

CHAPTER 21

MULLER: HOW COMMON ARE RECESSIVE LETHAL MUTATIONS IN POPULATIONS?

In 1927, Herman J. Muller developed a technique to detect recessive alleles, enabling him for the first time to assess their frequency in nature. By using a clever combination of genes on the Drosophila X chromosome, Muller was able to infer the presence of lethal recessives by examining only the sex of F₂ flies, a test so simple that large numbers of flies could be screened.

HOW ARE RECESSIVE LETHALS QUANTIFIED?

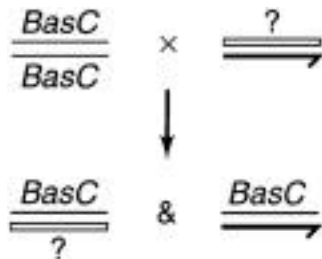
The presence of recessive lethals is detected essentially by their absence. Individuals being tested for the presence of recessive lethals are first crossed to special tester strains to obtain individual heterozygotes, which are then crossed so that the individual chromosome to be analyzed is either rendered homozygous in the case of autosomes or hemizygous (e.g., paired to the Y chromosome) in the case of X chromosomes. If a recessive lethal mutation was present in the original individual, the homozygous or hemizygous progeny will express the lethal gene and will not be detected among the offspring of the cross. In order to screen large numbers of individuals, the tester strains are designed for minimal manipulation and rapid scoring.

MULLER'S TESTER STRAINS

In *Drosophila*, the original tester strains were developed by Herman J. Muller in 1927 to screen for recessive lethals on the X chromosome. An optimal tester strain should contain three markers, each of which played an essential role in the screening procedure. Using the X chromosome as an example:

1. *sC*: a cross-over suppresser; in Muller's case an inversion near the "scute" locus that inhibited crossing-over along the length of the X chromosomes.
2. *B*: *Bar*, A dominant visible eye shape trait that mapped to the centromere end of the X chromosome.
3. *a*: *apricot*, a recessive visible eye color trait that mapped to the opposite end of the X chromosome.

An individual male fly to be tested for the presence of a recessive lethal mutation was crossed to females from one of the tester strains. The F₁ progeny of this cross were *BasC* males and females:



Nothing was done yet at this point in the experiment. The F₁ males and females were allowed to cross freely and produce F₂ progeny. But it was here that a critical point in the design came into play. It was very important that there be no crossing-over between the "wild" chromosomes and the *BasC* chromosome.

There were two ways in which such crossing-over interfered with the analysis, and they had opposite effects:

1. Recessive lethals on the wild chromosome may be lost to the analysis if recombined onto the tester chromosome.
2. Recombination may produce new combinations of alleles that did not work well together; crossing-over would have in effect produced a *synthetic lethal* by creating a subviable combination that was not present at the start of the experiment. The crossing-over suppressing inversion *C* is used to avoid the problems introduced by crossing-over. The recessive visible *apricot* is employed for the same reason. Any cross-over that *did* occur would immediately be apparent because it would result in *Bar*, not *apricot*, male progeny. If there was no crossing-over (and there should be very little because of the inversion), there were four types of F_1 progeny:



If the original “wild” X chromosome carried a recessive lethal mutation, due either to spontaneous mutation or to experimental mutagenesis, there would be no wild-type flies! All the investigator had to do was hold up the culture bottles one at a time and look for any in which all the males had *Bar*, *apricot* eyes. Any that were found indicated cases in which a recessive lethal was present on the X chromosome of the original male. Nor was the recessive lethal lost. The investigator had only to select the *Bar*, non*apricot* females, as each carried the original lethal-carrying wild chromosome.

In *Drosophila*, the spontaneous incidence of recessive lethal mutations detected in this fashion occurred in about 0.1 percent of the X chromosomes examined, and about 0.5 percent of II and III chromosomes. Overall, then, the recessive lethal mutation rate is about 0.01 per gamete per generation.