Segregation and the Principle of independent assortment

The Principle of Independent Assortment describes how different genes independently separate from one another when reproductive cells develop. Independent assortment of genes and their corresponding traits was first observed by Gregor Mendel in 1865 during his studies of genetics in pea plants. Mendel was performing dihybrid crosses, which are crosses between organisms that differ with regard to two traits. He discovered that the combinations of traits in the offspring of his crosses did not always match the combinations of traits in the parental organisms. From his data, he formulated the Principle of Independent Assortment.

We now know that this independent assortment of genes occurs during meiosis in eukaryotes. Meiosis is a type of cell division that reduces the number of chromosomes in a parent cell by half to produce four reproductive cells called gametes. In humans, diploid cells contain 46 chromosomes, with 23 chromosomes inherited from the mother and a second similar set of 23 chromosomes inherited from the father. Pairs of similar chromosomes are called homologous chromosomes. During meiosis, the pairs of homologous chromosome are divided in half to form haploid cells, and this separation, or assortment, of homologous chromosomes is random. This means that all of the maternal chromosomes will not be separated into one cell, while the all paternal chromosomes are separated into another. Instead, after meiosis occurs, each haploid cell contains a mixture of genes from the organism's mother and father.

Another feature of of independent assortment is recombination. Recombination occurs during meiosis and is a process that breaks and recombines pieces of DNA to produce new combinations of genes. Recombination scrambles pieces of maternal and paternal genes, which ensures that genes assort independently from one another. It is important to note that there is an exception to the law of independent assortment for genes that are located very close to one another on the same chromosome because of genetic linkage.

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Review

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Nonrandom segregation during meiosis: the unfairness of females

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Abstract. Most geneticists assume that chromosome segregation during meiosis is Mendelian (i.e., each allele at each locus is represented equally in the gametes). The great majority of reports that discuss non-Mendelian transmission have focused on systems of gametic selection, such as the mouse *t*-haplotype and Segregation distorter in *Drosophila,* or on systems in which postfertilization selection takes place. Because the segregation of chromosomes in such systems is Mendelian and unequal representation of alleles among offspring is achieved through gamete dysfunction or embryonic death, there is a common perception that true disturbances in the randomness of chromosome segregation are rare and of limited biological significance. In this review we summarize data on nonrandom segregation in a wide variety of genetic systems. Despite apparent differences between some systems, the basic requirements for nonrandom segregation can be deduced from their shared characteristics: i) asymmetrical meiotic division(s); ii) functional asymmetry of the meiotic spindle poles; and iii) functional heterozygosity at a locus that mediates attachment of a chromosome to the spindle. The frequency with which all three of these requirements are fulfilled in natural populations is unknown, but our analyses indicate that nonrandom segregation occurs with sufficient frequency during female meiosis, and in exceptional cases of male meiosis, that it has important biological, clinical, and evolutionary consequences.

Introduction

Mendel's law of segregation states that each pair of homologous chromosomes segregate at meiosis in each generation, ensuring maintenance of proper chromosome number in sexually reproducing organisms and resulting in equal transmission of each allele at each locus. Formulated in this way, there are three classes of observation that violate this law. The first is due to missegregation of chromosomes or chromatids, resulting in an aneuploid meiotic product. This type of violation is a discrete event (i.e., one may determine that the law has been violated in an individual meiotic product) that is often associated with strongly deleterious effects in humans, as well as other organisms (Boue et al. 1985; Jacobs and Hassold 1995). The second class of violation is gene conversion, in which the DNA sequence of one allele is changed to that of the other. This type of violation can also be observed as a discrete event if all of the products of an individual meiosis are available for analysis. The third class of violation is statistical in nature (i.e., it is observed as unequal representation of alleles among a population of gametes or offspring) and can result from many causes, including mitotic events that occur in proliferating germ cells, nonrandom segregation of chromosomes during meiosis, differential viability or functionality of gametes, or differential survival during development (Fig. 1). Here we address only violations in the third class that are due to nonrandom segregation of chromosomes or chromatids during meiosis. This type of violation must reflect abnormalities in the cellular mechanism that is the basis of Mendel's law of segregation.

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A general model for nonrandom segregation

Over the last 65 years a number of models have been proposed to explain the mechanism of nonrandom segregation in different systems, and some important predictions of these models have been confirmed experimentally (Sturtevant and Beadle 1936; Catcheside 1945; Rhoades 1952; Rhoades and Dempsey 1966; Novitsky 1967; Hewitt 1976). Collectively, these studies indicate that there are three requirements for nonrandom segregation of chromosomes to occur. However, we are unaware of any instance in which the complete set of conditions has been stated explicitly or formulated into a general model.

The following conditions are both necessary and sufficient for nonrandom segregation of a chromosome or chromosomes: a) asymmetry in the meiotic division(s) with respect to cell fate; b) functional asymmetry of the meiotic spindle poles; and c) functional heterozygosity at a locus that mediates attachment of a chromosome to the spindle.

