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Original Article

Study of Some Resistance Genes in Clinical *Proteus mirabilis*

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Abstract

Proteus mirabilis belongs to the family Enterobacteriaceae and is capable of transforming in shape from rod to elongated and swarming motility by flagella. It is an opportunity for bacteria and can cause different clinical diseases. Therefore, this study aimed to assay and detect a sequence of genes that encode for antibiotic resistance in multidrug resistance clinical isolates of *Proteus mirabilis*, including *blaTEM, aac(6')-Ib*, qnrA, *IntI2, IntI1* and secondly to investigate the relationship in the phylogenetic tree among these genes in Iraq comparison with global strains in NCBI. The study included the identifying of 500 clinical samples depending on morphological and biochemical tests and confirming *Proteus mirabilis* diagnosis by the VITEK-2 Compact system. The confirmed isolates of *Proteus mirabilis* were 95 clinical isolates (19%). Antibiotic susceptibility test of all these isolates was done using twelve antibiotics tested using Amoxicillin, Aztreonam, Imipenem, Cefoxitin, Amikacin, Ceftazidem, Ciprofloxacin, Nalidixic acid, Gentamicin, Sulphamethazol-trimethoprim, Cefotaxime, Amoxicillin-clavulanic acid. The results showed that multidrug resistance *Proteus mirabilis* isolates contained the genes in different levels as follow *blaTEM* gene (90%), *aac(6')-Ib* gene (80%) ,*IntI1* gene (100%), *IntI2* gene (80%). These genes were sequenced and detected phylogenetic relationships among these genes and global genes were documented in NCBI. The results showed that some Iraqi isolates contain genetic variation compared to global strains. Therefore, this variation was detected and registered in NCBI of all five antibiotic resistance genes mentioned above and accepted under accession numbers of *aacIb* gene (LC613168.1), *blaTEM* gene (LC613166.1), *IntI1* gene (LC613169.1), *IntI2 gene* (LC613170.1).

Keywords: Multidrug *Proteus mirabilis*, Antibiotic resistance genes, Integrons, Iraqi clinical samples, NCBI

1. Introduction

Proteus mirabilis belongs to the family *Enterobacteriacea*e and is capable of transforming in shape from rod to elongated and swarming motility by flagella. It is an opportunity bacteria and can cause different clinical diseases, including urinary tract infection, wound infection, meningitis in infants, rheumatoid, endocarditis, septicemia, and cystic fibrosis. This broad infection caused by *Proteus mirabilis* is produced due to the fact that it contains many virulence factors, including adhesion, toxins, flagella, enzyme production like urase, biofilm and highly resistant phenotype to antibiotics. The regulation of these virulence factor gene expressions is coordinated by signals in a phenomenon called quorum sensing (1-3).

In urinary tract infections, biofilm production leads to long-period infection (4-6).

The Proteus mirabilis genome contains different genes that encode proteins responsible for antibiotic resistance and develop multidrug and extensive resistance strains (7). These genes may be mobile genes located on chromosomes or plasmids called integrons (*IntI1*, *IntI2*) as well as other genes as included in this

study that leads to transfer antibiotic resistance horizontally among strains of these bacteria and able *Proteus mirabilis* to resist different groups of antibiotic (beta-lactam, quinolones, chloramphenicol, trimethoprim, aminoglycoside, rifampicin) in nosocomial infection that attract the attention of world health organization and put this multidrug resistance pathogen in a group of microorganisms that medically significant nosocomial and community-acquired pathogen (8, 9). So, this study was carried out to assay and detect a sequence of genes that encode for antibiotic resistance included (*blaTEM*, *aac(6')-Ib*, *IntI2*, *IntI1*), which considers resistance genes and include a mobile genetic element in multidrug resistance *P. mirabilis* in clinical samples and study of the relationship in the phylogenetic tree among these genes that responsible for the resistance of antibiotics.

