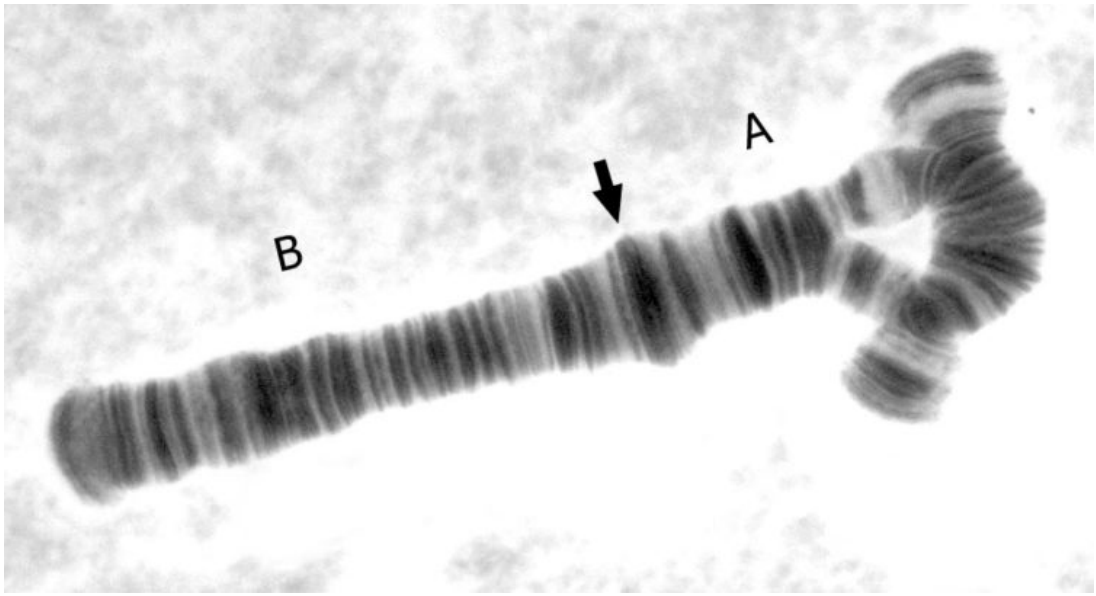
Segregation of Chromosomes with Inversions

See online here

Inversion is a type of chromosomal mutation which involves breakage and subsequent reunion of the same chromosomal segment but in reverse order. This article encompasses the basics of inversion and concludes with segregation characteristics and clinical implications of the same.



Definition of Inversion

Inversion refers to the rearrangement of a chromosome. Essentially, the chromosome is broken into three segments. The middle segment is inverted, i.e., turned 180 degrees, and then put back into place. The inversion forms a loop, where recombination occurs.

Inversions account for about 1-3 % of all genetic recombination in humans. The heterozygous carriers have no phenotypic abnormalities, but their gametes can have various combinations of deletions and duplications present. These may or may not be viable depending on the genes and the length of the chromosome involved.

History in Medical Science

The discovery of chromosomal inversion is credited to **Alfred Sturtevant,** who is known for the invention of genetic mapping. Inversions were recognized initially in the giant salivary chromosomes of Drosophila fly larvae. Indeed, inversions were one of the first genetic variation modalities ever studied.

Inversions do not result in the loss of any genetic material, and most are balanced; thus,

they initially appeared to be innocuous to many geneticists. Also, the analysis of inversions is complicated due to their inherent mediation through repeats. Hence, these mutations, even though discovered almost a century ago, have attracted little attention.

Types of Inversions

Inversions form a diverse group of **chromosomal mutations**. Some are silent phenotypically while others manifest in a stark manner. While most rearrangements are small, there are few very large inversions documented in the literature, such as the **3 RP inversion of the Drosophila melanogaster**. These inversions span thousands of genes and are multiple megabases in size.

There are **two types of inversions** described in the literature: paracentric and pericentric inversions.

Paracentric inversion

These inversion sequences occur in either chromosomal arm and do not include the **centromere**. Thus, recombination occurs in only one arm in part of the loop that forms because of the inversion. However, two other loops can form in the center of the chromosome, and a third loop forms near the centromere. Most chromosomal inversions in nature are paracentric.

