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Analysis of Acquired Antimicrobial Resistance Genes in Genomes of Iraqi *Acinetobacter baumannii*

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ABSTRACT

Objective: *This study aimed to investigate and analyze antimicrobial-resistant (AMR) genes in Acinetobacter baumannii isolates from Iraq, identify the frequency and proportions of resistant genes, and determine strains resistant to multiple antibiotics, including their genetic profiles based on protein-coded gene sequences.* ***Methods:*** *A total of 41 A. baumannii draft genome sequences were retrieved from the PATRIC database, spanning 2004–2018, and analyzed using ResFinder 4.0 for antibiotic resistance genes. Molecular typing was conducted via the Pasture MLST scheme targeting seven housekeeping genes (e.g., cpn60, fusA). Data were processed through the Center for Genomic Epidemiology for detailed resistance profiling.* ***Results:*** *Fifty-two known resistance genes were identified in 41 genomes. Most strains demonstrated multidrug resistance (MDR), while one strain exhibited extensive drug resistance (XDR). These findings underscore the concerning emergence of highly resistant A. baumannii strains in Iraq.* ***Novelty:*** *The study validates ResFinder 4.0 as an effective in silico tool for genetic analysis of AMR genes in A. baumannii, providing a comprehensive genomic epidemiological profile of Iraqi isolates. This is among the first studies to offer such detailed insights into the genetic resistance mechanisms of A. baumannii in Iraq.*

INTRODUCTION

One of the major global threats of the present century is the high levels of antimicrobial resistance. According to [1], it is predicted that 300 million premature deaths due to infections from resistant bacterial strains will occur by 2050.The Centers for Disease Control and Prevention (CDC) reported that antibiotic-resistant infections account for 2 million diseases and 23000 deaths annually in the United States, more than 20 billion dollars are spent on direct health care costs and 35 billion dollars are lost in productivity [2]. Bacterial strains can either be resistant to a certain antibiotic through natural means or by acquiring resistance genes [3].

The problem is further complicated by the lack of new and effective antibiotics in development against multi-drug resistant pathogens and with excessive use of antibiotics [4], [5], [6]. led to increased resistance to antibiotics for bacterial pathogens worldwide that are considered a public health risk while leaving the doctor with no increasingly therapeutic option [7]. One of the pathogens responsible for community-acquired infections in ESKAPE is Acinetobacter baumannii, a gram-negative, immovable, non-fermented, and non-porous bacteria of the Moraxellaceae family [8]. *A. baumannii* is equipped with multiple antibiotic resistance mechanisms to thrive in a variety of environments. Even in dehydrated environmental conditions, the ability to form biofilms is closely linked to survival Although Acinetobacter spp. causes pneumonia in the first place; They are also frequent causes of wound infections, burns, meningitis, urinary tract infections and sepsis [9].

In the early 1970s, it was assumed that A.baumannii isolates are sensitive and could be killed by most available antibiotics, such as ampicillin, gentamicin, carbenicillin and nalidixic acid [5]. The ESKAPE MDR now considers A.baumannii to be a part of the most problematic nosocomial pathogen. And reported to be resistant to wide range of antibiotic classes include beta_lactams, aminoglycosides, quinolines, tetracycline, polymyxin [10].

In 2017, the WHO introduced their initial list of antibiotic resistant 'priority pathogens', which comprises 12 bacterial genera that pose significant threats to public health. *A. baumannii* has been occupied at the top of the bacterial threat list and was classified as a 'critical pathogen' due to the increase in carbapenem-resistant isolates [11]. Globally, the Baumannia pathogen has become one of the most serious health concerns.

A therapeutic alternative is urgently needed for what has been designated as a top priority and critical agent [12]. The understanding of *A. baumannii* bacteria remains incomplete, with their virulence and non-antibiotic-associated resistance still requiring better characterization. Whole genome sequencing (WGS) is a tool that allows for a better understanding of the dynamics and genomic evolution of bacterial pathogens during infection [10]. Investigate the genetic similarity between strains isolated from the ward environment and inpatients in the hospital [13].

