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RESEARCH ARTICLE

Phenotypic and Genotypic Characterization of Some Virulence Factors among *Proteus mirabilis* Isolated from Clinical Samples in Al-Najaf Al-Ashraf/ Iraq

Anwar Kamel, Ahlam Kadhum Al-Yasseen*

Kufa University, Faculty of Education for Girls/Iraq.

***Corresponding Author: Ahlam Kadhum Al-Yasseen**

Abstract

The present study aimed to investigate the phenotypic and genotypic pattern of some virulence factors in *Proteus mirabilis* isolates from clinical samples. A total of 110 urine samples were collected from patients with urinary tract infection from both sexes and 100 vaginal swabs were collected of women with vaginal infections during the period from October 2017 to January 2018. The results of primary isolation and identification of bacterial isolates depending on microscopic, culturing on CHROM agar and biochemical test showed that 36.3% of isolates were belong to Proteus while the results of PCR techniques that used to confirmed identification using *16SrRNA* revealed that 27.2% of isolates were belong to *Proteus mirabilis*. Variable results in the ability of bacterial isolates to produce protease and hemolysin have been obtained in which 30% and 100% of bacterial isolates gave positive results respectively. Also the results of PCR technique showed that all isolates (100%) were possess *zap A, rsb A* and *mrp A* encoding for the production of protease, protein that regulates bacterial swarming behavior and mannose resistant pilli (MR /P) respectively by the appearance of amplicons with molecular weight 552, 485 and 366 bp.

Keywords: *Genotypic; Proteus mirabilis; Phenotypic; and Clinical Samples.*

Introduction

Proteus mirabilis, an important infectious agent of hospital and community acquired infection, is the third most common causes (after *Escherichia coli* and *Klebsiella pneumoniae*) of UTI [1], but it is represented as the most serious because it causes damage such as stone formation in the bladder and kidneys, acute and chronic pyelonephritis, catheter obstruction, cystitis, and bacteremia [2]. The ability of these bacteria to mediate urea hydrolysis, via the urease it produces, causing inflammation at the site of infection and tissue necrosis which lead to death so that the pathogen is inaccessible to antibiotics [3].

P. mirabilis has many morphological and virulence characters that distinguish it from the rest of the intestinal family, such as its ability to: swarm on certain solid culture media, adhere to the epithelial cells of humans by non-agglutinating fimbriae and production of enzymes and toxins. Moreover, its ability to produce Mannose resistance/ Proteus like fimbriae (MR / P) and Mannose resistance / Klebsiella like fimbriae (MR / K) [4, 5]. Metal proteases are a key group of proteolytic enzymes produced by *P. mirabilis* belong to serralysin family, which is encoded by *zapA* gene. ZapA is also a member of the metal proteases family that needs in its formation to zinc ion and a two-valence positive ion [6]. ZapA metalloproteases are associated with the differentiation of undulating cells and swarming (7, 8]. This protein also increases the ability of bacteria to sensitize surfaces and the formation of swarming cells, which lead to the formation of the bio-membrane in the artificial diuresis [9, 10].

Zap ABCD operon play an important role in formation of zapA and it has been founded that occurrence of mutations in *zap BCD* affect *zapA* production, also 13 founded that LD_{50} was less than 50% in ZapA producing strains compared to non- ZapA producer [11]. MR / P fimbria plays an important role in

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autoaglutination, heammaglutination, and biofilm formation [12]. It changes the immune response and interaction between the pathogen and the host [13].

MR / P operon consists of 8 genes; *mrpI, mrp A, mrpC, mrp D, mrpE, mrpF,* and *mrpG* [14]. *mrpH* gene is encoded for protein Mrp H, which is thought to be responsible for the adhesion, colonization, and formation of bio-membrane in the urinary tract [13]. Also, it's believed to be responsible for the agglutination of red blood cells treated with manganese sugar [15].

