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Bacterial DNA Recombination Events and Transposable Genetic Elements: Their Role in the Evolution of Bacterial Genetic Variability

Tariku Geinoro* and Wubshet Mulugeta

Hawassa University Faculty of Veterinary Medicine, Ethiopia

**Corresponding author*

Abstract

Bacterial DNA recombination, horizontal gene transfer, occurs by three basic mechanisms. Gene transfer by cell-to-cell contact (conjugation); gene transfer via virus particles (transduction), and bacterial cells take up free molecules of DNA (transformation). Transposable genetic elements (transposons, insertion sequences, integrons, and bacteriophage Mu) are segments of bacterial DNA that can move from one site to another site within or between genomes by a process called transposition. Recombination and transposable elements play important roles in the generation and transfer of new gene combinations. This results in the evolution of genetic variability in bacteria. This variation is due to mainly three strategies: (1) small local changes in the nucleotide sequence of the genome, (2) intragenomic reshuffling of segments of genomic sequences, and (3) the acquisition of DNA sequences from another organism. These alterations result in adaptation to novel ecological opportunities, acquisition of virulence genes, and drug resistance development. It needs due progressive attention for the evolution of virulent and drug-resistant varieties.

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Introduction

Transfer of genetic material is a common event in bacteria. The bacterial cell cycle involves the coordination of genome replication and segregation of replicated copies into daughter cells. In this way, the transmission of genetic material is "vertical" from one cell generation to the next (Anisimova, 2019). In addition to vertical transfer, genetic information can be transferred “horizontally” between unrelated cells via the processes of transformation, conjugation, or transduction (Frost *et al.*, 2005; Thomas and Nielsen, 2005). An event that transfers gene(s) between different species or cells by any of these three processes is referred to as a horizontal gene transfer (HGT) event (Anisimova, 2019).

Transposition is another process in which pieces of DNA in the chromosomes of bacteria move around the genome. The DNA segments that carry the genes required for this process and consequently move about chromosomes are transposable genetic elements (Prescott and Klein, 2002). Transposable genetic elements produce a variety of important effects. They can be inserted within a gene to cause a mutation or stimulate DNA rearrangement, leading to deletions of genetic material (Colonna and Fanti, 2022).

The genetic exchange, recombination, is known to be a major driving force in the evolution of most prokaryotes including bacteria (Didelot and Martin, 2010). Indeed, the lack of genetic exchange among bacteria can now be

regarded as an unusual situation, confined to a few lineages such as genetically monomorphic pathogens (Achtman, 2008).

Similarly, transposable genetic elements encoding the mechanisms for transmission between genomes (using virions or conjugation) or within genomes (insertion sequences, integron cassettes) are known to transfer genes at high rates and be rapidly lost. Thus, driving the rapid initial diversification of gene repertoires (Touchon *et al.*, 2020; Touchon and Rocha, 2007).

Likewise, a considerable number of researchers' investigations elaborate that both recombination events and transposable genetic elements contribute to the evolution of bacterial genetic variability. So, the focus of this paper is to review bacterial DNA recombination events and transposable genetic elements with a view of their role in the evolution of bacterial genetic variability.

Bacterial DNA Recombination Events

Recombination is a way process in prokaryotes: a piece of genetic material (the exogenote) is donated to the chromosome of the recipient cell (the endogenote) and integrated into it. This process occurs in three main ways: conjugation (the transfer of DNA from one bacterium to another via cell-to-cell contact), transformation (the uptake of exogenous DNA from the surrounding environment), and transduction (the virus-mediated transfer of DNA between bacteria) (Prescott and Klein, 2002).

Whatever the mode of transfer, the exogenote has only four possible fates in the recipient. First, when the exogenote has a sequence homologous to that of the endogenote, integration may occur; that is, it may pair with the recipient DNA and be incorporated to yield a recombinant genome. Second, the foreign DNA sometimes persists outside the endogenote and replicates to produce a clone of partially diploid cells. Third, the exogenote may survive, but not replicate, so that only one cell is a partial diploid. Finally, host cell nucleases may degrade the exogenote, a process called host restriction (Anisimova, 2019; Prescott and Klein, 2002).

