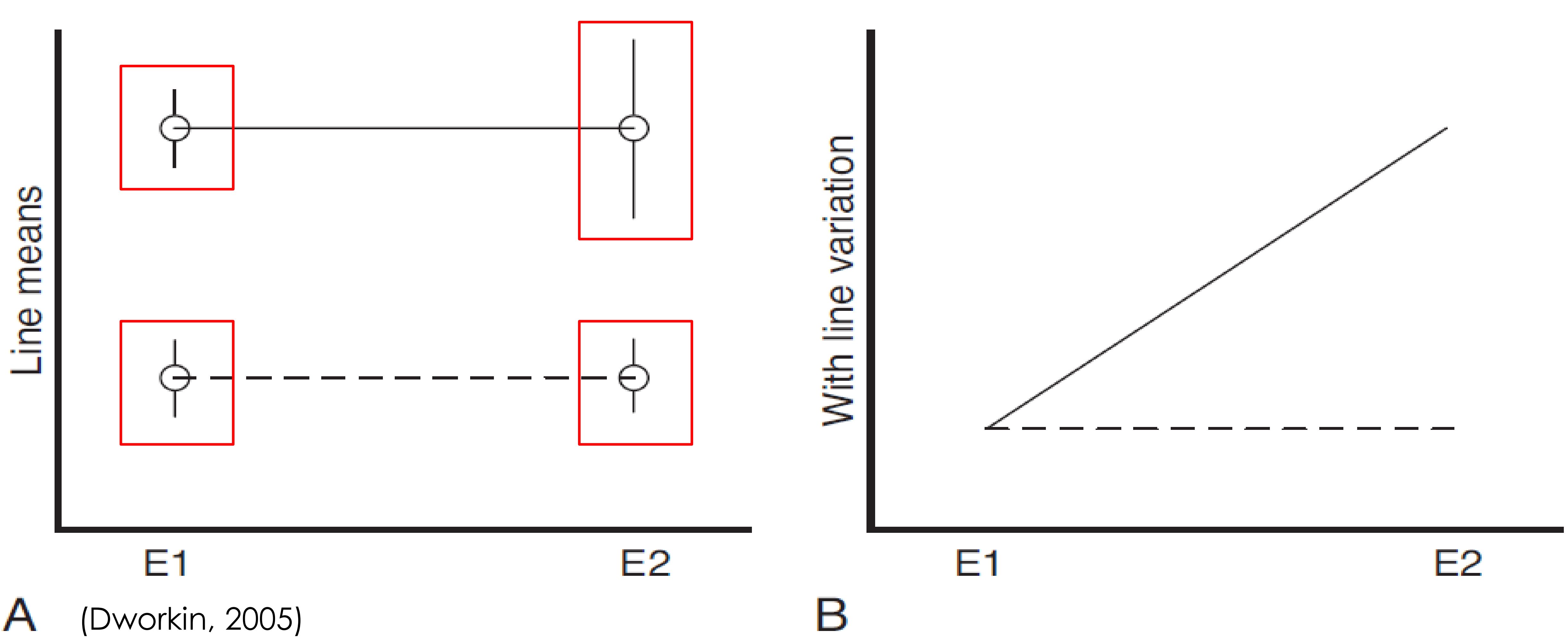
(Green et al. 2017)

REACTION NORM OF THE MEAN (BETWEEN LINE)



(Dworkin, 2005)

VARIATION APPROACH (WITHIN LINE)



(Dworkin, 2005)

OUR DATASET

- 5496 INDIVIDUALS
- S8 MUTANT ALLELES, 2 ALLELEIC SERIES
- SCALLOPED: SD[29.1], SD[1]. SD[E3], SD[ETX4]. SD[58D]
- BEADEX: BX[1], BX[2], BX[3]
- 20 DGRP LINES
- 2 REPLICATE BLOCKS

