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Muribaculaceae genomes assembled from metagenomes suggest genetic drivers of differential response to acarbose treatment in mice

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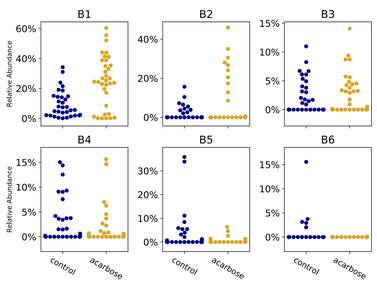
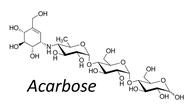
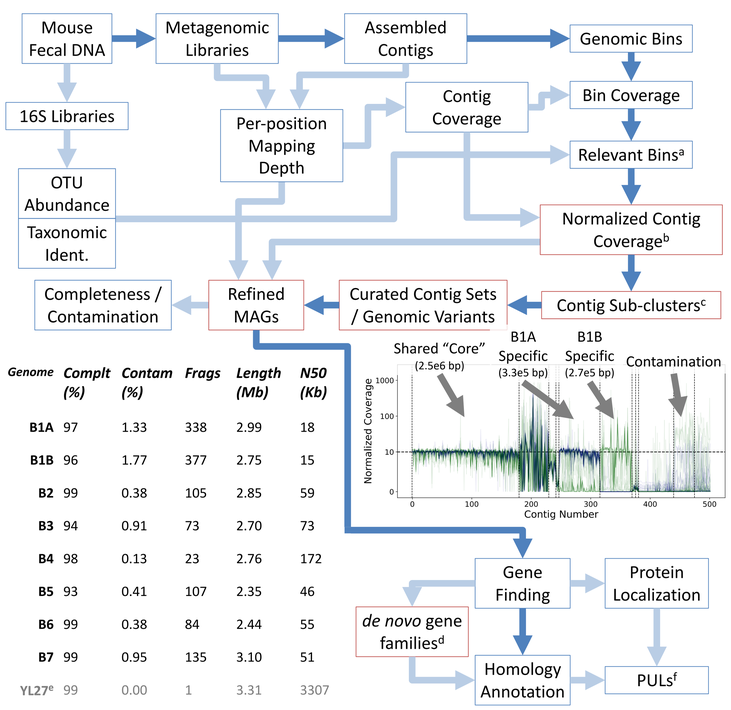
Introduction

Mice treated with the α-amylase and α-glucosidase inhibitor acarbose live longer[1] and have notably different fecal microbial communities and short-chain fatty acid concentrations[2], presumably due to increased starch entering the lower digestive system. The two bacterial taxa most dramatically enriched by this treatment are in the recently described family *Muribaculaceae* (also called: S24-7 or *Homeothermaceae*). However, other members of this clade decrease in abundance or do not respond. Previous studies of this bacterial family suggest that members specialize on a diversity of fibers including starch, plant polysaccharides, and glycans derived from their animal hosts[3,4]. However, these explorations have been limited by the availability of isolates, or have studied genomes assembled from metagenomes (MAGs) in the absence of experimental results. Here we compare 7 novel MAGs and find genomic features that may explain differences between *Muribaculaceae* that differentiate acarbose "responders", here referred to as B1 and B2, from non-responders, B3-B7.



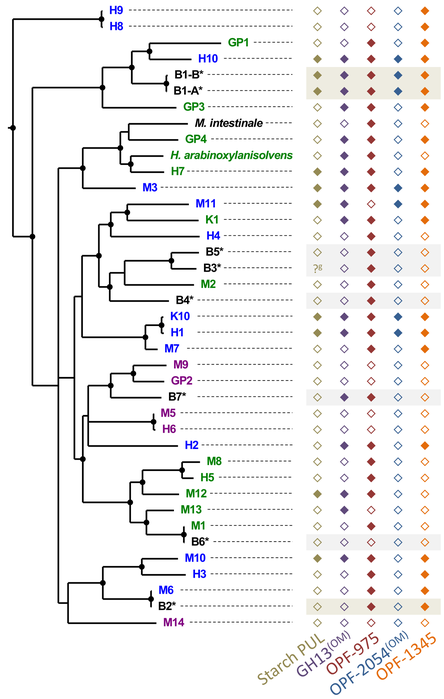


Methods

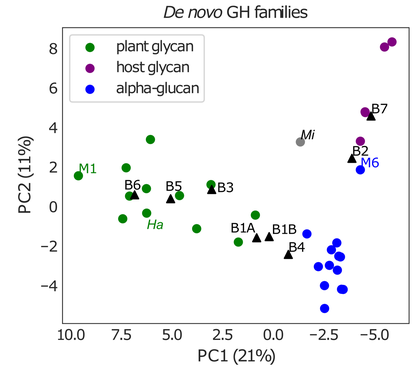


Genome	Complt (%)	Contam (%)	Frags	Length (Mb)	N50 (Kb)
B1A	97	1.33	338	2.99	18
B1B	96	1.77	377	2.75	15
B2	99	0.38	105	2.85	59
B3	94	0.91	73	2.70	73
B4	98	0.13	23	2.76	172
B5	93	0.41	107	2.35	46
B6	99	0.38	84	2.44	55
B7	99	0.95	135	3.10	51
YL27[e]	99	0.00	1	3.31	3307

