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Mechanisms of drug resistance: quinolone resistance

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Abstract

Quinolone antimicrobials are synthetic and widely used in clinical medicine. Resistance emerged with clinical use and became common in some bacterial pathogens. Mechanisms of resistance include two categories of mutation and acquisition of resistance-conferring genes. Resistance mutations in one or both of the two drug target enzymes, DNA gyrase and DNA topoisomerase IV, are commonly in a localized domain of the GyrA and ParE subunits of the respective enzymes and reduce drug binding to the enzyme-DNA complex. Other resistance mutations occur in regulatory genes that control the expression of native efflux pumps localized in the bacterial membrane(s). These pumps have broad substrate profiles that include quinolones as well as other antimicrobials, disinfectants, and dyes. Mutations of both types can accumulate with selection pressure and produce highly resistant strains. Resistance genes acquired on plasmids can confer low-level resistance that promotes the selection of mutational high-level resistance. Plasmid-encoded resistance is due to Qnr proteins that protect the target enzymes from quinolone action, one mutant aminoglycoside-modifying enzyme that also modifies certain quinolones, and mobile efflux pumps. Plasmids with these mechanisms often encode additional antimicrobial resistances and can transfer multidrug resistance that includes quinolones. Thus, the bacterial quinolone resistance armamentarium is large.

Keywords

topoisomerase; efflux pumps; plasmids; quinolone; DNA gyrase

Introduction

Quinolones have been a widely used class of synthetic antimicrobials.[1, 2] The initial member of the class, nalidixic acid, was identified as a byproduct of chloroquine synthesis in 1962 and had limited clinical use because it was only sufficient for treatment of urinary tract infections and because of the early emergence of resistance.[3] Chemical modifications of the core quinolone and related chemical scaffolds were, however, widely explored and generated compounds with greater potency, broader spectra of activity, improved pharmacokinetics, and lower frequency of development of resistance.[4] A key modification

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of a fluorine substituent at position 8 led to the development of many members of what became known as the fluoroquinolone class with the introductions of norfloxacin in 1986 and ciprofloxacin in 1987 that exhibited substantially greater potency against gram-negative bacteria. Subsequently other fluoroquinolones, such as levofloxacin and moxifloxacin, were developed with enhanced activity against gram-positive bacteria. Because of their potency, spectrum of activity, oral bioavailability, and generally good safety profile, fluoroquinolones were used extensively for multiple clinical indications throughout the world. Although still clinically valuable, fluoroquinolone use has become limited in some clinical settings, as bacterial resistance has emerged over time. In the sections that follow we review the range of molecular mechanisms that underlie quinolone resistance.

Quinolone resistance due to mutation in chromosomal genes

Alterations in target enzymes

Quinolones target two essential bacterial type II topoisomerase enzymes, DNA gyrase and DNA topoisomerase IV.[5] Each enzyme is a heterotetramer, with gyrase composed of 2 GyrA and 2 GyrB subunits and topoisomerase IV composed of 2 ParC and 2 ParE subunits. GyrA is homologous to ParC, and GyrB to ParE.[6] Both enzymes act by catalyzing a DNA double-strand break, passing another DNA strand through the break, and resealing the break.[7] The enzymes' DNA strand-passing domains are localized in GyrA and ParC, and the enzymes' ATPase activity, which drives the catalytic cycle, is localized in domains of GyrB and ParE. Quinolones block the resealing of the DNA double-strand break and in so doing inhibit enzyme activity as well as stabilize catalytic intermediate covalent complexes of enzyme and DNA that serve as a barrier to movement of the DNA replication fork and can be converted to double-strand DNA breaks, which correlate with quinolone bactericidal activity.[8–10]

Single amino acid changes in either gyrase or topoisomerase IV can cause quinolone resistance. These resistance mutations have most commonly been localized to the amino terminal domains of GyrA (residues 67 to 106 for *Escherichia coli* numbering) or ParC (residues 63 to 102) and are in proximity to the active site tyrosines (Tyr122 for GyrA, Tyr120 for ParC), which are covalently linked to DNA in an enzyme intermediate, in both enzymes.[11–14] This domain has been termed the *quinolone resistance determining region* (QRDR) of GyrA and ParC.[15] The most common site of mutation in GyrA of *E. coli* is at Ser83 followed by Asp87, with similar predominance of mutations at equivalent positions in other species.[7, 8, 16] There is conservation of an equivalent Ser and another acidic residue separated by four amino acids for GyrA in other species as well as for ParC, and likewise it is mutation in these residues that is most often present in resistant strains.[7] Ser83Trp and Ser83Leu mutations of *E. coli* GyrA have been associated with reduced binding of the quinolone norfloxacin and enoxacin to gyrase-DNA complexes.[17–19] Competition experiments with quinazolinediones and quinolones also suggest that the equivalent Ser81Phe resistance mutation in ParC of *Bacillus anthracis* causes selective decrease in quinolone affinity for the enzyme-DNA complex.[20] Ser mutations in GyrA appear to have little effect on the *E. coli* gyrase catalytic efficiency, but mutations in the adjacent Asp87 (or other equivalently positioned acidic residues in other species) decrease overall catalytic

efficiency five- to tenfold.[7, 21] A crystal structure of moxifloxacin with topoisomerase IV of *Streptococcus pneumoniae* (Fig. 1) positioned the quinolone in proximity with the Ser and nearby acidic residues but not sufficiently close to determine binding directly.[13] A subsequent structure of fused ParC-ParE fragments of topoisomerase IV of *Acinetobacter baumannii* with moxifloxacin, however, found positioning of the quinolone with a magnesium ion coordinating direct water interactions with Ser84 and Glu88, suggesting bridged contacts between drug and these conserved amino acids, contacts that are presumably disrupted when these amino acids are mutated.[7, 12]

Mutations in specific domains of GyrB and ParE have also been shown to cause quinolone resistance,[22, 23] although they are substantially less common in resistant clinical bacterial isolates than mutations in GyrA or ParC. GyrB resistance mutations have also been shown to have reduced binding of enoxacin to enzyme-DNA complexes.[17] The QRDR of GyrB (or ParE) appears to be distant from the QRDR of GyrA (or ParC) based on the x-ray crystallographic structure of the homologous enzyme, topoisomerase II of yeast.[24] Crystal structures of yeast topoisomerase II, however, identified other enzyme conformations in which the regions homologous to the QRDRs of GyrA and GyrB are in proximity,[25] and the C7 basic substituents of ciprofloxacin and moxifloxacin were shown to be facing the GyrB subunit and could be cross-linked to GyrB Cys466.[26] In addition, in the crystal structure of moxifloxacin and topoisomerase IV of *A. baumannii*, the quinolone C7 basic substituent is in proximity to Arg418, which is equivalent to Lys447 in *E. coli*.[12] Notably mutations in acidic residues in this domain of GyrB in *E. coli* (Asp426Asn) and other species as well as in ParE have been shown to confer quinolone resistance, suggesting that drug-enzyme contacts in this region may be mediated by charge interactions.[12] Thus, it appears that mutations in the QRDRs of both GyrA/ParC and GyrB/ParE act by reducing the affinity of quinolones for the enzyme-DNA complex. Although there are no direct quantitative data on quinolone binding to complexes of wild-type and mutant topoisomerase IV with DNA, the conservation of key resistance residues and the similarity of structures between gyrase and topoisomerase IV predict that resistance is also mediated by reduced drug affinity for the topoisomerase IV-DNA complex as it is for the gyrase-DNA complex.

