

## RESEARCH ARTICLE SUMMARY

## MICROBIOTA

## Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism

Vayu Maini Rekdal, Elizabeth N. Bess, Jordan E. Bisanz, Peter J. Turnbaugh\*, Emily P. Balskus\*

**INTRODUCTION:** Parkinson's disease is a debilitating neurological condition affecting more than 1% of the global population aged 60 and above. The primary medication used to treat Parkinson's disease is levodopa (L-dopa). To be effective, L-dopa must enter the brain and be converted to the neurotransmitter dopamine by the human enzyme aromatic amino acid decarboxylase (AADC). However, the gastrointestinal tract is also a major site for L-dopa decarboxylation, and this metabolism is problematic because dopamine generated in the periphery cannot cross the blood-brain barrier and causes unwanted side effects. Thus, L-dopa is coadministered with drugs that block peripheral metabolism, including the AADC inhibitor carbidopa. Even with these drugs, up to 56% of L-dopa fails to reach the brain. Moreover, the efficacy and side effects of L-dopa treatment are extremely heterogeneous across Parkinson's patients, and this variability cannot be completely explained by differences in host metabolism.

**RATIONALE:** Previous studies in humans and animal models have demonstrated that the gut microbiota can metabolize L-dopa. The major

proposed pathway involves an initial decarboxylation of L-dopa to dopamine, followed by conversion of dopamine to *m*-tyramine by means of a distinctly microbial dehydroxylation reaction. Although these metabolic activities were shown to occur in complex gut microbiota samples, the specific organisms, gene, and enzymes responsible were unknown. The effects of host-targeted inhibitors such as carbidopa on gut microbial L-dopa metabolism were also unclear. As a first step toward understanding the gut microbiota's effect on Parkinson's disease therapy, we sought to elucidate the molecular basis for gut microbial L-dopa and dopamine metabolism.

**RESULTS:** Hypothesizing that L-dopa decarboxylation would require a pyridoxal phosphate (PLP)-dependent enzyme, we searched gut bacterial genomes for candidates and identified a conserved tyrosine decarboxylase (TyrDC) in *Enterococcus faecalis*. Genetic and biochemical experiments revealed that TyrDC simultaneously decarboxylates both L-dopa and its preferred substrate, tyrosine. Next, we used enrichment culturing to isolate a dopamine-

dehydroxylating strain of *Eggerthella lenta*, a species previously implicated in drug metabolism. Transcriptomics linked this activity to a molybdenum cofactor-dependent dopamine dehydroxylase (Dadh) enzyme. Unexpectedly, the presence of this enzyme in gut bacterial genomes did not correlate with dopamine metabolism; instead, we identified a single-nucleotide polymorphism (SNP) in the *dadh* gene that predicts activity. The abundance of

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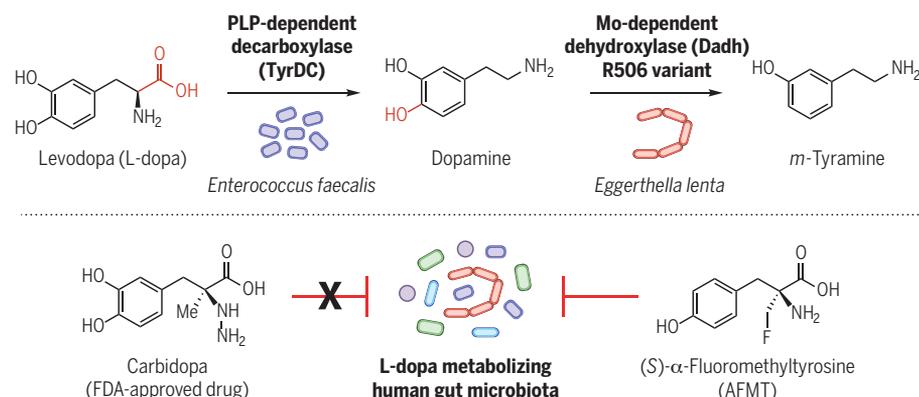
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*E. faecalis*, *tyrDC*, and the individual SNPs of *dadh* correlated with L-dopa and dopamine metabolism in complex gut microbiotas from Parkinson's patients, indicating that these orga-

nisms, genes, enzymes, and even nucleotides are relevant in this setting.

We then tested whether the host-targeted AADC inhibitor carbidopa affected L-dopa decarboxylation by *E. faecalis* TyrDC. Carbidopa displayed greatly reduced potency toward bacteria and was completely ineffective in complex gut microbiotas from Parkinson's patients, suggesting that this drug likely does not prevent microbial L-dopa metabolism in vivo. To identify a selective inhibitor of gut bacterial L-dopa decarboxylation, we leveraged our molecular understanding of gut microbial L-dopa metabolism. Given TyrDC's preference for tyrosine, we examined tyrosine mimics and found that (*S*)- $\alpha$ -fluoromethyltyrosine (AFMT) prevented L-dopa decarboxylation by TyrDC and *E. faecalis* as well as complex gut microbiota samples from Parkinson's patients. Coadministering AFMT with L-dopa and carbidopa to mice colonized with *E. faecalis* also increased the peak serum concentration of L-dopa. This observation is consistent with inhibition of gut microbial L-dopa metabolism in vivo.

**CONCLUSION:** We have characterized an interspecies pathway for gut bacterial L-dopa metabolism and demonstrated its relevance in human gut microbiotas. Variations in these microbial activities could possibly contribute to the heterogeneous responses to L-dopa observed among patients, including decreased efficacy and harmful side effects. Our findings will enable efforts to elucidate the gut microbiota's contribution to treatment outcomes and highlight the promise of developing therapies that target both host and gut microbial drug metabolism. ■



**Gut microbes metabolize the Parkinson's drug L-dopa.** Decarboxylation of L-dopa by *E. faecalis* TyrDC and human AADC likely limits drug availability and contributes to side effects. *E. lenta* dehydroxylates dopamine produced from L-dopa using a molybdenum-dependent enzyme. Although the host-targeted drug carbidopa did not affect gut bacterial L-dopa decarboxylation, AFMT inhibited this activity in complex human gut microbiotas.

