Chapter 5

Uropathogenic *Escherichia coli* and Fimbrial Adhesins Virulome

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Additional information is available at the end of the chapter

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Abstract

Urinary tract infections (UTIs) rank second among infectious diseases around the world, and this makes them significant. There are many microbial agents which may cause UTIs. *Enterobacteriaceae* family members are recognized as important UTI bacterial causative agents. Among them, uropathogenic *Escherichia coli* (UPEC) pathotypes are considered as the most important bacterial agents of UTIs. Today, genomics and bioinformatics explain us why UPEC strains are so considerable pathogens regarding UTIs. There is a diversity of *E. coli* strains involving commensal and pathogenic strains. Genomics shows that commensal strains of *E. coli* encompass the minimal amount of genome and genetic elements among *E. coli* populations, whereas the pathotypes of *E. coli* possess the maximal or a big portion of genomic elements. Previous studies confirm the presence of a vast range of virulence genes within the pool of *E. coli* pathotypes like UPEC. So, the pool of virulence genes (virulome) belonging to UPEC enables UPEC pathotypes to have huge genomes with the ability of different levels of pathogenesis. The more virulence factors, the more pathogenicity. Due to the presence of a mass of virulence factors within UPEC cellular structures, well-known fimbrial adhesins in UPEC pathotypes are discussed in this chapter.

Keywords: uropathogenic *Escherichia coli*, genomics, fimbriae, adhesins, virulence factors, urinary tract infections

1. Introduction

Every year, several million people suffer from urinary tract infections (UTIs), and of course it costs expensive for governments and healthcare medicine centres [1, 2].

UTIs with second ranking are one of the most dominant infectious diseases around the world. Although UTIs include vast etiological microbial agents, two pathogenic microorganisms

such as *Escherichia coli* (*E. coli*) (as a predominant pioneer bacterial agent) and Candida albicans (C. albicans) (as a predominant pioneer fungal agent) are the most recognized UTI etiologic pathogens [3–6].

The pangenomic and phylogenetic studies have revealed five different categories within the species of *E. coli*. These five categories involve A, B1, B2, D and E, which depending on their strains can cause extra- and intra-intestinal infections. The extra-intestinal pathogenic *E. coli* (ExPEC) may lead to a vast range of infectious diseases. So, uropathogenic *E. coli* (UPEC) represents one of the most important causative bacterial pathotypes of UTIs. Three phylogroups of A, B1 and E encompass intra-intestinal commensal and/or pathotypes of *E. coli*, whereas the B2 and D phylogroups involve, respectively, the most and the least numbers of UPEC pathotypes [7, 8].

1.1. Biology of urinary tract infections

There are different types of UTIs with a diversity of clinical demonstrations. Today, we know that the UTI syndromes are completely in association with hosts' immune system activities, type of causative microbial agent and the contributed microbial virulence factors. UTIs may be appeared as acute or chronic lower (typically known as cystitis) and/or upper (typically known as pyelonephritis) urinary tract infections, with symptomatic or asymptomatic manifestations and complicated or uncomplicated demonstrations. So, asymptomatic bacteriuria and simple cystitis with some ignorable irritations may be recognized as light and mild UTIs, respectively; while the urosepsis is known as a serious deathful type of UTI. Generally, the uncomplicated UTIs are recognized in patients with no previous background for UTIs, whereas the complicated UTIs normally happen in patients with previous problems in their urinary tracts. The remarkable point of view is the association between predisposing factors of diabetes, sexual intercourse, gender, catheterization, pregnancy, overweight, genetic factors, host's immune system responses and the type of UTIs and their severities [3, 5, 8–12].

In accordance with previous surveys, there are several numbers of microbial pathogens which can be identified as UTI pathogenic microorganisms. The microbial pathogens depending on the type of UTIs involve a vast number of pathogenic causative agents including Gram-negative bacteria, e.g. UPEC, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Citrobacter* spp., *Morganella morganii*, *Acinetobacter* spp., *Salmonella* spp. and *Pseudomonas aeruginosa*; Gram-positive bacteria such as Staphylococcus aureus (*methicillin-sensitive* S. aureus (*MSSA*) and/or *methicillin-resistant* S. aureus (*MRSA*)), Staphylococcus epidermidis (*methicillin-sensitive* S. epidermidis (*MSSE*) *and/or methicillin-resistant* S. epidermidis (*MRSE*)), *Staphylococcus saprophyticus*, *Streptococcus* spp., *Enterococcus faecium*, *Enterococcus faecalis*, diphtheroids and *Corynebacterium urealyticum* and fungal agents like C. albicans, Candida glabrata and Candida tropicalis. As aforementioned, some pathogens are predominant in complicated UTIs, and some others are responsible for uncomplicated UTIs; however, the UPEC strains are common causative agents in both types of complicated and uncomplicated UTIs. Moreover, the presence of living microbial cells determines the condition of UTIs. The usual threshold for UTI pathogens is estimated $\geq 10^5$ living cells per urine millilitre (ml). As each living cell can grow

and create its own colony, the 10^5 cells can be construed as 10^5 colony-forming units (CFUs). But we have to notice that, in some cases, the aforementioned threshold must be counted less than 10^5 CFUs/ml [3, 6, 10–14].