The magnitude of resistance caused by single amino acid changes in the subunits of gyrase or topoisomerase IV varies by bacterial species and by quinolone.[27, 28] The phenotype of a given resistance mutation is determined in part by the relative sensitivities of DNA gyrase and topoisomerase IV to a given quinolone. Because quinolone interaction with either target enzyme-DNA complex is sufficient to block cell growth and trigger cell death,[9] the level of susceptibility of a wild-type bacterium is determined by the more sensitive of the two target enzymes. For many quinolones in clinical use, gyrase is the more sensitive enzyme in gram-negative bacteria, and topoisomerase IV is the more sensitive enzyme in gram-positive bacteria, but exceptions occur.[28, 29] Target mutations occurring from first-step selection with quinolones are generally in the more sensitive target enzyme, constituting a genetic definition of the primary drug target enzyme.[23, 30, 31] The magnitude of the increase in resistance from such a first-step mutation can be determined by either the magnitude of the effect of the mutation on enzyme sensitivity or the intrinsic level of sensitivity of the secondary target enzyme. Thus, the sensitivity of the secondary target can set a ceiling on

the magnitude of resistance conferred by mutation in the primary target enzyme. This property implies that quinolones that have highly similar activities against both gyrase and topoisomerase IV of a given species may require mutations in both enzymes before the mutant bacterium exhibits a substantial resistance phenotype.[32–34] For fluoroquinolones currently in clinical use, which generally have differences in potency between the two target enzymes, single target mutations typically result in an eight- to 16-fold increase in resistance.

Sequential mutations in both target enzymes have been shown to provide increasing levels of quinolone resistance. In many species high-level quinolone resistance is often associated with mutations in both gyrase and topoisomerase IV.[35] There are also several species, *Mycobacterium tuberculosis*, *Helicobacter pylori*, and *Treponema pallidum*, for which genome sequencing has revealed the absence of genes for topoisomerase IV,[16] indicating that for these organisms gyrase is the only quinolone target. Thus, selection of mutations with substantial resistance phenotypes is predicted to occur readily in these pathogens, an inference that is supported by clinical data indicating the frequent occurrence of resistance with clinical use of quinolones without use of other active agents to treat patients with infections with *M. tuberculosis* and *H. pylori*.[36, 37]

Altered drug permeation

Because gyrase and topoisomerase IV are cytoplasmic enzymes, quinolones must traverse the bacterial envelope to reach their targets, and mutations that result in reductions in cytoplasmic drug concentrations can confer resistance. This reduction is accomplished by active transport of quinolones out of the cell, reduced quinolone uptake, or a combination of the two. In Gram-positive bacteria active efflux transporters are the principal means of reducing cytoplasmic drug concentrations, and reduced diffusion across the cytoplasmic membrane has not been demonstrated as a mechanism of resistance. In contrast, in Gram-negative bacteria reduction in outer membrane porin diffusion channels, through which quinolones enter the periplasmic space, can contribute to resistance and act in concert with basal or increased expression of efflux transporters.[38] Quinolones themselves in general do not induce expression of efflux pumps. Acquired quinolone resistance by altered drug permeation occurs largely by mutations in genes encoding regulatory proteins that control the transcription of efflux pump or porin genes.[39] Less often mutations in efflux pump structural genes have been associated with changes in pump substrate profiles that include quinolones.[40]

Altered permeation in Gram-positive bacteria

In Gram-positive bacteria, quinolone resistance by increased efflux has been most extensively studied in *Staphylococcus aureus*.[38, 41] Overexpression of each of three efflux pumps, NorA,[42, 43] NorB,[44] and NorC[45] has been shown to cause four- to eightfold increases in resistance to quinolones, with some variations in substrate profiles among the three pumps. All three pumps are members of the major facilitator superfamily (MFS) of transporters that are secondary transporters powered by the proton gradient across the cytoplasmic membrane. NorA expression confers resistance to hydrophilic quinolones, such as norfloxacin and ciprofloxacin, whereas NorB and NorC expression each confers

resistance to hydrophilic quinolones and hydrophobic quinolones, such as sparfloxacin and moxifloxacin; [43–45] these pumps also have substrate profiles extending beyond quinolones, in keeping with broad substrate profiles of many MFS transporters.

Regulation of expression of these transporters is complex and mediated by an interplay of several regulatory proteins. MgrA, has been most extensively studied, and it acts as a positive regulator of *norA* expression and a negative regulator of *norB* and *norC* expression.[44, 46] Post-translational phosphorylation of MgrA by the PknB kinase results in the loss of the ability of MgrA dimers to bind the *norA* promoter and an increase in their binding to the *norB* promoter.[47, 48] Acidic conditions alter the proportions of phosphorylated and unphosphorylated MgrA, and oxidative and aeration conditions also affect dimerization and promoter binding.[49–51] Thus, relative levels of expression of NorA, NorB, and NorC are modified in response to a variety of environmental conditions. Particularly notable is the increased expression of *norB* in an abscess environment in response to low-free iron conditions relative to growth in laboratory media and the contribution of NorB to fitness and bacterial survival in abscesses,[52] a common clinical manifestation of *S. aureus* infection. These findings imply that NorB, and likely NorA and NorC pumps, have natural substrates other than quinolones, which are synthetic agents. They also imply that susceptibility and response to quinolones may differ at sites of infection in vivo relative to standard clinical laboratory predictive susceptibility criteria, which are based on tests in vitro.

Other regulators such as NorG, a member of the GntR-like transcriptional regulators, can modulate pump expression and levels of quinolone resistance; it is a direct activator of *norA* and *norB* expression but a direct repressor of *norC* expression.[53, 54] ArlRS, a two-component regulatory system, has been shown to affect expression of *norA*.[55, 56] There are often hierarchies in regulatory networks, and other regulators can also affect expression of MgrA and NorG. Thus, there are additional complexities to the sum of various regulatory network contributors to what determines Nor pump expression under different conditions.

