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Infections caused by fluoroquinolone-resistant *Escherichia coli* following transrectal ultrasound-guided biopsy of the prostate

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Abstract

An increase in the number of infections with fluoroquinolone (FQ)-resistant *Escherichia coli* following transrectal ultrasound-guided biopsy of the prostate (TRUBP) was observed in Louis Stokes Cleveland Department of Veterans Affairs Medical Center. This study investigated whether these infections were caused by a single strain of *E. coli* possessing distinct resistance and virulence determinants. Of 15 patients with urinary tract infection, 5 were complicated with bacteraemia and 1 with prostate abscess. Thirteen FQ-resistant isolates demonstrated mutations in the quinolone resistance-determining regions (QRDRs) of *gyrA* and *parC* but did not contain plasmid-mediated quinolone resistance determinants; *bla*_{CTX-M} and *bla*_{CMY} as well as genes coding for extended-spectrum β -lactamases were also absent. Genes encoding aminoglycoside-

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modifying enzymes were discovered in an isolate that was gentamicin-resistant. The most prevalent sequence type (ST) was ST43 ($n = 7$), corresponding to ST131 in Achtman's multilocus sequence typing (MLST) scheme. These isolates (i) were distinguished as >95% similar by repetitive sequence-based PCR (rep-PCR), (ii) belonged to the virulent phylogenetic group B2 and (iii) contained plasmid types FIB, FIA and Frep. Several other strain types were present (ST2, ST27, ST30, ST44, ST472, ST494, ST511 and ST627). Non-ST43 isolates infected patients with more co-morbidities but contained similar virulence factors (*kpsMTII*, *iutA*, *papAH/papC* and *sfa/focDE*). In our hospital, *E. coli* isolates causing TRUBP-related infection are quite heterogeneous (ST131 and other ST types) and are part of phylogenetic groups containing multiple virulence factors.

Keywords

Escherichia coli; MLST; rep-PCR; Virulence; Prostate biopsy

1. Introduction

Each year, an estimated one million US men undergo transrectal ultrasound-guided biopsy of the prostate (TRUBP). *Escherichia coli* is the pathogen most commonly associated with infections occurring as a complication of this procedure [1]. Fluoroquinolones (FQs) are frequently administered as prophylactic antibiotics in order to prevent infections following TRUBP. Unfortunately, FQ resistance in *E. coli* and other Gram-negative bacilli has emerged steadily in recent years and there have been reports of increasing rates of infection due to FQ-resistant *E. coli* in patients undergoing TRUBP [2]. A particular strain of FQ-resistant *E. coli*, sequence type ST131, has a distinct virulence profile and frequently harbours CTX-M-type extended-spectrum β -lactamases (ESBLs). The enhanced virulence and antimicrobial resistance of *E. coli* ST131 has led to its emergence as a cause of community-onset urinary tract infections (UTIs) in the USA and globally [3,4].

On 30 December 2010, we became aware of four patients who required admission to the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCDVAMC) (Cleveland, OH) in the previous 2 months because of serious infections with FQ-resistant *E. coli* occurring after TRUBP. Concerned by what appeared to be a sudden increase in the number of cases, a case–case–control investigation was undertaken that did not identify increased exposure to antibiotics or other risk factors associated with the development of infection following TRUBP [5]. In the present analysis, we focused on the characteristics of the bacterial isolates causing infection after TRUBP. Given that *E. coli* ST131 has demonstrated the ability to disseminate into different locales, the present study investigated whether that particular strain type possessing distinct virulence and antibiotic resistance determinants was responsible for infections associated with TRUBP in this hospital.

