Genetic Variation in *Mycoplasma genitalium*

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*Mycoplasma genitalium* (MG) is the smallest self-replicating bacterium. Although small in size, unique MG genome induces distinctive and often serious characteristics in the infected cells. Due to its small genome and chronic symptomatic characteristics in the infected host, it first appears as a weak, insignificant, and easily controllable microbe. However, it is not a monotonous chrysalis, but rather a multicolored butterfly with various capabilities. Repetitive DNA sequence in MG’s immunodominant MgPa operon has been considered as an efficient strategy to evade the host immune surveillance and mediate MG’s genetic flexibility. Because of MG’s pathogenicity in multiple organs, various antimicrobials are prescribed, further exerting selection pressure on microbes. Consequently, a rapidly increasing drug resistance in macrolide and moxifloxacin has been frequently reported globally, radically decreasing the overall cure rate of infection. Re-infection can be defined as a new MG infection through antigenic variation, while persistent infection refers to recurring infections caused by the same MG isolate through acquisition of antimicrobial resistance. Therefore, we must differentiate between re-infection and persistent MG infection, and approach them accordingly. The genetic mechanisms of DNA variation in the MgPa operon and antibiotic resistance must be considered for the management of multicolored infection. In this respect, the unique genetic characteristics of MG will be described in detail. We hope that with this manuscript, clinicians can expand their understanding of recurrent MG infections and better choose an appropriate treatment for the infection in clinical setting.

**Keywords:** *Mycoplasma genitalium*; Genetics; Recurrence

INTRODUCTION

Sexually transmitted infections (STIs) remain to be one of the major health issues in both developed and under-developed countries, causing serious and adverse effects on reproductive health. Furthermore, they cause direct or indirect negative effects on the national socioeconomic systems [1].

Common bacterial pathogens for STIs include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomoniasis vaginalis*, and *Mycoplasma genitalium* (MG) [2]. Among them, *C. trachomatis* and *T. vaginalis* are relatively easy to treat using appropriate antibiotics due to their lower mutational frequencies [3,4]. Contrastingly, *N. gonorrhoeae* and MG pathogens are associated with multiple recurrences due to antibiotic resistance [5-12]. Therefore, efficiency of first-line therapies against these pathogens are declining, and consequently, the prevalence of these pathogens in the general population is increasing insidiously [7,10,12]. The pathogenicity or mechanisms for recurrent *N.
gonorrhoeae infections have been easily studied and documented, due largely to the ease in which the microbes are cultured in plates and Gram-staining method [13]. Furthermore, through conventional methods, the minimal inhibitory concentration (MIC) of antibiotics against N. gonorrhoeae was obtained. Nevertheless, unlike N. gonorrhoeae, MG microbes are not cultivable using the ordinary bacterial culture method [14,15]. Furthermore, only a limited amount of MG microbes may be harvested from infected patients for laboratory characterization [16]. Even if MG microbes were to be successfully isolated through specific time-consuming culture methods, the process usually requires a minimum of 6 months for stable cloning to properly evaluate the patterns of particular antimicrobial resistance [14,15]. Consequently, there have only been a few studies reporting on the antimicrobial MIC levels against MG infections, thereby requiring a transition from the current time-consuming culturing method to more rapid and straightforward methods for diagnosing MG [16].

The pathogenic microbes may infect host cells, proliferate rapidly, and cause diseases through specific host-pathogen interactions [17,18]. The unique transcription and translation machineries within the host cells allow these microbes to sustain their life cycles, divide rapidly, and initiate specific symptoms and signs [17,18]. Pharmaceutical drugs often have specific molecular targets in the host cells [19]. Similarly, various antimicrobials also target specific regions of the microbes [20-22]. Currently, almost all host-microbe or microbe-drug interactions at the molecular levels may be traced or estimated using precise molecular technologies [17-22]. Indeed, we can define the presence of uncultivated or poorly-cultivable microbes in the host cells and estimate these host-microbe interactions using molecular technologies, such as polymerase chain reaction [22,23].

The central dogma in prokaryotes is essential for the survival, proliferation, and self-replication of the bacteria [17,18]. Therefore, the fundamental pathways in bacterial transcription and translation may be targeted by antimicrobial agents [20-22]. For example, the specific molecular target site for macrolides is a large subunit of the bacterial ribosome [24], and fluoroquinolones can also bind to the bacterial gyrase and topoisomerase IV, preventing DNA synthesis [25]. Many cases of persistent MG infection are also attributed to the alterations of a specific DNA sequence in the target genes [6-11].

A recurrent infection is defined as an infection that appears again after a successful eradication of the antecedent infection. The term re-infection describes a new event associated with a re-introduction of the bacteria from the external environment. Bacterial persistence refers to a recurrent infection caused by the same bacteria re-emerging from a focus or through the acquisition of antimicrobial resistance [26,27]. According to this principle, once the initial MG infection is resolved, re-infection is believed to be the result of exposure to a new MG pathogen differing from the initial genotype. Contrastingly, persistent infections are those in which MG has not been completely eradicated in the first place, but rather submerge into a metabolically quiescent state. In the latter case, persistent infection, the inactivated MG pathogen may be reactivated under certain host conditions, leading to the disease phenotype. In both scenarios, there ought to be a specific method to distinguish between a persistent infection and new infection to decide on an appropriate treatment.

