INFECTION AND IMMUNITY, Sept. 1998, p. 4568–4571 Vol. 66, No. 9
0019-9567/98/$04.00+0
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papG Alleles among *Escherichia coli* Strains Causing Urosepsis: Associations with Other Bacterial Characteristics and Host Compromise

JAMES R. JOHNSON*

University of Minnesota and Minneapolis VA Medical Center, Minneapolis, Minnesota

Received 6 April 1998/Returned for modification 15 May 1998/Accepted 4 June 1998

Alleles I, II, and III of the P adhesin gene *papG* were sought by PCR among 75 *Escherichia coli* blood isolates from adults with urosepsis, and the *papG* genotype was compared with associated bacterial characteristics and host compromise status. Allele II predominated over allele III in the total population (71% of the strains versus 7% for allele III; $P < 0.01$). Allele I was not encountered. In comparison with allele II, allele III was significantly associated with the presence of *hly* and the absence of *iuc* (which encode hemolysin and aerobactin biosynthesis), nonagglutination of digalactoside-coated beads, absence of aerobactin production, membership in serogroups O6 and O18, and host compromise, particularly cancer and upper urinary tract abnormalities.

P fimbriae, the principal adherence organelles of uropathogenic *Escherichia coli*, mediate Gal(α1-4)Gal-specific binding via the adhesin molecule PapG (4, 16, 18–20, 22). PapG occurs in three molecular variants (I to III), which are encoded by distinct alleles of the adhesin gene *papG* (24) and exhibit subtly different receptor binding preferences (27). Whether the three *papG* variants differ with respect to associated bacterial traits, clinical syndromes, or host characteristics (the last being relevant to the development and deployment of possible future adhesin-based vaccines [23]) has only recently begun to be explored (3, 7, 12, 26).

Published data associate acute cystitis with *papG* allele III (3, 12) and acute pyelonephritis with allele II (3, 26). An initial study suggested the exclusive involvement of allele II in *E. coli* bacteremia also (26). However, a subsequent larger study found a substantial prevalence of allele III as well, independent of the source of the bacteremia (7).

Whereas the subjects in the former study were otherwise-healthy Swedish women with acute pyelonephritis (26), the subjects in the latter study, who were from Nairobi, Boston, and Long Beach, had bacteremia arising from diverse primary infections (7). Many also had underlying local or systemic compromising conditions (7, 25). These population differences, as well as the locale-specific differences in the *papG* allele mix between clinical centers noted in the latter study, suggested that host characteristics (notably, compromise status) and/or geographic locale might significantly influence the distribution of *papG* alleles in *E. coli* bacteremia. The availability of a well-characterized collection of *E. coli* urosepsis isolates from bacteremic subjects from yet another locale (Seattle, Wash.), for whom host compromise status has been carefully delineated (8–11), provided the opportunity to directly address these hypotheses in a new population.

Thus, the present study was undertaken to define the distribution of the three *papG* alleles among *E. coli* isolates from adults in Seattle with urosepsis, with specific attention to the influence of host compromise. Also explored were new and previously identified associations between the *papG* alleles and other relevant bacterial characteristics, including clonal structure (as revealed by O serogroup and O:K:H serotype) and selected virulence traits (7, 12).

Subjects and strains. Seventy-five blood culture isolates collected from 75 adults with urosepsis in Seattle, Wash., in the mid 1980s were studied. The clinical sources and associated host and bacterial characteristics (other than the *papG* allele distribution) of this collection have been previously reported (8–11). The presence of compromising host conditions (diabetes mellitus, cancer, immunosuppression, or uremia; known preexisting urinary tract abnormalities; and antecedent urinary tract instrumentation) was determined by medical record review (8–11).