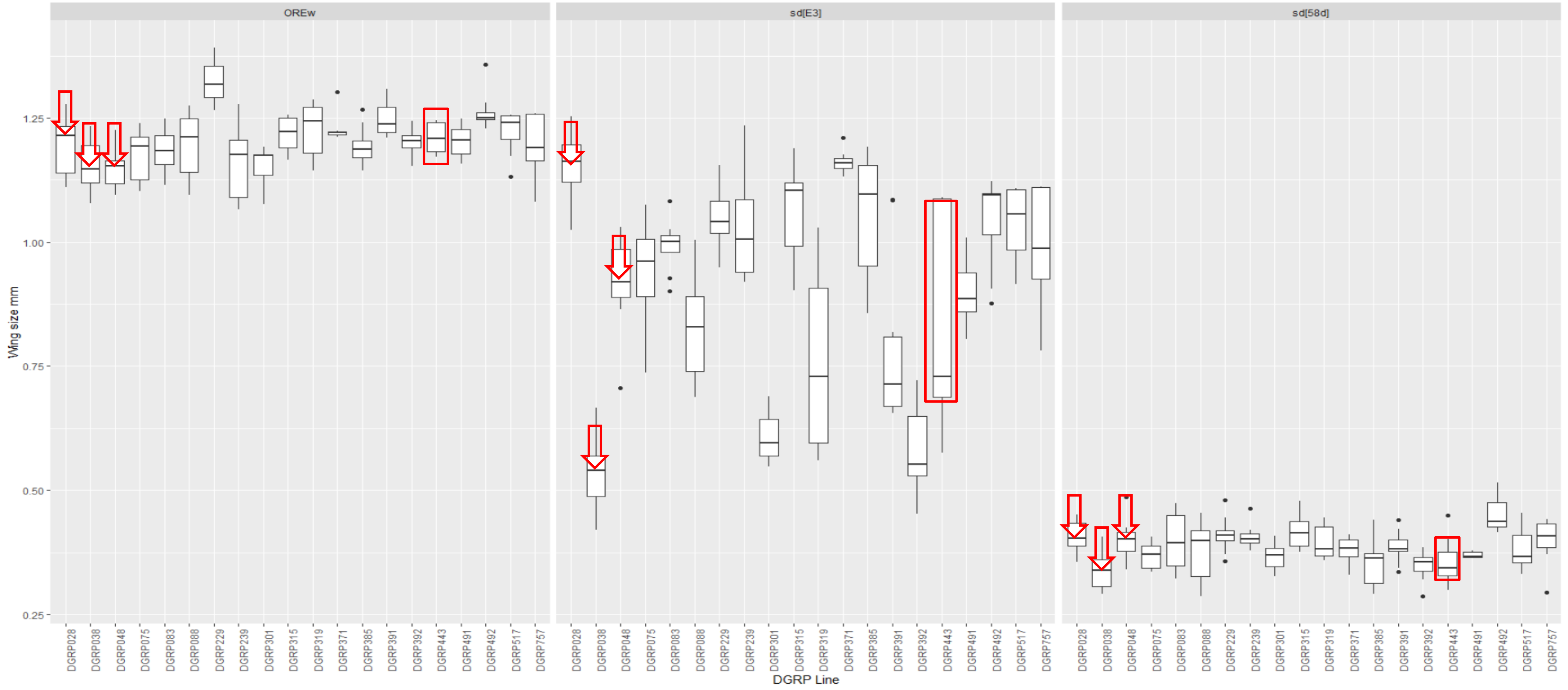
BIOLOGICAL QUESTIONS

- Our biological questions include:

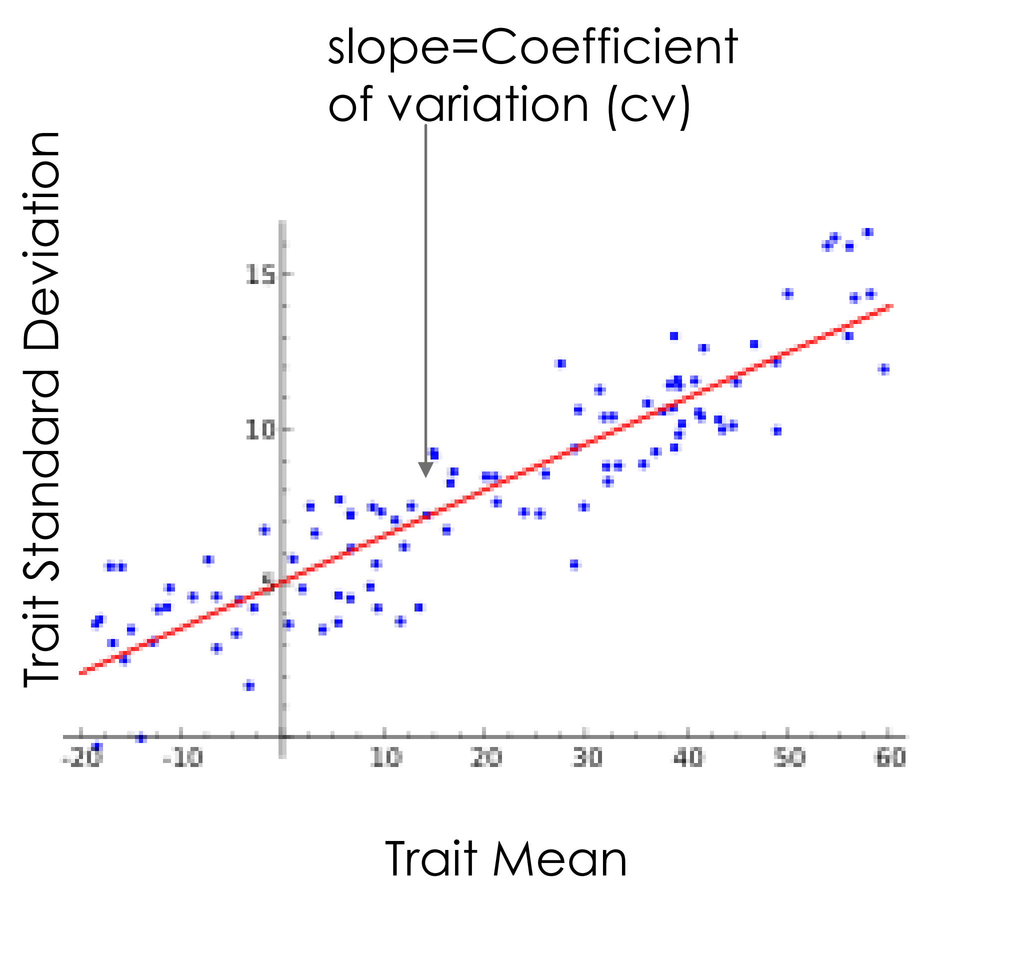
1) how the trait mean of wing size varies between DGRP lines crossed with different mutant alleles
2) How the variation around the trait mean of wing size varies between DGRP lines crossed with different mutant Alleles

