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## The gastrointestinal microbiome: a malleable, third genome of mammals

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### Abstract

The nonpathogenic, mutualistic bacteria of the mammalian gastrointestinal tract provide a number of benefits to the host. Recent reports have shown how the aggregate genomes of gastrointestinal bacteria provide novel benefits by functioning as the third major genome in mammals along with the nuclear and mitochondrial genomes. Consequently, efforts are underway to elucidate the complexity of the organisms comprising the unique ecosystem of the gastrointestinal tract, as well as those associated with other epidermal surfaces. The current knowledge of the gastrointestinal microbiome, its relationship to human health and disease with a particular focus on mammalian physiology, and efforts to alter its composition as a novel therapeutic approach are reviewed.

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In recent years there has been renewed interest in the enteric microorganisms that inhabit the mammalian gastrointestinal (GI) tract, commonly referred to as the GI microbiota. In particular, focus has been on the variation that occurs in the microbiota composition and on specific bacterial species that can antagonize or ease intestinal or other diseases. However, the idea that GI microorganisms are associated with a person's well-being is not new. Almost a century ago Ilya Ilyich Mechnikov (also known as Elie Metchnikoff), the 1908 Nobel Laureate in Physiology or Medicine for his work on phagocytosis, postulated in *Prolongation of Life: Optimistic Studies* that certain bacteria could improve the intestinal health of the host (Metchnikoff 1908). With the advent of genome-scale technologies and the ability to perform metagenomics, the dynamic interplay between a host and its GI microbiota and how these interactions contribute to disease are beginning to be elucidated (Turnbaugh et al. 2007).

The GI microbiota is a complex community of bacteria, archaea, and eukarya. The bacterial fraction is believed to contain more than 500 different species and can reach numbers of  $10^{12}$ – $10^{14}$  cells/ml of luminal contents (Ley et al. 2006; Whitman et al. 1998), with the highest densities residing in the colon. In addition to the numbers of bacteria in the GI tract being much greater, the diversity of phyla in the GI tract is also greater than in any other host environment like the skin, oral cavity, or reproductive tract (Dethlefsen et al. 2007; Grice et al. 2009; Nasidze et al. 2009; Zhou et al. 2009). In fact, the number of bacterial cells in the GI tract is greater than the total number of somatic cells in the mammalian body by an order of magnitude. With the exceptionally high numbers and such a diverse community of microorganisms, it is not surprising that the cumulative genomes of the GI microbiome are estimated to contain over 100 times as many genes as the mammalian nuclear genome (Gill et al. 2006). The microbiome harbors genes that code the components of many metabolic processes not found in mammalian cells but that are nonetheless essential for optimal health, such as the ability to degrade indigestible dietary components like fiber and plant cell wall polysaccharides (Brulc et al. 2009; Flint et al. 2007; Pryde et al. 2002). Consequently, the relationships between mammalian hosts and their GI microbiota are more mutualistic than commensal. The GI microorganisms have access to an unlimited supply of nutrition and in return the host is provided with readily absorbable nutrients (Rowland et al. 1985). Furthermore, the GI microbiota stimulate normal immune maturation (Bauer et al. 2006; Mazmanian et al. 2005), provide defense against pathogens through pathogen interference (Bernet-Camard et al. 1997), impart GI mucosal barrier stability (Gotteland et al. 2001), and alter the impact of toxicants and xenobiotics (Meinl et al. 2009; Swann et al. 2009). Since the well-being and phenotypic state of a host depends on the intimate association with its GI microbiota, it has been suggested that mammals can be considered as superorganisms, composed of an amalgam of both prokaryotic and eukaryotic cells (Goodacre 2007; Lederberg 2000).

## Coevolution of the GI microbiota with its host

More than 55 bacterial divisions exist on Earth, yet only two of these deep evolutionary phyla, *Bacteroidetes* and *Firmicutes*, are predominant in the GI microbiota, suggesting that the mammalian GI tract is a relatively exclusive environment (Backhed et al. 2005). However, there is an abundance of species from the two primary phyla represented in the mammalian microbiota. Supporting the idea of the GI tract as a unique environment is the fact that GI microorganisms are rarely found living independently outside their host. Conversely, studies on germ-free (GF) mice, which lack all microorganisms, demonstrate the host's dependence on the GI microbiota for normal physiological development and homeostasis. For example, GF mice exhibit elongated villi, an oversized cecum, and altered susceptibility to obesity (Backhed et al. 2007; Thompson and Trexler 1971), conditions that are reversed when GF mice are associated with a specific pathogen-free (SPF) microbiota. The inability of organisms to survive independently (GI microbiota) or to maintain normal health (mammalian hosts) is a strong indication of coevolved mutualism.