1.2. The genus of *Escherichia*: A great bacterial empire

The genus of *Escherichia* includes *E. albertii*, *E. coli*, *E. fergusonii*, *E. hermannii*, *E. marmotae* and *E. vulneris*. The familiarity of these species is shown in **Figure 1**. In addition to these species, there are some *Escherichia* strains which have no differences in their phenotypes; but from the genotypic aspects, they have different characteristics. These strains are named as cryptic clades, which are branched into five strains of C-I to C-V [15–18].

E. coli is the most famous member of Gram-negative bacterial family of *Enterobacteriaceae* which was identified by Theodor *Escherich*. This non-spore forming and generally motile (with a peritrichous flagellated arrangement) facultative anaerobic rod-shaped bacterium was named *E. coli* by the suggestion of Castellani and Chalmers in 1919 [7, 19, 20]. There are a diversity of *E. coli* strains which are divided into commensal types (intra-intestinal non-pathogenic strains) and pathotypes (intra-intestinal pathogenic *E. coli* (InPEC) and extra-intestinal pathogenic *E. coli* (ExPEC)). The commensal types of *E. coli* are able to be settled within the infants' alimentary canal just in some hours after birth as beneficial normal flora populations [21, 22].

The *E. coli* pathotypes are divided into a vast range of strains which may cause different types of infectious diseases. **Table 1** indicates the pathotypes and their related infections. In accordance with the table, the pathotypes have been divided into three groups: ExPEC, InPEC and ShiToPInPEC. Phylogenetic studies show a close relationship between *Shigella* spp. and *E. coli*. A close genetic similarity is recognized between *Shigella* spp. and enteroinvasive *E. coli* (EIEC) pathotypes [4, 7, 23–30].

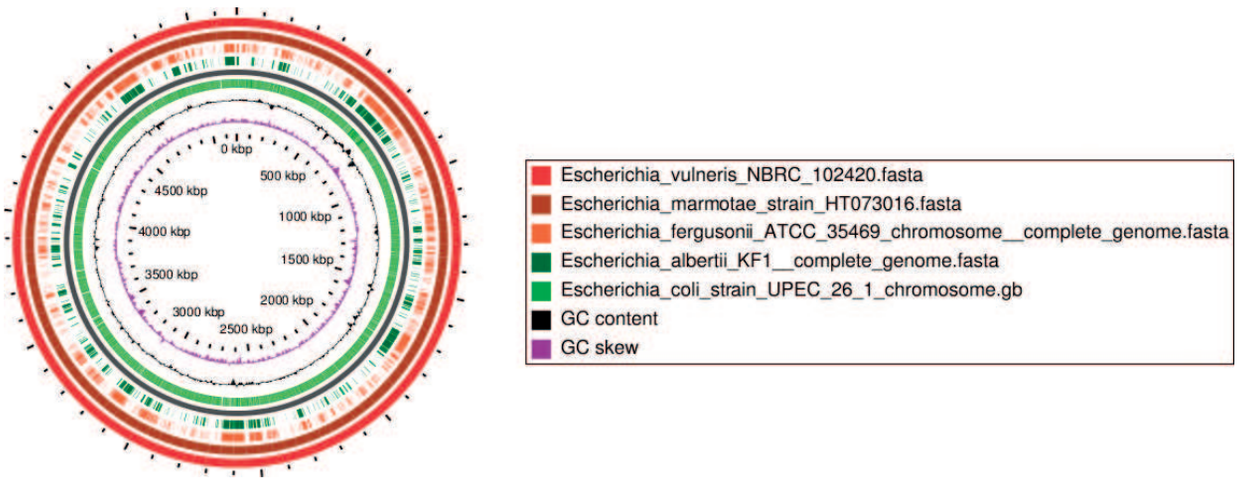

Figure 1. The genome of uropathogenic *E. coli* (UPEC) has been compared with *E. albertii*, *E. fergusonii*, *E. marmotae* and *E. vulneris* by the online GView Server system. The figure indicates genomic familiarities between the *Escherichia* species. As shown, the species of *E. marmotae* and *E. vulneris* have very close genomic similarities with UPEC, whereas there is some dissimilarity between genomic treasures of *E. albertii*, *E. fergusonii* and UPEC (GView Server; https://server.gview.ca/).