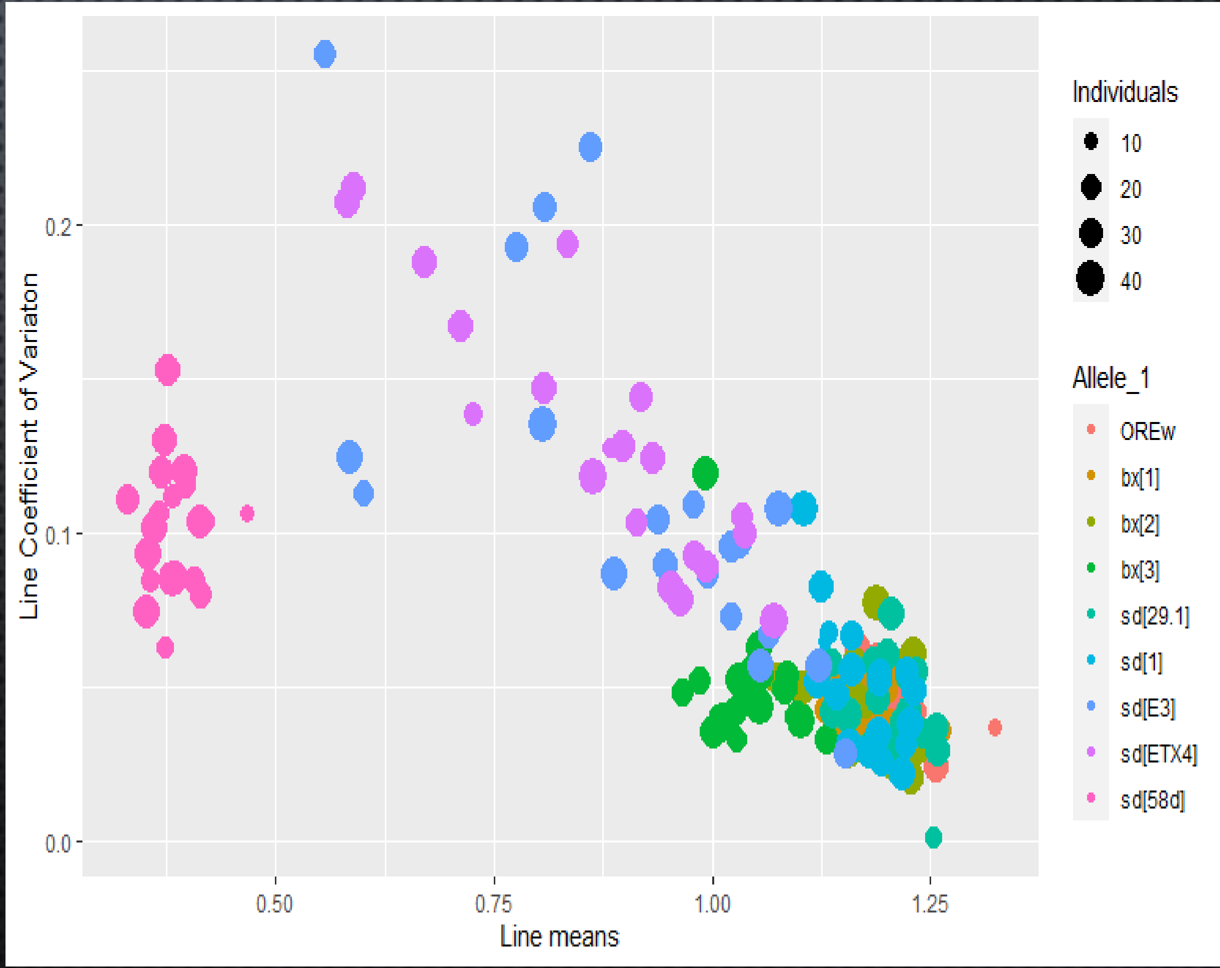
We hypothesize that mutant alleles with moderate phenotypic effects will display the greatest variability in mean wing size between dgrp lines crossed with mutant alleles. As well, they will display the greatest variability in within line wing size variability for dgrp lines crossed with mutant alleles.