Pericentric inversion

In this inversion sequence, the **centromere is a part of the segment that undergoes inversion,** and the breakpoints are on either side of the centromere. Thus, recombination occurs in two loops instead of one, and the chromosome can become shorter or longer. If there is a cross over with subsequent recombination in this segment, it forms an unbalanced gamete with either deletion, insertion, or two or zero centromeres, resulting in increased abnormal chromatids, which may lead to chromosomal imbalance. The end result is reduced fertility and overdominance of these inversions.

Other important terms associated with inversion can be described as follows:

- **Overdominance**: Inversions can lead to dominance and overexpression in some heterozygotes. This is usually a consequence of the effects of the breakpoints.
- **Associative overdominance**: This hypothesis propagates the formation of balanced polymorphism when inversion involves one or more recessive alleles. Such an inversion, when selected over other segments, results in the formation of recessive homozygotes, which leads to balanced polymorphism.

Mechanism of Inversion

The various mechanisms involved in the formation and propagation of inversions can be summarized as follows:

- Non-allelic homologous recombination (**NAHR**) between inverted repeats
- Double-stranded break repair mechanisms
- Non-homologous end-joining

- Processes based on replication conducted through **microhomology**, such as template switching or fork stalling.

Natural evolutionary drives, such as **natural selection** or **random drift,** are critical in repair or elimination of inversions with respect to their geographical distribution and prevalence in the population.

Diagnosis of Inversions

The different techniques for detecting inverted chromosomes are:

Technique	Explanation
Cytogenetic techniques	Meiotic chromosome cytology and mitotic chromosome analysis can be used to detect inversions using "**new arm ratios**" microscopically.
Genetic analysis	An **inversion loop** that forms during meiosis in inversion heterozygotes can reveal the inverted segment location. Entities like **recombination frequency** reduction and miniaturized fertility, secondary to unbalanced meiosis, are also useful.
Use of genetic markers	Mapped genetic markers can reveal an inverted segment's location when a cross-over demonstrates a consistently hindered recombination in part of the genome.
Human sperm studies	Human sperm often penetrate golden hamster eggs without fusion of the sperm nucleus in the egg cell. This is often followed by clear visibility of the human chromosomal set in the egg cell as an explicit group. This technique is often useful to study the meiotic yield of males with chromosomal segregation errors.
Chromosomal staining techniques	These techniques are helpful in visualizing inversions, but require great effort and often yield a poor resolution.
Significance of Polytene chromosomes	Larval salivary gland chromosomes reveal heterozygous inversions in species like Drosophila, which possess **polytene chromosomes**.

Clinical Implications of Inversions

There is **no loss of overall genetic material** in inversions. Most of the arrangements are balanced due to the existence of homologous chromosomes. Hence, inversions usually cause no phenotypical abnormalities in the carriers, which can make them difficult to detect. Indeed, current knowledge about chromosomal inversions is limited, and only a few inversions have been studied in detail in humans.

An unbalanced inversion is associated with problems such as retarded mental and physical growth and birth defects. Inversions may be involved in **pathological mutations** in a multitude of ways, such as direct altering of the gene structure, changing gene activity regulation, or predisposing the inversion heterozygote progeny to other secondary rearrangements with genetic significance.

Comparative genomics indicates that inversion may be one of the most significant mechanisms behind the evolution of the human genome. Inversions evolve by drift and selection mechanisms.

Chromosomes are structurally dynamic, and there are about 1,500 inversions that distinguish humans from chimpanzees. Inversions can also be critical in local adaptation and speciation. Some medical geneticists believe that fixed inversion differences might result in **incompatibility between species**.

The clinical implications of chromosomal inversions are summarized as follows:

Clinical scenario	Explanation
Chromosome 9 inversion	Inv (9) (p12 q13) is the most common inversion seen in humans. It is often innocuous in nature and phenotypical expression; however, equivocal evidence also indicates an increased risk of abortions and diminished fertility potential in affected individuals.