Category	Pathotype	Type of infection	Appearance	Phylogroup
ExPEC	Neonatal Meningitis E.coli (NEMEC)	Meningitis in neonates	Opportunistic	D, E
	Septic E.coli (SEPEC)	Sepsis	Opportunistic	B1
	Uropathogenic E.coli (UPEC)	Urogenital tract infections	Opportunistic	B2 , D
InPEC	Entero -Aggregative E.coli (EAEC)	Diarrhoea (bloody)	Pathogenic	A , B1 , D, E
	Entero -Pathogenic E.coli (EPEC)	Diarrhoea (bloody)	Pathogenic	
	Entero -Toxigenic E.coli (ETEC)	Diarrhoea (bloody)	Pathogenic	
Shigella Toxin Producer InPEC (ShiToPInPEC)	Entero -Hemorrhagic E.coli (EHEC)	Bloody Diarrhoea	Pathogenic	B1, D, E
	Entero -Invasive E.coli (EIEC)	Bloody Diarrhoea	Pathogenic	A, B1, E
	Adhesive -Invasive E. coli (AIEC)	Bloody Diarrhoea	Pathogenic	B2
	Diffused -Adhesive E.coli (DAEC)	Bloody Diarrhoea	Pathogenic	A, B2, D

Table 1. The categorization of *E. coli* pathotypes, the related infections and the condition of appearance.

2. *Escherichia coli* and pangenomics

E. coli is a quite diverse genus which involves a vast range of strains with different metabolic properties, pathogenesis, genomic treasure, virulence factors and ecological varieties. These characteristics make *E. coli* an important case in association with infectious diseases. The *E. coli* strains range from commensal strains (useful normal flora) to AIEC, DAEC, EAEC, EHEC, EIEC, EPEC, ETEC, NEMEC, SEPEC and UPEC pathotypes. The characteristic diversities among *E. coli* strains are completely pertaining to their specific pangenomes. The type of genes and the gene pool of microorganisms determine the quality and the quantity of genetic evolutionary properties [4, 7, 22].

The term pangenome was applied by Sigaux for a database with the content of tissues and tumour genomic data; but the application of pangenome with its microbial content was used by Tettelin and colleagues for the first time, and this refers to a collection of genes and genetic elements in a family group which can be recognized among species of a genus. According to genomic studies, each microbial genus encompasses a main genomic pool which is known as core genome. The core genome contains all those vital genes belonging to different species of a microbial genus. In addition to core genome, there is a group of genomic materials pertaining to species members of a genus which is named as extra genome (flexible or accessory genome). Sometimes some accessory genome pools contain unique genes which are completely related to specific strain. The extra genome possesses genes that are vital but varies in different genome pools. Some genera bear closed pangenomes, whereas the others contain open pangenomes. The open pangenomic microbial organisms involve a vast range of strains. In parallel with molecular techniques, bioinformatics has a key role in pangenomics. Computational analyses give us brilliant information regarding chromosomal genes and motile genetic elements such as plasmids, transposons and phages. Today, the bacterial genus of *E. coli* is known as the most progressive prokaryote with the highest detected genomic sets [7, 31–34].

The complete genomic data regarding *E. coli* (K12 strain) was reported in 1997 for the first time. Due to the recent aforementioned information regarding *E. coli* genomics, we now know that

each strain comprises core genome, accessory genome (extra genome and/or flexible genome) and some unique genes which are specific for each strain. Furthermore, the accessory genomic pool which is flexible may contain integrons, pathogenicity islands (PAIs), phages, plasmids, prophages and transposons. The presence of these genomic elements is related to the nature of the environment in which bacterial cells exist. So, the size of genome is completely dependent on the habitat of bacteria. In another word, the condition of genomic pool and sequence of the genome determine the biological characteristics of the bacteria. Therefore, genomics of *E. coli* strains reveal the needs of them in their own habitats [7, 23, 35].

The reported results from previous studies show that the commensal strains of *E. coli* bear the smallest pangenome (with no virulence genes or with minimal capacity), whereas the pathogenic strains of *E. coli* like UPEC pathotypes encompass large pangenomes (because of the presence of a mass of virulence genes). So, the added genes in pathotype pangenomes are recognized as virulence genes (virulome). It is estimated that UPEC pathotypes carry 10^5 bp much more than commensal strains within their pangenomes. This property gives a high plasticity to UPEC pathotype pangenomes. As shown in published reports, the pangenome of *E. coli* strains involve 4.6–5.9 Mbp and the chromosomal genomes are consisted of limited number of genes [7, 23, 26, 36].

Table 2 shows a number of well-known databases in which the genomic data regarding *E. coli* genomes are accessible.

