Microbial Genomic Island Discovery: Visualization and Analysis

4

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Abstract

Genomic Islands (GIs), the integrative part of the prokaryotic genomes which contain many genes with important biological functions. The islands are one of the main quests of today's concern as they frequently contain genes that are involved in adaptation in diverse environments by providing antimicrobial resistance, virulence, and pathogenicity. The frequency of occurrence of GIs within genome is directly proportional to organism's genomic plasticity and thus the motion of evolution. GIs of prokaryotes can be visualized by using many computational tools. Various databases are spectacularly involved in the analysis of GIs and predictions of their probable functions. Besides pathogenic and antibiotic resistant islands, thermophilic, psychrophilic, acidophilic, halophilic, metal-tolerating prokaryotes, etc., sufficiently harbour GIs within their genomes to adapt to the hectic environments. GIs acquisition through horizontal gene transfer (HGT) or change in frame of genome is supposed to be a driving force of prokaryotic evolution.

Keywords

Genomic Islands · Extremophiles · Databases · Tools · Symbiosis islands

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4.1 Microbial Genomic Islands (GIs): An Overview

For colonization perspective and adaptation within an environment, microbes use to reframe their genetic materials to compensate changing environmental scenario. Horizontal Gene Transfer (HGT) mechanisms like conjugation, transduction, and transformation are the crucial factors provide some clues to face the challenge of critical environmental circumstances (Dobrindt et al. 2004; Bellanger et al. 2014; Assaf et al. 2021). Chromosomal segments acquired through HGT carry some important genes that are responsible for providing adaptation potentialities and fitness to the organism, designated as genomic islands (GIs), and so these appears as a critical member of bacterial mobilome. Larger chromosomal segments coupled with a gene pool, sometimes encode their own transposase or integrase of tyrosine recombinase family, flanking with a few repeated structures and association of tRNA genes are typical characteristics of GIs (Dobrindt et al. 2004; Boyd et al. 2009). GIs containing genes are usually novel or their functions are not elucidated so far, but still they have some roles in adaptation in a specific condition.

It is now well established that GIs are one of the key regulators of bacterial diversity, adaptation within a particular habitat, and of course bacterial evolution (Vale et al. 2022). Its availability varies from species to species, sometimes within the same species inhabiting different habitats. To cope up with ever changing environments, and selection pressure of any contaminants like heavy metals or toxic organic and inorganic materials, antimicrobials, etc., are the crucial factors for acquisition of specific GIs within bacterial chromosomes. According to their functional roles, they could be classified as pathogenic islands, harbouring pathogenic genes; degradation islands, involving in degradation of complex molecules; metabolic islands, related to metabolism of carbon and nitrogenous compounds; and resistant islands, providing resistance capabilities against toxic compounds or antibiotics (van der Meer and Sentchilo 2003; Boyd et al. 2009; Juhas et al. 2009; Langille and Brinkman 2009; Carraro et al. 2014; Bertelli et al. 2019). In the very early 90s, scientists found some pathogenic genes within an *E. coli* strain which was devoid of other strains of *E. coli* (Langille and Brinkman 2009). This discovery may be called as a first step for GIs studies. A distinct difference between prokaryotic and eukaryotic organisms in context to their genetic element is predictable in terms of orthologous sequences which are not only found in the same species but also in the distinctly related eukaryotic species. But the scenario is quite different in prokaryotes where they conserve about 50% of their genome as core genome and genes of rest 50% accessory genome might be unique for the specific strain like., hundred of genome sequences of E. coli comprising of more than 45,000 gene families (Rodriguez-Valera et al. 2016).

For detecting GIs within bacterial genome, there are two basic approaches are available, such as depending on the sequence composition and another is based on comparative genomics. The first technique does not need any reference genome for detection; whereas the latter one needs a reference genome should be selected from the same species. After comparing with the reference genome, this approach finds

out GIs from target genome (Langille and Brinkman 2009; Bertelli et al. 2019). There are several programs like SIGI-HMM, PAI-IDA, Centroid, Alien_Hunter, IslandPick, etc., and these programs detect GIs by measuring codon adaptation index, dinucleotide bias, percentage of GC content, etc. (Langille et al. 2008).

After confirming presence of GIs within genome, it is necessary to visualize them for calculating their positions and numbers. So visualization is an important step for studying about GIs. In this chapter, we have discussed comprehensively about genomic island origin, distribution, types, role in adaptation in different hectic conditions in respect to microbial evolution and related tools and finally mentioned some of the relevant databases for studying GIs.