Conjugation

Conjugation was first discovered in 1946 by Edward Tatum and Joshua Lederberg, who showed that bacteria could exchange genetic information through the unidirectional transfer of DNA, mediated by a so-called F (Fertility) factor (Virolle *et al.*, 2020; Lederberg and Tatum, 1946). Conjugation is the process by which a donor bacterium transfers a copy of a plasmid to a recipient bacterium, through a pilus. The process requires cell-to-cell contact. The donor cell (F+) has a conjugative plasmid, an extrachromosomal piece of dsDNA that codes for the proteins necessary to make a thread like filament known as a pilus. The pilus is used to bind to the recipient (F-) cell, bringing it near the donor cell. It is believed that a channel is then opened between the two cells, allowing for a ssDNA copy of the plasmid to enter the recipient cells. Both cells then make the complimentary copy to the ssDNA, resulting in two F+ cells capable of conjugation (figure 1) (Virolle *et al.*, 2020; Quinn *et al.*, 2011).

Transformation

The second way in which DNA can move between bacteria is through transformation, discovered by Fred Griffith in 1928 (Griffith, 1928). Transformation is the uptake by a competent cell of a naked DNA molecule or fragment from the medium and the incorporation of this molecule into the recipient chromosome in a heritable form resulting in a genetically transformed recombinant cell (figure 2). In natural transformation, the DNA comes from a donor bacterium. The process is random, and any portion of a genome may be transferred between bacteria mediated by signaling and receptor proteins. (Das *et al.*, 2017; Quinn *et al.*, 2011). There is also artificially induced transformation through different techniques like electroporation, microshock waves, and local heat shock (Das *et al.*, 2017).

Transduction

Transduction is the transfer of bacterial genes by viruses (bacteriophages). Bacterial genes are incorporated into a phage capsid because of errors made during the virus life cycle. The virus-containing these genes then injects them into another bacterium, completing the transfer. There are two very different kinds of transduction: generalized and specialized (Maloy, 2019; Prescott and Klein, 2002).

Generalized transduction (figure 3): This occurs during the lytic cycle of virulent and temperate phages and can transfer any part of the bacterial genome. During the assembly stage, when the viral chromosomes are packaged into protein capsids, random fragments of the partially degraded bacterial chromosome also may be packaged by mistake. The resulting virus particle often injects the DNA into another bacterial cell but does not

initiate a lytic cycle. This phage is known as a generalized transducing particle or phage and is simply a carrier of genetic information from the original bacterium to another cell (Prescott and Klein, 2002). A successful integration changes the genotype and phenotype of the recipient, which is called a transductant. Two examples of generalized transducing phages are P1, which works on *E. coli*, and P22, which infects Salmonella. The ratio of transducing particles to live virus is about 1:100 in both cases; that is, for every 100 virus particles made, one will contain bacterial host DNA. The likelihood of the transduced DNA recombining into the recipient chromosome is roughly 1-2 in 100 (Maloy, 2019; Quinn *et al.,* 2011).

*In specialized or restricted transduction***,** the transducing particle carries only specific portions of the bacterial genome. Specialized transduction is made possible by an error in the lysogenic life cycle. For example, when bacteriophage lambda (*λ*) infects *E. coli*, it sometimes inserts its DNA into the bacterial chromosome (figure 4). This occurs at a single specific location, known as the lambda attachment site (*attλ*), which lies between the gal and bio genes. The integrated virus DNA is referred to as a prophage (Maloy, 2019; Quinn *et al.,* 2011). When a prophage is induced to leave the host chromosome, excision is sometimes carried out improperly. The resulting phage genome contains portions of the bacterial chromosome (about 5 to 10% of the bacterial DNA) next to the integration site. The transducing particle will inject bacterial genes into another bacterium, even though the defective phage cannot reproduce without assistance. The bacterial genes may become stably incorporated under the proper circumstances (Maloy, 2019; Quinn *et al.,* 2011).