Database	The main subject	URL	Reference
EcoCyc *E. coli* Database	*Escherichia coli* K-12 MG1655	https://ecocyc.org/	[37, 38]
EcoGene 3.0	*Escherichia coli* K-12	http://ecogene.org/	[39]
Kyoto Encyclopedia of Genes and Genomes (KEGG)	Genes, genomes, etc.	http://www.genome.jp/kegg/ http://www.genome.jp/kegg/	[40]
SHared Information of GENetic Resources (SHIGEN)	The profiling of *Escherichia coli* chromosome (PEC) database	https://shigen.nig.ac.jp/ecoli/pec/	[41]
Pfam 31.0	Protein family database	http://pfam.xfam.org/	[42]
Ensembl Genomes (The European Bioinformatics Institute (EMBL-EBI))	Genomes	http://ensemblgenomes.org/	[43]
The DNA Data Bank of Japan (DDBJ)	Nucleotide sequence database	http://www.ddbj.nig.ac.jp/	[44]
GenBank (National Center for Biotechnology Information (NCBI))	Nucleotide sequence database	http://www.ncbi.nlm.nih.gov/genbank/	[45]

Table 2. Some useful and helpful databases which can be used for *Escherichia coli* pangenome.

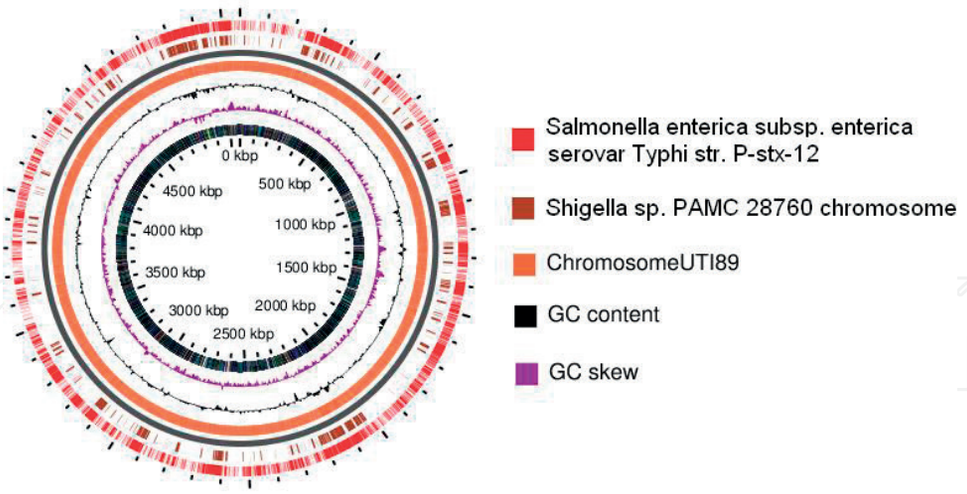

Figure 2. A chromosomal comparison between UPEC (UTI89), *Shigella* sp. and *Salmonella enterica*. The GC content and GC skew are shown, too (GView Server; https://server.gview.ca/).

The pangenomic studies reveal an interesting evolutionary relationship between *E. coli*, *Shigella* spp. and *Salmonella enterica*. It seems that *E. coli* is the ancestor of *Shigella* spp. The *Shigella* spp. have derivated from *E. coli* pathotypes within a duration of 270,000–35,000 years, whereas the origination of *E. coli* and *S. enterica* bacteria from a common progenitor goes back to 100,000,000 years ago [4, 46] (**Figure 2**).

3. Uropathogenic *Escherichia coli* (UPEC)

The UTIs are divided into community-acquired and nosocomial infectious diseases. The UPEC pathotypes are the most dominant causative bacterial agents of UTIs. As previous investigations show, about 50% of nosocomial and up to 95% of community-acquired UTIs are occurred by UPEC strains. So, the UPEC pathotypes are one of the most considered UTI causative agents worldwide. These reports lead us to a wide variety of virulence factors in UPEC pathotypes. Besides, the bioinformatic approaches and pangenomics confirm the presence of a giant treasure of virulence genes within the pangenome of UPEC [7, 8, 35, 47].

The spread of virulence genes among UPEC pathotypes is quite different. The range of UTIs varies from ignorable cases like asymptomatic bacteriuria to deathful cases like urosepsis. The severity of UTIs is completely in association with the UPEC virulence gene pool (virulome). Sometimes, pathotypes undergo mutations in their hosts' bodies which may lead to lose their own virulence genes. It seems that the UPEC pathotypes, which may cause asymptomatic bacteriuria, have undergone virulence gene deletions. On the other hand, strong uropathogenic strains encompass a mass of virulence genes which enable them to occur severe UTIs within their hosts' bodies. The occurrence of UTIs is associated with the host's genetic predisposing factors, immune system, gender, hospitalization, catheterization, social behaviour, sexual activities, personal hygiene and the presence of virulence factors in uropathogenic microbial agents [3, 7, 11, 13, 22, 48–50].

