

Non-additive extreme effects of gene expression on anthropometric traits

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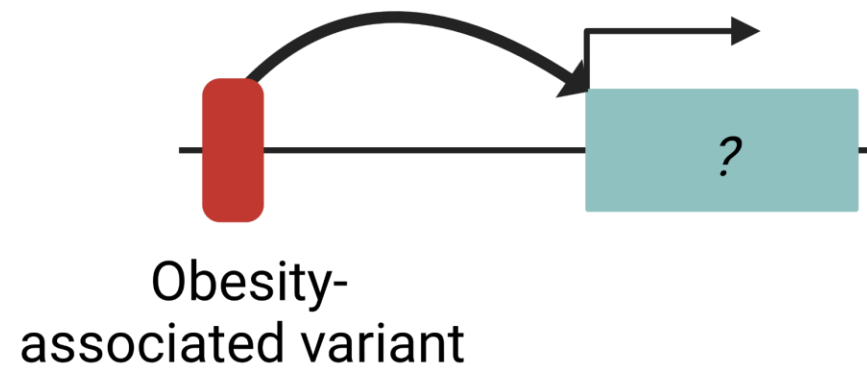
Disclosure

I am currently a full-time employee of Roche

Genetic effects on molecular traits

- Hundreds to thousands of genetic variants associated with complex traits
- > 90% of disease-associated variants in non-coding parts of the genome and of uncertain function
- eQTL mapping to find genetic variants with effects on expression identity intermediate processes underlying the mechanism

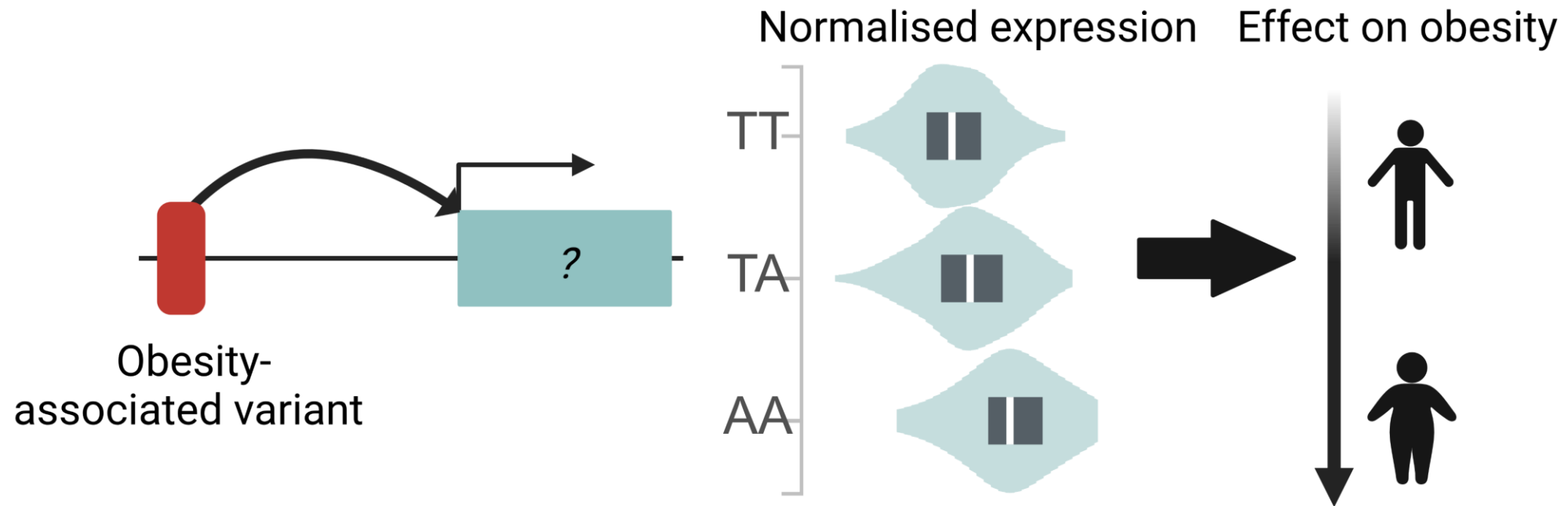
Genetic effects on molecular traits



Effect on obesity

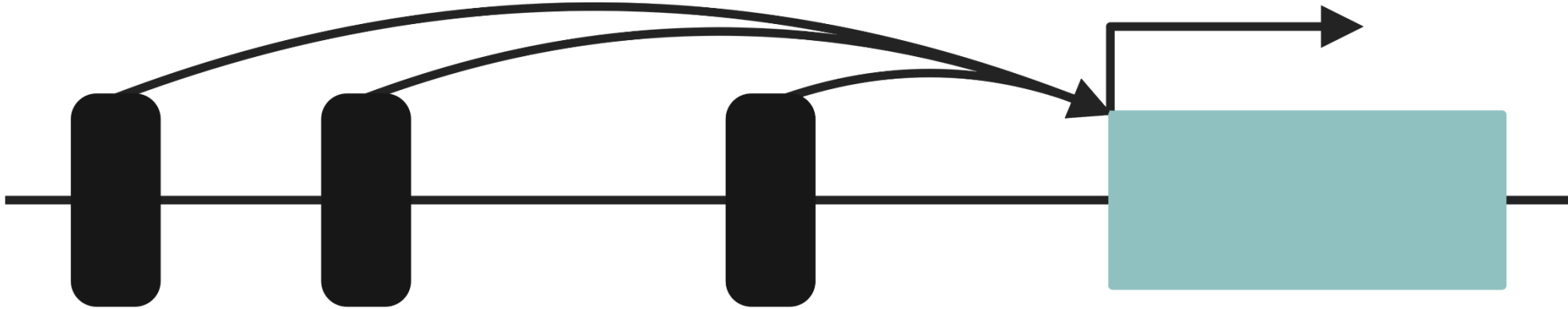


Genetic effects on molecular traits



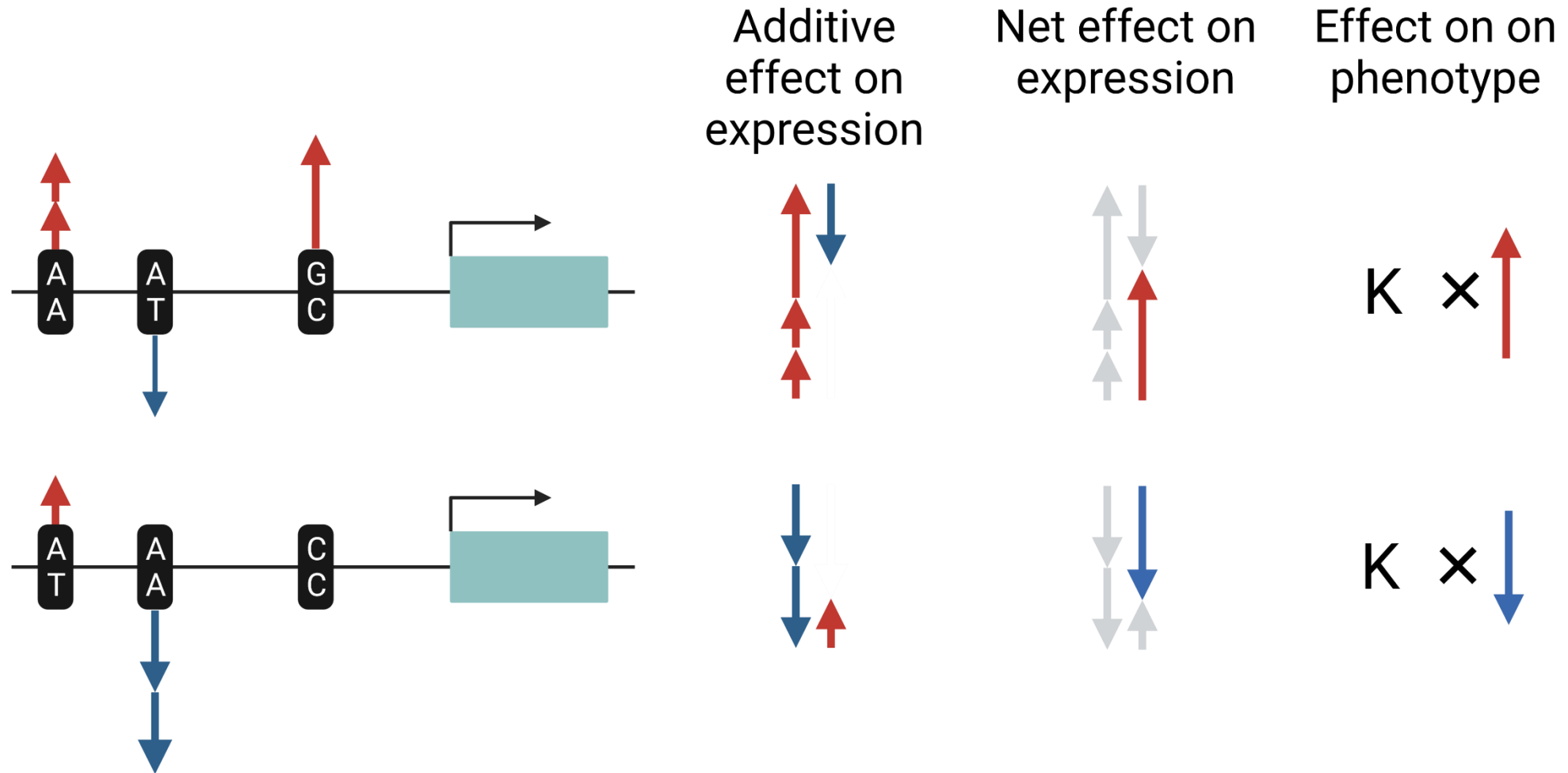
*Adapted from GTEx portal

Many genes are regulated by multiple eQTLs



When multiple eQTLs regulate expression of a causal gene we expect their effect on disease risk to be consistent