Transposable Genetic Elements

Transposable genetic elements, mobile genetic elements (MGEs), are segments of DNA that encode enzymes and other proteins. These elements mediate the movement of DNA within genomes (intracellular mobility) or between bacterial cells (intercellular mobility) through a process called transposition (Quinn *et al.,* 2011; Frost *et al.,* 2005).

They are also known as transposable elements, transposons, translocatable elements, mobile sequences, movable sequences, insertion elements, jumping elements, parasitic elements, or selfish DNA (Colonna and Fanti, 2022; Tomar, 2014). Some literature classifies the mobile genetic elements in bacteria as insertion sequences (IS), transposons, and integrons (Mahillon and Chandler, 1998). The insertion sequences are also considered the simplest transposons (Quinn *et al.,* 2011). Besides, as reviewed by (Babakhani and Oloomi, 2018), TEs (DNA Tns) are categorized in bacteria as insertion sequences (IS), transposons (simple Tns (Tn3 family), composite Tns, complex Tns, conjugate Tns), and transposable phage Mu (table 1), but can also embrace integrons (In) and introns (Clark *et al.,* 2019; reviewed in Siguier *et al.,* 2014).

Transposons and Transposition

These genetic elements, sometimes called 'jumping genes' can move from one location to another in the genome. They can also become integrated into plasmid DNA (Babakhani and Oloomi, 2018). All DNA-based transposons possess two essential features. First, they have inverted repeats at either end. Second, transposons must have at least one gene that encodes the transposase, the enzyme needed for movement (figure 5). The transposase recognizes two different DNA sequences. First, it recognizes the inverted repeats at the transposon ends, and this tells it which piece of DNA must be moved. In addition, the transposase must also recognize a specific sequence on the DNA molecule it has chosen as its future home. This is known as the target sequence and is usually from 3 to 9 base pairs long (Clark *et al.,* 2019).

The movement of a transposon, a process of transposition, is initiated when an enzyme cuts DNA at a target site. The transposase recognizes the inverted repeats and moves the segment of DNA bounded by them from one site to another. The frequency of transposition varies from one transposon to another. Typically, it ranges from 1 in 1000 to 1 in 10,000 per transposon per cell generation. Transposition is generally classified as replicative (copy and paste) and non-replicative or conservative (cut and paste) forms. Transposition is important in genetic engineering, as other genes can be relocated along with the transposon DNA (Colonna and Fanti, 2022; Clark *et al.,* 2019).

Composite transposons

A composite transposon consists of two inverted repeats from two separate transposons moving together as one unit and carrying the DNA between them (figure 6) (Quinn *et al.,* 2011). For example, consider a segment of DNA flanked at both ends by two identical insertion sequences. The transposase will move any segment of

DNA surrounded by a pair of the inverted repeats that it recognizes. Consequently, transposition occurs in several possibilities. First, each of the insertion sequences may move independently. Second, the whole structure between the two outermost inverted repeats may move as a unit, that is, as a composite transposon.

Many of the well-known bacterial transposons that carry genes for antibiotic resistance or other useful properties are composite transposons. Three of the best-known are Tn5 (kanamycin resistance), Tn9 (chloramphenicol resistance), and Tn10 (tetracycline resistance) (Colonna and Fanti, 2022; Quinn *et al.*, 2011).

Complex transposons

Complex (replicative) transposons have a gene for resolvase and an internal resolution site, in addition to the gene for transposase and two flanking inverted repeats. They have additional genes such as those encoding antibiotic resistance which can ensure survival in the face of antimicrobial therapy (Clark *et al.*, 2019; Quinn *et al.*, 2011).

Conjugative transposons

Conjugative transposons, found in bacteria, are hybrid elements that can both transpose and can move from cell to cell, like a transmissible plasmid. The first of these to be discovered, Tn916, confers tetracycline resistance and was found in the bacterium *Enterococcus faecalis*. Tn916 carries several genes needed for conjugative transfer and is therefore much larger than most transposons.