Other transporters in Gram-positive bacteria have also been shown to have effects on susceptibility to quinolones, but have been less extensively studied than the Nor pumps. In *S. aureus* overexpression of MFS transporters MdeA (norfloxacin, ciprofloxacin),[57] SdrM (norfloxacin),[58] QacB(III) (norfloxacin, ciprofloxacin),[59] and LmrS (gatifloxacin)[60] has also been shown to reduce susceptibility to quinolones. One member of the Multiple Antibiotic and Toxin Extrusion (MATE) family of secondary transporters, MepA, also confers resistance to norfloxacin, ciprofloxacin, moxifloxacin, and sparfloxacin in addition other antimicrobials and dyes.[61] MepA is negatively regulated by MepR, and pentamidine, a MepA substrate, reduces MepR binding to the *mepA* promoter thereby increasing *mepA* expression. [62, 63] Thus, exposure to other agents may also affect quinolone susceptibility by upregulating broad-spectrum pumps. MFS transporters in other Gram-positive bacteria have also been shown to include quinolones in their substrate profiles. These transporters include those in the MFS group, Bmr, Bmr3, and Blt of *Bacillus subtilis*;[64, 65] PmrA[66] of *Streptococcus pneumoniae*; LmrP[67] of *Lactococcus lactis*, and Lde[68] of *Listeria monocytogenes* as well as those in the ABC transporter group, which are energized by ATP hydrolysis, PatAB[69] of *S. pneumoniae*, SatAB[70] of *S. suis*, and LmrA[71] of *L. lactis*. In *L. monocytogenes* in addition, the FepA pump of the MATE family is overexpressed in

quinolone-resistant strains and is regulated by the FepR transcriptional regulator of the TetR family, mutation in which accounted for pump overexpression and the resistance phenotype.[72]

Altered permeation in Gram-negative bacteria

In Gram-negative bacteria, the expression levels of a number of efflux pumps, most in the Resistance-Nodulation-Division (RND) superfamily, have been shown to confer increased quinolone resistance.[73] The RND pumps have three structural components, a pump protein localized in the cytoplasmic membrane, an outer membrane channel protein, and a membrane fusion protein that links the pump and the outer membrane protein.[74] Some outer membrane components may link to more than one pump-fusion protein pair.[38] This structure allows for export of substrates across both inner and outer membranes that is coupled to movement of protons in the opposite direction, termed antiport exchange. Best studied has been the AcrAB-TolC pump complex of *E. coli*. Crystal structures of the complex have revealed a trimer of AcrB pump monomers that rotate around a central axis perpendicular to the membrane, with each monomer assuming a different conformation associated with substrate binding and extrusion through the channel as its rotation position changes.[75] The drug access point is the periplasmic space between the inner and outer membranes or the outer leaflet of the inner membrane. Binding sites for ciprofloxacin and other substrates of diverse chemical types have been identified in the central cavity of the periplasmic domain of AcrB,[76–78] accounting for the multidrug resistance properties of this pump. Fluoroquinolones as zwitterionic compounds are presumed to cross the outer membrane through porin diffusion channels OmpF and OmpC, and downregulation of these channels or mutation in their structural genes may also contribute as a resistance mechanism. Notably quinolone resistance mutations in the MarR regulator result in both an increase in *acrB* expression as well as a decrease in *ompF* expression.[79] Thus, reduced quinolone influx through porin channels acts in concert with increased effux to generate a resistance phenotype. In addition to the Mar regulon, mutations in the *E. coli* SoxRS[80, 81] and Rob[82] regulons can also effect resistance to fluoroquinolones in part related to reductions in OmpF and in a manner that is dependent on AcrAB-TolC, similar to what occurs in *mar* mutants. Although initially quinolone and other antimicrobial resistances conferred by AcrAB-TolC were the phenotype most studied, this pump complex also confers resistance to bile salts and its expression is induced by bile salts,[83] suggesting that one of its natural functions is to facilitate the ability of *E. coli* to thrive in its natural habitat, the lower gastrointestinal tract.

In *Pseudomonas aeruginosa* the OprF porin channel has permeability two orders of magnitude lower than that of OmpF in *E. coli*,[84] accounting in part for its intrinsic relative resistance to quinolones and other antimicrobial agents. In addition, the MexAB-OprM efflux pump, an RND pump similar to AcrAB-TolC, is expressed in wildtype strains and acts in concert with the low permeability OprF to increase further the intrinsic level of resistance to fluoroquinolones, which is higher in *P. aeruginosa* than in *E. coli*.[85] Both *mexA* and *oprM* structural gene mutants exhibit increased uptake of norfloxacin and increased susceptibility to fluoroquinolones.[86] Overexpression of MexAB-OprM due to mutations in the MexR negative regulator causes increased resistance to ciprofloxacin and nalidixic acid, and *mexR* mutants can be selected with exposure to fluoroquinolones.[87] *P. aeruginosa* also

has three other efflux pump systems that include quinolones in their substrate profiles, MexCD-OprJ, MexEF-OprN, and MexXY-OprM.[88] These pumps have limited or variable expression in wildtype strains expressing MexAB-OprM,[89] but mutants overexpressing these pumps can be selected with fluoroquinolones and other antimicrobial substrates.[90] Mutation in the NfxB repressor, which is encoded upstream of the *mexCD-oprJ* operon, results in increased expression of MexCD-OprJ and increased resistance to fluoroquinolones.[91] MexEF-OprN expression varies inversely with the level of expression of MexAB-OprM, as does MexCD-OprJ expression. [89] Mutation in *nfxC* results in overexpression of MexEF-OprN, but details of the regulatory mechanism remain to be elucidated.[92] Mutations in the global regulator MvaT, which affects quorum sensing and virulence, also causes increased expression of *mexEF-oprM* and resistance to norfloxacin. [93] Mutations in the MexZ repressor cause overexpression of MexXY-OprM and resistance to fluoroquinolones in addition to resistance to aminoglycosides and other pump substrates.[94, 95] Notably, specific quinolones differ in which mutations they most commonly select. [90] Quinolones with a fluorine at position 6 and a positively charged substituent at position 7 (e.g., norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin), which characterizes most quinolones currently in clinical use, tend to select *nfxB*-type mutants. In contrast, quinolones lacking a positive charge at position 7 (e.g., nalidixic acid) tend to select *mexR* and *nfxC*-type mutants, differences presumably reflecting differences in the relative efficiencies of efflux of different quinolones by the pumps overexpressed by a given mutation.