BETWEEN LINE VARIATION AND WITHIN LINE VARIATION



TO USE THE LOG TRANSFORMATION, OR NOT TO USE THE LOG TRANSFORMATION?

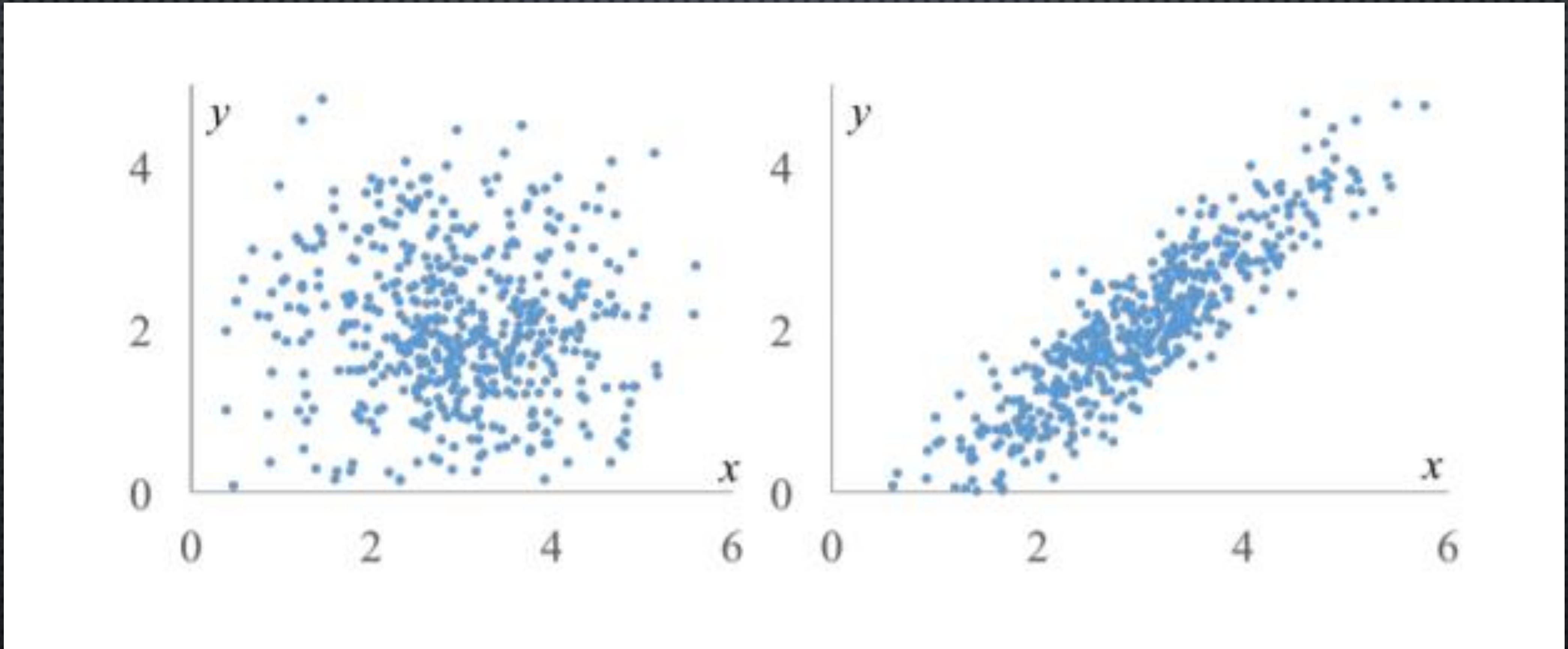




CALCULATING THE LEVENE'S STATISTIC

```
wing_table_lev_raw <- wing_table_clean %>%
  mutate (lev_stat = LeveneDeviates(y = wing_size_mm,
                                    group = Mutant:DGRP, med = TRUE))
```

COVARIANCE VS CORRELATION



VARIANCE-COVARIANCE PLOT

CORRELATION PLOT

COVARIANCE VS CORRELATION

COVARIANCE CAN BE DEFINED AS:

Cov(X,Y) = E[(X − E[X])(Y − E[Y])]

CORRELATION CAN BE DEFINED AS:

P(X,Y) = COV(X,Y) /(SQRT (VAR(X) VAR(Y))), WHERE X AND Y ARE TWO RANDOM VARIABLES

(Monroe, 2017)

GENERALIZED MIXED LINEAR MODEL: SINGULARITY ISSUE

$$C = \begin{bmatrix} 2.5 & 1.0 & 0 & 0 \\ 1.0 & 2.5 & 0 & 0 \\ 0 & \boxed{0} & 2.5 & 2.0 \\ 0 & 0 & 2.0 & 2.5 \end{bmatrix}$$

VARIANCE-COVARIANCE MATRIX

$$Correlation = \begin{pmatrix} 1 & 0.80 & 0 \\ 0.80 & 1 & \pm 0.60 \\ 0 & \pm 0.60 & 1 \end{pmatrix} \Rightarrow Cholesky = \begin{pmatrix} 1 & 0 & 0 \\ 0.8 & 0.6 & 0 \\ 0 & \boxed{\pm 1} & 0 \end{pmatrix}$$

CORRELATION MATRIX

("Chapter 3…", n.d.)