Antibiotic Resistance Mechanisms in *A. baumannii*

A. baumannii has developed a variety of mechanisms for resistance to the antibiotics that are most commonly used. This pathogen has the ability to acquire mobile genetic elements, such as AbaR1 resistance island-element. which contains a cluster of genes coding for more than 45 resistance genes, including those coding for Β-lactams, aminoglycoside-modifying enzymes, and efflux pumps [14].

The most known mechanism of resistance found in *A. baumannii* to the β-lactam class of antibiotics is the presence of β-lactamases. β-lactamases resistance was recorded in Gram negative local enteric bacteria isolates [15]. β-Lactam antibiotics act as bactericidal agents that interrupt the peptidoglycan synthesis covalently and irreversibly binding to penicillin-binding proteins (PBPs), an enzyme contributing to the formation of the bacterial cell wall, thus resulting in lysis of bacterial cells and death [16]. The β-lactamases are enzymes that have been categorized into four molecular A, B, C and D classes. The four β-lactamase classes have been found in *A. baumannii* [17].

Colistin antibiotic causes bacteria to die by penetrating the inner membrane and separating the lipid A bilayers of the lipopolysaccharides (LPS) away from each other, leading to the dysfunction and defects of bacterial outer membrane proteins and outer membrane breakdown [18]. Colistin is one of the options for alternative combinations therapies for treating *A. baumannii* pathogens, particularly MDR and XDR *A. baumannii* infections, according to [19].

In recent studies, it has been reported that Colistin resistance has emerged in *A. baumannii* isolates worldwide [20], [21], with Iraq being one of them [22]. The resistance to Colistin antibiotic in *A. baumannii* can be attributed to the loss of LPS through the inactivation of lipid A biosynthesis chromosomal genes (lpxA, lpxC, or lpxD), thus preventing the interactions of Colistin with its binding target sites on the LPS [23]. Another mechanism of resistance is the decrease in the transcription of the mgrB gene, which results in modifications in the structure of LPS [24].

Aim of study is investigation and analysis of acquired antimicrobial-resistant genes in Iraq's *Acinetobacter baumannii* isolates, Know the proportions and frequency of resistant genes in this bacteria and know the strains resistant to more than one type of genetically antibiotic and know the antibiotic resistant varieties, Mechanical and epidemiological knowledge of genes resistant to these bacteria by taking advantage of their complete genetic relay and Knowledge of the genetic profiling of Iraqi isolates through knowledge of the sequences of protein-coded genes.

RESEARCH METHOD

The Draft Genome Sequences of *A. baumannii*

A total of 36 draft whole genome sequenced strains belonging to *A. baumannii* originally isolated from clinical sources from that obtained from the PATRIC database [25] as of January, 2024 were included in this study. The sequences were downloaded and saved in a fasta-type file for further analysis.

Antibiotic Resistance Genes and Resistance Phenotypes Prediction

The new platform of ResFinder 4.0 tool [26] was used to detect the antibiotic resistance genes in the draft genome sequences. The ResFinder 4.0 contains a database that translate of sequence genotypes into resistance phenotypes which displays the results in created tables. As default all the antimicrobial databases is selected with threshold for 98% identity and a minimum hit length of 80% for the best matching resistance antimicrobial genes in the ResFinder 4.0 databse and the input *A. baumannii* genome sequences.

Table 1. Resistance Genes Detected in the 41 Whole Genome Sequences Of *A. baumannii* Strain by Resfinder.