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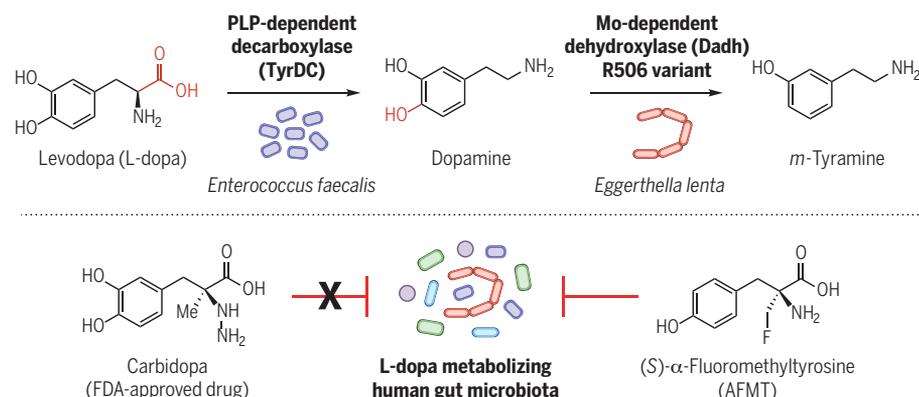
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# Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism

Vayu Maini Rekdal<sup>1</sup>, Elizabeth N. Bess<sup>2,3,4</sup>, Jordan E. Bisanz<sup>2</sup>, Peter J. Turnbaugh<sup>2,5\*</sup>, Emily P. Balskus<sup>1\*</sup>

The human gut microbiota metabolizes the Parkinson's disease medication Levodopa (L-dopa), potentially reducing drug availability and causing side effects. However, the organisms, genes, and enzymes responsible for this activity in patients and their susceptibility to inhibition by host-targeted drugs are unknown. Here, we describe an interspecies pathway for gut bacterial L-dopa metabolism. Conversion of L-dopa to dopamine by a pyridoxal phosphate-dependent tyrosine decarboxylase from *Enterococcus faecalis* is followed by transformation of dopamine to *m*-tyramine by a molybdenum-dependent dehydroxylase from *Eggerthella lenta*. These enzymes predict drug metabolism in complex human gut microbiotas. Although a drug that targets host aromatic amino acid decarboxylase does not prevent gut microbial L-dopa decarboxylation, we identified a compound that inhibits this activity in Parkinson's patient microbiotas and increases L-dopa bioavailability in mice.

A growing body of evidence links the trillions of microbes that inhabit the human gastrointestinal tract (the human gut microbiota) to neurological conditions, including the debilitating neurodegenerative disorder Parkinson's disease (1, 2). Gut microbes from Parkinson's patients exacerbate motor deficits when transplanted into germ-free mouse models of disease (2). This effect is reversed with antibiotic treatment, suggesting a causal role for gut microbes in neurodegeneration. Multiple studies have revealed differences in gut microbiota composition in Parkinson's disease patients compared with healthy controls that may correlate with disease severity (3–9). However, the influence of the human gut microbiota on the treatment of Parkinson's and other neurodegenerative diseases remains poorly understood.

The primary treatment for Parkinson's disease is Levodopa (L-dopa) (10), which is prescribed to manage motor symptoms that result from dopaminergic neuron loss in the substantia nigra. After crossing the blood-brain barrier, L-dopa is decarboxylated by aromatic amino acid decarboxylase (AADC) to give dopamine, the active

therapeutic agent. However, dopamine generated in the periphery by AADC cannot cross the blood-brain barrier, and only 1 to 5% of L-dopa reaches the brain, owing to extensive presystemic metabolism in the gut by enzymes such as AADC (11–13). Peripheral production of dopamine also causes gastrointestinal side effects, can lead to orthostatic hypotension through activation of vascular dopamine receptors, and may induce cardiac arrhythmias (14, 15). To decrease peripheral metabolism, L-dopa is coadministered with AADC inhibitors such as carbidopa. Despite this, 56% of L-dopa is metabolized peripherally (16), and patients display highly variable responses to the drug, including loss of efficacy over time (17).

Multiple lines of evidence suggest that gut microbial interactions with L-dopa influence treatment outcomes (18). Administering broad-spectrum antibiotics improves L-dopa therapy, suggesting that gut bacteria interfere with drug efficacy (19, 20). The gut microbiota can also metabolize L-dopa, potentially reducing its bioavailability and leading to side effects (21–24). The major proposed pathway involves an initial decarboxylation of L-dopa to dopamine followed by a distinctly microbial dehydroxylation reaction that converts this neurotransmitter to *m*-tyramine by selectively removing the para hydroxyl group of the catechol ring (Fig. 1A) (25, 26). When we began our work, the gut microbial species, genes, and enzymes involved in these transformations were unknown because previous studies examined undefined and uncharacterized consortia. The clinical relevance of this pathway was also unclear given the potential effects of coadministered inhibitors of host periph-

eral L-dopa metabolism on these gut microbial activities.

## The human gut bacterium *Enterococcus faecalis* decarboxylates L-dopa

We sought to elucidate the genetic and biochemical bases for gut microbial L-dopa metabolism and understand how coadministered AADC inhibitors affect this pathway. Using a genome-mining approach, we first identified strains that encode candidate L-dopa decarboxylating enzymes. Aromatic amino acid decarboxylation is typically performed by enzymes using pyridoxal-5'-phosphate (PLP), an organic cofactor that provides an electron sink (27). Recently, a PLP-dependent tyrosine decarboxylase (TyrDC) from the food-associated strain *Lactobacillus brevis* CGMCC 1.2028 was shown to have promiscuous activity toward L-dopa in vitro (28). To locate TyrDC homologs in human gut bacteria, we performed a BLASTP (Protein Basic Local Alignment Search Tool) search against the complete set of Human Microbiome Project (HMP) reference genomes available through the National Center for Biotechnology Information (NCBI). The majority of hits were found in the neighboring genus *Enterococcus*, with some hits within lactobacilli and Proteobacteria (Fig. 1B, fig. S1, and data file S1). We selected 10 representative gut strains that contain TyrDC homologs (29 to 100% amino acid ID) and examined their ability to decarboxylate L-dopa in anaerobic culture. Although both *Enterococcus faecalis* and *Enterococcus faecium* displayed activity, only *E. faecalis* showed complete decarboxylation across all strains tested (Fig. 1C). All *E. faecalis* strains tested share the highly conserved four-gene *tyrDC* operon (fig. S2), and we found *tyrDC* in 98.4% of the *E. faecalis* assemblies deposited in NCBI with a median amino acid identity of 99.8 (range 97.0 to 100). This high degree of sequence conservation and prevalence is consistent with tyrosine decarboxylation being a common phenotypic trait of *E. faecalis* (29). We therefore chose this prevalent, genetically tractable gut organism as a model for characterizing L-dopa decarboxylation (30).

Although lyophilized *E. faecalis* cells decarboxylate L-dopa (31) and the *tyrDC* operon's role in tyrosine decarboxylation in *E. faecalis* is well-characterized (32), the connection between *tyrDC* and L-dopa decarboxylation was unknown. We used genetics and in vitro biochemistry experiments to confirm that TyrDC is necessary and sufficient for L-dopa decarboxylation by *E. faecalis*. *E. faecalis* MMH594 mutants carrying a 2-kb Tet-cassette disrupting *tyrDC* could not decarboxylate L-dopa (Fig. 1D and fig. S3) and displayed no growth defects compared with wild type (fig. S4). In vitro characterization of TyrDC revealed a five-fold higher catalytic efficiency toward L-tyrosine compared with L-dopa, suggesting that drug metabolism arises from promiscuous enzyme activity (Fig. 1E, fig. S5, and table S1). This selectivity contrasts sharply with that of AADC, which displays very low activity toward L-tyrosine (33). Although TyrDC from *E. faecalis* was previously shown to decarboxylate tyrosine and phenylalanine

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(34–37), its ability to accept L-dopa had not been demonstrated. A recent, independent report also corroborates this finding (38).