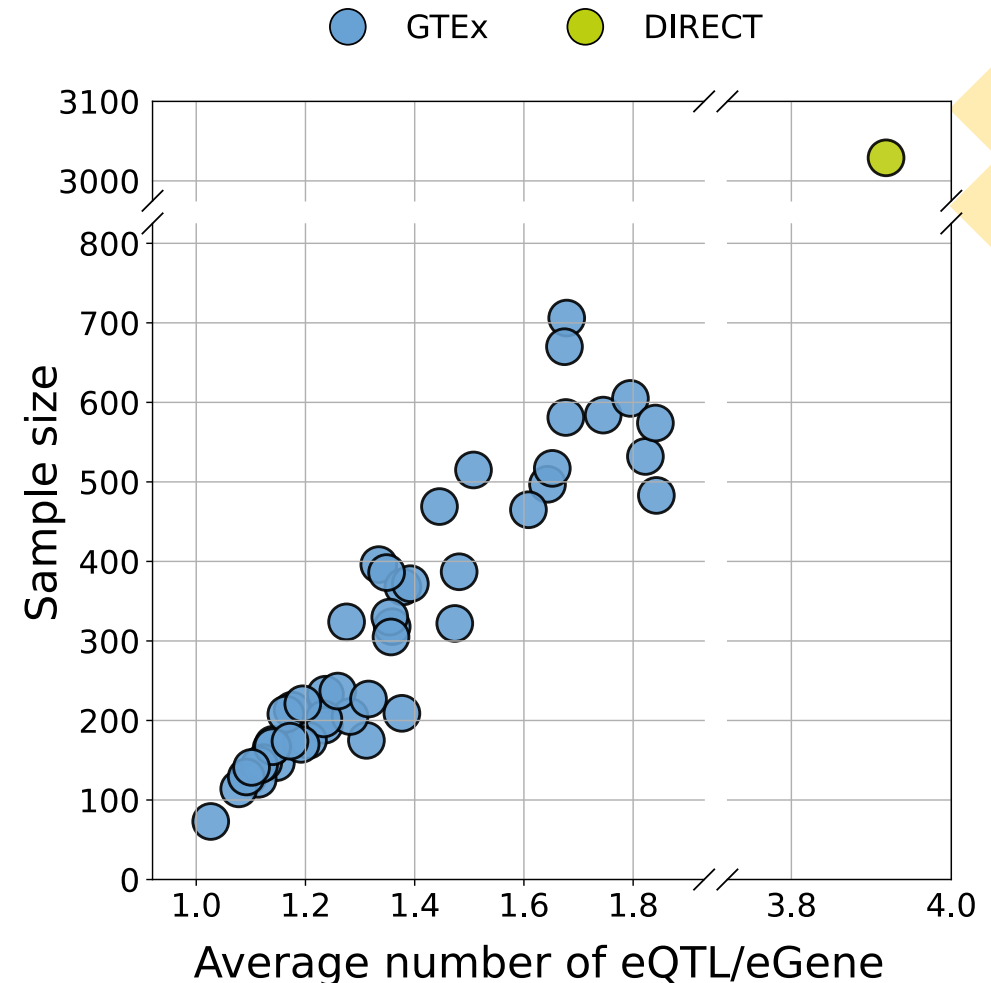
Additive genetic effects on gene expression



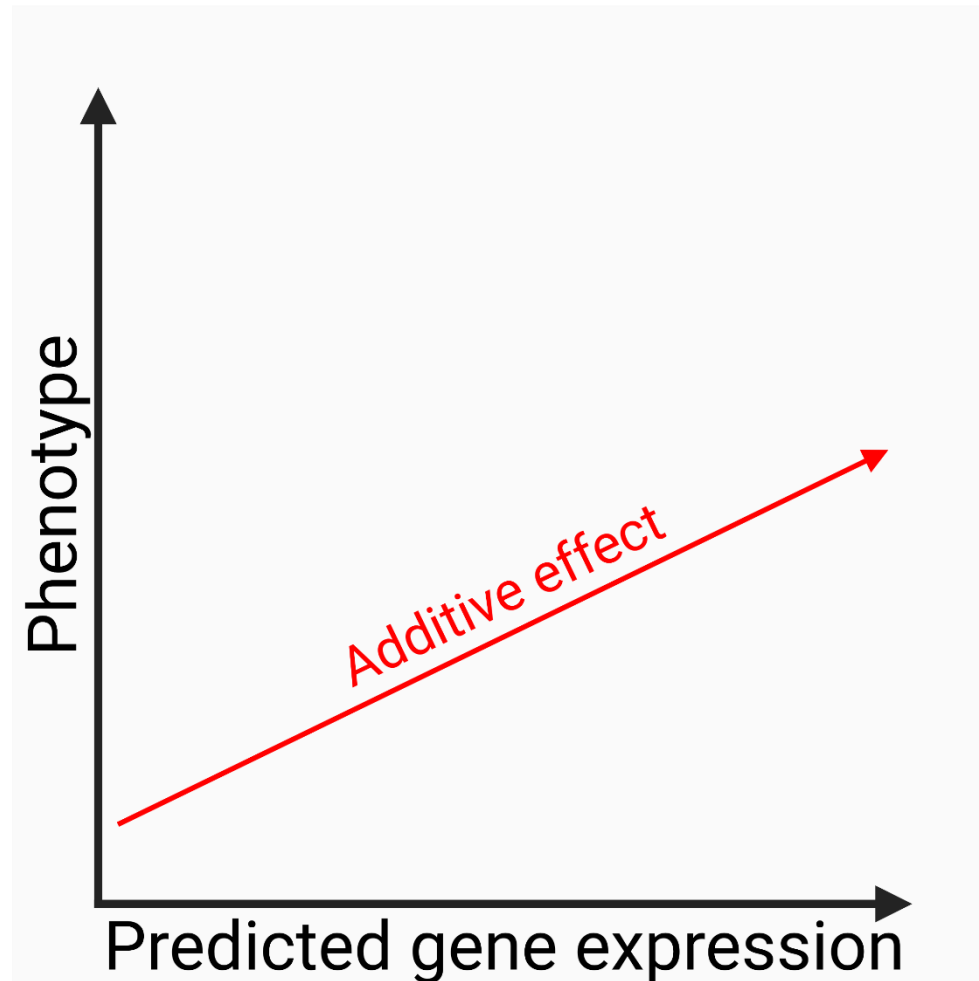
Multiple eQTLs help to find mediating genes

- Methods using intermediate phenotypes to identify causal genes rely on this assumption of additive proportional effects (*e.g.* multi-instrument MR, TWAS)
- In DIRECT (whole blood)¹
 - At least one significant genetic effect on expression in ~95% protein coding genes (*i.e.* eGenes)
 - 2/3 of genes with 2+ eQTLs

