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REVIEWS

Spotlight

Host Genetics, Diet, and Microbiome: The Role of AMY1

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Host gene variants selected by diet adaptation have been associated with the microbiome. Poole *et al*. (*Cell Host Microbe* 2019;25;553–564. E7) reported that *AMY1* copy number, associated with obesity, also impacts microbiome composition and function. Complex genetics–diet–microbiome interactions and their effect on obesity could eventually translate into personalized nutrition.

Hosts and their microbiome have coevolved, shaping phenotypes in our ancestral lineages [1]. Several studies suggest that transition to agriculture led to the selection of human-genetic variants with greater capability of obtaining energy from foods [2]. This, in turn, could have caused selection of gut microbes, further benefiting the host. In fact, one of the strongest signs of recent selection in humans is observed for variants allowing persistence of lactase activity into adulthood. Interestingly, in lactose-intolerant individuals, the abundance of lactose-hydrolyzing bacteria, such as bifidobacteria, is increased [3]. It is thus reasonable to assume that other host loci, selected through diet adaptation, could also modify the composition and function of the gut microbiota. This is likely the case with the salivary α-amylase gene (*AMY1*), as increased *AMY1* copy numbers (CNs) could have been selected by adaptation to high-starch diets during the Neolithic agriculture transition [4], interacting with gut microbiota for complex carbohydrate digestion.

In an effort to understand the interaction between host *AMY1*-CN variation and the gut microbiome, Poole and colleagues [5] recently assessed structural differences in gut microbial communities of individuals with low and high *AMY1*-CN. In order to maximize power, they analyzed 50 normal-weight individuals at each extreme of predicted difference in *AMY1*-CN from the Twins UK cohort; they found that high *AMY1*-CN was associated with a distinctive gut microbial profile enriched mainly in members of the family Ruminococcaceae.

To dissect the possible confounding effect of diet, the authors sought associations of *AMY1*-CN variation with both oral and gut microbiota in an independent group receiving a 2-week standardized diet intervention ensuring availability of carbohydrate-rich foods. While higher *AMY1*-CN was associated with greater oral microbiome richness, oral profiles seemed to be diet-independent. Interestingly, high *AMY1*-CN was associated with a higher abundance of *Porphyromonas endodontalis*, previously known to be associated with periodontitis. Because amylase activity has been found to be increased in chronic periodontitis [6], in the light of this finding, the role of *AMY1*-CN in oral health deserves further investigation.

Regarding gut microbiota, differences in certain taxa according to *AMY1*-CN converged after dietary intervention, while differences in other taxa remained. It is noticeable that the intervention study confirmed the association of high *AMY1*-CN with Ruminococcaceae abundance observed in the UK twin study, suggesting that this association is diet-independent. Previous studies have suggested that higher *AMY1*-CN and salivary amylase activity (SAA) allow faster digestion of starch-rich foods [7]. Because *Ruminococcus* has been linked to resistant starch degradation, the authors suggest that a higher content of resistant starch reaches the colon in high-*AMY1*-CN individuals, leading to selection and a higher abundance of these bacteria. Moreover, the study of Poole *et al*. [5] is consistent with a recent study in Mexican children and adults reporting an association of high *AMY1*-CN with *Prevotella copri* abundance [8], also involved in complex carbohydrate fermentation.

To further understand the functional differences, Poole *et al*. [5] performed deep metagenomic sequencing and quantified fecal short-chain fatty acids (SCFAs) at different time points during the dietary intervention. Remarkably, the gut microbiota of low-*AMY1*-CN individuals was enriched in glycoside hydrolases and polysaccharide lyases, enzymes involved in overall complex carbohydrate degradation. The authors speculate that this results from a greater load of complex carbohydrates reaching the distal gut. Interestingly, a previous study reported that individuals with low *AMY1*-CN had increased fasting breath methane, suggesting that this is not necessarily related to the presence of less-digestible starch but to a different microbiome with an increased abundance of methane-producing organisms [7]. Although Poole *et al*. [5] did not report an increased abundance of methanogens in low-*AMY1*-CN individuals, it is clear that further studies are required to explore whether different starch types in the distal gut, microbiome profile, or other yet unknown mechanisms mediate the effect of low *AMY1*-CN on complex carbohydrate metabolism.