Other less extensively studied efflux pump systems that can confer quinolone resistance have been identified in many Gram-negative bacteria.[38] In *E. coli*, EmrAB-TolC, a MFS pump that functions in tripartite structure like the RND pumps, is negatively regulated by EmrR and can confer resistance to nalidixic acid but not fluoroquinolones.[96] MdfA, another MFS pump that was originally termed CmlA because of its ability to confer resistance to chloramphenicol, also confers resistance to fluoroquinolones.[97] In *Klebsiella pneumoniae*, the OqxAB-TolC RND pump has been found on the chromosomes of most strains.[98] Although originally identified on plasmids in *E. coli* isolated from pigs due to its ability to cause resistance to olaquindox, a growth promotant used in swine production, it also confers resistance to quinolones (see section on plasmid-mediated quinolone resistance below). Both *Salmonella* spp. [99] and *Enterobacter aerogenes*[100] have AcrAB homologs the increased expression of which has been associated with quinolone resistance. The CmeABC RND pump of *Campylobacter jejuni* has been shown to contribute to the resistance of enrofloxacin-selected mutants.[101, 102] The NorM MATE family pump can confer quinolone resistance in *Vibrio parahaemolyticus*.[103] The NorA pump[104] of *Bacteroides fragilis* and the BexA pump[105] of *B. thetaiotaomicron* have also been shown to efflux fluoroquinolones.

Among non-enteric bacteria, in *A. baumannii* the AdeIJK RND pump[106] is constitutively expressed and confers resistance to a large number of agents, including fluoroquinolones. In addition, overexpression of the AdeABC and AdeFGH RND pumps due to mutation in their respective regulators, AdeRS, a two-component sensor-regulator system, and AdeL, a LysR family regulator, can also confer a similarly broad resistance profile. Notably pump-overexpressing mutants exhibited decreased ability to form biofilms and accept plasmid

DNA transfer.[107, 108] In *Stenotrophomonas maltophilia* the SmeDEF RND pump[109, 110] has been shown to contribute to resistance based on knock-out mutants with increased susceptibility and resistant strains with increased expression as well as its ability to confer quinolone resistance when overexpressed in *E. coli*.

In addition, there have been other examples in both Gram-positive and Gram-negative bacteria in which a relevant pump, its regulator, or a specific mutation have not been identified specifically but in which there is evidence of efflux in quinolone-resistant isolates determined by either reduction in resistance with addition of a broad efflux pump inhibitor or reduced quinolone accumulation in resistant cells.[38, 75] Information on efflux mechanisms and resistance in over 50 bacterial species has recently been extensively reviewed and is beyond the scope of this review.[38] Thus, efflux-mediated resistance to quinolones and many other antimicrobials is widespread, and since most efflux pumps effecting quinolone resistance have broad substrate profiles, efflux generally links quinolone resistance to multidrug resistance, as often also occurs with plasmid-mediated quinolone resistance discussed in the next section.

Plasmid-mediated quinolone resistance

Plasmid-mediated quinolone resistance was discovered inadvertently while studying β-lactam resistance produced by a multiresistance plasmid on transfer to a porin-deficient strain of *K. pneumoniae*. Ciprofloxacin resistance was evaluated as a control with the unexpected finding that it increased from 4 to 32 μg/ml on plasmid acquisition.[111] The increase in resistance was much less marked in *E. coli* or *K. pneumoniae* with intact porins, but the plasmid was readily transferred and decreased quinolone susceptibility in strains of Citrobacter, Salmonella, and even *P. aeruginosa*. The responsible resistance gene was named *qnr*, later amended to *qnrA*, as additional alleles were discovered. Investigation of a *qnrA* plasmid from Shanghai that conferred more than the expected level of ciprofloxacin resistance resulted in the discovery of a second plasmid-mediated mechanism: modification of certain quinolones by a particular aminoglycoside acetyltransferase, AAC(6′)-Ib-cr.[112] A third mechanism of plasmid-mediated quinolone resistance (PMQR) was added with the discovery of plasmid-mediated quinolone efflux pumps QepA [113, 114] and OqxAB.[115] In the last decade PMQR genes have been found in bacterial isolates worldwide. They reduce bacterial susceptibility to quinolones, usually not to the level of clinical nonsusceptibility, but facilitate the selection of mutants with higher level quinolone resistance and promote treatment failure.

Qnr structure and function

Cloning and sequencing *qnrA* disclosed that it coded for a protein of 218 amino acids with a tandem repeat unit of five amino acids indicating membership in the large (more than 1000 member) pentapeptide repeat family of proteins.[116] Knowledge of the sequence allowed search for *qnrA* by PCR, and it was soon discovered in *E. coli*, *K. pneumoniae*, and *S. enterica* strains from around the world.[117–121] *qnrA* was followed by the discovery of plasmid-mediated *qnrS*,[122] *qnrB*,[123] *qnrC*,[124] *qnrD*,[125] and most recently *qnrVC*.[126, 127] These *qnr* genes generally differ in sequence by 35% or more from *qnrA* and from each other. Allelic variants differing by 10% or less have also been described in almost every

family: currently a single allele for *qnrC*, 2 for *qnrD*, 7 each for *qnrA* and *qnrVC*, 9 for *qnrS*, and 78 for *qnrB*.[128]

The first pentapeptide repeat protein to have its structure determined by X-ray crystallography was MfpA, encoded by the chromosome of mycobacterial species, where its deletion increases and its overexpression decreases fluoroquinolone susceptibility.[129] MfpA is a dimer linked C-terminus to C-terminus and folded into a right-handed quadrilateral β helix with size, shape, and charge mimicking the B-form of DNA.[130] The 5 unit repeat occupies one face of the quadrilateral with each of the 8 helical coils of the MfpA monomer thus consisting of 20 residues. The central, usually hydrophobic, amino acid (*i*) of the pentapeptide repeat and the first polar or hydrophobic residue (*i*-2) generally point inward forming the core of the molecule, while the remaining amino acids (*i*-1, *i*+1, *i*+2) are oriented outward, presenting an anionic surface. Hydrogen bonding between backbone atoms of neighboring coils stabilizes the helix, which is just the size to fit into the cationic G segment DNA binding saddle of DNA gyrase and topoisomerase IV.[130]

The three-dimensional structure of three Qnr proteins has been determined by x-ray crystallography: chromosomally-encoded EfsQnr from *Enterococcus faecalis*, [131] chromosomally encoded AhQnr from *Aeromonas hydrophila*,[132] and plasmid-mediated QnrB1.[133] All are rod-like dimers (Fig. 1). The monomers of QnrB1 and AhQnr have projecting loops of 8 and 12 amino acids that are important for their activity. Deletion of the smaller A loop reduces quinolone protection, while deletion of the larger B loop or both loops destroys protective activity. Deletion of even a single amino acid in the larger loop compromises protection.[134] Other essential residues in QnrB are found in pentapeptide repeat positions *i* and *i*-2 where alanine substitution for the native amino acid eliminates protection as does deletion of more than 10 amino acids at the N-terminus or as few as 3 amino acids from the dimerization module at the C-terminus.[134] MfpA and EfsQnr lack loops, but EfsQnr differs from MfpA in having an additional β-helical rung, a capping peptide, and a 25-amino acid flexible extension that interacts with a lengthwise grove along the β-helix and is required for full protective activity.[131]

