REVIEW PAPER

URINARY TRACT INFECTIONS

Uropathogenic *Escherichia coli* virulence genes: invaluable approaches for designing DNA microarray probes

Nadia Jahandeh[1], Reza Ranjbar[1], Payam Behzadi[1], Elham Behzadi[2]

[1]*Molecular Biology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[2]*Department of Microbiology, College of Basic Sciences, Shahr-e-Qods Branch, Islamic Azad University, Tehran, Iran*

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Corresponding author
Payam Behzadi
Molecular Biology Research Center
Baqiyatallah University of Medical Sciences
Tehran, Iran
phone: +98 218 803 98 83
behzadipayam@yahoo.com

Introduction The pathotypes of uropathogenic *Escherichia coli* (UPEC) cause different types of urinary tract infections (UTIs). The presence of a wide range of virulence genes in UPEC enables us to design appropriate DNA microarray probes. These probes, which are used in DNA microarray technology, provide us with an accurate and rapid diagnosis and definitive treatment in association with UTIs caused by UPEC pathotypes. The main goal of this article is to introduce the UPEC virulence genes as invaluable approaches for designing DNA microarray probes.

Material and methods Main search engines such as Google Scholar and databases like NCBI were searched to find and study several original pieces of literature, review articles, and DNA gene sequences. In parallel with *in silico* studies, the experiences of the authors were helpful for selecting appropriate sources and writing this review article.

Results There is a significant variety of virulence genes among UPEC strains. The DNA sequences of virulence genes are fabulous patterns for designing microarray probes. The location of virulence genes and their sequence lengths influence the quality of probes.

Conclusions The use of selected virulence genes for designing microarray probes gives us a wide range of choices from which the best probe candidates can be chosen. DNA microarray technology provides us with an accurate, rapid, cost-effective, sensitive, and specific molecular diagnostic method which is facilitated by designing microarray probes. *Via* these tools, we are able to have an accurate diagnosis and a definitive treatment regarding UTIs caused by UPEC pathotypes.

Key Words: uropathogenic *E.coli* ‹› DNA microarray ‹› virulence genes ‹› microarray probe designing

INTRODUCTION

Escherichia coli (E.coli), the flagellated member of *Enterobacteriaceae* is an important component of the normal microbial flora in the human gastrointestinal tract. However, there are several *E.coli* pathotypes with a vast range of virulence factors, which may lead to different clinical symptoms. The *E.coli* pathotypes and their related infections are shown in Table 1 [1–5].

ExPEC pathotypes include septicemia causing *E.coli* (SCEC), neonatal meningitis causing *E.coli* (NMEC) and uropathogenic *E.coli* (UPEC) that leads to septicemia, pediatric meningitis and urinary tract infections (UTIs), respectively. Although, ExPEC strains cause a wide range of infections; UTIs are the most considerable bacterial infections which may lead to several types of symptoms [1, 2].

The pathogenicity of *E.coli* pathotypes such as UPEC is completely in association with virulence genes and other related genomic elements. Simultaneously, the increase of dissemination of antimicrobial resistance genes *via* mobile genetic particles including integrons (usually located in transposons and plasmids), transposons, and plasmids has brought up a main concern for providing definite diagnostic

Table 1. *Escherichia coli (E.coli) pathotypes and their related infections*

Diseases	*E.coli* Pathotype
Intestinal infections	Cell detaching *E.coli* (CDEC), Diffusely adherent *E.coli* (DAEC), Enteroaggregative *E.coli* (EAEC), Enterohemorrhagic *E.coli* (EHEC), Enteroinvasive *E.coli* (EIEC), Enteropathogenic *E.coli* (EPEC), Enterotoxigenic *E.coli* (ETEC), Necrotoxic *E.coli* (NTEC)
Extraintestinal infections	Extraintestinal pathogenic *E.coli* (ExPEC)

tools and therapeutic alternatives. The application of traditional and preliminary molecular diagnostic techniques for detecting UPEC strains and the antimicrobial resistant UPEC pathotypes is not sufficient or reliable. Thus, the development of modern molecular techniques which can lead to an accurate diagnosis and a definitive treatment is urgently needed. There are some routine molecular diagnostic methods such as polymerase chain reactions (PCRs) which may cover a portion of deficiencies relating to detection and identification of a limited number of UPEC virulence and antimicrobial resistance genes. However, the PCR tools are suitable only for small gene subsets, not for determining several hundreds or thousands of genes at the same time [2, 3, 6, 7].

