Resistance integrons; A mini review

Abstract
Integrons are a segment of dsDNA that play a major role in bacterial adaptation and evolution. These genetic determinants are known by the presence of three necessary apparatuses: an integrase (intI gene), Pc (a promoter) and attI (a recombination site). These elements are able to acquire gene cassettes, which can carry antibiotic resistance factors, via site-specific recombination mechanism. The most common types of resistance integrons are class I (Tn402 derivatives), followed by class II and III. In recent years, the role of integrons as an important factor in the transmission and spread of resistance factors has been considered. Therefore, the ongoing threats posed by integrons require an understanding of their origins and evolutionary history. This review examines the functions and activities of integrons. It shows how antibiotics use selected particular integrons from the environmental pool, so that integrons carrying resistance genes are now present in the majority of Gram-negative pathogens.

Keywords: Integron, gene cassettes, antibiotic resistance

H orizontal Gene Transfer (HGT) in the bacterial species means the movement of genetic material between bacteria from a similar genus (1). The HGT plays an important role in evolution, diversity, recombination and multi-drug resistant strains (2, 3). Antibiotic-resistant determinants in resistance bacteria are usually carried on mobile genetic elements (MGEs), such as the plasmids, transposons (TEs), integron (Int), and multidrug resistance genomic islands. Integrons are conserved dsDNA sequences (3′-CS and 5′-CS) of DNA that are able to obtain gene cassettes, which can carry drug resistance genes, by site-specific recombination. (4-8). In this review article, we described an integron structure, types and their distribution in antibiotic resistance bacteria.

Integrons and gene cassettes: These elements are immobilized but located on the transferrable plasmids which can disseminate in the intra- and inter-bacterial species (figure 1) (9).

These elements have three main components: (1) IntI which encodes integrase gene and it is the part of tyrosine kinases family. The coding protein derived from this gene plays an important role in the recombination of genetic cassettes (2) attI is recognized by the integrase, so is a receptor site for gene cassette integration by site-specific recombination (10-13). (3) Pc is a promoter which is necessary for the transcription and expression of genetic cassettes in integron (14-16). The circular gene cassettes are DNA segments which can integrate between attI and attC by integrase (figure 2). This process can also be reversible, leading to gene cassette deletion (17-19).
Resistance integrons: A Mini Review

Figure 1. Transfer of antibiotic resistance elements through integrons: the figure gives a schematic representation of transmission of integrons. Transposons (Tn) containing integrons can transfer into a microbial strains from natural sources. The int1 and the attI are corresponded for attachment and integration of the gene cassettes. Resistance to sulfonamides and quaternary ammonium compounds were encoded by the sul1and qacEΔ1 genes, respectively. The grey zones showed the gene cassettes with different functions. The Pint and Pc are integrase (int1) and gene cassette promoters respectively (9).

Figure 2. Acquisition of gene cassettes. Integrons obtain a new gene cassette by the site-specific recombination between attC in the circular gene cassette and attI site in integron. These insert cassettes are at the position proximal to int gene and its embedded promoter. Cassette arrays can enlarge by repeated cassette acquisition, but cassettes can also be excised as closed circles by attC × attI or attC × attC recombination (10).

Integron types

Two main groups of integrons are identified including: mobile integrons (MIs) and chromosomal integrons (CIs). CIs are found in marine bacterial chromosome, such as Vibrio species. The other name for this class is super-integrons (SIs), because they can carry more than 200 cassettes and usually encode proteins with unknown function (20). On the other hand, CIs can carry a numerous number of...
gene cassettes, which are commonly not involved in drug resistance. MIs are located on the mobile genetic elements (MGEs) such as plasmids and transposons, and carry only a few cassettes. MIs can carry antibiotic resistance cassettes, because of this function; they called resistance integrons (RIs) (21).

**Resistance integrons**

These integrons are divided into five groups based on the similarity of amino acid sequences. These elements are most commonly found in gram-negative bacteria (22-26). Class I integrons differ widely between gram-negative bacteria and are transmitted through Tn402. The integron–integrase gene (intI1) is identical in all class I integron, and the left-hand end of all class I of integrons contains a conserved noncoding sequence that terminates in a 25-bp sequence (IRi), which is an inverted repeat of another sequence (IRt) located at the right-hand end of most extant class I integrons (27). The common ancestor of all clinical class I of integrons was likely same to a Tn402-like transposon, consisting of IRi, intI1, attI1, gene cassette(s) and their associated recombination sites (attC, or59-base elements), a qacE cassette (quaternary ammonium compound E; which encodes resistance to biocides), a complete transposition module and IRt, respectively (28). The class II of integrons has a IntII gene which is terminated by stop codon. This class is transmitted by Tn7 and its derivatives (29). The integrons class III is less important but found in clinical isolates and transmitted by Tn402 (30, 31). The integrons class IV and V are found in *Vibrio* and PRSV1 plasmid.

