

# The genetic architecture of behavioral response to methylphenidate predicted from gene networks

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## Why

**Drug response** phenotypes are **genotype dependent**. Treatment of psychiatric disorders have heterogeneous success. **Personalized medicine** has the potential to target and **improve treatment**.

## Aim

Use ***Drosophila melanogaster* as a model** to investigate the genetic basis for **genotype-specific response to treatment (GSRT)** of **methylphenidate (MPH)** which is commonly used to **treat ADHD**.

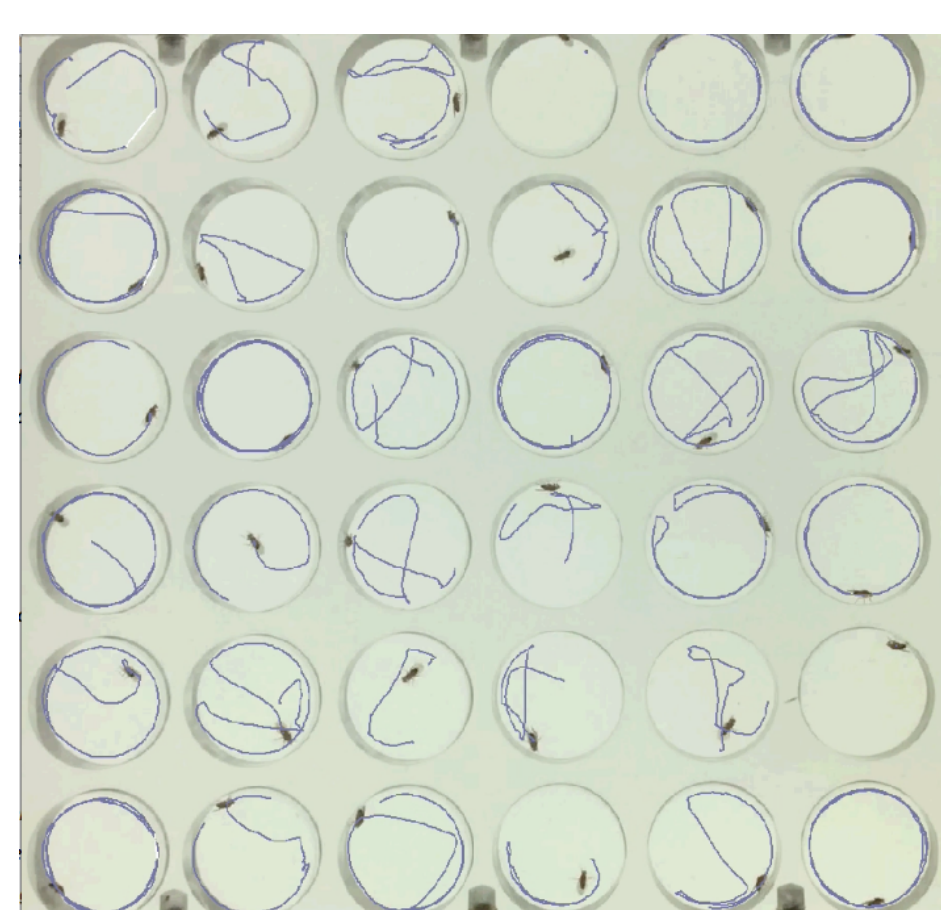
## Methods

### 1 Behavioral assay



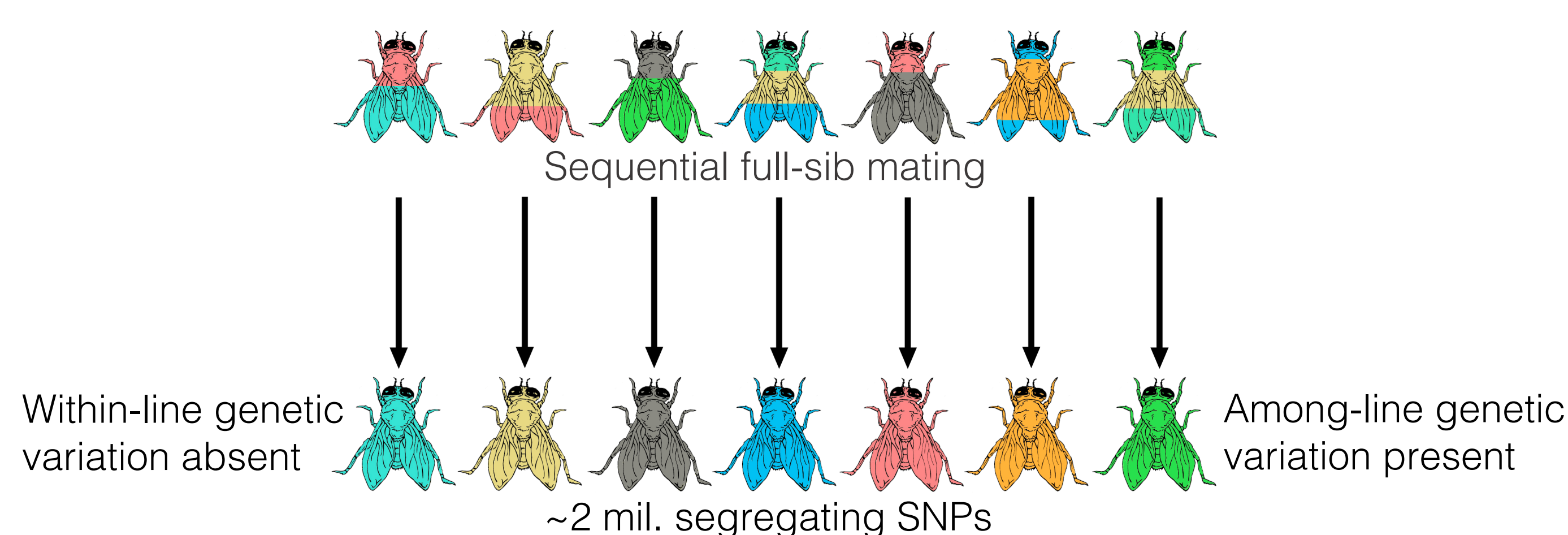