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The outcomes of several studies reveal the presence of a huge number of virulence factors which have been expanded among different strains of UPEC. Here, the most considerable virulence factors are mentioned and the most considerable filamentous adhesins are explained one by one.

4. Uropathogenic *Escherichia coli* (UPEC) virulome

The severity of UPEC pathogenesis is completely in association with diversity of virulence genes in their pangenomes. **Figure 3** shows the pangenome of UTI89. The virulence genes may be located on chromosomes (added through vertical gene transfer) or plasmids, transposons, integrons and phages (added via horizontal gene transfers). Previous studies indicate that the majority of virulence genes belonging to UPEC are located on pathogenicity islands (PAIs) where many of genes are transferred from other species rather than *E. coli* through the feature of horizontal genomic exchange. UPEC pathotypes are effective pathogens due to their high capacity of virulome. The diversity of virulence factors enables UPEC to manifest different types of UTIs in their human hosts. Adhesion, immune system escape mechanisms, iron uptake systems, protease enzymes and toxins are the most significant mechanisms that UPEC pathotypes should utilize them to survive in the human host urinary tract [22, 51–53].

Because of the vast variety of pathogenicity potentials in UPEC strains, only hair-like structures of afimbrial adhesins (including curli and Afa) and fimbrial adhesins (comprising Dr, Type 1 fimbriae, Type 3 fimbriae, F1C fimbriae, S fimbriae, P fimbriae, Auf and F9 fimbriae) are discussed in this chapter. There are some useful databases such as Center for Genomic Epidemiology (https://cge.cbs.dtu.dk/services/VirulenceFinder/) and Virulence Factors of Pathogenic Bacteria (http://www.mgc.ac.cn/VFs/) which may be used for detection and identification virulence genes within the *E. coli* strain populations' genomes [54].

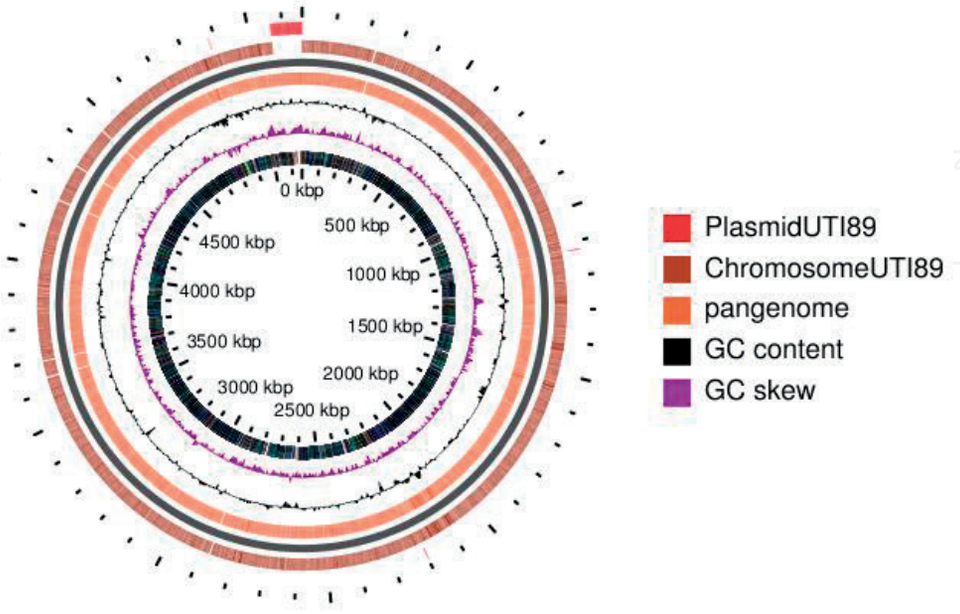

Figure 3. The pangenome map (chromosomal and plasmid genomes) of UPEC (UTI89). The GC content and GC skew are shown, too (GView Server; https://server.gview.ca/).

4.1. Filamentous adhesin virulome

Each microorganism either pathogen or non-pathogen needs to be adhered for colonization. Indeed, colonization of pathogenic microorganisms results in pathogenesis within human body's host. For this reason, UPEC has a range of superficial proteins and adhesins (**Table 3**). However the hair-like structured fimbriae are invaluable virulence factors which enable UPEC pathotypes to have successful attachment, colonization, biofilm formation and virulence [7, 22, 53, 55–65].