Coevolution is defined as the mutual evolutionary influence between species and has been extensively documented for humans and infectious microorganisms (Brunham et al. 1993). For example, the adaptation of *Helicobacter pylori* with its human host has been used to

independently trace the migration of early humans from northern Africa (Linz et al. 2007). The coevolution of hosts with their GI microbiota has resulted in a cooperative relationship that has shaped the biology and genomes of these mutualistic partners (Ley et al. 2006).

In order to reside in the unique, relatively exclusive GI niche, microorganisms must contain a battery of genes that are dedicated to their persistence, such as genes coding for bile-salt hydrolases and mucus/fibronectin binding proteins. These are evident in the genome sequence of *Bacteroides thetaiotaomicron*, a prominent member of the GI microbiota, where the representation of predicted glycosylhydrolases far exceeds that of any other sequenced bacterial genome (Xu et al. 2003). In addition, *B. thetaiotaomicron* has the ability to utilize host-derived glycans. Thus, a symbiotic relationship exists where a prominent member of the GI microbiota can break down dietary components for host use, while the host provides an ecosystem with a rich energy source in the form of glycans and other dietary components. Additional evidence for coevolution of GI microbiota and their hosts is displayed in the genomes of *Lactobacillus acidophilus* (Altermann et al. 2005) and *L. johnsonii* (Pridmore et al. 2004). The genomes of these two *Lactobacillus* species harbor a number of genes coding for proteins that process indigestible dietary components that can be utilized by the host but lack genes responsible for the synthesis of amino acids and purine nucleotides, indicating a strong dependence on the host.

Similar to the influence of the host on the microbiota, the microorganisms inhabiting the GI tract likely affected mammalian evolution. It has been demonstrated that the human GI microbiome is significantly enriched with genes for the metabolism of glycans, amino acids, and xenobiotics when compared to the human genome (Gill et al. 2006; Meini et al. 2009; Swann et al. 2009). Thus, the GI microbiome has genes that the mammalian host did not need to evolve independently and allows the host to obtain nutrients from food sources that would otherwise be indigestible (Brulc et al. 2009; Flint et al. 2007; Pryde et al. 2002). Supporting the strong link between the GI microbiome and its host is the fact that the composition of the GI microbiota changes with age, mirroring changes in diet that occur between milk-fed infants and adults and into the elderly years (Mariat et al. 2009; Sela et al. 2008). It is therefore likely that the GI microbiome aided the acceleration of early mammalian evolution by supporting consumption and use of novel food constituents (Ley et al. 2008).

## The gastrointestinal microbiome

Most species of bacteria that inhabit the mammalian GI tract are currently unculturable and amenable only to molecular analysis (Eckburg et al. 2005; Hayashi et al. 2005; Table 1). Until recently, the majority of nucleic acid sequences obtained from analysis of the mammalian GI microbiome were from the 16S rDNA genes, which have been widely used for the qualitative and quantitative analyses of the microbiota constituents (Alexander et al. 2006; Heilig et al. 2002; Sarma-Rupavtarm et al. 2004). Analysis of the mammalian GI microbiome has now entered the metagenomic era (characterization of complex bacterial populations). Metagenomic analysis on the human distal colonic microbiome identified distinctive functional attributes encoded by the member microorganisms (Gill et al. 2006). Thousands of GI microbiome sequences were analyzed from random DNA libraries

generated from fecal specimens collected from one male and one female subject with no known health problems or antibiotic exposure. The GI microbiome of both subjects displayed an enrichment of genes specific to metabolic processes such as energy production and conversion, transport, and metabolism of carbohydrates, amino acids, and coenzymes as well as secondary metabolite biosynthesis, transport, and catabolism. In addition, a metagenomic study of the microbiomes from adults and children at various ages demonstrated that preweaned infants have simpler but more variable microbiota than weaned children or adults, who are more complex but also more uniform (Kurokawa et al. 2007). An important example is *Bifidobacterium longum* subsp. *infantis*, which has adapted to utilize milk-borne molecules that have little nutritive value to the neonatal host (Sela et al. 2008). New high-throughput sequencing technologies have even supported interrogation of ancient human microbiomes from preserved paleofecal deposits (Tito et al. 2008).