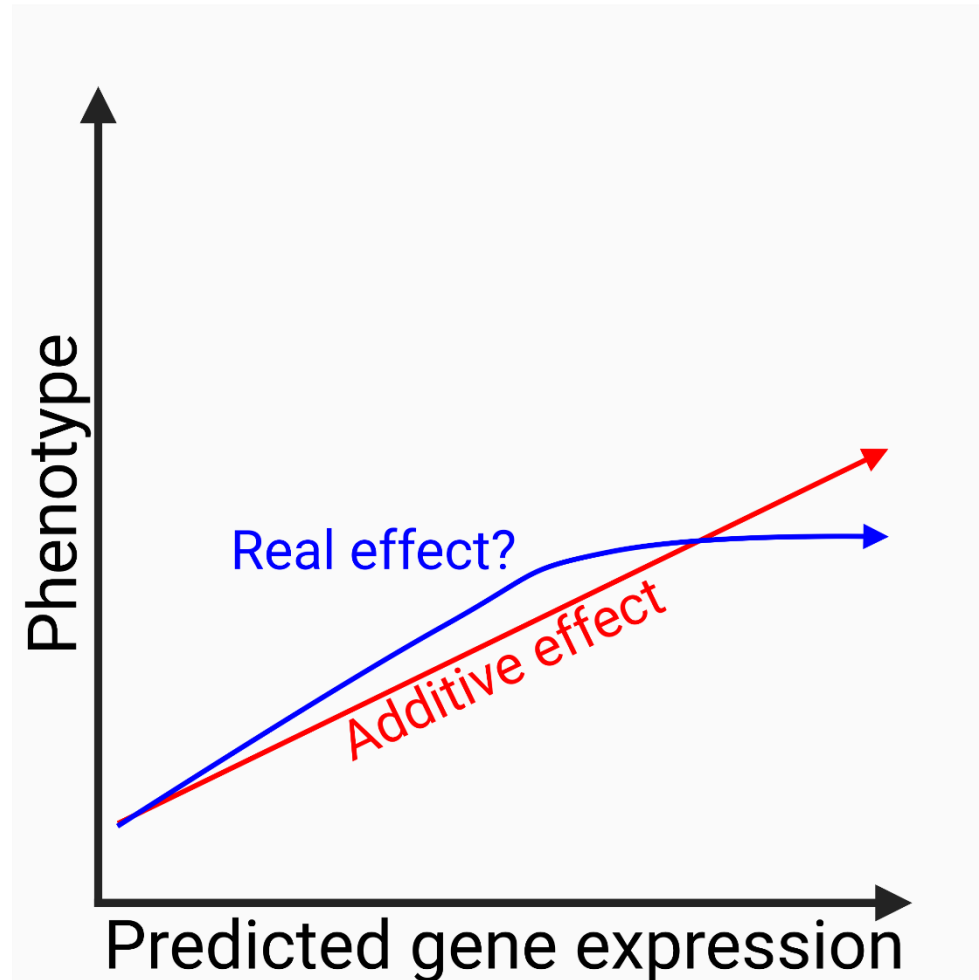
1: Viñuela *et al*, 2021 medRxiv



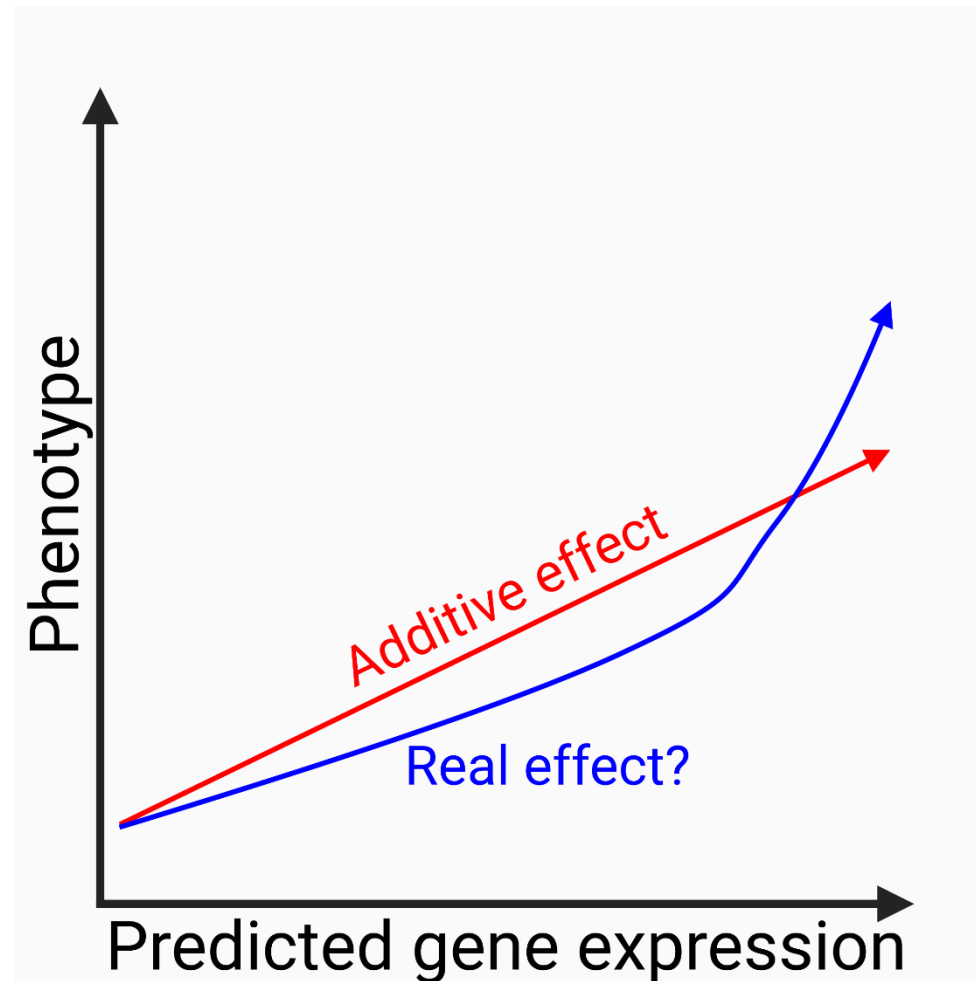
Additive genetic effects on gene expression (TWAS model)



Additive models can miss the relation between expression and phenotype

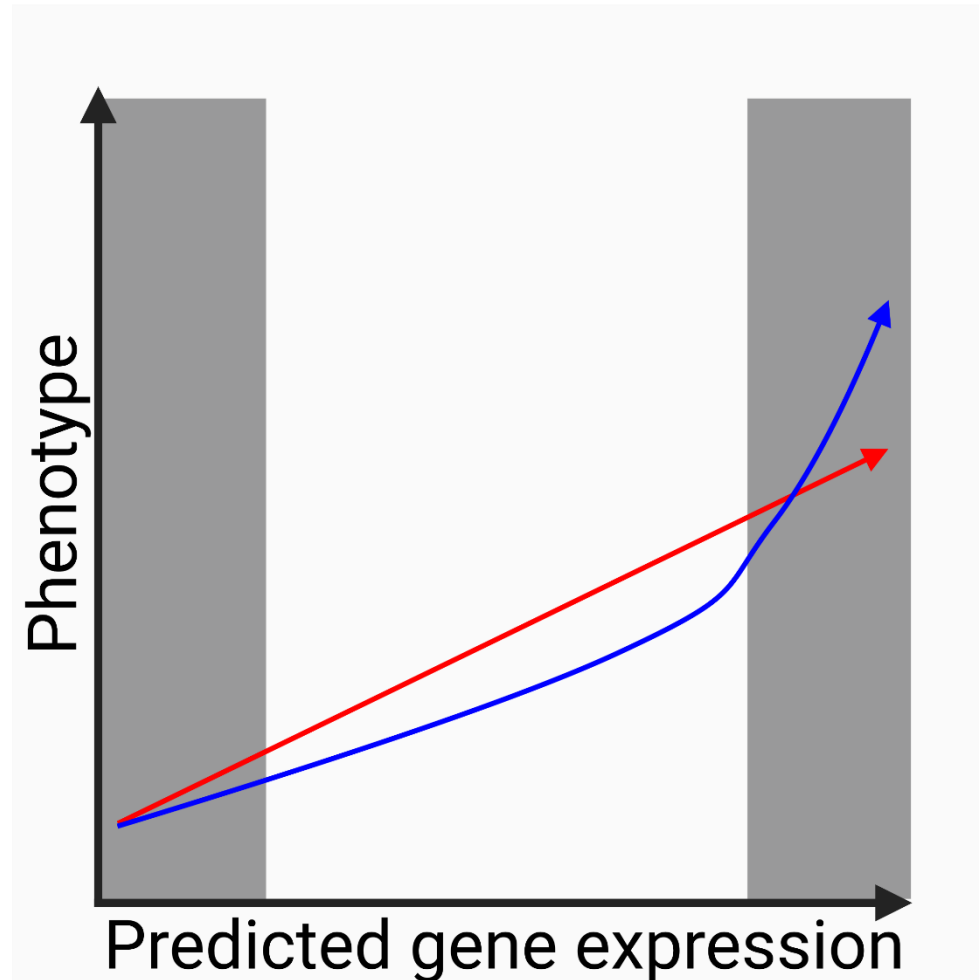


Additive models can miss the relation between expression and phenotype





Can we see additive genetic effects on gene expression resulting in non-additive consequences for phenotypes?