2. Materials and Methods

2.1. Isolation and Identification of *Proteus mirabilis*

The study collected 500 clinical infections from urine, wound, burn and otitis. All these samples were distributed among six governorates in Iraq, including Baghdad, Babylon, Al-Anbar, Al- Muthanna, Wasit, and Diyala, from October 2020 to January 2021. Identification of these samples depended on morphological and biochemical tests through appearance swarming, non-lactose fermentation on selective and differentialMacConkey and enriched condition on blood agar to another step that included confirmation of *Proteus mirabilis* diagnosis by VITEK-2 Compact system (Biomerieuxm France). The confirmed isolates of *Proteus mirabilis* were 95 clinical isolates.

2.2. Antibiotic Susceptibility Test

All *Proteus mirabilis* isolates were tested by using"Amoxicillin 10µg/ml, Aztreonam 30µg/ml, Imipenem 10µg/ml, Cefoxitin 30µg/ml, Amikacin30µg/ml, Ceftazidem 30µg/ml, Ciprofloxacin 5µg/ml, Nalidixic acid 30µg/ml, Gentamicin 10µg/ml, Sulphamethazol-trimethoprim 25µg/ml, Cefotaxim 30µg/ml, Amoxicillin-clavulanic acid 20/10 µg/ml". Then isolates were considered resistant or sensitive depending on the previously published regulation (10).

2.3. Molecular Study of Target Genes

2.3.1. Multidrug Resistance *Proteus mirabilis*

Ten more resistant isolates of *Proteus mirabilis* PM1, PM2, PM3, PM4, PM5, PM6, PM7, PM8, PM9, and PM10 were selected and used for genomic DNA extraction according to manufacturer protocol (Geneaid Extraction Promega, USA). The extracted DNA was concentrated at 27 ng/µl.

2.3.2. Primers Used in This Study

Specific primers for the detection of genes responsible for the resistance of antibiotics, as shown below in table 1, were used.

2.4. Sequencing of Resistance Genes

PCR products of resistance genes (*aacIb*, *qnrA*, *blaTEM*, *IntI1*, *IntI2*) were electrophoresis on gel against 100 bp marker of DNA ladder. Then, nucleotide sequencing of these genes and selecting some important sequences of genes are registered in NCBI.

Table 1. Primers used in amplification target genes in this study

Primer Name	Seq.	Annealing Temp. (˚C)	Product Size (bp)
aacIb-F aacIb-R	5`-TTGCGATGCTCTATGAGTGGCTA-3` 5`-CTCGAATGCCTGGCGTGTTT-3	54	482 (11)
blaTEM-F blaTEM-R	5`-TACGATACGGGAGGGCTTAC-3 5`-TTCCTGTTTTTGCTCACCCA-3	52	716 (12)
IntI1-F IntI1-R	5`-CAGTGGACATAAGCCTGTTC-3 5`-CCCGAGGCATAGACTGTA-3	59	160 (13)
IntI2-F IntI2-R	5`-CACGCATATGCGACAAAAAGGT-3 5`-GTAGCAAACGAGTGACGAAATG-3	55	788 (13)

3. Results

3.1. Identification of *Proteus mirabilis* in Clinical Samples

Standard methods and biochemical tests tested all 500 clinical samples, and then identification was confirmed by VITEK-2 Compact System. The results showed that 95 isolates (19%) belong to *Proteus mirabilis* from different regions in Iraq (Table 2).

3.2. Antibiotic Resistance Pattern

Ninety-five *Proteus mirabilis* isolates were examined to detect multidrug and extensive drug-resistant against twelve antibiotics, including amoxicillin, Aztreonam, Imipenem, Cefoxitin, Amikacin, Ceftazidem, Ciprofloxacin, Nalidixic acid, Gentamicin, Sulphamethazol-trimethoprim, Cefotaxim, and Amoxicillin-clavulanic acid. The results of antibiotics resistance exhibited the ability of *Proteus mirabilis* to resist antibiotics at different levels, as shown in table 3, then 10 more resistant isolates were selected (Table 4) for molecular study. The results of the antibiotic resistance pattern are shown in table 3.