Although quinolones can bind gyrase alone in some species,[135] DNA enhances and increases the binding specificity to the enzyme-DNA complex.[136, 137] Thus, a molecule like MfpA that mimics and competes with DNA can decrease quinolone susceptibility by reducing the number of lethal double stranded breaks that result from quinolone stabilization of the cleavage complex. It lacks a protective effect against ciprofloxacin and only inhibits DNA gyrase *in vitro*.[130, 138] In contrast QnrA,[116, 139] QnrB,[123, 134, 138] QnrS,[140] AhQnr,[132] and EfsQnr[131] have been shown to protect purified DNA gyrase from quinolone inhibition . Protection occurs at low concentrations of Qnr relative to quinolone. For DNA gyrase inhibited by 6 μM (2 μg/ml) ciprofloxacin, half protection required only 0.5 nM QnrB1, and some protective effect was seen with as little at 5 pM.[123] At high Qnr concentrations (25–30 μM) gyrase inhibition is observed. [123, 138] EfsQnr is intermediate in effect. It partially protects *E. coli* gyrase against ciprofloxacin inhibition but also inhibits ATP-dependent supercoiling activity of gyrase with an IC_{50} of 1.2 μM.[131] Evidently added structural features (loops, N-terminal extension) of Qnr proteins allow interactions with regions of

gyrase besides the DNA binding groove[132] and could allow more specific binding to and destabilization of the topoisomerase-DNA-quinolone cleavage complex.[133]

Qnr Origin

Qnr homologs can be found on the chromosome of many γ-Proteobacteria, Firmicutes, and Actinomycetales, including species of *Bacillus*, *Enterococcus*, *Listeria*, and *Mycobacterium*, as well as anaerobes such as *Clostridium difficile* and *Clostridium perfringens*.[141–144] Nearly 50 allelic variants have been found on the chromosome of *S. maltophilia*.[141, 145–148] Aquatic bacteria are especially well represented, including species of *Aeromonas*, *Photobacterium*, *Shewanella*, and *Vibrio*.[149–151] QnrA1 is 98% identical to the chromosomally determined Qnr of *Shewanella algae*.[151] QnrS1 is 83% identical to Qnr from *Vibrio splendidus*,[152] and QnrC is 72% identical to chromosomal Qnr in *V. orientalis* or *V. cholerae*.[124] QnrB homologs, on the other hand, are encoded by the chromosome of members of the *Citrobacter freundii* complex of both clinical[153] and environmental[154] origin. The small, nonconjugative plasmids that carry *qnrD* can be found in other Enterobacteriaceae but are especially likely to be found in *Proteeae*, such as *Proteus mirabilis*, *Proteus vulgaris*, and *Providencia rettgeri* [155] and may have originated there.[156, 157]

The worldwide distribution of *qnr* suggests an origin well before quinolones were discovered Indeed, *qnrB* genes and pseudogenes have been discovered on the chromosome of *C. freundii* strains collected in the 1930s.[158]

Qnr Plasmids

PMQR genes have been found on plasmids varying in size and incompatibility specificity (Table 1), indicating that the spread of multiple plasmid types has been responsible for the dissemination of this resistance around the world. Such plasmid heterogeneity also indicates that plasmid acquisition of *qnr* and other quinolone resistance determinants occurred independently multiple times. *qnr* genes are almost invariably associated with a mobile or transposable element, especially IS*CR1* and IS*26* (Table 1). *qnrD* and *qnrS2* are located within mobile insertion cassettes, elements with bracketing inverted repeats but lacking a transposase,[157, 159] while *qnrVC* is so far the only *qnr* gene located in a cassette with a linked *attC* site.[159a]

qnr genes are usually found in multiresistance plasmids linked to other resistance determinants. β-lactamase genes, including genes for extended spectrum β-lactamases (ESBLs), AmpC enzymes, and carbapenemases, have been conspicuously common, (reviewed in Ref. 160). *qnrB* alleles are also frequently found in plasmids linked to variable portions of the operons for *psp* (phage shock protein) and *sap* (peptide ABC transporter, ATP-binding protein) genes. These genes flank *qnrB* on the chromosome of several *Citrobacter* spp., and their co-acquisition with *qnrB* is one of the arguments for *Citrobacter* as the source of *qnrB* alleles.[153]

Spread of qnr plasmids

PMQR genes have been found in a variety of Enterobacteriaceae, especially *E. coli* and species of *Enterobacter, Klebsiella*, and *Salmonella* (reviewed in Ref. 160). They have been conspicuously rare in non-fermenters but have occasionally been reported in *P. aeruginosa*, other *Pseudomonas* spp., *A. baumannii*, and *S. maltophilia*. *qnr* genes are found in a variety of Gram-positive organisms but are chromosomal and not plasmid-mediated. Of the various *qnr* varieties, *qnrB* seems somewhat more common than *qnrA* or *qnrS*, which are more common than *qnrD*.[161–163] Only a single isolate of *qnrC* is known.[124] The earliest known *qnr* outside of *Citrobacter* spp., dates from 1988.[164] Studies in the last decade suggest that *qnr* detection is increasing but is still usually less than 10% in unselected clinical isolates with the exception of a *qnr* prevalence of 39%, which was reached in an unselected sample of *E. cloacae* isolates at one hospital in China.[165] Higher frequencies result if samples are preselected for ESBL or other resistance phenotypes.[163, 165, 166]

Although most prevalence studies have surveyed hospital isolates, animals have not been neglected. PMQR genes have been found in a great variety of wild and domestic animals, including samples from birds, cats, cattle, chickens, dogs, ducks, fish, geese, horses, pigs, reptiles, sheep, turkeys, and zoo animals (reviewed in Ref.160).

Regulation of qnr

Environmental conditions affect expression of *qnr* genes and may offer clues concerning the native function of these genes. Expression of the *qnrA* gene of *S. algae*, an organism adapted to growth at low temperature, is stimulated up to 8-fold by cold shock but not by other conditions such as DNA damage, oxidative or osmotic stress, starvation, or heat shock. [167] Expression of *qnrB* alleles, on the other hand, is augmented up to 9-fold by exposure to DNA damaging agents such as ciprofloxacin or mitomycin C via an upstream LexA binding site and the classical SOS system.[168, 169] *qnrD* and the chromosomal *qnr* of *S. marcescens* are similarly regulated.[170] Expression of plasmid-mediated *qnrS1* or the related chromosomal *qnrVS1* of *V. splendidus* is also stimulated by ciprofloxacin up to 30-fold, but by a mechanism independent of the SOS system. No LexA binding site is found upstream from these *qnr* genes, but upstream sequence is required for quinolone induction to occur.[171] Some naturally occurring quinolone-like compounds such as quinine, 2-hydroxyquinoline, 4-hydroxyquinoline, or the *Pseudomonas* quinolone signal for quorum sensing also induce *qnrS1*, but not *qnrVS1*.[172]