Complementary investigations have focused on the metabolic properties of specific *Bacteroides* spp. since they account for a large proportion of the constituents of the GI microbiota. The genome sequence of *B. thetaiotaomicron*, which represents 12% of GI *Bacteroides* and 6% of the entire GI microbiota based on 16S rDNA analysis, proves its unique niche in the host GI tract (Xu et al. 2003); *B. thetaiotaomicron* contains an unusually large number of genes responsible for the metabolism of carbohydrates. In addition, the genome sequences of *B. vulgatus* and *B. distasonis*, which represent 31 and 0.8% of total GI *Bacteroides*, respectively, prove that many genes in the microbiome are dedicated to the acquisition, breakdown, or synthesis of carbohydrates (Xu et al. 2007).

The importance of the metabolic activities encoded by the GI microbiome is reflected in the fact that the composition of the GI microbiota is strongly influenced by the host's diet. For example, a reduction in dietary carbohydrates leads to reduced levels of *Roseburia* spp., *Eubacterium rectale*, and *Bifidobacterium* spp., but there is no change in *Bacteroides* spp. (Duncan et al. 2007). The levels of some constituents of the GI microbiota can be altered indirectly by diet because of their dependence on the metabolic production of other constituents that are directly affected by diet (Belenguer et al. 2006).

Although diet has a pronounced influence on the GI microbiota, a growing body of evidence suggests that host genetics can also influence the composition of the GI microbiota (Zoetendal et al. 2001). Comparisons of microbiota from mono- and dizygotic twins indicate that host genetic factors may influence the composition of the microbiota (Stewart et al. 2005; Van de Merwe et al. 1983). Host-influenced changes in the composition of the microbiota may be a mechanism by which host genetics contributes to obesity if the selected microbiota have increased capacity for energy harvest from the diet (Turnbaugh et al. 2006). Importantly, individuals with shared phenotypic characteristics, e.g., obesity, can have different microbiota while sharing a “core microbiome” at the gene level (Turnbaugh et al. 2009). The role of host genetics in modulating GI microbiota composition has been confirmed using mice in controlled environments. Inbred strains of mice differ in the quantity of various members of the GI microbiota and these differences are maintained even when mice from different strains cohabitate (Alexander et al. 2006). Similar experiments indicate that gender, age, and presence of pathogenic bacteria in the GI tract influence colonization dynamics (Ge et al. 2006).

## The GI microbiota and disease

Although the GI microbiota is essential for the health of the host, it is also associated with a number of intestinal disorders and susceptibility to systemic diseases. The mutualistic relationship of the mammalian host with its GI microbiota is based on tolerance. Reduced or altered host tolerance to GI microorganisms can lead to inflammatory disorders such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Moreover, studies have also correlated the composition of the microbiota with systemic diseases like cancer and obesity.

### IBD

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as IBD, are disorders of unknown cause and are characterized by recurrent intestinal inflammation. IBD is believed to result from one or a combination of factors including genetic-based host susceptibility, the GI microbiota, and a dysfunctional immune response (Sartor 1997). The GI microbiota, which are thought to be a major source of antigens contributing to abnormal immune responses, differ among individuals at different stages of CD and UC (Bibiloni et al. 2006). Differences in the GI microbiota may precede the onset of inflammation (Nones et al. 2009). More recent analyses have found that a subset of individuals with CD and UC have a depletion of commensal bacteria from the phyla *Bacteroidetes* and *Firmicutes*, suggesting that IBD may represent a spectrum of disease states (Frank et al. 2007). The most convincing evidence for the association of GI microbiota with IBD comes from gnotobiotic (defined microbiota) studies in mouse models of colitis (Kuhn et al. 1993), which demonstrated that mucosal inflammation results when interleukin-10 (*Il10*)-deficient mice are colonized by normal members of the GI microbiota. Confirming this association, inflammation is absent from these mutant mice when they are maintained GF.

