Characterization and detection of a widely distributed gene cluster that predicts anaerobic choline utilization by human gut bacteria.

Title	Characterization and detection of a widely distributed gene cluster that predicts anaerobic choline utilization by human gut bacteria.
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Abstract	**UNLABELLED:** Elucidation of the molecular mechanisms underlying the human gut microbiota's effects on health and disease has been complicated by difficulties in linking metabolic functions associated with the gut community as a whole to individual microorganisms and activities. Anaerobic microbial choline metabolism, a disease-associated metabolic pathway, exemplifies this challenge, as the specific human gut microorganisms responsible for this transformation have not yet been clearly identified. In this study, we established the link between a bacterial gene cluster, the choline utilization (cut) cluster, and anaerobic choline metabolism in human gut isolates by combining transcriptional, biochemical, bioinformatic, and cultivation-based approaches. Quantitative reverse transcription-PCR analysis and in vitro biochemical characterization of two cut gene products linked the entire cluster to growth on choline and supported a model for this pathway. Analyses of sequenced bacterial genomes revealed that the cut cluster is present in many human gut bacteria, is predictive of choline utilization in sequenced isolates, and is widely but discontinuously distributed across multiple bacterial phyla. Given that bacterial phylogeny is a poor marker for choline utilization, we were prompted to develop a degenerate PCR-based method for detecting the key functional gene choline TMA-lyase (cutC) in genomic and metagenomic DNA. Using this tool, we found that new choline-metabolizing gut isolates universally possessed cutC. We also demonstrated that this gene is widespread in stool metagenomic data sets. Overall, this work represents a crucial step toward understanding anaerobic choline metabolism in the human gut microbiota and underscores the importance of examining this microbial community from a function-oriented perspective. **IMPORTANCE:** Anaerobic choline utilization is a bacterial metabolic activity that occurs in the human gut and is linked to multiple diseases. While bacterial genes responsible for choline fermentation (the cut gene cluster) have been recently identified, there has been no characterization of these genes in human gut isolates and microbial communities. In this work, we use multiple approaches to demonstrate that the pathway encoded by the cut genes is present and functional in a diverse range of human gut bacteria and is also widespread in stool metagenomes. We also developed a PCR-based strategy to detect a key functional gene (cutC) involved in this pathway and applied it to characterize newly isolated choline-utilizing strains. Both our analyses of the cut gene cluster and this molecular tool will aid efforts to further understand the role of choline metabolism in the human gut microbiota and its link to disease.
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