2. Materials and methods

2.1. Study setting and case definition

LSCDVAMC is a 265-bed acute-care facility with 13 associated outpatient clinics that serve more than 100 000 patients from northeast Ohio (USA). Between December 2009 and February 2012, 752 patients underwent TRUBP (ca. 30 procedures/month). Among these, 30 patients (4.0%) were found to have infection; 25 patients were infected with FQ-resistant *E. coli* and 5 patients with FQ-susceptible *E. coli*. For the present retrospective study, it was possible to collate bacterial isolates from 15 patients. UTI associated with TRUBP was defined as a urine culture with >100 000 CFU/mL of *E. coli* in addition to fever, dysuria, urinary frequency, urgency, suprapubic pain or tenderness within 30 days of the procedure. Bacteraemia was defined as growth of *E. coli* in a blood culture and signs of systemic infection (e.g. fever/hypothermia, tachycardia, tachypnoea, leukocytosis/leukopenia). Medical records were reviewed, noting demographic characteristics, hospital admissions, use of antibiotics in the past year, medical conditions (i.e. diabetes mellitus, systemic steroids, immunodeficiency, cerebrovascular or chronic kidney disease, spinal cord injury and previous urological abnormalities) and biopsy-related factors (i.e. prior biopsy, prostate size at the time of procedure and type of antibiotic prophylaxis). A co-morbidity index was determined according to Charlson, including adjustment for age [6].

2.2. Bacterial isolates and antimicrobial susceptibility testing

Isolates of *E. coli* associated with infection after TRUBP, including blood isolates in five patients with bacteraemia, were analysed in the clinical microbiology laboratory. Bacteria were identified as *E. coli* and antimicrobial susceptibility testing was performed using a VITEK® 2 system (bioMérieux, Inc., Durham, NC) and results were interpreted according to breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) [7].

2.3. Analysis of the quinolone resistance-determining regions (QRDRs) and detection of plasmid-mediated quinolone resistance (PMQR) determinants, aminoglycoside-modifying enzymes (AMEs) and β -lactamase genes

Detection of mutations in the QRDRs of *gyrA* and *parC* genes as well as analyses of PMQR, AMEs and *bla* genes were performed by PCR and sequencing of amplicons. Genomic DNA extraction, amplification and sequencing were performed using primers and methods described elsewhere [8–10]. Genes screened to investigate PMQR were *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *qepA*, *oqxA* and *oqxB*. AME genes included were *aac(6')-Ib-cr*, *aacC1*, *aacC2*, *aadA1*, *aadB* and *aphA6*. The β -lactamase genes investigated were *bla_{SHV}*, *bla_{TEM}*, *bla_{CTX-M}* and *bla_{CMY}*.

2.4. Repetitive sequence-based PCR (rep-PCR)

Genomic DNA was extracted from bacterial isolates using an UltraClean® Microbial DNA Isolation Kit (MO BIO Laboratories, Carlsbad, CA). PCR amplification was performed using a DiversiLab® (bioMérieux, Athens, GA) *E. coli* fingerprinting kit, and rep-PCR amplicons were separated by electrophoresis on microfluidic chips and were analysed with an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Resulting band

patterns were compared by Pearson's correlation and isolates that were >95% similar were considered the same strain type [11].

2.5. Multilocus sequence typing (MLST)

Gene amplification and sequencing of eight housekeeping genes (*dinB*, *icdA*, *pabB*, *polB*, *putP*, *trpA*, *trpB* and *uidA*) was performed, and allele and sequence types (STs) were determined using the platform for *E. coli* MLST maintained at the Institut Pasteur (Paris, France) [12].

2.6. Plasmid replicon typing and phylogenetic group classification

Plasmid replicon typing was performed using the PCR-based method developed by Carattoli et al., employing primers that detect unique areas in 18 plasmid replicons frequently found in Enterobacteriaceae [13]. All *E. coli* strains were assigned to one of the four main phylogenetic groups (A, B1, B2 and D) using a previously described multiplex PCR-based method [14].

2.7. Virulence factor detection

To classify isolates as extraintestinal pathogenic *E. coli* (ExPEC) or non-ExPEC, isolates were screened for five common virulence factors (*afa/draBC*, DR-binding adhesins; *kpsMTII*, group II capsular polysaccharide synthesis, *iutA*, aerobactin receptor; *papAH/papC*, P fimbriae subunit and assembly; and *sfa/focDE*, adhesin genes of S and FIC fimbriae). The presence of two or more of these virulence factors defined an isolate as ExPEC [15].

2.8. Statistical analysis

Comparison of characteristics, clinical outcomes and molecular analyses between patients infected with ST43 (ST131) and non-ST43 *E. coli* isolates was performed. Fisher's exact test was used to compare proportions of categorical variables, Student's *t*-test to compare mean values, and the Mann–Whitney *U*-test to compare median values of ordinal variables (i.e. Charlson index). Analyses were performed using R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria). *P*-values of <0.05 were considered significant.