Here, the current status of MG infections and their resistant phenotypes are discussed. We hope that this manuscript benefits clinicians to broaden their understanding of recurrent MG infections and subsequently better allow them to decide on appropriate treatments for this multi-potential infection.

MATERIALS AND METHODS

1. Overview

Mycoplasmataceae family includes Candidatus Hepatoplasma, Candidatus Marinoplasma, Candidatus

| Table 1. Taxonomical classification of Mycoplasmataceae family |
|---------------------------------|-----------------|-----------------|-----------------|
| Bacteria                        | Terrabacteria group | Tenericutes | Mollicutes  |
| Mycoplasmataceae               | Candidatus Hepatoplasma | Candidatus Marinoplasma | Candidatus Moeniiplasma |
| Mycoplasma (329 species)       | Mycoplasma genitalium | Mycoplasma hominis | Mycoplasma pneumoniae |
| Ureaplasma (24 species)        | Ureaplasma pavum | Ureaplasma urealyticum |

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Moeniplasma, Mycoplasma, and Ureaplasma (Table 1) [28].

Several species in the Mycoplasma genus, including MG, Mycoplasma pneumoniae, Mycoplasma hominis, and others, are commonly diagnosed (Table 1). MG is genetically different from Ureaplasma urealyticum and Ureaplasma parvum, which are two species that cause certain urogenital infections (Fig. 1). MG is genetically similar to M. pneumoniae rather than M. hominis. Because of this genetic similarity, cross-reactive antibodies or cross-hybridizing DNA probes between two pathogens may be observed (Fig. 1).

Nevertheless, despite the phylogenetic similarity, respiratory infections caused by M. pneumoniae in the human respiratory tract have been insufficient to induce immune response against a vaginal MG infection [29,30].

In 1995, the complete genome of MG had been published, MG genome is approximately 580 kb in size with about 480 coding genes [31]. Therefore, among the self-replicable organisms with metabolic mechanisms, MG has the smallest genome [31]. It is believed to have been evolved from Gram-positive bacteria that are phylogenetically most closely related to clostridia through genomic reduction mechanisms [32]. Thus, the MG genome carries a high percentage of essential conserved genes and minimal genomic redundancy. It also has minimal spacer regions between the coding sequences (Table 2) [31,32].

It could be suggested that a genome reduction may have benefitted the organism through enhanced reproductive efficiency and reduced metabolic requirements under nutrient-deficient environments [33]. Under these conditions, bacteria must retrieve some essential nutrients from the infected cells during their life cycle [34]. MG follows a more chronic course, and the infected hosts are usually lesser symptomatic or even asymptomatic. Therefore, MG may be considered as an optimal parasite for the host-bacterial interaction.

Even with relatively limited genomic information, MG has extraordinary flexibility under various conditions. Therefore, it would be worthwhile to investigate MG in the human intestinal tract, oral cavity, as well as urogenital tract (Table 3) [35,36]. In the near future, we must define whether MG’s tissue tropism has a certain role in spreading the infection and developing drug resistance in homosexual, as well as in heterosexual individuals (Table 3).

The dimensions of MG are as follows: a length of 0.6 to 0.7 μm and widths of 0.3 to 0.4 μm at the broadest part, and 0.06 to 0.07 μm at the tip. A small terminal projection (7 to 8 nm) in MG (Fig. 2) acts like certain toxins with respect to the method in which it invades the the host cells [37], ultimately allowing MG to glide and attach onto the host cells. This attachment is mediated largely

Table 2. Structural characteristics of Mycoplasma genitalium

| Organisms               | Size (μm) | Genome size (base pair) | Protein coding gene (no) |
|-------------------------|-----------|-------------------------|--------------------------|
| Escherichia coli        | 2.0-6.0   | 5,000,000,000-4,000,000 | 5,400-4,300              |
| Neisseria gonorrhoeae   | 0.6-1.0   | 2,232,025 (NCCP11945)   | 2,662                    |
| Chlamydia trachomatis   | 0.3       | 1,044,282 (FM872307)    | 2,032-1,052              |
| M. genitalium           | 0.3       | 580,070                 | 480                      |
| Eukaryotic cell         | 10-100    | 3,000,000,000,000       | 19,000-20,000            |

Table 3. Tissue tropisms of Mycoplasmas

| Species                        | Primary site of colonization | Pathogenicity |
|--------------------------------|------------------------------|---------------|
| Mycoplasma hominis             | Y                            | Y             |
| Ureaplasma urealyticum         | Y                            | Y             |
| Mycoplasma pneumonia           | Y                            | N             |
| Mycoplasma genitalium          | ?                            | Y             |
by MG200 (heat shock protein motif) and MG386 (cytadherence-accessory protein) genes, which are involved in MG motility [31]. The specialized terminal structure also seems important for the gliding and attachment process [31,37].

In one study, when MG came in contact with human lung fibroblasts, the plasma membrane of the host cells appeared to be forced inward to form a cup or depression. These host pockets resembled clathrin-coated pits, suggesting that, similar to chlamydiae, the mycoplasma may attach to and enter the cells by host-mediated events [38]. The ability of intracellular invasion and survival may allow MG to evade the host immune surveillance system and acquire a specific antimicrobial resistance.

