

Evidence of Adaptive Evolution Provides the Achilles-Heel of Pathogen Genomes: Candidates for Drug and Vaccine Targets

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Previous studies have shown that certain virulence factors of pathogenic bacteria e.g. adhesins and outer membrane proteins, appear to be under positive selection. . To determine whether new virulence-associated genes may be identified using screening for adaptive selection, we have performed an intraspecies search between orthologous genes that contain regions for which the rate of nonsynonymous (K_A) substitution is greater than the rate of synonymous substitution (K_S). We have analyzed pairs of strains of *Helicobacter pylori* and *Neisseria meningitidis*. A total of 85 genes undergoing pathoadaptive evolution were identified, of which a large proportion (41/85) code for known or potential virulence genes. Interestingly, it appears that specific cellular processes in *N. meningitidis* are under strong selection, as we have detected multiple genes involved in iron acquisition and DNA-repair that have acquired adaptive mutations. Furthermore, of 21 *H. pylori* knockout mutants 5 had decreased colonization efficiency and 8 were fatal and thus classified as being ‘putative essential’. Due to the demonstrated ability of our system to identify known and potential virulence factors, and the fact that 61% of *H. pylori* genes tested in gene-knockout experiments were shown to play important roles in the organism’s biology, we conclude that it may be an important tool for novel drug and vaccine targets.