Results



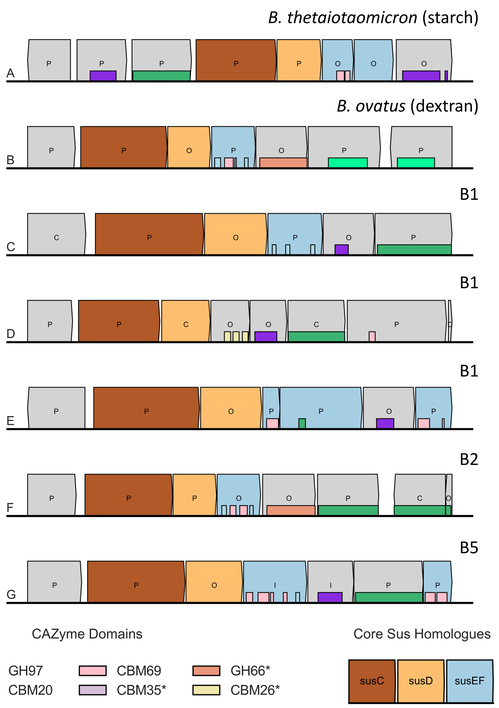
Reconstructed MAGs differ in their encoded glycoside hydrolases (GHs) and carbohydrate binding domains, many of which are encoded in apparent polysaccharide utilization loci (PULs). Given the dramatic increase in the relative abundance of B1 and B2 in mice treated with acarbose, we predicted that these taxa shared traits with starch degradation specialists. An ordination based on the predicted complement of glycoside hydrolases in each genome confirmed that both responders were similar to other members of this putative "guild", one of three hypothesized in previous studies of the *Muribaculaceae*[3].



Indeed, the B1 genome includes three separate PULs encoding numerous starch-active domains, including GH13 containing proteins predicted to be localized to the outer membrane (OM). None of the non-responders encode a starch-active PUL[g], nor a GH13 localized to the OM. Surprisingly, the B2 genome also had no apparent PULs for starch, nor GH13 enzymes on the OM.

Since traditional, best-match based annotations may split functionally orthologous groups and combine functionally distinct groups, we applied *de novo* clustering of protein sequences to produce operational protein families (OPFs) potentially reflecting more relevant relationships between proteins. This approach identified several families that appear to differentiate starch specialists from others, including OPF-1345, a periplasmic GH13 containing enzyme shared by both B1 and B2, but by none of the non-responders.

B1 has two distinct genomic variants, B1A and B1B, with differences in gene content including numerous PULs. However, starch active enzymes do not seem to be included in these variable regions.



Conclusions

- We have reconstructed **eight high-quality *Muribaculaceae* genomes** from metagenomes.
- Members of this family are **taxonomically and functionally diverse** in the mouse gut microbiome, and may specialize in the degradation of complex carbohydrates.
- Differential response to acarbose treatment reflects **variation in encoded polysaccharide utilization loci and glycoside hydrolases**.
- The most abundant taxon, B1, is composed of **two distinct genomic variants**, differentiated by more than 600 protein coding genes.
- High-quality MAGs can be recovered from microbial communities currently under-represented in strain collections, and provide a **powerful platform for ecological discovery**.

Footnotes and Citations

• [a] Bins were matched to OTUs based on a partial least squares cross-decomposition of coverage and relative abundance. • [b] Contig coverage was normalized to the mean coverage of contigs confidently identified as part of the core genome based on manual inspection. • [c] Contigs were clustered based on normalized coverage across samples, effectively partitioning between contigs in the core genome, in particular genomic variants, or in other, "contaminating" genomes. • [d] *De novo* gene families were assigned based on an all-by-all protein BLAST using the MCL algorithm. • [e] *Muribaculum intestinale* YL27 • [f] PULs were defined as a *susC* homolog within 5000 bases of, on the same strand as, and upstream of a *susD* homolog. • [g] While B3 does encode a possible starch-active PUL, the GH13 lipoprotein is predicted to localize to the inner membrane, rather than the OM. • [1] Harrison, D. E. *et al.* (2014). *Aging Cell*, *13*(2), 273–282. doi:10.1111/acel.12170 • [2] Smith, B. J. *et al.* (2019). *BMC Microbiology*, *19*(130), 16. doi:10.1186/s12866-019-1494-7 • [3] Ormerod, K. L. *et al.* (2016). *Microbiome*, *4*(1), 36. doi:10.1186/s40168-016-0181-2 • [4] Lagkouvardos, I. *et al.* (2019). *Microbiome*, *7*(1), 1–15. doi:10.1186/s40168-019-0637-2

Acknowledgments & Contact

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