ORIGINAL ARTICLE

Comparative genomic analysis of *Myroides odoratimimus* isolates

Shaohua Hu | Lin Cao | Yiyin Wu | Yajun Zhou | Tao Jiang | Liqiang Wang

School of Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, Fujian, China

College of Computer Science and Technology, Huaqiao University, Xiamen, Fujian, China

Department of Neurosurgery, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong, China

Department of Clinical Laboratory, Quanzhou First Hospital Affiliated to Fujian Medical University, Fujian, China

Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI, USA

Correspondence
Mingxi Wang, Yun Leung Laboratory for Molecular Diagnostics, School of Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, Fujian 361021, China. Email: mxwang@hqu.edu.cn

Qiujing Wang, Department of Neurosurgery, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong 518101, China Email: qiujingwang1@126.com

Desong Ming, Department of Clinical Laboratory, Quanzhou First Hospital Affiliated to Fujian Medical University, Fujian 362000, China Email: mds6430@126.com

Shicheng Chen, Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI 48824, USA Email: shicheng@msu.edu

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Abstract

*Myroides odoratimimus* is an important nosocomial pathogen. Management of *M. odoratimimus* infection is difficult owing to the multidrug resistance and the unknown pathogenesis mechanisms. Based on our previous genomic sequencing data of *M. odoratimimus* PR63039 (isolated from a patient with the urinary tract infection), in this study, we further performed comparative genomic analysis for 10 selected *Myroides* strains. Our results showed that these *Myroides* genome contexts were very similar and phylogenetically related. Various prophages were identified in the four clinical isolate genomes, which possibly contributed to the genome evolution among the *Myroides* strains. CRISPR elements were only detected in the two clinical (PR63039 and CCUG10230) isolates and two environmental (CCUG12700 and H1bi) strains. With more stringent cutoff parameters in CARD analysis, the four clinical *M. odoratimimus* contained roughly equal antibiotic resistance genes, indicating their similar antibiotic resistance profiles. The three clinical (CCUG10230, CCUG12901, CIP101113) and three environmental (CCUG12700, L41, H1bi) *M. odoratimimus* strains were speculated to carry the indistinguishable virulent factors (VFs), which may involve in the similar pathogenesis mechanism. Moreover, some VFs might confer to the high capacity of dissemination, attacking tissue cells and induction of autoimmune complications. Our results facilitate the research of antibiotic resistance and the development of therapeutic regimens for the *M. odoratimimus* infections.

KEYWORDS
antibiotic resistance genes, comparative genomics, *Myroides odoratimimus*, virulence factors
1 | INTRODUCTION

*Myroides odoratimimus* is a gram-negative and opportunistic pathogen. It causes a variety of serious infections mainly reported in China (summarized by Hu et al., 2016) and outbreak of urinary tract infection (Ktari et al., 2012). Recently, the increasing infections emerged in patients with the recurrent calcaneal ulcer (Pompilio et al., 2017), fulminant erysipelas and sepsis (Willems, Muller, Verhaegen, Saegeman, & Desmet, 2017), bacteremia (Belloir, Billy, Hentgen, Fille, & Barrans, 2016), or prosthesis joint infection (Jover-Sáenz, Pérez-Villar, & Barcenilla-Gaité, 2016).

*M. odoratimimus* infections are life-threatening due to its multi-drug resistance and unknown pathogenicity (as summarized in Hu et al., 2016). In our previous report (Hu et al., 2017), to some extent, we correlated the phenotype in antibiotic susceptibilities and infectivity of *M. odoratimimus* with the genomic findings of a variety of resistance genes, virulence factor (VF) genes. To better accomplish these purposes and verify the possibility of infection source of environmental strains, here, we further performed comparative genomic analysis of 10 *Myroides* strains, including four clinically pathogenic (PR63039, CCUG10230, CCUG12901, CIP101113), four environmental (CCUG 3837 CCUG 12700 H1bi L41), and two human-associated *Myroides* isolates (CCUG39352, *Myroides* sp. A21) by focusing on their antibiotic resistance and pathogenesis mechanisms.

2 | MATERIALS AND METHODS

2.1 | Genome sequences

In the NCBI Genome RefSeq Assembly Database, only nine genomic sequences of *M. odoratimimus* were found (Table 1). They included four clinically pathogenic strains, a human-associated strain, and four environmental isolates. Only PR63039 genome (Hu et al., 2017) was complete. Strain PR63039 (Hu et al., 2017) and CCUG12901 were isolated from the urine of patients with postinjury urinary tract infection. CCUG10230 and CIP101113 were isolated from skin wounds. Human-associated strain CCUG39352 was collected and sequenced by Shandong University. *M. odoratimimus* H1 bi, L41, CCUG 12700, and CCUG 3837 are environmental isolates. For the phylogenetic tree analysis of *Myroides* genomes, another human-associated strain *Myroides* sp. A21 (CP010327) (Burghart et al., 2015) with highly homologous 16S rRNA gene sequence to strain PR63039 (coverage 100%, identity 100%, 1,388 bp) (GenBank No. KR349266) was also included. *Myroides* sp. A21 was isolated from the urethral catheter of a patient without symptoms of a urinary tract infection, had extensive drug resistance; its full genomic sequence was available.