Resistance gene	Accession NO.	Frequency N=41	Percentage 100%	Predicted phenotype
		Aminoglycoside		
aph(3'')-Ib	AF321551	10	24.3%	streptomycin
aph(6)-Id	M28829	20	48.7%	streptomycin
aadA1	JX185132	15	36.5%	spectinomycin,streptomycin
aac(3)-Ia	X15852	14	34.1%	gentamicin,astromicin,fortimicin
ant(2'')-Ia	AY139599	9	21.9%	gentamicin,tobramycin
aph(3')-VIa	X07753	15	36.5%	kanamycin,neomycin,paromomycin,ribostamycin, butirosin,gentamicin,amikacin
aph(3')-Ia	X62115	13	31.7%	neomycin,kanamycin,lividomycin,paromomycin ,ribostamycin
aadA24	DQ677333	1	2.4%	spectinomycin,streptomycin
aph(3')-VIb	AJ627643	1	2.4%	kanamycin,neomycin,paromomycin ,ribostamycin,butirosin,gentamicin,amikacin
aac(6')-Ib-cr	EF636461	3	7.3%	ciprofloxacin
armA	AY220558	4	9.7%	amikacin,gentamicin,tobramycin,isepamicin, netilmicin
aac(6')-Ib3	X60321	3	7.3%	amikacin,tobramycin
aadA2b	D43625	1	2.4%	spectinomycin,streptomycin
		Folate pathway antagonist		
sul1	DQ143913	20	48.7%	sulfamethoxazole
sul2	AY034138	16	39%	sulfamethoxazole
dfrA1	X00926	11	26.8%	trimethoprim
dfrA7	AB161450	1	2.4%	trimethoprim
		Aminocyclitol		
aadA1	JQ414041	15	36.5%	spectinomycin,streptomycin
aadA24	DQ677333	1	2.4%	spectinomycin,streptomycin
aadA2b	D43625	1	2.4%	spectinomycin,streptomycin
		Tetracycline		
tet(B)	AJ277653	15	36.5%	doxycycline,tetracycline,minocycline
tet(39)	KT346360	4	9.7%	doxycycline,tetracycline
tet(A)	AY196695	2	4.8%	doxycycline,tetracycline
		Beta-lactam		
blaADC-25	EF016355	32	78%	unknown beta-lactam
blaTEM-1D	AF188200	4	9.7%	amoxicillin,ampicillin,cephalothin,piperacillin,ticarcillin
blaOXA66	AF188200	6	14.6%	unknown beta-lactam
blaOXA-23	AY795964	19	46.3%	imipenem,meropenem
blaOXA-144	FJ872530	2	4.8%	unknown beta-lactam

blaOXA-124	EU255293	1	2.4%	unknown beta-lactam
blaOXA-528	KX599407	1	2.4%	unknown beta-lactam
blaOXA-71	AY750913	2	4.8%	unknown beta-lactam
blaOXA-64	AY750907	1	2.4%	unknown beta-lactam
blaOXA-69	AY859527	13	31.7%	amoxicillin,ampicillin
blaPER-1	GU944725	1	2.4%	moxicillin,amoxicillin+clavulanic acid,ampicillin,ampicillin+clavulanic acid,cefotaxime,cefoxitin,cefepime,ceftazidime,piperacillin,piperacillin+tazobactam,ticarcillin,ticarcillin+clavulanic acid,aztreonam
blaOXA-90	EU547443	11	2.4%	unknown beta-lactam
blaOXA-78	AY862132	39	2.4%	unknown beta-lactam
blaCARB-2	M69058	30	2.4%	ampicillin,amoxicillin,piperacillin
blaPER-7	HQ713678	30		amoxicillin,amoxicillin+clavulanic acid,ampicillin,ampicillin+clavulanic acid,cefotaxime,cefoxitin,cefepime,ceftazidime,piperacillin,piperacillin+tazobactam,ticarcillin,ticarcillin+clavulanic acid,aztreonam
blaOXA-144	FJ872530	1	2.4%	unknown beta-lactam
blaOXA-317	KF057034	1	2.4%	unknown beta-lactam
blaOXA-508	KU596972	1	2.4%	unknown beta-lactam
blaOXA-260	APOR01000009	1	2.4%	unknown beta-lactam
blaGES-11	FJ854362	1	2.4%	amoxicillin,amoxicillin+clavulanic acid, ampicillin,ampicillin+clavulanic acid,cefoxitin, ceftazidime,piperacillin,ticarcillin
blaOXA-500	JMNQ01000002	1	2.4%	unknown beta-lactam
blaOXA-323	KF203097	1	2.4%	unknown beta-lactam
Streptogramin b				
msr(E)	FR751518	8	19.5%	erythromycin,azithromycin,quinupristin,pristinamycin ia,virginiamycin s
Amphenicol				
catB8	AF227506	2	4.8%	chloramphenicol
cmlA1	AB212941	1	2.4%	chloramphenicol
Macrolide				
mph(E)	DQ839391	8	19.5%	erythromycin
msr(E)	FR751518	8	19.5%	erythromycin,azithromycin,quinupristin,pristinamycin ia,virginiamycin s
Quinolone				
aac(6')-Ib-cr	EF636461	2	4.8%	ciprofloxacin
Quaternary ammonium compound				

qacE	X68232	21	51.2%	benzylkonium chloride,ethidium bromide,chlorhexidine,cetylpyridinium chloride