2. Multi-potential \textit{M. genitalium}

1) MgPa and MgPar

Despite its small genome, 4.7% of the MG genomic sequence is devoted for MgPa adhesin operon and repetitive chromosomal sequences (MgPar) [31]. The gene for MgPa is composed of one operon that contains three genes: MG190 (mgpA), MG191 (mgpB), and MG192 (mgpC), with minimal inter-spacer regions among them (Fig. 3) [31,39,40]. The gene for MgPa is a single, continuous copy; however, there are nine repetitive MgPar elements in the truncated copies of MG191 and MG192 genes dispersed throughout the genome (Fig. 3) [31,39,40]. The MgPar DNA sequences have a partial similarity with the B, EF, and G areas in the MgPa gene, suggesting the possibility of genetic recombination [31,39-42].

Serological studies have shown that the MgPa protein is an important immunodominant epitope [43-45]. Additionally, mutants lacking MG191 or MG192 genes in the MgPa operon have revealed that the two genes are crucial for the proper assembly and development of the terminal organelle in MG [45]. Therefore, the flask-shaped terminal structure in MG might be an important organelle for the survival and/or self-replication of MG.

The immune system may resolve infections and prevent recurrence through the innate and active surveillance systems [46]. Specifically, a critical step to prevent the infectious process involves the immune systems recognizing the molecular patterns of the pathogens for future reference, including the information on the specific antigens that characterize these pathogens [46]. However, to overcome these defensive mechanisms, some microbes undergo a genetic modification, in which their DNA sequences on the immunodominant site(s) are altered, allowing them to evade the host immune surveillance system. For example, genetic varieties or mutations in the immune determining areas can provide functional diversity of cell-surface antigens, which allow these pathogens to rapidly adapt to the environment or the host and avoid the host immune system [47]. Therefore, genetic variations are critical in the evasion of the host immune responses, as well as in the optimization of the bacterial surface for host colonization [46-48].

The role of MgPa protein in MG includes the attachment of bacteria onto the host epithelium, invasion into the host cells, and provide an immunogenic role for the host immune system [33,37,39,40]. We performed a multiple comparison analysis with 20 different MG191 partial DNA sequences from the National Center for Biotechnology Information (NCBI) database (Supplementary Table 1) [49]. Some areas, such as B, EF, and G, from the MG191 gene revealed frequent genetic alterations or diversity (Fig. 4).

Because the MgPa gene consists of a single operon, the MG192 gene is co-transcribed with the MG191 gene [31], and both genes elicit a strong immune response in both animal and human models during the process of host and \textit{M. genitalium} interaction [43-45]. Because most MgPars contain not only regions homologous to MG191 but also
regions homologous to MG192, it is particularly interesting that in addition to MG191, MG192 also undergoes multiple genetic and antigenic variations. The anterior half of the MG192 gene (130-910 bp in Fig. 5) in the aligned DNA sequences reveals frequent variations in their sequences (Supplementary Table 2). Therefore, MG192 of the MgPa...

![Figure 4](image)

**Fig. 4.** Twenty mgpB DNA sequences from the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/nuccore/) are evaluated for their homology using the Clustal W alignment algorithm (http://www.genome.jp/tools/clustalw/). Locations in the MG191 gene are indicated in the upper area. There are three areas of hot genetic variety in the mgpB gene (520-1,040 bp for B area, 2,340-2,990 bp for EF area, 3,250-3,640 bp for G area). The gray colors represent matching, while the black colors represent mismatching (http://multalin.toulouse.inra.fr/). MG: *Mycoplasma genitalium*.

![Figure 5](image)

**Fig. 5.** Sixty-four partial mgpC DNA sequences (Supplementary Table 2) from the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/nuccore/) are collected and evaluated for their homology using the Clustal W alignment algorithm (http://www.genome.jp/tools/clustalw/). Locations in the mgpB gene are indicated in the upper area. The gray colors represent matching, while the black colors represent mismatching (http://multalin.toulouse.inra.fr/).

**Table 4.** Sequential cultures of *Mycoplasma genitalium* (MG) from two infected parents and unique MG192 variants

| Patient no. | Date       | Clones’ no. | Unique MG192 sequences variant(s) |
|-------------|------------|-------------|-----------------------------------|
| 61          | 11/20/2000 | 8           | 61.0a                             |
|             | 5/7/2001   | 6           | 61.2b, 61.2c, 61.2d, 61.2e, 61.2f |
| 126         | 10/23/2001 | 10          | 126.0a, 126.0b, 126.0c, 126.0d    |
|             | 1/15/2002  | 10          | 126.1e, 126.1f, 126.1g, 126.1h, 126.1i, 126.1j, 126.1k |
|             | 6/26/2002  | 10          | 126.2l, 126.2m, 126.2n, 126.2o, 126.2p |
|             | 9/17/2002  | 10          | 126.3q, 126.3r, 126.3s, 126.3t, 126.3u, 126.3w, 126.3x |
|             | 12/3/2002  | 10          | 126.4.1, 126.4.2, 126.4.3, 126.4.4, 126.4.5, 126.4.6, 126.4.7, 126.4.8, 126.4.9 |

All unique variants in table reveal different sequences. Modified from the article of Ma et al. Infect Immun 2014:82:1326-34 [50].