Deviations from the additive model for extreme expression



Data: independent eQTLs

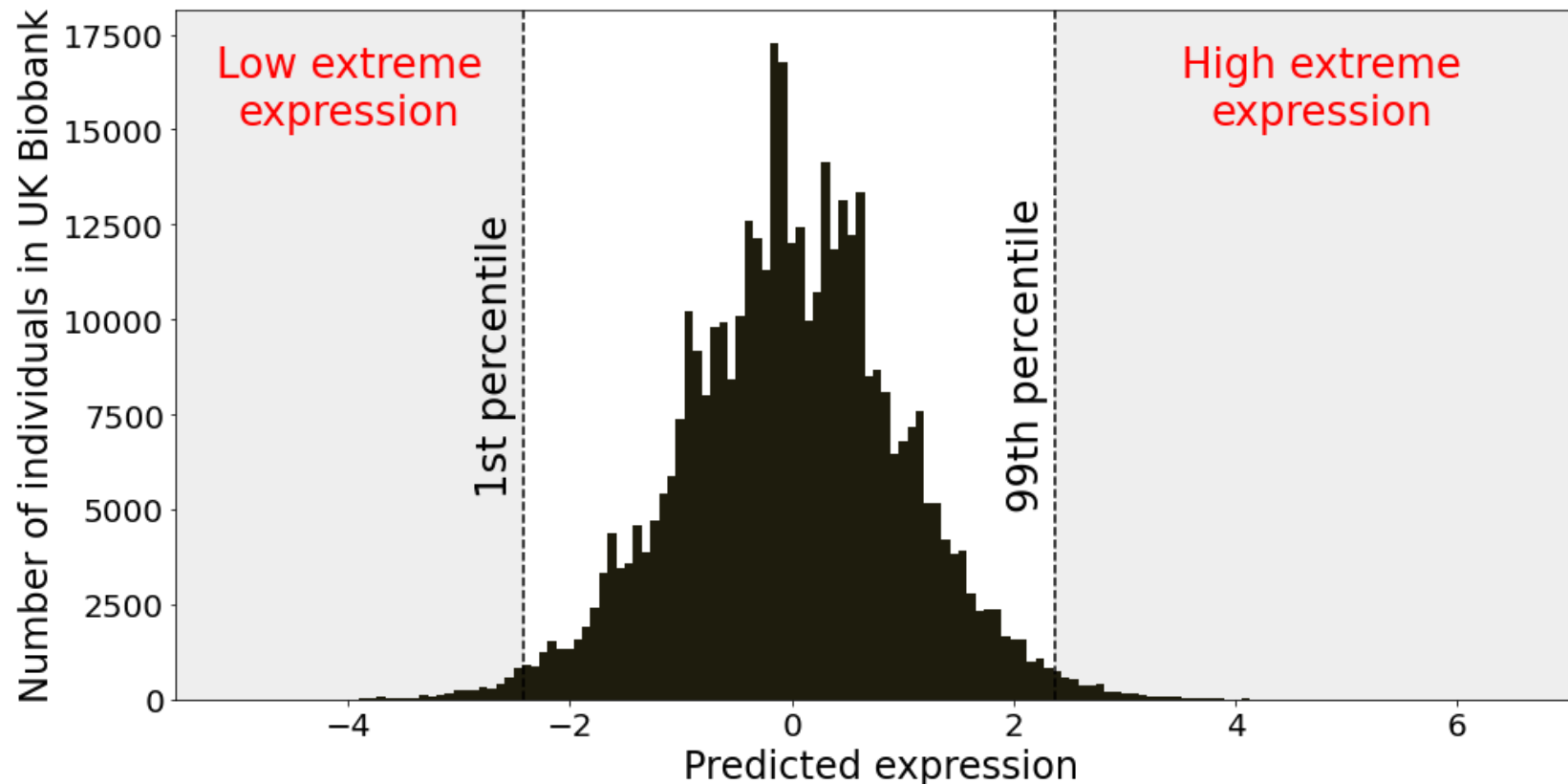
	 (GTEx v8)	 DIRECT <small>DIABETES RESEARCH ON PATIENT STRATIFICATION</small>
Independent eQTLs	~499k	59,971
Tissues	44 tissues	Whole blood
Sample size	73-706 (mean=323)	3029
Number of gene-tissue pairs with 2+ eQTLs	~109k	12,824

Data: UK Biobank

Predicted expression in 45 tissues for 406k UK Biobank individuals

Genetically predicted extreme expression

For each gene-tissue pairs, individuals with predicted expression in top or bottom percentiles are considered to have extreme expression.



Testing the consequences of extreme expression

Additive model:

$$phenotype^* \sim predicted\ expression + covariates^{**}$$

*: Blood pressure, BMI, grip strength, standing height, waist-hip ratio

** : age, sex, genotype PCs, other technical

Testing the consequences of extreme expression

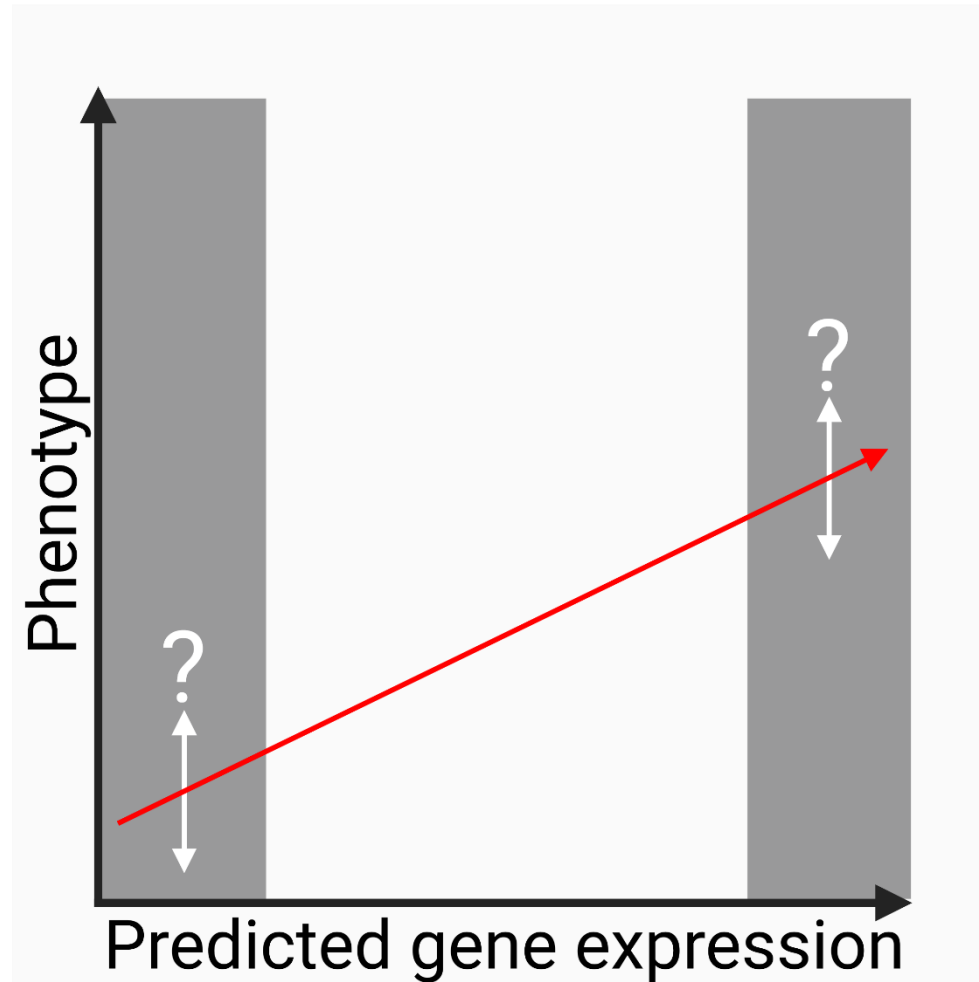
Our model:

$$phenotype^* \sim predicted\ expression + extreme\ expression + covariates^{**}$$

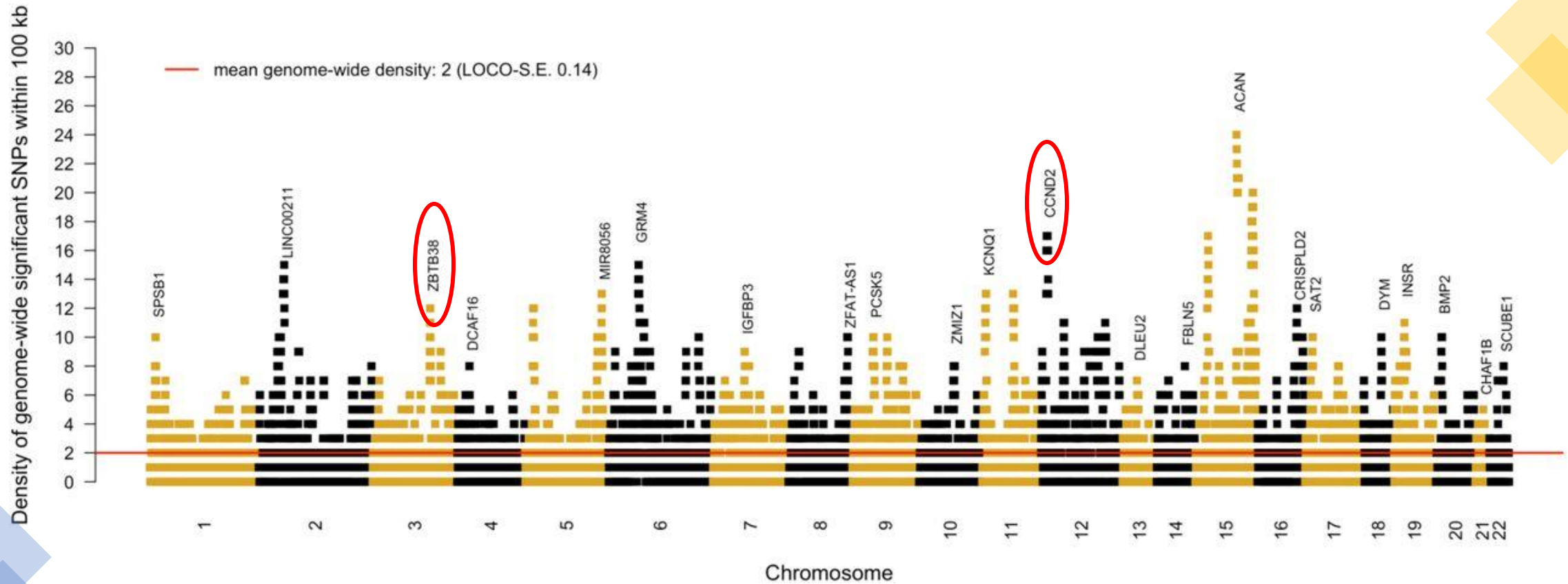
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Deviations from the additive model for extreme expression