Flies were fed with sucrose or MPH for 24h.

Activity measurements obtained using video tracking (10 min. periods).



### 2 Genetic basis for GSRT

*Drosophila* Genetic Reference Panel (DGRP)



- Quantify GSRT for 172 DGRP lines as the within-line difference between treatments ( $n=30$ /line/treatment).
- Identify gene networks (see BOX 1) associated with GSRT, as those networks that increased prediction of unobserved phenotypes from observed genotypes.

### 3 Functional validation of hub-genes

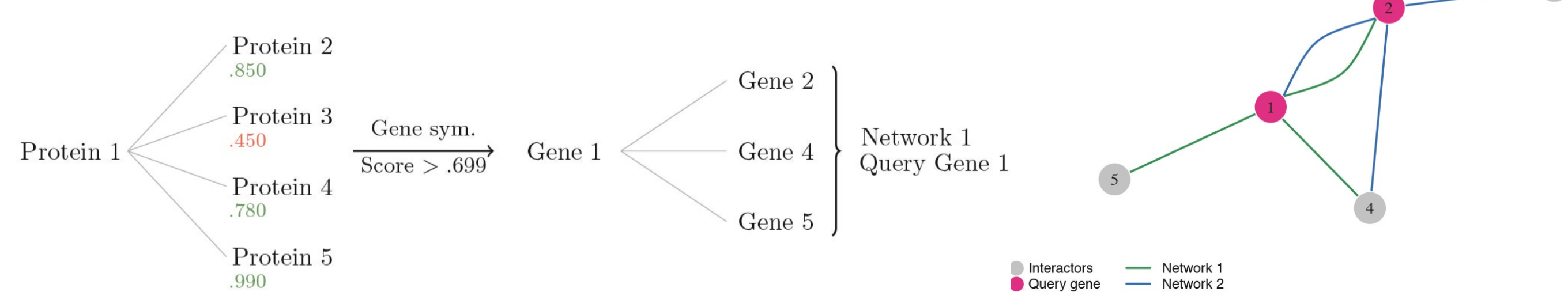
- Central genes in the predictive network were functionally validated by gene expression knockdown using the *UAS*-RNAi system.