3. Results and discussion

3.1. Clinical characteristics of cases

Fifteen cases of infection following TRUBP caused by *E. coli* as well as the corresponding isolates were identified and included in the study. According to protocols followed at LSCDVAMC, all patients received ciprofloxacin as antibiotic prophylaxis [16]. The mean patient age was 63 years (range 52–70 years) and patients had a median Charlson weighted index of 3 (range 2–7) (Table 1). Only two patients (13%) had a history of TRUBP within 5 years of the current episode, and five patients (33%) were prescribed antibiotics within the preceding year. The majority of patients (67%) were eventually found to have prostate cancer. All patients were diagnosed with UTIs; five were complicated with bacteraemia and one with prostate abscess. Eleven patients (73%) required hospitalisation, ranging in

duration between 2 days and 8 days. Four patients had recurrent infection and two had to be re-admitted to the hospital. All of the patients survived.

3.2. Bacterial isolates and antimicrobial susceptibility testing

As seen in other centres, FQ-resistant *E. coli* was identified as the overwhelming cause of infection following TRUBP [87% of isolates (13/15) were ciprofloxacin-resistant] [2]. Susceptibility to ampicillin and trimethoprim/sulfamethoxazole occurred in 33% (5/15) and 53% (8/15) of the isolates, respectively. One isolate was resistant to gentamicin, but all were susceptible to amikacin. Of note, nitrofurantoin retained very good activity (87% susceptibility). All *E. coli* isolates demonstrated susceptibility to extended-spectrum cephalosporins and carbapenems, and two isolates had decreased susceptibility to piperacillin/tazobactam (TZP) (Table 2).

3.3. Analysis of quinolone-resistance determining regions and detection of plasmid-mediated quinolone resistance determinants, aminoglycoside-modifying enzymes and β -lactamase genes

Analysis of the QRDRs and examination of AME genes were consistent with the phenotypic profiles of the strains. All FQ-resistant *E. coli* isolates were found to have mutations in *gyrA* and *parC*, whilst the isolate that expressed gentamicin resistance was found to have *aac(6')-Ib-cr* (also conferring ciprofloxacin resistance), *aacC1*, *aadA1* and *aadB* genes, and an *aacC2* gene [4,8]. The analysis did not detect any of the eight PMQR genes, as described in other studies of *E. coli* ST131 [4].

All of the isolates from this study were susceptible to extended-spectrum cephalosporins, and PCR amplification did not detect *bla*_{CTX-M}, *bla*_{CMY} or *bla*_{SHV} genes. Previous studies from the USA have reported the co-existence of ESBL genes with FQ resistance, especially in *E. coli* ST131 [3]. Similar to the current study, Mavroidi et al. recently found that the majority of FQ-resistant ST131 *E. coli* (12/21; 57%) from Central Greece did not carry ESBL genes [17]. In the nine ampicillin-resistant isolates studied here, the presence of *bla*_{TEM} was detected. Two isolates displayed decreased susceptibility to TZP and harboured only *bla*_{TEM-1}. Sequencing of the promoter region did not identify either a P4 or P5 promoter, which are associated with *bla*_{TEM} upregulation and serve as a mechanism of resistance to TZP [18]. Mutations conferring resistance to inhibitors in this *bla*_{TEM} gene were not found. The presence of *bla*_{AmpC} other than *bla*_{CMY} and *bla*_{OXA_s} was not ruled out. It must be noted that in North America CMY is the predominant AmpC cephalosporinase in *E. coli* [19].

3.4. rep-PCR, multilocus sequence typing and plasmid replicon typing

As shown in Fig. 1, six different clones of *E. coli*, as defined by rep-PCR, were identified. This corresponded to eight different MLST types, the most common of which was ST43 [detected in 7 isolates (47%)]. ST43 corresponds to ST131 in Achtman's MLST scheme [20]. Other types present were ST2, ST27, ST30, ST44, ST472, ST494, ST511 and ST627 (one isolate each). Of note, there were three instances of different STs classified under the same rep-PCR group (>95% similarity): ST43 and ST627 (a ST first reported in this study),

with three common alleles; ST27 and ST30, sharing one allele; and ST511 and ST494, with seven alleles in common.