Determination of *papG* alleles. Determination of *papG* alleles was done by an allele-specific PCR assay (6, 14). Primers were as follows: for allele I, j96-193f (5′-TCGTGCTCAGGT CCGGAATTT-3′) and j96-653r (5′-TGGCATCCCCCAACA TTATCG-3′) (461-bp product); for allele II, ia2-383f (5′-GG GATGAGCGGGCCTTTGAT-3′) and ia2-572r (5′-CGGGC CCCCAAGTAACTCG-3′) (190-bp product); and for allele III, prs-198f (5′-GGCCTGCAATGGATTTACCTGG-3′) and prs-455r (5′-CCACCAAATGACCATGCCAGAC-3′) (258-bp product) (6). In control experiments, with rare exceptions, the *papG* PCR assay yielded results comparable to those of dot blot hybridization with allele-specific DNA probes (12).

Determination of other bacterial characteristics. Determination of other bacterial characteristics was done as previously reported for this collection (8–11). *papEFG* (*pap*) and *hlyA* (*hly*) were detected by colony blot hybridization (9). Aerobactin biosynthesis determinants (*iuc*) were detected by colony blot hybridization combined with Southern hybridization of plasmid DNA to resolve the plasmid-versus-chromosomal location of *iuc* when present (9). Expression of the P agglutination phenotype was defined as macroscopic agglutination of digalactoside-coated latex beads (P beads) (11). Hemolysin production was detected with sheep's blood agar (11). Aerobactin production was determined by a cross-feeding bioassay (9). Antimicrobial resistance was defined as reduced susceptibility to ≥1 of 12 antimicrobial agents (9, 11). Carboxylesterase B electrophoretic phenotype (B_1 versus B_2) was determined by Phillipe Goullet and Bertrand Picard, as previously described (8). O:K:H serotypes were determined by The International Escherichia and Klebsiella Centre (World Health Organiza-

* Mailing address: Infectious Diseases Section (111F), Minneapolis V.A. Medical Center, 1 Veterans Dr., Minneapolis, MN 55417. Phone: (612) 725-2000, ext. 4185. Fax: (612) 725-2273. E-mail: johns007@maroon.tc.umn.edu.

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TABLE 1. Distribution of *papG* alleles by geographical locale among *E. coli* strains causing bacteremia in adults[a]

Syndrome	Locale (*n*)	No. (%) of strains with allele(s):						
		I + III	III only	II + III	II only	Any III[b,e]	Any II[b,e]	None
Urosepsis[c,d]	Seattle (75)	0	4 (5)	1 (1)	52 (69)	5 (7)	53 (71)	18 (24)
Unselected bacteremia[d]	Boston (115)	2 (2)	25 (22)	6 (5)	32 (29)	33 (29)	38 (33)	50 (43)
	Long Beach (51)	0	7 (14)	2 (4)	17 (33)	9 (18)	19 (37)	25 (49)
	Nairobi (21)	0	0	1 (5)	9 (4)	1 (5)	10 (48)	11 (52)
	Total (187)	2 (1)	32 (17)	9 (5)	58 (31)	43 (23)	67 (36)	86 (46)
Bacteremic pyelonephritis[e]	Sweden (15)	0	0	0	14 (93)	0	14 (93)	1 (7)

[a] All populations except Swedish pyelonephritis cohort included compromised hosts.
[b] Sums of "any III" plus "any II" are greater than total number of *papG*-positive strains, since strains with both alleles II and III are counted both as any III and any II. (Adapted, with permission, from reference 7.)
[c] Present study.
[d] Alleles were determined by PCR assay. Data are from reference 7.
[e] Alleles were determined by DNA probe hybridization. Data are from reference 26.

tion) (10). Ten urinary tract infection (UTI)-associated O serogroups (O1, O2, O4, O6 to O8, O16, O18, O25, and O75) were designated O-UTI, and 10 pyelonephritis-associated O:K:H serotypes were designated O:K:H-pyelo (10).

Statistical analyses. Comparisons of proportions were tested by Fisher's exact test or McNemar's test (2). *P* values of <0.05 were considered significant.