### 4 Transcriptomic analysis of MPH effect in wildtype flies

- Phenotypic assessment of wildtype flies ( $n=72$ /treatment).
- Identifying differentially expressed genes from full-genome transcriptomic data of assayed flies.

#### BOX 1

Genes are not independent units, but interact through networks. Gene networks were established from known protein-protein interactions. SNPs within the genes coding for the proteins were then used in the phenotypic prediction models.



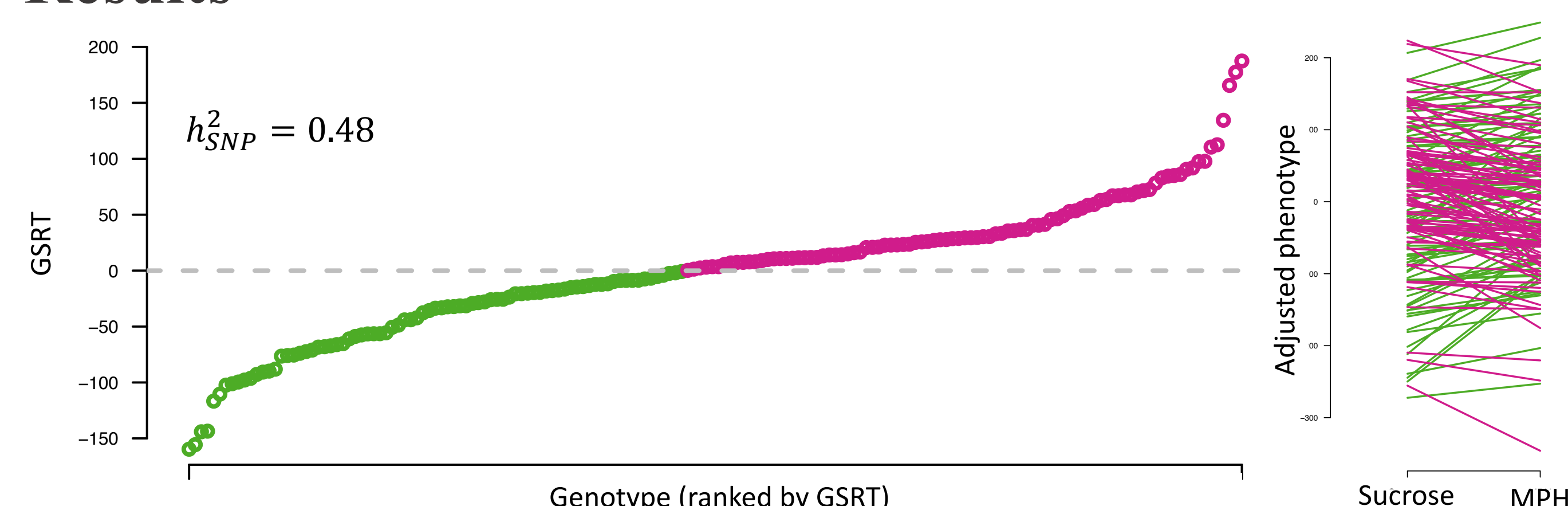
## Main findings

We found **genetic variation for GSRT** (Fig. 1), and identified a large **gene network predictive of GSRT**.