MODELS THAT SUFFER FROM SINGULAR FIT

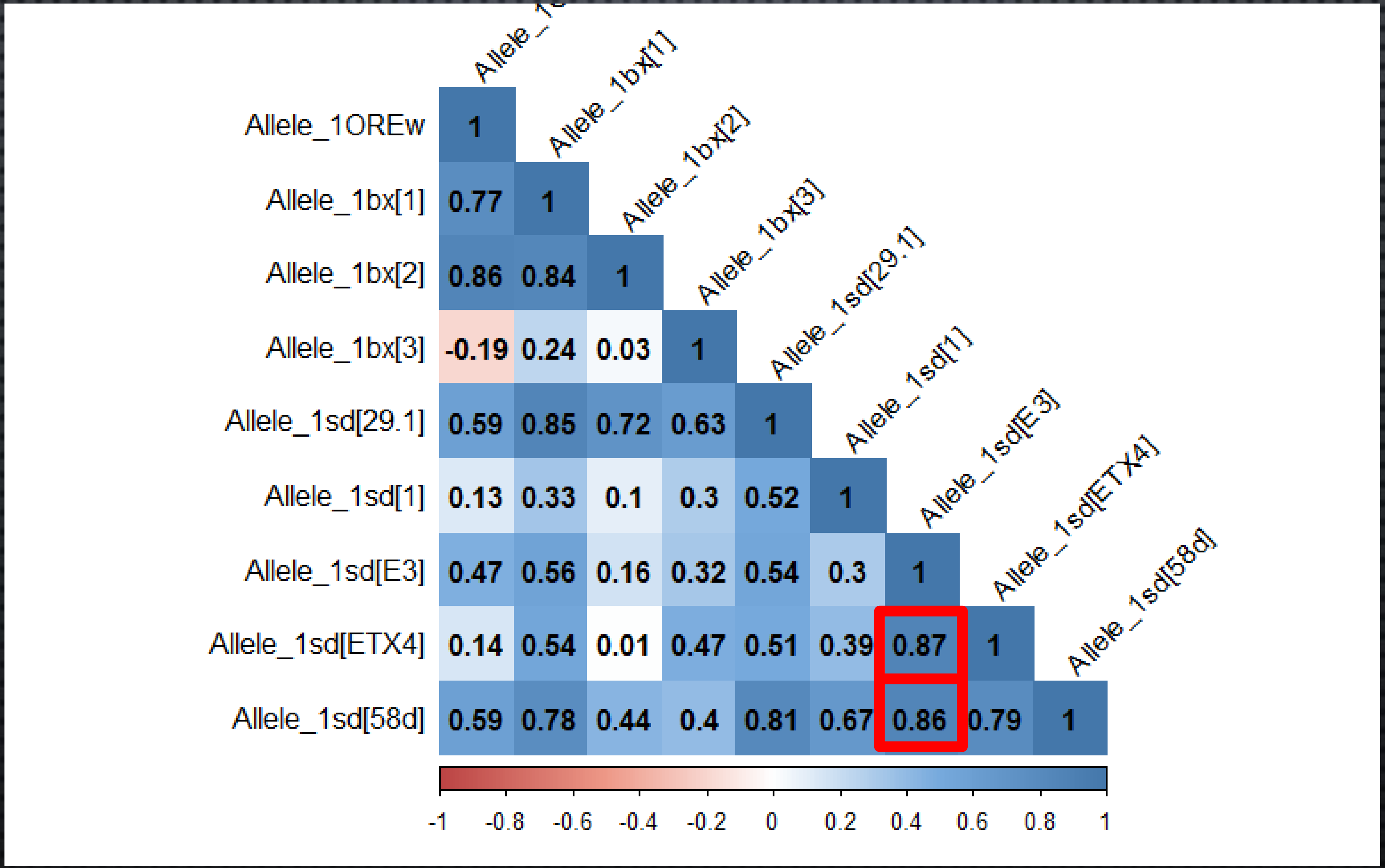
```
lmer(wing_size_mm ~ Mutant + (0 + Mutant | DGRP)
     + (1|Replicate),
     data = wing_table_clean)
```

```
lmer(wing_size_mm ~ Mutant + (0 + Mutant | DGRP)
     + Replicate,
     data = wing_table_clean)
```