Table 3 summarises the plasmid replicon types found in the isolates. Interestingly, isolates from different geographical origins contained plasmids of the same incompatibility types, including FIA, FIB, I1, N and Frep; these have been previously associated with a variety of ESBLs, AmpC cephalosporinases and carbapenemases [21]. Of particular note, a previous study reported the association of the *bla*_{CTX-M-15} gene with FII, FIB and FIA (87%, 44% and 42%, respectively) in ST43 (ST131) isolates, the predominant ST in this collection [4].

3.5. Phylogenetic group and virulence factor determination

Phylogenetic analysis showed that the majority of *E. coli* isolates belonged to phylogenetic groups B2 and D (10 and 4 isolates, respectively) (Fig. 1), which have been associated with severe clinical disease [15]. In fact, virulence factors were detected more often among isolates belonging to phylogenetic groups B2 and D. Only one of the isolates (EC1) belonged to phylogenetic group A. Six *E. coli* isolates (40%) with two or more virulence factors were found, consistent with the ExPEC definition (Table 1). These included *kpsMTII*, *iutA*, *papAH/papC* and *sfa/focDE* genes. None of the isolates was found to contain the *afa/draBC* gene.

3.6. Comparison of clinical characteristics, outcomes and molecular analyses of patients infected with ST43 (ST131) and non-ST43 *Escherichia coli* isolates

To gain a deeper insight into the impact of this particular clonal lineage, the molecular characteristics of the bacteria and the clinical profiles of patients infected with ST43 (ST131) were compared with those infected with non-ST43 isolates (Table 1). In this series, there was a trend towards more frequent, albeit significantly shorter, hospital admissions in patients infected with ST43 (ST131) despite their lower co-morbidity score. Interestingly, patients with ST43 (ST131) had less frequent antibiotic exposure and previous UTIs. All ST43 (ST131) isolates belonged to phylogenetic group B2, often associated with virulence and severe disease, and harboured, with one exception, three plasmid replicon types (FIA, FIB and Frep). Differences in the proportion of ExPEC strains between the ST43 (ST131) and non-ST43 isolates were not found. The presence of *papAH/papC*, *sfa/focDE* and *kpsMTII* was found to be more common in non-ST43 isolates. In contrast, *iutA* occurred predominantly in ST43 (ST131) isolates. None the less, these associations were not statistically significant. Importantly, we emphasise the absence of *bla*_{CTX-M}, which frequently converges with FQ resistance and virulence factors in *E. coli* ST131 in the USA [3,22], although not necessarily in other parts of the world as recently demonstrated in Greece [17].

The most common aetiology of infection following TRUBP in the current case series, namely FQ-resistant *E. coli* ST43 (ST131), is well recognised as a pandemic multidrug-resistant (MDR) strain [3,4]. A frequent cause of UTI, ST131 was also identified as a cause of infection after TRUBP in a recent study from New Zealand [22]. There is growing awareness of the clinical impact of *E. coli* ST131, often leading to serious infections in patients with healthcare exposures. In many instances, *E. coli* ST131 is found as a truly

‘community-acquired’ pathogen [3]. This important change in the epidemiology of *E. coli* may dictate a re-assessment of antibiotic prescribing practices to treat UTIs. Broader antibiotic therapy may be required initially in seriously ill patients, anticipating the MDR phenotype of these high-risk clonal lineages, and in order to avoid the potential dire consequences of inappropriate antimicrobial therapy.

The series of infections following TRUBP seen at LSCDVAMC may reflect the increasing incidence of *E. coli* ST131 and other FQ-resistant strains in the community served, following national and global patterns. In 2011, we documented through rectal swab screening that the prevalence of colonisation with FQ-resistant *E. coli* at our facility was 16%, whereas surprisingly it was only 1% for ESBL-producing *E. coli* [23]. Unfortunately, the standard prophylaxis for TRUBP used at our hospital, ciprofloxacin, may have contributed to select populations of FQ-resistant *E. coli*, which translocated to the prostate and bloodstream as the needle passed through the rectum. Given the morbidity we observed from infectious complications after TRUBP, screening for colonisation with MDR and FQ-resistant *E. coli* and subsequent adjustment of antibiotic prophylaxis was implemented in LSCDVAMC. Through these measures, the rate of FQ-resistant *E. coli* infections following TRUBP has decreased significantly ($P < 0.05$), from 4.3% (23/541) before the intervention to 1.6% (9/571) in the subsequent 18-month period [23]. We foresee that the advent of more sensitive and rapid diagnostic methods in the clinical setting will facilitate the early detection of certain MDR strains with defined virulence profiles, such as FQ-resistant *E. coli* ST131. This, in turn, may help optimise tailored pre-operative and post-operative infection control and antibiotic stewardship measures in order to prevent infectious complications related to TRUBP and other invasive procedures.