2.2 | Softwares and databases used for comparative genomics analysis

The analyses of whole-genome phylogenetic tree, circular genome mapping, insertion sequence elements (IS), multiple genome alignment, prophage, CRISPR, antibiotic resistance genes, and VF genes in the *M. odoratimimus* genomes were performed with the softwares and databases listed in Table 2.

We should mention that, for identifying the resistance genes using CARD Resistance Gene Identifier (RGI) software (Jia et al., 2017; Mcarthur et al., 2013), we performed BLASTp search (collaborated with Beijing Novogene Bioinformatics Technology Co., Ltd, BNNT) of the protein sequences of *M. odoratimimus* (downloaded from RefSeq assembly) against the CARD reference sequences, and more stringent parameters were set up [Query ID, Chromosome, Gene start, Gene end, Direction, ARO ID, ARO name, Category, Query length, Query start, Query end, Subject length, Subject start, Subject end, Gap, Mismatch length, Match length, Bit score, E value ≤ 1e-30, Identity (%), Query coverage, Subject coverage]. The stringency of extracting antibiotic resistance genes from the primary output was improved by setting the cutoff parameters [Protein identity >50%, Query coverage >50%, and Subject coverage >50%].

The genes coding for the virulence factors was predicted by performing BLAST search (collaborated with Beijing Novogene Bioinformatics Technology Co., Ltd) of the protein sequences of *M. odoratimimus* against the VFDB protein Set B database (Chen, Xiong, Sun, Yang, & Jin, 2012; Chen, Zheng, Liu, Yang, & Jin, 2016). The stringent parameters were set up (Gene ID, VFDB internal ID, VF ID, VF name, Genes, Characteristics, Structure features, Functions, Mechanisms, Descriptions, Query length, Query start, Query end, Subject length, Subject start, Subject end, Match length, Mismatch length, Gap, Identity, E value, Bit score, Query coverage, Subject coverage). The cutoff parameters for extracting VF genes from the primary outputs were same as the extracting resistance genes as the above.

3 | RESULTS

3.1 | The basic genome statistics of 10 *Myroides* genomes

The general features of 10 *Myroides* genomes, including four clinically pathogenic *M. odoratimimus* (PR63039, CCUG12901, CCUG10230, CIP101113), four environmental (CCUG 12700, L41, H1bi, CCUG 3837), and two human-associated *Myroides* strains (CCUG 39352, *Myroides* sp. A21) were similar (summarized in Table 1). Their GC contents were approximately 34%. The sizes of the genomes varied from 3.88 to 4.46 Mb. The numbers of genes, proteins, and tRNAs in PR63039 genome were larger than that of the other nine genomes. We should mention that eight *Myroides* genomes were incomplete, and the sequencing of the plasmids in PR63039 strains were not completed even its chromosome was fully sequenced (Figure 1 in Hu et al., 2016, 2017).

3.2 | Phylogenetic analysis of 10 *Myroides* genomes

Whole-genome phylogenetic tree of the 10 *Myroides* genomes was created (Figure 1). It showed that PR63039 formed a different clade
| Sources | Strain | Site of isolation | Type | Assembly No. | Level | Scaffold | Size (Mb) | GC (%) | Gene | Protein | rRNA | tRNA | Other RNA | Pseudo gene |
|---------|--------|-------------------|------|--------------|-------|----------|-----------|--------|------|---------|------|------|-----------|-------------|
| Clinically pathogenic <i>M. odoratimimus</i> | PR63039 | Urine | GCA_001481655.1 | 2 | 4.46 | 34.14 | 4,084 | 3,840 | 27 | 105 | 4 | 108 |
|         |        |                   | NZ_CP013690.1 | Complete | 4.37 | 34.20 | 3,988 | 3,745 | 27 | 105 | 4 | 107 |
|         |        |                   | NZ_CP013691.1 | 0.09 | 31.30 | 96 | 95 | - | - | - | 1 |
|         | CCUG 10230 | Skin wound | Chr | GCA_000242075.2 | Scaffold | 7 | 4.03 | 34.10 | 3,610 | 3,458 | 5 | 76 | 4 | 67 |
|         | CCUG 12901 | Urogenital tract | Chr | GCA_000242095.1 | Scaffold | 3 | 4.07 | 34.20 | 3,653 | 3,505 | 9 | 75 | 4 | 60 |
|         | CIP 101113 | Skin wound | Chr | GCA_000242135.1 | Scaffold | 3 | 4.14 | 34.10 | 3,673 | 3,516 | 8 | 71 | 4 | 74 |
| Environmental <i>M. odoratimimus</i> | CCUG 3837 | N/A | Chr | GCA_000297855.1 | Scaffold | 4 | 4.14 | 34.40 | 3,611 | 3,459 | 11 | 72 | 4 | 65 |
|         | CCUG 12700 | N/A | Chr | GCA_000413415.1 | Scaffold | 7 | 4.04 | 34.30 | 3,581 | 3,423 | 7 | 87 | 4 | 60 |
|         | H1bi | Carnivorous plant Phytotelma | Chr | GCA_000633375.1 | Contig | 183 | 3.88 | 34.00 | 3,549 | 3,260 | 4 | 85 | 4 | 196 |
|         | L41 | Lake water | Chr | GCA_000812825.1 | Contig | 168 | 4.16 | 33.60 | 3,802 | 3,599 | 82 | 4 | 114 |
| Human-associated <i>Myroides</i> | CCUG 39352 | Wound | Chr | GCA_001485415.1 | Contig | 65 | 4.24 | 33.90 | 3,789 | 3,650 | 74 | - | - |
|         | Myroides sp. A21 | Urethral catheter | Chr | GCA_000807225.1 | Complete | 1 | 4.16 | 34.10 | 3,750 | 3,554 | 24 | 101 | 4 | 67 |