Table 2. Percentage of infection with *P. mirabilis*

Type of Clinical Sample	Number of isolates	Percentage
Infection of burn	21	22.1%
ear swabs	22	23.25%
Midstream urine	52	54.7%
Total	95	100%

Table 3. Pattern of resistance *Proteus mirabilis* against antibiotics

Antimicrobial Agent	*Proteus mirabilis* (95 isolates)			
	Resistance		Sensitive	
	NO.	%	NO.	%
Amoxicillin (AMX) 10µg/ml	47	49.47%	48	50.5%
Aztreonam (ATM) 30µg/ml	6	6.3%	89	93.68)
Imipenem (IPM) 10µg/ml	0	0%	95	100%
Cefoxitin (FOX) 30µg/ml	17	17.89%	78	82.1%
Amikacin (AK)30µg/ml	10	10.5%	85	89.47%
Ceftazidem (CAZ) 30µg/ml	29	30.5%	66	69.47%
Ciprofloxain (CIP) 5µg/ml	8	8.4%	87	91.57%
Nalidixic acid(NA) 30µg/ml	42	44.2%	52	54.73%
Gentamicin (CN) 10µg/ml	24	25.26%	71	74.73%
Sulphamethazol-trimethoprim (SXT) 25µg/ml	64	67.36%	31	32.63%
Cefotaxim (CTX) 30µg/ml	42	44.2%	53	55.78%
Amoxicillin-clavulanic acid (AUG) 20/10 µg/ml	45	47.36	50	52.63

Table 4. Multidrug resistance *Proteus mirabilis* clinical isolates

No. of isolate	Antimicrobial Agent											
	AMX 10µg/ml	ATM 30µg/ml	IPM 10µg/ml	FOX 30µg/ml	AK 30µg/ml	CAZ 30µg/ml	CIP 5µg/ml	NA 30µg/ml	CN 10µg/ml	SXT 25µg/ml	CTX 30µg/ml	AUG 20/10 µg/ml
PM 1	R	R	S	R	S	R	S	R	R	R	R	R
PM 2	R	R	S	R	R	R	R	R	S	R	R	R
PM 3	R	S	S	S	S	R	S	R	R	R	R	R
PM 4	R	R	S	R	R	R	R	R	R	R	R	R
PM 5	R	S	S	S	S	R	R	R	S	R	R	R
PM 6	R	R	S	R	S	R	S	R	R	R	R	R
PM 7	R	S	S	R	R	R	S	R	R	R	R	R
PM 8	R	R	S	R	R	R	R	R	S	S	R	R
PM 9	R	S	S	S	S	R	R	R	R	R	R	R
PM 10	R	S	S	S	S	R	R	R	S	R	R	R

R = resistant S = Sensitive

3.3. DNA Extraction from Multidrug Resistance *Proteus mirabilis*

The 10 multidrug-resistant isolates of *Proteus mirabilis* tabulated in table 4 were used for more molecular investigation. The results showed all ten multidrug resistance *Proteus mirabilis* contain these genes in different levels *blaTEM* gene (90%), *aac(6')-Ib* gene (80%), *IntI1* gene (100%), *IntI2* gene (80%) as shown in figures (1, 2, 3 and 4).

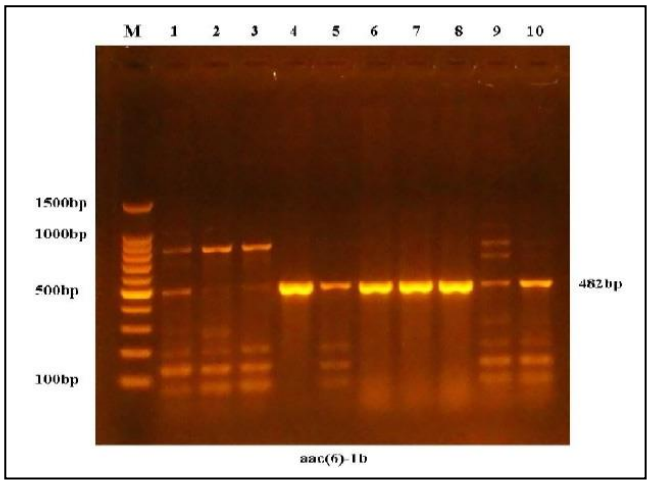

Figure 1. *aac(6)-lb* (482bp) resistant *P. mirabilis* comparison with stander marker (1500 bp)