Overall distribution of *papG* alleles. *papG* was detected by PCR in 57 (76%) of the 75 urosepsis strains (Table 1). Fifty-two strains (69%) had allele II only, four (5%) had allele III only, and one (1%) had both alleles II and III. Allele I, which is associated with a J96-like clonal group of *E. coli* O4:H5 (10, 13, 14), was not detected. Thus, allele II predominated overwhelmingly over allele III, occurring in 53 (71%) of the 75 strains, versus only 5 strains (7%) for allele III, and in 93% of *papG*-positive strains versus only 9% for allele III ($P < 0.01$ by McNemar's test).

***papG* alleles versus bacterial characteristics.** Consistent with previous findings in this collection as derived for *pap* with an allele-inclusive *papEFG* probe (8–11), in the total population *papG* positivity per se was significantly associated with the presence of *pap* (98 versus 6%) and P bead agglutination (88 versus 0%), the presence and expression of *hly* (54 versus 17%), the presence of chromosomal *iuc* (67 versus 28%) but absence of plasmid *iuc* (12 versus 50%), the absence of antimicrobial resistance (44 versus 89%), the B_2 carboxylesterase B phenotype (70 versus 39%), and membership in O-UTI serogroups (77 versus 44%) and O:K:H-pyelo serotypes (42 versus 0%).

Among *papG*-positive strains, those containing only allele III differed significantly from those containing only allele II with respect to the proportion exhibiting P bead agglutination, *hly*, aerobactin production, the combined *pap*$^+$ *hly*$^+$ *iuc* genotype, and membership in serogroups O6 or O18 (Table 2). Nearly half of the II-only strains, but none of the III-only strains, exhibited a pyelonephritis-associated O:K:H serotype (Table 2). The sole II-plus-III strain aligned with the II-only strains with respect to most bacterial characteristics (Table 2).

The single largest serogroup, O6, accounted for 15 strains, 10 of which belonged to a single O:K:H clone (O6:K2:H1) (not shown). All 10 O6:K2:H1 strains contained *papG* allele II only. The five non-O6:K2:H1 strains in serogroup O6, which exhibited three different O:K:H patterns, included two with only *papG* allele III. Exclusion of the (allele II-associated) O6:K2:H1 clone from serogroup O6 yielded a much stronger association of allele III with serogroups O6 and O18 (Table 2).

***papG* alleles versus host characteristics (Table 3).** Consistent with previous findings in this collection for *pap* as detected by an allele-inclusive probe (9), in the total population *papG* positivity per se was associated with consistent trends toward a reduced likelihood of host compromise. These trends approached statistical significance ($0.05 < P < 0.10$) specifically for any host compromise, immunosuppression, and urinary tract abnormalities.

Stratification of the *papG*-positive strains according to specific *papG* alleles (Table 3) revealed marked host compromise differences between allele II-only and allele III-only strains.

TABLE 2. *papG* alleles versus other bacterial characteristics among 57 *papG*$^+$ *E. coli* urosepsis isolates

Associated bacterial characteristic (*n*)	No. (%) of strains with associated characteristic		
	II only (*n* = 52)	III only (*n* = 4)	II + III (*n* = 1)
pap$^+$ (57)	51 (98)	4 (100)	1
P bead agglutination (50)	48 (92)[a]	1 (25)[a]	1
hly$^+$ (34)	26 (50)	4 (100)	1
Hemolysin production (32)	24 (46)	3 (75)	1
iuc$^+$ (59)	43 (83)[a]	1 (25)[a]	1
Plasmid (16)	7 (13)	0	0
Chromosomal (43)	36 (69)	1 (25)	1
Aerobactin production (51)	37 (71)	1 (25)	0
pap$^+$ *hly*$^+$ *iuc* (6)	3 (6)[a]	3 (75)[a]	0
Antimicrobial resistance (41)	22 (42)	2 (50)	1
B_2 carboxylesterase B phenotype (47)	36 (71)	3 (75)[b]	1
10 O-UTI serogroups (52)	40 (77)	3 (75)	1
O6 or O18 (17)	14 (27)	3 (75)	0
O6 (non-O6:K2:H1) or O18 (7)	4 (8)[a]	3 (75)[a]	0
10 O:K:H-pyelo serotypes (24)	24 (46)	0	0

[a] For II only versus III only, $P < 0.05$.
[b] Carboxylesterase B result was not available for one II-only strain; proportions shown are based on actual number tested.