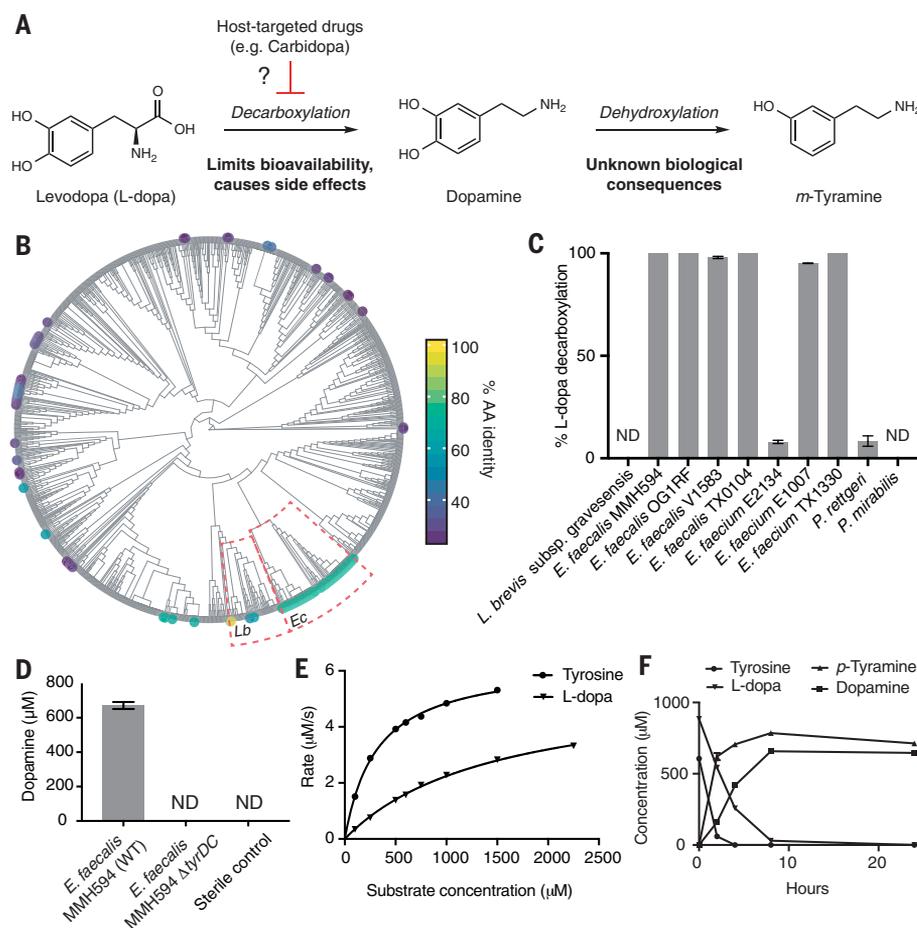
We next tested whether tyrosine, which is the preferred substrate for TyrDC and is present in the small intestine, could interfere with L-dopa decarboxylation by *E. faecalis* (39, 40). In competition experiments, purified TyrDC (fig. S6) and anaerobic *E. faecalis* cultures decarboxylated L-dopa and tyrosine simultaneously (500  $\mu$ M tyrosine, approximating the resting small intestinal concentration) (Fig. 1F and fig. S7) (40). This observation sharply contrasts with previous investigations of phenylalanine, which is metabolized by *E. faecalis* only when tyrosine is completely consumed (36). Simultaneous decarboxylation of L-dopa and tyrosine also occurred in *E. faecalis* MMH594 cultures that contained higher tyrosine concentrations (1.5 mM, approximating the small intestinal post-meal concentration) (fig. S8) and in three human fecal suspensions (fig. S9). As observed previously for tyrosine, L-dopa decarboxylation occurred more rapidly at lower pH across all strains tested (figs S7 and S8), suggesting that this metabolism is likely accelerated at the lower pH of the upper small intestine (41, 42). Because the Michaelis constant ( $K_m$ ) of TyrDC for L-dopa (1.5 mM) is below the estimated maximum in vivo small intestinal L-dopa concentration even at its lowest clinically administered dose (5 mM), these data strongly suggest that peripheral decarboxylation is performed by both host and gut bacterial enzymes.

### *Eggerthella lenta* dehydroxylates dopamine using a molybdenum-dependent enzyme

Having identified a gut bacterial L-dopa decarboxylase, we next examined the conversion of dopamine to *m*-tyramine because this activity may influence the side effects associated with peripheral L-dopa decarboxylation. *E. faecalis* did not further metabolize dopamine, indicating that this step was performed by a different microorganism. Dehydroxylation of dopamine has not been reported for any bacterial isolate, and a screen of 18 human gut strains failed to uncover metabolizers. Therefore, we used enrichment culturing to obtain a dopamine-dehydroxylating organism. Recognizing the chemical parallels between this reductive dehydroxylation and reductive dehalogenation of chlorinated aromatics, which enables anaerobic respiration in certain bacteria (43), we inoculated a stool sample from a human donor into a minimal growth medium containing 0.5 mM dopamine as the sole electron acceptor (figs. S10 and S11). Passing over multiple generations enriched for active strains, as assessed by means of a colorimetric assay for catechol dehydroxylation (fig. S11). This effort identified a strain of the gut Actinobacterium *Eggerthella lenta* (referred to herein as strain A2) that is capable of selectively removing the para hydroxyl group of dopamine to give *m*-tyramine (fig. S12). Because *E. lenta* also inactivates the cardiac drug digoxin, our finding suggests a wider role for this gut organism in drug metabolism (44, 45).

Catechol dehydroxylation is a chemically challenging reaction that has no equivalent in synthetic chemistry and likely involves unusual enzymology. To identify the dopamine-dehydroxylating enzyme, we first searched the *E. lenta* A2 genome for genes that encode homologs of the only characterized aromatic *para*-dehydroxylase, 4-hydroxybenzoyl-CoA reductase (46), but found no hits. Assays with *E. lenta* A2 cell lysates showed dopamine dehydroxylation required anaerobic conditions and was induced by dopamine (fig. S13). We therefore used RNA-sequencing of *E. lenta* A2 to identify the de-

hydroxylase. This experiment revealed >2500-fold up-regulation of three colocalized genes in response to dopamine (Fig. 2A and table S2). These genes encode a predicted bis-molybdopterin guanine dinucleotide cofactor (moco)-containing enzyme belonging to the dimethyl sulfoxide reductase family. Moco-dependent enzymes catalyze a wide variety of oxygen-transfer reactions but have not been demonstrated to catalyze catechol dehydroxylation in vitro (47). We therefore hypothesized that this enzyme was a dopamine dehydroxylase (Dadh).



