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Tooth Be Told, Genetics Influences Oral Microbiome

Emily R. Davenport[1,*]
[1]Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY 14853, USA
*Correspondence: ed379@cornell.edu
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The mix of bacteria that coat our teeth impact oral health, but it remains unclear what factors govern their composition. In this issue of *Cell Host & Microbe*, Gomez et al. (2017) examine the relationship between host genetics and the oral microbiome in the context of health and disease.

The oral cavity houses many environments for microbes to colonize. The tooth surface in particular serves as a tethering point, allowing bacterial biofilms to develop. When not kept in check, these communities contribute to poor oral health. For instance, several bacterial taxa tend to associate with dental caries, including *Streptococcus mutans* and Lactobacillus species. Your dentist tells you to brush, floss, and avoid sugar, but are there other factors that determine which bacteria live in your mouth?

In a study published in this issue of *Cell Host & Microbe*, Gomez et al. demonstrate the role of host genetics in determining composition of the bacteria that live on tooth surfaces right next to the gums (supragingival plaque) and further from the gum line. They collected microbiome, dental caries, and sugar consumption data for 485 twins aged 5–11. By comparing the microbiomes of monozygotic (identical; MZ) and dizygotic (fraternal; DZ) twin pairs, they estimate heritability (h^2), which is the difference in the correlation of MZ and DZ twin pairs, for the relative abundances of microbial taxa present in at least half of their samples. Of the 91 common bacteria examined, almost half show heritability of at least 0.2. Of these, the heritability estimates of many taxa are fairly high, including *Prevotella pallens* (h^2 = 0.65), a Veillonella species (h^2 = 0.60), and *Corynebacterium durum* (h^2 = 0.54), clearly demonstrating the contribution of the host genome to oral colonization by these bacteria.

These results mesh well with the first genome-wide association study of microbiomes, which examined multiple body sites profiled by the Human Microbiome Project (HMP) (Blekhman et al., 2015). For both saliva and supragingival plaque microbiomes from the HMP, the more similar a pair of individuals' genomes, the more similar their microbiome composition—pointing to a role of host genetics. However, given that the HMP samples consist of unrelated individuals, heritability could not be directly measured. The results of Gomez et al. fill in this gap. Moreover, specific results from the two studies support each other. Several taxa that Blekhman et al. observed to be associated with host genetic variation are now reported as heritable by Gomez et al. In supragingival plaque from the HMP study, genus *Aggregatibacter* was associated with genetic variants on chromosomes 3 and 11, while in the twin study an *Aggregatibacter* OTU is heritable (h^2 = 0.35). Additionally, in saliva from the HMP study, genus *Leptotrichia* was associated with genetic variants on chromosome 15, while in the twin study a *Leptotrichia* OTU is highly heritable (h^2 = 0.54).

The role of the host genetics in determining oral microbiomes seems to differ from its role in the gut, the most well-studied body site to date. Typically, a much smaller percentage of bacteria in the gut have heritable abundances, somewhere between 10% and 20%. Those also tend to have lower heritability estimates, usually no more than 0.4 (Goodrich et al., 2016). However, one caveat worth pointing out is the difference in the ages of participants between the gut and oral studies. Gut studies typically include adults, many of whom are older. Not only does the new oral microbiome study from Gomez et al. focus on younger participants than the gut studies, but heritability estimates *decrease* with age for the most heritable taxon, *Prevotella pallens*. Would the heritability of gut microbe abundances be higher in children than in the current estimates from adults?

Another difference between gut and oral sites is the relationship of heritable taxa to the rest of the microbial