4.2 Origin and Acquisition of GIs

GIs are often considered as the clusters of functionally related genes that are acquired via HGT and have a great impact on the evolutionary lineage of prokaryotes (Jani and Azad 2021). In the late 1980s, the concept of genomic islands (GIs) was first stricken in the mind of J. Hacker and his colleagues as pathogenicity islands (PAIs), who deeply studied the genetic background of the virulence factor of *Escherichia coli* (Hacker et al. 1990). Notably, they observed that the PAIs were unstable regions of chromosomes having variable virulence factors associated with different characteristics and phenotypes (Phillips-Houlbracq et al. 2018). These PAIs islands are of 10 kb–100 kb in size and can be up to 500 kb large. GIs of below 10 kb size are known as genomic islets (Juhas et al. 2009). The evolutionary relationships between different GIs are based on specific sequence and functional homologies. The coding region of genomic islands is not only confined to pathogenicity, but it also comprises other traits like symbiosis aromatic compound and sucrose metabolism (Bertelli et al. 2019), siderophore synthesis (Bertelli et al. 2019), and mercury resistance (Norambuena 2020). This could suggest that GIs evolved for selected adaptive and auxiliary functions.

The acquisition of GIs has happened via horizontal gene transfer. GIs have self-mobility capability; they could excise from their chromosomal region, can transfer itself independently into a different cell, and integrate into the specific target site of host's chromosome (Juhas et al. 2009). GIs are also acquired into the host cell through a well-defined group of the genetic element known as integrative and conjugative elements. It also includes conjugative transposons with multiple integration sites into the host cell (Burrus and Waldor 2004). A group of GIs does not have any self-mobility capability and they transfer via phage packaging, release, and infection (Juhas et al. 2009). In the detailed mechanism of GIs acquisition, it is sometimes inserted into the 30-end of tRNA genes by a phage-like recombinase, named as integrases which acts site specifically (Juhas et al. 2009). Other than GIs, different tRNA could also be inserted by integrases (Williams 2002). Specifically, GI-encoded integrases are related to the lambda, XerD, or P4 families (Juhas et al. 2009). The integrase coding gene, *int* may be located at one extreme part of the island and adjacent to the tRNA gene where they are integrated into GIs. The phage

packaging GIs are often observed in staphylococcal pathogenicity islands (SaPIs) (Pantůček et al. 2018; Jin et al. 2021). SaPIs are involved in phage-induced excision, integration, replication, and proliferation resulting in acquisition of GI.

4.2.1 Islands Related to Pollution Degradation

Natural and manmade organic chemicals sometimes cause environmental pollution. Potent bacteria associated with some important adapted genes are responsible for chlorobenzene, nitrobenzene, phenoxyalkanoic acids and atrazine degradation for their own metabolism. Pollutant degrading metabolic genes (referred as 'evolutionary greenhouse') harboured by GIs are intrinsic factors responsible for environmental sustainability (van der Meer and Sentchilo 2003). Tn*4371*-like integrative or conjugative elements harboured in GIs of *Cupriavidus* and *Ralstonia* genera are responsible for toluene degradation (Van Houdt et al. 2012).

4.2.2 Islands Related to Pathogenicity

Genomic islands associated with pathogenicity may be the most studied topic among genomic islands and associated with environmental adaptations. Host organisms usually produce or secrete some chemical compounds that inhibit the growth of pathogens. On the other hand, pathogens adapted to be associated with their own host by producing some toxin degrading proteins. Not only *Yersinia*, a well-known pathogen bears GIs associated pathogenic genes, but also harmless bacteria *E. coli* and *Klebsiella* sometimes acquire pathogenic islands and cause disease (Hacker and Carniel 2001). *E. coli* is a well-known commensal organism present in the intestine of many organisms helping in metabolism, but when it acquires pathogenic islands (PAI), causes diseases. Loss of pathogenic genes from a genome of plasmid sometimes leads to produce non-pathogenic strains. For example, thermophilic strain *Bacillus anthracis* PFAB2 is a novel strain without common virulence genes (Banerjee et al. 2020).

4.3 Islands in Extremophiles

4.3.1 Thermophiles

Horizontal gene transfer mainly provides the advantages to bacteria to adapt in punitive environment (da Silva Filho et al. 2018), one of the example is high temperature. Horizontal gene transfer enlightens the evolutionary explanation on extreme thermophilic bacteria as model for ancient bacteria (Gogarten and Townsend 2005).

