Aneuploidy & chromosomal rearrangement

Aneuploidy and nondisjunction. Down syndrome and related disorders. Chromosomal rearrangements.

Introduction

Some things just work well in pairs. Everyday examples include shoes, gloves, and the ear-buds on a music player. If you're missing one member of a pair, it's likely to be a nuisance, and might even be a serious problem (for instance, if you're already late for school!).

Pairs are important in genetics, too. Most of your cells contain 46 chromosomes, rod-like structures made of DNA and protein that come in 23 perfectly matched pairs. These chromosomes carry tens of thousands of genes, which told your body how to develop and keep it functioning from moment to moment during your lifetime.

Image credit: "Human genome," by Webridge (CC BY 2.0)

If a chromosome pairs loses or gains a member, or even part of a member, the delicate balance of the human body may be disrupted. In this article, we'll examine how changes in chromosome number and structure come about, and how they can affect human health.

Aneuploidy:

Extra or missing chromosomes Changes in a cell's genetic material are called mutations. In one form of mutation, cells may end up with an extra or missing chromosome.

Each species has a characteristic chromosome number, such as 46chromosomes for a typical human body cell. In organisms with two full chromosomes sets, such as humans, this number is given the name 2n. When an organism or cell contains 2n chromosomes (or some other multiple of n), it is said to be euploid, meaning that it contains chromosomes correctly organized into complete sets (eu- = good). If a cell is missing one or more chromosomes, it is said to be aneuploidy (an- = not, "not good"). For instance, human somatic cells with chromosome numbers of (2n − 1) = 45or (2n + 1) = 47are aneuploid.

Similarly, a normal human egg or sperm has just one set of chromosomes (n = 23). An egg or sperm with (n − 1) = 22or (n + 1) = 24chromosomes is considered to be aneuploid.

Two common types of aneuploidy have their own special names:

Monosomyis when an organism has only one copy of a chromosome that should be present in two copies (2n − 1).

Trisomyis when an organism has a third copy of a chromosome that should be present in two copies (2n + 1).

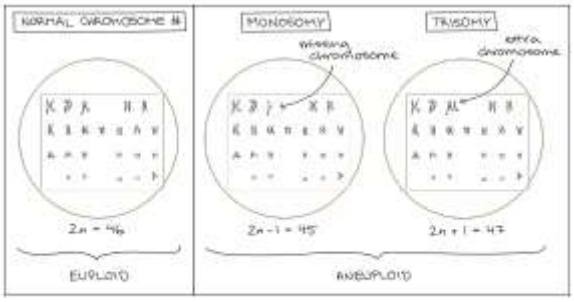


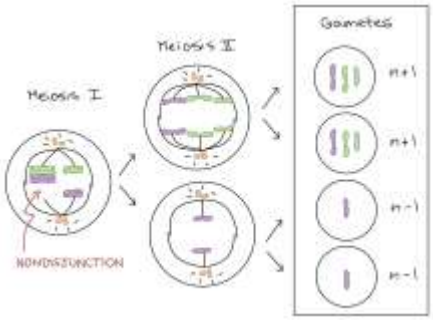
Image modified from "NHGRI human male karyotype," by the National Human Genome Research Institute (public domain.

Aneuploidy also includes cases where a cell has larger numbers of extra or missing chromosomes, as in (2n − 2), (2n + 3), etc. However, if there is an entire extra or missing chromosome set (e.g., 3n), this is not formally considered to be aneuploidy, even though it may still be bad for the cell or organism. Organisms with more than two complete sets of chromosomes are said to be polyploid.

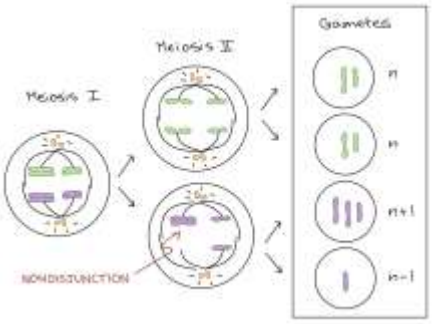
Nondisjunction of chromosomes Disorders of chromosome number are caused by nondisjunction, which occurs when pairs of homologous chromosomes or sister chromatids fail to separate during meiosis I or II (or during mitosis).

Meiosis I.

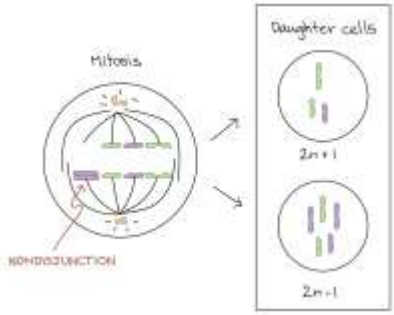
The diagram below shows how nondisjunction can take place during meiosis I if homologous don't separate, and how this can lead to production of aneuploid gametes (eggs or sperm):



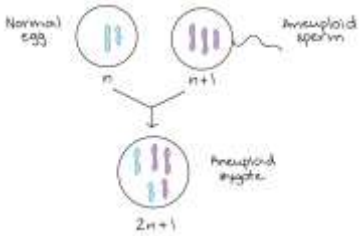
Meiosis II. Nondisjunction can also happen in meiosis II, with sister chromatids (instead of homologous chromosomes) failing to separate. Again, some gametes contain extra or missing chromosomes:



Mitosis. Nondisjunction can also happen during mitosis. In humans, chromosome changes due to non-disjunction during mitosis in body cells will not be passed on to children (because these cells don't make sperm and eggs). But mitotic non-disjunction can cause other problems: cancer cells often have abnormal chromosome numbers.