**Fig. 1. *E. faecalis* metabolizes L-dopa using a PLP-dependent tyrosine decarboxylase.** (A) Proposed major pathway for L-dopa metabolism by the human gut microbiota and potential for interaction with host-targeted drugs. (B) Phylogenetic distribution of TyrDC in the human microbiota. Human Microbiome Project reference genomes were queried by means of BLASTP for homologs of the *L. brevis* TyrDC, and the results are visualized on a cladogram of phylogeny [based on 16S ribosomal RNA (rRNA) alignment]. TyrDC homologs found sporadically within *Lactobacillus* spp. (*Lb*) are widely distributed among *Enterococcus* (*Ec*; average amino acid identity 67.8% over 97.6% query length). (C) Testing representative gut microbial strains encoding TyrDC reveals that *E. faecalis* strains reproducibly convert L-dopa to dopamine. Strains were cultured for 48 hours anaerobically. Bar graphs represent the mean  $\pm$  SEM of three biological replicates. (D) Deletion of *tyrDC* abolishes L-dopa decarboxylation by *E. faecalis*. Dopamine was detected in culture supernatants after 48 hours of anaerobic growth with 0.5 mM L-dopa. Bar graphs represent the mean  $\pm$  SEM of three biological replicates. (E) Kinetic analysis of *E. faecalis* TyrDC reveals a preference for tyrosine. Error bars represent the mean  $\pm$  SEM of three biological replicates. ND, not detected. (F) L-dopa and tyrosine are simultaneously decarboxylated in anaerobic cultures of *E. faecalis* MMH594 grown at pH 5 with 1 mM L-dopa and 0.5 mM tyrosine. Bar graphs represent the mean  $\pm$  SEM of three biological replicates.

To assess Dadh's role in dopamine dehydroxylation, we first explored whether this activity was molybdenum-dependent by culturing *E. lentia* A2 in the presence of tungstate. Substitution of molybdate with tungstate during moco biosyn-

thesis generates an inactive metallocofactor (fig. S14) (48). Treating cultures of *E. lentia* A2 with tungstate inhibited dopamine dehydroxylation without affecting growth (Fig. 2B and fig. S15), whereas incubating cell lysates with tungstate had no ef-

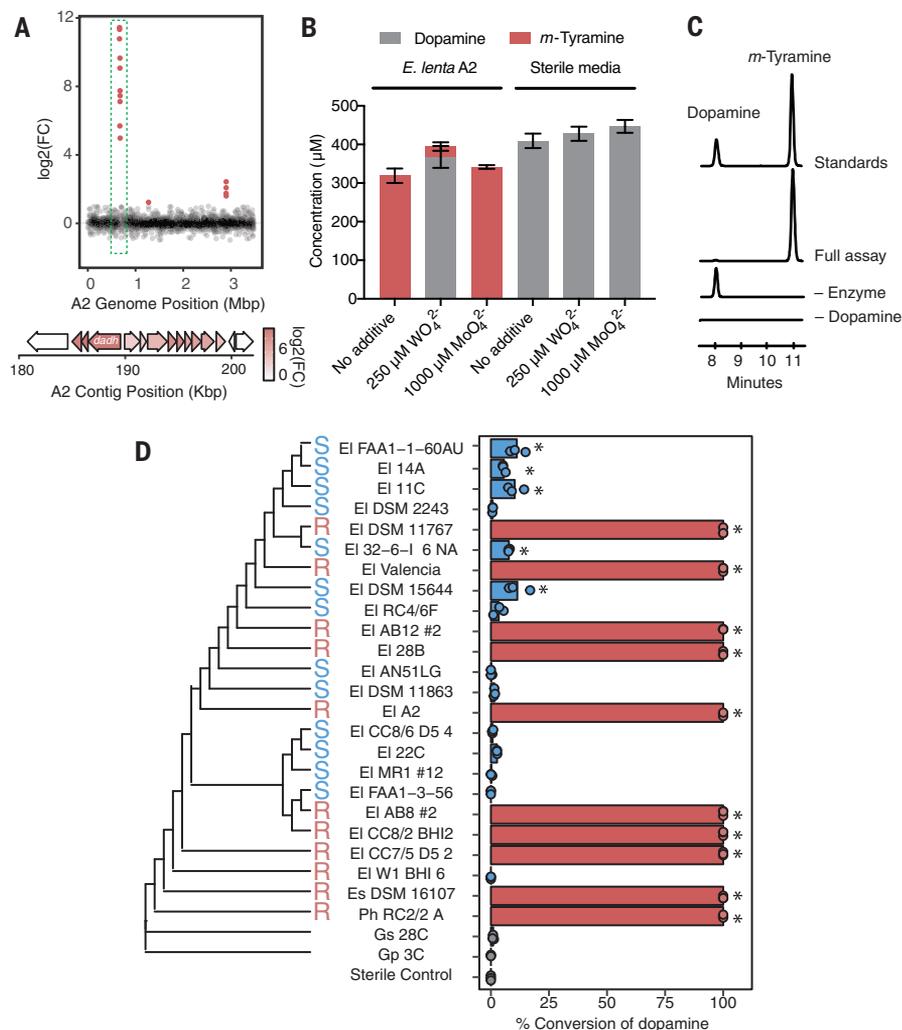
fect, which is consistent with inhibition requiring active moco biosynthesis (fig. S16). We next confirmed the activity of Dadh in vitro. Heterologous expression of >20 constructs in multiple hosts failed to provide active enzyme, prompting us to pursue native purification. Anaerobic activity-guided fractionation of *E. lentia* A2 cell lysates yielded a dopamine-dehydroxylating fraction containing four proteins as assessed by means of SDS-polyacrylamide gel electrophoresis (Fig. 2C, fig. S17, and table S3). Dehydroxylation activity correlated with a 115-kDa band that was confirmed with mass spectrometry (MS) to be Dadh. Dadh was the only isolated protein up-regulated in the presence of dopamine (tables S2 and S3). Together, these data strongly support the assignment of this enzyme.

We next assessed whether the presence of *dadh* in microbial genomes correlated with dopamine dehydroxylation. A BLASTP search revealed that this enzyme is restricted to *E. lentia* and its close Actinobacterial relatives (table S4), prompting us to screen a collection of 26 gut Actinobacterial isolates (49) for their ability to dehydroxylate dopamine in anaerobic culture. Although Dadh appeared to be encoded by 24 of the 26 strains (92 to 100% amino acid ID) (fig. S18 and table S5), only 10 *Eggerthella* strains quantitatively converted dopamine to *m*-tyramine, with low (<11%) or no metabolism in the others (Fig. 2D). This strain-level variability in dopamine metabolism reinforces that gut microbial species identity is often not predictive of metabolic functions (49, 50).