The selection of genomic island is controlled by some internal mechanisms which may be a random manner or controlled by specific selection procedure, but it is till date remain mystery. Relative age and movement of genomic island had been studied to analyse the competence level of *Thermus* spp. Several horizontally transferred genomic islands had been studied in genome of *Thermus* spp. by Kumwenda et al. (2014). Genomic island incorporation in chromosome is responsible for DNA amelioration and oligonucleotide distance pattern calculation determining reletive aquisition time (Kumwenda et al. 2014). From the point of evolution it had been found that *Deinococcus* lineage had acquired GI from *Thermus* species. Hence, it can be said that genomic island is most likely to play an evolutionary role in case of *Thermus* species lineage (Kumwenda et al. 2014). On the other hand, GI has also important role in holding the genes responsible for adaptation in extreme environment like high temperature. As per example, in one study done by Mercer et al. (2015)) heat resistance food isolate *Escherichia coli* AW1.7 showed more than 6 min D_{60}-value (highly resistant to heat). A ~14 Kb genomic island consists of many putative heat shock proteins present in 16 open reading frames encoding protease, responsible for highly heat resistance. Hence, this genomic island was converted to locus of heat resistance (LHR) that could help foodborne pathogens to withstand heat (Mercer et al. 2015). An LHR of 15–19 kb comprise of yfdX2, *yfd*$X1_{GI}$, *hde*D_{GI}, *orf*11, *kef*B, *trx*$_{GI}$, etc. genes that confers heat resistance in *Enterobacteriaceae* (Mercer et al. 2017). Genomic island PYG1 of 21.4 kb had been identified in the genomic sequence of the hyper-thermophile *Pyrococcus yayanosii*. The ΔPYG1 mutant strain had shown reduced growth at 100 °C compared to the wild one (Li et al. 2016).

4.3.2 Psychrophiles

Microorganisms have evolved diverse cold-adaptation mechanisms to survive and proliferate in the Earth's cold biosphere like cold aquatic and terrestrial ecosystems, or seasonally cold environments. The GIs provided us valuable insight into the unique characteristics of cold-adapted genome that assessed possible HGT events for cold adaptation (Penn et al. 2009; Murray and Grzymski 2007; De Maayer et al. 2014; Bowman 2017). A psychrophilic archaeon, *Methanosarcina burtonii* was reported with 125 genomic islands that represented >50% of the genome. Whereas, the GIs of mesophilic *Methanosarcina* genomes were represented ≤40% of its genome. The high proportion of unclassified genes harboured in genomic island denotes genes from unknown organisms that were perhaps acquired through HGT event. The GIs were overrepresented with different cellular parts such as cell wall and cell membrane (outer part); envelope biogenesis and signal transduction mechanisms (inner metabolism) and these are related to cold adaptation (Allen et al. 2009). Likewise, the GIs of an extreme psychrophilic bacterium *Psychroflexus torquis* harboured most of the genes to dwell in a sea-ice environment. A majority of 44 GIs were represented with insertional elements, addiction modules, and pseudogene. Some GIs were flanked by tRNA genes that are well-known hot-spot

for site-specific recombination (Ou et al. 2006; Feng et al. 2014). The GIs of a flavobacterial epiphyte *Psychroflexus torquis* habituating in sea ice algal assemblages harboured genes that encode proteins or enzymes to synthesize poly-unsaturated fatty acids, exopolysaccharides, putative antifreeze proteins, and to uptake compatible solutes (Feng et al. 2014; Bowman 2017). The genome of an *Alteromonas* species was represented by 15 specific GIs with genes to provide the ecological fitness in a cold marine environment (Math et al. 2012). An Antarctic deep lake habituating *Halobacterium* species acquired unique gene features like gas vesicle, polyhydroxyalkanoate, bacteriorhodopsin biosynthesis genes to survive in the cold ecosystem (DeMaere et al. 2013).

4.3.3 Halophiles

Halophiles are organisms that grow in saline environment. They can be found in various habitats like hypersaline water, saltern pond crystallizers, salt lakes, saline soil (Dutta and Bandopadhyay 2022). Horizontal acquisitions of various osmoresponsive genes might be a consequence of improving tolerance to salinity stress. Extremely halophilic archaea, *Haloarcula hispanica* possesses insertion element (IS), terminal inverted repeat (TIR), transposase gene (without TIRs) (Woods et al. 1999). 50% of the megaplasmid genes including two prophage regions were reported from GIs of moderately halophilic bacteria, *Pontibacillus*. Most of the chemotaxis genes (*mcp*/*che*) and flagellar motility genes (*fliG*/*M*/*N* and *motA*/*B*) are present in the megaplasmid. These environment sensing genes are harboured in two prophages regions (von Hoyningen-Huene et al. 2021). *Salinicoccus halodurans* genome contained 11 GIs, no CRISPR repeat region. One gene cluster involved in *N*α-acetyl-α-lysine biosynthesis. Genes encoding several hydrolases, stress responsive proteins, i.e., choline and betaine transporters, cold-shock protein, as well as chaperones are also noted (Jiang et al. 2015). Three larger horizontal gene transfer (HGT)-GIs are harboured in *Salinibacter ruber*, flanked by tRNAs and phage-related recombinase, which may participate in HGT events. Metalloresistence island, antibiotic resistance islands are associated with adaptive processes (González-Torres and Gabaldón 2018).