Fimbrial adhesins are superficial peritrichous arranged exterior proteinaceous appendages which target special motifs upon the cell surface receptors to join them in the manner of key-and-lock operation. These adhesins are able to attach onto biotic (e.g. host cells) and abiotic (e.g. catheter) surfaces. The aforementioned characteristics make UPEC bacteria functional and effective pathogenic microorganisms. The attachment of bacterial cells of UPEC onto the host cells is a complicated process which may be caused by important proteinaceous molecules of adhesins. Adhesins prepare suitable condition for a successful signalling controlled communication between UPEC cells and human body cells. In other words, the fimbrial adhesins act as signal molecules. As shown in **Table 3**, the most studied and recognized superficial filamentous adhesins are Curli, Dr, AFA, Type 1 fimbriae, Type 3 fimbriae, F1C fimbriae, S fimbriae, P fimbriae, F9 fimbriae and Auf. Some of these superficial fimbrial organelles involving F1C, P, S, Auf, Type 1, Type 3 and F9 fimbriae are categorized into chaperone-usher (CU) proteins [8, 27, 53, 59, 62, 66].

4.1.1. Curli adhesins

Curli adhesins of UPEC are known as types of fragile exterior proteinous coiled fibrous appendages which contribute in linking the UPEC cells onto related receptors situated upon the human body cells such as endothelial cells, epithelial cells, matrix proteins, urothelial cells, mucosal cells, blood cells, etc. In addition to UPEC pathotypes, curli adhesins are recognized in *Salmonella* spp. too. The affinity between curli organelles and Congo red makes it easy to observe these tiny adhesins by microscope. Curli adhesins with up to 12 nm width and 1 μm length are made of CsgA (curlin as major content with amyloid property) and CsgB (as minor content with amyloid property and nucleator activity) proteins. The highly conserved curli gene clusters in UPEC pathotypes are organized into *csgBAC* and *csgDEFG* operons. Curli molecules are effective structures to adhere UPEC cells onto the urine bladder and kidney urothelial cells within human bodies [50, 52, 53, 57, 67–69] (**Table 3**).

4.1.2. Dr/Afa adhesins

The Dr and Afa adhesins are the members of DR family. Dr adhesins (with a homology rate of ≥70%) and Afa molecules are able to bind to the Dr^a blood group antigen molecules situated onto the decay-accelerating factors (DAFs). The DAF molecules are located upon the surface of different types of cells such as urothelial cells. The Dr gene operons consisted of five genes, including *draA–draE*, which are detectable in 7% of the UPEC populations. The *draE* gene is responsible for Dr haemagglutinin production, which is contributed in type IV collagen attachment. *draA–draG* genes are highly conserved and produce the accessory

proteins, whereas the *draE* genes with lower conserved sequences are responsible for adhesin structural subunits. Moreover, the AFA adhesins are encoded by a five-member gene operon including *afaA*, *afaE*, *afaD*, *afaB* and *afaC*. The proteins of AFAI and AFAIII are known as Dr family members. In accordance with previous studies, some of Dr and AFA adhesins have close similarities with chaperone-usher pathway adhesins. The AFA adhesins are recognized in up to 65% of UPEC pathotypes causing cystitis, 26% causing pyelonephritis and 6% asymptomatic bacteriuria (ABU) [7, 8, 22, 55, 61, 70, 71] (**Table 3**).

4.2. Chaperone-usher fimbrial adhesins

There are varieties of fimbriae which are produced by Gram-negative bacteria such as *Enterobacteriaceae* family members. The subunits of these fimbriae are assembled by different pathways like CU pathway. Those fimbriae produced via CU pathway are the most frequent filamentous organelles among Gram-negative bacteria populations. The CU pathway is a kind of common bacterial secretion system with a high conservancy. In a fimbrial CU pathway, chaperone (a periplasmic protein molecule) together with a pore-forming protein of usher (situated within bacterial outer membrane) orchestrate this secretion system. So through the CU pathway, the usher protein plays its role as platform assembler by employing a chaperone to produce and secrete subunits of CU fimbriae class. F1C, P, S, Auf, Type 1, Type 3 and F9 fimbriae in UPEC pathotypes are known as CU pathway proteinaceous adhesins [62, 66, 72–75] (**Table 3**).

4.2.1. Type 1 fimbriae

Type 1 fimbriae as mannose-sensitive adhesins (belonging to chaperone-usher class) are able to attach to those receptors with mannose residues. Uroplakin molecules with high frequency in human urine bladder are known as one of the most important Type 1 fimbriae receptors. Furthermore, there are different types of Type 1 fimbriae receptors which are located on human ureter and Henle's tubules. These fimbriae are encoded in 99% of commensal and pathogenic strains of *E. coli* including UPEC pathotypes. As important virulence factors, Type 1 fimbriae have peripheral arrangement upon the microorganisms' surfaces with a number of 1–5 hundred. Type 1 fimbriae with up to 10 nm width and up to 2 μm length are able to perform haemagglutination. The Type 1 fimbriae are encoded by the highly conserved gene operon consisted of nine genes of *fimBEAICDFGH*. The FimH protein which is located on the top of Type 1 fimbria is recognized as the main adhesin. FimG, Fim F and FimA protein molecules are, respectively, situated under the FimH molecule. FimC and FimD play their roles as chaperone and usher proteins, respectively. The recombinase enzymes of FimB and FimE activate as bidirectional switching molecules for turning on and/or turning off the cluster gene expression. The activities of FimB and FimE are directly associated with environmental factors [7, 22, 50, 53, 55, 60, 62, 68, 71, 74, 76, 77] (**Table 3**).