### IBS

IBS is a chronic GI disorder characterized by abdominal pain, cramping, diarrhea, and/or constipation (Quigley 2006; Ringel et al. 2001). Traditionally, IBS has been considered a disorder that is associated with GI hypersensitivity, which leads to pain, and GI motor dysfunction, which leads to diarrhea or constipation. Randomized studies have implicated various factors in this GI disorder, including food allergy, serotonin levels, pathogenic bacterial infection and inflammation, alterations in the normal GI microbiota, and host genetics (Talley 2006). Because IBS is a heterogeneous disorder, it is possible that there are heterogeneous etiologies for the different subtypes of the disorder: diarrhea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), mixed-bowel-habit IBS (MIBS), or postinfectious IBS (PI-IBS). Recent investigations have demonstrated that the composition of the GI microbiome of individuals with IBS differs from that of healthy controls (Kassinen et al. 2007), implicating intestinal bacteria in the pathogenesis of this disorder. Moreover, intestinal inflammation has been demonstrated in patients with IBS (Liebregts et al. 2007; O'Mahony et al. 2005), further implicating GI microbiota in the pathogenesis of IBS. However, to date there is no clear picture of how an altered GI microbiota is associated with intestinal inflammation, altered GI hypersensitivity, or motor dysfunction.

## Cancer

As might be expected, cancers of the colon are most strongly associated with the GI microbiota. Germ-free *Il10*-deficient mice are resistant to IBD and subsequent colitis-associated colon cancer (CAC), but if conventionalized, they are highly susceptible to CAC development with the azoxymethane carcinogen model (Uronis et al. 2009). Similarly, transforming growth factor  $\beta 1$  (*Tgfb1*) null mice that are colonized by a conventional microbiota develop colon cancer, while those that are raised GF do not (Engle et al. 2002). The susceptibility to colon cancer of mice with perturbed transforming growth factor  $\beta$  (TGFB) signaling, like the *Smad3* null, *Rag2* null, and *Tgfb1* null mouse models (Erdman et al. 2009; Maggio-Price et al. 2006), has been attributed to *Helicobacter* spp. or other proinflammatory bacteria in the colon. Unlike the TGFB-driven models, *Apc<sup>Min</sup>* mice, raised under GF conditions, show only a modest reduction in the number of intestinal polyps (Dove et al. 1997), suggesting that the microbiota can have differential influences on molecularly distinct colon cancers. In addition to modulating the inflammatory system, the GI microbiota also produces butyrate, a potent histone deacetylase inhibitor that can alter epigenetic programming of colonocytes and has been implicated in the prevention of colon cancer (Balamurugan et al. 2008). Differences in the composition of the GI microbiota may also contribute to ethnic differences in colon cancer incidence (O'Keefe et al. 2007). The role of the GI microbiota in cancer susceptibility may even extend beyond the colon; it was recently reported that members of the GI microbiota can increase susceptibility to mammary adenocarcinomas in mice (Rao et al. 2006).

## Obesity

The traditional view of obesity is centered on nutrition and host genetics (Rankinen et al. 2006). However, studies using mouse models of obesity as well as GF and gnotobiotic mice have shown a contributing role of the GI microbiota to obesity (Backhed et al. 2007; Ley et al. 2005; Turnbaugh et al. 2007). Consistent with the diet-linked changes in the GI microbiota described above, the ratio of the two predominant bacterial divisions, *Bacteroides* and *Firmicutes*, shifts significantly when comparing normal to diet-induced obese mice (Ley et al. 2005). Furthermore, in leptin-deficient obese mice, the number of *Bacteroides* is 50% lower with a subsequent rise in the quantities of *Firmicutes* compared to normal littermates. This observation was also found in obese humans where the numbers of organisms from the *Bacteroidetes* division increased in dieting subjects and correlated with weight loss (Kurokawa et al. 2007). These observations did not demonstrate whether a change in the *Bacteroidetes* division is the cause of weight gain or whether it was the effect of consuming specific dietary components that selectively enhances the members of this bacterial division. However, a recent study demonstrated that an "obese microbiome" can promote weight gain in ex-GF mice when compared to ex-GF mice associated with a "lean microbiome," demonstrating that the obesity phenotype can be transmissible through the microbiome (Turnbaugh et al. 2008).

