The Case of the Cumbersome Chromosomes: An Introduction to Workshop Genetics.

Tammy Tobin-Janzen

Biology Department
Susquehanna University
Selinsgrove, PA 17870

Tammy is an associate professor of biology. She received her bachelor's degree in animal science from Cornell University in 1985, and her Ph.D. in genetics from Texas A&M University in 1990. Following postdoctoral work at the National Institutes of Health, she moved to central Pennsylvania where she is currently studying soil bacterial communities in the Centralia mine fire area using both genetic and physiological tests.

Reprinted From: Tobin-Janzen, T. 2003. The case of the cumbersome chromosomes: An introduction to workshop genetics. Pages 253-258, in Tested studies for laboratory teaching, Volume 24 (M. A. O'Donnell, Editor). Proceedings of the 24th Workshop/Conference of the Association for Biology Laboratory Education (ABLE), 334 pages.

Introduction

The goal of the Workshop Genetics Project is to increase student comprehension of and enthusiasm for genetics. Genetics is a highly quantitative subject that is frequently a stumbling block for biology majors. Studies show that students enroll in genetics with misconceptions regarding everything from the cell cycle and mitosis to evolution. Furthermore, students have a particularly hard time relating many genetics concepts to their everyday lives. Nonetheless, most initiatives to improve science education have focused on introductory and general education courses. In order to rectify these problems, the "Workshop Biology" project, which was developed for a large general education class at the University of Oregon, was adapted for implementation in our smaller, mid-level genetics class.

Workshop Genetics consists of four basic types of activities: "Class Assemblies" that replace traditional large lectures, short "Concept Activities" that teach key biological concepts, "Investigative Activities" that allow students to design experiments and discover science concepts for themselves, and "Issues Activities" that allow students to use both scientific knowledge and their own values to address modern dilemmas. The course is broken down into four subject modules, which vary based on the text we use. Each subject module is introduced using an engaging module mystery that the students must solve during concept and investigative activities that are also

designed to teach key genetics concepts. More course details can be found on the workshop homepage: (http://www.susqu.edu/facstaff/t/tobinjan/Workshop%20Genetics%20Folder/Workshophome.html).

The Case of the Cumbersome Chromosomes is a "mini mystery" concept activity that we have developed to help students visualize the process by which large chromosomal aberrations such as inversions and translocations can have dramatic effects on individual fertility, even when they have no deleterious effects on viability. This activity also reinforces student understanding of meiosis, and lays the groundwork for understanding how chromosomes behave during meiosis in interspecific hybrids.

The Mini Mystery – Student Materials

The Mystery

Martin and Mary Cumbersome have been married for three years, and have not yet had any children. They are concerned that one of both of them may be infertile, and have come to your genetic counseling clinic for consultation and advice. Most other forms of infertility have been ruled out, but cytogenetic analyses have not yet been performed. During this activity, you will be introduced to the effects that large chromosomal aberrations can have on fertility and viability, and you will use this information to counsel the Cumbersomes.

Background Information

Chromosomal aberrations are large, generally irreversible changes to chromosomes. They include such physical changes as duplications, deletions, inversions and translocations. In duplications, a large part of a chromosome has been copied, and can be found either adjacent to the original gene, as shown in Figure 2, or in another part of the genome altogether. Conversely, deleted chromosomes have lost a large region. Translocations move a part of a chromosome to a non-homologous chromosome. The translocation shown Figure 1, which is a reciprocal translocation, occurs when two non-homologous chromosomes swap parts (Figure 1A). Finally, inversions are generated when a chromosome is broken in two places, and the affected chromosomal region is flipped 180º before the breaks are resealed (Figure 1B).

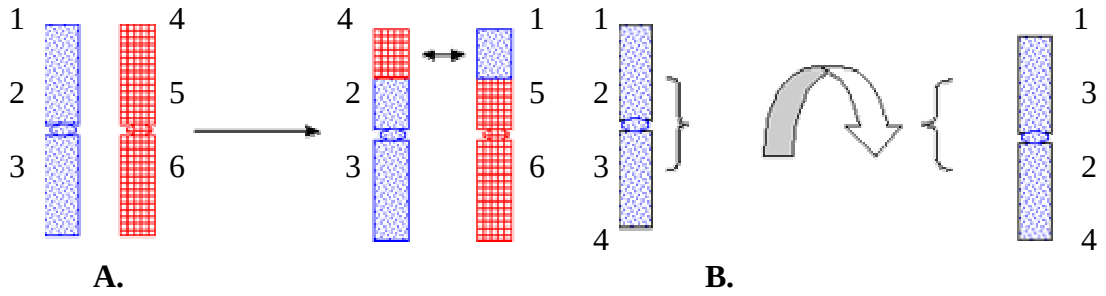

Figure 1. Generation of reciprocal translocations (Panel A) and Inversions (Panel B). Homologous chromosomal regions are designated by the numbers 1-6.