AAC(6′)-Ib-cr

AAC(6′)-Ib-cr is a bifunctional variant of a common acetyltransferase active on such aminoglycosides as amikacin, kanamycin, and tobramycin but also able to acetylate those fluoroquinolones with an amino nitrogen on the piperazinyl ring, such as ciprofloxacin and norfloxacin.[112] Compared to other AAC(6′)-Ib enzymes, the –cr variant has two unique amino acid substitutions: Trp102Arg and Asp179Tyr, both of which are required for quinolone acetylating activity. Models of enzyme action suggest that the Asp179Tyr replacement is particularly important in permitting π-stacking interactions with the quinolone ring to facilitate quinolone binding. The role of Trp102Arg is to position the Tyr

face for optimal interaction[173] or to hydrogen bond to keto or carboxyl groups of the quinolone to anchor it in place.[174]

The *aac(6′)-Ib-cr* gene is usually found in a cassette as part of an integron in a multiresistance plasmid, which may contain other PMQR genes. Association with ESBL CTX-M-15 is particularly common. A mobile genetic element, especially IS*26*, is often associated.[175] *aac(6′)-Ib-cr* may also be chromosomal.[176, 177] The gene has been found world-wide in a variety of Enterobacteriaceae and even in *P. aeruginosa*.[178] It is more prevalent in *E. coli* than other Enterobacteriaceae,[179–182] and is more common than *qnr* alleles in some samples.[183 184]

QepA and OqxAB

QepA is a plasmid-mediated efflux pump in the major facilitator (MFS) family that decreases susceptibility to hydrophilic fluoroquinolones, especially ciprofloxacin and norfloxacin.[113, 114]*qepA* has often been found on plasmids also encoding aminoglycoside ribosomal methylase *rmtB*.[114, 185–187] Substantial differences in quinolone resistance produced by different *qepA* transconjugants suggest variability in the level of *qepA* expression, by mechanisms as yet to be defined. [186]

OqxAB is an efflux pump in the RND family that was initially recognized on transmissible plasmids responsible for resistance to olaquindox used for growth enhancement in pigs.[188, 189] It has a wide substrate specificity, including chloramphenicol, trimethoprim, and quinolones such as ciprofloxacin, norfloxacin, and nalidixic acid.[115] *oqxAB* has been found on plasmids in clinical isolates of *E. coli* and *K. pneumoniae* and in the chromosome and on plasmids of *S. enteritis* flanked in both locations by IS*26*-like elements.[190–195] In *E. coli* isolates from farms in China where olaquindox was in use, *oqxAB* was found on transmissible plasmids in 39% of isolates from animals and 30% of isolates from farm workers.[192] Linkage of *oqxAB* with genes for CTX-M-14 and other plasmid-mediated CTX-M alleles has been noted.[196] It is common (usually 75% or more) on the chromosome of *K. pneumoniae* isolates, where up to 20-fold variation in expression implies the presence of regulatory control.[191, 194, 197–199] In *K. pneumoniae* overexpression of the nearby *rarA* gene is associated with increased *oqxAB* expression, while increased expression of adjacent *oqxR* gene down regulates OqxAB production.[200, 201]

Resistance produced by PMQR determinants

Table 2 shows the minimum inhibitory concentration (MIC) produced in an *E. coli* strain by PMQR genes. *qnr* genes produce about the same resistance to ciprofloxacin and levofloxacin as single mutations in *gyrA*, but have less effect on susceptibility to nalidixic acid. Thus, reduced susceptibility to fluoroquinolones combined with susceptibility to nalidixic acid is a clue to the presence of PMQR and potentially resistance to other agents because of their linkage to *qnr*.[202, 203] *aac(6′)-Ib-cr* and *qepA* give lower levels of resistance, which is confined to ciprofloxacin and norfloxacin in the case of *aac(6′)-Ib-cr* because of its substrate specificity. All provide a decrease in susceptibility that does not reach the clinical breakpoint for even intermediate resistance, but PMQR genes are important because they facilitate the selection of higher levels of quinolone resistance.

If *E. coli* J53 pMG252 is exposed to increasing concentrations of ciprofloxacin, a diminishing number survives until a concentration of more than 1 μg/ml ciprofloxacin is reached. This limiting concentration has been termed the mutant prevention concentration (MPC), and the concentration between the MIC and MPC at which mutants are selected is the mutant selection window.[204] PMQR genes exert their influence by widening the mutant selection window and elevating the MPC, as shown for *qnr*,[205, 206] *aac(6′)-Ib-cr*,[112, 207] and *oqxAB*.[207] Surprisingly, in *qnr*-harboring *E. coli gyrA* resistance mutants are rarely selected,[208] although resistance produced by *qnr* and *gyrA* is additive.[209–211] Rather higher level ciprofloxacin resistant derivatives of *E. coli* J53 pMG252 (*qnrA1*) have mutations in regulatory genes *marR* or *soxR* leading to increased expression of the AcrAB pump or mutations in *rfaD* or *rfaE* associated with defects in lipopolysaccharide biosynthesis.[212]

It should be noted that higher levels of quinolone resistance are seen if a plasmid or strain carries two or more genes for quinolone resistance, such as both *qnr* and *aac(6′)-Ib-cr* , and that ciprofloxacin MICs of 2 μg/ml can be reached with *qnrA* in *E. coli* overexpressing the AcrAB multi-drug efflux pump.[213] A fully resistant *E. coli* with a ciprofloxacin MIC of 4 μg/ml has been reported with plasmid-mediated *qnrS1* and *oqxAB* as well as overexpression of AcrAB and other efflux pumps.[214]

Areas for future study

Much has been learned about the mechanisms of quinolone resistance over many years, but a number of areas await further studies. Because quinolones are synthetic compounds, those efflux pumps and plasmid-encoded proteins that confer resistance, although advantageous to the bacterium in the presence of quinolone use in humans and animals, likely have functions in addition to resistance mediation in Nature. Further understanding of their natural functions, the determinants of their mobilization, and the regulation of their expression should better inform the links between bacterial physiology, adaptation to environmental conditions, and virulence with antimicrobial resistance, an understanding that will be important for future strategies for optimizing antimicrobial use.