Chr, chromosome; Plsm, plasmid; N/A, not available.
from *Myroides* sp. A21 even although they had highly homologous 16S rRNA gene sequence (100% identity). The clinically pathogenic strain CCUG 10230 and the environmental strain CCUG 39352 were closest. Strain CCUG3837, CIP101113, and CCUG12700 formed a clade, while strain H1bi was located alone. It seemed that strain CCUG3837, CIP101113, and CCUG12700 were phylogenetically closer and H1bi might have a different origin compared to the above three strains.

Collectively, these 10 *Myroides* strains were related phylogenetically, indicating that there might similarly evolve to some pathogenic traits. However, further study to illuminate the evolution pathway is warranted.

### 3.3 Genomic variants among four clinically pathogenic *M. odoratimimus* strains

We compared the genomes of three clinically pathogenic *M. odoratimimus* strains (CCUG12901, CCUG10230, CIP101113) with the clinically pathogenic PR63039 genome as the reference (Table 2). Many highly variable regions were found (Figure 2). Specifically, the following regions on the above three genomes were absent or had low identity with our strain PR63039: from 150 to 250 kb, 700 to 780 kb, 1,650 to 1,700 kb, 2,300 to 2,450 kb, 2,680 to 2,720 kb, 3,370 to 3,530 kb, 3,720 to 3,800 kb, 4,110 to 4,200 kb, 4,250 to 4,270 kb, and 4,350 to 4,560 kb. Interestingly, the region from 1,650 to 1,700 kb was predicted to be located in one prophage locus of CCUG-12901 genome. Circular map of the genome comparisons indicated that there were a number of conserved or diverged genome segments among the genomes of these four clinically pathogenic *M. odoratimimus*.

In addition, the abovementioned variable regions were partially accompanied by several insertion elements, which might assist the integration of resistance- and pathogenesis-related genes and facilitate the transfer of drug resistance and pathogenic genes among *M. odoratimimus* strains. Furthermore, IS elements may enhance drug resistance and virulence by promoting gene expression (Herlitzi, Poirel, & Nordmann, 2006; Higgins, Dammhayn, Hackel, & Seifert, 2010).

#### 3.4 Synteny analysis among four clinically pathogenic and three environmental *M. odoratimimus* strains

Genome alignments can identify evolutionary traits. To study the genome synteny and rearrangements in four clinically pathogenic (PR63039, CCUG10230, CCUG12901, and CIP101113) and three environmental (CCUG12700, L41, and H1bi) *M. odoratimimus* bacteria (Table 2), the genome alignment software progressive MAUVE (Darling, Mau, & Perna, 2010) was used (Figure S1). The synteny between the PR63039 genome and *Myroides* sp. A21 was approximately 83.7% (Hu et al., 2017). The genome arrangement of these four clinically pathogenic isolates mimics each other. Similarly, the genome context and arrangement in the three environmental strains exhibited great similarity. However, the genome synteny between the clinically pathogenic and environmental isolates was relatively low.

The alignment of the four genomes of clinically pathogenic isolates showed that their genome rearrangements were similar although there were inversions in some regions. Moreover, the chromosomal alignments of CCUG12901 and CIP101113 were nearly identical with large segments of high similarity. There were some white areas not aligned well because they might contain elements specific to a particular genome.

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**Table 2** The softwares and databases used for comparative analysis

| Analysis | Software/database | References | Clinically pathogenic strains |
|----------|------------------|------------|-------------------------------|
| Sequence level | | | PR63039 | CCUG 10230 | CCUG 12901 |
| Phylogenetic tree | REALPHY | Bertels, Silander, Pachkov, Rainey, & van Nimwegen, 2014; | Yes | Yes | Yes |
| CG | CG viewer | Grant & Stothard, 2008; | Yes | Yes | Yes |
| ISs | IS Finder | Siguier, Perochoen, Lestrade, Mahillon, & Chandler, 2006; | Yes (43) | Yes (169) | Yes (117) |
| Synteny | Progressive mauve | Darling et al., 2010; | Yes | Yes | Yes |
| Prophage | PHAST | Zhou, Liang, Lynch, Dennis, & Wishart, 2011; | Yes (2 incomplete) | Yes (2) | Yes (5) |
| CRISPR | CRISPR Finder | Bland et al., 2007; | Yes (3) | Yes (4) | Yes (ND) |
| Antibiotic resistance genes | CARD Resistance Gene identifier | Mcarthur et al., 2013; Jia et al., 2017; | Yes | Yes | Yes |
| Virulence factors | VFDB protein Set B database | Chen et al., 2012, 2016 | Yes | Yes | Yes |

CG, Circular genome maps (Genomic variants); ISs, insertion sequence elements; Yes, analyzed; (): number of the predicted; ND, not detected.
Overall, the four clinically pathogenic strain genomes were similar although the genome synteny in the latter three (CCUG10230, CCUG12901, and CIP101113) was more related than that in PR63039.