P. mirabilis characterized by a phenomenon called swarming on the solid and liquid media and even inside the body of the organism because of the migration of the bacterial cells after their differentiation [16]. Many theories have shown the role of swarming and the consolidation phenomenon in bacteria. The colony centered by actively growing and dividing cells that produce toxic metabolic products spread in the medium and create a descending gradient concentration away from the colony.

When the concentration reaches a critical level, the normal short cells converted into swarming cells by inhibiting cell division and stimulating the synthesis of fimbria. These long mobile cells are capable of detecting toxic products swimming or swarming away from the center of the colony as a negative chemotactic response.

When the swarming cells reach a zone of low-metabolic enzymes they stop moving, become short and multiply again [17, 18]. By repeating the process, a concentric circle pattern will appear on the agar medium called the bull's eye pattern and a change in cell form results from changes in the nature of LPS, Peptidoglycan and formation of membrane fatty acids [19, 20]. Other theories have shown that the periodic nature of the swarming in *Proteus mirabilis* is due to the population density of the bacteria or the aqueous activity in the vicinity of the cells [21, 22, 23].

Also, *rsbA gene* organizes swarming in *P. mirabilis* is because it senses the surrounding environmental conditions. Moreover many different genes are organized during the swarming, including the genes that are not required for the swarming (24). Researchers' interests on *P. mirabilis* have been increasing due to its pathogenesis and the appearance of multiple antibiotic resistant strains so that this study aims at detecting the genotype and phenotype of *P. mirabilis*.

Methodology

Samples Collection

One hundred and ten urine samples have been collected from patients with UTIs whom admitted Al-Sadr City Educational Hospital from October 2017 to January 2018 and 100 vaginal swabs from upper-cervical infections of patients of Al-Hakim General Hospital and al-Zahraa Maternity Teaching Hospital in Najaf from October 2018 to January 2018.

Isolation and Initial Diagnosis of *P. mirabilis*

All specimens were planted on different cultures include Blood Agar Base and Macconkey agar, for initial isolation and diagnosis of bacterial isolates, while further identification has been carried out based on cultural characteristics and biochemical tests [25].

Molecular Diagnosis

PCR technique was used to confirm diagnosis of *P. mirabilis* isolates based on *16SrRNA* and for the detection of *zapA*, *rsbA*, and *mrpA* responsible for the virulence of bacterial isolates.

DNA Extraction

Extraction of bacterial DNA using Boiling method has been follow as described previously [26]. Briefly bacterial cell suspension boiled for 5 minutes then incubated in water bath at boiling temperature for 5 minutes, then, ice bath incubation for another 5 minutes. The lyses mixture was centrifuge at 15000 rpm/min then, the DNA was precipitate by mixing with isopropanol for 24 hrs and centrifuged again at 10000 rpm/min. The DNA precipitate was conserve in TE solution and DNA concentration was measure by DNA-RNA spectrophotometer (Bio-Droop).

Amplification Reaction

The oligo-synthesis nucleotide sequences (iNtRON, Korea) that used in PCR technique were mention in table 1. PCR mixture was prepared to the final volume of 20µl by adding 3µl of the forward and revers primer

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and 6µl of DNA template to the reaction mixture of PCR (PCR- Premix kit-i-Taq), then the volume was completed to 20µl of Nuclease-free water. The thermo-cyclic conditions of each gene were set by thermo cycler (Biometra, Germany) as shown in Table 2. The amplification products were electrophoresing on 1% agarose gel stained with ethidium bromide at 70 V volts for 50 min. Then, the results were record using a gel documentation system (Biometra, Germany).

Phenotypic Detection of Protease Production

The ability of 10 bacterial isolates to produce protease was detect as described previously [27] in which milk agar plates were inoculated with bacterial spots (O.D. = 1) and incubated at 37 ° C for 24 h. Positive results were determine by appearance of transparent areas around the holes.