*Indicate the starting points in serial MG cultures.
adhesion operon demonstrates that the MG192 gene is highly variable among and within MG strains (Fig. 5).

Interestingly, Ma et al. [50] reported an extensive in vitro variation and rapid shift of the MG192 sequence in the MG strains from a patient with chronic infection (Table 4). They isolated MG strains from selected patients and serially cultured the isolates. Finally, they examined the DNA sequence changes in the MG192.

Initially, of eight cloned plasmids from patient no. 61, only one had unique MG192 sequence (61.0a). Nonetheless, in six months, the one clone had evolved into five different variants. The patient no. 126 had 4 unique MG192 sequences at the starting point (10/23/2001) (126.0a, 126.0b, 126.0c, 126.0d) from 10 cloned plasmids. During the sequential

Fig. 6. Twenty-four partial mgpC DNA sequences (Supplementary Table 3) from patient no. 126 are evaluated from the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/nuccore/) to investigate the homology using the Clustal W alignment algorithm (http://www.genome.jp/tools/clustalw/). Ma et al. [50] serially examined the DNA sequence changes in the mgpC gene in serial culturing periods (from the starting point to 4th subculturing period). The DNA sequences of MG192 changed rapidly in vitro within a short period of time. The gray colors represent matching, while the black colors represent mismatching (http://multalin.toulouse.inra.fr/multalin/multalin.html). MG: Mycoplasma genitalium.

Fig. 7. Phylogenetic analysis of the MG192 variable sequences from serially cultured in vitro samples from MG infected patients no. 61 and no. 126. Time intervals are described in Table 4. There are greater variations in the MG192 gene during sequential cultures, but the variances are more closely related within an individual patient than between the patients. MG: Mycoplasma genitalium.
cultures, the MG evolved very rapidly within limited intervals (Fig. 6, 7, Supplementary Table 3) [50].

In addition, Ma et al. [51] intraurethrally inoculated one cloned MG strain G37 into one male chimpanzee’s urethra. The infected samples were serially recovered at 5 weeks, 9 weeks, and 11 weeks. Finally, they extracted the MG DNA from the samples and examined the in vivo DNA sequence variations in the MG192. The DNA sequence in MG192 had evolved rapidly in vivo within a short period of time (Fig. 8, Supplementary Table 4) [51].

2) Recombination between the MgPa gene and the MgPar gene; ability to generate unlimited variants from its minimized genome

The DNA sequences in the mgpB and mgpC regions of the MgPa gene are highly variable (Fig. 4, 5), and the DNA sequence in MG192 changes rapidly within a short interval, both in vitro and in vivo (Fig. 6-8) [50,51]. These mechanisms may aid MG attachment onto the host cells and evade host immune responses through antigenic variation mechanisms.

These variations could be explained by a homologous recombination or by gene conversion between the MG191 and MG192 sites and various MgPar DNA sequences [33]. The recombination events between the repetitive elements and MgPa operon could have created an unlimited amount of new sequence variants from the limited genome in MG (Fig. 9, 10).

Except for MgPar 6, which has homologous only to the region EF in MG191, all MgPars contain 3-5 discrete minicassettes that are homologous to different regions of MG191 and MG192 [39].

[Diagram or image of homologous recombination between MG192 and MgPar 8 in the MG type strain G37 during in vitro passage.]

A schematic view of homologous recombination between MG192 and MgPar 8 in the MG type strain G37 during in vitro passage.

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In addition to their homology to mgpB, most MgPar regions contain intervening sequences that are AT rich and/or that are homologous to the mgpC gene (MG192 in the TIGR database) located downstream of the mgpB gene in the MgPa operon (Fig. 10) [33,39,40]

2. Genetic Mutation in Determining Sites for Antimicrobials Resistance

MG is an important cause of non-chlamydial, non-gonococcal (NCNG) urethritis in men [8,10,52,53]. In the past, doxycycline or tetracycline had been applied for MG-caused NCNG urethritis, albeit with poor efficiency [53,54]. Azithromycin has been the preferred treatment for this infection, and it has been used extensively for several years around the globe. Unfortunately, certain MG pathogens have become resistant to the primary azithromycin treatment. Some fluoroquinolones have revealed to be highly active against azithromycin-resistant MG [53-57], yet cases of moxifloxacin treatment failures have been reported recently in Japan, Australia, and some other developed countries in Europe [55-57]. Because of the current lack of a specific treatment strategy for macrolide-resistant and fluoroquinolone-resistant MG, multi-drugs resistant MG infections will likely become a major problem in the near future [54].

Some strong and consistent associations between the presence of 23S rRNA gene mutations and azithromycin treatment failure, as well as between the presence of type II topoisomerase gene mutations and fluoroquinolone treatment failure have been reported around the world [54-56,58].