One mechanism by which the microbiome contributes to obesity appears to be through modulation of host metabolism. Ex-GF mice that are conventionalized with a normal GI microbiota have a dramatic increase in weight compared to their GF littermates, even though they consume less food. The GI microbiota suppress expression of angiopoietin-like 4

(*Angpt14*, formerly called fasting-induced adipose factor or *Fiaf*), which causes the deposition of triglycerides in adipocytes. GF mice lacking *Angpt14* lose resistance to diet-induced obesity (Backhed et al. 2007), which implicates the GI microbiota as a contributor to obesity not only by increasing the capacity for harvesting sugars from the diet, but also by modulating the host's processing and storage of fats. The GI microbiota can also have direct effects on host physiology. For example, the GI microbiota can convert choline into methylamines, thus reducing the availability of choline in mice maintained on a high-fat diet (Dumas et al. 2006). Consequences of choline metabolism by the microbiota are mimicking choline-deficient diets and inducing nonalcoholic fatty liver disease.

### Other systemic diseases

The GI microbiota also has pronounced effects on host physiology beyond the intestinal tract. Metabolomic differences in the urine of GF and normal microbiota-colonized rats (Nicholls et al. 2003) and among humans with different microbiota compositions (Li et al. 2008) can be readily detected. A more detailed metabolic analysis of various biofluids showed that the microbiota impact the homeostasis of a variety of organ systems in mice, including altering liver levels of glycine and bile acids and kidney levels of hippurate, betaine, and choline (Claus et al. 2008). Similarly, the microbiota cause changes in a variety of blood metabolites (Wikoff et al. 2008). The blood metabolomic changes elicited by the GI microbiota are similar to those of a drug-like phase II response in the host, suggesting that the microbiota may also impact drug metabolizing-capability of the host. The type of microbiota also can have differential influences on host physiology (Martin et al. 2007). Colonization of GF mice with human neonatal GI microbiota, as opposed to adult GI microbiota, causes changes in a highly correlated metabolome network in the plasma and urine, indicative of lipid metabolism.

With the range of physiological and metabolic changes to the host attributed to the GI microbiota, it is not surprising that systemic diseases can also be influenced by members of the GI microbiota. Epidemiological studies have shown that allergic diseases correlate with the use of antibiotics and alterations to the GI microbiota (Shreiner et al. 2008). Confirming the link between antibiotic use and allergic diseases, mice with antibiotic disruption of the GI microbiota have elevated sensitivity to T-cell-mediated airway allergic response that requires IL13 (Noverr et al. 2005). More striking are the potential links between the GI microbiota and cardiovascular and neurological diseases (Ordovas and Mooser 2006; Parracho et al. 2005). For example, the GI microbiota influence myocardial metabolism in response to nutrient deprivation (Crawford et al. 2009) and diet-induced improvements in hypercholesterolemia (Martinez et al. 2009). In addition, children with autistic spectrum disorders have higher levels of *Clostridium histolyticum*, a known toxin-producer, than healthy controls (Parracho et al. 2005).

### Microbiota-based therapies

Because the microbiota play an important role in GI and other diseases, numerous studies have attempted to exploit beneficial bacteria (probiotics) or compounds that stimulate beneficial bacteria (prebiotics) as therapies. Probiotics are live microorganisms that when administered in adequate numbers confer a health benefit on the host. It is believed that

increasing the numbers of specific organisms within the GI microbiota can have a beneficial effect, either directly by regulating the host immune system (O'Mahony et al. 2001; Peran et al. 2005; Vinderola et al. 2005) or indirectly by altering the composition or activity of the GI microbiota (Tannock et al. 2000).

Most probiotic-mediated therapies to date have focused on IBD. Many different probiotics are effective at reducing inflammation in various mouse models of IBD (Prisciandaro et al. 2009), demonstrating that there is no generalized mode of action for the beneficial effects of probiotics. Modulation of the microbiota as a treatment for IBD has been confirmed in clinical trials where antibiotics can alleviate inflammatory symptoms and it is a common treatment for IBD patients (Bibiloni et al. 2005). Although early probiotic trials in human patients with IBD were criticized for their experimental design, a number of double-blind placebo-controlled trials for IBS have been performed and clearly demonstrate the beneficial effects of probiotics (Gawronska et al. 2007; Guyonnet et al. 2007).