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Fig. 1. Dendrogram illustrating clusters of similar isolates of *Escherichia coli* determined by repetitive sequence-based PCR (rep-PCR), with corresponding multilocus sequence typing (MLST) (Pasteur scheme) strain type and phylogenetic group. Sequence type ST43 isolates (corresponding to ST131 in Achtman's MLST scheme) are highlighted.

Table 1

Comparison of clinical characteristics, outcomes and molecular analyses of patients infected with *Escherichia coli* sequence type ST43 (ST131) and non-ST43 strains

	ST43 (ST131) [n (%)] ^a	Non-ST43 [n (%)] ^a	P-value
No. of patients	7	8	
Age (mean) (years)	62.1	63.5	0.64
Charlson index (median)	0	3	0.009 *
Age-adjusted Charlson index (median)	2	5	0.02 *
PSA (ng/mL)	5.5	8.2	0.3
Race			
Caucasian	6 (86)	7 (88)	1
TRUBP result			
Prostate cancer	5 (71)	5 (63)	1
Benign prostatic hypertrophy	2 (29)	3 (38)	1
Clinical outcome			
Admission	6 (86)	5 (63)	0.57
Length of stay (mean) (days)	3.7	6.4	0.057
Bacteraemia	2 (29)	3 (38)	1
Phylogenetic group B2	7 (100)	3 (38)	0.026 *
Virulence factors			
<i>kpsMTIII</i>	2 (29)	6 (75)	0.13
<i>papAH/papC</i>	0	3 (38)	0.2
<i>sfa/focDE</i>	0	1 (13)	1
<i>iutA</i>	7 (100)	4 (50)	0.077
ExPEC	2 (29)	4 (50)	0.6
Plasmid replicon typing			
FIA	7 (100)	3 (38)	0.026 *
FIB	7 (100)	3 (38)	0.026 *
Frep	6 (86)	5 (63)	0.57
FIA, FIB, Frep	6 (86)	1 (13)	0.01 *

PSA, prostatic specific antigen; TRUBP, transrectal ultrasound-guided biopsy of the prostate; ExPEC, extraintestinal pathogenic *E. coli*.

^aData are n(%) unless otherwise stated.

* Associations occurring at $P < 0.05$ were considered statistically significant.

Table 2

Results of antibiotic susceptibility testing for *Escherichia coli* associated with infections after transrectal ultrasound-guided biopsy of the prostate