Phenotypic Detection of Haemolysin Production

The ability of 10 bacterial isolates to produce hemolysin was detected by culturing these isolates on blood agar base, incubating at 37 ° C for 24 hours, then the decomposition pattern was determined according to [28].

Table 1: The oligo-synthesis nucleotide sequences

Genes	Sequences 5' → 3'	Size (bp)	References
16SrRNA	F - GAGTTTGATCCTGGCTCAG R - GGTTACCTTGTTACGACTT	1500	29
zapA	F- ACGCAGGTCAGAATGTTCCA R –TATCCTGTCCACGACCACCA	552	Designed in this research
rsbA	F – CCACAGGACAGCAGAGTGTT R –CTGATAATCAACTTGGAAGTT	485	
mrpA	F – GTTGTTGCGGGTTCTGCTTT R – GTTTTGAGCAGCACTTGGG	366	

Table 2: The thermocycler condition

Gene	Initial Denaturation (°C/min)	No. of Cycle	The condition of one cycle			Final extension (°C/min)
			Denaturation	Annealing	Extension	
16SrRNA	94 °C /2 min.	35	94 °C /2 min.	55 °C /1min.	72°C/1 min.	72 °C /5 min.
zapA	95 °C /2 min.	30	95 °C /30 sec.	58°C/30 sec.	72°C/1 min.	72 °C /5 min.
rsbA	95 °C /2 min.	30	95°C/30 sec.	59°C/30 sec.	72°C /50 sec.	72 °C /5 min.
mrpA	95 °C /2 min.	30	95°C/30 sec.	58°C/30 sec.	72°C /40 sec.	72 °C /5 min.

Results and Discussion

Isolation and diagnosis of P. mirabilis

The results of isolation and initial diagnosis based on phenotypical, cultural and biochemical characteristics showed that out of 88 isolates of Gram negative, the percentage of *P. mirabilis* isolates was 27.2%. The highest isolation percentage was 43.7% from urine of women with urinary tract infection. Meanwhile, isolation percentage from women with vaginal infection was 25%, and *P. mirabilis* isolation percentage in males was 29.1%.The results of agarose gel electrophoresis for *16SrRNA* amplicon showed that 24 isolates were belong to *P. mirabilis* by appearance of amplicon with molecular weight 1500 bp (Fig. 1).

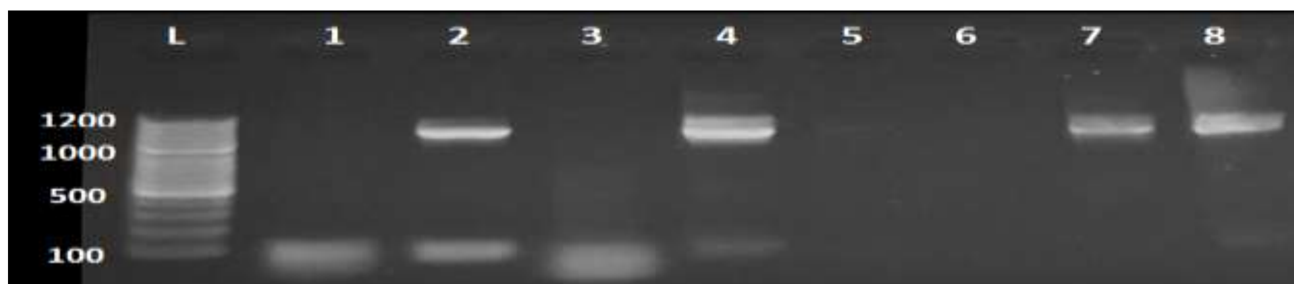

Figure 1: Agarose gel electrophoresis of the *16SrRNA* gene amplification products (1500 bp) in *Proteus mirabilis* isolates (% 1 agarose at70 volt. /70 min).Line L: DNA Ladder (100 bp). Line 2, 4, 7, 8: Positive results of *16SrRNA* amplification. Line 1, 3, 5, 6: Negative results

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Several studies have shown inconsistency in the percentage *P. mirabilis* isolates from different clinical sources [30, 34]. The difference in isolation rates may be due to the different isolation areas of infected persons taken from different hospitals in different locations and the different methods of collection and conditions.