4.3.4 Acidophiles and Alkaliphiles

Acidophiles are organisms that thrive in acidic and sulphur rich environments, acid mine drainage (AMD), and relied on chemoautotrophic production by iron and sulphur oxidation. They are widely distributed in AMD Río Tinto of Spain (Amaral-Zettler et al. 2011), Iron Mountain hot springs in California, USA (Wilmes et al. 2008), and stromatolites (Sriaporn et al. 2020). One of the most studied bacterial genus *Acidithiobacillus* grows at optimum pH <4. Comparative genomics

study revealed the genes responsible for survival in the acidic environment, viz., amino acid decarboxylases, deiminase/deaminases group, K^+ transporters, Na^+/H^+ antiporters, modified proton-efflux P-type ATPases (Baker-Austin and Dopson 2007). The genes are mostly present in GIs, are often associated with mobility genes (integrases and transposase), prophage, flanking repeats, plasmid mobilization elements along with atypical GC content (Beard et al. 2021).

Alkaliphiles are organisms that grow efficiently at pH >9. Alkaliphiles are inhabited in various environments like ocean hydrothermal vents, river, soda lakes, and alkaline soils (Grant 2006). GIs of extremely alkaliphilic *Bacillus halodurans* contain transposases, insertion sequences (IS) that facilitate HGT in the course of evolution and also in internal rearrangement of the genome (Takami et al. 2000). *Bacillus pseudofirmus* has phosphoserine aminotransferase, ABC type siderophore transporter, Na + coupled Npt type phosphate transporters, Ktr-type potassium uptake system, and cation/proton antiporters genes whose products contributed adaptations to alkaliphily (Janto et al. 2011).

4.4 Antibiotic Resistance Islands

Advancement in genome sequencing leads to the discovery of involvement of GIs in making antibiotic resistant phenotype within bacterial community. Antibiotic resistant islands often carry more than one antibiotic resistant genes integrated within tRNA gene. These GIs are characterized by terminal integrase or recombinase or insertion sequences, as consequences, GIs are less stable element (Dobrindt et al. 2004). Antibiotic resistant GIs can take part in genetic transfer events like conjugation, transformation, and transduction. GIs that actively participate in conjugation are termed as integrative conjugative elements (ICEs) and thus become the keen interest of modern research (Johnson and Grossman 2015). These ICEs are highly transmissible mobile genetic elements (MGE) and additively self-transmissible due to the presence of insertion sequences. They can exist as an integrated part of nucleoid or may be excised independently, self-replicable extrachromosomal DNA. ICEclc from *Pseudomonas knackmussii*, SXT from *Vibrio cholerae*, pKLC102 from *P. aeruginosa* Tn4371 from *Ralstonia oxalatica* are among the well-defined ICEs (Botelho et al. 2020). For Enterobacteria and other group of bacteria, typical GIs that impart numerous antibiotic resistance features have been reported. Clinically relevant methicillin-resistant *S. aureus* strains have emerged from the so-called SCCmec islands (MRSA). SCCmec islands can range in size from 20 kb to >60 kb, and they could harbour extra resistance features. In certain Proteobacteria, another sort of genomic island provides antibiotic resistance. The SXT island and R391 island of *Vibrio cholerae* and *Providencia rettgeri*, respectively, are the most well-known members of this category. A comparison of these elements indicated a conserved backbone with dedicated areas to the integration, transmission, etc., for these components. However, extra variable regions are also to be noted within these components. SXT-related components have also been discovered in natural settings. The pMERPH element (from *Shewanella putrefaciens*) got

from river sediments of UK is an example of antibiotic resistant islands. *V. cholerae* lives a portion of its life cycle in water, suggesting that this group of GIs may have additional, some unidentified features that improve its fitness and/or survival, involved in adaptation and evolution of the species (Dobrindt et al. 2004).