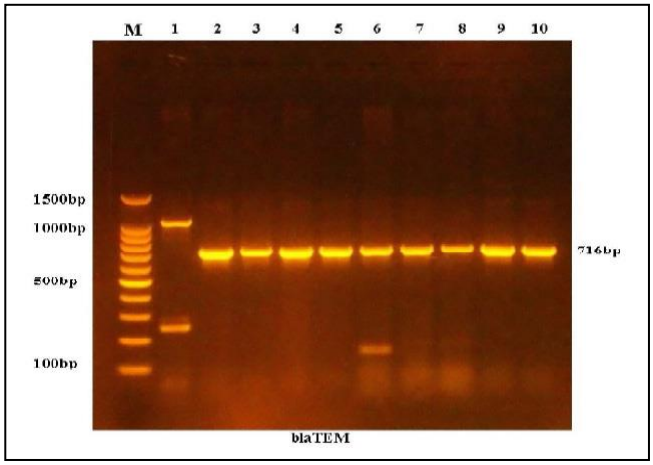

Figure 2. *blaTEM* (716 bp) in *resistant P. mirabilis* comparison with stander marker (1500 bp)

3.4. Sequence of MDR *P. mirabilis* genes

The sequencing of multidrug resistance *Proteus mirabilis* (32 isolates) containing genes including*aacIb, blaTEM, IntI1, and IntI2* were sent for Sanger sequencing to Macrogen Corporation – Korea. Geneious software analyzed the results to detect a mismatch with *P. mirabilis* in NCBI, as shown in figures 5, 6, 7 and 8.

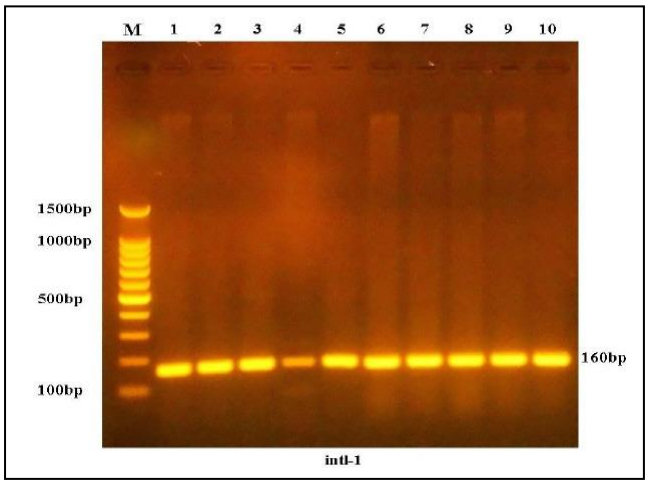

Figure 3. *IntI-1*(160 bp) in *resistant P. mirabilis* comparison with stander marker (1500 bp)

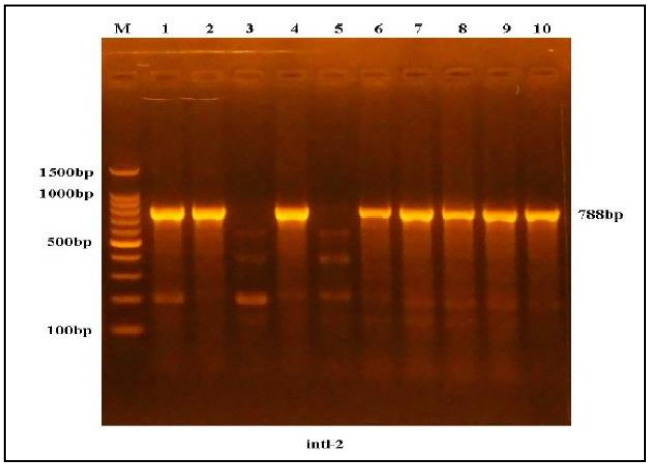

Figure 4. *IntI-2 (*788bp) in *resistant P. mirabilis* comparison with stander marker (1500 bp)