### 3.5 | Prophages in four clinically pathogenic M. odoratimimus strains

All the four clinically pathogenic isolates genomes contained incomplete prophage elements (Figure 3). In our strain PR 63039, two incomplete prophages were identified (Hu et al., 2017). CIP101113 contained one prophage with 54 CDs extending from 985,588 bp to 1,032,415 bp (46.8 kb). CCUG10230 was predicted to carry two prophages (9 CDs, 9.2 kb and 12 CDs, respectively). CCUG12901 had five prophages. The region length was 9.2, 9.7, 9.9, 10.1, and 9 kb, respectively, and the number of CDs was 9, 8, 7, 6, 6, respectively. CIP101113 contained only one prophage, but it was larger and more complete than any other prophages. It consisted of hypothetical proteins, phage-like proteins, attachment sites, tail shafts, and proteases. Among these predicted prophages, attachment sites and proteases only existed in CIP101113 prophage. In bacterial genomes, integrases are useful markers for mobile DNA elements, such as prophages, integrative plasmids, and pathogenicity islands (Liu et al., 2015). However, no integrase was identified in these predicted prophages.

### 3.6 | CRISPR prediction in the genomes of four clinically pathogenic and three environmental M. odoratimimus strains

CRISPR is well known to contribute to the antibiotic resistance and prevent the foreign virulence genes from invading into pathogens.

**FIGURE 1** Whole-genome phylogenetic tree of 10 Myroides isolates. This Whole-genome phylogenetic tree was produced by REALPHY with the default parameters. Strain L41 was used as the root.
It may be involved in the bacterial evolution, regulation of virulence gene expression, and the enhancement of pathogenicity (Hatoum-Aslan & Marraffini, 2014). Particularly, in the pathogen, CRISPR is able to edit genome and modulate gene functions as an adaptive immune system (Arras et al., 2016; Sontheimer & Barrangou, 2015). Comparative analysis of the seven strain genomes (PR63039, CCUG10230, CCUG12901, CIP101113, CCUG12700, L41, and H1bi) showed that PR63039 genome contained three types of CRISPRs.
CCUG10230 genome contained four types of CRISPRs. CCUG12700 and H1bi contained only one CRISPR. However, no CRISPRs were identified in the genomes of CCUG12901, CIP101113, and L41 (Table S1).

### 3.7 Comparative analysis of antibiotic resistance genes in the genomes of four clinically pathogenic *M. odoratimimus* strains

With CARD RGI software (Jia et al., 2017; McArthur et al., 2013), all the genomes of four clinically pathogenic *M. odoratimimus* strains PR63039, CCUG10230, CCUG12901, and CIP101113 were predicted to contain a number of genes related to antibiotic resistance, including the β-lactam resistance gene, fluoroquinolone resistance gene, antibiotic target replacement protein, antibiotic inactivation enzyme, triclosan resistance gene, dianmonopyrimidine resistance gene, phenicol resistance gene, elfamycin resistance gene, and efflux pumps conferring antibiotic resistance (Table 3).

Overall, more resistance genes were predicted in the fully sequenced clinically pathogenic PR63039 genome than in the other three partially sequenced strains, such as, cat gene variant catB2, catB3, catB6, catB7, catB8, catB9, and catB10, tetracycline resistance gene tetX, sulfonamide resistance gene sul1, sul2, and sul3, and β-lactam resistance gene OXA-209, OXA-347. Moreover, in PR63039 genome, the resistance genes tetX, cat, OXA-347, and OXA-209 were clustered in an approximately 6 kb region, called MY63039-RR (Hu
et al., 2017). No similar resistance gene cluster could be identified in the genomes of other three clinically pathogenic M. odoratimimus strains.

Among CCUG12901, CIP101113, and CCUG10230, the identified resistance genes were almost similar. By comparing with PR63039 genome, CCUG12901 genome contained mefC (efflux pump conferring antibiotic resistance) and antibiotic inactivation enzyme (mphD and mphG), but lacked the resistance gene cat. The gene catll, catIII in CCUG10230, and catl in CIP101113 were also not predicted in PR63039 genome.

3.8 Virulence factors in the genomes of three clinically pathogenic and three environmental M. odoratimimus strains

With the help of VFDB protein Set B database (Chen et al., 2012, 2016) and more stringent cutoff parameters, we obtained the VF genes in the genome of three clinically pathogenic (CCUG.12901, CCUG.10230, CIP.101113) and three environmental (H1bi, L41, CCUG.12700) M. odoratimimus isolates (Table 4).