**Evolutionary History**

SIs are present as the pioneers of the old incubators (30). In contrast to other integrons, SIs are always related to chromosomes. They are large in size and carry more than twenty gene cassettes. For the first time, they were found in the small chromosome of *Vibrio cholerae* but today they are found in many bacterial species (32-34). Gillings et al, detected intI1 gene from the environmental samples including, sediments, soils, and biofilms (27).

These MGEs are classified into broad groups based on the phylogeny of the *int* gene (1). Proteobacteria found in water and soil, which mostly consists of integrons class I and III (2) γ-Proteobacteria, found in marine environments including the class II integrons (3). Integrons that integrase gene have revers origin with the above categories found in *Spirochetes* and *Acinetobacter*. The categorization of integrons based on the type of environment, contrary to their identification by the host, indicates that the transfer of integrons between species occurs in similar environments. These findings are based on phylogenetic tree of 16sRNA and IntI (14, 30, 35). The miniature inverted-repeat transposable elements (MITEs) are a group of non-autonomous Class II transposable elements found in *Acinetobacter* and *Enterobacter* that rearrangement or displacement of these regions can cause integron transfer in the chromosome (36, 37).

**Integrons and antibiotic resistance**

Integrons act as a pool of gene cassettes. These cassettes play a role in antibiotic resistance. In general, about 130 different genetic cassettes have been identified which are different in the codon patterns and attC site. These cassettes are usually small in the mobile integrons. The longest known row of gene cassettes is 8 gene cassettes. Perhaps one of the reasons is that the cassettes are controlled by a promoter (38, 40).

**Class I integron**

The left conserved sequence is 107- bp that is located under Int1 stop codon and the right conserved sequence is 43-bp located under aatC site. Class I integrons harbor various antimicrobial resistance gene cassettes encoding dfr (dihydroflavonol-4-reductase), broad-spectrum β-lactamase, qacEΔ1 (quaternary ammonium compound disinfectant), sul1 (sulfonamide), and aminoglycoside-modifying enzymes (AMEs). Recently, its hybrid types consist of class I integron and cassettes, which still carry inverted repeat sequences (41-43). Class I integrons can capture and distribute gene cassettes among other integron classes. This broadcast happened via the natural conjugation or transformation (44, 45). This class has been observed in gram-negative organisms such as Acinetobacter, Aeromonas, Alcaligenes, Burkholderia, Campylobacter, Citrobacter, Pseudomonas, Klebsiella, Salmonella (46-52). The studies indicate a strong relation between cassettes and expression of the integrase (53-62).

**Class II integron**

Similar to the class I integron, class II integron is also found on Tn7 transposon family. Its 3’ conserved section (3’-CS) contains 5 *ms* genes, which acts in transposon movement. Compared to Class I integrons, the *int* gene in the class II is less active and, consequently, class II is more limited in gene cassette acquisition. In addition, these integrons can carry unusual cassettes that encode the lipoprotein signal peptidase (63). The sequence of amino
acid in class II is less than 50% identical to class I integron and this is due to the displacement of internal stop codon at position 179 in triplet coding for glutamic acid. This integron has Dfr1, sul1, aadA1 (aminoglycoside adenyllytransferase) gene cassettes. This class is most commonly found in Escherichia coli, Acinetobacter baumannii, Salmonella enterica, and Burkholderia (64-67).

**Class III integron**

It was first identified in 1993, in Japan from Serratia marcescens. This class is transferred by Tn402, but it is not active as well as other classes. The 3’ end of class III integrons are similar to the class I and contain the qacEΔ1, sul1 and orf genes, with the only difference being the lack of transposition genes in the class III. There are several cassettes in this class that include: bla-IMP-1 (enceodes for Metallo-β-lactamase enzymes), aacA4 (tobramycin resistance gene). However, class III integron has been recently identified containing blaGES-1 (an extended-spectrum β-lactamase (ESBL) encoded gene) within the IncQ plasmid from E. coli. To date, this class has been identified within a few microorganisms including Escherichia coli, Acinetobacter spp., Salmonella spp., Citrobacter freundii, Alcaligenes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Pseudomonas putida, and Serratia marcescens (68, 69).

