Nondisjunction — Definition and Examples

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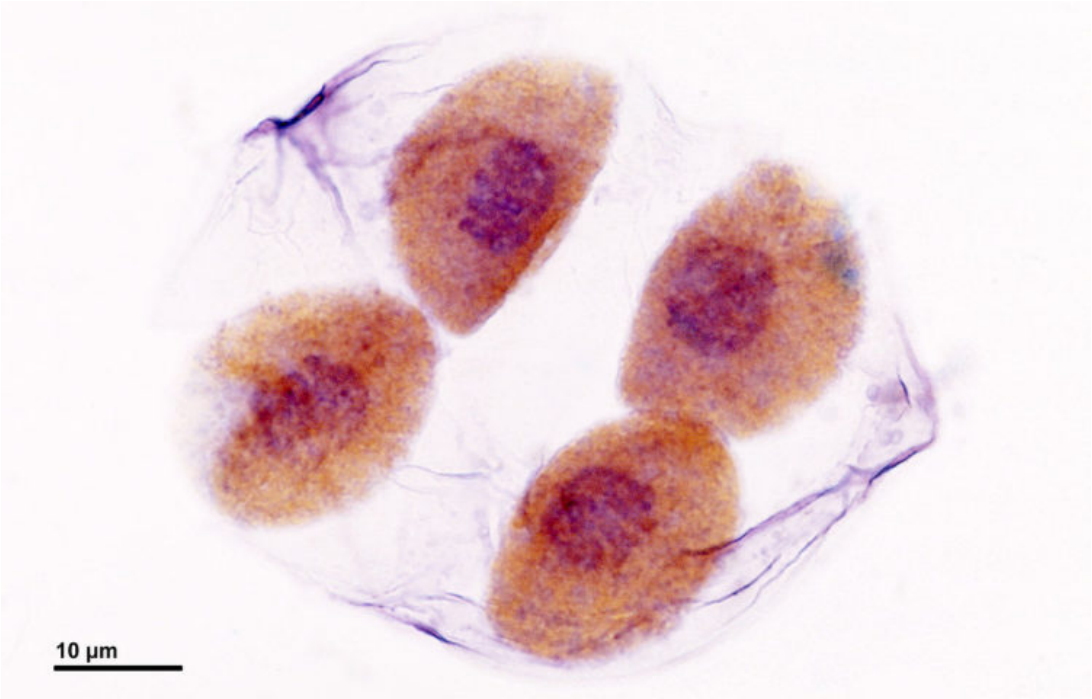
Nondisjunction connotes the failure of the separation of homologous chromosomes during cell division. It has significant repercussions and is culpable for a large share of chromosomal anomalies like aneuploidy and various hereditary syndromes. With a brief introduction to the basic structure of a chromosome and characteristics of nondisjunction, this article focuses on clinical implications of the same.



Basic Structure of Chromosomes

A **chromosome** is the carrier of genes, the molecules ultimately responsible in carrying forward the hereditary set of information about protein synthesis and, in turn, the functioning of the entire cell.

Every chromosome consists of a **pair of chromatids**. Similar chromosomes exist in pairs and are termed as **homologous chromosomes**.

A normal structural human cell carries two sets, 23 pairs of homologous chromosomes, which is 46 chromosomes in total. These are the **diploid cells**.

The male and female **gamete cells** responsible for reproduction have only one set of homologous chromosomes, the total is 23 and is termed as **haploid cells**.

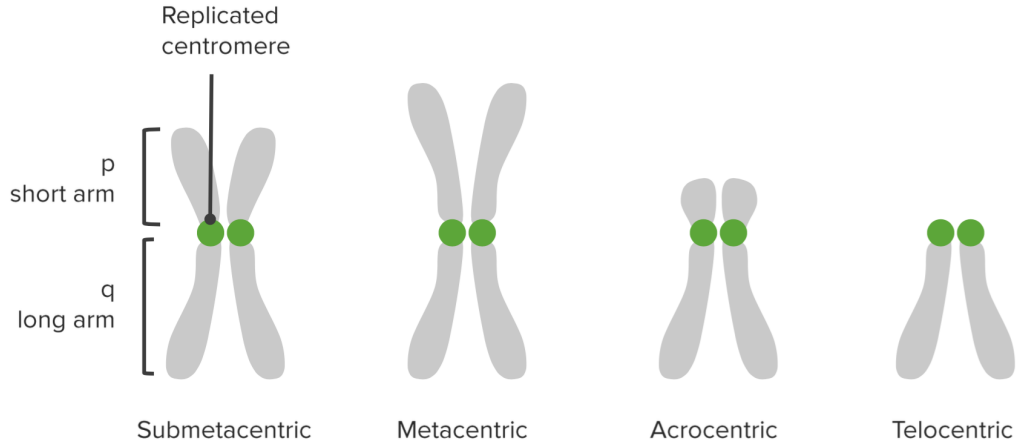
The **centromere** is the part of the chromosome where the sister chromatids are linked. Through the **kinetochore**, the spindle fibers attach at the centromere during cell