4.5 Catabolic Genomic Islands

Heavy metals are the key toxicant in the environment as they are hazardous, incremental, and tenacious. The heavy metal toxicity effect was shown in every hierarchical level of life including microbes. It could disrupt the cell membrane structure, damage proteins and nucleic acids, and hamper various enzymatic pathways and transcription processes (Chandrangsu et al. 2017) in the microbial cell. To cope with the toxic effect of heavy metals, microbial communities have evolved genetic programs encoding selective function that allows for efflux or sequestration of the heavy metals resulting in reduction of toxic effects. In the efflux system various heavy metal transporters like cation diffusion facilitators (CDF) and PIB-type ATPases were involved, which translocate the metal ions from cytoplasm to periplasmic space (Nies 2016). Notably, the P-type is known as the most relevant heavy metal transporter that uses ATP to efflux heavy metals against their concentration gradients (Nies 2016). In addition, heavy metals are exported from the periplasmic space to the extracellular space across the outer membrane via resistance-nodulation-division (RND)-transport (Greene and Koronakis 2021). The RND transporter is a multi-component system composed of 6 membrane fusion proteins (MFPs), 3 RND transport proteins, and 3 outer membrane factor proteins (Greene and Koronakis 2021). Bacteria have an astonishing potential to confer the heavy metal resistance (HMR) genes within bacterial species through HGT, conjugative plasmids, transposons, and genomic islands (Li et al. 2018b). Genomic islands associated with HMR were described in many bacterial species. For example, the presence of PIB1-ATPase, PIB3-ATPase, PIB4-ATPase, RND-type metal transporter, and metal binding chaperones in *Mucilaginibacter rubeus* and *M. kameinonensis* makes the strain put forward for HMR (Li et al. 2018b). An aquatic ecosystem strain *Listeria welshimeri* harboured a novel LGI2-like genomic island from *L. monocytogenes* that transfers cadmium (Cd) tolerance proteins CadA and makes the strain resistant to Cd (Lee et al. 2021). Different heavy metal related genes are found to be situated within islands of environmental multi-metal resistant strain of *Bordetella petrii*. Arsenic resistant genes like *arsC*, *arsI*, *arsH*, *arsM*, etc., were present in GIs of the strain (Halder et al. 2022). These genes are involved in arsenic tolerance in bacteria by arsenic reduction, methylation, etc. (Kabiraj et al. 2022).

Reactive azo dyes are refractory pollutant containing –N=N– (azo bond) group linked with carbonated skeleton. This reactive azo dye laden textile effluent is being discharged in the aquatic ecosystem with consequent deleterious repercussion (Sarkar et al. 2017).

Genomic Island had important role in harbouring genes related to metabolic process, catabolic expression which have role in environmental adaptation for

bacterial isolates. *Shewanella* is known for its high potentiality in dye containing textile effluent bioremediation. As per example, *Shewanella* algae 2NE11, isolated from industrial effluent in Peru, had shown ~97% decolourization against high concentration of anthraquinone dye and ~ 89% decolourization rates for azo dye (Lizárraga et al. 2022). It was also reported to harbour two genomic islands related to horizontal gene transfer showing role in environmental adaptation (Lizárraga et al. 2022). Dye decolourizing genes are associated with this genome, like NADPH-dependent oxidoreductase genes (HU689_04585; HU689_21345; HU689_04700), an FMN-dependent NADH-azoreductase gene (HU689_20695), and heme-dependent Dyp peroxidase gene (HU689_05310) (Lizárraga et al. 2022). In one bacterial consortium SCP (*Stenotrophomonas acidaminiphila* APG1, *Pseudomonas stutzeri* APG2 and *Cellulomonas* sp. APG4) it was found that, APG4 CDS associated category for transport and catabolism could be related with dye (mono-azo dye, Reactive blue 28) degradation (Chen et al. 2020). Maximum number of functional genes had been identified basically in APG2; however, APG1 and APG4 are also associated with it. This scenario further indicates the catabolic reaction related to azo dye degradation (Nanjani et al. 2021). Azo bond breakdown could be noticed by the APG genome due to the presence of a redox mediator. It was found that APG4 contains more number of ORF for NADH:DCIP oxidoreductase which lead to greater functionality (nearly 18 folds higher reductase activity) compared to APG1 and APG2 in azo dye degradation (Nanjani et al. 2021).

4.6 Symbiosis Islands

The role of genomic island is not limited to pathogenicity but have diverse role in symbiosis, aromatic compound metabolism, siderophore synthesis, etc. (Juhas et al. 2009). Many bacteria form symbiotic association with eukaryotic host with the help of symbiotic island. The mosaic structure of island suggests that multiple recombination events have occurred during evolution in a stepwise fashion. Presence of this type of island is also uncertain, i.e. they may not be present in closely related strain of same or different species. This type of island contains nodulation genes, genes related to nitrogen fixation, and other types of genes required for transfer of the island, nodule metabolism, several regulatory genes, etc. Transfer of symbiotic island to a nonsymbiotic mesorhizobia converts their behaviour as symbionts and they could get the ability of nitrogen fixation. A chromosomally integrated element (502 kb), a symbiotic island, from the genome of *Mesorhizobium loti* strain R7A have the ability to transform nonsymbiotic mesorhizobia in the environment to Lotus symbionts (Sullivan et al. 2002). The island also contains several operons that are not required for transfer including operon for vitamin (biotin, thiamine, and nicotinamide) biosynthesis. These operons are not directly linked with symbiosis but they may help bacteria for better competition in rhizospheric environment. Symbiotic nitrogen fixing bacterium *Bradyrhizobium japonicum* harbours a symbiotic island of 681 kb in size that carry cluster of symbiotic genes which are structurally inserted into a val-tRNA gene on the genome (Itakura et al. 2009). Symbiotic nitrogen fixing