Overall, all these M. odoratimimus genomes had similar VF profiles with a little difference. The VFs included capsule/capsular polysaccharide (GalE, GlmU, wbjD/wecB, ugd, uppS, RmlA, RmlB, capL, wecC), intracellular survival and invasion factors (katA, clpP, EF-Tu, sodB), molecular chaperone (hsp60, Dnak), urease (ureA, ureB, ureG), acinetobactin (bauE), Streptococcus colonal enolase (eno), heme biosynthesis (hemB, hemL), acyl carrier protein (acpxL), and T4SS effectors (Trans-2-enoyl-CoA reductase).

4 DISCUSSION

4.1 Genomic evolution, variants, synteny of M. odoratimimus

To some contents, the 10 Myroides genomes had similar general features. However, the genomes of four clinically pathogenic M. odoratimimus strains (PR63039, CCUG12901, CCUG10230, and CIP101113) contained highly variable regions. The genome arrangement, rearrangements of the four clinically pathogenic isolates, and the three environmental strains were similar, respectively. These data implied that they might be evolutionarily related. All four clinically pathogenic isolate genomes contained prophage elements. CRISPRs were not always identified in all the genomes of four clinically pathogenic and three environmental M. odoratimimus strains. Complete genomic sequencing of these M. odoratimimus strains and their plasmids are indispensable for confirming these analyses.

4.2 Resistance genes in clinically pathogenic M. odoratimimus

All these four clinically pathogenic strains (PR63039, CCUG12901, CCUG10230, CIP101113) contained a number of antibiotic resistance genes. PR63039 genome might have several possibly unique resistance genes, including catB2, catB3, catB6, catB7, catB8, catB9, catB10, tetX, OXA-209, OXA-347, sul1, sul2, and sul3. Some were already discussed to be involved in drug resistance in our previous report (Hu et al., 2017). Here, we mainly discuss mph and cat genes (catB2, catB3, catB6, catB8) with clear functions in antibiotic resistance described by literatures.

The mphD and mphG genes provide a high level of resistance to 14- and 15-membered-ring macrolides via coding for a macrolide 2′-phosphotransferase (https://card.mcmaster.ca/). Cat (chloramphenicol acetyltransferase gene) has many variants in a variety of bacteria, such as Staphylococcus aureus, Staphylococcus haemolyticus, Enterococcus faecium, and Bacillus clausii (Bruckner & Matzura, 1985; Galopin, Cattoir, & Leclercq, 2009; Grady & Hayes, 2003; Schwarz & Cardoso, 1991). All the above identified catB genes (as well catl, catll, catIII) are plasmid, chromosome, or integron-mediated cat variants (https://card.mcmaster.ca/). The cat variants usually participate in the composition of gene cassette or integron, and confer to the ability of antibiotic resistance. For instance, catB2, aacC4, and aadA1 form the gene cassettes aacC4-aadA1-catB2, which confers multidrug and broad-spectrum cephalosporin resistance in Salmonella clinical isolates (Villa et al., 2002). CatB3, one member of gene cassette aacA7-catB3-aadB-oxa2-orfD, can be mobilized by the integron-encoded DNA integrase and plays a role in chloramphenicol resistance of plasmid pBW3013 (Bunny, Hall, & Stokes, 1995; Houang, Chu, Lo, Chu, & Cheng, 2003). CatB6, a chloramphenicol acetyltransferase-encoding allele of the catB family inserted in integron In31, functions to decrease the in vitro antibiotic susceptibilities of Pseudomonas aeruginosa strains (Laraki et al., 1999). CatB8 consists of a resistance gene cassette aacA4-catB8-aadA1 which is prevalent in many clinical antibiotic-resistant bacteria, such as carbapenem-resistant Klebsiella pneumoniae (Ou, Li, Li, & Yu, 2017) and carbapenem-resistant Acinetobacter baumannii (Farshadzadeh et al., 2015; Lin, Liou, Tu, Yeh, & Lan, 2013).

We could not further correlate these predicted antibiotic resistance gene profiles to the antibiotic susceptibility of the other three clinically pathogenic strains (CCUG12901, CCUG10230, CIP101113) due to the lack of these related data. However, the conservation of the antibiotic resistance genes among the clinically pathogenic M. odoratimimus strains indicated that these predicted antibiotic resistance gene profiles potentially provide the guidance for treating M. odoratimimus infections later.

4.3 Pathogenicity of clinically pathogenic and environmental M. odoratimimus indicated by the predicted virulence factors

The VFs in M. odoratimimus were identified using VFDB protein Set B database which curates the experiment-verified and predicted virulence factor genes (Table 4). The finding of similar VFs in both clinically pathogenic and environmental M. odoratimimus genomes might explain the pathogenicity of the three clinically pathogenic M. odoratimimus isolates and indicate that the three environmental
**M. odoratimimus** isolates are also potentially pathogenic. We only discuss the experimentally verified VF genes (in bold/italic, Table 4).

bauE encodes the ferric siderophore ABC transporter/ATP-binding protein BauE with a high-affinity iron-chelating capacity, belonging to acinetobactin. In a mouse sepsis model, the expression of a fully active acinetobactin-mediated iron uptake apparatus by *Acinetobacter baumannii* was verified to be vital for the bacteria to establish infection and kill mouse, by competing with host cells for iron (Gaddy et al., 2012). Thus, bauE should be a survival factor of *M. odoratimimus* during infection.