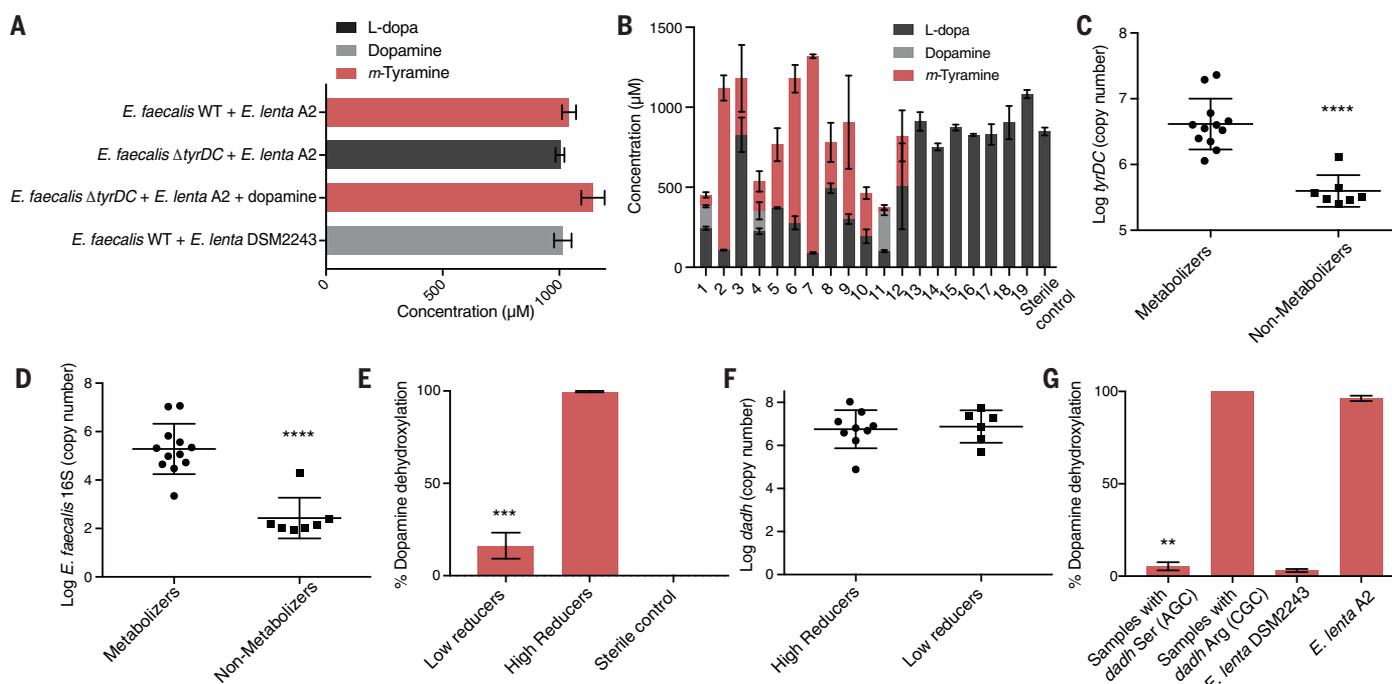
To better understand this variation, we first performed RNA-sequencing experiments with metabolizing (*E. lentia* 28B) and nonmetabolizing (*E. lentia* DSM2243) strains in the presence and absence of dopamine. Surprisingly, *dadh* was up-regulated in response to dopamine in both strains, indicating that lack of activity in *E. lentia* DSM2243 did not arise from differences in transcription (tables S6 and S7). Aligning the Dadh protein sequences, we instead found a single amino acid substitution that almost perfectly predicted metabolizer status: Position 506 is an arginine in metabolizing strains and a serine in inactive strains (Fig. 2D and fig. S19). This change arises from a single-nucleotide polymorphism (SNP) in *dadh*. The only exception, *E. lentia* W1BHI6, has the Arg<sup>506</sup> variant and an additional substitution nearby (Cys<sup>500</sup>) (fig. S19). Thus, specific amino acid residues in the Dadh enzyme, rather than presence or transcription of *dadh*, predict dopamine dehydroxylation among gut bacterial strains. The Dadh variants do not correlate with *E. lentia* phylogeny (Fig. 2D), suggesting that this activity has been gained and/or lost multiple times.

### *E. faecalis* and *E. lentia* metabolize L-dopa in human gut microbiotas

Having identified organisms and enzymes that perform the individual steps in the L-dopa pathway, we next tested whether *E. faecalis* and *E. lentia* generated *m*-tyramine in coculture. Wild-type *E. faecalis* grown with *E. lentia* A2



**Fig. 2. *E. lentia* dehydroxylates dopamine using a molybdenum-dependent enzyme.** (A) RNA-sequencing identifies a putative molybdenum (moco)-dependent dopamine dehydroxylase (Dadh) in *E. lentia* A2. Differentially expressed candidate genes (false discovery rate < 0.1 and fold change > |2|) are plotted as a function of genome position, revealing three discrete loci of differentially expressed genes. (Inset) Analysis of the largest cluster of differentially expressed genes at 0.665 Mbp in the scaffolded assembly (190 kb base pairs in the reference contig) revealed that a putative *dadh* was up-regulated by 2568-fold in response to dopamine. (B) Tungstate treatment inhibits dehydroxylation of dopamine by *E. lentia* A2. Cultures were grown anaerobically with tungstate (WO<sub>4</sub><sup>2-</sup>) or molybdate (MoO<sub>4</sub><sup>2-</sup>) for 48 hours with 0.5 mM dopamine. Bar graphs represent the mean ± SEM of three biological replicates. (C) In vitro activity of Dadh-containing fractions purified from *E. lentia* A2. Extracted LC-MS/MS ion chromatograms for simultaneous detection of dopamine and *m*-tyramine after 12 hours of anaerobic incubation of enzyme preparation with 500 µM dopamine and artificial electron donors at room temperature. Peak heights show the relative intensity of each mass, and all chromatograms are shown on the same scale. (D) A single amino acid variant predicts dopamine metabolism by *E. lentia* and related strains ( $P = 0.013$  Fisher's exact test) and does not correlate with phylogeny. Strains were cultured anaerobically with 500 µM dopamine for 48 hours (*El*, *E. lentia*; *Es*, *Eggerthella sinensis*; *Gs*, *Gordonibacter* sp.; and *Gp*, *Gordonibacter pamelaeeae*; *Ph*, *Paraeggerthella hongkongensis*). High (100% conversion) and low (<11% conversion) metabolizers are denoted in red and blue. For each strain, data points represent biological replicates (\* $P < 0.05$  analysis of variance with Dunnett's test versus sterile controls).



**Fig. 3. *E. faecalis* and *E. lenta* Dadh predict L-dopa metabolism in complex human gut microbiotas.** (A) Metabolism of L-dopa by cocultures of *E. faecalis* and *E. lenta* strains cocultured for 48 hours with 1 mM *D*<sub>3</sub>-phenyl-L-dopa or 1 mM dopamine. Results are mean  $\pm$  SEM ( $n = 3$  replicates).

(B) Metabolism of *D*<sub>3</sub>-phenyl-L-dopa by 19 unrelated human gut microbiota samples ex vivo. Samples were cultured anaerobically with *D*<sub>3</sub>-phenyl-L-dopa (1 mM) for 72 hours. Results are mean concentration  $\pm$  SEM ( $n = 3$  replicates).

(C) The abundance of *tyrDC* predicts L-dopa decarboxylation in human gut microbiota samples. Data represent the average *tyrDC* abundance (as assessed with qPCR) across the three replicates for samples in (B). Results are mean  $\pm$  SEM (\*\*\*\* $P < 0.0001$ , one-tailed Mann-Whitney test).