The effects of these aberrations depend on a variety of factors. First, the original break in the chromosomal material could have a dramatic effect on gene expression if it occurs in a regulatory region or in a coding region. In fact, Burkitt's lymphoma is often associated with a translocation of the *MYC* oncogene on chromosome 8 to chromosome 14. This translocation changes the expression of the gene, causing cancer. Since duplications and deletions almost always result in the gain or loss

of gene copies, they tend to have more dramatic effects on the individual than do translocations and inversions, which only change the arrangement of the genetic material, rather than its content.

Nevertheless, even translocations and inversions can have a dramatic effect on individual fertility, particularly in individuals heterozygous for the aberration. In this activity, you will use pipe cleaner chromosomes to model meiosis in such duplication, translocation and inversion heterozygotes.

Procedure:

Duplication Heterozygotes: Practicing Synapsis

1. Get a duplication chromosome set, and remove the handle, separating the two chromosomes. Write down the sequence of gene regions on both homologs. Which region is duplicated?
2. Synapse the homologs, remembering that chromosomes are flexible, and regions that cannot pair will simply loop out. Check your synapsis with the correctly synapsed duplication heterozygote shown in Figure 2 below.

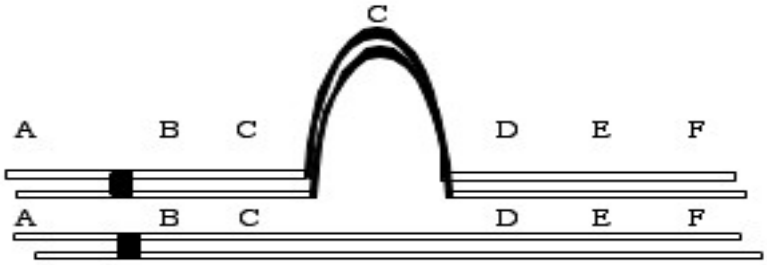

Figure 2. Synapsis in a duplication heterozygote. The duplicated region (C) is shown in black. Homologous chromosomal regions are labeled A-F.

Translocation Heterozygotes

1. Get a translocation chromosome set, and remove the handle, separating the four chromosomes. Write down the sequence of gene regions on all four chromosomes. Note that only one member of each homologous pair is translocated. Thus, this individual is referred to as a translocation heterozygote.
2. Synapse the chromosomes, remembering that chromosomes are flexible, and that all gene segments must align with their match (A with A, B with B, etc). Show your instructor your synapsed chromosomes.
3. Perform anaphase I. That is, pull any two centromeres towards one pole, and the other two towards the other pole. Show your instructor your results, then complete meiosis and draw the chromosomes that would be found in the resulting gametes in the space below. Are these gametes normal, or would they have deletions and duplications?
4. Repeat this process for all three possible segregation types (see the figure in your textbook for help), and write down the gametes you would get in each case. What proportion of the gametes in an inversion heterozygote would be expected to generate viable offspring?
5. Would you expect to see the same results if this person was a translocation homozygote?

Inversion Heterozygotes

1. Get an inversion heterozygote chromosome set, and remove the handle. You should have two homologous chromosomes, one of which has an inverted region. Each chromosome consists of two sister chromatids, attached at the centromere. Make sure that the centromere is located between A and B on each chromosome.
2. Synapse the homologs again, remembering that your goal is to align each and every gene region with its homolog. Show your synapsed chromosomes to your instructor.
3. Now, simulate a single crossover in the inversion loop by unhooking loops "2" and "4" and reattaching them to the non-sister chromatid loops "3" and "1" as shown in figure 3 below. It is critical that you keep your chromosomes synapsed in an inversion loop during this process, or you will not get the correct results,

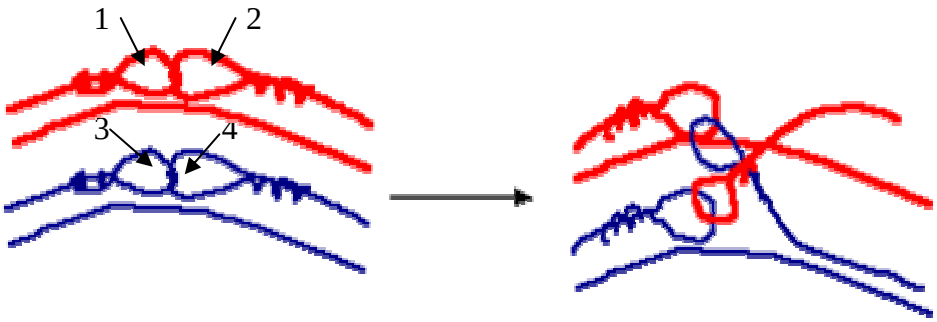

Figure 3. Diagram of crossing over in inversion heterozygote. A single loop is opened in each homologous pair, the strands are exchanged, and the loops are resealed.