bacteria, *Mesorhizobium* and *Bradyrhizobium* are involved in root nodule formation with specific types of plants. There are *sym*-genes for regulation of root nodule formation in different stages of plant growth. So, these types of important islands are devoted with nitrogen fixation. More studies also required to know about the stability of these important genes within the bacterial chromosome (Roumiantseva et al. 2018).

4.7 Prediction of GIs

In this Era, robust genome sequencing and emerging interest on role of GIs on bacterial adaptation and evolution drive us to grow interest to assume genomic islands, their position, related genes, etc. Several tools and databases are now available to predict genomic islands. In this section, we will discuss briefly the tools and databases related to GIs identification.

4.7.1 Tools

Bacteria may now be studied by studying their genomic sequences owing to the high sequencing methods. Comparative genome sequence analysis, for example, can identify phenomena like gene gain or loss, or exchange in a genome. Gene gain by horizontal gene transfer makes a bacterium more selective to that particular environment. The study of GIs is crucial for biological and bioinformatics research. So, identifying GIs is one of the most important jobs in genome evolution and gene transfer mechanism research. Nowadays, several tools are available (Table 4.1) for GIs prediction.

4.7.2 Databases

Other than GI prediction tools there are several databases (Table 4.2) available that can be used directly for comparative study. These databases serve as resource to identify integrase site specificity and its evolution (Bertelli et al. 2017).

4.8 Significance of GIs in Prokaryotic Evolution

In 1965, Zuckerkandl and Pauling had found that there is a relationship between nucleotide as well as protein sequences and organism's evolution. Different parameters like codon bias, point mutation, changes in nucleotide sequences, etc., were considered for driving force of evolution. But there are some sudden changes that can be occurred within the genome of prokaryotic cells that cannot be imagined through the grammar of evolution. An example of this sudden change is horizontal gene transfer of genomic islands (Lima et al. 2008).

Table 4.1 List of computational tools used for Genomic Island prediction in Prokaryotes

Tool names	Tool links	Special features	References
IslandPath	http://www.pathogenomics.sfu.ca/islandpath	Aid in detection of genomic islands with genome annotation features	Hsiao et al. (2003)
PAI-IDA	http://compbio.sibsnet.org/projects/pai-ida/	Simple analysis to detect pathogenicity islands and anomalous gene cluster	Tu and Ding (2003)
SIGI (score-based identification of genomic islands)	https://www.uni-goettingen.de/en/research/185810.html	Detect genomic island with high sensitivity	Merkl (2004)
ORFcurator	http://www.genomecurator.org/ORFcurator/	Used for molecular organization of genes and gene clusters	Rosenfeld et al. (2004)
GC-Profile	http://tubic.tju.edu.cn/GC-Profile/	Study for visualization and analysis of the variation of GC percentage and GIs	Gao and Zhang (2006)
MobilomeFINDER	http://mml.sjtu.edu.cn/MobilomeFINDER (Upon request)	High-throughput tools for identification and characterization of island through exploitation of emerging sequence data and PCR-dependent profiling of un-sequenced strains	Ou et al. (2007)
PredictBias	www.davvbiotech.res.in/PredictBias (Upon request)	Genomic and pathogenic islands detection in prokaryotes by analysing sequence composition, insertion elements, and genes associated with virulence factors.	Pundhir et al. (2008)
Design-Island (Detection of Statistically Significant Genomic Island)	http://www.geocities.com/raghuchatterjee/Design-Island.html	This tool does not require any previous data sets and used Monte-Carlo statistical tests	Chatterjee et al. (2008)
INDeGenIUS (Improved N-mer based Detection of Genomic Islands Using Sequence-Clustering)	Upon request	Identification of unique functional islands in complete-sequence of organism	Shrivastava et al. (2010)
EGID (Ensemble Algorithm for Genomic Island Detection)	http://www5.esu.edu/cpsc/bioinfo/software/EGID (Upon request)	Used in horizontal gene transfer and molecular evolution study	Che et al. (2011)
IGIPT (integrated genomic island prediction tool)	http://bioinf.iiit.ac.in/IGIPT/	Allows the users to analyse GIs by simultaneously using	Jain et al. (2011)