The fact that these requirements can be stated in a way that relates mechanistic features of meiosis to the process of nonrandom segregation allows one to make mechanistic inferences about one nonrandom segregation system from knowledge gained in another. In contrast, knowledge of the biochemical mechanism by which gametes are rendered nonfunctional in one gametic selection system has little power to explain the mechanism by which gametes are rendered nonfunctional in any other gametic selection system.

a) Asymmetrical meiotic division. Meiosis is a special type of cell division that results in the formation of haploid gametes from diploid cells. In mammals (and many other organisms), cells from the diploid germ line undergo two consecutive rounds of cell division, without intervening DNA replication, to produce haploid gametes (Fig. 1). At the first meiotic division (MI), each homologous chromosome segregates to opposite poles of the spindle. At the second meiotic division (MII), each chromatid of an individual dyad undergoes a similar segregation to opposite poles of the spindle. Because recombination (the exchange of DNA between non-sister chromatids of homologous chromosomes) takes place during prophase of MI, the subsequent segregation of chromosomes/chromatids dictates that each product of meiosis is genetically distinct. (However, there are exceptional meioses in which

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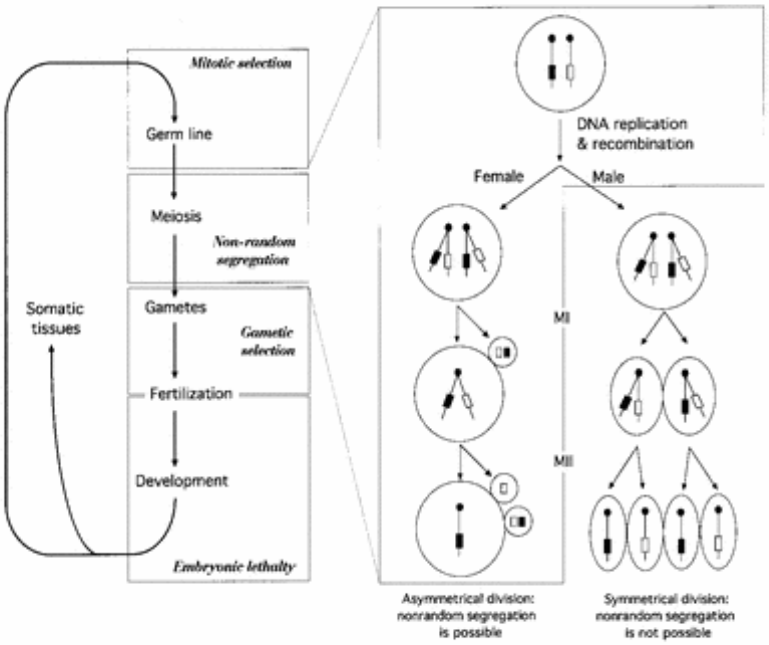

Fig. 1. Multiple origins of true and apparent violations of Mendel's law of segregation. The basic life cycle of sexually reproducing organisms is shown at the left. At each stage the mechanisms that may cause transmission ration distortion are shown in italics. Although mitotic selection is shown as taking place before meiosis, it may also occur after meiosis in organisms that have post-meiotic mitotic divisions before formation of the gametes. Missegregation and gene conversion represent two additional types of true violation of Mendel's law of segregation occurring at meiosis. However, they are not shown because they are discrete events, and the mechanisms responsible for either one are distinct from nonrandom segregation (see text). The right side of the figure shows a schematic of meiosis in males and females. Note that meiotic divisions are asymmetric with respect to cell fate in females but symmetric in males. The processes of DNA replication, recombination, and chromosome/chromatid segregation are shown for only one chromosome. MI, first meiotic division. MII, second meiotic division.

recombination does not occur, i.e., males of many species of insects, including *Drosophila*).

Although the same basic process occurs in both males and females, there are important differences between meiosis in each sex. The most relevant for nonrandom segregation is the number of functional meiotic products generated from each gonocyte. The number of functional products is determined by the symmetrical or asymmetrical nature of MI and MII with respect to cell fate. As a general rule, MI and MII are symmetrical divisions in males, and meiosis generates four functionally equivalent gametes (Fig. 1). In contrast, each of the two meiotic divisions in females is asymmetric and results in an oocyte and a polar body, each having a different morphology and developmental fate, such that only one functional gamete is generated per primary oocyte (Fig. 1).

This asymmetry of female meiosis establishes a crucial difference between the sexes in the mechanisms by which Mendel's law of segregation can be violated. Note that at the onset of male meiosis (Fig. 1), there are as many chromatids as there will be meiotic products. Therefore, in the absence of gene conversion, it is not possible to have unequal representation of alleles among euploid MII products (gametes). In contrast, only one chromatid out of the initial four will be selected during the two asymmetrical divisions of a female meiosis and be transmitted to offspring. Therefore, any factor that influences the randomness with which chromosomes are partitioned between the oocyte and polar body will result in unequal representation of alleles.