Among several useful nucleic acid diagnostic approaches, DNA microarray technology is a rapid, accurate, cost-effective, reproducible, and reliable technique for a definitive diagnosis and an appropriate treatment. The robust platforms belonging to DNA microarray technologies accommodate a wide range of abilities for detecting a huge number of virulence and antimicrobial resistance genes within a single clinical test *via* molecular epidemiology investigations. For this reason, virulence genes are valuable approaches for designing DNA microarray probes [1, 6–10].

Although this literature review considers several factors including UPEC genomics, UPEC virulence factors, antimicrobial resistant UPEC strains, the main goal of this article is to introduce the UPEC virulence genes as valuable approaches for designing DNA microarray probes.

Host and UPEC Genomics

UPEC is the predominant bacterial agent responsible for up to 50% and 75–95% of nosocomial and community acquired UTIs, respectively. This pathotype causes a variety of deleterious effects including morbidity, increased costs of healthcare, and even mortality [6, 11].

Depending on UPEC strains and human immune systems, UTIs vary from acute/chronic, asymptomatic/symptomatic, to complicated/uncomplicated, and lower/upper UTIs [1, 6, 8, 9, 10, 12, 13].

Age, catheterization, genetics, hospitalization, immune system condition, individual hygiene, infectious and non-infectious diseases, sex and social behavior are the most reported host specific factors which contribute to occurrence of UTIs [12, 23, 14].

Genomics is a modern and proper science for determining virulence and virulence-dependent factors in UPEC throughout pan-genomic investigations. Pan-genomic surveys reveal the structures of virulence genes belonging to UPEC [15, 16, 17].

Recent phylogenetic analyses have categorized *E.coli* strains into 5 groups; A, B1, B2, D and E [18]. The major members of UPEC strains belong to group B2 and the remaining minor strains are from group D. The A, B1 and E group members are in association with intestinal strains of *E.coli* [18]. As mentioned before, the physiological presence of commensal *E.coli* is recognized in the human gastrointestinal tract. Therefore, the presence of *E.coli* strains (UPEC) in the urinary tract is related to extra-intestinal virulence factor genes. The virulence genes guarantee the survival of UPEC within the urinary tract. The pan-genomic analyses show that, the *E.coli* genome is made up of a core and a flexible genomic pool. The core genome is detectable in all strains of *E.coli* while the flexible gene pool is identified only in pathogenic intestinal strains of *E.coli* and ExPEC strains such as UPEC. The core genome consists of essential genetic data for normal vital activities of the cell and the flexible gene pool [named as mobile genetic elements including transposons, plasmids, integrons, phages, and pathogenicity islands (PAIs)] includes genetic information which is needed for the cell's adaptation to its surrounding conditions [5, 11, 17–20].

The genomic content of *E.coli* is estimated to be in the range of 4.5–5.5 Mb. The intestinal commensal *E.coli* possesses a lower genomic content (≈4.5 Mb) than the intestinal pathogenic *E.coli*, while ExPEC (such as UPEC) contains more genomic components (≥5 Mb) than the aforementioned strains. Thus, the genome sizes of *E.coli* strains are as follows [11, 19]: commensal < intestinal pathogen < UPEC antimicrobial sensitive < UPEC antimicrobial resistant.

The noticeable point relating to mobile genetic elements is that, they are able to replicate by themselves or be inserted into the chromosomal gene pools [11, 19].

Presentations of UTIs vary from asymptomatic bacteriuria (ABU) to cystitis and from acute pyelone-

Table 2. *Different aspects of uropathogenic Escherichia coli (UPEC) virulence factors*