4.2.2. Type 3 fimbriae

Type 3 fimbriae are encoded by *mrk* gene operon of *mrkABCDEF* in UPEC and other members of *Enterobacteriaceae* family such as Klebsiella pneumoniae. The highly conserved gene

of *mrkB* encodes chaperone protein of MrkB, whereas the MrkC plays role as usher protein. MrkA and MrkF are the major and minor subunits in Type 3 fimbriae, respectively. The adhesin molecule of Type 3 fimbria is recognized as MrkD and MrkE plays its role as a regulator protein. It seems that *mrk* gene cluster originally belongs to K. pneumoniae which has been horizontally transferred into UPEC pathotypes by plasmids. The role of Type 3 fimbriae in biofilm formation regarding catheter-associated urinary tract infections (CAUTs) is significantly considered [53, 56] (**Table 3**).

4.2.3. F1C fimbriae

The F1C fimbriae are encoded by a gene operon consisting of seven genes of *focAICDFGH*. F1C fimbriae are expressed by up to 30% of UPEC pathotypes. The F1C fimbria is composed of FocA (major fimbrin subunits), FocF and FocG (minor fimbrin subunits) proteins. On the top of F1C fimbria, FocH monomer is located which acts as an adhesin. So, F1C fimbriae adhere onto the receptors with galactosylceramide (situated on the surfaces of urothelial cells of the urinary bladder, kidneys and ureters) and globotriaosylceramide (located in kidneys) residues. Previous surveys indicate a strong attraction between F1C fimbriae and Gal-NAc-beta-1-4-Gal-beta structure of glycolipids. FocC and FocD proteins are recognized as chaperone and usher molecules, respectively. Due to prior scientific investigations, the F1C fimbriae are able to bind to their specific receptors upon the whole zone of the urinary tract. There is a close homology between F1C and S fimbriae [7, 53, 55, 62, 66, 78] (**Table 3**).

4.2.4. S fimbriae

In addition to FIC, the S fimbriae organelles have also a close morphology to F9, P and Type 1 fimbriae and are detected in ≥22% of the UPEC pathotypes. The S fimbriae are encoded by *sfa* gene operon with nine genes. SfaA, SfaS and SfaH proteins contribute in S fimbrial adhesion. The SfaA protein is a dominant subunit, and the minor subunits are composed of SfaG, SfaH and SfaS. SfaS is located on the top of S fimbriae and adhere to alpha-sialyl-2,3-alpha-galactose residues upon the glycoproteins of urothelial tissues of the urinary bladder and kidneys. The presence or absence of S fimbriae is determined by environmental factors. The related regulations and phase variations are done by SfaB and SfaC [7, 22, 35, 50, 53, 55, 62, 66, 71, 77, 79] (**Table 3**).

4.2.5. P fimbriae

P fimbriae as considerable adhesins are encoded by 11 genes within a gene operon of *papA-K* in up to 70% of UPEC pathotypes. The predominant subunit in P fimbria is PapA fimbrin placed in the basis of the fimbrial stalk. PapG is known as the main adhesin which is linked to the stalk by PapE, PapF and PapK proteins. PapD and PapC have chaperone and usher roles, respectively. There are some isoclasses for PapG (PapGI, PapGII (major isoclass in UPEC strains) and PapGIII) in different UPEC pathotypes. The related receptor epitopes of P fimbriae are alpha-D-galactopyranosyl-(1-4)-beta-D-galactopyranoside which are located on the surface of entire urothelial cells covering the human urinary tract. P fimbriae are recognized as significant virulence factors in UPEC virulome [7, 22, 50, 53, 62, 66, 71, 77] (**Table 3**).

4.2.6. Auf fimbriae

Auf (acronym for another UPEC fimbria) fimbriae are detected in 67% of isolated UPEC pathotypes. The Auf fimbriae are encoded by the gene operon of *aufABCDEFG*. AufA protein is predominant subunit in Auf fimbria, whereas AufC is known as an usher protein. The Auf protein receptors are still unknown in human body cells [7, 22, 53, 62, 74] (**Table 3**).

4.2.7. F9 fimbriae

The F9 fimbriae encoded by *f9* gene operon including *c1931–c1936* are detectable in 78% of UPEC populations. The C1931 protein is the major subunit identified in F9 fimbriae. The genetic and structural characteristics of F9 fimbriae are very close to Type 1, F1C and S fimbriae. Gal-beta-(1-3)-Glc-NAc and lacto-N-tetraose glycans are recognized as the main F9 fimbriae receptors [22, 53, 59, 60] (**Table 3**).