Capsular LPS is the predominant virulence determinant in many gram-negative and -positive bacteria (García & López, 1997). It inhibits complement-mediated lysis, phagocytosis, and immune recognition in host (Rowe & Huntley, 2015). Several genes involved in capsular LPS biosynthesis pathway were found in the *M. odoratimimus* genomes, such as GalE, GlmU, ugd, wbjD/ wecB, uppS, RmlA, RmlB. UDP-sugar 4-epimerase (GalE) plays an

| Table 3 | The predicted resistance genes in the genomes of four clinically pathogenic *M. odoratimimus* strains |
|----------------|-------------------------------------|-------------------------------------|-------------------------------------|
| **Category** | **PR63039** | **CCUG12901** | **CCUG10230** | **CIP101113** |
| Efflux pump complex or subunit conferring antibiotic resistance | abeS | abeS | abeS | abeS |
| KPC-2 | KPC-2 | KPC-2 | KPC-2 |
| - | mefC | - | - |
| msrB | msrB | msrB | msrB |
| qacH | qacH | qacH | qacH |
| rosA | rosA | rosA | rosA |

| Determinant of elfamycin resistance | basS | basS | basS | basS |
| LpxC | LpxC | LpxC | LpxC |
| SPM-1 | SPM-1 | SPM-1 | SPM-1 |

| Determinant of phenicol resistance | catB2 | - | - | - |
| catB6 | - | - | - | - |
| catB7 | - | - | catB7 | - |
| catB8 | - | - | - | - |
| catB9 | - | - | - | - |
| catB10 | - | - | catI | - |

| Determinant of diaminopyrimidine resistance | dfrE | dfrE | dfrE | dfrE |
| Determinant of triclosan resistance | MexR | MexR | MexR | MexR |

| Antibiotic inactivation enzyme | catB3 | - | - | - |
| - | catlI | - | - |
| - | mphD | - | - |
| - | mphG | - | - |
| OXA-78 | OXA-78 | OXA-78 | OXA-78 |

| tetX | VIM-2 | VIM-2 | VIM-2 |
| VIM-2 | - | - | - |

| Antibiotic target replacement protein | sul1 | - | - | - |
| sul2 | - | - | - | - |
| sul3 | - | - | - | - |

| Determinant of fluoroquinolone resistance | oqxB | oqxB | oqxB | oqxB |
| rpsJ | rpsJ | rpsJ | rpsJ |
| tet(35) | tet(35) | tet(35) | tet(35) |
| tetB(48) | tetB(48) | tetB(48) | tetB(48) |

| Determinant of beta-lactam resistance | OXA-209 | - | - | - |
| OXA-347 | - | - | - | - |

| TLA-3 | TLA-3 | TLA-3 | TLA-3 |

*not predicted
### TABLE 4  The VFs predicted in three clinically pathogenic and three environmental *M. odoratimimus* genomes

| Classification                  | Definition                                                                 | Genes coding for virulence factors | Clinically pathogenic *M. odoratimimus* | Environmental *M. odoratimimus* |
|---------------------------------|---------------------------------------------------------------------------|-----------------------------------|----------------------------------------|---------------------------------|
|                                 |                                                                           | CCUG. 12901                      | CCUG. 10230                           | H1bi   | L41   | CCUG. 12700 |
| Capsular polysaccharide         | UDP-N-acetyl-D-galactosamine 6-dehydrogenase                               | capL (hasB2)                     | capL                                   | capL   | -     | capL         |
|                                 | UDP-glucose 4-epimerase                                                   | galE                              | galE                                   | galE   | galE  | galE         |
|                                 | Bifunctional UDP-N-acetylglucosamine pyrophosphorylase/glucosamine-1-phosphate N-acetyltransferase | glmU                              | glmU                                   | glmU   | glmU  | -            |
|                                 | UDP-glucose 6-dehydrogenase                                                | ugd                               | ugd                                    | -       | ugd   | -            |
| Capsule sialic acid             | UDP-N-acetylglucosamine 2-epimerase                                        | wbjD/wecB                         | wbjD/wecB                              | wbjD/wecB | - | wbjD/wecB |
| Cell wall Peptidoglycan         | Undecaprenyl diphosphate synthase                                          | uppS                              | uppS                                   | uppS   | uppS  | uppS         |
|                                 | Glucose-1-phosphate thymidylyltransferase                                  | rmlA                              | rmlA                                   | rmlA   | rmlA  | rmlA         |
|                                 | dTDP-glucose 4,6-dehydratase                                               | rmlB                              | rmlB                                   | rmlB   | -     | -            |
|                                 | UDP-N-acetyl-D-mannosaminuronic acid dehydrogenase                         | wecC                              | wecC                                   | -       | -     | wecC         |
| Intracellular survival factors  | Catalase katA                                                              | katA                              | katA                                   | katA   | katA  | katA         |
|                                 | ATP-dependent Clp protease proteolytic subunit                             | clpP                              | clpP                                   | clpP   | clpP  | clpP         |
|                                 | Elongation factor Tu                                                       | EF-Tu                             | EF-Tu                                   | EF-Tu   | EF-Tu  | EF-Tu         |
|                                 | Superoxide dismutase                                                       | sodB                              | sodB                                   | sodB   | sodB  | sodB         |
| Molecular chaperones            | CT396 molecular chaperone DnaK                                              | DnaK                              | DnaK                                   | DnaK   | DnaK  | DnaK         |
|                                 | 60k heat-shock protein HtpB                                                 | Hsp60                             | Hsp60                                  | Hsp60   | Hsp60  | Hsp60         |
| Urease                          | Urease                                                                     | ureA                              | ureA                                   | ureA   | ureA  | ureA         |
|                                 | Urease/hydrogenase-associated predicted GTPase                             | ureE                              | ureE                                   | ureE   | ureE  | ureE         |
|                                 | Acinetobactin ABC-type enterochelin transport system, ATPase component     | bauE                              | bauE                                   | bauE   | -     | bauE         |
| Streptococcal enolase           | Streptococcal enolase                                                      | eno                               | eno                                    | eno     | eno   | eno          |
| Pantothenate synthesis          | Aspartate 1-decarboxylase                                                   | panD                              | panD                                   | panD   | panD  | panD         |
| Heme biosynthesis               | Porphobilinogen synthase                                                   | hemB                              | hemB                                   | hemB   | hemB  | hemB         |
|                                 | glutamate-1-semialdehyde aminotransferase                                  | hemL                              | hemL                                   | hemL   | hemL  | hemL         |
| Acyl carrier protein            | Acyl carrier protein                                                       | acpXL                             | acpXL                                  | acpXL   | acpXL  | acpXL         |
| T4SS effectors                  | Trans-2-enoyl-CoA reductase (no unique name)                               | +                                 | +                                      | +       | +     | +            |