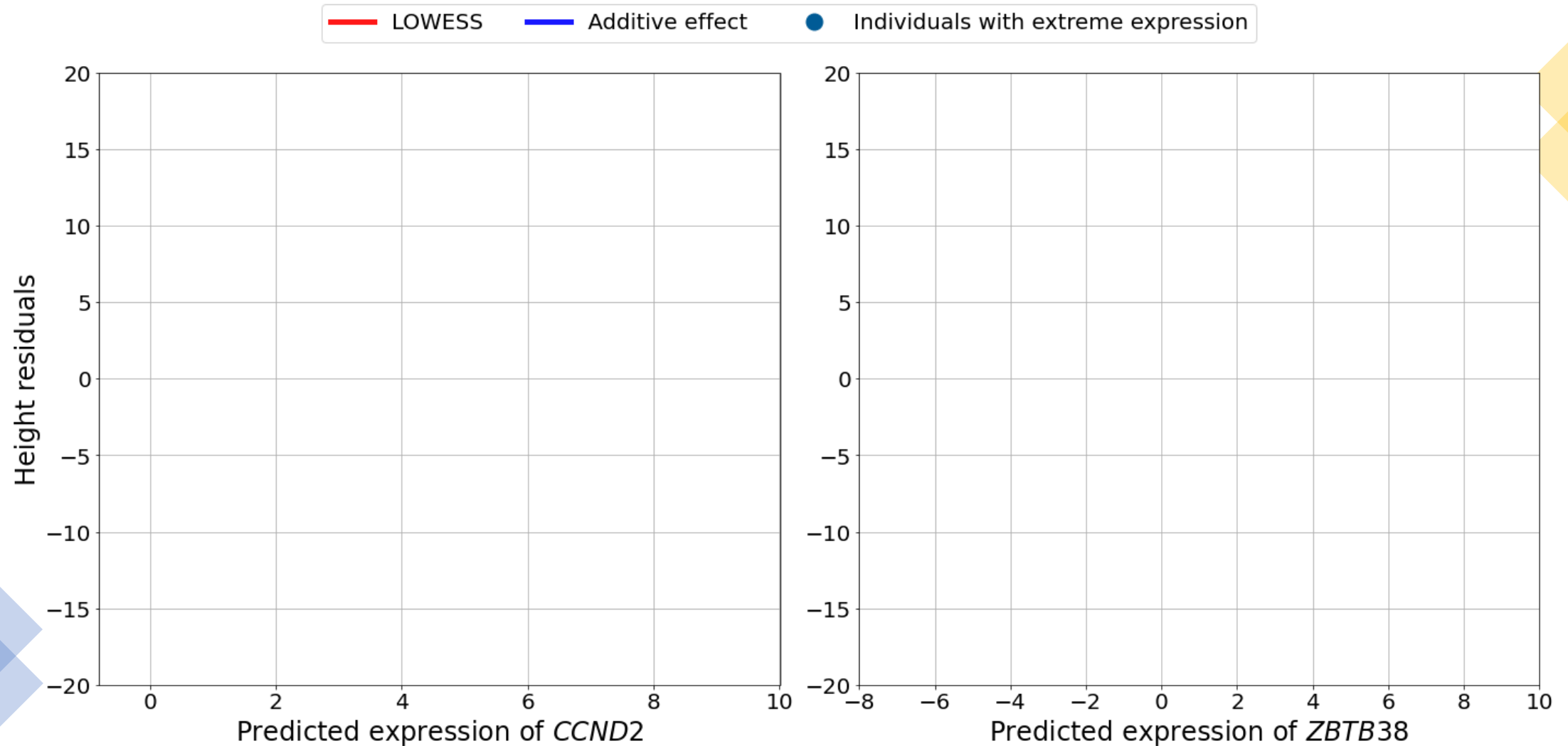


Examples of extreme expression effects on height

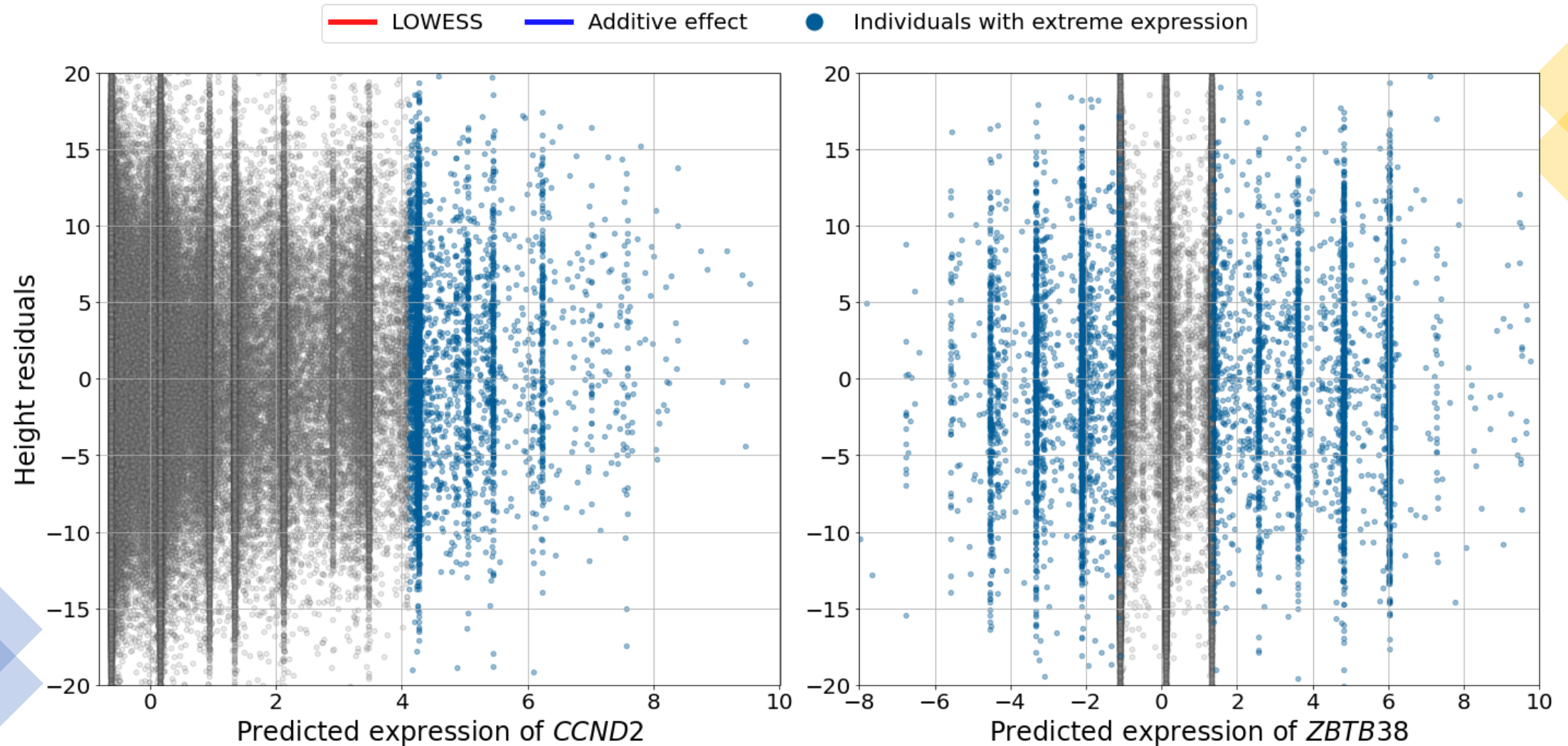


GWAS of height with 5.4M individuals. GIANT + 23andme. Yengo *et al*, BiorXiv 2022

