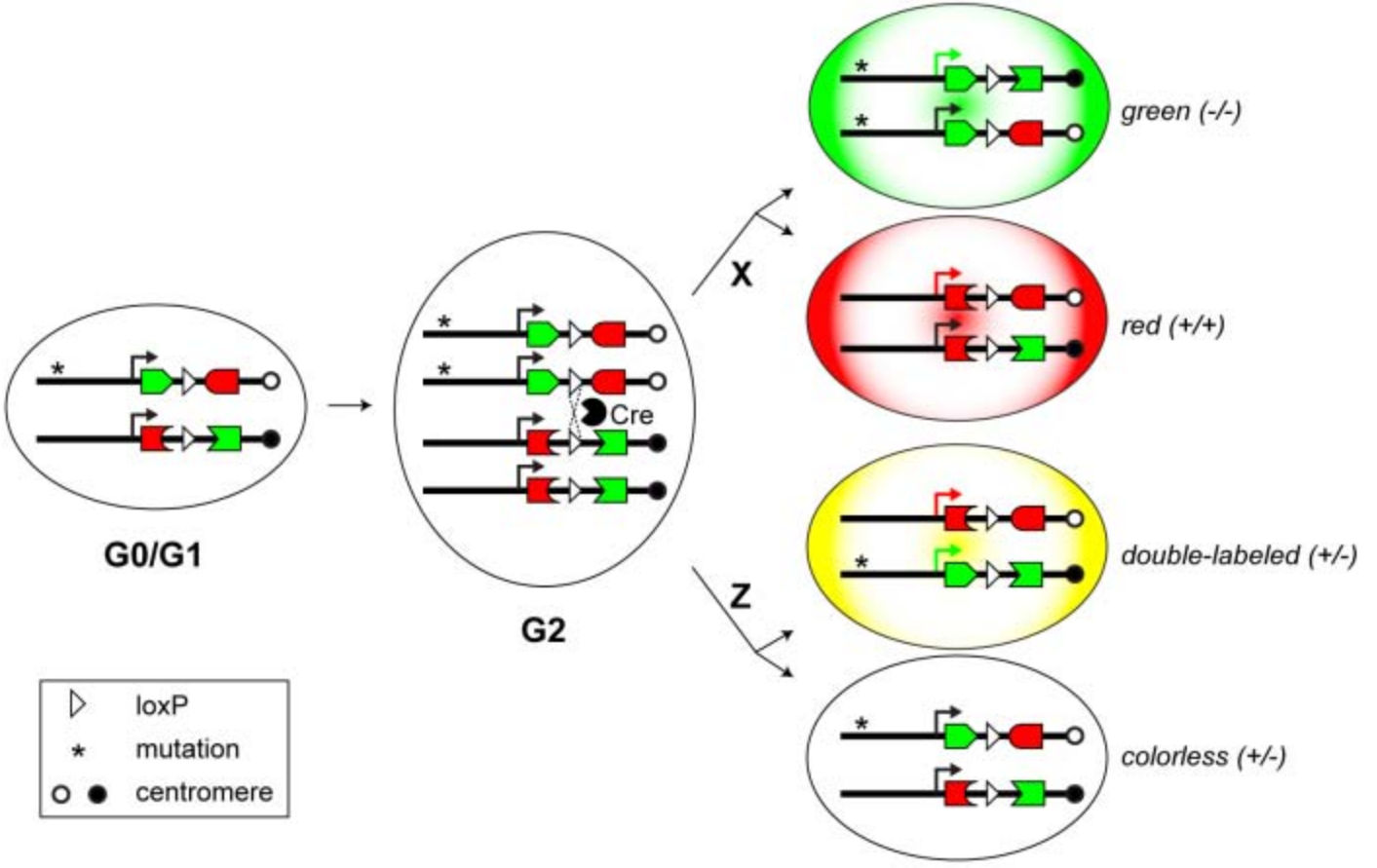
G0/G1
G2
Cre
X
Z
green (-/-)
red (+/+)
double-labeled (+/-)
colorless (+/-)
loxP
mutation
centromere

Image above modified with permission from Tasic et al 2012 PLoS One 7(3): e33332 "Extensions of MADM (Mosaic Analysis with Double Markers) in Mice"

MADM-6

This is an example if breeding $R26^{GT}$ mice (Stock No. 017912) with $R26^{TG}$ mice (Stock No. 017921).

The resulting GT/TG offspring have one copy of each reciprocal mutation on homologous chromosomes ("trans-heterozygous"). Prior to Cre or FLP-induced recombination, double mutant mice do not have fluorescent protein expression/colored cells: the chimeric genes do not produce functional proteins because their coding sequences are interrupted by the beta-actin intron in different reading frames.

After DNA replication (G2 phase) in double mutant mice, introduction of Cre- or FLP-recombinase that facilitates inter-chromosomal recombination will align the respective N- and C-terminal coding sequences for each of the reporter genes on the same chromosome.

The subsequent chromatid segregation (X or Z) determines daughter cell phenotype: congregation of recombinant sister chromatids into the same daughter cell (a G2-Z event) leads to double reporter expression or no reporter expression, while segregation into separate daughter cells (a G2-X event) leads to expression of either mut4EGFP or tdTomato-3Myc.

If an additional targeted mutation of interest (*) is introduced distal to the *Gt(ROSA)26Sor* locus on chromosome 6, only homozygous cells will be singly labeled following Cre- or FLP-recombinase expression in G2. The homozygous mutant and wildtype cells can then be distinguished by which single reporter they express. Most heterozygous cells will be unlabeled, but some heterozygous cells will be yellow (both markers expressed). Reporter protein tissue specificity, expression levels, and frequency of recombination are thus determined by the promoter controlling Cre- or FLP-recombinase expression.