In this table describe 45 type of antimicrobial resistance gene and accession number of them and detect frequency and percentage in 41 whole genome sequence of A.baumannii and predicted phenotype of antibiotics

Sequence Type of *A. baumannii* Sequenced Genomes

Molecular typing of *A. baumannii* from the draft genome sequences was carried out using the Pasture multilocus sequence typing (MLST) scheme (*cpn60*, *fusA*, *gltA*, *pyrG*, *recA, rplB* and *rpoB*) [27]. The sequenced genomes in a fasta format were uploaded to the public databases MLST (PubMLST) which contains 3356 allele sequences [28]. According to PubMLST If an exact match of any locus is not found, the closest partial matches is identified.

RESULTS AND DISCUSSION

Result

Draft genome analysis of all *A. baumannii* strains isolated between 2004 and 2018 from different samples in Iraq was conducted through the Center for Genomic Epidemiology and the Bacterial and Viral Bioinformatics Resource Center (BV-BRC) programs. After the download draft genome for 41 *A.baumannii* strains in iraq bacterial and viral bioinformatics resource center programme from 2004_2018 year then all of one in center for genomic epidemiology to analyze sequencing data to give information to antibiotics resistance

A.baumannii isolates exhibited remarkable resistance pattern to various antimicrobial classes including B-lactam 80.4% (n=33), aminoglycoside 73.1% (n=30), folate pathway antagonist 60.9%(n=25), and tetracycline, quaternary ammonium compound were 51.2% (n=21).The isolate tested displayed intermediate resistance to aminocyclitole 41.4% (n=17), streptogramin b, macrolide were 19.5%(n=8), amphenicol 7.3% (n=3), quinoline 4.8% (n=2).

Table 2. Class of Antibiotics and Percentage *A.baummannii* Strain Resist to Each Class.

Class of antibiotic	Percentage%
Aminoglycoside	73.1%
Folate pathway antagonist	60.9%
Aminocyclitol	41.4%
Tetracycline	51.2%
Beta-lactam	80.4%
Streptogramin b	19.5%
Amphenicol	7.3%
Macrolide	19.5%
Quinolone	4.8%
Quaternary ammonium compound	51.2%

These pathogens are classified as multi-drug resistant bacteria because they show resistance to antibiotics such as fluoroquinolones, aminoglycosides, vancomycin, methicillin, and B-lactamases [29]. Numerous MDR, XDR, and PDR strains were found in the Acinetobacter baumannii whole genome sequences of the isolated Iraqi patient.

This strain resist of amonge class of antibiotic such B- lactums, aminoglycoside, tetracycline. the antimicrobial susceptibility result ten antimicrobial drug indicate that fifteen strains including CI77, MRSN1309, MRSN1990, MRSN11846, MRSN32954, MRSN32941, MRSN32942, MRSN32943, MRSN32927, MRSN32959, MRSN32956, ZQ1, ZQ2, ZQ7 were resistant to six out of ten tested antibiotics including B- lactum, tetracycline aminocyctiole, folate aminoglycoside, quaternary. so they were designated MDR ; while ZQ1 high resist that resist to nine antimicrobe from ten antibiotic that consider XDR ; While appear one strain (ZQ7) high resist to all microbe that consider PDR ; compare to less antimicrobial resistance such IS-123, CI86 strain resist quinolone, aminoglycoside, tetracycline, B- lactum which sensitive aminocyclitol, macrolide, Amphenicol, Streptogramin b.

Disscusion

The most commonly encountered pathogens in human infections are *A.baumannii*, which is known to be a significant repository of MDR genes [30]. Because contain many virulance factor including porine, enzymes, capsules, cellwall, lipopolysaccaride, biofilm production,motility, iron aquisition mechansim[31]. The majority of studies concerning A.baumannii focus on phenotypic, genotypic, and epidemiological characterization [32]. Genotyping techniques such as PCR-based oligotyping are generally limited to identifying a single or multiple genetic determinants associated with resistance or virulance [33]. NGS provides an extraordinary insight into the genomic organization of pathogens that cause outbreaks and detects antimicrobial resistance genes in multiple bacterial genomes.