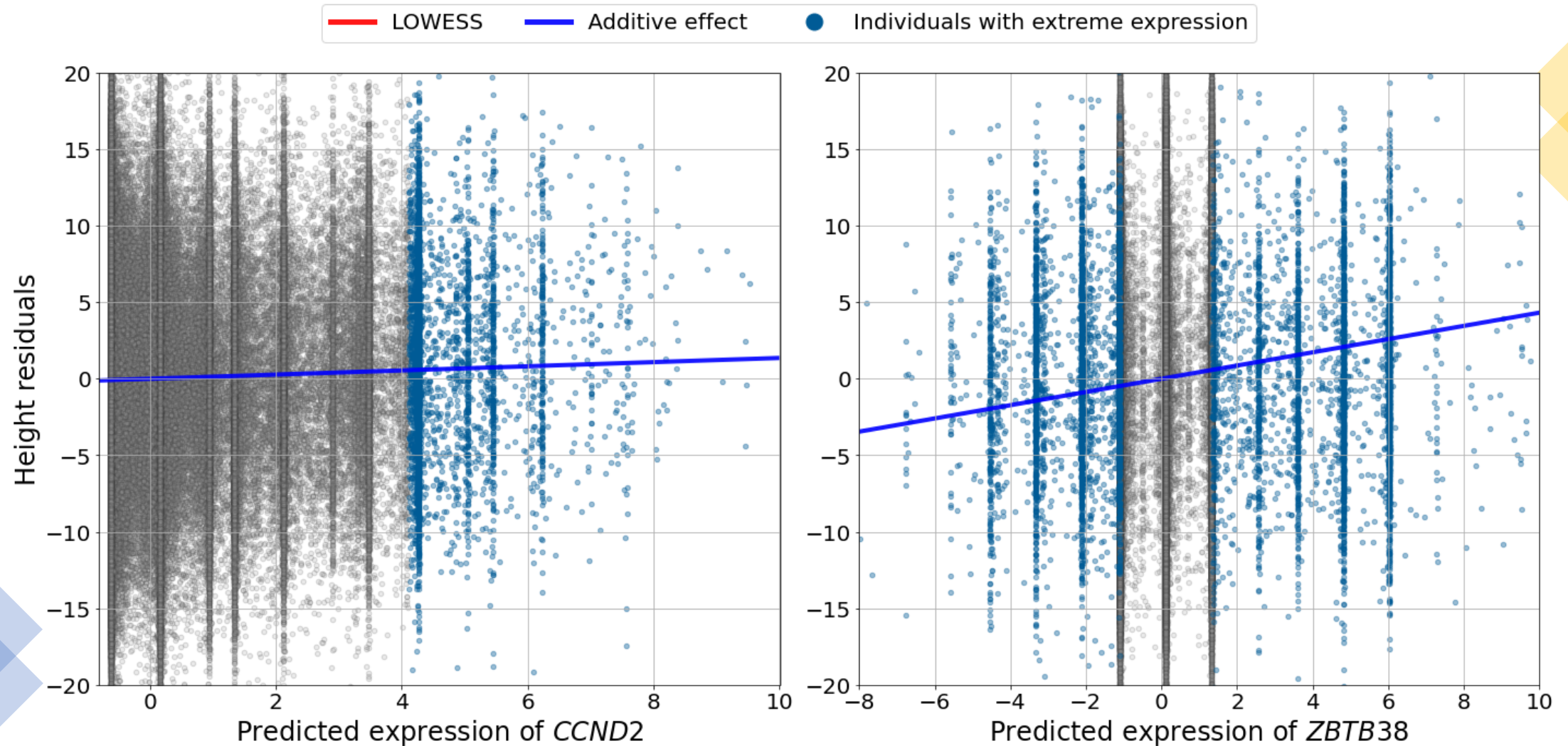
Examples of extreme expression effects



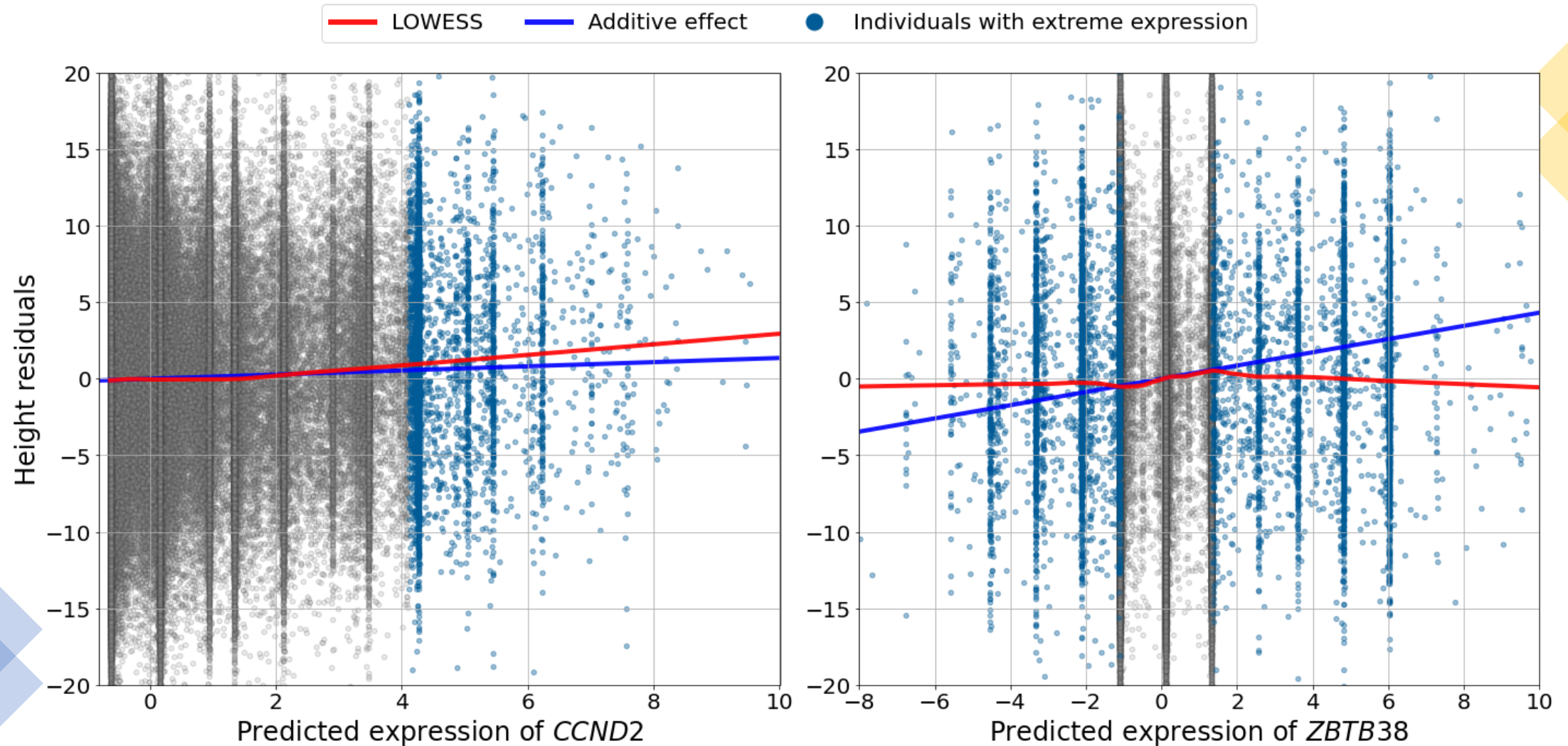
Examples of extreme expression effects



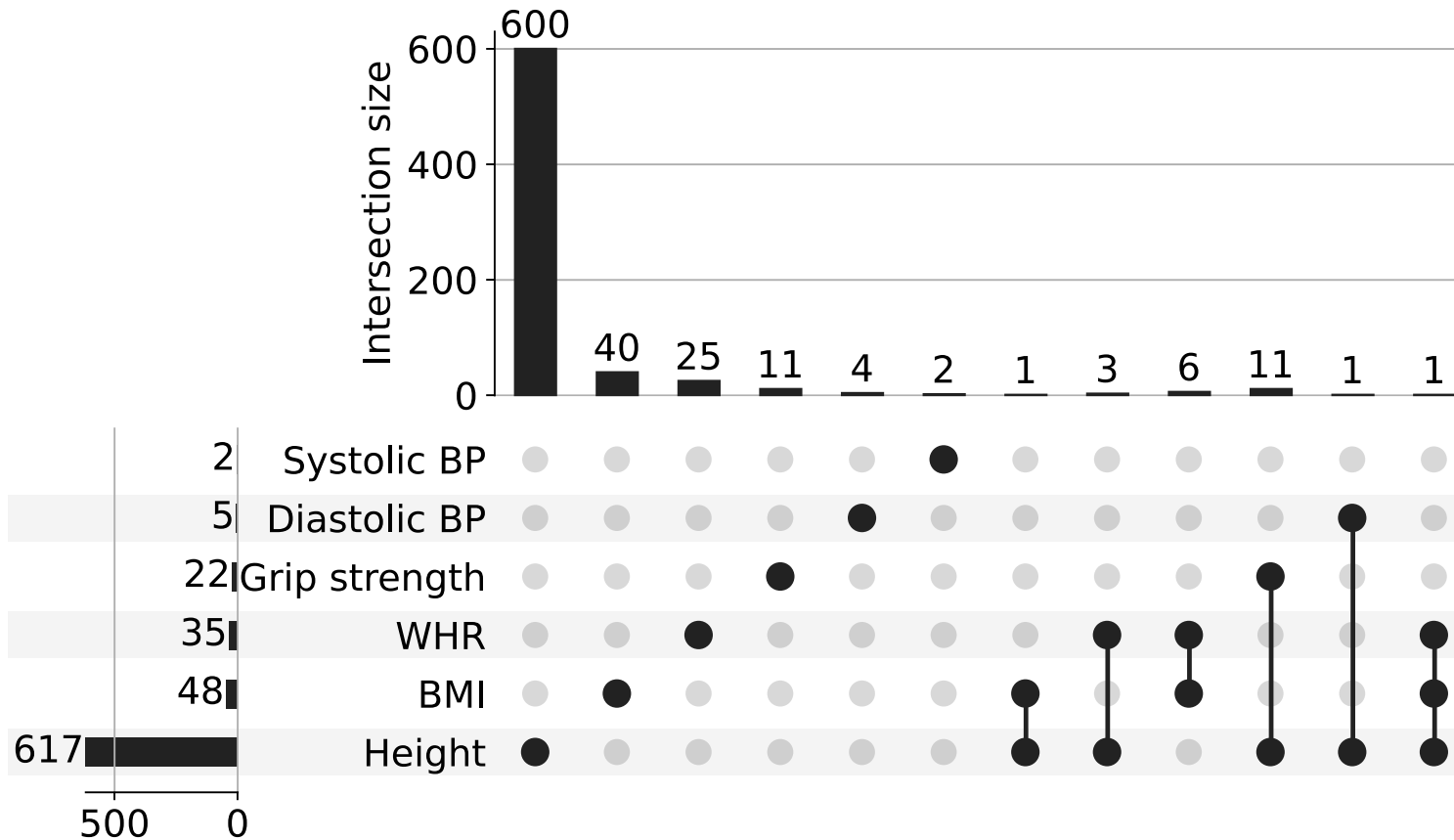
Examples of extreme expression effects



Examples of extreme expression effects



Polygenic traits show more non-additive effects



729 significant extreme effects on phenotype (qvalue < 5%)