When moving from one bacterial cell to another, Tn916 is thought to excise itself temporarily from the DNA of the original cell. It then transfers itself into the recipient and, once inside, it transposes into the DNA of the new host cell (Clark *et al.*, 2019).

Insertion sequences

The simplest and shortest autonomous transposons, known as insertion sequences, were first found in bacteria. They are designated IS1, IS2, etc. Typical insertion sequences are 750-1500 base pairs long with terminal-inverted repeats of 10-40 base pairs. Insertion sequences only encode a single enzyme, the transposase, the enzyme needed for movement. Between the inverted repeats is a region that contains two open reading frames, orfA and orfB. The transposase itself is derived from both open reading frames by a frame shift that occurs during translation (figure 7) (Clark *et al.*, 2019; Babakhani and Oloomi, 2018).

Bacteriophage Mu

It is not about a virus that carries a transposon inserted within its DNA but about a genetic element that behaves as both a virus and a transposon in its entirety. When Mu DNA enters E. coli, its bacterial host, it integrates at random into the host chromosome by transposition. In other words, the whole of the Mu genome is a transposable element. If Mu inserts into the middle of a host gene this will be inactivated. Early investigators noticed that infection with this virus caused frequent mutations and therefore named it Mu for "mutator" phage (Babakhani and Oloomi, 2018).

Integrons

Integrons are other mobile DNA elements with the ability to capture genes (cassettes), notably those encoding antibiotic resistance, by site-specific recombination (Quinn *et al.*, 2011). An integron consists of a recognition region, the *attI* site, into which a variety of gene cassettes may be integrated, plus a gene encoding the enzyme responsible for insertion, the integrase. The *attI* site is flanked by two 7 bp sequences that act as recognition sites for the integrase (figure 8).

Two promoters, facing in different directions, are situated between the integrase gene and the *attI* site. One is for the integrase gene; the other faces the gene collection region and drives transcription of whatever gene has been integrated (Clark *et al.*, 2019).

Role of DNA Recombination and Transposable Genetic Elements in the Evolution of Bacterial Genetic Variability

Genetic (DNA) recombination and transposition are considered to be the causes of the evolution of genetic variations in bacteria (figure 9). Thus, plasmids, bacteriophages, and transposable elements may contribute additional genetic information, some of which may influence phenotypic expression (Quinn *et al.*, 2011; Davison, 1999). These processes can pose bacterial genetic variation through three main strategies: (1) small local changes in the nucleotide sequence of the genome, (2) intragenomic reshuffling of segments of genomic sequences, and (3) the acquisition of DNA sequences from another organism (Arber, 2000).

Table.1 Transposable genetic elements and their basic characteristics

Type of element	Length (base pair)	Terminal repeats	Mechanism of mobility	Mechanism to exit the cell
Insertion sequence	750-1,500	Inverted	Cut and paste	No
Simple transposon	1,300-5,000	Inverted	Cut and paste	No
Composite transposon	2,500-10,000	Insertion sequence	Cut and paste	No
Complex transposon	5,000	Inverted	Replicative	No
Bacteriophage Mu	37kb	Inverted	Replicative	Virus particle
Conjugate transposon	30-150kb	None	Transfer pilus integration	Conjugation
Integrons and casettes	1,500	None	Accumulation of casettes	No

Source: (Clark *et al*., 2019; Babakhani and Oloomi, 2018)

Fig.1 Conjugation(Frost *et al*., 2005)