Although recent clinical trials have demonstrated the therapeutic benefit of probiotics for treating GI illnesses, the underlying mechanisms contributing to their beneficial effects remain relatively unknown. An emerging aspect of probiotic therapy is the heterologous expression of novel therapeutic molecules in natural constituents of the GI microbiota. Because probiotics in their natural form can reduce symptoms of GI disease in mouse models and in human clinical trials (Ouwehand et al. 2002), it is tempting to speculate that more effective probiotics can be created through genetic engineering. Initial studies using genetically engineered probiotics demonstrated how recombinant lactic acid bacteria can enhance lipid digestion (Drouault et al. 2002) and prevent HIV infection (Chang et al. 2003) and be used to deliver foreign antigens to mucosal surfaces (Seegers 2002). In addition, it has been demonstrated that a recombinant strain of *Lactococcus lactis* producing mouse IL10 is capable of reducing inflammation in the *IL10*-deficient mouse model (Steidler et al. 2000). Although this approach failed as a therapeutic in clinical trials, this study demonstrated the power of probiotics as delivery vehicles for replacing molecules depleted in vivo. Similarly, heterologous expression of trefoil factors in *L. lactis* acts as a potent prophylactic for the treatment of acute colitis in a chemically induced mouse model of colitis (Vandenbroucke et al. 2004). More recently, *Lactobacillus gasseri*, genetically engineered to overexpress the antioxidant superoxide dismutase, was shown to decrease inflammation and disease in the *IL10* mouse model of colitis (Carroll et al. 2007).

## Future prospects

Renewed appreciation for the role of GI microorganisms in health and disease has led to the Human Gut Microbiome Initiative (Turnbaugh et al. 2007). The objective of this program is to sequence and compare the genomes of hundreds of species representing the bacterial divisions known to comprise the human distal GI microbiota. Analyzing the combined genomes of numerous GI microorganisms will answer important questions about the evolution and flexibility of the GI microbiome, including the extent of lateral gene transfer between autochthonous (permanent) and allochthonous (transient) GI microorganisms, the identification of essential genes required for survival in the GI ecosystem, and the mechanisms of interaction between the GI microbiota and the host immune system. Equally



important will be the insights gained into the mechanisms by which the GI microbiota modulate a diverse array of host phenotypes. Many phenotypes that have been attributed to the host in functional genomic studies may in fact result from host-microbiota interactions. The GI microbiome is the most malleable of the mammalian “genomes,” whose composition has important implications for mammalian functional genomics and links to health and disease outcome. An improved knowledge of the composition and function of the GI microbiota of humans and model organisms will allow this important third genome of mammals to be exploited for new therapeutic approaches to prevent or treat not only GI diseases but also systemic diseases like cancer and obesity.

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**Table 1**  
**Comparison of human and mouse GI microbiota composition**

Phylum	Percentage of total sequences	
	Human	Mouse
Aquificae		
Thermotogae		
Thermodesulfobacteria		
Deinococcus-Thermus	0.01	1.15
Chrysiogenetes		
Chloroflexi	0.003	
Thermomicrobia		
Nitrospira		
Deferribacteres	0.03	
Cyanobacteria	0.014	
Chlorobi		
Proteobacteria	3.7	15.2
<b>Firmicutes</b>	<b>65</b>	<b>52.5</b>
Actinobacteria	2	0.35
Planctomycetes	0.005	
Chlamydiae	0.008	0.01
Spirochaetes	0.63	0.3
Fibrobacteres		
Acidobacteria		
<b>Bacteroidetes</b>	<b>26.7</b>	<b>28.2</b>
Fusobacteria	0.12	0.75
Verrucomicrobia	1.5	1.25
Dictyoglomi		
Gemmatimonadetes		
Lentisphaerae	0.005	
BRC1		
OP10		
OP11		
TM7	0.14	0.15
WS3		
Dehalococcoides		
SR1		
OD1		
Unclassified bacteria	0.09	0.05

Bold = major phyla