1) 23S rRNA

The central dogma may be simplified into the following statement: “DNA makes RNA, and RNA makes protein.” The mature mRNA goes into a ribosome, where it gets translated. The complexes of initiation factors and elongation factors bring aminoacylated transfer RNAs (tRNAs) into the ribosome-mRNA complex, matching the codon in the mRNA to the anti-codon on the tRNA. Each tRNA bears the appropriate amino acid residue to add to the polypeptide chain being synthesized. As the amino acids get linked into the growing peptide chain, the chain begins folding into the correct conformation [59,60].

The 23S rRNA in *Escherichia coli* is about 2,900 nucleotides long component of the large subunit (50S) of the bacterial ribosome [61]. The ribosomal peptidyl transferase activity resides in the V domain of the 23S rRNA, where peptide bonds between adjacent amino acids are formed using tRNA during protein biosynthesis [62]. This domain is the most common binding site for antibiotics that target and inhibit translation. In addition to inhibiting growing amino acid chains, macrolide antibiotics may also inhibit peptidyl transferase through the ribosomal elongation mechanism [63,64]. Some nucleotide sites in the 23S rRNA areas have hot spots that are critical in determining the azithromycin resistance of MG: mutational changes in these hot spots inhibit macrolide binding, which leads to the development of macrolide resistant infections [54-57]. Nucleotide positions 2058 and 2059 in the V region of the 23S rRNA gene have been well documented as important binding sites by macrolide. Therefore, their mutations are critical for deciding macrolide resistance in the bacterial class, *Mollicutes*, such as *M. pneumonia* and MG [65].

Anagrius et al. [66] reported that the prevalence of macrolide resistant MG has been increasing in a Swedish STD clinic, and the mutation rates in the 23S rRNA regions are as follows: wild type (A2058A and A2059A type-59%), A2058G (23%), A2058T (2%), A2059G (13%), and insufficient results (3%). However, the prevalence of macrolide resistance-associated 23S rRNA gene mutation in selected cities of Russia and Estonia are slightly different; 3.3% in A2059G, 1.6% in A2058G, 0.1% in A2058C, 0.1% in A2058T, 0.1% in A2062G, and 0.1% in C2055G [6]. Unlike Sweden, where the A2058G type is the most common mutant, followed by A2059G mutant, the A2059G mutant is the most prevalent type in selected Russian and Estonian cities [6].

Although there have only been a handful of studies reporting on the sequential antimicrobial treatments and genetic mutation status in MG, Couldwell and Lewis [67] and Coulwdwell et al. [68] from Australia reported that clinical failures of antimicrobials treatment in MG infections is well matched with genetic mutations in the 23S rRNA hot spots.

2) Topoisomerase IIA

Although fluoroquinolone-resistance in MG appears to be increasing globally, this phenomenon is especially remarkable in Eastern Asia, Kikuchi et al. [69] from Japan reported that in 27 MG specimens in 2011 and in 24 in 2012, no macrolide resistance-associated mutations in the
Table 5. Topoisomerase IIA family in *Mycoplasma genitalium*

| Enzyme      | Type                | Structure               | Genes                  | Annotations           | Locationa) | Gene name    |
|-------------|---------------------|-------------------------|------------------------|-----------------------|-------------|--------------|
| Gyrase      | Topoisomerase IIA   | Heterodimer             | gyrA                   | DNA gyrase subunit A  | 4812..7322  | AFQ04307.1  |
|             | (AB/AB)             | gyrB                    | DNA gyrase subunit B   |                       | 2845..4797  | AFQ04306.1  |
| Topo IV     | Topoisomerase IIA   | Heterodimer             | ParC                   | DNA topoisomerase IV, A subunit | 242059..244404 | AFQ04524.1 |
|             | (AB/AB)             | ParE                    | DNA topoisomerase IV, B subunit |                   | 240158..242059 | AFQ04523.1 |

a)CP003773; *Mycoplasma genitalium* M2288, complete genome from https://www.ncbi.nlm.nih.gov/nuccore/CP003773.

Table 6. List of common DNA mutations in topoisomerase IIA genes that change their amino acid sequences, which may inactivate moxifloxacin treatment in *Mycoplasma genitalium* infection [67-69]

| Gene | Position | Mutation | AA change |
|------|----------|----------|-----------|
| ParC | 234      | C to T   | No change |
|      | 241      | G to T   | Glt to Cys|
|      | 244      | G to A   | Asp to Asn|
|      | 247      | G to T   | Ser to Arg|
|      | 248      | G to A   | Ser to Ile|
|      | 259      | G to A   | Asp to Asn|
|      | 260      | A to G   | Asp to Tyr|
|      | 261      | A to G   | Lys to Met|
|      | 290      | A to G   | Lys to Met|
|      | 307      | G to A   | Val to Ile|
|      | 351      | T to C   | No change |
|      | 356      | C to A   | Ala to Val|
| GyrA | 237      | G to T   | No change |
|      | 267      | C to T   | No change |
|      | 270      | C to T   | No change |
|      | 285      | G to A   | No change |
|      | 285      | G to C   | Met to Ile|

AA: amino acid.