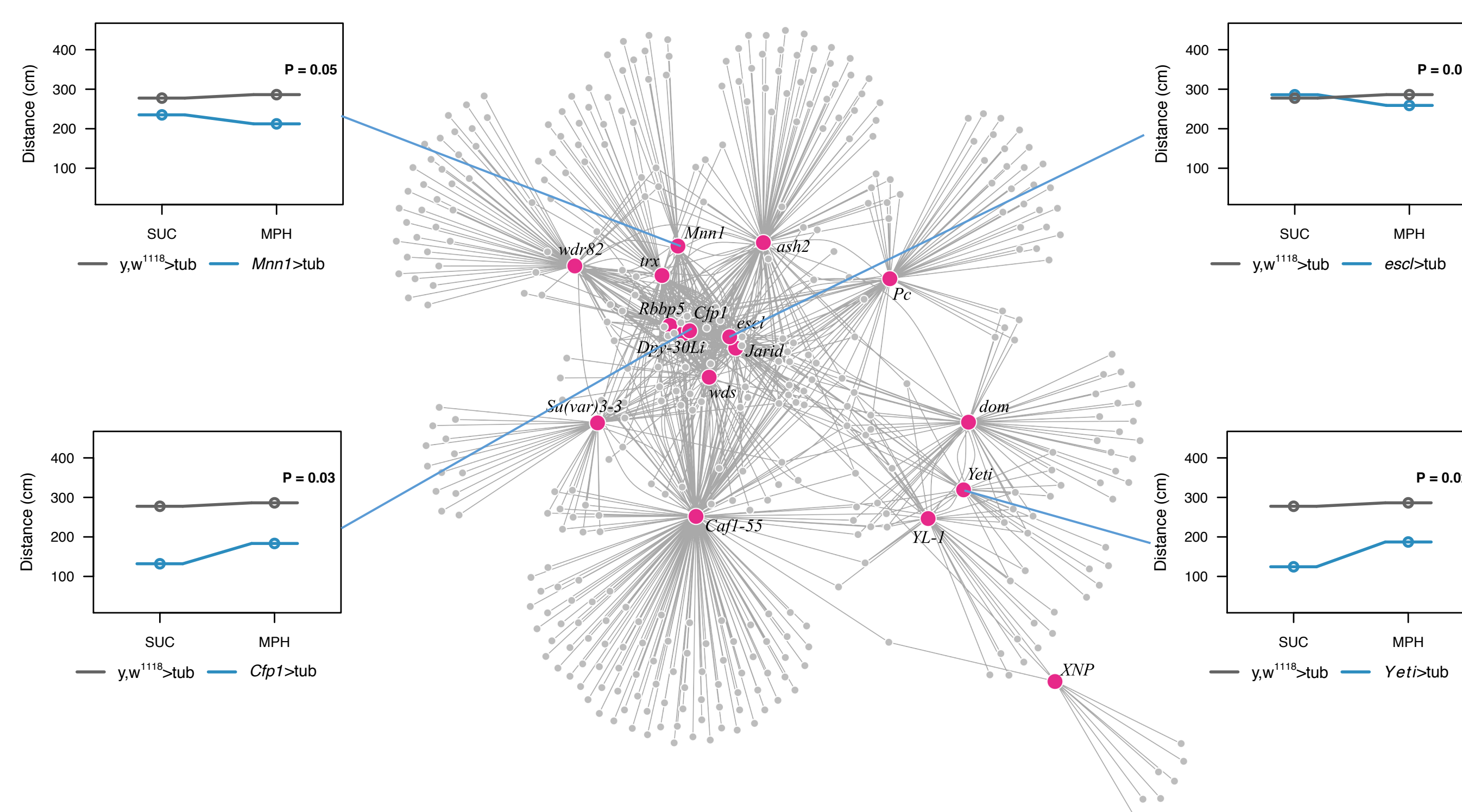
20% of the **hub genes were histone modifying genes**, of which we **functionally validated** 4/7 of the top candidate genes (Fig. 2).

The genes within the **predictive network** were **differentially expressed in a wildtype population** when treated with either sucrose or MPH (Fig. 3).