In addition, it could be because the patients had taken wide-spectrum antibiotics before taking samples, which prevented the appearance of bacteria [35]. Vaginal hormone changes also play a major role in the natural structure of the vagina, where the normal level of estrogen is necessary to maintain the balance to resist bacterial diseases on the basis that this hormone stimulates and activates the growth and integration of the vaginal epithelial membrane [36]. Meanwhile, hydrogen peroxide produced by *Lactobacillus* strains plays a vital role in maintaining the microbial environment of the vagina and inhibiting possible pathogens [37].

Detection of zap A, *rsb A* and *mrp A*

The results of agarose gel electrophoresis of *zapA, rsbA* and *mrpA* amplification products of *P. mirabilis* showed that 24 isolates (100%) were possess these gene by appearance of amplicons with a molecular weight of 552,487 and 366 bp (Fig. 2, 3 and 4).

Figure 2: Agarose gel electrophoresis of *zapA* amplification products (552 bp) in *Proteus mirabilis* isolates (1% agarose gel at 70 volt./ 50 min.). Line L: DNA Ladder (100 bp). Line 12-1: Positive results of *zapA* amplification

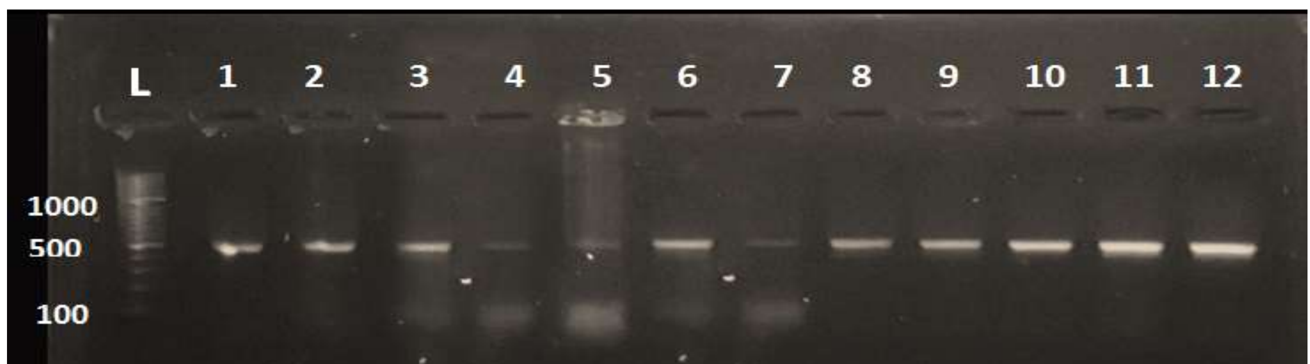

Figure 3: Agarose gel electrophoresis of *rsbA* amplification products (485 bp) in *Proteus mirabilis* isolates (1% agarose at 70 volt./ 50 min.).Line L: DNA Ladder (100 bp). Line 12-1: Positive results of *rsbA* amplification