Although this distinction between female and male meiosis applies to most multicellular eukaryotic organisms, it is noteworthy that there are cases of asymmetrical division in male meiosis (Crouse 1960). In such males nonrandom segregation is not only theoretically possible, but has been observed (Table 1).

Although a requirement for asymmetrical cell division in nonrandom segregation has been recognized for many years (Sturtevant and Beadle 1936), the further cytological implications of this requirement have not been explored in detail. Known examples of asymmetrical cell division involve the establishment of a cellular gradient of a product(s) that determines the differential fate of the two cells after cell division (Fig. 2a). Such gradients can have a differential effect on the products of cell division only if the spindle is oriented in such a way that the daughter cells receive unequal amounts of the product (Fig. 2a). This, in turn, requires the precise orientation of the spindle with respect to the gradient (Fig. 2a). In several examples of asymmetrical cell division, the orientation of the spindle is mediated by the interaction of one of its poles with the gradient (Schober et al. 1999; Hoyt 2000; Wodarz et al. 2000).

b) Functional asymmetry of the meiotic spindle poles. Nonrandom segregation may be described as the preferential passing of a specific chromosome to a specific pole (Rhoades 1942). As emphasized by Catcheside (1945), such an event requires a dual inequality; first, a difference must exist between the two poles of the spindle (Fig. 2b), and second, the pair of homologous chromosomes exhibiting the bias must be different (Fig. 2c).

Although the logical requirement for functional asymmetry of the spindle poles is unassailable, direct experimental evidence for functional asymmetry also exists. The grasshopper *Myrmeleotettix maculatus* carries variable numbers of B chromosomes. Transmission of these B chromosomes through males is Mendelian, but there is a significant excess of offspring that inherit B chromosomes through females (Hewitt 1976). This example of transmission ratio distortion ("TRD": a statistically significant departure from the Mendelian inheritance ratio expected regardless of the cause; see Description of Terms) is owing to nonrandom segregation of B chromosomes at the first meiotic division of oogenesis. Hewitt (1976) demonstrated that the meiotic spindle of this organism is asymmetric, with the egg side being much larger than the polar body side (Fig. 2b2). Because the B chromosomes are distributed along the entire length of the spindle in a volume-dependent manner, they are more likely to be located on the egg-pole side of the plate at the onset of anaphase. Remarkably, the level of nonrandom segregation among the progeny is identical to the ratio of B chromosomes located in the egg-pole versus the polar body-pole. A similar result has been reported for the B chromosome of the plant *Lilium callosum* (Kayano 1957).

Another example has been reported in the Dipteran fly, *Sciara* (and related organisms, including *Trichosia*). In this insect, male meiosis is asymmetric with respect to cell fate (Crouse 1960). The nonrandom segregation observed derives from functional differ-

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Principal Investigator: Juraj Gregan

How does the cell ensure that during cell division each daughter cell inherits one copy of every chromosome? Meiosis is a specialized cell division which produces haploid gametes from diploid cells, how is this reduction of chromosome number achieved? We want to understand how cells accurately segregate their chromosomes during mitosis and meiosis. It is important to understand this process because defects in chromosome segregation (missegregation) during mitosis result in cells with abnormal number of chromosomes. Such cells are hallmarks of cancer. Moreover, defects during meiosis cause miscarriages, infertility and genetic diseases such as Down's syndrome

Chromosome segregation during meiosis

The reduction of chromosome number during meiosis is achieved by two successive rounds of chromosome segregation, called meiosis I and meiosis II. While meiosis II is similar to mitosis in that sister kinetochores are bi-oriented and segregate to opposite poles, recombined homologous chromosomes segregate during the first meiotic division. Formation of chiasmata, mono-orientation of sister kinetochores and protection of centromeric cohesion are three major features of meiosis I chromosomes which ensure the reductional nature of chromosome segregation. In our studies we use the fission yeast *S. pombe*, which is an excellent model organism amenable to both genetic and cell biology techniques, to identify new proteins required for proper segregation of chromosomes during meiosis. In order to decipher molecular functions of identified proteins, we combine biochemical and cell biology techniques. To test the possible

functional conservation of identified proteins, we plan to analyze the function of the respective homologs in mammalian cells.

Chromosome segregation during mitosis.

Accurate chromosome segregation in mitosis depends on the establishment of correct (amphitelic) kinetochore orientation. Merotelic kinetochore orientation is an error which occurs when a single kinetochore is attached to microtubules emanating from opposite spindle poles. Recent studies showing that merotelic kinetochore attachment represents a major mechanism of aneuploidy in mitotic cells and is the primary mechanism of chromosomal instability in cancer cells underline the importance of studying merotely. We focus on fission yeast proteins required to prevent and correct merotelic attachments in order to understand how cells ensure high fidelity of chromosome segregation.