division.

The centromere abscinds each chromosome into two arms: the short arm being called **“p”** and the longer one the **“q”** arm. (p for “petit“ in French which means small.)

Based on the location of the centromere, different types of chromosomes are described:

Type	Explanation
Metacentric	Centromere is in the middle; p and q arms are equal in length.
Submetacentric	P and q arms are almost equal.
Telocentric	Centromere is present near to one end; the p arm is very small.
Acrocentric	The P arm is small, but slightly longer compared to telocentric chromosomes.



Cell division consists of the division of genetic material and cytogenesis. Genetic material can either undergo **mitosis** or **meiosis**.

Mitosis

In mitosis, one diploid cell gives rise to two diploid cells. The two daughter cells thus produced are genetically identical to the mother cell.

The table shows the various stages of mitosis:

Stage	Explanation
Interphase	In cell division, mitotic phase alternates with interphase – the time when the cell prepares itself for the division. Synthesis of proteins, cytoplasmic organelles, and genetic material is the hallmark of this phase.
Prophase	Chromosomal condensation and initiation of mitotic spindle formation mark the prophase.
Metaphase	Chromosomal separation after attachment of microtubules at the centromere and proper alignment along the metaphase plate or the equatorial plate occurs in metaphase. Metaphase checkpoints ensure equal distribution of the chromosomes at the end of the mitotic phase of cell division.
Anaphase	Anaphase culminates in the formation of identical daughter chromosomes. Cohesins that bind the sister chromatids together are cleaved in this phase. The microtubules shorten with a resultant pull of a set of newly-formed daughter chromosomes towards opposite ends of the cell.
Telophase	Derived from the Greek word “telos” which signifies the end, telophase is the end of the mitotic phase of cell division. It is a reversal of prophase in many ways. Two daughter nuclei with an identical set of chromosomes are formed at the end of telophase.

Meiosis

There are two phases of meiosis, namely phase I and phase II.

Reductive division occurs in phase I. **Chromosomal crossover**, also a unique feature of phase I, leads to an exchange of genetic material between homologous chromosomes. The end result of meiosis is the formation of **four genetically distinct haploid cells**. Two haploid gametes fusion during fertilization re-establishes the diploid nature of the

embryo.

Error in meiosis like nondisjunction is one of the most prevalent causes of **miscarriage** and **developmental disabilities** secondary to a genetic cause.

Phase I of meiosis can be summarized as follows:

Stage	Explanation
Prophase I	This is the longest phase of meiosis. **Chromosomal crossover** leading to genetic variation in the resultant daughter haploid cells takes place in prophase. Prophase is divided into the following stages: • **Leptotene** • **Zygotene** • **Pachytene** • **Diplotene** • **Diakinesis**
Metaphase I	Homologous chromosome pairs move along the metaphase plate in this stage.
Anaphase I	Homologous chromosomes move towards opposite poles secondary to the shortening of kinetochore microtubules in this phase.
Telophase I	This stage marks the end of the first meiotic division. Two daughter cells genetically distinct from the mother cell are formed with half the number of chromosomes. Each chromosome consists of a pair of chromatids.

Phase II of meiosis is identical to mitosis. It involves the separation of sister chromatids along the equatorial plane; thus, at the end of meiosis, four haploid cells are formed.

With this basic insight of normal chromosomal anatomy and cell division, we are fit to progress to nondisjunction.

Definition of Nondisjunction

Failure of proper separation of two homologous chromosomes or the sister chromatids during cell division is termed as **nondisjunction**.