**Class IV integron**

It was identified in 1998. On the small chromosome of Vibrio cholerae and was named SIs. The size of this class is large (~126 kb) and contains at least 178 gene cassettes. This class has been found in Vibrionaceae, Shewanella, Xanthomonas and other marine proteobacteria group. These integrons are also found in Geobacter sulfurreducens, Pseudomonas, Nitrosomonas, Listonella and Treponema denticol. To date, class IV integrons have been found to carry gene cassettes imparting resistance to the fosfomycin and chloramphenicol (17, 23, 70-75). It can be concluded that the gene cassettes in integrons are one of the compatible components of bacteria with environment. The ability of integrons to acquire new cassettes and their ability to recombine cassette rows emphasizes the adaptation of their diversity in bacteria. Integrons have the ability to carry cassettes with a variety of functions and are also compatible with the acquisition and expression of resistance components. In addition, most studies about integrons have been limited to class I integron in gram-negative bacteria, but this class has also been observed in gram-positive bacteria. There are a lot of questions about the organisms carrying these integrons, gene cassettes, and the outbreak of them in particular species of bacteria.

**Ethical Consideration**

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the author.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

**References**

1. Ochman H, Lawrence JG, Groisman EA. Lateral gene transfer and the nature of bacterial innovation. Nature 2000; 405: 299-304.
2. Nakamura Y, Itoh T, Matsuda H, Gojobori T. Biased biological functions of horizontally transferred genes in prokaryotic genomes. Nat Genet 2004; 36: 760-6.
3. Thomas CM, Nielsen KM. Mechanisms of and barriers to, horizontal gene transfer between bacteria. Nat Rev Microbiol 2005; 3: 711-21.
4. Hall RM, Collis CM. Mobile gene cassettes and integrons: capture and spread of genes by site specific recombination. Mol Microbiol 1995; 15: 593-600.
5. Stokes HW, Hall RM. A novel family of potentially mobile DNA elements encoding site-specific gene-integration functions: integrons. Mol Microbiol 1989; 3:1669-83.
6. Ahangarkani F, Rajabnia R, Shahandashti EF, Bagheri M, Ramez M. Frequency of class 1 integron in escherichia coli strains isolated from patients with urinary tract infections in North of Iran. Mater Sociomed 2015; 27: 10-12
7. Asgharpour F, Rajabnia R, Ferdosi SE, et al. Investigation of class I integron in salmonella infantis and its association with drug resistance. Jundishapur J Microbiol 2014; 7: e10019.
8. Moradian Kouchaksaraei F, Ferdosi Shahandashti E, Molana Z, et al. Molecular detection of integron genes and pattern of antibiotic resistance in pseudomonas aeruginosa strains isolated from intensive care unit, Shahid Beheshti hospital, North of Iran. Int J Mol Cell Med 2012; 1: 209-17.
9. Ravi A, Avershina E, Ludvigsen J, L'Abée-Lund TM, Rudi K. Integrons in the intestinal microbiota as reservoirs for transmission of antibiotic resistance genes. Pathogens 2014; 3: 238-48.
10. Gillings MR. Integrons: past, present, and future. Microbiol Mol Biol Rev 2014; 78: 257-77
11. Messier N, Roy PH. Integron integrases possess a unique additional domain necessary for activity. J Bacteriol 2001; 183: 6699-706.
12. Partridge SR, Recchia GD, Scaramuzzi C, et al. Definition of the attI site of class 1 integrons. Microbiology 2000; 146: 2855-64.
13. Collis CM, Hall RM. Expression of antibiotic resistance genes in the integrated cassettes of integrons. Antimicrob. Agents Chemother 1995; 39: 155-62.
14. Lévesque C, Brassard S, Lapointe J, et al. Diversity and relative strength of tandem promoters for the antibiotic-resistance genes of several integron. Gene1994; 142: 49-54.