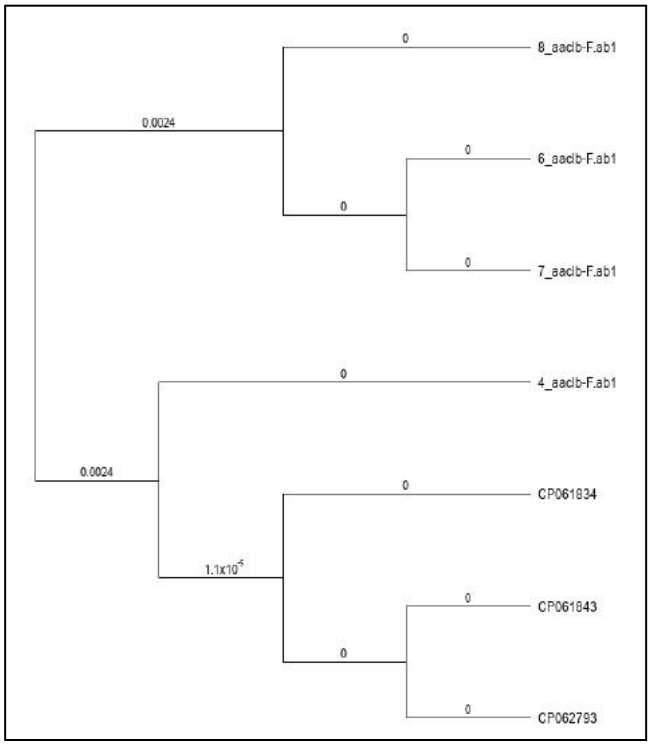

Figure 5. Dendrogram of sequence *aacIb in P. mirabilis* (4, 6, 7, 8) comparison with world *Proteus mirabilis* in NCBI (CP061834, CP061843, CP062793)

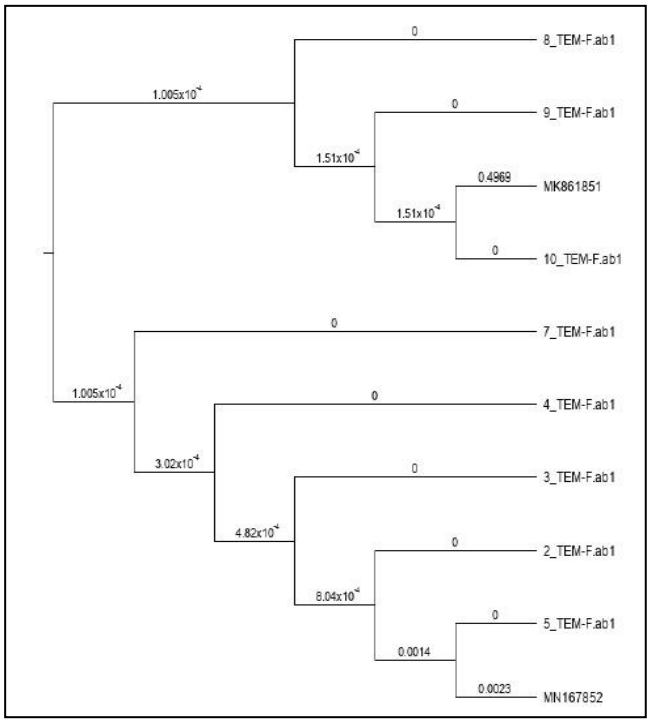

Figure 6. Dendrogram of sequence *TE M*in *P. mirabilis* (2, 3, 4, 5, 7, 8, 9, 10) comparison with world *Proteus mirabilis* in NCBI (MK861851, MN167852)