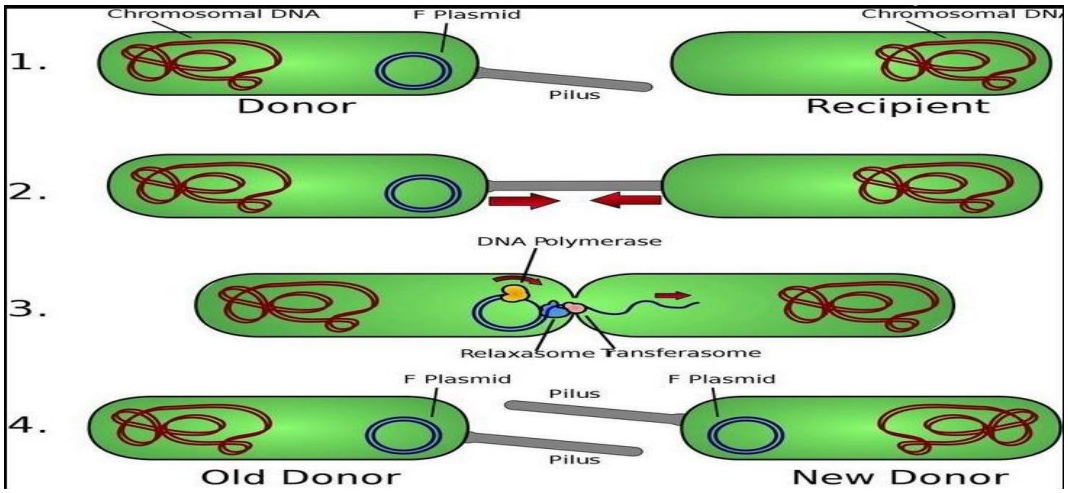


Fig.2 Transformation (Das *et al*., 2017)

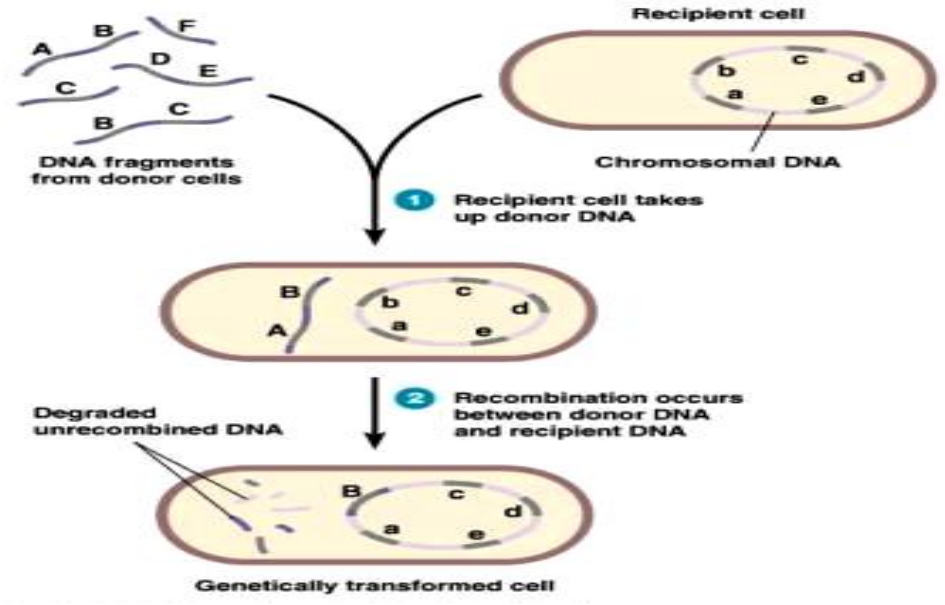


Fig.3 Generalized transduction (Prescott and Klein, 2002)