`not predicted; *, predicted; bold/italic, were discussed.`
essential role in LPS synthesis (Beereens, Soetaert, & Desmet, 2015; Fry et al., 2000) by catalyzing the interconversion of UDP-galactose and UDP-glucose (Fry et al., 2000), is a critical virulence factor in many gram-negative bacteria (Beereens et al., 2015; Fry et al., 2000). N-acetylgalcosamine-1-phosphotransferase/glucosamine-1-phosphate-acytetransferase (GlmU) is involved in the synthesis of peptidoglycan and LPS in Gram-negative and -positive bacteria (Sharma & Khan, 2017). The bifunctional enzyme UDP-N-acetylglucosamine 2-epimerase/MannNac kinase (encoded by wbjD/wecB, also known as siaA or neuC) catalyzes biosynthesis of Escherichia coli K1 capsule, an alpha-2,8-linked polymer of sialic acid, and is a vital meningitis virulence factor for this pathogen (Vann et al., 2004). Both mammals (Chou, Hinderlich, Reutter, & Tanner, 2003) and bacteria (Murkin, Chou, Wakarchuk, & Tanner, 2004) produce this bifunctional enzyme. Both source of this enzyme can catalyze the conversion of UDP-GlcNac into ManNac and UDP, the first two steps in the sialic acid biosynthesis in mammals (Chou et al., 2003) and the first step of sialic acid (N-acety neuraminic acid) biosynthesis in bacteria (Murkin et al., 2004). UDP-glucose 6-dehydrogenase (UGD) has an indispensable role in hyaluronic acid capsule production and pathogenicity in Group A Streptococcus (Cole et al., 2012), is required for bacterial growth inside macrophages (Mouslim & Groisman, 2003). Undecaprenyl diphosphate synthase (UPPS) is involved in cell wall biosynthesis (peptidoglycan and wall teichoic acid synthesis) by catalyzing the synthesis of a polysaccharoid, becoming an attractive antibacterial drug target (Farha et al., 2015). Glucose-1-phosphate thymidylyltransferase (RmlA) is vital for bacterial survival (Mansuri et al., 2016). It participates in L-rhamnose synthesis (Alphey et al., 2013; Mansuri et al., 2016), a critical linker of peptidoglycan and arabinogalacton in bacterial cell wall (Mansuri et al., 2016), by catalyzing the generation of dTDP-D-glucose and pyrophosphate (PPI) (Alphey et al., 2013; Mansuri et al., 2016). dTDP-D-glucose 4,6-dehydratase (RmlB) is also involved in L-rhamnose biosynthesis, by catalyzing the conversion of dTDP-D-glucose into dTDP-4-keto-6-deoxy-D-glucose in cell wall (Allard et al., 2002). Bacteria with truncated LPS molecules due to the L-rhamnose synthesis failure could not prevent clearance by the host cells and become avirulent (Allard et al., 2002). The presence of capsular LPS biosynthesis genes in six M. odoratimimus indicates their infectivity. The presence of these LPS biosynthesis genes in both the three clinically pathogenic and the three environmental M. odoratimimus isolates is in concert with the fact that M. odoratimimus is gram-negative and confer it this bacterium with in infectivity.