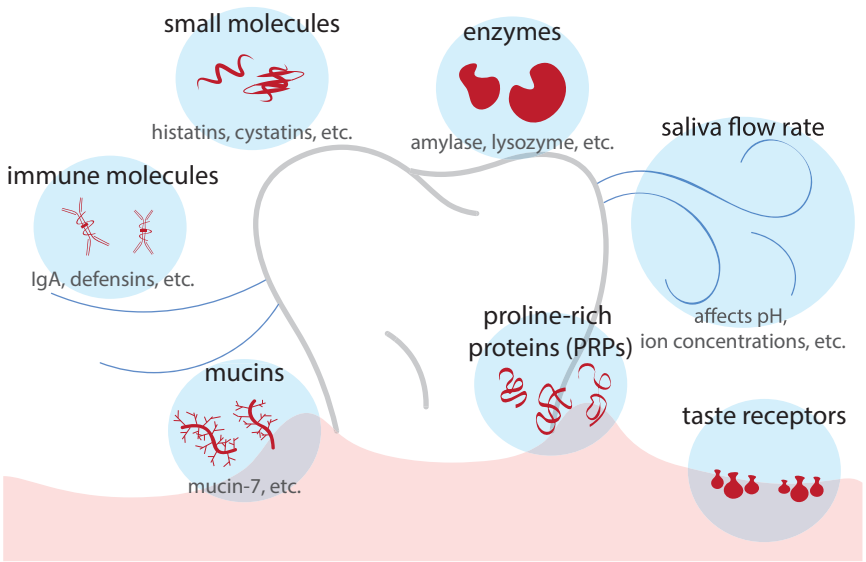

Figure 1. Candidate Host Secreted Molecules that May Influence Heritability of the Oral Microbiome

Saliva and epithelial tissues in the mouth contain a number of molecules with known genetic variation. Proline-rich proteins (PRPs) make up a major component of saliva and influence bacterial attachment to tooth surfaces. Mucins act as tethering and energy sources for particular microbes. Immune molecules and other small molecules (histatins, defensins, etc.) regulate bacterial composition in the mouth and prevent pathogen colonization. Taste receptors contribute to dietary preferences and certain enzymes break down food, such as amylase. Both of these classes of molecules create different nutritional content available for oral bacteria. Finally, salivary flow rate determines the concentrations of these molecules and electrolytes.

community. Heritable oral taxa tend to lie on the periphery of microbiome networks and do not co-occur with each other (Gomez et al., 2017). In contrast, in the gut most heritable taxa co-occur with each other, forming a clique (Goodrich et al., 2016). The genetic and environmental factors that contribute to these differences remain unknown.

Those discrepancies aside, one similarity between the two body sites is that the most heritable bacteria tend to be more highly abundant in states of health rather than disease. For instance, in the gut, increased abundance of the most heritable taxa, Christensenellaceae, is associated with leanness (Goodrich et al., 2016). In the oral cavity, higher abundances of *Prevotella pallens* and other heritable taxa occur in individuals lacking dental caries. Whether increased abundances of the heritable taxa at other body sites associate with health rather than disease is another open question.

Given that a sizeable proportion of common oral microbe abundances are heritable, the next question is which host genes, genetic variants, and physiological processes potentially underlie this heritability? Human saliva and mucosal surfaces contain a number of molecules encoded by the host genomes that likely play a role in the process, including mucins, immune compounds, enzymes, and taste receptors (Figure 1). Top candidates include proline-rich proteins, or PRPs. These proteins make up the largest component of human saliva and contain putatively functional polymorphisms (Azen, 1993). Another candidate is salivary amylase, an enzyme responsible for breaking down starches. This enzyme exists in variable copy number across human populations and is capable of binding several bacterial species common in oral microbiomes (Oppenheim et al., 2007; Perry et al., 2007). Other candidates include histatins, which are unique to saliva and have antimicrobial properties in vitro (Kavanagh and Dowd, 2004); immune molecules, such as IgA or defensins; and taste receptor genes, such as *TS2R38*, *TAS1R2*, and *GNAT3*.

Recently, genetic variation near a mucin gene, *MUC7*, was found to be significantly associated with oral microbiome composition. *MUC7* encodes one of the most abundant proteins in saliva, MUCIN-7. It contains variable numbers of proline, threonine, and serine (PTS) repeats that act as the primary sites for O-glycosylation, which is a target for microbes in saliva. Variants near *MUC7* are associated with *Neisseria* abundance in supragingival plaque (Xu et al., 2017). Meanwhile, in Gomez et al., a *Neisseria* OTU is also heritable (h^2 = 0.38) (Gomez et al., 2017). Copy-number variation (CNV) of PTS repeats in *MUC7* potentially explains a portion of this heritability, highlighting the understudied role that CNVs might play underlying heritability of microbial abundance.

In addition to what host genetic variants and physiological processes underlie oral microbiome heritability, the results of this study open up a floodgate of other questions to be addressed. For example, are the non-bacterial members of the oral microbiome, such as *Candida albicans*, which is an indicator of oral health, also heritable? Do the heritable oral bacteria identified in children remain heritable in adults? How do modern oral hygiene practices affect estimates of heritability? Would oral microbiomes collected from populations that do not regularly visit dentists or use toothpastes with antimicrobial compounds show different estimates of heritability? Finally, how does heritability relate to the placement of microbes in 3D space in the oral cavity? A recent study identified hedgehog structures in oral microbiomes using imaging techniques. Stalks made of *Corynebacterium* connected the structure to the tooth, while the periphery consisted of *Streptococcus* and other species (Mark Welch et al., 2016). Given that *Corynebacterium* species are heritable while *Streptococcus* species are not, is it more than coincidence that the heritable species lie close to the human structures to which they attach? This research clearly opens up many doors for future study. In the meantime, I'll be taking the advice of the inspirational poster hanging in my dentist's office: Keep calm and floss on.