In comparison almost 78k significant additive effect

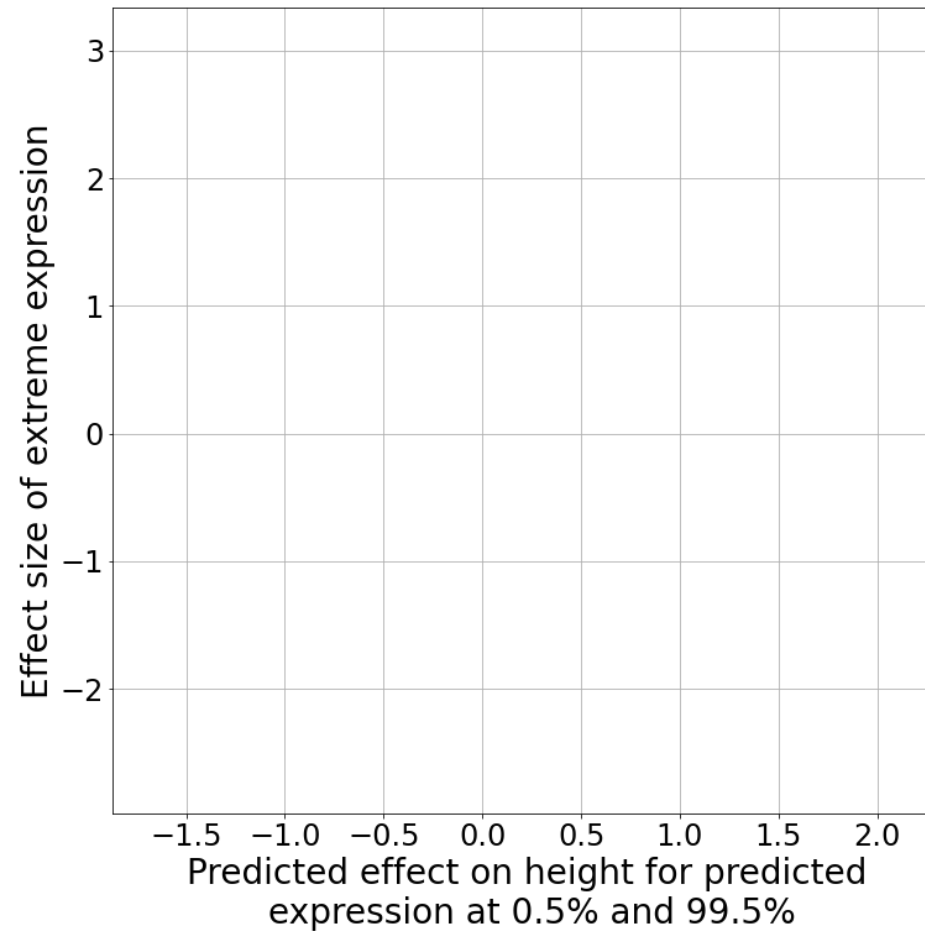
609/729 additive effect significant as well

Most associations for height: more polygenic

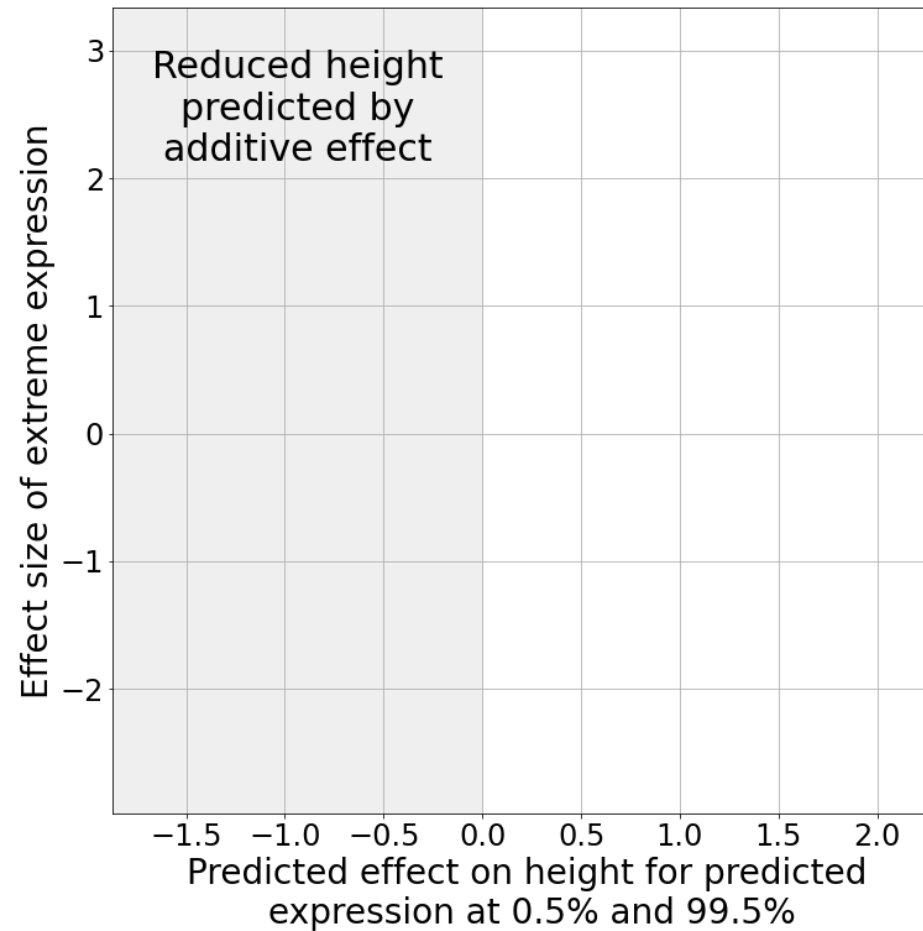


Does extreme expression exacerbate
or attenuate the additive effect?

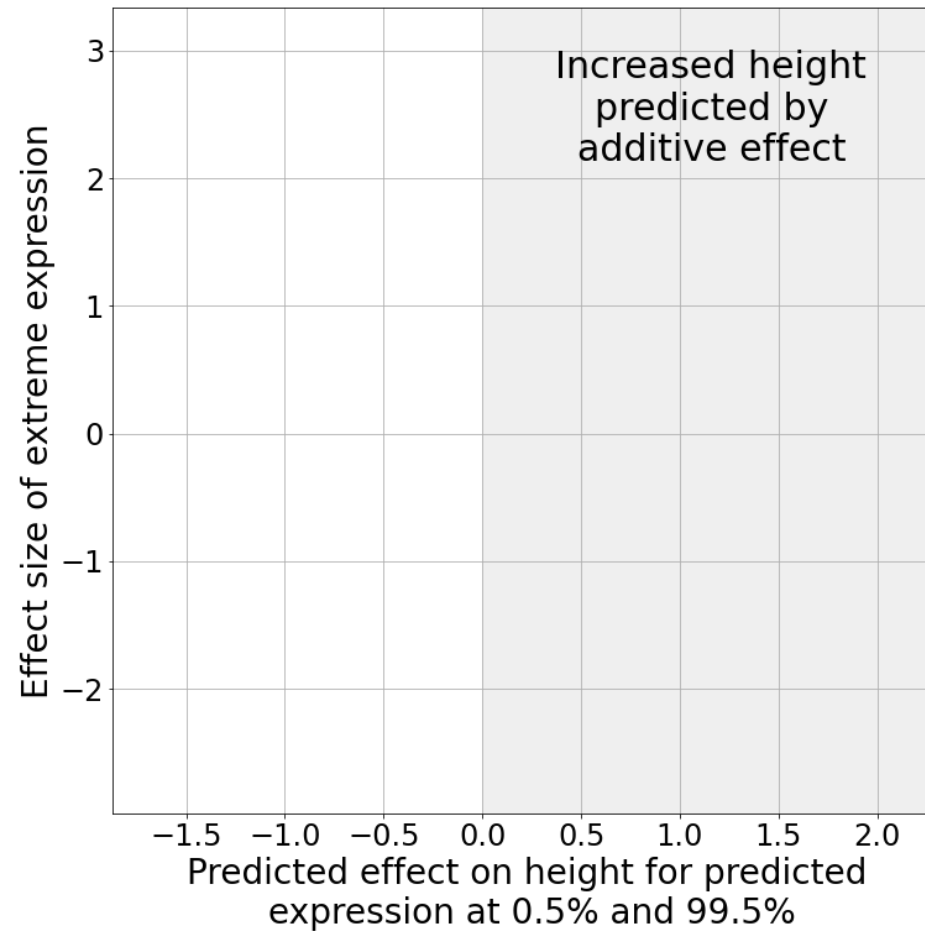
Comparison between the effect size of the extreme expression effect vs additive effect at the tails