23S rRNA gene were observed. However, 5 of 17 specimens in 2013 had carried 23S rRNA mutations. Three isolates of 15 in 2011, 6 of 19 in 2012, and 8 of 17 in 2013 had fluoroquinolone resistance-associated variations in ParC. Moreover, three isolates in 2013 coincidentally carried both antibiotic resistance-associated phenotypes. As the case of macrolide resistance with 23S rRNA mutations, fluoroquinolone resistance in MG is frequently associated with the mutations of the molecular target genes in MG.

During prokaryotic DNA replication and transcription, DNA strands are subjected to various conformational stresses. Due to the intertwined structure, the double-stranded DNAs are twisted throughout the process of replication, generating large amounts of steric hindrance that may prevent the entire process. The supercoiled DNA strings must be relieved to prevent damaging or disrupting DNA structures. Therefore, the appropriate control or relief of supercoiled string is essential for the replication and transcription in the cell cycles of bacteria. The topoisomerase family of enzymes catalyzes the passage of one strand of double strand DNA by nicking the second strand. Among various topoisomerase family, DNA gyrase and DNA topoisomerase IV are important genes for relieving the over-twisted MG DNA strands (Table 5) [25,70]. Therefore, both genes are ideal targets for fluoroquinolone family of drugs in the treatment of MG infection.

Some quinolones, such as moxifloxacin, have potent activity in vivo and in vitro against MG, and treatment with moxifloxacin is considered as an effective second-line treatment for azithromycin-resistant, persistent or recurrent MG infections [54,71]. The antibacterial activities of the quinolones may be due to their inhibitory activities against bacterial type II topoisomerases, such as DNA gyrase and topoisomerase IV (Table 6) [54,67-69,71,72]. Therefore, it has been reported that mutations in the quinolone resistance-determining regions of the type II topoisomerases contribute to quinolone resistance in various bacterial species, including MG [67-69].

CONCLUSIONS

MG displays features that are commonly observed in other pathogenic bacteria that allow it to cause disease, evade host immune responses through antigenic variability, and readily develop resistance to antimicrobial agents. It is not a monotonous chrysalis, but a multicolored butterfly with various capabilities, with natural tendency to evolve rapidly. Therefore, it is near impossible to control or eradicate MG infections in current clinical practice with outdated methods. Furthermore, some empirical therapies against MG infection may aggravate drug resistance. Unfortunately, the lists of currently available antibiotics against MG are quickly being exhausted, and fewer new antimicrobial agents are being introduced for MG treatment. In this regard, the unique genetic characteristics in the antigenic variation and target
gene mutations for antimicrobials must be taken into account. To do so, specific molecular tests for determining antimicrobial resistance and appropriate antimicrobial prescriptions to recurrent MG infected patients are important. Complete eradication of the disease must then be confirmed with highly sensitive diagnostic methods, while sexual partners must be made aware of the situation to prevent the spread of new infection. Clinical guidelines are in need of updates and changes, but more importantly, they must be administered on an international scale. Finally, some national or international research centers must be established to curb this volatile target. We hope that this manuscript offers clinicians a deeper understanding of recurrent MG infections and can provide guidance in deciding on an appropriate treatment for the infection clinical setting.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://euti.org/src/sm/uti-12-65-s001.pdf.

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Supplementary Table 1.

*Mycoplasma genitalium mgpB* sequences from the National Center for Biotechnology Information

> CP003773.1:221365-225744 Mycoplasma genitalium M2288, complete genome
> GU226203.1:1247-5599 Mycoplasma genitalium isolate 6286 MgPa operon, complete sequence
> GU226202.1:1247-5569 Mycoplasma genitalium isolate M6285 MgPa operon, complete sequence
> GU226200.1:1250-5593 Mycoplasma genitalium isolate M6283 MgPa operon, complete sequence
> GU226201.1:1250-5578 Mycoplasma genitalium isolate M6284 MgPa operon, complete sequence
> FJ872591.1:1152-5510 Mycoplasma genitalium strain New Orleans 64 MgPa operon, complete sequence
> FJ872584.1:1206-5537 Mycoplasma genitalium strain M2282 MgPa operon, complete sequence
> KP318806.1 Mycoplasma genitalium strain Seattle2 MgpB adhesin gene, complete cds
> FJ872588.1:1257-5615 Mycoplasma genitalium strain M2341 MgPa operon, complete sequence
> FJ872592.1:1152-5501 Mycoplasma genitalium strain New Orleans 64 MgPa operon, complete sequence
> FJ872586.1:1260-5585 Mycoplasma genitalium strain M2300 MgPa operon, complete sequence
> FJ872589.1:1143-5465 Mycoplasma genitalium strain New Orleans 199 MgPa operon, complete sequence
> GU226196.1:1250-5581 Mycoplasma genitalium isolate M30 MgPa operon, complete sequence
> FJ872587.1:1245-5588 Mycoplasma genitalium strain M2321 MgPa operon, complete sequence
> M31431.1:1066-5400 M. genitalium attachment protein (MgPa) gene, complete cds
> FJ872590.1:1143-5465 Mycoplasma genitalium strain New Orleans 199 MgPa operon, complete sequence
> GU226199.1:1250-5593 Mycoplasma genitalium isolate M6282 MgPa operon, complete sequence
> GU226197.1:1063-5388 Mycoplasma genitalium isolate M6257 MgPa operon, complete sequence
> GU226198.1:1250-5584 Mycoplasma genitalium isolate M6280 MgPa operon, complete sequence
> KP318805.1 Mycoplasma genitalium strain Seattle1 MgpB adhesin gene, complete cds
Supplementary Table 2.