The presence of bacterial intracellular survival factors katA, clpP, EF-Tu, and sodB in the six M. odoratimimus genomes suggested that this bacterium might be able to survive within host cells, increase the antibiotic therapy difficulty and thus explain the reported high death rate of M. odoratimimus infections (summarized in Hu et al., 2016). Catalase katA is a critical virulence factor for Campylobacter jejuni, a facultatively intracellular microbe and the principal pathogen of human gastroenteritis. Its resistance ability to the bactericidal activity from host cell-produced hydrogen peroxide and intramacrophage persistence/growth is dependent on this catalase (Day, Sajecki, Pitts, & Joens, 2000). ClpP, a highly conserved protease in prokaryotes and eukaryotes, is involved in the rapid adaption capacity during infection for Listeria monocytogenes, another facultative intracellular pathogen (Gaill0t, Bregenholt, Jaubert, Di Santo, & Berche, 2001; Gaill0t, Pellegrini, Bregenholt, Nair, & Berche, 2000). By interacting with host surface nucleolin, the bacterial surface EF-Tu (elongation factor Tu), a GTP-binding protein involved in protein translation in Franciscella tularensis, a highly infectious intracellular gram-negative bacterium, plays a crucial role in its invasion to host tissues (Barel et al., 2008). It is also an adhesion/invasion factor secreted by microbes during infection by bacteria (like Helicobacter pylori) (Chiu, Wang, Tsai, Lei, & Liao, 2017) and fungi (Marcos et al., 2016) through binding (Mycobacterium avium subsp. paratuberculosis) with fibronectin on host cells (Viale et al., 2014). Superoxide dismutases (SODs) protect the bacteria from oxidative damage by converting endogenously generated superoxide radicals into hydrogen peroxide and oxygen, are indispensable for intraphagocytic viability for pathogenic bacteria (Dhar, Gupta, & Virdi, 2013), SodB is required for colonization of Helicobacter pylori in the stomach (Tsugawa et al., 2015).

The presence of bacterial DnaK (known as Hsp70 in eukaryotes) and Hsp60 in M. odoratimimus imply that the autoimmunological response might be complicated by the infection. Heat-shock proteins are ubiquitous proteins with high homology between eukaryotes and prokaryotes. Bacterial DnaK is crucial bacterial virulence factor. Both host Hsp70 and bacterial DnaK mediate bacterial attachment to host cells. After infection, bacterial DnaK switches on bacterial survival processes and arouses autoimmune sequelae (Ghazaei, 2017). Hsp60 is also involved in Clostridium difficile attachment to host cells (Hennequin et al., 2001), and the strong proinflammatory reaction (IL8) of monocytes cells induced by Helicobacter pylori (Lin et al., 2005). Chlamydia pneumonia Hsp60 can help to spread Chlamydial infection of blood monocytes to vascular wall cells (Rupp et al., 2005), and increase the pathogenesis and severity of Chlamydia infection-correlated atherosclerosis because of sequence homology between bacterial and human Hsp60 (mitochondria in endothelial cells) and subsequent induction of a strong autologous humoral and cellular immune responses (Kalayoglu et al., 2000; Mehta et al., 2005).

The presence of ureA, ureB, ureG in M. odoratimimus implies that this bacterium might be pathogenic in human stomach. Urease is a principal virulence factor of human gastric bacterium Helicobacter pylori (Stingl et al., 2008). It has oligomeric Ni2+-containing heterodimer of UreA and UreB subunits involved in converting gastric juice urea into NH3 in bacterial periplasm which maintains an optimal pH, inner membrane potential and proton motive force, being critical for colonization within the human stomach (Sachs, Weeks, Melchers, & Scott, 2003). Urease activity needs an assembly of a lysine-carbamate functional group with two Ni2+ ions facilitated partially by GTP hydrolysis by UreG (Martin-Diaconescu, Bellucci, Musiani, Ciurli, & Maroney, 2012; Zambelli, Turano, Musiani, Neyroz, & Ciurli, 2009).

The surface enolase (eno) of bacteria, a glycolytic pathway enzyme, can bind human plasminogen and convert it into active
plasmin (Cork et al., 2009) to facilitate bacterial adherence to host cells and destruction of host tissues through plasmin degrading intercellular junctions and extracellular matrix components (Attali, Durmort, Vernet, & Di Guilmi, 2008), like cellulitis (Bachmeyer et al., 2008), necrotizing fasciitis (Crumb-Cianflone, Matson, & Ballon-Landa, 2014), and make the bacterial infection life-threatening (Cork et al., 2009). The containing eno in M. odoratimimus genome might explain the high death rate of patients infected by M. odoratimimus (as summarized in Hu et al., 2016).

In brief, M. odoratimimus not only possesses common virulence factors, like using bauE gene to compete the iron with host, general LPS synthesis genes, adherence factors (DnaK, Hsp60), but also can survive intracellularly (katA, clpP, EF-Tu, and sodB), even in human stomach (ureA, ureB, ureG), but also disseminate easily, destroy human tissues, induce autoimmune diseases. So, the M. odoratimimus is a life-threatening pathogen as reported (summarized in Hu et al., 2016).

5 | CONCLUSION

The genomic analysis demonstrated that these M. odoratimimus isolates are closely related. Our analyses provided some insights in bacterial pathogenicity and antibiotic resistance mechanisms of M. odoratimimus and contribute to future development of the therapeutics in M. odoratimimus infections.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors.

CONFLICT OF INTEREST

None declared.

ORCID

Mingxi Wang https://orcid.org/0000-0002-8093-0384

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information section at the end of the article.