(continued)

Table 4.1 (continued)

Tool names	Tool links	Special features	References
		thirteen different measures that give a more precision for prediction	
PIPS (Pathogenicity Island Prediction Software)	http://www.genoma.ufpa.br/lgcm/pips	Using multiple tools for detection of pathogenic island in blended mode	Soares et al. (2016)
GIV (Genomic Island Visualization)	http://www5.esu.edu/cpsc/bioinfo/software/GIV	Detection of the location of GIs in a genome and also gives the supportive features information for GIs	Che and Wang (2013)
GI-POP	http://gipop.life.nthu.edu.tw/	Draft genomes can be submitted in contigs or scaffolds to get highly probable GIs	Lee et al. (2013)
Genomic Island Hunter	http://www.esu.edu/cpsc/che_lab/software/GIHuanter	GI projection method for sequenced bacterial and archaeal genomes. This tool uses sequence composition, mobile gene information, and integrase.	Che et al. (2014)
MSGIP (Mean Shift Genomic Island Predictor)	http://msgip.integrativebioinformatics.me/	Precisely predicted the complete reservoir of GIs in a genome	de Brito et al. (2016)
GI-SVM (Genomic Island-Support Vector Machine)	https://github.com/icelu/GI_Prediction	Highly sensitive tools for prediction of GIs in unannotated sequence of a single genome	Lu and Leong (2016)
GIPSy (genomic island prediction software)	https://www.bioinformatics.org/groups/?group_id=1180	Identify GIs in bacterial genome based on variation of the GC content, tRNA, genomic codons, transposase, etc.	Soares et al. (2016)
Zisland Explorer	http://tubic.tju.edu.cn/Zisland_Explorer/	GIs detection by utilizing both homogeneity and heterogeneity properties	Wei et al. (2017))
Islandviewer4	http://www.pathogenomics.sfu.ca/islandviewer/	Prediction of GIs with their products and features via three integrated tools like IslandPick, SIGI-HMM, and IslandPath-DIMOB	Bertelli et al. (2017)

(continued)

Table 4.1 (continued)

Tool names	Tool links	Special features	References
XenoGI	http://www.cs.hmc.edu/xgiWeb/	Study the history of GIs insertions in a clade of microorganism	Bush et al. (2018)
Vrprofile	http://bioinfo-mml.sjtu.edu.cn/VRprofile	Rapid investigation of antibiotic resistance and virulence gene clusters in pathogenic bacteria	Li et al. (2018b)
MTGIpick	https://github.com/bioinfo0706/MTGIpick	GIs identification from a single, unannotated genome with prior information	Dai et al. (2018)
IslandCafe	https://github.com/mehuljani/IslandCafe	Novel island detection by comparing frequently used tools for GIs analysis	Jani and Azad (2019)
panRGP	https://github.com/labgem/PPanGGOLiN	Prediction of genomic islands diversity via Pangenome analysis	Bazin et al. (2020)
2SigFinder	https://github.com/bioinfo0706/2SigFinder	Statistical analysis for GIs detection from a single genome.	Kong et al. (2020)
SSG-LUGIA	https://nibtehaz.github.io/SSG-LUGIA/	Analysis of new-sequence based genomes and independent of functional annotation of genomes	Ibtehaz et al. (2021)

Secretion systems, encoded by GIs, are not only responsible for release of GIs and GIs encoded products from microbial cells, but also GIs associated chromosomal segments of the host organism. Acquisition of chromosomal segments through GIs is associated with rapid microbial evolution and diversification. A magnificent metabolic change is to be found in recipient microbes (Juhas et al. 2009) as GIs contain huge numbers of genes (Dobrindt et al. 2004). Acquisition of new genes associated with GIs usually counterbalanced by reduction of negative genes which sometimes considered as extra advantage for the organisms. These genetic and metabolic changes ultimately drive organisms to evolve (Juhas et al. 2009). GIs within the recipient microbial chromosome acquire, replace, or disintegrate chromosomal core genes. Gain or loss of genes makes distinct features of a particular strain from rest other strains of the same species. Species like *E. coli,* after acquiring pathogenic islands had become able to cause different diseases in intestine and extraintestine of human beings and other animals (Desvaux et al. 2020). Bacteriophages are sometimes considered as the driving force for bacterial evolution. Bacteria use to develop CRISPR-Cas system to escape itself from viral attack; on the other hand, viruses also modulate their genetic elements which help them to survive against bacterial 'sword'

Table 4.2 Databases related to GIs prediction with some important characteristics