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TABLE 3. *papG* alleles versus host characteristics among 57 *papG*$^+$ *E. coli* urosepsis isolates

Associated host characteristic (*n*)	No. (%) with associated characteristic		
	II only (*n* = 52)	III only (*n* = 4)	II + III (*n* = 1)
Any host compromise (47)	29 (56)	3 (75)	0
Illness			
Any (26)	15 (29)	3 (75)	0
Diabetes (9)	6 (12)	0	0
Cancer (13)	7 (13)[a]	3 (75)[a]	0
Immunosuppression (14)	6 (12)	2 (50)	0
Uremia (8)	5 (10)	1 (25)	0
Urinary tract abnormality			
Any (31)	18 (35)	2 (50)	0
Upper urinary tract (8)	2 (4)[a]	2 (50)[a]	0
Urinary tract instrumentation (16)	8 (15)	2 (50)	0
Multiple compromising conditions			
≥2 medical illnesses (15)	8 (15)[a]	3 (75)[a]	0
≥2 medical illnesses plus urinary tract abnormality or instrumentation (11)	5 (10)[a]	3 (75)[a]	0

[a] For II only versus III only, $P < 0.05$.

Except for diabetes mellitus (which occurred only in association with allele II), all categories of host compromise were numerically more common among hosts with allele III-only strains. Cancer ($P < 0.05$), upper urinary tract abnormalities ($P < 0.05$), multiple medical illnesses ($P < 0.05$), and combined medical-plus-urological impairments ($P < 0.01$) all were significantly associated with allele III, and similar trends approaching statistical significance ($0.05 < P < 0.10$) were observed for immunosuppression and any medical illness. The sole II-plus-III strain, like most allele II-only strains, was from a noncompromised host (Table 3).

Clinical implications of the observed *papG* allele distribution. The observed distribution of *papG* alleles in the present Seattle urosepsis cohort (allele II > allele III > allele I), when compared with host compromise status and with the results of previous epidemiological studies of the *papG* alleles (3, 7, 12, 26), suggests three major conclusions. First, allele II is reconfirmed (in a new population) as the predominant *papG* variant in *E. coli* bacteremia. This is consistent with the reported predominance of allele II in acute pyelonephritis (3, 26) and contrasts with allele III's reported predominance in acute cystitis (3, 12). These observations suggest that strains containing allele II are particularly fit for the pathogenesis of bacteremia during UTI and other extraintestinal infections, whether this is due to the allele II PapG variant per se or to other bacterial properties more closely associated with *papG* allele II than with allele III.

Secondly, in *E. coli* bacteremia, allele III-containing strains are associated with host compromise. This hypothesis was initially suggested by the observation that in the two previous studies that examined *papG* allele genotypes among bacteremia isolates of *E. coli*, allele III was identified only in populations containing compromised hosts (7, 26). The hypothesis was directly confirmed by the finding in the present study of statistically significant associations between allele III and several compromising host conditions. In view of the reported predominance of allele III in acute cystitis (3, 12), a unifying hypothesis would be that allele III (or associated bacterial properties), although well suited for the pathogenesis of lower-tract or noninvasive UTI, may be insufficient for bloodstream invasion in the absence of host compromise. This would be analagous to the well-documented association of *pap* negativity with host compromise among strains causing pyelonephritis or bacteremia (4).

Thirdly, although host compromise may be an important determinant of the distribution of *papG* alleles in *E. coli* bacteremia, other factors (e.g., geographic locale) probably are also important. This conclusion is suggested by the marked discrepancies between different clinical centers with respect to *papG* allele distribution observed in a previous study (7) and between subjects in that study (7) versus those in the present Seattle cohort (Table 1). Since in the previous study the clinical source of bacteremia was not predictive of *papG* allele distribution (7), differences in primary clinical syndrome are unlikely to explain the observed variability in *papG* allele mix between bacteremic populations. Instead, geographical differences in the distribution of virulent *E. coli* clones (7) may significantly influence the *papG* allele mix among bacteremia isolates from different centers.