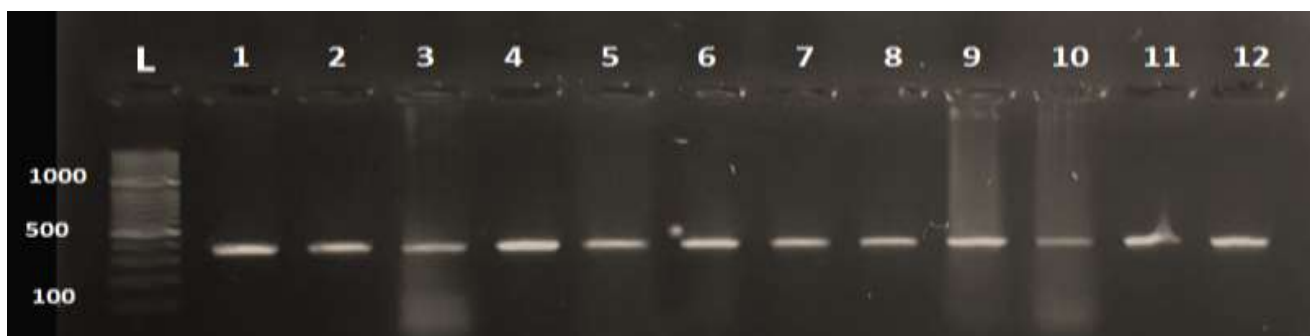

Figure 4: Agarose gel electrophoresis of *mrpA* amplification products (366 bp) in *Proteus mirabilis* isolates (1% agarose at 70 volt. / 50 min).Line L: DNA Ladder (100 bp). Line 12-1: Positive results of *mrpA* amplification

Most *P. mirabilis* strains produce the metalloprotease enzyme encoded by *zapA* gene, which destroys host proteins and releases amino acids to use as nutrients for growing bacterial cells.

It also decomposes many other proteins such as IgA and IgG, which contribute to defending the host [38]. The enzyme divides IgA2, IgG1, IgA and destructs antimicrobial peptides such as Human β-definsin1 (hBD1)

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and LL-37, which are the body defenses produced by distal tubules, Henle's loop, and collecting duct at the beginning of Urinary tract infection, This helps bacteria hide from the body's immune system, as well as to break down IgG and IgA immunoglobulins, which helps bacteria to avoid the immune system in the host's body. It also increases the effectiveness of other virulence factors such as urease hemolysin production and flagellation [39]. ZapA is an important virulence factor of P. mirabilis carried by the chromosome. Several studies have indicated that the genomes of all P. mirabilis isolates are carriers of zap [35, 40] which improved the importance of zapA in the pathogenicity of P. mirabilis, including prostatitis at the acute and chronic stages [41]. The occurrence of genetic mutation in zapA gene leads to a significant change in the phenotypic traits of the bacteria, reduce in the number of bacteria, and cause sharp anatomical changes in laboratory mice infected with P. mirabilis bacteria carrying zapA gene in comparison with wild type [42].

RSBA encodes into a regulated protein for the behavior of the organism. The gene encodes into the intermediate transporters of phosphorus, which play an important role in regulating swarming [43]. The appearance of genetic mutations in this gene leads to hyper swarming; a phenomenon similar to swarming, which results from increased gene expression of the flagin protein [44].Such mutations also lead to increased virulence factors associated with swarming such as the production of heamolysin and protease [45]. Furthermore, this protein mediates other metabolic pathways related to saturated fatty acids, which play an important role in the formation of biomass and swarming [46].MRPA encodes Manose Resistance Proteus Like Fimbriae (MR/P), which is responsible for blood agglutination with human red blood cells with the presence of mannose sugar. It is important in the adhesion of bacteria in to epithelial cell that coating the urinary duct [47]. All P. mirabilis strain have identical sequences of nitrogen bases of mrpA gene which indicating that these fimbriae proteins maintain their sequences in different isolates indicating the possibility using them as vaccines [48]. mrpA mutation leads to bacterial failure to stick to the host surface, but bacterial cells survive inside the host body compared to non-mutant P. mirabilis [49].

Protease Production

Ten isolates of *P. mirabilis* were selected to investigate their ability of protease production, depending on their genetic characteristics, which showed the presence of the genes responsible for coding to produce this enzyme. The results showed that the ratio of protease producing isolates was 30% and the diameter of the decomposition area for the medium was 30 mm, while the diameters for the other isolates 21 and 18 mm respectively (Figure 5 and Table 3).