15. Boucher Y, Labbate M, Koenig JE, Stokes HW. Integrons: mobilizable platforms that promote genetic diversity in bacteria. Trends Microbiol 2007; 15: 301-9.
16. Cameron FH, Groot Obbink DJ, Ackerman VP, Hall RM. Nucleotide sequence of the AAD (2) aminoglycoside adenylyl transferase determinant aadB. Evolutionary relationship of this region with those surrounding aadA in R538-1 and dhfrII in R388. Nucleic Acids Res 1986; 14: 8625-35.
17. Rowe-Magnus DA, Guérout AM, Mazel D. Super-integrons. Res Microbiol 1999; 150: 641-51.
18. Collis CM, Hall RM. Gene cassettes from the insert region of integrons are excised as covalently closed circles. Mol Microbiol 1992; 6: 2875-85.
19. Collis CM, Hall RM. Site-specific deletion and rearrangement of integron insert genes catalyzed by the integron DNA integrase. J Bacteriol 1992; 174: 1574-85.
20. Hocquet D, Llanes C, Thouverez M, et al. Evidence for induction of integron based antibiotic resistance by the SOS response in a clinical setting. PLoS Pathog 2012; 8: e1002778.
21. Cambray G, Guerout AM, Mazel D. Integrons. Annu Rev Genet 2010; 44: 141-66.
22. Naas T, Mikami Y, Imai T, Poirel L, Nordmann P. Characterization of In53, a class 1 plasmid and composite transposon-located integron of Escherichia coli which carries an unusual array of gene cassettes. J Bacteriol 2001; 183: 235-49.
23. Fluit AC, Schmitz FJ. Resistance integrons and super-integrons. Clin Microbiol Infect 2004; 10: 272-88.
24. Petersen A, Guardabassi L, Dalsgaard A, et al. Class I integrons containing a dhfrI trimethoprim resistance gene cassette in aquatic Acinetobacter spp. FEMS Microbiol Lett 2000; 182: 73-6.
25. Gallego L, Towner K.J. Carriage of class 1 integrons and antibiotic resistance in clinical isolates of Acinetobacter baumannii from northern Spain. J Med Microbiol 2001; 50: 71-7.
26. Chang CY, Chang LL, Chang YH, Lee TM, Chang SF. Characterisation of drug resistance gene cassettes associated with class 1 integrons in clinical isolates of Escherichia coli from Taiwan. ROC J Med Microbiol 2000; 49: 1097-102.
27. Gillings M, Boucher Y, Labbate M, et al. The evolution of class 1 integrons and the rise of antibiotic resistance. J Bacteriol 2008; 190: 5095-100.
28. Mazel D, Dychinco B, Webb VA, Davies J. Antibiotic resistance in the ECOR collection: integrons and identification of a novel aad gene. Antimicrob Agents Chemother 2000; 44: 1568-74.
29. Hansson K, Sundström L, Pelletier A, Roy PH. IntI2 integron integrase in Tn7. J Bacteriol 2002; 184: 1712-21.
30. Paulsen IT, Littlejohn TG, Rådström P, et al. The 3 conserved segment of integrons contains a gene associated with multidrug resistance to antiseptics and disinfectants. Antimicrob Agents Chemother 1993; 37: 761-8.
31. Mazel D. Integrons: Agents of bacterial evolution. Nat Rev Microbiol 2006; 4: 608-20.
32. Hochhut B, Lotfi Y, Mazel D, et al. Molecular analysis of antibiotic resistance gene clusters in vibrio cholerae O139 and O1 SXT constins. Antimicrob Agents Chemother 2001; 45: 2991-3000.
33. Mazel D, Dychinco B, Webb VA, et al. Distinctive Class of Integron in the Vibrio cholerae Genome. Science 1998; 280: 605-8.
34. Rowe-Magnus DA, Guerout AM, Ploncard P, et al. The evolutionary history of chromosomal super-integrons provides an ancestry for multiresistant integrons. Proc Natl Acad Sci USA 2001; 98: 652-7.
35. Clark CA, Purins L, Kaewrakon P, Focareta T, Manning PA. The Vibrio cholerae O1 chromosomal integron. Microbiology 2000; 146: 2605-12.
36. Wu YW, Doak TG, Ye Y. The gain and loss of chromosomal integron systems in the Treponema species. BMC Evol Biol 2013; 13: 16.
37. Gillings MR, Labbate M, Sajjad A, et al. Mobilization of a Tn402-like class 1 integron with a novel cassette array via flanking miniature inverted-repeat transposable element-like structures. Appl Environ Microbiol 2009; 75: 6002-4.