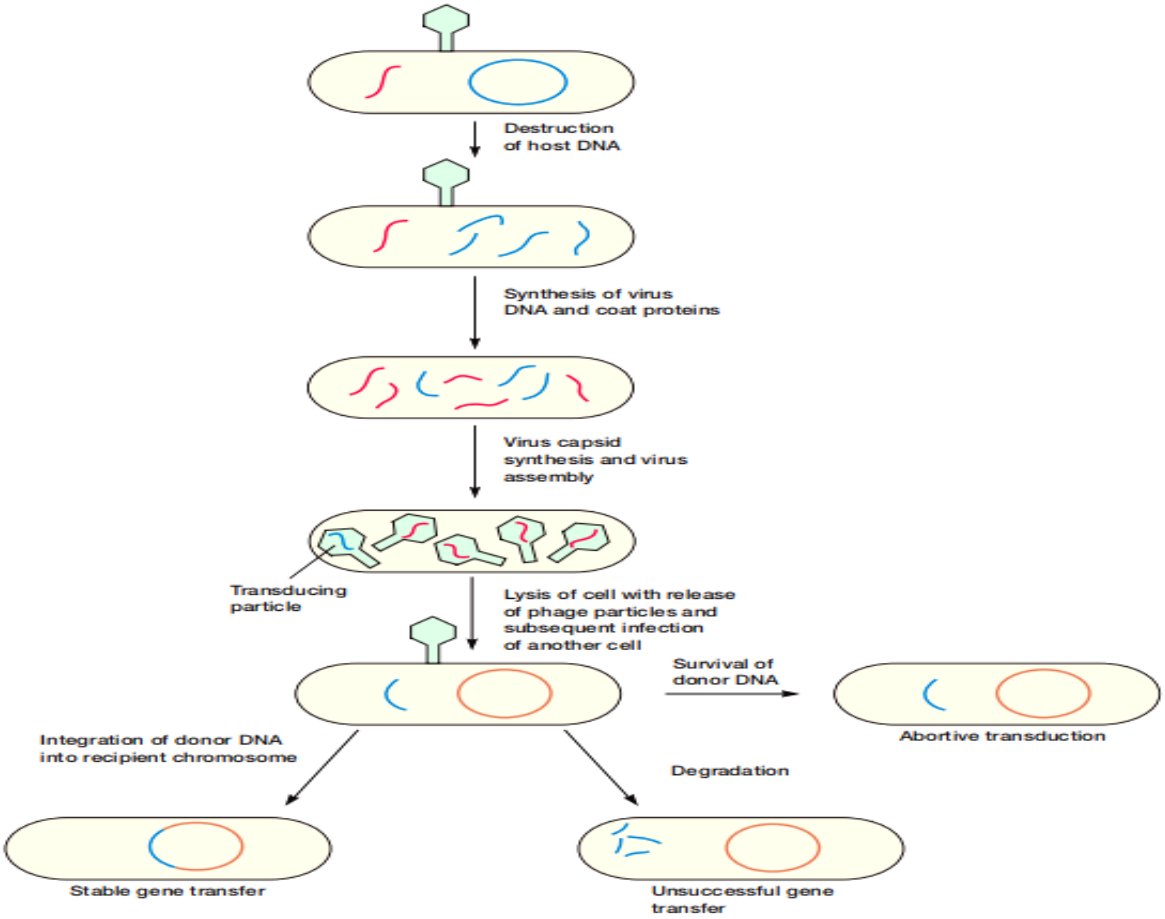


Fig.4 Specialized transduction (Maloy, 2019)

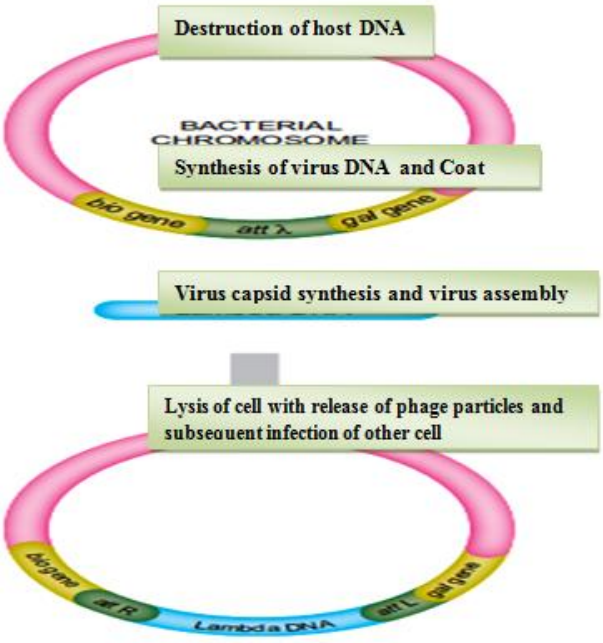


Fig.5 Essential parts of transposon (Clark *et al*., 2019)