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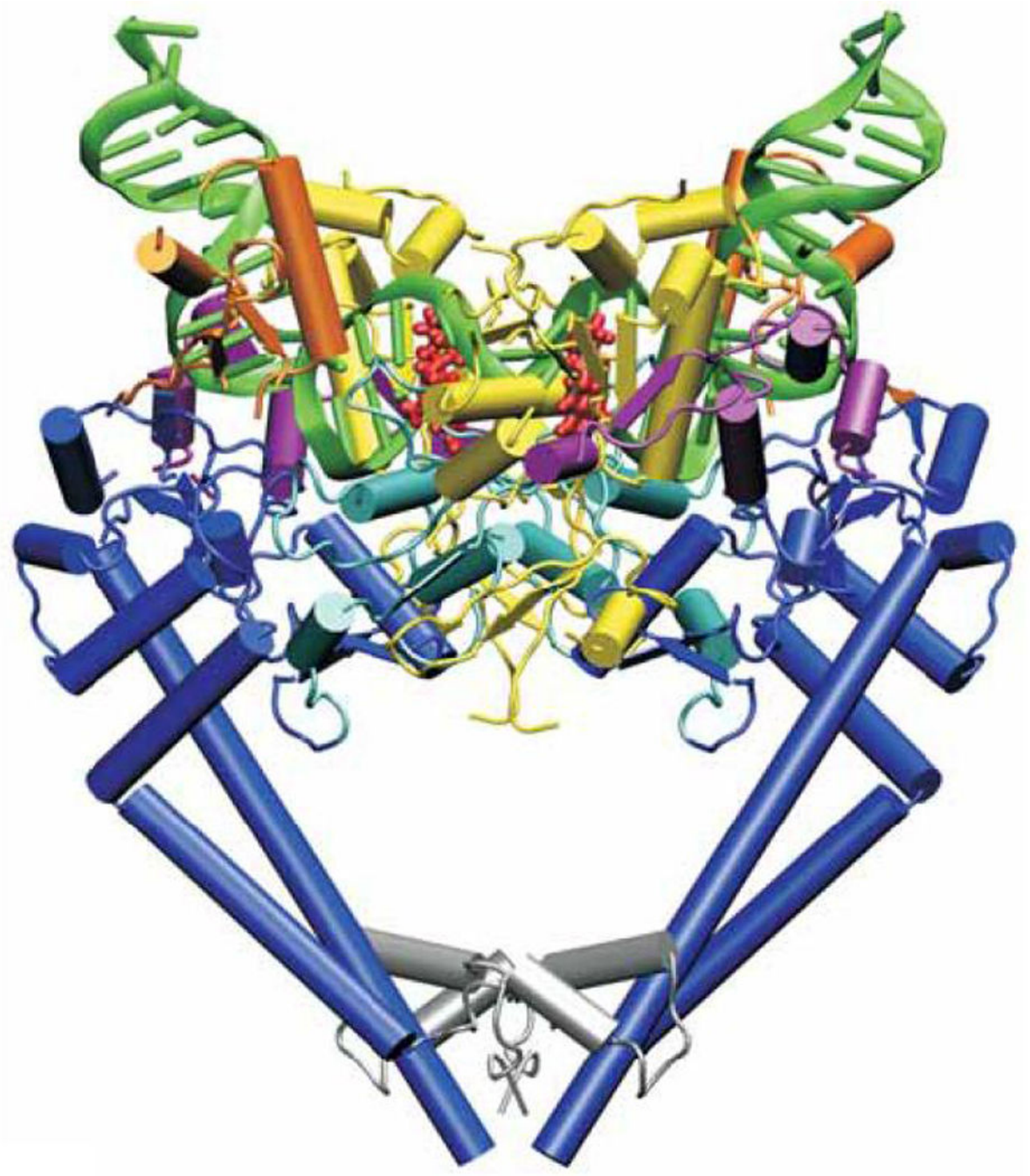

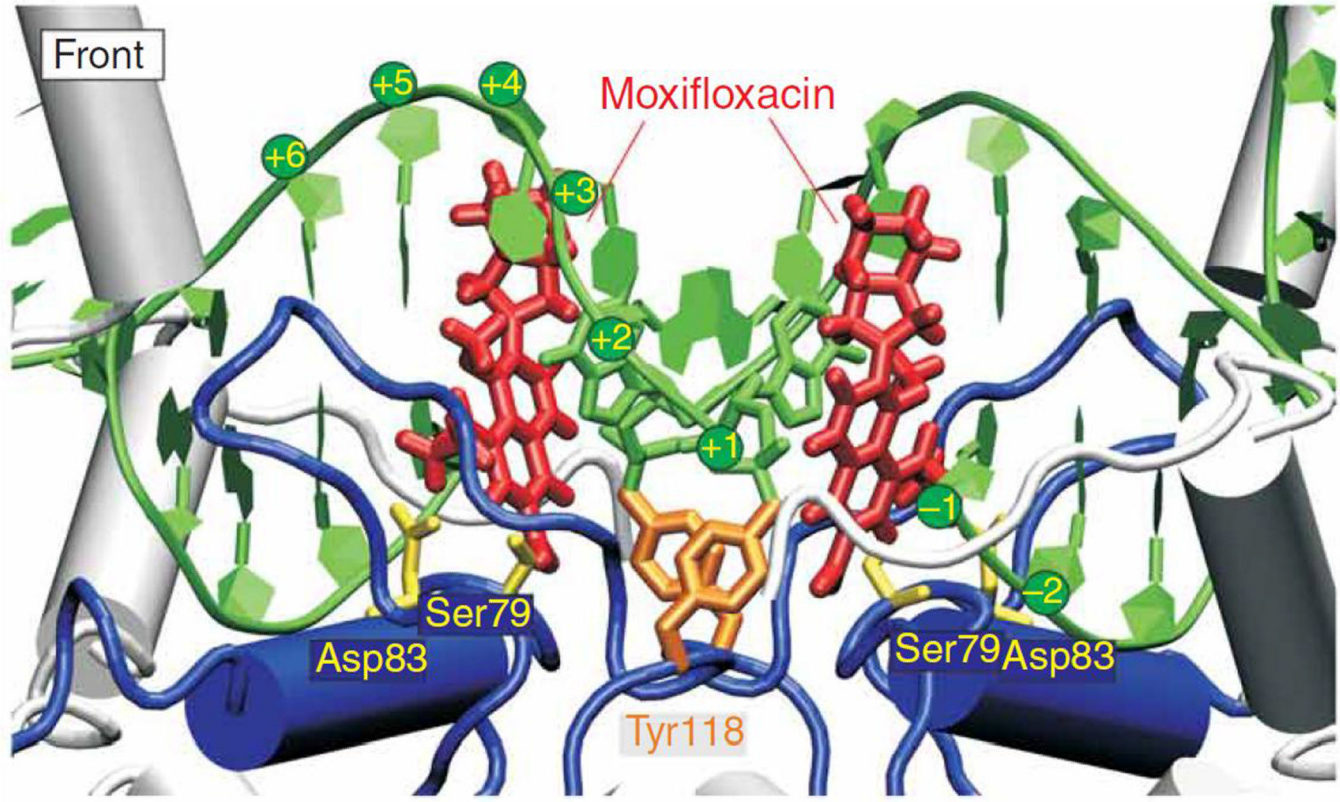

Figure 1.
Structure of *Streptococcus pneumoniae* topoisomerase IV-DNA-moxifloxacin complex. From reference 13.