*Mycoplasma genitalium* mgpC sequences from the National Center for Biotechnology Information

- EF117280.1 Mycoplasma genitalium strain G37 adhesion protein (mgpC) gene, partial cds
- EF117281.1 Mycoplasma genitalium strain TW10-5 adhesion protein (mgpC) gene, partial cds
- JX869102.1 Mycoplasma genitalium strain A52.0A adhesion protein MG192 (mgpC) gene, partial cds
- JX869118.1 Mycoplasma genitalium strain 1125.5b adhesion protein MG192 (mgpC) gene,
- JX869119.1 Mycoplasma genitalium strain 1125.5c adhesion protein MG192 (mgpC) gene, partial cds
- JX869103.1 Mycoplasma genitalium strain A52.5B adhesion protein MG192 (mgpC) gene, partial cds
- EF117282.1 Mycoplasma genitalium strain TW48-5 adhesion protein (mgpC) gene, partial cds
- JX869120.1 Mycoplasma genitalium strain 1125.5d adhesion protein MG192 (mgpC) gene, partial cds
- JX869104.1 Mycoplasma genitalium strain A52.5C adhesion protein MG192 (mgpC) gene, partial cds
- JX869122.1 Mycoplasma genitalium strain 1125.5f adhesion protein MG192 (mgpC) gene, partial cds
- JX869123.1 Mycoplasma genitalium strain 1125.5g adhesion protein MG192 (mgpC) gene, partial cds
- JX869105.1 Mycoplasma genitalium strain A52.5D adhesion protein MG192 (mgpC) gene, partial cds
- JX869124.1 Mycoplasma genitalium strain 1125.5h adhesion protein MG192 (mgpC) gene, partial cds
- AY679761.1 Mycoplasma genitalium strain TW10-5 cytadherence-related protein p110 gene, partial cds
- JX869114.1 Mycoplasma genitalium strain A52.13M adhesion protein MG192 (mgpC) gene, partial cds
- JX869126.1 Mycoplasma genitalium strain 1125.11 adhesion protein MG192 (mgpC) gene, partial cds
- JX869128.1 Mycoplasma genitalium strain 1125.11l adhesion protein MG192 (mgpC) gene, partial cds
- JX869127.1 Mycoplasma genitalium strain 1125.11k adhesion protein MG192 (mgpC) gene, partial cds
- JX869116.1 Mycoplasma genitalium strain A52.13O adhesion protein MG192 (mgpC) gene, partial cds
- JX857935.1 Mycoplasma genitalium isolate 126.4.1 adhesion protein MG192 (mgpC) gene, partial cds
- JX869129.1 Mycoplasma genitalium strain 1125.1m adhesion protein MG192 (mgpC) gene, partial cds
- JX857936.1 Mycoplasma genitalium isolate 126.4.2 adhesion protein MG192 (mgpC) gene, partial cds
- JX869115.1 Mycoplasma genitalium strain A52.13N adhesion protein MG192 (mgpC) gene, partial cds
- JX857927.1 Mycoplasma genitalium isolate 126.3q adhesion protein MG192 (mgpC) gene, partial cds
- JX857922.1 Mycoplasma genitalium isolate 126.2l adhesion protein MG192 (mgpC) gene, partial cds
- JX857929.1 Mycoplasma genitalium isolate 126.3s adhesion protein MG192 (mgpC) gene, partial cds
- JX869131.1 Mycoplasma genitalium strain 1125.1o adhesion protein MG192 (mgpC) gene, partial cds
- JX869108.1 Mycoplasma genitalium strain A52.10G adhesion protein MG192 (mgpC) gene, partial cds
- JX869125.1 Mycoplasma genitalium strain 1125.9i adhesion protein MG192 (mgpC) gene, partial cds
- JX857901.1 Mycoplasma genitalium isolate 61.2c adhesion protein MG192 (mgpC) gene, partial cds
- JX869110.1 Mycoplasma genitalium strain A52.10l adhesion protein MG192 (mgpC) gene, partial cds
- JX869109.1 Mycoplasma genitalium strain A52.10H adhesion protein MG192 (mgpC) gene, partial cds
- JX857925.1 Mycoplasma genitalium isolate 126.2o adhesion protein MG192 (mgpC) gene, partial cds
- JX857939.1 Mycoplasma genitalium isolate 126.4.5 adhesion protein MG192 (mgpC) gene, partial cds
- JX869111.1 Mycoplasma genitalium strain A52.10J adhesion protein MG192 (mgpC) gene, partial cds
- JX857899.1 Mycoplasma genitalium isolate 61.0a adhesion protein MG192 (mgpC) gene, partial cds
- JX857928.1 Mycoplasma genitalium isolate 126.3r adhesion protein MG192 (mgpC) gene, partial cds
- JX869121.1 Mycoplasma genitalium strain A52.10K adhesion protein MG192 (mgpC) gene, partial cds
- JX857921.1 Mycoplasma genitalium isolate 126.1k adhesion protein MG192 (mgpC) gene, partial cds
- JX857904.1 Mycoplasma genitalium isolate 61.2f adhesion protein MG192 (mgpC) gene, partial cds
- JX857914.1 Mycoplasma genitalium isolate 126.0d adhesion protein MG192 (mgpC) gene, partial cds
- JX857900.1 Mycoplasma genitalium isolate 61.2b adhesion protein MG192 (mgpC) gene, partial cds
- JX857934.1 Mycoplasma genitalium isolate 126.3x adhesion protein MG192 (mgpC) gene, partial cds
- JX857932.1 Mycoplasma genitalium isolate 126.3v adhesion protein MG192 (mgpC) gene, partial cds
- JX857903.1 Mycoplasma genitalium isolate 61.2e adhesion protein MG192 (mgpC) gene, partial cds
- JX857926.1 Mycoplasma genitalium isolate 126.2p adhesion protein MG192 (mgpC) gene, partial cds
- JX857881.1 Mycoplasma genitalium isolate 64.0a adhesion protein MG192 (mgpC) gene, partial cds
- JX857924.1 Mycoplasma genitalium isolate 126.2n adhesion protein MG192 (mgpC) gene, partial cds
- JX857915.1 Mycoplasma genitalium isolate 126.1e adhesion protein MG192 (mgpC) gene, partial cds
Supplementary Table 3.