38. Poirel L, Carrer A, Pitout JD, Nordmann P. Integron mobilization unit as a source of mobility of antibiotic resistance genes. Antimicrob Agents Chemother 2009; 53: 2492-8.
39. Partridge SR, Tsafnat G, Coiera E, Iredell JR. Gene cassettes and cassette arrays in mobile resistance integrons. FEMS Microbiol Rev 2009; 33: 757-84.
40. Stokes HW, Nesbo CL, Holley M, et al. Class 1 integrons potentially predating the association with Tn402-like transposition genes are present in a sediment microbial community. J Bacteriol 2006; 188: 5722-30.
41. Gillings MR, Krishnan S, Worden PJ, Hardwick SA. Recovery of diverse genes for class 1 integron-integrases from environmental DNA samples. FEMS Microbiol Lett 2008; 287: 56-62.
42. Rosewarne CP, Pettigrove V, Stokes HW, Parsons YM. Class 1 integrons in benthic bacterial communities: abundance, association with Tn402-like transposition modules and evidence for coselection with heavy-metal resistance. FEMS Microbiol Ecol 2010; 72: 35-46.
43. Sajjad A, Holley MP, Labbate M, Stokes HW, Gillings MR. Preclinical class 1 integron with a complete Tn402-like transposition module. Appl Environ Microbiol 2011; 77: 335-7.
44. Nardelli M, Scalzo PM, Ramirez MS, et al. Class 1 integrons in environments with different degrees of urbanization. PLoS One 2012; 7:e39223.
45. Liebert CA, Hall RM, Summers AO. Transposon Tn21, flagship of the floating genome. Microbiol Mol Biol Rev 1999; 63: 507-22.
46. Partridge SR, Brown HJ, Stokes H, Hall RM. Transposons Tn1696 and Tn21and their integrons In4 and In2 have independent origins. Antimicrob. Agents Chemother 2001; 45: 1263-70.
47. Clark NC, Olsvik O, Swenson JM, Spiegel CA, Tenover FC. Detection of a streptomycin/ spectinomycin adenyltransferase gene (aadA) in Enterococcus faecalis. Antimicrob Agents Chemother 1999; 43: 157-160.
48. Nandi S, Maurer JJ, Hofacre C, Summers AO. Gram-positive bacteria are a major reservoir of Class 1 antibiotic resistance integrons in poultry litter. Proc. Natl. Acad. Sci. 2004; 101: 7118-22.
49. Nesvera J, Hochmannová J, Pátek M. An integron of class 1 is present on the plasmid pCG4 from gram-positive bacterium Corynebacterium glutamicum. FEMS Microbiol Lett 1998; 169: 391-395.
50. Tauch A, Götker S, Pühler A, Kalinowski J, Thierbach G. The 27.8-kb R-plasmid pTET3 from Corynebacterium glutamicum encodes the aminoglycoside adenyltransferase gene cassette aadA9 and the regulated tetracycline efflux system Tet 33 flanked by active copies of the widespread insertion sequence IS6100. Plasmid 2002; 48: 117-29.
51. Lee MD, Sanchez S, Zimmerman M, et al. Class 1 integron-associated tobramycin-gentamicin resistance in Campylobacter jejuni isolated from the broiler chicken house environment. Antimicrob. Agents Chemother 2002; 46: 3660-4.
52. Arakawa Y, Murakami M, Suzuki K, et al. A novel integron-like element carrying the metallo-beta-lactamase gene blalMP. Antimicrob. Agents Chemother 1995; 39: 1612-5.
53. Ruiz L, Domínguez MA, Ruiz N, Viñas M. Relationship between clinical and environmental isolates of Pseudomonas aeruginosa in a hospital setting. Arch Med Res 2004; 35: 251-7.
54. Guérin E, Jové T, Tabesse A, Mazel D, Ploy MC. High-level gene cassette transcription prevents integrase expression in class 1 integrons. J Bacteriol 2011; 193: 5675-82.
55. Lin MF, Liou ML, Tu CC, Yeh HW, Lan CY. Molecular epidemiology of integron-associated antimicrobial gene cassettes in the clinical isolates of acinetobacter baumannii from Northern Taiwan. Ann Lab Med 2013; 33: 242-7.
56. Akram F, Shahandashti E, Yahyapur Y, et al. Integron types, gene cassettes and antimicrobial resistance profile of Acinetobacter baumannii isolated from BAL samples in Babol, North of Iran. Microb Phatog 2017; 109: 35-8.
57. Çiçek A, Ö Düzgün A, Saral A, et al. Detection of class 1 integron in Acinetobacter baumannii isolates collected from nine hospitals in Turkey. Asian Pac J Trop Biomed 2013; 3: 743-7.