One of the main contributions of the study was the functional approach in determining microbiota-derived metabolites. SCFAs in the stool were associated more strongly with host SAA levels than with *AMY1*-CN, likely because SAA varied daily throughout the intervention [5]. The authors suggest that SCFA availability derives from the fermentation of resistant starch by bacteria such as *Ruminococcus*,

whose abundance is increased in high-*AMY1*-CN individuals. SCFA profiles and the abundance of SCFA-producing microbiota may differ according to the source of resistant starch [9] (Figure 1). In this regard, it remains to be determined whether SCFAs resulting from the interaction between SAA/*AMY1* copy number and dietary starch is dependent on the source of the starch (cereal, tubers, legumes, and others).

Finally, in order to assess the effect of gut microbiota selected by *AMY1*-CN variation on host physiology, the authors compared adiposity in germ-free mice fed a polysaccharide-rich diet and transplanted with microbiota from high- and low-*AMY1*-CN human donors [5]. Interestingly, in mice with a constant *AMY1*-CN ($n = 2$), microbiota from high-*AMY1*-CN donors gained more adiposity. This is intriguing, given that high *AMY1*-CN has been associated with a lower body mass index (BMI) in several human studies [10]. The authors cautiously point out that their experiment does not necessarily resemble human physiology, and that increased SAA activity in humans with high *AMY1*-CN may be mediating the effect of the selected microbiome on metabolic traits. These findings reveal the complexity of the relationship between the *AMY1* gene, diet, and the microbiome. To confirm that