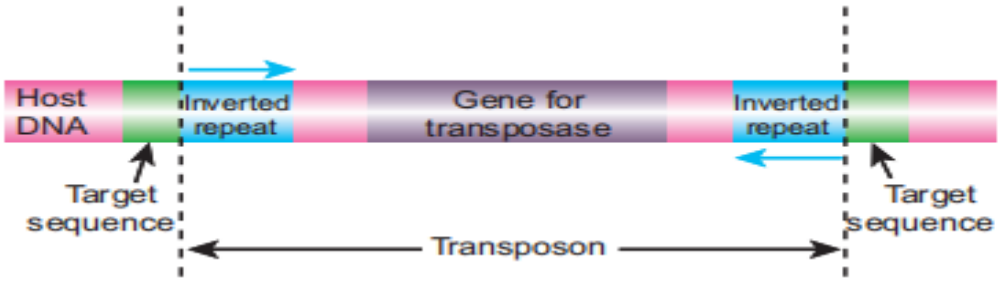


Fig.6 Structure of composite transposon (Colonna and Fanti, 2022)

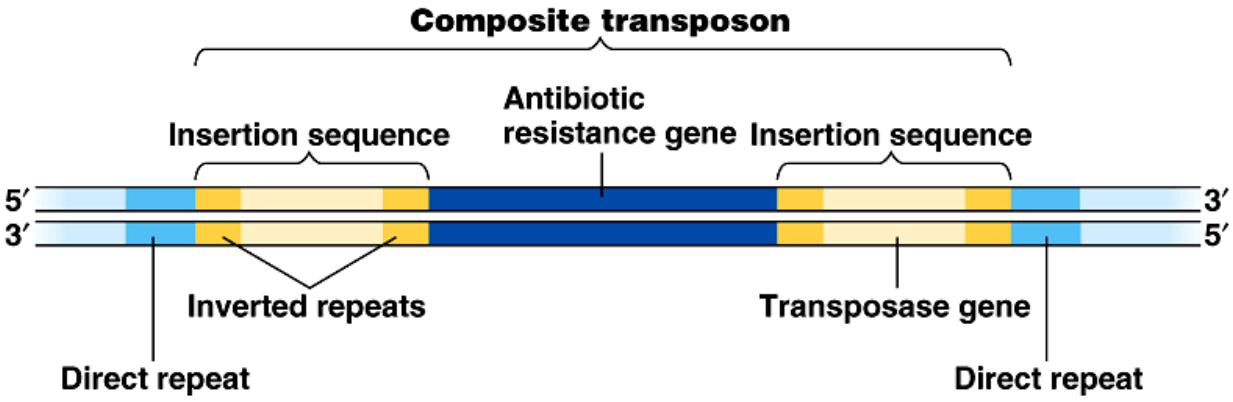


Fig.7 Structure of insertion sequence (Clark *et al*., 2019)

Fig.8 Integron structure (Clark *et al*., 2019)