When an aneuploid sperm or egg combines with a normal sperm or egg in fertilization, it makes a zygote that is also aneuploid. For instance, if a sperm cell with one extra chromosome (n + 1) combines with a normal egg cell (n), the resulting zygote, or one-celled embryo, will have a chromosome number of 2n + 1.



Genetic disorders caused by aneuploidy Human embryos that are missing a copy of any autosome (non-sex chromosome) fail to develop to birth. In other words, human autosomal monosomies are always lethal. That's because the embryos have too low a "dosage" of the proteins and other gene products that are encoded by genes on the missing chromosome.

Most autosomal trisomies also prevent an embryo from developing to birth. However, an extra copy of some of the smaller chromosomes (13, 15, 18, 21, or 22) can allow the affected individual to survive for a short period past birth, or, in some cases, for many years. When an extra chromosome is present, it can cause problems in development due to an imbalance between the gene products from the duplicated chromosome and those from other chromosomes. The most common trisomy among embryos that survive to birth is Down syndrome, or trisomy 21. People with this inherited disorder have short stature and digits, facial distinctions including a broad skull and large tongue, and developmental delays. Here is a karyotype, or image of the chromosomes, from a person with Down syndrome, showing the characteristic three copies of chromosome 21:

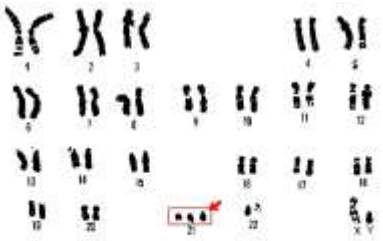


Image credit: "21 trisomy - Down syndrome," by the U.S. Department of Energy Human Genome Program (public domain).

About 1in every 800 newborns is born with Down syndrome. However, the likelihood that a pregnancy will result in an embryo with Down syndrome goes up with a woman's age, particularly above 40years. This is probably because of more frequent nondisjunction in the developing eggs of older women.

Why is this the case?

Human genetic disorders can also be caused by aneuploidies involving sex chromosomes. These aneuploidies are better-tolerated than autosomal ones because human cells have the ability to shut down extra X chromosomes in a process called X inactivation. You can learn more in the article on X chromosome inactivation.

Chromosomal rearrangements

In another class of large-scale mutations, big chunks of chromosomes (but not entire chromosomes) are affected. Such changes are called chromosomal rearrangements. They include:

A duplication, where part of a chromosome is copied.

A deletion, where part of a chromosome is removed.

An inversion, where chromosomal region is flipped around so that it points in the opposite direction.

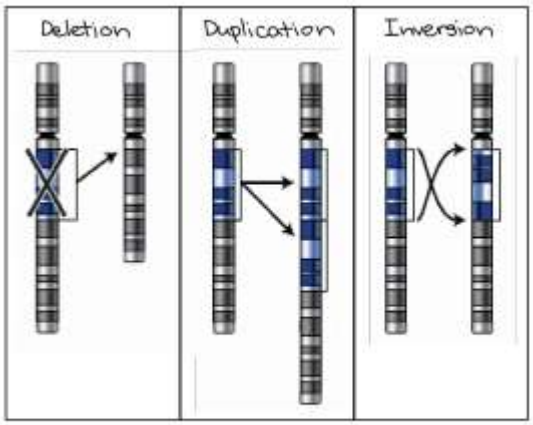


Image modified from "Chromosomenmutation," by Deltzel66, modified from NIH Talking Glossary of Genetics (public domain).

A translocation, where a piece of one chromosome gets attached to another chromosome. A reciprocal translocation involves two chromosomes swapping segments; a nonreciprocal translocation means that a chunk of one chromosome moves to another.

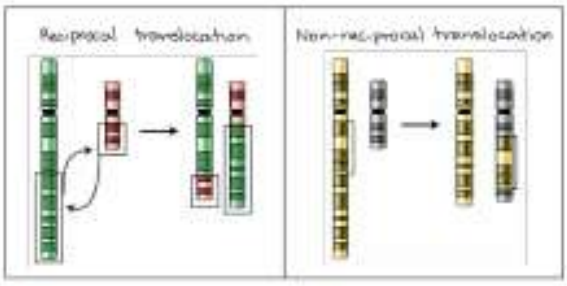


Image modified from "Chromosomenmutation," by Deltzel66, modified from NIH Talking Glossary of Genetics (public domain).

In some cases, a chromosomal rearrangement causes symptoms similar to the loss or gain of an entire chromosome. For instance, Down syndrome is usually caused by a third copy of chromosome 21, but it can also occur when a large piece of chromosome 21moves to another chromosome (and is passed on to offspring along with a regular chromosome 21). In other cases, rearrangements cause unique disorders, ones that are not associated with aneuploidy.