Class III: Genetic Modifiers
"The plus race shows no white except on the underside and sometimes along the flank."

"The minus race shows no black except a short hood lying anterior to the shoulders..."

$hd$: a hypomorphic allele of $kit$.

Cross both strains to a wild-type strain and recover hooded pheontype in F2 generation.
Scenario: It’s Monday, and my weekend plans are as follows:
- Saturday: go fishing (but need a new rod to do so)
- Sunday: write MGG QE written exam

If I get rod and go fishing, I will be in a good mood, and I’ll write a fair exam and everyone will pass.

If don’t get the rod, I won’t go fishing, I’ll be cranky, I’ll write a really hard exam...

But, what if I have allergies and my hearing is diminished by 50%?
Genetic modifier screen: Genetic dissection of expected RTK signaling (Simon and Rubin, 1991)

**Known:** Receptor tyrosine kinases implicated in cancer (e.g. v-erbB)
Many proteins known to be phosphorylated in response to RTK activation (e.g., raf and ras), but few if any were known to transduce the RTK signal.

**Model:** Most receptor tyrosine kinases signal through common downstream factors, but none identified yet.

**Question:** What genes act downstream of receptor tyrosine kinases?
How do you create a sensitized sevenless genetic background?

Start with a rescuing wild-type sev transgene

Use known temperature sensitive mutations in v-src as a guide to make five sev[TS] mutations

Wild-type sev\[^{[wt]}\] sev\[^{[B4]}\] sev\[^{[B4]}\] /+ 22.7°C 24.3°C

Wild-type

Mutant

90% R7

90% No R7
Logic of Dominant Genetic Modifier Screen

- **sev**$^{[B4]}$
- **sev**$^{d2}/Y; P[sev^{[B4]}]/+$
- 22.7°C
- 24.3°C

Wild-type: 90% R7
Mutant: 90% No R7

Level of **sevenless** activity below which you don’t see R7.

- **sevenless**$^{B4}$ function at 22.7°C
- **sevenless**$^{B4}$ function at 24.3°C

Gene A
Gene B
Gene C
R7
No R7
Sev2/Y; +/+; +/+ × Sev2/sev2; +/+; TM3 Sb P[sevB4]/Cxd

\[\text{Sev2/sev2; +*/+; +*/TM3 Sb P[sevB4]}\]

Screened 30,000 F1 flies for loss of R7

29,980 flies have R7

22.7°C

R7

20 flies lack R7: 1 in 1500 flies

22.7°C

No R7

7 complementation groups
Now what?

1) In a wild-type background, are the alleles recessive?
   Yes, all of them.

2) What is the loss of function phenotype of each Enhancer of sevenless in the eye and the animal?
   - 4 of 7 required for the development of all photoreceptors
   - 4 of 7 are homozygous lethal (die before late larval stage)

3) Do they act downstream of other RTKs?
   - Ellipse: gain of function allele of EGFR.
     - Ellipse/def = wild-type
     - Ellipse/wt = rough eye
     - Ellipse/Ellipse = very rough eye
   - 4 of the 7 Enhancers of sev suppress Ellipse phenotype
If a loss of function mutation enhances a loss of function phenotype, the two genes act in the same direction.

If a loss of function mutation suppresses a gain of function phenotype, then the two genes act in the same direction.

If a loss of function mutation suppresses a loss of function phenotype, do the two genes act in the same direction?

If a loss of function mutation enhances a gain of function phenotype, do the two genes act in the same direction?