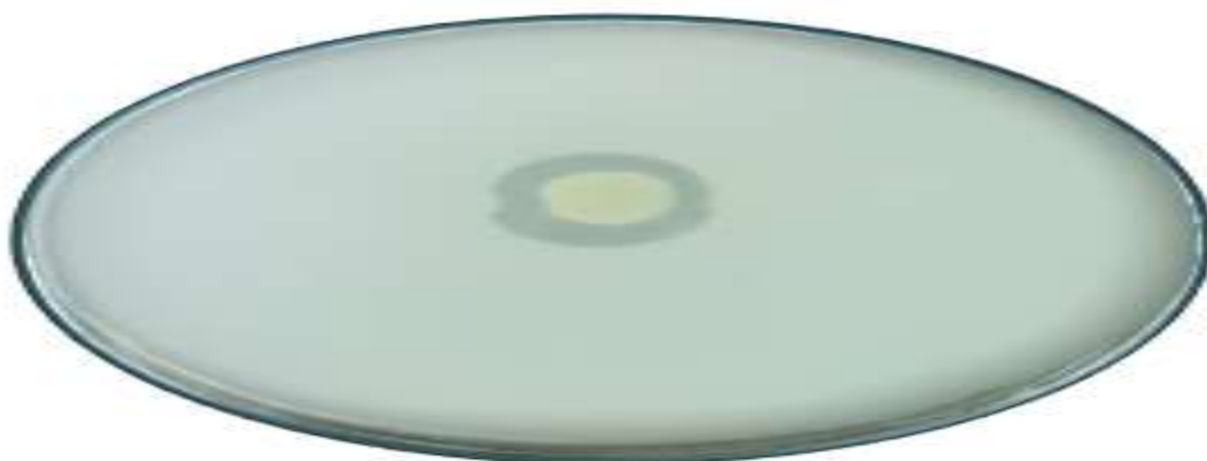

Figure 5: The efficacy of protease decomposition produced by *Proteus mirabilis*

Table 3: Proportion of diameters of the protease

Isolate No. (Vaginal Infection)	Decomposition Area Diameter(mm)	Isolate No UTI	Decomposition Area Diameter (mm)
13	-	3	-
19	-	5	-
21	-	9	-
22	(18)	10	(30)
24	(21)	12	-

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Protease breaks down the peptide bonds between protein-forming amino acids and thus leads the proteolysis, which helps bacterial isolates to penetrate the host's defensive system(breaks down the peptide bonds that bind the heavy and light chains of the immune proteins) and cause injury [50].

Inconsistency of isolates in the production of protease was attributing to the efficiency of the *zapA* gene, which encoded to produce this enzyme, where the enzyme is produce extracellular in the period in which the cells differentiate from swimming cells into swarming cells. The results of this study show that all the selected isolates were carrying a *zapA* gene while no capability was shown to produce protease; this was attributed to the loss of gene during the period of cell differentiation, which leads to failure to produce the enzyme or the failure of gene expression during this period [33].

Heamolysin Production

The results of testing ten isolates of *P. mirabilis*, showed capability of two of these isolates (20%) to produce α –hemolysin, which causes partial hemolysis. The decomposed region appears to be greenish, while 8 (80%) isolates produced ß-hemolysin, which causes complete hemolysis, where a transparent aura appeared around the bacterial growth. Hemolycin is an important toxin of *P. mirabilis*. It causes damage to the host's tissues directly by breaking the red blood cells and releasing hemoglobin, which increases the pathogenicity of the bacteria and causes infection [51]. It was produce at the end of the logarithmic stage and the onset of the dormancy phase, where it analyzes the phosphorylation of the cell membranes [52].

It was associated with fatty-protein receptors on the surface of the target cell to make holes in the host cell membrane. The bacteria also use hemolysin as a route to obtain host nutrients such as iron, which is a specific factor for the growth of bacterial pathogens. The variation in the ability of bacterial isolates to produce hemolysin may due to the fact that genes encoded for the production of hemolycin are silent genes, which expressed only in the host's body [53].

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