Situation of Virulence Factors	Type of Virulence Factors	Virulence factors	Gene	Role	Association in UTIs
Superficial virulence factors	Afimbrial Adhesins	AFA-I, AFA-II, AFA-III, AFA--IV, AFA-V, AFA-VII, AFA-VIII	*afa*	Adhesion, Colonization, High tropism to kidney	Chronic cystitis/pyelonephritis, Recurrent cystitis/pyelonephritis, rarely in ABU
		Curli	*csg*	Adhesion, Colonization, Biofilm formation	All types of UTIs
	Fimbrial Adhesins	P fimbriae	*pap*	Adhesion, Colonization, Cytokine production, Invasion, Inflammation, Pain, Renal tropism, Pathogenesis	Most recognized in upper UTIs, Acute UTIs, Acute Pyelonephritis, renal failures, Acute Cystitis, Rarely in ABU
		Type 1 fimbriae	chaperone-usher class fimbrial genes: *fim*	Adhesion, Biofilm formation, Colonization, Growth, Invasion, Rapid replication, Inflammation, Intracellular survival	All types of UTIs
		Type 3 fimbriae	chaperone-usher class fimbrial genes: *mrk*	Biofilm formation	Mostly in catheter associated UTIs
		Dr	*dra*	Adhesion, High tropism to kidney	Chronic cystitis/pyelonephritis, Recurrent cystitis/pyelonephritis, rarely in ABU
		F1C	*foc*	Adhesion, Biofilm formation, Colonization	All types of UTIs, renal failure
		S fimbriae	*sfa*	Adhesion, Colonization, Dissemination, Bacterial ascending factor	Meningitis, Septicemia, Mostly severe upper UTIs
		F9 fimbriae	chaperone-usher class fimbrial genes: *c*	Adhesion Biofilm formation	UTIs, Mostly pyelonephritis
		Auf fimbriae	chaperone-usher class fimbrial genes: *auf*	Adhesion Biofilm formation	All types of UTIs
	Capsule	K polysaccharides including: K1, K2, K3, K5, K12, K13, K20, K51/KspMT	*kps*	Adhesion, Biofilm formation, Antimicrobial resistance, Anti-phagocytosis, Anti-serum and anti bactericidal complement activity	All types of UTIs
	Lipopolysaccharide	O serogroups UPEC including: O1, O2, O4, O6-O8, O15, O16, O18, O21, O22, O25, O75, O83	*rf*	Adjuvant, Anti-phagocytosis, Anti bactericidal complement activity, Induction of human cytokine production, Endotoxin activity, Acute inflammation pain	All types of UTIs
	Motility	Flagella protein H antigen	*flic*	Biofilm formation, Colonization, Facilitated ascending (dissemination), Invasion, Chemotaxis	Mostly cystitis and pyelonephritis
	Outer membrane proteins	OmpA, OmpC, OmpF, OmpT, OmpX	*ompA, ompC, ompF, ompT ompX*	Porin, transportation, Facilitating factor for UPEC intracellular virulence	Mostly chronic UTIs
	Serum Resistance	Serum resistant proteins	*iss, traT, cvaC*	Neutralization of anti-bactericidal effect of serum	Mostly cystitis and pyelonephritis, bacteremia
	Siderophores	Aerobactin/Enterobactin/ Salmochelin/Yersiniabactin	*aer,iutA/entS/ iroN/ fyuA, ybtP, ybtQ*	Growth, Iron uptake	Severe UTIs
		Hemin uptake system	*chuA, hma, ireA, iha,iutA*	Biofilm formation, Growth, Iron uptake	All types of UTIs
Discharged virulence factors	Autotransporter adhesins (Type V secretion system proteins)	Secreted Autotransporter Toxin (SAT)	*sat*	Colonization, Cytotoxic effect on bladder and kidney, Pathogenesis	Mostly pyelonephritis, UTIs
		Ag43 (outer membrane protein antigen), Upab, UpaC, Upag and UpaH proteins	*ompA, upab, upaC, upaG, upaH*	Adhesion, Biofilm formation, Intracellular survival, Long term infection	Chronic UTIs
	Toxins	Cytolethal Distending Toxin	*cdt*	Cytolethal factor, Human cell apoptotic factor	UTIs
		Cytotoxic Necrotizing Factor 1 (CNF1)	*cnf1*	Invasion, Apoptosis in cell bladder, Host cell malfunction	Severe UTIs
		α-Haemolysin	*hlyA*	Host cell lysis, Hemolysis, Growth, Adhesion, Inflammation	Mostly in severe and symptomatic UTIs
		Serine protease autotransporter toxin (Sat)	*sat*	Cytotoxic effect on bladder and kidney	Mostly pyelonephritis
		Vacuolating autotransporter toxin (Vat)	*vat*	Cytotoxic effect on bladder and kidney endothelial tissue	Mostly pyelonephritis
		TosA	*tosA*	Adhesion, Colonization	UTIs
		Shigella enterotoxin-1	*set-1*	Invasion, Inflammation	Severe UTIs
		Arginine succinyltransferase	*astA*	Invasion, Cytotoxin, Inflammation	Severe UTIs
		Toll/interleukin receptor domain containing protein (Tcp)	*tcpC*	Bacterial survival, Human avoidance system, Cytopathic effect on kidney	Mostly pyelonephritis
	Multi-functional factors	Usp	*usp*	Invasive, Inflammation	Severe UTIs

phritis to advanced renal failure. The pan-genomic studies have elucidated that the presence and expression of UPEC virulence and virulence-associated genes in asymptomatic UTIs are weaker than acute UTIs [1, 8, 11, 19, 20].