(D) The abundance of *E. faecalis* (as assessed with qPCR) predicts L-dopa decarboxylation in human gut microbiota samples. Each data point is the average abundance across three biological replicates for each sample shown in (B). Results are mean  $\pm$  SEM (\*\*\*\* $P < 0.0001$ , one-tailed Mann-

Whitney test). (E) Dopamine dehydroxylation by gut microbiota samples of 15 unrelated individuals. Samples were cultured for 48 hours with 0.5 mM dopamine. Bars are mean  $\pm$  SEM of  $n = 6$  for low reducers (<50%) and  $n = 9$  for high reducers (>50%) (\*\*\*\* $P = 0.0002$ , one-tailed Mann-Whitney test).

(F) *Dadh* abundance does not correlate with dehydroxylation by human gut microbiotas. Data represent qPCR with *Dadh*-specific primers. Each data point is the *dadh* abundance in each sample shown in (E). Bars represent the mean and SE. (G) *Dadh* sequence variants predict dopamine dehydroxylation ex vivo. Full-length *dadh* from each culture in (E) was sequenced by using primers specific for the region containing position 506. Samples in which a mix of variants were present ( $n = 5$ ) were removed. Bars represent the mean and SEM [ $n = 3$  for samples encoding the Arg506 *Dadh* variant,  $n = 7$  for samples encoding the Ser506 *Dadh* variant.,  $n = 3$  for DSM2243, and  $n = 3$  for A2] (\*\* $P = 0.0083$ , one-tailed Mann-Whitney test. CGC samples versus AGC samples).

(Arg<sup>506</sup>) fully converted L-dopa to *m*-tyramine (Fig. 3A). Although a coculture containing the *E. faecalis tyrDC* mutant could not consume L-dopa, *m*-tyramine was produced when exogenous dopamine was added to this culture, revealing that *E. lenta* A2 was still metabolically active. Incubating wild-type *E. faecalis* with the nonmetabolizing *E. lenta* DSM2243 (Ser506) strain produced only dopamine, indicating that this *Dadh* variant is also inactive in a coculture setting (Fig. 3A).

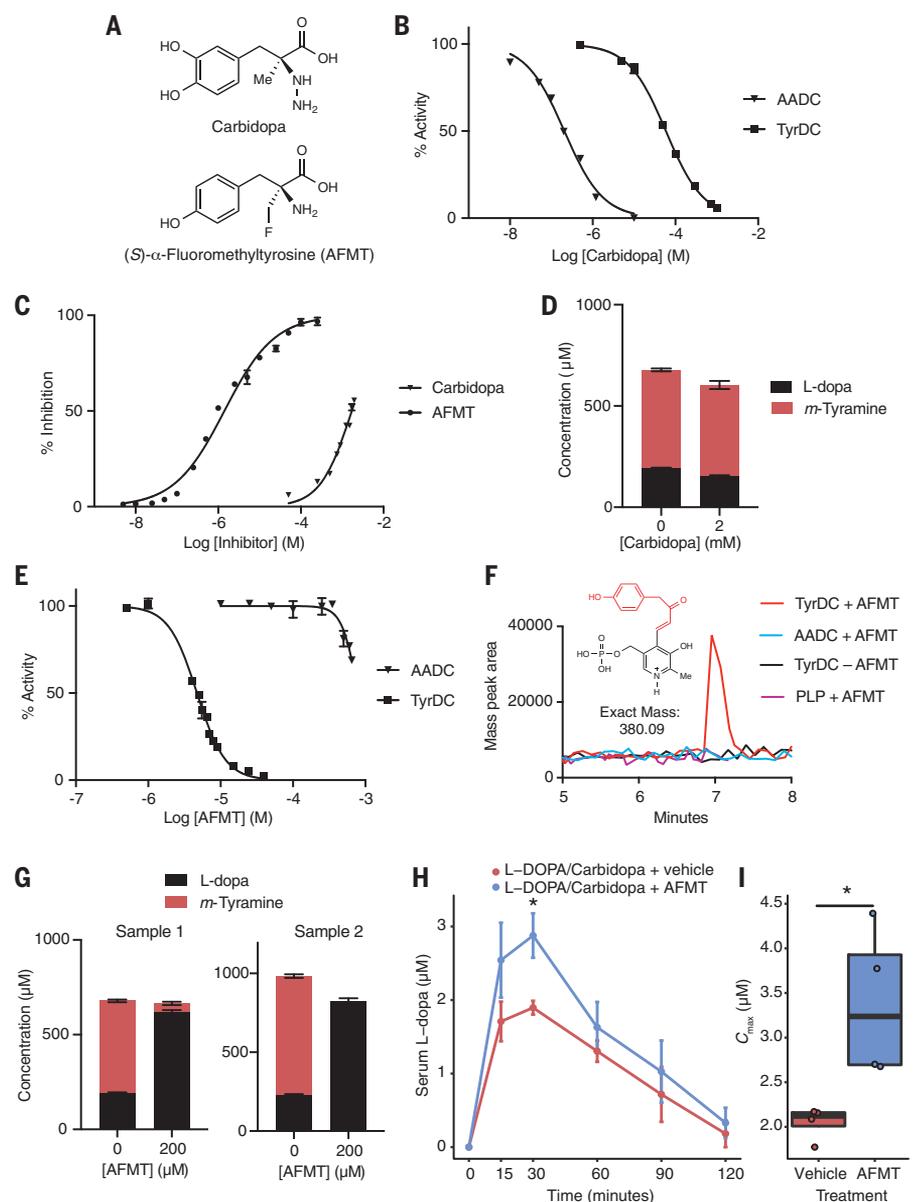
To investigate whether *E. faecalis* and *E. lenta* transform L-dopa in the human gut microbiota, we assessed the metabolism of deuterated L-dopa by fecal suspensions ex vivo. Whereas 7 of 19 samples did not show detectable depletion of L-dopa, the remaining samples displayed substantial variability in metabolism, ranging from partial (25%) to almost full conversion (98%) of L-dopa to *m*-tyramine (Fig. 3B). We next asked whether the abundance of *tyrDC* predicted metabolism in these samples. Quantitative polymerase chain reaction (qPCR) enumeration of *tyrDC*

(51) and *E. faecalis* discriminated metabolizing and nonmetabolizing samples ( $P < 0.0001$ , one-tailed Mann-Whitney test) (Fig. 3, C and D). By contrast, *E. lenta* abundance showed no association with L-dopa metabolism (fig. S20). We found a strong linear correlation between *tyrDC* abundance and *E. faecalis* abundance [coefficient of determination ( $R^2$ ) = 0.99,  $P < 0.0001$ ] (fig. S21), which likely reflects the high conservation of *tyrDC* in *E. faecalis* genomes. These data also suggest that *E. faecalis* is the dominant microorganism responsible for L-dopa decarboxylation in these complex human gut microbial communities. Consistent with this, *E. faecalis* abundance significantly correlated with *tyrDC* abundance in 1870 human gut microbiomes ( $R^2 > 0.812$ ,  $P < 2.2 \times 10^{-16}$ , Pearson's correlation) (fig. S22).