Databases	Feature	Availability	References
Islander	A database associated with integrases and their specific DNA sites in the genomic islands of prokaryotes	http://bioinformatics.sandia.gov/islander (Upon request)	Mantri and Williams (2004)
IslandPick datasets	Investigate the sequence composition-based GIs	http://www.pathogenomics.sfu.ca/islandpick_GI_datasets/	Langille et al. (2008)
PAIDB (Pathogenicity Island Database)	Detection and analysis of antibiotic resistance and pathogenicity islands	http://www.paidb.re.kr/	Yoon et al. (2015)
ICEberg	Study the bacterial mobile genetic elements such as integrative and conjugative elements (ICEs)	http://db-mml.sjtu.edu.cn/ICEberg/	Liu et al. (2019)
VRprofile	Exploration of antibiotic resistance and virulence gene cluster	http://bioinfo-mml.sjtu.edu.cn/VRprofile	Li et al. (2018a)
VCGIDB (*Vibrio cholerae* Genomic Island Database)	Prediction of phylogeny-based upgraded features in a large genome	http://leb.snu.ac.kr/vcgidb	Hur et al. (2019)
DarkHorse	Strong and flexible collection of tools using for prediction of phylogenetically related protein families in both individual HGT in a single genome and large-scale HGT in large genome	http://darkhorse.ucsd.edu/	Podell et al. (2008)
Islandviewer 4	Interactive visualization of GIs in bacterial and archaeal genomes for large-scale datasets	http://www.pathogenomics.sfu.ca/islandviewer/	Bertelli et al. (2017)
DGI	A dataset that comprises GIs derived from 2000 different bacterial genome including PAIs depicted as circular graphical images	http://www5.esu.edu/cpsc/bioinfo/dgi (Upon request)	Che et al. (2014)
GI-POP	Microbial genome annotation dataset including non-coding RNAs, ORF, and GIs. Also, GI-GPS based system is used for genomic islands prediction.	http://gipop.life.nthu.edu.tw/	Lee et al. (2013)
MOSAIC	Study the conserved and diverse segments (i.e., GIs) in the genome	http://genome.jouy.inra.fr/mosaic (Upon request)	Chiapello et al. (2008))

(Vale et al. 2022). However, evolution of GIs itself is quite distinct from the evolutionary lineages of other integrative elements (Boyd et al. 2009). From the analysis of GIs analogous structural and functional characteristics along with their phylogenetic relatedness revealed that GIs may be evolved multiple times.

Bacteriophages usually attack bacteria at different times of bacterial life cycle, integration of viral genome, commonly called as prophage, can acquire more supplementary genes and can be considered as genomic island (Boyd et al. 2009). Cell-wall less small bacterium, *Mycoplasma* is also associated with some genomic islands. Among *Mycoplasma* related bacteriophages, φMFV1 and φMAV1 contain *mem* and *vir* genes, which preferentially encode some membrane anchored surface proteins. *mem* generates a coiled protein, whereas *vir* is responsible for a lipoprotein, eventually acts as putative virulence factor (Citti et al. 2020). Super-integrons are specific types of integron with the ability to stockpile a number of genes that might be associated with antibiotic resistance and can be converted themselves to GIs leading towards development of antibiotics resistant microbes (Dobrindt et al. 2004). After critical review on antibiotics resistance by *Salmonella enterica*, an author reported that this pathogenic bacterium is associated with a class 1 integron. *Salmonella* genomic island 1 (SG1) comprised of 15 kb integron and 27.4 kb backbone with five antibiotic resistant genes (Hall 2010). SGI1 and SGI1-REs were found to be members of large family of integrative genomic elements (IGE) and due to random evolutionary events like insertion, deletion, mutation, etc., their structural shape becomes altered. When members of Gammaproteobacteriaceae catch up these GIs, they distribute GIs easily and more frequently to their related species for adaptation against antimicrobial agents (Cummins et al. 2020). Urease producing bacterium, *Proteus mirabilis* is associated with a novel GI, named as PmGRI1 also responsible for antibiotic resistance (Lei et al. 2020).

Studies on genomic islands of archaea is not as frequent as bacteria, a very few reports are available till date, although archaea are very closely related with bacteria and eukaryotic organisms both genetically and evolutionarily (Makarova et al. 1999).

4.9 Conclusion

Prokaryotes can thrive in all kinds of biomes. In order to adapt in the diverse kinds of environment, they have evolved over time during a variety of events, namely gene rearrangements, mutations, horizontal gene transfer, etc. This evolutionary pattern may contain specific sequence. The horizontal transfer of large gene clusters as genomic islands contains accessory genes for adapting in a specific environmental niche. As evolution is a random and continuous process and GIs have tremendous role in prokaryotic evolution, the question is raised about its stability. Beside developing new tools and databases for genomic islands, now focus is needed on identifying the factors that provide its stability within the bacterial genome.

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