History

Time attests to the discovery of nondisjunction in the spring of 1910 at the hands of **Calvin Bridges** and **Thomas Hunt Morgan**. They found aberrant chromosomal behavior while studying Drosophila melanogaster sex chromosomes.

Types of Nondisjunction

Type	Explanation
Meiotic nondisjunction phase I	All haploids derived from the primary cell are abnormal. For example all sperms derived from a primary spermatocyte will have a total of 22 or 24 chromosomes rather than the usual 23.
Meiotic nondisjunction phase II	Only half of the haploids derived from the primary cell will be abnormal. For example: If nondisjunction affects a secondary spermatocyte undergoing meiosis II, only half the sperms are abnormal.
Mitotic nondisjunction	Secondary to the break of the spindle fibers during metaphase or anaphase, mitotic nondisjunction results in the formation of trisomic and monosomic daughter cells, which give rise to mosaic cell lines in an individual.

Etiogenesis of Nondisjunction

Molecular mechanisms behind nondisjunction can be briefly summarized as follows:

Mechanism	Explanation
Sex-specific differences in meiosis	Maternal oocytes are prone to have segregation errors as there is documented arrest of oocytes in prophase I of meiosis. As a corollary, the fact remains that **most of the human aneuploidy syndromes are maternally derived**.
Age-related loss of Cohesin ties	Cohesin is responsible for the attachment of spindle fibers to the sister chromatids and subsequent normal separation of the same. Prolonged maternal oocyte arrest in meiosis leads to a loss of cohesion ties; a higher possibility of incorrect spindle kinetochore-microtubule attachment with resultant segregation errors.

Spindle Assembly Checkpoint (SAC) malfunction	The SAC ensures normal chromosomal separation and alignment during anaphase of cell division. Aberrant functioning of the SAC can lead to nondisjunction.

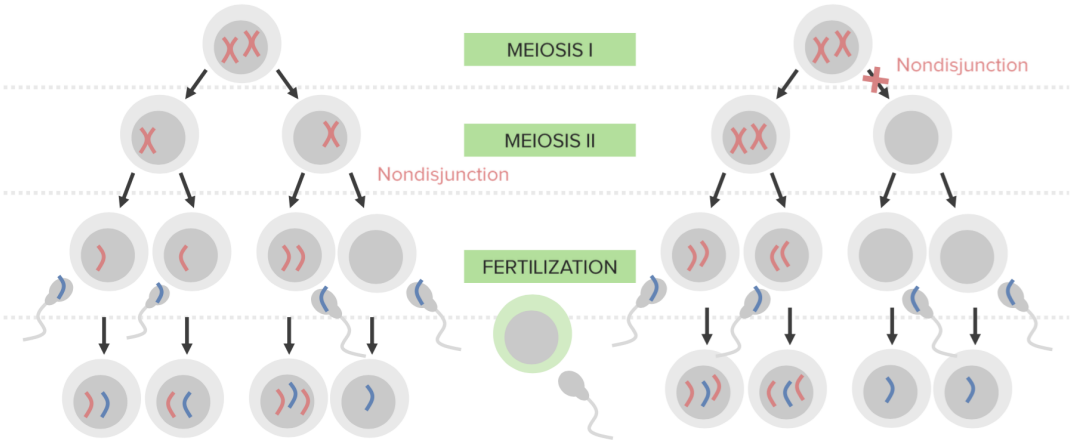
Diagnosis of Nondisjunction

Nondisjunction can be clinically identified using a battery of tests as shown in the table below:

Test	Explanation
Polar body diagnosis	Used to detect maternally derived chromosomal aneuploidies.
Karyotyping	A technique using light microscopy to study unborn fetus cells obtained through amniocentesis.
Blastomere biopsy	Involves removal of blastomeres from zona pellucida to detect aneuploidy. This procedure is not without risks.
Preimplantation genetic diagnosis	Used in couples with a family history of genetic disorders who opt for in-vitro fertilization.

Clinical Implications of Nondisjunction

Nondisjunction results in **aneuploidy** – a state of chromosomal imbalance. Loss of a single chromosome is termed as **monosomy**, while the gain of a single chromosome is referred to as **trisomy**. The majority of thus produced chromosomal aberrations are **incompatible with life** and are the reason for the majority of **first trimester spontaneous abortions**.



aneuploid

The study of nondisjunction reveals links between increasing maternal age and increased chances of recombination. It also provides validation of the **chromosomal theory of heredity** (Bridges 1916).

