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Class 1 integrons as invasive species

Michael R Gillings

Clinical class 1 integrons are a major contributor to the evolution and dissemination of antibiotic resistance. The conserved motifs of these integrons suggest that a single, recent ancestor gave rise to all current variants. They have had a spectacular increase in distribution and abundance over the last 100 years, exhibiting many similarities to invasive species that prosper under human impacts. They have spread into over 70 bacterial species of medical importance, are commonly resident in the gut of humans and domesticated animals, and have invaded every continent, including Antarctica. They have done so via linkage with transposons, metal, disinfectant and antibiotic resistance genes. As a consequence of their invasive nature they have now become significant pollutants of natural environments.

Address
Department of Biological Sciences, Macquarie University, Sydney, NSW 2109, Australia

Corresponding author: Gillings, Michael R (michael.gillings@mq.edu.au)

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Introduction

Humans influence the entire biosphere, significantly changing the distribution and abundance of species and genes. Many species have declined during the Anthropocene, while domesticated and invasive species have flourished because of their usefulness to humans, or their ability to prosper in human-dominated ecosystems. Human influence extends even into the microbial world, affecting our own microbiota, and changing the dynamics of bacterial genome evolution.

One group of microorganisms that have prospered in the modern world are those that exhibit resistance to antimicrobial compounds. They have done so because they carry genes that confer advantageous phenotypes, and in turn, these genes have also vastly increased in abundance, generating a crisis for modern medicine [1]. Understanding the evolution, selection and dispersal of resistance determinants is critical to predicting and controlling this phenomenon [2•], and examining the history of particularly successful DNA elements might help identify the properties behind their success [3–5].

One major player in the dissemination of antibiotic resistance is the class 1 integron. Although this element does not itself confer resistance, it has been extraordinarily successful at capturing and expressing diverse resistance genes in clinical contexts. This review examines the evolutionary history of the class 1 integron, and investigates the properties that have allowed it to prosper, despite attempts by humans to control the host bacteria in which it now resides.

General properties of integrons

Integrons are genetic platforms that acquire exogenous genes in the form of mobile gene cassettes. All integrons share three core characters, these being: the integron-integrase gene, *intI*, encoding a tyrosine recombinase; a recombination site, *attI*, where the integrase catalyses insertion of newly acquired gene cassettes; and a promoter, Pc, that drives expression of the inserted genes. Sequential acquisition of multiple gene cassettes can result in arrays that contain hundreds of genes (see Ref. [6]).

Integrons are diverse and ancient elements that can be recovered from a wide range of environments. They have been found in more than 15% of genome-sequenced bacteria, where they usually reside on chromosomes. Based on the sequence diversity of the integron-integrase gene, there are many hundreds of integron classes in environmental bacteria. Of this diverse group, only a handful of integron classes have become significant in clinical contexts, and of these, the class 1 integron is the most important [6].

Class 1 integrons in the environment

Class 1 integrons comprise a diverse family, united on the basis of amino acid homology of the integron-integrase protein. This homology distinguishes class 1 integrons from their nearest sister taxon, the class 3 integrons, and helps define the clade [6]. Class 1 integrons are commonly found on the chromosomes of non-pathogenic *Betaproteobacteria* that inhabit soil, freshwater and biofilms. They exhibit some mobility between chromosomal locations, at least on evolutionary timescales [7], and can actively acquire gene cassettes from a diverse environmental pool of these elements. Environmental gene cassettes usually

encode unknown functions, rather than antimicrobial resistance [8]. One notable exception are cassettes encoding the *qac* family of efflux pumps [9].

In summary, the 'wild' version of the class 1 integron exhibits a number of characteristics that might have pre-adapted it to a world where humans attempt to control bacteria with antimicrobial agents. It is present in 1–5% of bacterial cells in soil, freshwater and biofilms, and consequently intersects with the human food chain; it is able to sample diverse gene cassettes that confer adaptive phenotypes; it can mobilize into new locations; and often carries *qac* cassettes that confer resistance to disinfectants (see Ref. [6]).