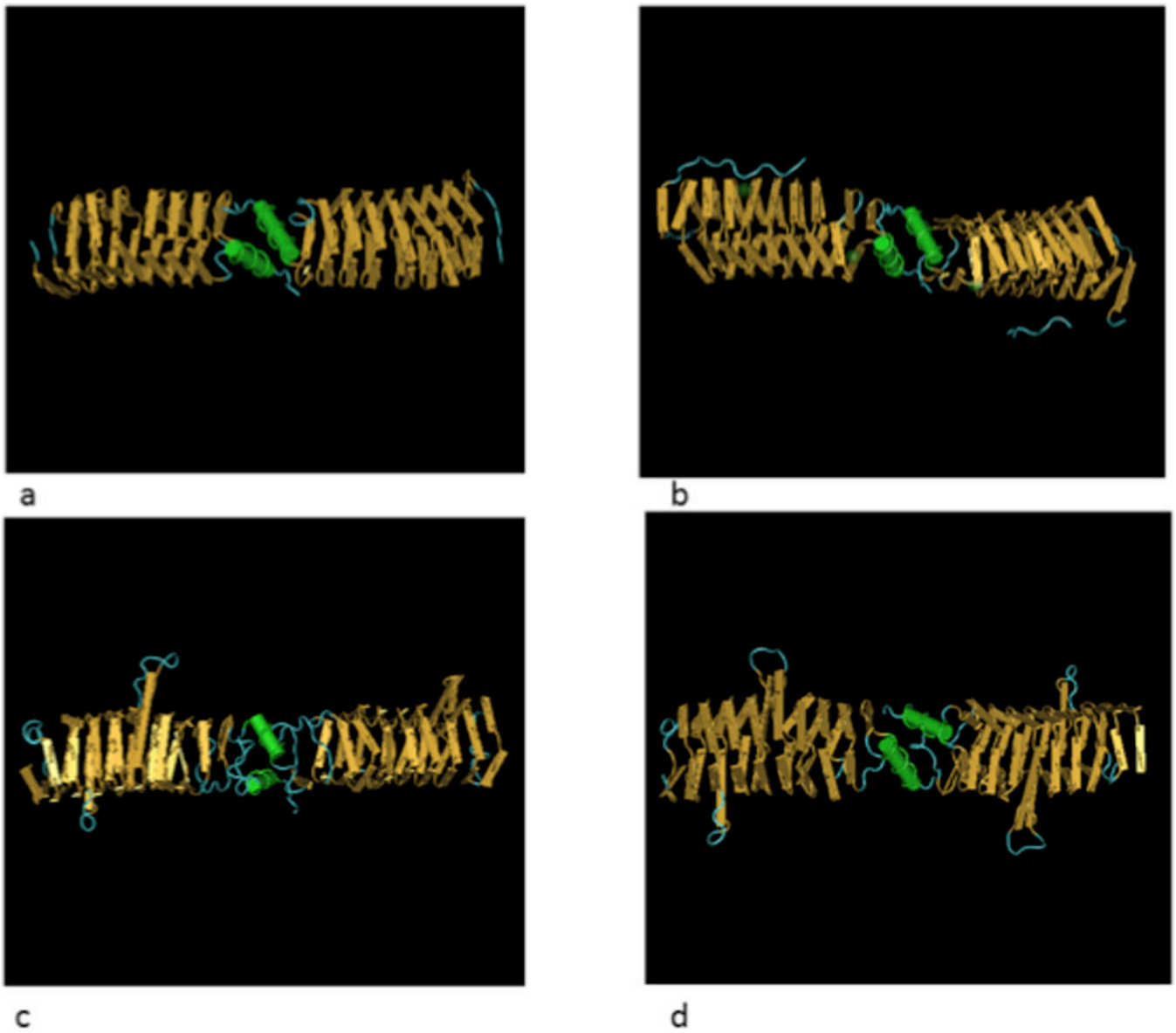

Figure 2.

3-D representation of pentapeptide repeat proteins. (A) MfpA from *M. tuberculosis (*PDB ID: 2BM6), (B) EfsQnr from *E. faecalis* (PDB ID: 2W7Z), (C) AhQnr from *A. hydrophila* (PDB ID: 3PSS) and (D) plasmid-mediated QnrB1 (PDB ID: 2XTW)

Table 1

Plasmids and mobilizing elements associated with PMQR genes

PMQR gene	Plasmid Inc groups	Mobilizing element	References
qnrA1	A/C2, FII, HI2, I1, L/M, N	IS*CR1*	111, 116, 215–217
qnrA3	N	IS*CR1*, IS*26*	216, 218
qnrA6	A/C	IS*CR1*	219
qnrB1	FII_K, H family, L/M	Orf1005, IS*26*	123, 199, 216, 220, 221
qnrB2	FIA, FII, L/M, N	IS*CR1*	199, 216, 222–224
qnrB4	FIA, FIIAs, L/M, R	IS*CR1*	216, 225, 226
qnrB6	FIIAs	IS*CR1*	216, 227
qnrB10	UT[a]	IS*CR1*	199, 228
qnrB19	ColE, L/M, N	IS*Ecp1*, IS*26*	199, 216, 223, 228, 229
qnrB20		Orf1005, IS*26*	230
qnrS1	ColE, FI, HI1, HI2, I1, L/M, N, NT, R, UT, X1, X2	IS*2*, IS*26*, IS*Ecl2*	122, 199, 215, 223, 224, 228, 231–234
qnrS2	Q, U	mic[b]	216, 235
qnrC		IS*Pmi1*	124
qnrD1	UT	mic	125, 155, 157, 236
qnrVC1		*attC*	126,159a
qnrVC4		IS*CR1*	237
aac(6')-Ib-cr	ColE, FII, L/M, N, R	IS*26*, *attC*	175, 216, 226, 238–240
oqxAB	F, FII, HI2, N, X1	IS*26*	190, 195, 240–242
qepA1	FII, HI2	IS*26*, IS*CR3C*	113, 228, 243, 244
qepA2	FI	IS*CR3C*	216, 243

[a] UT= untypable

[b] mic = mobile insertion cassette

Table 2

Effect of different quinolone resistance mechanisms on quinolone susceptibility of*E. coli*

***E. coli* Strain**	**MIC (μg/ml)**		
	Ciprofloxacin	**Levofloxacin**	**Nalidixic acid**
J53	0.008	0.015	4
J53 *gyrA* (S83L)	0.25	0.5	≥256
J53 pMG252 (q*nrA1)*	0.25	0.5	16
J53 pMG298 (*qnrB1)*	0.25	0.5	16
J53 pMG306 *(qnrS1)*	0.25	0.38	16
J53 pMG320 *(aac(6')-Ib-cr)*	0.06	0.015	4
J53 pAT851 (*qepA)*	0.064	0.032	4
CLSI susceptibility breakpoint	≤1.0	≤2.0	≤16