UPEC virulence factors

It has been recognized that UPEC possesses a diverse repertoire of virulence and virulence-associated factors, which support the occurrence of UTI manifestations. Not only the presence and contribution of virulence genes but also the levels of gene expression determine the form of infection. First of all, adhesins are essential factors for the beginning of the pathogenesis process. The UPEC bacterial pathogen needs a suitable condition for colonization and biofilm formation. According to previous investigations, there are complex balances between different proteomic and genomic capabilities of UPEC (Table 2) [9, 10, 11, 18–32].

In this study, the type of virulence factors are categorized into ten groups including afimbrial adhesins, fimbrial adhesins, capsule, lipopolysaccharide (LPS), motility, outer membrane proteins, serum resistance, siderophores, autotransporter adhesins and toxins. The presence of chaperone-usher system, type V secretion system, type IV pili, autotransporter proteins system, iron-uptake system, and flagella genes shows an intense contribution of gene clusters and the related triggering system which may lead to increase or decrease of the level gene expressions. Moreover, the antibiotic resistance genes may be seen in the gene pool of some UPEC strains [9, 10, 11, 18–31, 33].

Table 2 highlights the role of virulence factors in UPEC strains. The diversity of virulence and virulence-associated factors involves a wide range of genomic information; as mentioned before, the presence of virulence genes and the level of their expressions determine the bacterial characteristics in association with the clinical demonstrations of UTIs such as ABU, cystitis and pyelonephritis in an individual patient. Previous studies revealed that the plasticity of the gene pool and genomic assemblages illuminate the quality and the quantity of the bacterial pathogenesis. Among the aforementioned factors in Table 2, there are some significant virulence genes such as *afa, aer, cnf 1, hly, pap* and *sfa* which contribute in severe UTIs caused by UPEC pathotypes; Also, the genes including *astA, fim, foc, iha, iroN, iutA, kpsMT, set-1, traT* and *usp* contribute in UPEC pathotypes' pathogenicity. Furthermore, the situation of some virulence genes is variable. For example, *cnf-1, hly, pap, sfa* genes can occur in pathogenicity island clusters. However, these genes are also recognized in plasmids [19, 32, 33, 34].

In recent years, virulence genes have been recognized as suitable target sequences in microarray technology. The DNA microarray technique enables us to detect hundreds of thousands of genes simultaneously. The selection of unique sequences relating to UPEC virulence genes helps us to prepare and design appropriate microarray probes for detecting and identifying *E.coli* strains which may lead to UTIs [3, 7, 16, 33, 35, 36, 37].

In parallel with virulence factors, the increase of antimicrobial resistance genes among UPEC strains has complicated the emergence condition for definite treatment [11].

Antimicrobial resistant UPEC strains

The antimicrobial resistance phenomenon has been an urgent global problem since the 1990s. However, bacterial drug resistance genes go back to several thousand years ago. Detection and identification of antibiotic resistant gene subsets as a necessary and complementary gene profiles in association with virulence and virulence related gene profiles, accommodates a stronger and more accurate spectacle for drug resistant UPEC (DRUPEC) pathotypes. The presence of DRUPEC and in particular, multidrug resistant UPEC (MDRUPEC) has led to unsuccessful treatments or prolonged, long-term treatments [34]. The misuse and inappropriate consumption of antibiotics has led to progression of antimicrobial resistant bacteria around the world. The most dangerous outcome from antimicrobial resistant bacteria like UPEC is a considerable increase in death because of failed treatment procedures. The antimicrobial resistance genes may occurred *via* DNA mutations or horizontal transfer mechanisms among UPEC strains [38]. Similarly to virulence genes, the antimicrobial resistance genes are located on chromosomal DNA or plasmids. Moreover, the antimicrobial resistance genes are also recognized in transposons and integrons. Therefore, the association between antimicrobial resistance and virulence genes and the level of their expressions are understood. Simultaneously, the antimicrobial resistance genes are recognized as appropriate target sequences for designing microarray probes [2, 6, 32, 34, 38–41].

Several scientific surveys indicate a global dissemination of antimicrobial resistant UPEC strains including β-lactam resistance, extended-spectrum β-lactamase (ESBL), plasmid mediated AmpC β-lactamase and metallo-β-lactamase [11, 40, 42, 43].