5. Diagnostic methods for virulence genes of filamentous adhesins

Detection and identification of genes such as virulence genes of filamentous adhesins may be achieved by a vast range of molecular techniques. PCR tools from conventional and multiplex to real time are the commonest molecular diagnostic techniques which can be used for limited samples [80–86].

Furthermore there are advanced pangenomic techniques like microarray technology which can be applied for detection and identification of different types of genes, when there are huge numbers of specimens. Microarray technology is divided into three types of DNA, protein and RNA microarray tools. The outcome of microarray technology is reliable, sensitive, specific, flexible and rapid with high accuracy [4, 7, 8, 87–93].

6. Conclusion

UPEC strains are expanded pathogenic microorganisms which are able to carry a mass of virulence genes within their genomes. The environmental condition and the genomic abilities and capacity determine the expression of virulence genes and factors. The UPEC strains bear different types of virulence factors in different parts of their cellular structures. These properties make UPEC pathotypes interesting pathogenic microorganisms which can appear a vast range of UTIs: from acute to chronic, from light to severe, from complicated to uncomplicated, from lower to upper and from asymptomatic to symptomatic signs and syndromes. So, knowing the genotypic and phenotypic characteristics of UPEC strains in different regions of world helps us to recognize the probable UPEC strains with their local clinical demonstrations. This enables us to have an accurate diagnosis with a definite treatment to reduce the healthcare costs around the world. Moreover, equipped microbiology laboratories with normal molecular tools and techniques like PCR or advanced pangenomic technologies support us to have specific, sensitive and reliable outcome.

Adhesins	Type of adhesins	Genes	Role	Target structure	Type of UTIs
Curli	Afimbrial adhesin	*csgA, csgB,csgC, csgD, csgE,csgF,csgG*	Adhesion for colonization (biofilm formation) and invasion	Matrix Proteins like Fibronectin, Laminin and Plasminogen, Mucosal cells	Severe UTIs; Cystitis in particular
Dr	Fimbrial adhesin	*dra* gene family including: *draA, draB, draC, draD, draE, draP*	Adhesion for colonization, Preparing invasion	A vast range of cells with Dr blood group antigen on their surfaces like urothelia, Neutrophil cells, Connective tissues in upper part of human urinary tract	(Recurrent and/or chronic) Cystitis and pyelonephritis (mostly in pregnant women), Asymptomatic Bacteriuria (ABU) in few cases
AFA	Afimbrial adhesin	*afa* gene family including: *afaI, afaII, afaIII ,afaIV,nfa1 ,drII*			
Type 1 fimbriae	Fimbrial adhesin (sensitive to mannose)	*fim* gene family including: *fimA, fimB, fimC, fimD, fimE, fimF, fimG, fimH, fimI*	Adhesion for colonization (biofilm formation), invasion	Red Blood Cells (RBCs), Mucosal membrane and Epithelium cells, Uroplakin receptors in urine bladder	UTIs
Type 3 fimbriae	Fimbrial adhesin	*mrk gene familyincluding: mrkA, mrkB, mrkC, mrkD, mrkE, mrkF*			UTIs in catheterized patients
F1C fimbriae	Fimbrial adhesin	*focA, focC, focD, focf, focG, focH, focI*	Adhesion for colonization (biofilm formation)	Glycolipids of endothelia, Mucosal membrane and Glomeruli	UTIs, Pyelonephritis in particular
S fimbriae	Fimbrial adhesin	*sfaA, sfaB, sfaC, sfaD, sfaE, sfaF, sfaG, sfaH, sfaS, sfaX, sfaY*	Adhesion and colonization	Sialic acid molecules on kidneys and glomeruli endothelial, epithelial and mucosal cells	Upper UTIs in most cases
P fimbriae	Fimbrial adhesin Resistance to mannose	*papa, papB, papC, papD, papE, papF, papG, papH, papI, papJ, papK*	Adhesion and colonization	vascular epithelia, urothelia and Mucosal cells	Acute forms of UTIs (particularly Pyelonephritis), ABU in few cases
F9 fimbriae	Fimbrial adhesin	*c1931, c1932, c1933, c1934, c1935, c1936*	Adhesion for colonization (biofilm formation) ?	Urothelial cells ?	UTIs ?
Auf fimbriae (Another UPEC Fimbriae)	Fimbrial adhesin	*aufA, aufB, aufC, aufD, aufE, aufF, aufG*	Adhesion for colonization (biofilm formation)	unknown	UTIs

Table 3. The UPEC fimbrial and afimbrial adhesins and their characteristics within human bodies [7, 22, 53, 55–64, 71].

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