Spontaneous abortions	Inversions manifest in the affected heterozygous parent's offspring as either duplication or deletion genotypically. The gamete's phenotypical viability depends on the genes that make up the inverted segment and the segment length. Some of these inversions result in non-viability and spontaneous abortion.
Heterozygous chromosomal inversion	There is an increased propensity for the formation of abnormal chromatids, and subsequent lowered fertility, in individuals who are heterozygous for a particular inversion. The propensity increases when the chiasmal cross over of prophase I of meiosis takes place in this segment, producing unbalanced gametes. Some specific inversions show a propensity to be involved in meiosis; more than 50% of the time, they are encountered in the resultant haploid gametes.
Break within a gene	If inversion, with breakage and rapprochement, inculpates a gene with an indispensable function, a lethal gene mutation will form. It cannot be made homozygous.
Inversion loop formation with the omission of cross-over products	Abridged recombination in the daughter cells formed from an inversion heterozygote.
Inhibition of pairing of homologous chromosomes in the inversion segment	There is economized recombination and higher chances of genetically incomplete gametes.
Experimental use	Pericentric inversions at the tip, and paracentric inversions with overlapping breakpoints, have been put to experimental use to generate a specific desired chromosomal segment's duplication.
Duplication q-deletion p recombinant chromosome	This inversion, with the subsequent duplication of the q arm and deletion of the p arm, culminates in abnormal offspring. The deletion of the longer q segment is incompatible with life.
Sex chromosomes	Evidence suggests that a series of overlapping inversions could enlarge the non-homologous part of the Y chromosome. Some also believe that inversions may be instrumental in the origin of the sex chromosomes.
Other alterations in the genome	Inversions might lead to the following changes in an individual's genome: Nocent outcomes of genomic alteration, secondary to inversion, can lead to human genetic diseases. Adaptive mutation Disruption of an open reading frame with subsequent alteration of cell proteonomics. Alteration of gene expression in many ways such as silencing, truncation of protein synthesis, the altered, diminished, or complete absence of protein synthesis.

Inversions have been instrumental in evolution; thus, they have been explored in various studies involving diversified flora and fauna, such as:

- The size and developmental time in Drosophila
- Flowering time in plants
- Adaptation to freshwater in sticklebacks

Genetic counseling and testing: affected families or individuals with known inversions could be offered genetic counseling.

Summary

A chromosomal mutation involving breakdown and subsequent, almost simultaneous, recombination in reverse orientation, is known as "inversion." The prevalence of inversions is about 2 %. It is one of the oldest and most overlooked genetic rearrangements in the literature.

Most inversions are balanced and phenotypically invisible, so they do not alter health. An unbalanced inversion is associated with problems, such as birth defects, limited growth, and developmental delays. However, human studies are scarce, and these mutations' true clinical potential requires further examination.

There are paracentric and pericentric inversions. Paracentric inversions spare the centromere, while pericentric inversions occur on either side and include the centromere.

Various mechanisms have been proposed to establish the causes of inversions.

Inversions can be detected by a multitude of cytogenetic analysis techniques and chromosomal studies.

While some inversions are connected with reduced fertility and abortions in the offspring of inversion heterozygotes, other inversions may have a role in evolution, speciation, and local adaptation.

Inversions have also found a place in experimental genetics because they could be used to generate highly specific desired chromosomal segment's duplication.

Families with known inversions could be offered genetic counseling and testing. Like all chromosomal segregation errors, no cure is available.

References

Gardner, R.J.M; Sutherland, Grant R.; Shaffer, Lisa G. (2011). "9 Inversions". Chromosome Abnormalities and Genetic Counseling (4th ed.). Oxford University Press. pp. 161–182.

Griffiths AJF, Miller JH, Suzuki DT, et al. New York: W. H. Freeman; 2000. An Introduction to Genetic Analysis. 7th edition.

Kirkpatrick M (2010) How and Why Chromosome Inversions Evolve. PLoS Biol 8(9): e1000501.

Hoffmann A. A, Rieseberg L. H (2008) Revisiting the impact of inversions in evolution: From population genetic markers to drivers of adaptive shifts and speciation? Annu Rev Ecol Evol Syst 39: 21–42.

Sturtevant A. H, Mather K (1938) The interrelations of inversions, heterosis and recombination. Am Nat 72: 447–452.

Charlesworth B (1991) The evolution of sex chromosomes. Science 251: 1030–1033

Puig M, Casillas S, Villatoro S, Cáceres M. Human inversions and their functional consequences. Brief Funct Genomics. 2015 Sep;14(5):369-79.

Notes