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Rendering of *Neisseria gonorrhoeae*
(Image credit: Centers for Disease Control and Prevention)

A Missense Mutation in the *acnB* Gene Indirectly Affects the Growth, Metabolism and Biological Fitness in a Spontaneous Compensatory Mutant of Antibiotic-resistant *Neisseria gonorrhoeae*

Neisseria gonorrhoeae, the causative agent of the sexually transmitted infection gonorrhea, has developed resistance to every antimicrobial used against it. The CDC currently recommends a dual therapy of ceftriaxone and azithromycin, however multiple strains with high-level resistance to either ceftriaxone or azithromycin have been isolated. Ceftriaxone-resistant *N. gonorrhoeae* strains tend to harbor mosaic *penA* alleles that encode highly mutated forms of Penicillin-Binding Protein 2 (PBP2), the lethal target of ceftriaxone. When bacteria develop resistance to a particular antibiotic, they often incur a fitness cost as a result, which they must overcome. Wild-type strains harboring a mosaic *penA* allele (*penA41* from the multi-drug resistant strain H041) have reduced fitness both *in vitro* and *in vivo*, but our collaborators have isolated compensatory mutants with increased biological fitness. In one such strain, a mutation (G348D) was identified in *acnB*, which encodes a variant of the aconitase enzyme that functions in the tricarboxylic acid (TCA) cycle, and this mutation appears to offset the cost of carrying the *penA41* allele. The hallmark of this compensatory mutant is that it grows rapidly during log-phase growth, but then plateaus early as it enters into stationary phase growth. The *acnB*-G348D mutation is both necessary and sufficient to impart the growth phenotype characteristic of compensatory mutant. Western blots of AcnB during the growth cycle show that wild-type AcnB increases in abundance as the cells enter stationary phase, whereas in the AcnB mutant, expression decreases by 2- to 3- fold. Interestingly, AcnB mRNA levels do not account for changes in AcnB protein levels. These data suggest that *acnB*-G348D is a functional knockout in regards to the role of AcnB in the TCA cycle. Any fitness benefits associated with this mutation do not appear to be directly associated with the activity of AcnB in the TCA cycle.