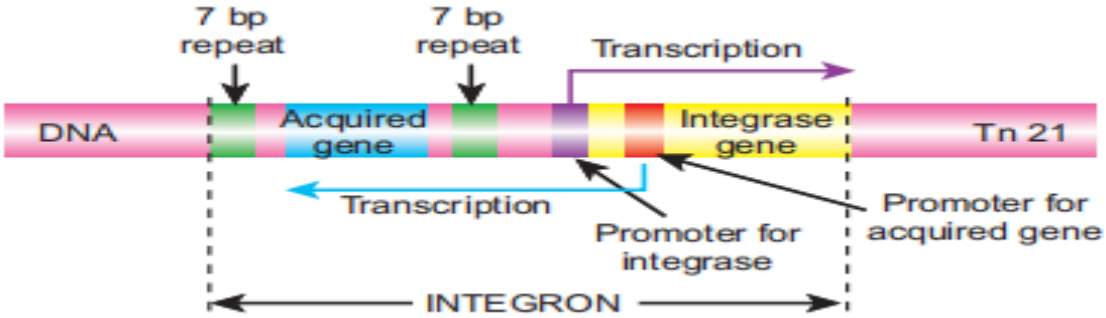
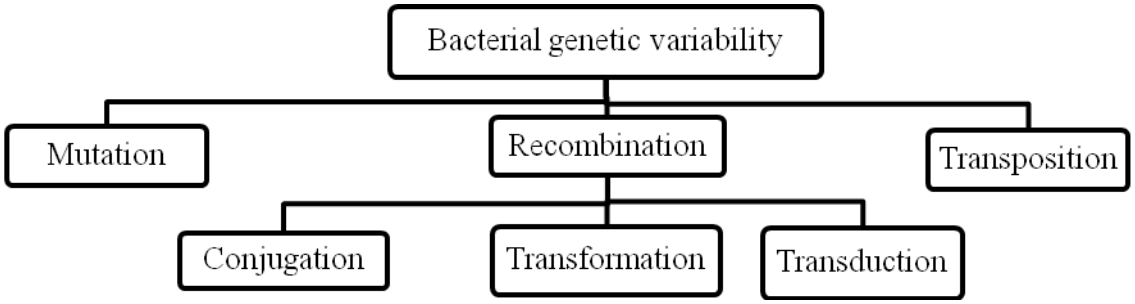


Fig.9 Bacterial genetic variation (Quinn *et al*., 2011)



Role of recombination

It induces an unexpected inheritable change due to the introduction of new genetic material from a different cell (Quinn *et al.,* 2011; Prescott and Klein, 2002). Genetic diversity, created by HGT, recombination, affects a species' ability to adapt to novel ecological opportunities. The higher the diversity of gene repertoires in a population, the more likely that one of those genes will prove helpful in the face of environmental challenges such as antibiotics (Belkum *et al.,* 2015). On the contrary, there is also the possibility of the acquisition of virulence genes from virulent species/strains of bacteria as in the case of *Streptococcus pneumonae* which inherits pathogenic characteristics (Griffith, 1928). Similarly, the development of antibiotic resistance is possible through conjugative transfer of plasmid (containing drug resistance gene) (Maloy, 2019; Quinn *et al.,* 2011).

Role of transposable genetic elements

Almost in a similar manner, the transposable genetic elements can play a very big role in the activation and inactivation of bacterial genes, the best explanation derived from the work of Barbara McClintock in corn, who won the Nobel Prize for her research in 1983 (Mccljntock, 1929). These DNA sequences can change their position within a genome, sometimes creating or reversing mutations and altering the cell's genetic identity and genome size (Bourque *et al.,* 2018). For this reason, on the one hand, TEs can induce deleterious

mutations, causing dysfunction, disease, and even lethality in individuals. On the other hand, TEs can increase genetic variability, making populations better equipped to respond adaptively to environmental change (Colonna and Fanti, 2022).

These elements can transfer from a plasmid to other plasmids or from a DNA chromosome to a plasmid and vice versa causing the transmission of antibiotic resistance genes in bacteria (Babakhani and Oloomi, 2018). There is also horizontal gene transfer mainly in the case of conjugative transposons and bacteriophage Mu by conjugation, transformation, and transduction (Clark *et al.,* 2019).

Conclusion

Bacterial genomes are in a constant state of flux, and any segment of DNA in a large bacterial population might have the opportunity to be horizontally transferred; similar to transposition. This induces an unexpected inheritable change due to the introduction of new genetic material within or between cells that are likely to be maintained in the new host over generations. The emergence of virulent species/strains and the development of drug resistance in bacteria are more or less attributed to these issues. So, it needs due progressive attention for the evolution of the varieties.

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