Isolate	MIC (µg/mL) (susceptibility category)											
	CIP	AMP	SAM	CFZ	CRO	FEP	TZP	IPM	SXT	GEN	AMK	NIT
EC1	4 (R)	32 (R)	32 (R)	4 (S)	1 (S)	1 (S)	64 (I)	1 (S)	320 (R)	2 (S)	4 (S)	64 (I)
EC2	4 (R)	32 (R)	32 (R)	16 (I)	1 (S)	1 (S)	4 (S)	1 (S)	320 (R)	2 (S)	4 (S)	16 (S)
EC3	0.25 (S)	32 (R)	32 (R)	64 (R)	1 (S)	1 (S)	128 (R)	1 (S)	320 (R)	1 (S)	2 (S)	16 (S)
EC5	4 (R)	2 (S)	2 (S)	4 (S)	1 (S)	1 (S)	4 (S)	1 (S)	20 (S)	1 (S)	2 (S)	16 (S)
EC7	4 (R)	32 (R)	16 (I)	4 (S)	1 (S)	1 (S)	8 (S)	1 (S)	320 (R)	1 (S)	2 (S)	16 (S)
EC8	0.25 (S)	4 (S)	4 (S)	4 (S)	1 (S)	1 (S)	4 (S)	1 (S)	20 (S)	1 (S)	2 (S)	16 (S)
EC9	4 (R)	2 (S)	2 (S)	4 (S)	1 (S)	1 (S)	4 (S)	1 (S)	20 (S)	1 (S)	2 (S)	16 (S)
EC10	4 (R)	32 (R)	16 (I)	4 (S)	1 (S)	1 (S)	8 (S)	1 (S)	320 (R)	16 (R)	2 (S)	16 (S)
EC11	4 (R)	8 (S)	8 (S)	4 (S)	1 (S)	1 (S)	8 (S)	1 (S)	20 (S)	1 (S)	2 (S)	16 (S)
EC12	4 (R)	32 (R)	16 (I)	4 (S)	1 (S)	1 (S)	8 (S)	1 (S)	20 (S)	1 (S)	4 (S)	16 (S)
EC13	4 (R)	32 (R)	32 (R)	16 (I)	ND	ND	ND	ND	20 (S)	ND	ND	16 (S)
EC14	4 (R)	32 (R)	8 (S)	4 (S)	1 (S)	1 (S)	4 (S)	1 (S)	20 (S)	1 (S)	2 (S)	16 (S)
EC15	4 (R)	32 (R)	32 (R)	4 (S)	1 (S)	1 (S)	ND	1 (S)	320 (R)	1 (S)	2 (S)	16 (S)
EC16	4 (R)	2 (S)	2 (S)	4 (S)	1 (S)	1 (S)	8 (S)	1 (S)	320 (R)	1 (S)	2 (S)	16 (S)
EC17	4 (R)	16 (I)	4 (S)	4 (S)	1 (S)	1 (S)	8 (S)	1 (S)	20 (S)	1 (S)	2 (S)	64 (I)
% susceptible	13	33	47	80	100	100	85	100	53	93	100	87

MIC, minimum inhibitory concentration; CIP, ciprofloxacin; AMP, ampicillin; SAM, ampicillin/sulbactam; CFZ, cefazolin; CRO, ceftriaxone; FEP, cefepime; TZP, piperacillin/azobactam; IPM, imipenem; SXT, sulfamethoxazole/trimethoprim; GEN, gentamicin; AMK, amikacin; NIT, nitrofurantoin; I, intermediate; R, resistant; S, susceptible; ND, no data.

Table 3

Sequence types (STs), virulence factors (VFs), plasmid replicon types and quinolone resistance determining region (QRDR) analysis

Isolate	ST	VFs				No. of VFs	Plasmid replicon type	QRDR mutations	
		<i>afa/draBC</i>	<i>kpsMTII</i>	<i>iutA</i>	<i>papAH/papC</i>	<i>sfafocDE</i>		<i>gyrA</i>	<i>parC</i>
EC1	ST2	-	-	-	-	-	0	FIA, FIB, Frep, II	S83L, D87N S80I
EC2	ST43 (ST131)	-	-	+	-	-	1	FIA, FIB, Frep	S83L, D87N S80I, E84V
EC3	ST27	-	+	-	+	+	3	Frep	No changes No changes
EC5	ST494	-	+	+	+	-	3	FIA	S83L, D87N S80I
EC7	ST511	-	+	+	+	-	3	FIA, FIB	S83L, D87N S80I
EC8	ST30	-	+	+	-	-	2	Frep	D87G No change
EC9	ST43 (ST131)	-	-	+	-	-	1	FIA, FIB	S83L, D87N S80I, E84V
EC10	ST627	-	-	+	-	-	1	FIB, Frep	S83L, D87N S80I
EC11	ST472	-	+	-	-	-	1	None	S83L, D87N S80I
EC12	ST43 (ST131)	-	-	+	-	-	1	FIA, FIB, Frep	S83L, D87N S80I, E84V
EC13	ST43 (ST131)	-	-	+	-	-	1	FIA, FIB, Frep, II, N	S83L, D87N S80I, E84V
EC14	ST43 (ST131)	-	+	+	-	-	2	FIA, FIB, Frep	S83L, D87N S80I, E84V
EC15	ST43 (ST131)	-	+	+	-	-	2	FIA, FIB, Frep, II	S83L, D87N S80I, E84V
EC16	ST43 (ST131)	-	-	+	-	-	1	FIA, FIB, Frep	S83L, D87N S80I, E84V
EC17	ST44	-	+	-	-	-	1	Frep	S83L, D87N S80I