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Choline Theft—An Inside Job

Marina Mora-Ortiz[1] and Sandrine Paule Claus[1,*]
[1]Department of Food and Nutritional Sciences, University of Reading, Whiteknights Campus, PO Box 226, Reading RG6 6AP, UK
*Correspondence: s.p.claus@reading.ac.uk
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Choline is a crucial methyl donor necessary for epigenetic regulation. In this issue of *Cell Host & Microbe*, Romano et al. (2017) demonstrate that choline-utilizing gut bacteria compete with their host for this essential resource, calling for a systematic consideration of gut microbial composition for personalized diet recommendations.

Choline is an essential nutrient abundant in diet, especially in high-protein-containing food such as eggs, red meat, soy beans, and wheat germs. It is critical for neurotransmission (as it is the precursor of the neurotransmitter acetylcholine), for epigenetic regulation via the synthesis of the major methyl donor S-adenosylmethionine (SAM), and is necessary to produce phosphatidylcholine, the ubiquitous phospholipid that ensures the integrity of cell membranes (Zeisel, 2000). Choline's essential nature has been widely evidenced by studies in which choline deficiency results in abnormalities in epigenetic regulation and lipid metabolism (Lombardi et al., 1968; Pogribny and Beland, 2009). Following ingestion, some dietary choline is transformed by the gut microbial enzyme, choline trimethylamine (TMA) lyase, into TMA and acetaldehyde. TMA is then absorbed through the portal blood system and reaches the liver, where it is oxidized into trimethylamine-*N*-oxide (TMAO) by the host flavin monooxygenase 3 (FMO3) (Baker and Chaykin, 1962; Lang et al., 1998) (Figure 1).

In an elegant investigation published in this issue of *Cell Host & Microbe*, Romano et al. (2017) demonstrate that choline metabolism by gut bacteria plays a significant role in modulating host access to this resource (Romano et al., 2017). They first identified a choline-utilization gene cluster, *cut*, in a strain of *E. coli* (MS 200-1) isolated from the ileum of a healthy human donor. They show that this "type II" *cut* gene cluster encodes all the proteins required for anaerobic choline metabolism, including CutC and CutD, the choline-TMA lyase and its activase, respectively. Inspection of the genetic context of the *cut* gene cluster in γ-Proteobacteria (of which *E. coli* is a member) allowed them to identify other genes potentially linked to choline usage absent in the type I *cut* cluster, which is abundant in Firmicutes, Actinobacteria, and δ-Proteobacteria. Romano et al. (2017) then confirmed the role of the *E. coli cut* gene cluster in choline metabolism by knocking out *cut*C and *cut*D. These mutants were unable to grow on a restricted medium containing choline as the sole carbon source and failed to convert choline into TMA, demonstrating their essential involvement in TMA production from dietary choline. Next, they determined that the respiratory electron acceptors fumarate, nitrate, DMSO, and TMAO supported bacterial growth on choline as a carbon source in anaerobic conditions. Given that nitrate is known to be released into the lumen during gut inflammation and that some *E. coli sp*. use it as an electron acceptor during anaerobic growth, Romano et al. (2017) hypothesized that the bacterial strains able to couple nitrate respiration with choline usage could bear an evolutionary advantage in the inflamed gut as previously suggested (Winter et al., 2013).

Romano et al. (2017) further hypothesized that choline-consuming bacteria may have a significant impact on host choline-utilization pathways. To test this hypothesis, they developed a gnotobiotic model consisting of adult germ-free mice associated with a simplified gut microbiota composed of five bacteria common in the human gut that are unable to metabolize choline and added either a wild-type choline-consuming *E. coli* (CC^+) or a *cutC* knockout (Δ*cut*C) non-choline consuming mutant strain (CC^-). Deletion of the *cut*C gene significantly impaired *E. coli* colonization, suggesting that choline-consuming *E. coli* receive a fitness advantage *in vivo* and that choline metabolism modulates the composition of gut bacterial communities. Importantly, CC^+ colonization resulted in an altered host plasma metabolome, in which circulating levels