|Mycoplasma genitalium mgpC sequences from patient No. 126 from the National Center for Biotechnology Information|
|-------------------------------------------------------------|
|>JX857935.1 Mycoplasma genitalium isolate 126.4.1 adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857936.1 Mycoplasma genitalium isolate 126.4.2 adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857927.1 Mycoplasma genitalium isolate 126.3q adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857929.1 Mycoplasma genitalium isolate 126.3s adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857925.1 Mycoplasma genitalium isolate 126.2o adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857939.1 Mycoplasma genitalium isolate 126.4.5 adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857928.1 Mycoplasma genitalium isolate 126.3r adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857921.1 Mycoplasma genitalium isolate 126.1k adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857914.1 Mycoplasma genitalium isolate 126.0d adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857934.1 Mycoplasma genitalium isolate 126.3x adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857932.1 Mycoplasma genitalium isolate 126.3v adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857926.1 Mycoplasma genitalium isolate 126.2p adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857924.1 Mycoplasma genitalium isolate 126.2n adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857915.1 Mycoplasma genitalium isolate 126.1e adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857941.1 Mycoplasma genitalium isolate 126.4.7 adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857923.1 Mycoplasma genitalium isolate 126.2m adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857920.1 Mycoplasma genitalium isolate 126.1j adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857912.1 Mycoplasma genitalium isolate 126.0b adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857943.1 Mycoplasma genitalium isolate 126.4.9 adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857933.1 Mycoplasma genitalium isolate 126.3w adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857916.1 Mycoplasma genitalium isolate 126.1f adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857922.1 Mycoplasma genitalium isolate 126.2l adhesion protein MG192 (mgpC) gene, partial cds |
|>JX857931.1 Mycoplasma genitalium isolate 126.3u adhesion protein MG192 (mgpC) gene, partial cds |
Supplementary Table 4.

*Mycoplasma genitalium* mgpC sequences from patient No. 1125 from the National Center for Biotechnology Information

> JX869118.1 Mycoplasma genitalium strain 1125.5b adhesion protein MG192 (mgpC) gene, partial cds
> JX869119.1 Mycoplasma genitalium strain 1125.5c adhesion protein MG192 (mgpC) gene, partial cds
> JX869120.1 Mycoplasma genitalium strain 1125.5d adhesion protein MG192 (mgpC) gene, partial cds
> JX869122.1 Mycoplasma genitalium strain 1125.5f adhesion protein MG192 (mgpC) gene, partial cds
> JX869123.1 Mycoplasma genitalium strain 1125.5g adhesion protein MG192 (mgpC) gene, partial cds
> JX869124.1 Mycoplasma genitalium strain 1125.5h adhesion protein MG192 (mgpC) gene, partial cds
> JX869126.1 Mycoplasma genitalium strain 1125.11j adhesion protein MG192 (mgpC) gene, partial cds
> JX869128.1 Mycoplasma genitalium strain 1125.11l adhesion protein MG192 (mgpC) gene, partial cds
> JX869127.1 Mycoplasma genitalium strain 1125.11k adhesion protein MG192 (mgpC) gene, partial cds
> JX869129.1 Mycoplasma genitalium strain 1125.11m adhesion protein MG192 (mgpC) gene, partial cds
> JX869131.1 Mycoplasma genitalium strain 1125.10 adhesion protein MG192 (mgpC) gene, partial cds
> JX869125.1 Mycoplasma genitalium strain 1125.9i adhesion protein MG192 (mgpC) gene, partial cds
> JX869121.1 Mycoplasma genitalium strain 1125.5e adhesion protein MG192 (mgpC) gene, partial cds
> JX869132.1 Mycoplasma genitalium strain 1125.11p adhesion protein MG192 (mgpC) gene, partial cds