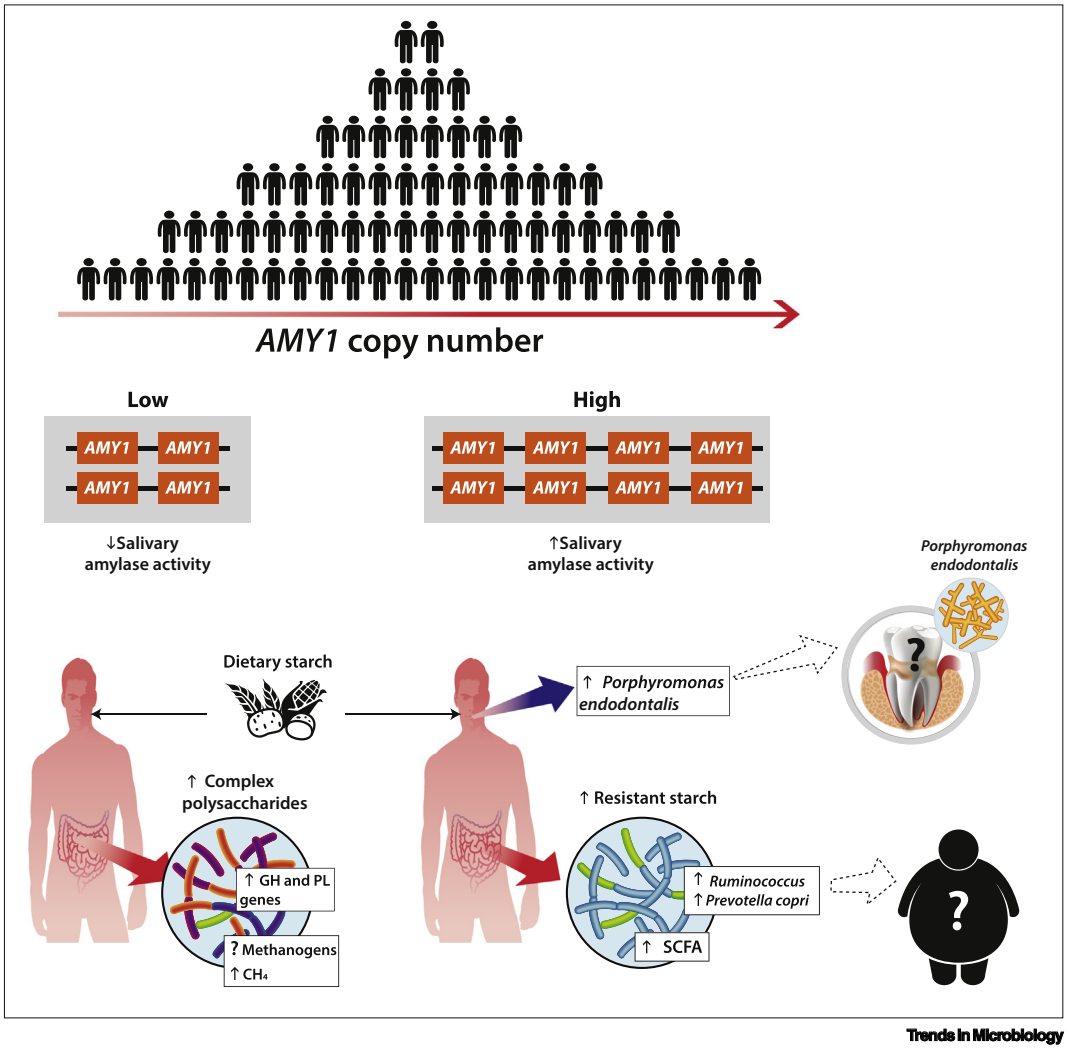

Figure 1. *AMY1* Copy Number (CN) Drives the Oral and Gut Microbiota Profile. Low *AMY1*-CN and salivary amylase activity (SAA) are associated with a higher proportion of genes involved in complex carbohydrate degradation [glycoside hydrolases (GHs) and polysaccharide lyases (PLs)], and higher fasting breath methane. This may be due to enrichment of complex carbohydrates in the distal gut. Alternatively, low *AMY1*-CN could favor the growth of methanogens. In individuals with high *AMY1*-CN, oral microbiota is enriched in *Porphyromonas endodontalis*, while gut microbiota produces increased levels of short-chain fatty acids (SCFAs) and is enriched in taxa such as *Ruminococcus* and *Prevotella copri*. This gut microbiota profile probably results from a higher content of resistant starch selected by higher *AMY1*-CN. Whether these findings are related to oral health or obesity, or could aid in the development of personalized nutrition, warrants further research.

this effect is, in fact, dependent on SAA, as the authors suggested, it would be necessary to humanize the mouse model, simulating variable levels of SAA, perhaps by modifying carbohydrate hydrolysis with amylase supplementation of the polysaccharide-rich diet.

In summary, the study of Poole *et al*. [5] elegantly dissects the interaction between host genetics and the gut microbiome, providing solid evidence of the role of *AMY1*-CN and SAA in the oral and gut microbiomes. Their findings urge to conduct future studies to unravel the complex interactions between *AMY1* genetics, diet (starch sources), and the microbiome, and the effect of these interactions on obesity and other traits which could eventually translate into personalized nutrition.

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Spotlight

A Common Receptor Found for Echoviruses

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It has remained a puzzle why infants, during the first weeks of life, are especially prone to enterovirus infections. New work (*Proc. Natl. Acad. Sci. U. S. A.* 2019;116: 3758–3763) shines light on this matter by showing that the neonatal Fc receptor, prevalent in several tissues, acts as a pan receptor for several echoviruses.

Echoviruses belong to the genus *Enterovirus* within the family Picornaviridae [1]. Echoviruses are very small viruses, approximately 30 nm in diameter, and do not contain a lipid envelope. This feature makes these viruses quite stable as they are not as easily killed by normal hand washing and disinfectants as enveloped viruses such as influenza viruses. Echoviruses consist of 30 different serotypes and have been associated with a high number of acute infections worldwide, EV9 and EV30 being the most common serotypes. Echovirus infections can cause mild symptoms but also severe diseases such as meningitis and encephalitis [1,2]. Neonates and young infants are especially susceptible to severe enterovirus diseases that may turn fatal [1,3]. Echoviruses and their close relatives, coxsackieviruses, have also been associated with chronic diseases such as type I diabetes and atherosclerosis, further stressing their importance [2].

The transmission of enteroviruses occurs via the fecal–oral route where the mucosal cells of the gastrointestinal tract serve as the place for primary infection [4]. Carolyn Coyne's group pinpointed earlier that enterocytes promoted primary infection, based on their *in vitro* studies from human fetus-derived enteroids [5]. However, at that point, the receptor responsible for the primary infection was not yet determined [5]. From the primary infection site, enteroviruses typically cause secondary infections in other tissues such as liver, heart, pancreas, and nerve tissue, when the viruses spread systemically via the bloodstream and lymphatic system. Infection in secondary infection sites depends on the presence of specific cellular receptors and other host factors, for example, in helping to attach the virus particles onto the cell surface [4].

Several molecules have been identified to act as cell-surface receptors for enteroviruses (Table 1): poliovirus receptor (PVR) for three types of poliovirus; coxsackie–adenovirus receptor (CAR) for several coxsackie B viruses; and integrins for coxsackievirus A9 and echovirus 1 [1]. In addition to the primary receptors, enteroviruses often bind to other molecules that act as coreceptors, such as the decay-accelerating factor (DAF) – which has been found to bind some coxsackieviruses and echoviruses – or β_2 microglobulin (β2M), which was shown to be important for the entry of echovirus 1 and 7 [1,6,7]. In particular, it has been suspected that β2M has a role *in vivo* due to the strong inhibitory effect of anti-β2M antibodies on the binding of several different enteroviruses to cells, which prevents infection by those viruses *in vitro*.