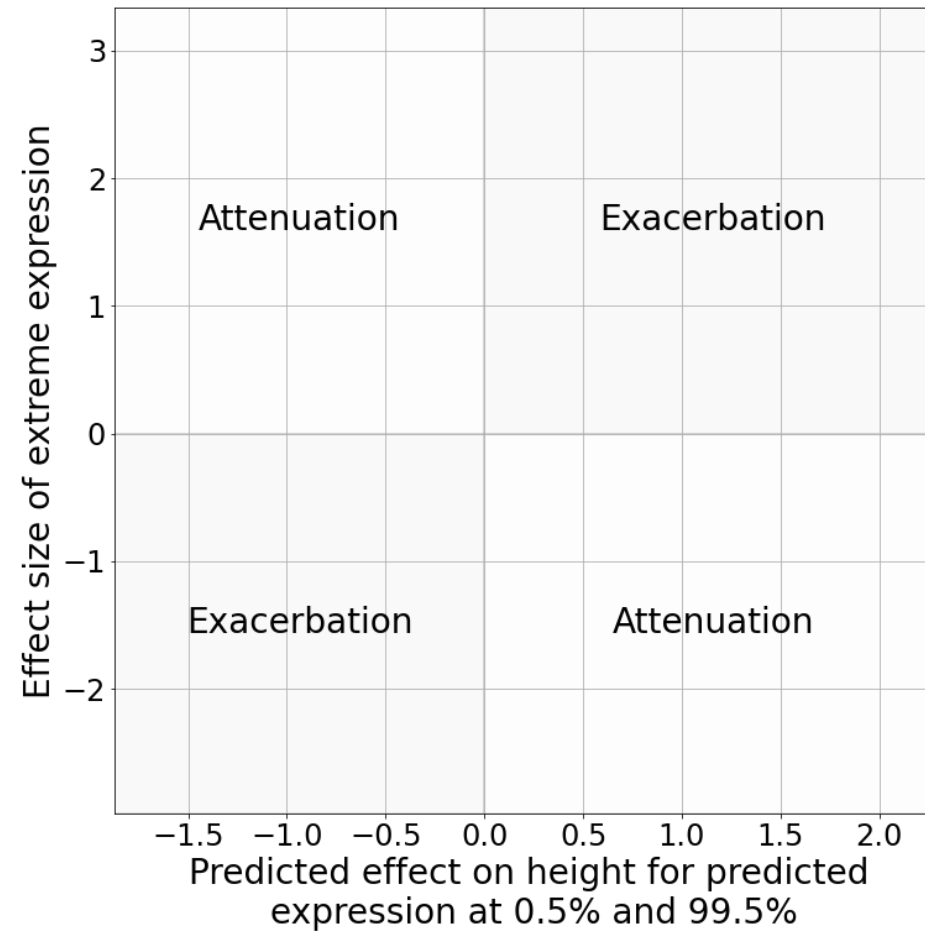
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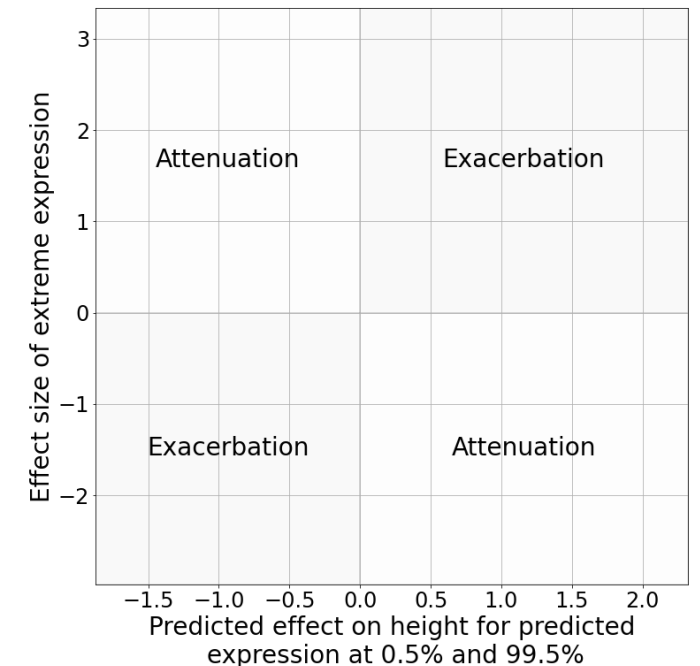
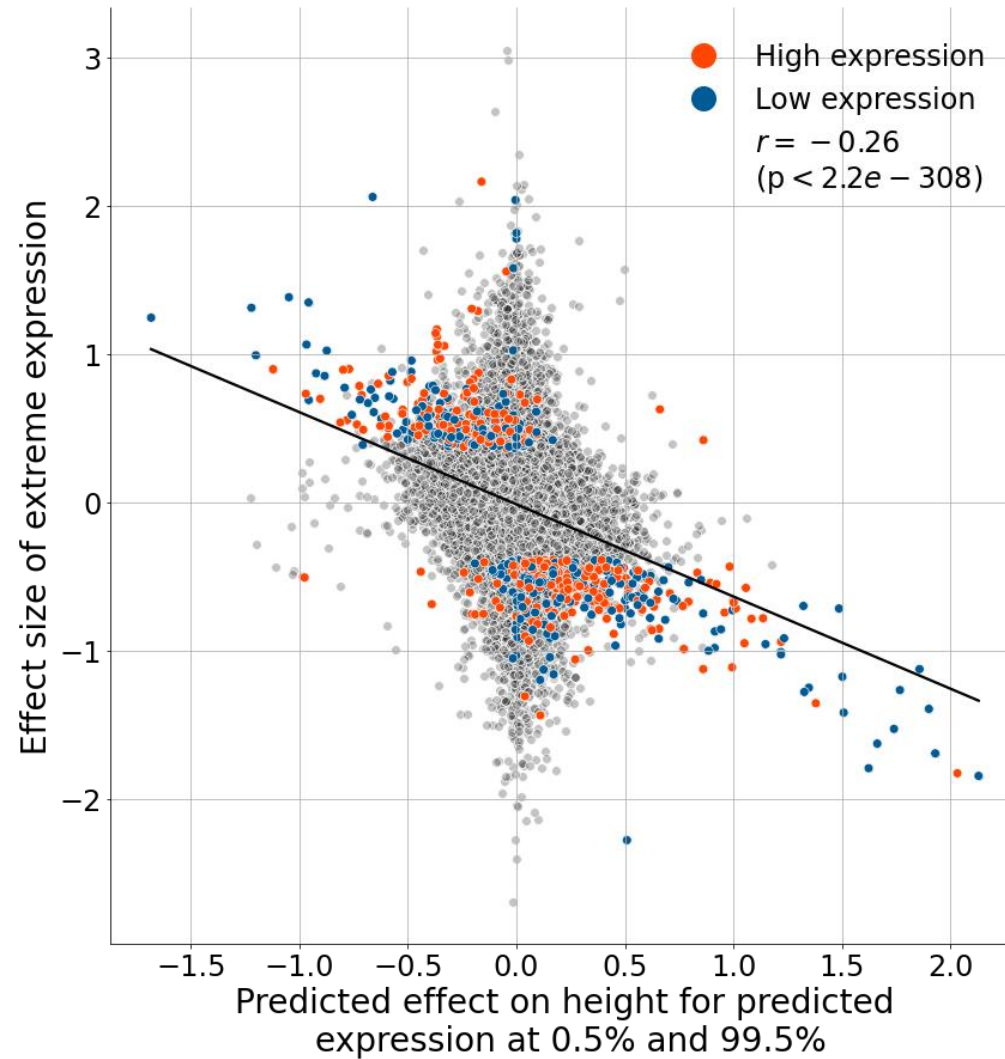
Comparison between the effect size of the extreme expression effect vs additive effect at the tails



Comparison between the effect size of the extreme expression effect vs additive effect at the tails



Comparison between the effect size of the extreme expression effect vs additive effect at the tails



Conclusion

- Most models assume additive proportional effects on intermediate phenotype and whole-organism traits
- We found that additive effect on expression may not always result in additive effects on phenotype
- If confirmed, the frequent attenuation of gene expression effects on downstream phenotypes would highlight how epistasis is not always caused by a physical interaction between gene products but by any process resulting in non-additive consequences

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Some figures created with Biorender



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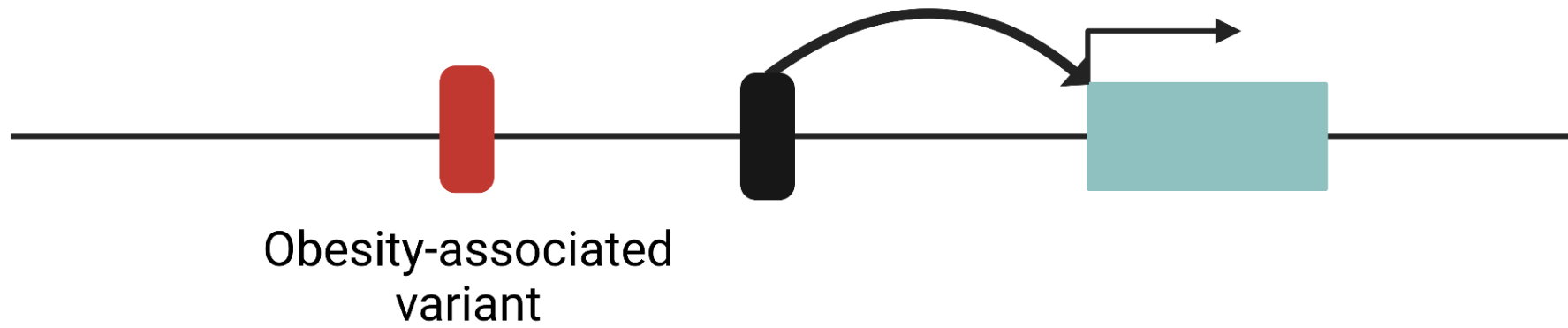
Additional slides

Predicted expression

$$\textit{Predicted expression} (G, T, I) = \sum_{k=1}^{\textit{Number of eQTLs}_{G,T}} \textit{dosage}_{I,k} \times \textit{effect size}_k$$

G = gene, T = tissue, I = individual

Caveats: linkage disequilibrium



Caveats: pleiotropy