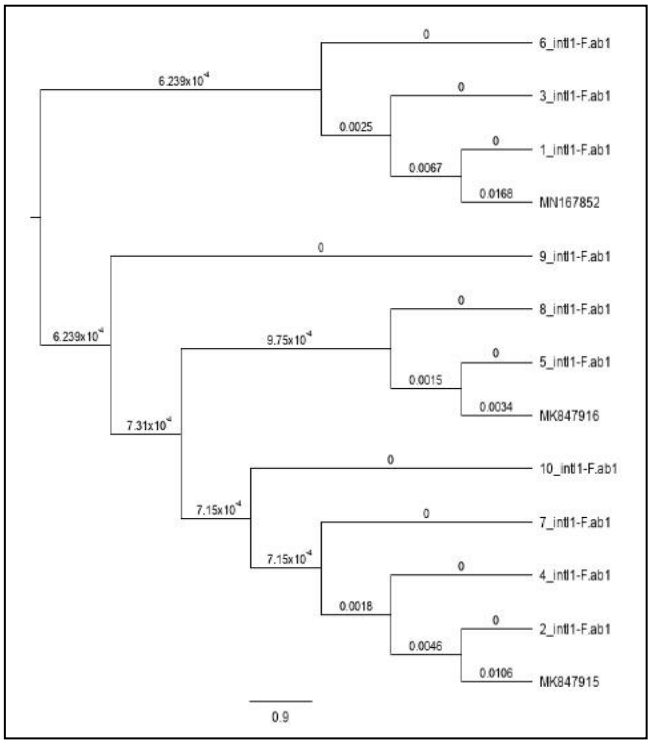

Figure 7. Dendrogram of sequence *IntI1* in *P. mirabilis* (1, 2, 3, 4, 5, 6, 7, 8, 9, 10) comparison with world *Proteus mirabilis* in NCBI (MN167852, MK847916, MK847915)

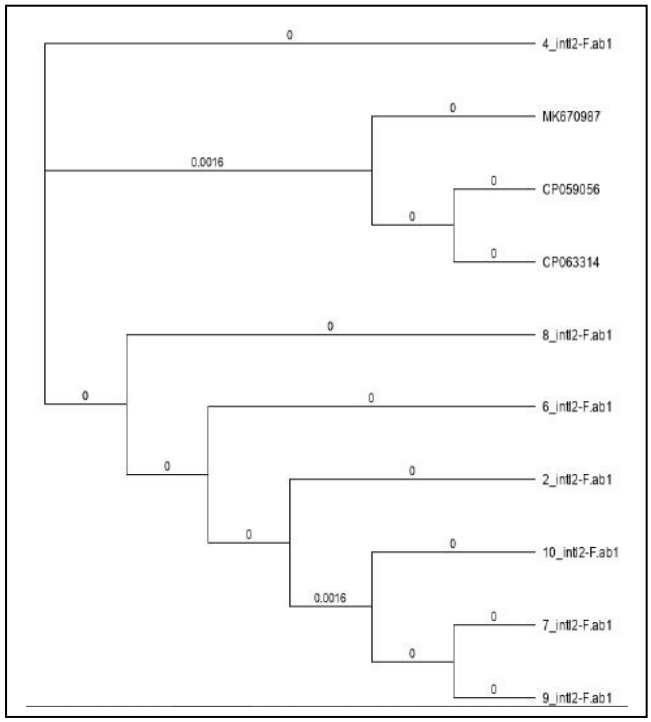

Figure 8. Dendrogram of sequence *IntI2* in *P. mirabilis* (2, 4, 5, 6, 7, 8, 9, 10) comparison with world *Proteus mirabilis* in NCBI (MK670987, CP059056, CP063314)

Documentation of genes from Iraqi multidrug-resistant clinical isolates of *Proteus mirabilis* carried out as new Iraqi strains. They selected five isolates of multidrug resistance *Proteus mirabilis* with specific sequences of nucleotides with genetic variation compared with world strain. The results showed an accepted sequence of five genes for five isolates in NCBI, including the following genes *aacIb* (LC613168.1), *blaTEM* (LC613166.1), *IntI1* (LC613169.1), *IntI2* (LC613170.1). All mentioned strains in this research are named (Iraq 2-4-5-6).

4. Discussion

Proteus mirabilis became a prevalent opportunistic pathogen agent in clinical infection worldwide and is associated with UTI especially among patients with long-term indwelling catheters, burn infections, ear infections, and septicemia (14, 15). In Iraqi clinical isolates, infections with *Proteus mirabilis* were burned infection 21 (22.1%), ear infection 22 (23.25%), and urinary tract infection 52 (54.7%). The spreading of infection with these bacteria belongs to many virulence factors and a high ability to resist different antibiotics (16).