58. Rezai MS, Ahangarkani F, Rafie A, et al. Extended-spectrum beta-lactamases producing pseudomonas aeruginosa isolated from patients with ventilator associated nosocomial infection. Arch Clin Infect Dis 2018; 13: e13974.

59. Rezai MS, Rafiei A, Ahangarkani F, et al. Emergence of extensively drug-resistant acinetobacter baumannii-encoding integrons and extended-spectrum beta-lactamase genes isolated from ventilator-associated pneumonia patients. Jundishapur J Microbiol 2017; 10. Available at: http://jjmicrobiol.com/en/articles/14377.html

60. Rezai MS, Bagheri-Nesami M, Hajaibeig A, et al. Multidrug and cross-resistance pattern of ESBL-producing enterobacteriaceae agents of nosocomial infections in intensive care units. J Mazandaran Univ Med Sci 2017; 26: 39-49.

61. Bagheri-Nesami M, Rezai MS, Ahangarkani F, et al. Multidrug and co-resistance patterns of non-fermenting Gram-negative bacilli involved in ventilator-associated pneumonia carrying class 1 integron in the North of Iran. Germs 2017; 7: 123-131.

62. Bagheri-Nesami M, Rafiei A, Eslami G, et al. Assessment of extended-spectrum β-lactamases and integrons among Enterobacteriaceae in device-associated infections: multicenter study in North of Iran. Antimicrob Resist Infect Control 2016; 5: 52.

63. Márquez C, Labbate M, Ingold AJ, et al. Recovery of a functional class 2 integron from an Escherichia coli strain mediating a urinary tract infection. Antimicrob. Agents Chemother 2008; 52: 4153-4.

64. Labbate M, Case RJ, Stokes HW. The integron/gene cassette system: an active player in bacterial adaptation. Methods Mol Biol 2009; 532: 103-25.

65. Ramírez MS, Morales A, Vilacoba E, Márquez C, Centrón D. Class 2 integrons dissemination among multidrug resistance (MDR) clones of acinetobacter baumannii. Curr Microbiol 2012; 64: 290-3.

66. Correia M, Boavida F, Grosso F, et al. Molecular characterization of a new class 3 integron in Klebsiella pneumoniae. Antimicrob. Agents Chemother 2003; 47: 2838-43.

67. Laroche E, Pawlak B, Berthe T, Skurnik D, Petit F. Occurrence of antibiotic resistance and class 1, 2 and 3 integrons in Escherichia coli isolated from a densely populated estuary (Seine, France). FEMS Microbiol Ecol 2009; 68: 118-30.

68. Poirel L, Carattoli A, Bernabeu S, et al. A novel IncQ plasmid type harbouring a class 3 integron from Escherichia coli. J Antimicrob Chemother 2010; 65: 1594–8.

69. Deng Y, Bao X, Ji L, et al. Resistance integrons: class 1, 2 and 3 integrons. Ann Clin Microbiol Antimicrob 2015; 14: 45.

70. Deylam Salehi M, Ferdosi-Shahandashti E, Yahyapour Y, et al. Integron-mediated antibiotic resistance in acinetobacter baumannii isolated from intensive care unit patients, Babol, North of Iran. Biomed Res Int 2017; 2017: 7157923.

71. Rowe-Magnus DA, Guerout AM, Mazel D. Super-integrons. Res Microbiol 1999; 150: 641-51.

72. Smith AB, Siebeling RJ. Identification of genetic loci required for capsular expression in Vibrio vulnificus. Infect Immun 2003; 71: 1091–7.

73. Ogawa A, Takeda T. The gene encoding the heat-stable enterotoxin of Vibrio cholerae is flanked by 123-base pair direct repeats. Microbiol Immunol 1993; 37: 607–16.

74. Holmes AJ, Gillings MR, Nield BS, et al. The gene cassette metagenome is a basic resource for bacterial genome evolution. Environ Microbiol 2003; 5: 383-94.

75. Gillings MR. Integrons: past, present, and future. Microbiol Mol Biol Rev 2014; 78: 257-77.14 Jun;78(2): 257-77.