To confirm that *E. faecalis* could decarboxylate L-dopa in complex gut microbiotas, we added this organism to nonmetabolizing samples. Although introducing the *tyrDC*-deficient strain did not change L-dopa levels, including the wild-type strain led to complete depletion of L-dopa

(fig. S23, B to E). In some samples, addition of wild-type *E. faecalis* was sufficient to yield quantitative production of *m*-tyramine, indicating the presence of dopamine-dehydroxylating organisms in these communities (fig. S23, B and D). Last, addition of both the wild-type *E. faecalis* and the metabolizing strain *E. lenta* A2 to nonmetabolizing samples or the addition of *E. lenta* A2 alone to a decarboxylating sample generated *m*-tyramine (fig. S23, A and C to E). Taken together, these data indicate that the abundance of *E. faecalis* and its encoded *tyrDC* predicts the considerable interindividual variation in L-dopa metabolism observed in complex human gut microbiota samples.

As expected from our previous experiments, neither the abundance of *E. lenta* nor *dadh* predicted dopamine dehydroxylation in complex gut microbial communities (Fig. 3, E and F, and fig. S24). However, when we amplified *dadh* from these cultures and determined the SNP status at position 506, we found samples that contained the Arg<sup>506</sup> variant quantitatively



**Fig. 4. L-dopa decarboxylation by *E. faecalis* is inhibited by AFMT but not the host-targeted drug carbidopa.** (A) Carbidopa and AFMT. (B) Carbidopa preferentially inhibits human AADC over TyrDC. AADC or TyrDC were incubated with inhibitor, and reaction rates were measured with LC-MS/MS. “% Activity” represents the rate relative to a no inhibitor (vehicle) control. Results are mean  $\pm$  SEM ( $n = 3$  replicates). (C) Activity of carbidopa and AFMT in cultures of *E. faecalis* grown for 16 hours anaerobically with 0.5 mM L-dopa. Error bars represent the mean  $\pm$  SEM for three biological replicates. (D) Activity of carbidopa in a human fecal microbiota from a Parkinson’s patient. The sample was cultured anaerobically with carbidopa and 1 mM  $d_3$ -phenyl-L-dopa for 72 hours. Error bars represent the mean  $\pm$  SEM for three biological replicates. (E) AFMT preferentially inhibits TyrDC over AADC in vitro. AADC or TyrDC were incubated with inhibitor, and reaction rates were measured with LC-MS/MS. “% Activity” represents the rate relative to a no inhibitor (vehicle) control. Error bars represent the mean  $\pm$  SEM for three biological replicates. (F) Detection of an AFMT-PLP covalent adduct after incubation of TyrDC or AADC with AFMT for 1 hour. The data shown is the extracted ion chromatogram of the mass of the predicted covalent adduct. (G) Action of AFMT in human fecal microbiotas from Parkinson’s patients incubated anaerobically with AFMT and 1 mM  $d_3$ -phenyl-L-dopa for 72 hours. Error bars represent the mean  $\pm$  SEM for three biological replicates. (H) Pharmacokinetic analysis in gnotobiotic mice colonized with *E. faecalis* and given L-dopa + carbidopa + AFMT demonstrates higher serum L-dopa relative to vehicle controls. Error bars represent the mean  $\pm$  SEM. (I) The maximum serum concentration ( $C_{max}$ ) of L-dopa is significantly higher with AFMT relative to vehicle controls. In (H) and (I), \* $P < 0.05$ , Mann-Whitney U test;  $n = 4$  to 5 mice per group.

metabolized dopamine, whereas the activity of samples that carried the Ser<sup>506</sup> variant was indistinguishable from the nonmetabolizing *E. lenta* DSM2243 strain (Fig. 3G). These findings indicate that a single amino acid residue in a gut microbial enzyme predicts dopamine metabolism in complex communities. Given that *dadh* is highly prevalent (>70%) in gut microbiomes from human subjects and the two *dadh* variants are present among this population (figs. S22 and S25), we speculate that SNPs may influence xenobiotic metabolism in the context of both the host genome (52) and the human gut microbiome (53).

To further explore the clinical relevance of our findings, we assessed the metabolism of dopamine and L-dopa by fecal suspensions from Parkinson’s disease patients ex vivo. Similar to control subjects, these individuals displayed substantial variability in metabolism of L-dopa (fig. S26A). qPCR assays revealed that *tyrDC* abundance and *E. faecalis* abundance discriminated between L-dopa decarboxylating and nondecarboxylating samples ( $P < 0.005$ , one-tailed Mann-Whitney test) (fig. S26, C and D). We also observed depletion of L-dopa without corresponding production of dopamine or *m*-tyramine in three samples (fig. S26A). Instead, L-dopa was converted to hydroxyphenylpropionic acid (fig. S26B), a pathway thought to make a minor contribution to drug metabolism in vivo (22, 25, 26). Last, we found that the *dadh* SNP predicted dopamine dehydroxylation in these samples (fig. S27). Overall, these data support a role for gut bacteria in the extensive interindividual variability in L-dopa decarboxylation observed in Parkinson’s patients (13). A recent study reported that stool *tyrDC* abundance is positively correlated with L-dopa dosage in patients (38) but did not demonstrate a connection between *tyrDC* and L-dopa decarboxylation in these samples. Our findings indicate this metabolic activity may indeed affect L-dopa therapeutic efficacy.

### (S)- $\alpha$ -Fluoromethyltyrosine (AFMT) inhibits gut microbial L-dopa metabolism

Having shown that *E. faecalis* and *E. lenta* enzymes predict L-dopa metabolism by complex patient gut microbiotas, we next investigated whether this interspecies pathway was susceptible to inhibition by drugs that target peripheral L-dopa decarboxylation. In the United States, Parkinson’s patients are coprescribed carbidopa (Fig. 4A), an L-dopa mimic that inhibits AADC by forming a stable, covalent hydrazone linkage with its PLP cofactor (54). We found carbidopa was 200 times less active toward purified *E. faecalis* TyrDC [half maximal inhibitory concentration ( $IC_{50}$ ) = 57  $\mu$ M] relative to *H. sapiens* AADC ( $IC_{50}$  = 0.21  $\mu$ M) and showed only ~50% inhibition of L-dopa decarboxylation by *E. faecalis* cultures at the solubility limit of 2 mM (Fig. 4, B and C, and table S8), which is consistent with recently reported findings (38). Additionally, carbidopa did not affect growth of *E. faecalis* or metabolism or growth of *E. lenta* (figs. S28 to S30). Given the maximum

predicted gastrointestinal concentration of carbidopa (0.4 to 9 mM), these data suggest that this drug does not fully inhibit gut bacterial L-dopa decarboxylation in Parkinson's patients. We found that 2 mM carbidopa did not alter the kinetics of L-dopa degradation (fig. S31) or endpoint *m*-tyramine production in stool samples from both Parkinson's patients and neurologically healthy controls (Fig. 4D and fig. S32). These observations support previous findings that carbidopa administration does not affect *m*-tyramine production in patients (55).