Multidrug resistance ten *Proteus mirabilis* isolates have different levels of all resistance genes (*blaTEM, aac(6')-Ib, IntI2, IntI1*). Genome of nine isolates of these bacteria contain *blaTEM* gene (90%), eight isolates contain *aac(6')-Ib* gene (80%) ,all isolates contain *IntI1* gene (100%), eight isolates contain *IntI2* gene (80%) .These above genes make *Proteus mirabilis* isolates able to resist different groups of antibiotics likeβ-lactam, aminoglycoside, and quinolones, as shown in table 4. Analysis sequencing of the above target genes may be referred to as these genes' horizontal transport among *Proteus mirabilis* subspecies because it is located in some groups in a phylogenetic tree.

Also, the phylogenetic tree exhibited sequences of genes variable comparison with global strain in NCBI of the same bacteria locally. The selected five Iraqi strains were to interpret the origin of this genetic variation that may occur due to mutation or integrons (17, 18) and accepted as Iraqi strains in NCBIincluded*aacIb* (LC613168.1), *blaTEM* (LC613166.1), *IntI1* (LC613169.1), *IntI2* (LC613170.1).

Proteus mirabilis produces extended-spectrum β-lactamase enzyme developed as a result of a mutation that occurs in β-lactamase like (TEM-1, CTX-M, SHV-1), and this mutation may be point mutation leading to a change in type and sequence amino acid in protein peptide. These enzymes consider primary causal agents that lead to increased resistance against the β-lactam group, especially cephalosporins antibiotics that include (cefotaxime, ceftazidime), and aztreonam (19, 20). All that spreading of multidrug resistance in these bacteria in the clinical environment is due to the random use of antibiotics (21, 22).

The ability of *Proteus mirabilis* to resist quinolones may occur because chromosomal mutation affects *gyr A, topoisomerase* genes and plasmid genes like *qnr* genes (23, 24). These genes encode proteins that act on the target site to quinolones and cause the inhibition effect of this group of antibiotics, especially norfloxacin and ciprofloxacin (11, 25-27).

The aminoglycoside group is significant in treatment because it includes a broad spectrum of antibiotics (28, 29). The isolates *Proteus mirabilis* contain *aac(6')-Ib* gene that encodes to an aminoglycoside-modifying enzyme that acts inhibition effect against antibiotics in this group like amikacin and gentamycin, then isolates of these pathogenic bacteria become resistant against antibiotic of aminoglycoside group (30-32).

The genome of *Proteus mirabilis* contains mobile genetic elements like integrons, including *IntI1* and*IntI1* genes. These integrons contain three regions, a gene encoding to production integrase enzyme, the primary site for the recombination stage, and a promotor regulating the transcription process of captured genes that encode proteins, making these bacterial isolates able to resist antibiotics (33-35).

Analysis of the phylogenetic tree showed genetic variation between Iraqi clinical *Proteus mirabilis* and

global, documented in NCBI. Genetic variation in the sequence of *aacIb* gene from Iraq – 4 infection UTI documented clinically data NCBI (LC613168.1). Sequencing of the *blaTEM* gene refers to found genetic variation in Iraq 2 strain that was isolated from midstream urine and accepted in NCBI (LC613166.1). The nucleotides of *the IntI1* gene detected in Iraq 5 strain isolated from burn infection and registered in NCBI (LC613169.1). The difference between Iraqi and global sequencing in*IntI2* was achieved in Iraq 6strain, isolated from midstream urine, and then documented in NCBI (LC613170.1). Found a high degree of similarity in the sequence of antibiotic resistance genes (*blaTEM*, *aac(6')-Ib*, *IntI2*, *IntI1*) from locally clinical isolates *Proteus mirabilis* may be referred to horizontal transport of these genes among species of these pathogenic bacteria.

Authors' Contribution

Study concept and design: A. S. H.
Acquisition of data: E. A. G.
Analysis and interpretation of data: A. S. H.
Drafting of the manuscript: E. A. G.
Critical revision of the manuscript for important intellectual content: W. F. H.
Statistical analysis: A. S. H.
Administrative, technical, and material support: A. S. H.

Conflict of Interest

The authors declare that they have no conflict of interest.

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