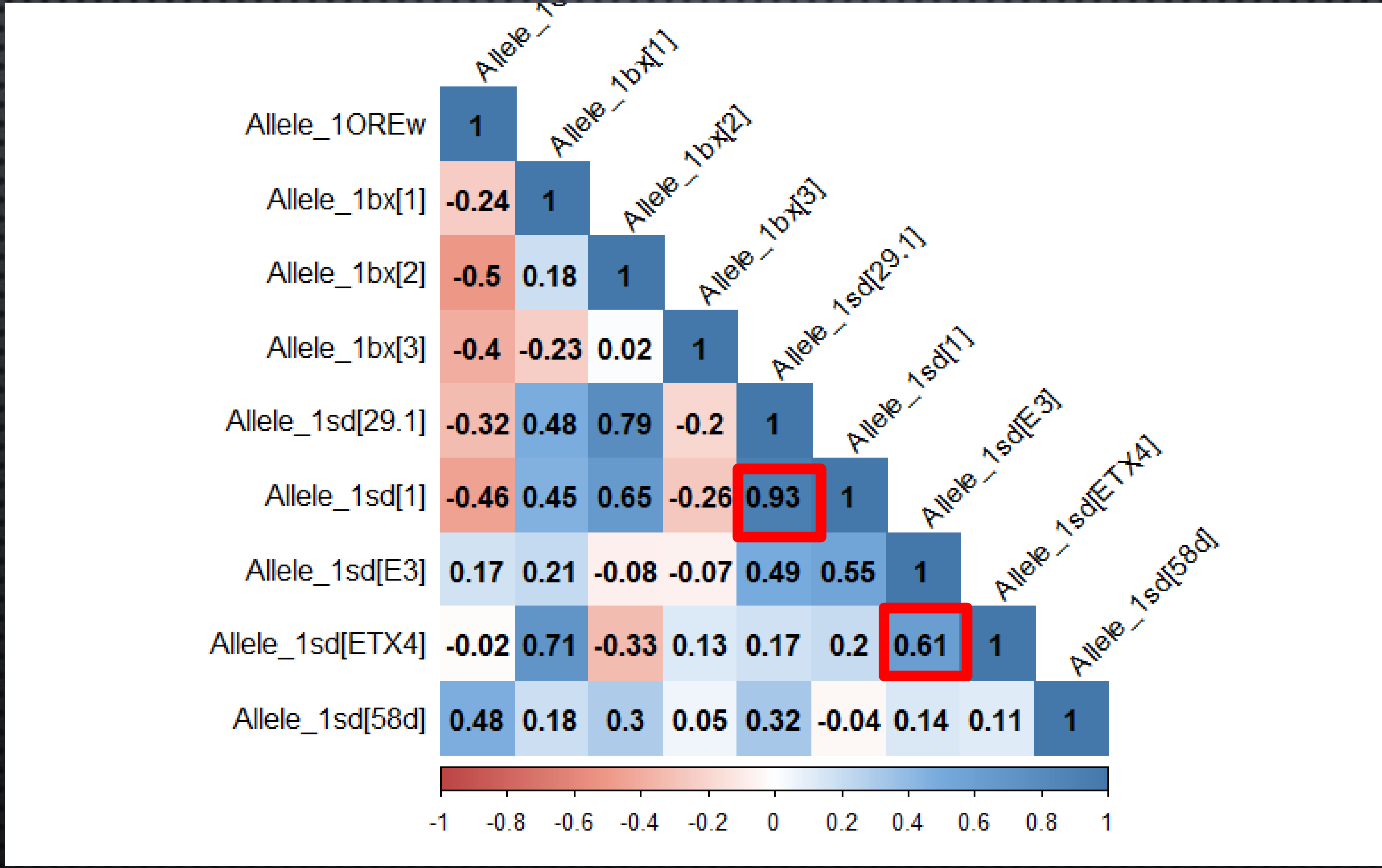
EUREKA!: RANK-REDUCED MODEL

```
glmmTMB(wing_size_mm ~ Allele_1 + rr(0 + Allele_1 | WT_Background,5) +
            Replicate,
        data=wing_table_clean,
        control=glmmTMBControl(optCtrl=list(iter.max=1000,eval.max=1000)))
cov2cor(VarCorr(m5)$cond[[1]])
```