4. Perform anaphase I by slowly pulling the centromeres towards opposite poles. What do you observe? Can meiosis complete itself normally?
5. Complete meiosis by unwinding the centromere to allow the sister chromatids to separate. Write down the sequence of gene regions that you would see in each gamete. Which gametes would you expect to produce viable offspring?
6. Reassemble your chromosomes, but place the centromere between C and D. This type of inversion is calle a pericentric inversion. The previous inversion, which did not include the centromere, is called a paracentric inversion. Repeat steps 2-5.

Discussion Questions

1. Inversions are sometimes called "crossover suppressors," even though they do not decrease the frequency of crossing over. Why is this?
2. Describe how you might determine if translocations or inversions have caused the Cumbersomes' fertility difficulties.

The Mini-Mystery – Instructor Materials

While the length of this activity – approximately 2 hours – is far longer than most of us would normally spend on a discussion of chromosomal aberrations, we have found that the opportunity to really see, feel and model what is happening in these unusual meioses is an invaluable review of meiosis as a whole, and well worth the time. We also often include an issues activity in which the students have to simulate a counseling appointment with the Cumbersomes. Two excellent web resources that we use to guide this activity are listed in the Web References section below.

Materials Needed per Group of Four Students

- 1 translocation kit (16 chromosomes, two colors)
- 1 Inversion kit (16 chromosomes, three colors)
- 1 duplication kit (four pipecleaners, two colors)

Translocation Kit. The translocation kit consists of two pairs of homologous pipe cleaner chromosomes that have undergone a reciprocal translocation. For ease of synapsis, each chromosome arm consists of a full pipe cleaner, and each homolog is a different color. Additionally, the translocation itself consists of an entire chromosome arm, so the translocated chromosomes will be half one color and half the other, as shown in the figure below. Chromosome regions are labeled using masking tape and a sharpie.

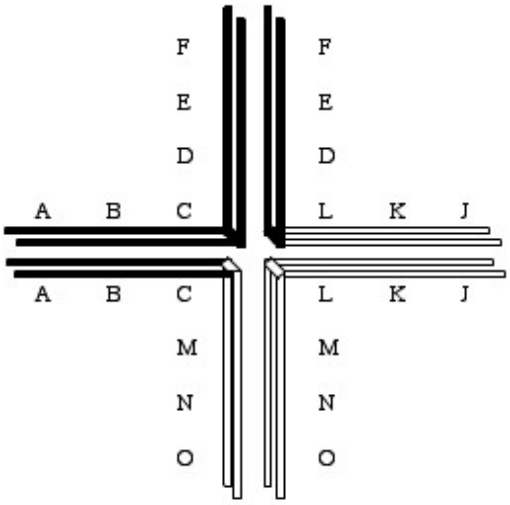

Figure 4. Pairing of homologs in a translocation heterozygote.

Inversion Kit. The inverted chromosomes must be much longer than the others, if the crossing over exercise is to work. I generally twist together four pipe cleaners, with the inverted region represented by the middle two. The centromeres and the inverted chromosomal region use different color pipe cleaners than the rest of the chromosome.

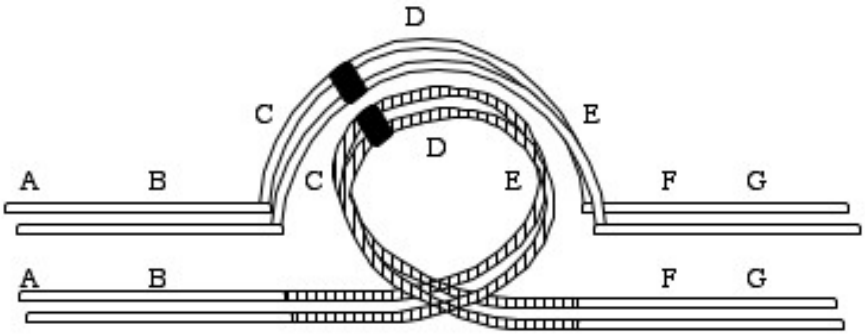

Figure 5. Pairing of homologs in a pericentric inversion heterozygote. The inverted region, (CDE), is shown with vertical stripes.

Duplication Kit. The duplication kit is shown in Figure 2 in the student materials.

Web References

Workshop Biology Homepage
http://yucca.uoregon.edu/wb/

American Medical Association Family History Tools
http://www.ama-assn.org/ama/pub/category/2380.html

Debra Collins Simulated Genetic Counseling Activity
http://www.kumc.edu/gec/gcsim/html