Clonal segregation of *papG* alleles. The concept that the *papG* alleles are clonally distributed within the *E. coli* population (7, 24) is supported by the observed serogroup- and serotype-specific associations of the *papG* alleles. The present study confirms the previously noted concentration of allele III in serogroups O6 and O18 (7, 12). It demonstrates that the clonal split within serogroup O6 previously revealed by multilocus enzyme electrophoresis (7), with an associated segregation of *papG* alleles II and III (7), is also apparent by O:K:H serotyping. In addition, the sole II-plus-III strain in the present study was an O2, consistent with the previously demonstrated association of the II-plus-III *papG* allele pattern with serogroup O2 (7). Finally the observed trend toward an association of *papG* allele II with the O:K:H-pyelo serotypes (Table 2) is consistent with allele II's recognized association with clinical pyelonephritis (3, 26).

Phenotypic and genotypic correlates of *papG* alleles. The decreased frequency of P bead agglutination observed among III-only strains, as previously noted among cystitis isolates (3, 12), was probably due to the allele III PapG adhesin's decreased affinity for digalactoside-coated latex beads (21) and illustrates the limitations of this assay as a broad screen for the expression of *papG*-encoded adhesins. Other agglutination assay systems may be more useful for epidemiological studies, although even with these a precise correspondence between *papG* genotype and adherence phenotype cannot be expected (5, 15). Allele III's association with *hly* confirms a previous similar finding in a different population (7) and may be attributable to a preferential genetic linkage of *hly* with allele III over allele II within the pathogenicity-associated islands of virulence genes that are prominent among uropathogenic *E. coli* (1, 17, 28). The observed associations of allele III with the absence of aerobactin production and with a distinctive combined virulence factor genotype (*pap*$^+$ *hly*$^+$ *iuc*) are novel findings of the present study, which is the first to examine the *papG* alleles in relation to aerobactin phenotype and genotype. Since, in contrast to *pap* and *hly*, *iuc* and *iut* are not known to reside on pathogenicity-associated islands (1, 17, 28, 29), the basis for the latter associations remains to be determined.

Limitations of the present study. The small number of allele III-containing strains, although itself an important finding, limits the robustness of the observed statistically significant associations of allele III with other bacterial and host characteristics. Nonetheless, many of these associations replicate similar findings in other populations (7, 12) and hence can be considered externally validated. Those that are unique to the present

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study await future confirmation. The use of multiple comparisons introduces the risk of spuriously significant *P* values. However, 8 (31%) of the 26 comparisons between alleles II and III with respect to bacterial and host characteristics (Tables 2 and 3) yielded *P* values of <0.05, whereas only one such result would be expected by chance alone. Finally, the strains studied were from a limited geographical area, period, and disease category, which may limit the generalizability of the results.

Summary. Although *papG* allele II predominated among *E. coli* urosepsis isolates from adults in Seattle, Wash., allele III did occur and was significantly associated with serogroups O6 and O18, specific virulence genotypes and phenotypes, and host compromise. Despite allele II's predominance, *papG* allele III and/or its associated bacterial properties may contribute to the pathogenesis of urosepsis, particularly in compromised hosts.

Jennifer J. Brown assisted in the laboratory. Diana Owensby helped prepare the manuscript. Todd deFors helped with the statistical analysis. O:K:H serotyping was done by The International Escherichia and Klebsiella Centre (World Health Organization), and carboxylesterase B phenotyping was done by Phillipe Goullet and Bertrand Picard. Detection of *iuc*, *pap*, *hly*, and aerobactin production was done in the laboratory of Steve L. Moseley. Phenotyping for hemolysin and P fimbriae was done in the laboratory of Walter E. Stamm. Robin Olsen helped review medical records.

Support was provided by NIH grant R01-DK47504.

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