The genesis and rise of the 'clinical' class 1 integron

When humans first started to use antimicrobial agents, the stage was set for selection of resistance. Genes that conferred resistance, and DNA elements that could move these resistance genes between species, were at a significant advantage. The class 1 integrons fulfilled both these requirements, and as a consequence, were amongst the earliest elements to move from the environmental resistome into human ecosystems. They have gone on to become one of the most clinically important vectors of antibiotic resistance in modern medicine.

The clinical class 1 integron, and the accessory DNA elements closely linked to it, were assembled from diverse environmental sources. It is likely that the component elements, captured from the resistome or mobilome, each had their original homes in diverse taxa. The unique properties and activities of these elements combined synergistically to pre-adapt the clinical class 1 integron for survival in human-dominated ecosystems (Figure 1).

Class 1 integrons are able to acquire and express gene cassettes from very diverse sources, because of their ability to recognize a wide range of *attC* recombination sites [10]. Gene cassettes generate genomic complexity, allow rapid adaptation and confer selective advantages under specific environmental pressures (Figure 1). In the immediate ancestor of the clinical version of the class 1 integron, the possession of a gene cassette encoding the versatile QacE efflux pump conferred resistance to cationic compounds used as disinfectants. Subsequently, this ancestral integron acquired the *sul1* gene that conferred resistance to sulfonamides, the first true antibiotic (Figure 1).

The class 1 integron family must exhibit at least a limited ability to move between chromosomal locations and species, because it can be found embedded in different chromosomal landscapes in various species of environmental bacteria [7]. However, the insertion of the class 1 integron into a Tn*402*-like transposon provided enhanced mobility, enabling the integron to rapidly spread into many different genomic locations. Tn*402* targets the *res* sites of other transposons and plasmids, and this ensures that its cargo class 1 integron could spread rapidly into a diversity of plasmids and transposons. One of these insertions was into a transposon encoding mercury resistance, to spawn the highly successful Tn*21* family of transposons (see Ref. [6]).

The final assembly of the compound element that was the immediate ancestor to clinical class 1 integrons probably occurred at a single point of time, and in a single cell, because all extant clinical class 1 integrons have identical, or near identical DNA sequences across many of the components schematically illustrated in Figure 1. Initial movement of this ancestral integron into humans probably occurred via the food chain, since phyllosphere and rhizosphere bacteria known to harbor such ancestral structures can also be commensals in the human gut [11]. Acquisition might have occurred via agricultural or companion animals (Figure 2), but this is less likely given that exposure to selective agents such as disinfectants, mercury, and sulfonamide antibiotics occurred at a much earlier date in human populations.

Once resident in the human gut, the *res* hunting activity of the Tn*402* transposon allowed transfer onto broad host-range plasmids, driving their diversification [12], and allowing spread by conjugation to new bacterial species. As a consequence, the clinical class 1 integron has spread into at least 72 different bacterial species, the majority of which are of medical importance [13]. Subsequent association of the class 1 integron with mobile IS elements and miniature inverted repeat transposable elements (MITEs) promotes the ongoing generation of diversity and new gene combinations [14–16].

The clinical class 1 integron, carried by various host species, has become an almost universal inhabitant of human gut microbiota [17••]. Humans are colonized with clinical class 1 integrons soon after birth [18], and humans also drive the dissemination of these integrons via migration and international travel [19,20], such they can now be found in at least 74 countries, covering all continents, including Antarctica [13,21]. Lateral gene transfer and sharing of microbiota also ensured that the clinical class 1 integron became a universal feature of the microbiota of domesticated animals [22,23].

Human activities also promote the diversification and dissemination of class 1 integrons. The abundance of *sul1*, strongly associated with clinical integrons, increases in sewage in proportion to the volume of antibiotic prescriptions, demonstrating the direct effect of antibiotic selection on its abundance in human populations [24]. Clinical class 1 integrons are often linked to metal

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