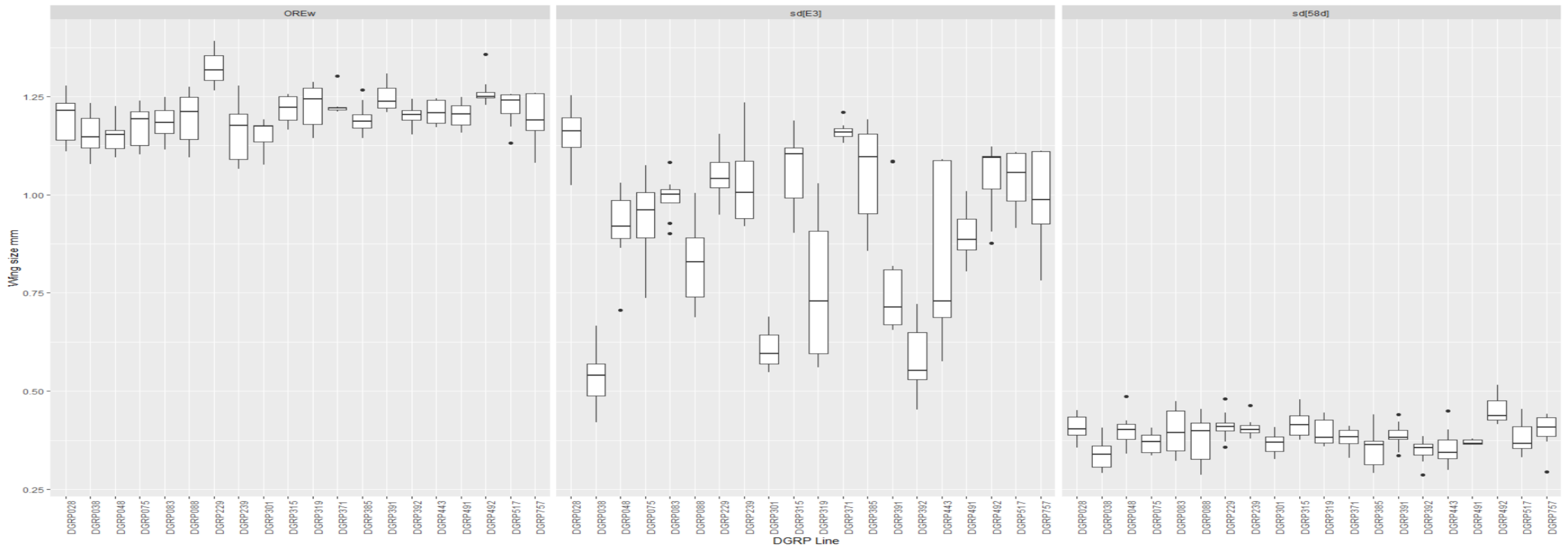
CORRELATION PLOT FOR BETWEEN LINE VARIATION



WITHIN LINE VARIATION (USING LEVENE STAT)



SHORTCOMINGS OF THE RANK-REDUCED MODEL



- Based on this graphical depiction, it appears as though the residual variation is different between the different groups

SHORTCOMINGS OF THE RANK-REDUCED MODEL

```
Random effects:
 Groups    Name            Variance  Std.Dev.
 DGRP      mutantOREw      0.0096997 0.09849
           mutantbx[1]     0.0101421 0.10071
           mutantbx[2]     0.0099196 0.09960
           mutantbx[3]     0.0106359 0.10313
           mutantsd[29.1]  0.0102938 0.10146
           mutantsd[1]     0.0082081 0.09060
           mutantsd[E3]    0.1029471 0.32085
           mutantsd[ETX4]  0.0458258 0.21407
           mutantsd[58d]   0.0001753 0.01324
 replicate (Intercept)     0.0114822 0.10715
 Residual                  0.0165275 0.12856
```

- This model assumes that residual variation is the same amongst the different groups, when we are in fact interested in looking at variation in residual variation (within line variation)

MARKOV CHAIN MONTE CARLO GENERALIZED LINEAR MIXED MODEL (MCMCGLMM)