Our results also highlight the possibility of therapeutically targeting gut microbial L-dopa decarboxylation to increase L-dopa efficacy. To selectively manipulate gut bacterial TyrDC in complex microbiotas, we turned to  $\alpha$ -fluoromethyl amino acids, which are known mechanism-based inhibitors of PLP-dependent decarboxylases (33). A survey of potential amino acid substrates revealed that TyrDC requires a *p*-hydroxyl group for robust activity, whereas AADC prefers a *m*-hydroxyl substituent (fig. S33), leading us to hypothesize that the L-tyrosine analog (*S*)- $\alpha$ -fluoromethyltyrosine (AFMT) (Fig. 4A) might selectively inhibit the microbial enzyme. In vitro, AFMT strongly inhibited L-dopa decarboxylation by TyrDC (IC<sub>50</sub> = 4.7  $\mu$ M) but not AADC (~20% inhibition at solubility limit of 650  $\mu$ M) (Fig. 4E and table S8). Consistent with this selectivity, AFMT formed a covalent PLP adduct only in the presence of TyrDC (Fig. 4F). AFMT was also effective in *E. faecalis* cultures (EC<sub>50</sub> = 1.4  $\mu$ M) (Fig. 4C), outperforming carbidopa by 1000-fold without affecting growth (table S8 and fig. S29). It also reduced L-dopa decarboxylation by cocultures of *E. faecalis* and *E. lenta* without affecting growth or metabolism of *E. lenta* (figs. S29, S30, and S34). Last, AFMT completely inhibited L-dopa decarboxylation in gut microbiota samples from Parkinson's disease patients and neurologically healthy control subjects (Fig. 4G and fig. S35) and was nontoxic to eukaryotic cells (fig. S36).

To investigate AFMT activity in vivo, we administered either AFMT (25 mg/kg) or a vehicle control in combination with L-dopa (10 mg/kg) and carbidopa (30 mg/kg) to gnotobiotic mice colonized with *E. faecalis* MMH594 (Fig. 4H). We found that AFMT significantly increased the peak serum concentration (C<sub>max</sub>) of L-dopa compared with vehicle (*P* < 0.05, two-tailed Mann Whitney test) (Fig. 4I), which is consistent with inhibition of first-pass gut microbial metabolism in the intestine. Although we cannot rule out the possibility that AFMT modulates additional, uncharacterized targets, this observation is consistent with our in vitro inhibition data. This result also aligns with a recent report that small intestinal *tyrDC* abundance negatively correlates with plasma L-dopa levels in conventional rats receiving L-dopa and carbidopa (38). Overall, these data suggest that AFMT could be a promising tool compound for the study of bacterial L-dopa metabolism (56) and highlight the promise of developing L-dopa-based combination therapies containing drugs that target both host and gut microbial decarboxylation.

## Conclusions

We have used chemical knowledge and interdisciplinary tools to decipher the molecular mechanisms by which gut bacteria interfere with the treatment of Parkinson's disease. The decarboxylation of L-dopa by *E. faecalis* mirrors host drug metabolism and, together with human AADC, likely limits drug availability and contributes to interindividual variation in efficacy. Together with recent work dissecting host and gut microbial contributions to the antiviral drug brivudine (57), our findings show that gut bacterial metabolism need not be chemically distinct from host activities to alter drug efficacy and suggest that such interactions may be underappreciated. Moreover, carbidopa's failure to prevent L-dopa decarboxylation by *E. faecalis* implies that additional host-targeted drugs may lack efficacy toward activities also present in the gut microbiota. Although a recent, independent study also characterized *E. faecalis* TyrDC's role in L-dopa decarboxylation and its lack of susceptibility to carbidopa (38), it did not show that this activity occurs in human gut microbiotas or identify strategies for inhibiting the bacterial enzyme. By contrast, we demonstrate that TyrDC predicts drug metabolism in Parkinson's patient microbiotas and use an understanding of its substrate specificity to identify a small molecule that prevents L-dopa decarboxylation in patient samples and increases L-dopa bioavailability in vivo. Through discovery of predictive biomarkers for L-dopa metabolism and identification of an inhibitor of this activity, this work will enable efforts to elucidate the contribution of the gut microbiota to drug availability, patient drug response, and treatment outcomes.

We also show that *E. lenta* further metabolizes the dopamine produced by L-dopa decarboxylation using a distinctly microbial reaction, catechol dehydroxylation. It is possible that this transformation influences the multiple side effects of L-dopa administration linked to dopamine production. This discovery also raises questions about the biological consequences of gut microbial metabolism of endogenous dopamine, which is present in the gastrointestinal tract and has been linked to phenotypes ranging from gut motility to pathogen colonization (58–60). The biological activity of the gut microbial metabolite *m*-tyramine in the host and the benefits of this metabolism for *E. lenta* are also poorly understood. Our findings will enable further study of these phenomena. Given that gut microbes dehydroxylate catechol groups found in numerous aromatic drugs and dietary compounds (18, 61–63), the discovery of Dadh will enable identification of additional catechol dehydroxylases and help to elucidate the biological role of this enigmatic transformation. Uncovering the unexpected effect of SNPs on gut microbial dopamine metabolism suggests that simply detecting functional genes may not accurately predict the activities encoded by the human gut microbiome and underscores the importance of studying enzymes from this community.

## Materials and methods summary

Our methods for the identification and biochemical characterization of *E. faecalis* TyrDC; characterization of anaerobic L-dopa metabolism by *E. faecalis* and gut microbiota samples; enrichment culturing for dopamine dehydroxylating organisms; RNA-sequencing; culture-based assays; purification of Dadh; assays of anaerobic dopamine metabolism by Actinobacteria and complex gut microbiota samples; PCR and qPCR assays; liquid chromatography–MS (LC-MS) methods; and assays for evaluating inhibitors in vitro, ex vivo, and in vivo are provided in the supplementary materials. Additional information about our protocols, including references to the supplementary materials, can be found throughout the main text.

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**Competing interests:** E.P.B. has consulted for Merck, Novartis, and Kintai Therapeutics; is on the Scientific Advisory Boards of Kintai Therapeutics and Caribou Biosciences; and is an Associate Member of the Broad Institute of Harvard and MIT. P.J.T. is on the scientific advisory board for Kaleido, Seres, uBiome, and WholeBiome. **Data and materials availability:** The *E. lentis* A2 genome has been deposited into GenBank (PRJNA412637). RNA-sequencing data has been deposited

into the Sequence Read Archive available by way of BioProject PRJNA507796. The small-molecule AFMT was obtained under a materials transfer agreement with Merck.

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## Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism

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### The dope on l-dopa metabolism

The efficacy of l-dopa treatment for Parkinson's disease is hugely variable between individuals, depending on the composition of their microbiota. l-Dopa is decarboxylated into active dopamine, but if the gut microbiota metabolize l-dopa before it crosses the blood-brain barrier, medication is ineffective. Maini Rekdal *et al.* found that different species of bacterium are involved in l-dopa metabolism (see the Perspective by O'Neill). Tyrosine decarboxylase (TDC) from *Enterococcus faecalis* and dopamine dehydroxylase (Dadh) from *Eggerthella lenta* A2 sequentially metabolized l-dopa into *m*-tyramine. The microbial l-dopa decarboxylase can be inactivated by (S)- $\alpha$ -fluoromethyltyrosine (AFMT), which indicates possibilities for developing combinations of Parkinson's drugs to circumvent microbial inactivation.

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