Knudson's 2 hit hypothesis for malignant transformation of cells propagates the existence of a 2-step metamorphosis of the normal cell. While the first hit is supposed to be inborn, the second hit may be caused by mitotic nondisjunction.

The few viable **syndromic chromosomal aberrations** can be summarized as follows:

Chromosomal aberration	Explanation
Monosomy	Turner syndrome (XO) is the only viable monosomy compatible with life in humans.
Autosomal aneuploidy	
Patau syndrome (trisomy 13)	Trisomy of chromosome 13 results in Patau syndrome. It is characterized by microcephaly, intellectual disability, ocular issues, urogenital and musculoskeletal disturbances.
Edwards' syndrome (trisomy 18)	Edwards' syndrome is marked by the presence of extra segment-part or whole of chromosome 18. Its characteristic features are growth retardation, heart defects, micrognathia, severe mental retardation and clenched fists with overlapping fingers.

Down syndrome	Trisomy 21 is one of the most common chromosomal segregation errors in humans. Notoriously known as “Down syndrome,” it is characterized by growth retardation, intellectual disability, and multiple neurological and cardiovascular issues.
Sex chromosome aneuploidy	
Turner syndrome (XO)	As already mentioned, this is the only monosomy compatible with life in humans. It is characterized by a short webbed neck, normal intelligence, short stature, and a higher risk of vision and hearing issues.
Klinefelter syndrome (XXY)	This syndrome is characterized by the presence of 2 or more X chromosomes in males. It is marked by primary sterility, aggressive behavior and often normal intelligence with minor speech and reading difficulties.
Supermales (XYY)	Characterized by XYY genotype, this condition is marked at an incidence of about 1 in 1,000 male births. Many patients are phenotypically normal with greater height, occasional aggressive behavior and learning disabilities. It is a result of nondisjunction in paternal meiosis phase II.
Superfemales (XXX)	Trisomy X, also termed as superfemales, have mild neuropsychological disturbances. The majority of these are a culmination of nondisjunction in maternal meiosis.
Uniparental disomy	This is a unique combination of nondisjunction leading to autosomal trisomy and subsequent loss of the unpaired chromosome, leading to the existence of 2 copies of a chromosome of uniparental origin. Examples include **Prader-Willi syndrome** and **Angelman syndrome**.
Mosaicism syndromes	Early fetal mitotic nondisjunction leads to the simultaneous existence of different cell lines in the same individual. **Hypomelanosis of Ito** is an illustration of such mosaicism syndromes.

Summary

Chromosomes consist of **pairs of chromatids**. Homologous chromosomes exist in pairs. The failure of proper separation of homologous chromosomes or chromatids during cell division is termed as nondisjunction.

Nondisjunction can occur during **meiosis phase I or phase II**, or **mitosis**.

There are **many tests** available to diagnose nondisjunction.

Nondisjunction results in **aneuploidy**. While most of these chromosomal segregation errors lead to **spontaneous abortions** in the first trimester, few are compatible with life and lead to **variable autosomal and sex chromosomal aneuploid syndromes**.

Review Questions

The correct answers can be found below the references.

1. In acrocentric chromosomes, which of the following statements is true?

A. The centromere is present near to one end; the p arm is very small.
B. P and q arms are almost equal.
C. P arm is small but slightly longer as compared to telocentric chromosomes.
D. The centromere is in the middle; p and q arms are equal in length.

2. Which of the following syndromes is a result of uniparental disomy?

A. Hypomelanosis of Ito.
B. Prader-Willi syndrome.
C. Turner syndrome.
D. Klinefelter syndrome.

3. Which of the following statements is false?

A. Most of the human aneuploidy syndromes are maternally derived.
B. Aberrant functioning of the SAC can lead to nondisjunction.
C. Mitotic nondisjunction results in the formation of trisomic and monosomic daughter cells which give rise to mosaic cell lines in an individual.
D. In meiotic nondisjunction phase II, all haploids derived from the primary spermatocyte are abnormal.

References

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Correct answers: 1C, 2B, 3D

Notes