This study analysize 41 of *A.baumannii* strains submitted to the NCBI from different hospital across the Iraq (B) these strain were appear resistant to more than one antimicrobial agent that detected using the Resfinder tool they include : aminoglycoside, folate, aminocyclitol, tetracycline, B_lactum, quinolone, streptogramine B, macrolide, amphenicole.

Analysing the core genome of the 41 *A. baumannii* indicate R total 54 types of antimicrobial resistance genes (ARGs) providing resistance to type antibiotic were identified by Insilico Method. Aminogiycoside resistance was associated with various genes that encoding aminoglycoside –modifying enzyme and 16SrRNA methylase that contribute to resistance to many type aminoglycoside (streptomycin, gentamicin, ciprofloxacin, amikacin) that resistance associated sequence type 412, 3, 25, 2, 1, 1090, 513, 414, 136, 575, 717.

Our study revealed that Acinetobacter spp. Have a diverse range of OXA- type β-lactamases,particularly *A. baumannii*, which suggests that *A. baumannii* may be the main host of blaOXA genes. The majorty of the OXA-type β-lactamase found in our study were carbapenem-hydrolyzing-β-lactamase was a major reason for of Acinetobacter spp, to resist carbapenem in different degrees [34], [35].

Within the large diversity of OXA-type carbapenemase genes identified by the ResFinder tool, the genes for blaOXA-66 and blaOXA-23 types were the most predominant. According to studies [36], [37], [38], *A. baumannii* strains carrying one or both of these genes are resistant to all β-lactam antibiotics, including carbapenems. Furthermore, there are serious concerns regarding the limited number of antimicrobial treatment options available due to the emergence of multidrug-resistant *A. baumannii* strains that are resistant to carbapenems globally [39], [40].

Moreover, upstream sequences of ISAba1 or ISAba4 that boost the expression of the blaOXA-66 and blaOXA-23 genes have been linked to them [41]. Additional resistance genes linked to isolates resistant to cephalosporins, such as blaTEM, blaPER, and blaVEB, which encode extendedspectrum β-lactamases (ESBLs) [38].

Within the wide diversity of OXA- type genes found by the resfinder tool, the genes for blaOXA-87, blaOXA-23, blaOXA-69 of 95.1%,46.3%, 31.7% in respectively, types were the most predominant studies have demonstrated that *A. baumannii* strains harbouring one or both of the these genes are resistant to most b-lactam antibiotic. Resistance to sulphonamide is conferred by (sul1, sul2) in 48% and 39% of the strains, respectively; additionally, 36% of the strains exhibit tetB gene resistance to tetracycline. These outcomes concur with previous research [38], [42], [43], [44], [45] this author disagree with it, less than 36% oppose ((aac(6')-Ib-cr) Quinolone, (mph(E),msr(E)) Macrolide, (catB8, cmlA1) Amphenicol). which suggest that *A. baumannii* possesses a diverse range of genes that contribute to resistance against a broad spectrum of antimicrobial agents. Amphenicol resistance is conferred by the presence of catB8 and CmlA1 in (4.8%) and 2.4% of cases, respectively.

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CONCLUSION

Fundamental Finding : This study demonstrates that the RestFinder bioinformatics tool is an effective in silico genetic analysis tool for identifying acquired antimicrobial resistance (AMR) genes in the genomes of *Acinetobacter baumannii*, with fifty-two resistance genes identified across forty-one complete WGS from Iraqi strains. **Implication :** The findings highlight the worrying emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *A. baumannii* strains, emphasizing the need for heightened surveillance and targeted therapeutic strategies to combat these resistance patterns. **Limitation :** Despite its accuracy, this study was limited to the genetic analysis of a specific population of *A. baumannii* and focused primarily on complete genomes, which may not fully represent the genetic diversity of strains in broader regions. **Future Research :** Further studies should expand the geographical scope, explore resistance mechanisms in partial genomes, and investigate the functional impact of dominant sequence types, such as ST unknown and ST 1090, on clinical outcomes and epidemiological trends.

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