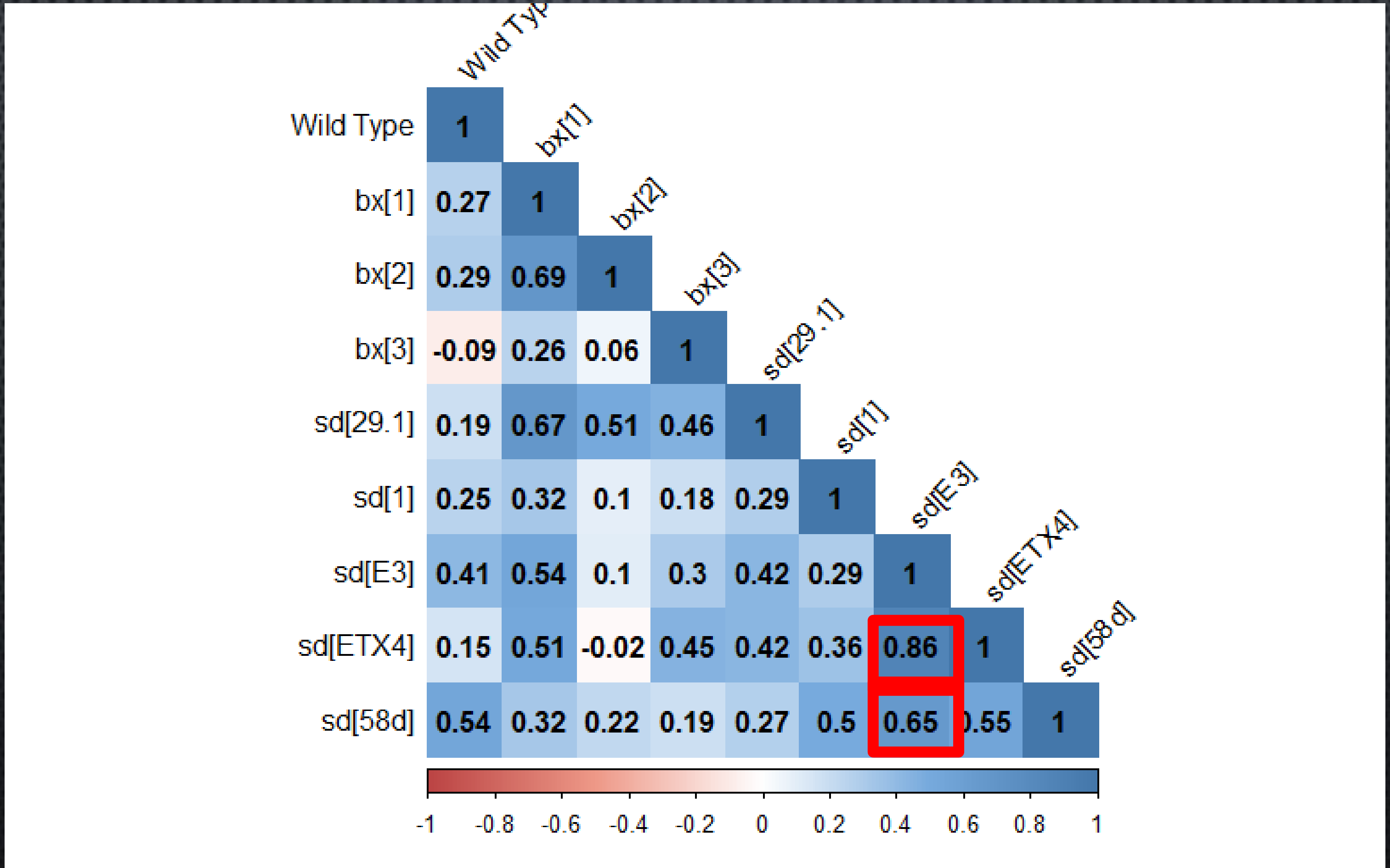
- Uses a Bayesian approach
- Does not assume that residual variances are the same amongst all of the different groups

```
prior <- list( R = list(V=diag(9)/9, nu=0.004),
               G = list(G1=list(V=diag(9)/9, nu=0.004)))

summary(MCMCglmmmTotal)

MCMCglmmmTotal <- MCMCglmm(fixed = wing_size_mm ~ 1 + Allele_1,
                           random =~ us(Allele_1):WT_Background,
                           rcov = ~idh(Allele_1):units,
                           data = wing_table_clean, prior=prior,
                           nitt = 20000, burnin = 5000, thin = 10)
```

BETWEEN LINE VARIATION CORRELATION PLOT FOR MCMCGLMM



Next Steps

- Creating AIC models to compare the two different models types that we've created
- Plotting confidence intervals
- Doing what we've done so far with both allelic series separately

REFERENCES

Chandler, C. H., Chari, S. & Dworkin, I. Does your gene need a background check? How genetic background impacts the analysis of mutations, genes, and evolution. *Trends Genet.* **29**, 358–366 (2013).

Chandler, C. H. *et al.* How well do you know your mutation? Complex effects of genetic background on expressivity, complementation, and ordering of allelic effects. *bioRxiv* 1–25 (2017) doi:10.1101/139733.

Chapter 3: Introduction to Brownian motion. (n.d.). Retrieved April 13, 2021, from https://lukejharmon.github.io/pcm/chapter3_bmintro/

Dworkin, I. CHAPTER 8 - Canalization, Cryptic Variation, and Developmental Buffering: A Critical Examination and Analytical Perspective, Editor(s): Benedikt Hallgrímsson, Brian K. Hall, Variation, Academic Press, 2005, Pages 131-158, ISBN 9780120887774, https://doi.org/10.1016/B978-012088777-4/50010-7.(https://www.sciencedirect.com/science/article/pii/B9780120887774500107)

Félix, M. A. & Barkoulas, M. Pervasive robustness in biological systems. *Nat. Rev. Genet.* **16**, 483–496 (2015).

Green, R. M. *et al.* Developmental nonlinearity drives phenotypic robustness. *Nat. Commun.* **8**, (2017).

Monoe, W. (2017, July 21). Covariance and Correlation. Retrieved April 13, 2021, from
WADDINGTON, C. Selection of the Genetic Basis for an Acquired Character. *Nature* **169**, 625–626 (1952). https://doi.org/10.1038/169625b0

https://web.stanford.edu/class/archive/cs/cs109/cs109.1178/lectureHandouts/150-covariance.pdf