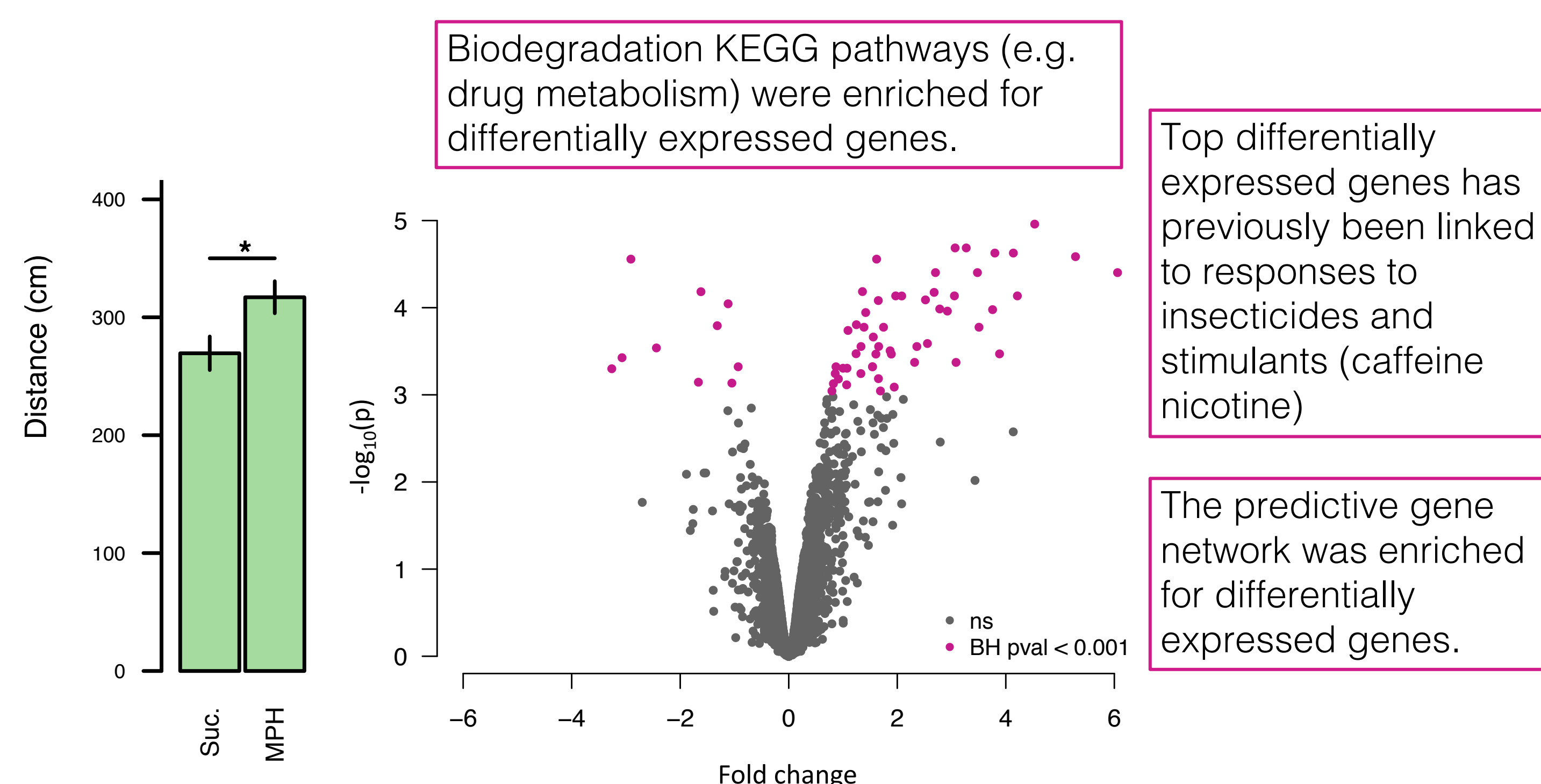
## Results



**Fig. 1** Genotype-specific response to treatment (GSRT, left panel) was highly variable among the DGRP lines. GSRT was quantified as the phenotypic difference between the two treatments (right panel).



**Fig. 2** Sub-network with histone modifying hub-genes (pink nodes). 7/16 *UAS*-RNAi lines survived gene expression knockdown, and 4/7 showed significant genotype-by-treatment interaction.



**Fig. 3** Left panel shows the significant phenotypic effect of MPH on wildtype flies, and right panel shows the fold change in gene expression, where pink dots indicates significantly differentially expressed genes.