There are many different antibiotics such as β-lactams, chloramphenicol, gentamicin, quinolones, streptomycins, sulfonamides, tetracyclines, and trimethoprims, used in UTI treatment. However, the most commonly prescribed drugs for nosocomial and community acquired UTI therapies are reported as penicillins, trimethoprim-sulfamethoxazole, fluoroquinolones and cephalosporins. Table 3 shows the most often encountered antimicrobial resistance genes which have been reported by previous studies [2, 11, 32].

Today, the close link between virulence genes and antimicrobial resistance genes can be distinguished. Additionally, these genes are able to influence each other through their levels of expression. As a fact, there are some plasmid families such as Inc F which have a vast contribution among *E.coli* pathotypes like UPEC. The plasmids pertaining to Inc family carry a great portion of ESBL and quinolones resistance genes together with bacterial virulence factors involving serum resistance proteins, iron uptake system components, etc. On the other hand, the presence of quinolones resistance genes affects the level of virulence factor gene expression. This field is directly linked to molecular epidemiology studies [34].

Virulence genes: excellent approaches for designing DNA microarray probes

Virulence genes are hidden pearls which help us to design appropriate microarray probes with the best functional and structural characteristics. The UPEC virulence genes including adhesins, capsular antigens, toxins and other unique virulence genes are extraordinary molecular patterns which can be used for designing high quality microarray probes. It is important to know the selected locus position and the length of virulence genes because these parameters determine the quality of microarray probes. The gene DNA sequences are accessible by NCBI, GenBank database (http://www.ncbi.nlm.nih.gov/genbank/) and weit is possible to analyze the related DNA sequences *via* BLAST tool offered by the NCBI (http://blast.ncbi.nlm.nih.gov/Blast.cgi) [16, 33, 36, 37, 44].

AllelID software (http://premierbiosoft.com/bacterial-identification/index.html) helps us to detect conserved sequences within the genes as prompt microarray probes candidates and oligoanalyzer tool (https://eu.idtdna.com/calc/analyzer) analyzes the physicochemical characteristics in association with the designed probes [33, 36, 37, 44].

The quality of microarray probes guarantees the flexibility, accuracy, sensitivity and specificity of DNA microarray techniques as a reliable and reproducible diagnostic method [36, 37, 44].

Microarray probe designing *via* virulence genes enables us to detect and identify the different strains of UPEC and to have accurate knowledge of the level of bacterial pathogenicity as early as possible. In recent studies, microarray probes designed by virulence genes have allowed for the identification of new UPEC strains [33, 36].

Table 3. *The most frequent antimicrobial resistance genes*

Antimicrobial drugs	*Antimicrobial resistance genes*
β-lactams	*bla_{CTX-M}, bla_{OXA-7}, bla_{PSE-4}, bla_{SHV}, CITM*
Chloramphenicol	*cat1, cmlA*
Gentamicin	*aac(3)-IIA, aac(3)-IV*
Kanamycin	*aph(3')-Ia*
Quinolones	*qnr*
Streptomycins	*aadA1,ant(3'')-IIa*
Sulfonamides	*sul1, sul2*
Tetracyclines	*Tet(A), tet(B), tet(C), tet(D)*
Trimethoprims	*dhfr1, dhfrVII*

CONCLUSIONS

Virulence genes in different microorganisms and in particular in UPEC pathotypes, are excellent molecular patterns which enable us to design effective and flexible microarray probes. The collections of designed microarray probes may lead to the creation of an appropriate microarray chip involving a diversity of virulence genes for detecting and identifying different strains of UPEC. This opportunity is useful in molecular epidemiological investigations. Moreover, the use of virulence genes for designing microarray probes offers us a wide range of probes.

Recently, the application of DNA microarray technology has increased as an invaluable diagnostic technique in advanced hospitals, laboratories and medical health care centers.

On the other hand, there are some problems regarding the use of DNA microarray technology as a routine diagnostic method in small and limited laboratories. For example, this technology is very expensive for small labs with limited samples and patients. The application of DNA microarray technology requires experts and specialists which is not cost effective for small labs and limited medical health care centers, while the use of DNA microarray technology is brilliant and outstanding for reference labs and important hospitals with huge numbers of patients and clinical samples.

Despite the aforementioned limitations, DNA microarray technology provides us with an accurate, rapid, cost-effective, reliable, reproducible, flexible, sensitive and specific molecular diagnostic method which is facilitated by designing microarray probes. This technology enables us to obtain an accurate diagnosis with a definitive treatment regarding UTIs caused by UPEC pathotypes.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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