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Escherichia coli is the most important etiological agent of urinary tract infections (UTIs). Unlike uropathogenic E. coli, which causes symptomatic infections, asymptomatic bacteriuria (ABU) E. coli strains typically lack essential virulence factors and colonize the bladder in the absence of symptoms. While ABU E. coli can persist in the bladder for long periods of time, little is known about the genetic determinants required for its growth and fitness in urine. To identify such genes, we have employed a transposon mutagenesis approach using the prototypic ABU E. coli strain 83972 and the clinical ABU E. coli strain VR89. Six genes involved in the biosynthesis of various amino acids and nucleobases were identified (carB, argE, argC, purA, metE, and ilvC), and site-specific mutants were subsequently constructed in E. coli 83972 and E. coli VR89 for each of these genes. In all cases, these mutants exhibited reduced growth rates and final cell densities in human urine. The growth defects could be complemented in trans as well as by supplementation with the appropriate amino acid or nucleobase. When assessed in vivo in a mouse model, E. coli 83972carAB and 83972argC showed a significantly reduced competitive advantage in the bladder and/or kidney during coinoculation experiments with the parent strain, whereas 83972metE and 83972ilvC did not. Taken together, our data have identified several biosynthesis pathways as new important fitness factors associated with the growth of ABU E. coli in human urine.