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Original Article

Absence of the candidate intestinal modifier ortholog *Slc6a14* alters the gut microbiome and delays intestinal obstructions in CF mice

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ABSTRACT

Background: Genetic association studies identify hypothesis-free relationships between genomic variants and measurable phenotypes, identifying physiologic mechanisms elusive by traditional hypothesis testing. *SLC6A14* variants were previously found to associate with meconium ileus. Mouse models provide opportunities to verify modifying effects and investigate their mechanisms.

Methods: Cftr and *Slc6a14* intestinal mRNA was profiled to establish temporal and spatial gene expression during development and postnatally. Double mutant mice were used to evaluate the effects on intestinal physiology and survival. Histology and mRNA were profiled quantitatively and spatially. Functional characteristics, intestinal transit and bacterial 16S rRNA were measured.

Results: Absence of SLC6A14 alone had no significant effect on mortality or growth. F508del mice had earlier but limited mortality compared to G542X, which continued to weaning. Both displayed CF-like increases in circular and longitudinal smooth muscle, small intestinal crypt depth and villus length. Both double mutants saw a significant shift in survival, delaying obstructions in the G542X mice and reducing overall mortality of F508del mice. Profiling prenatal intestines for *Slc6a14* and *Cftr* expression showed varying expression onset and duration. Transit differences were observed and attributed to CF mutation and diet. 16S rRNA analysis of mice show microbiome differences in both alpha and beta diversity across all examined genetic lines and diets.

Conclusions: This approach provides an example of how to evaluate modifier candidates and demonstrates the importance of assessing physiologically relevant timepoints. Our studies show that microbiome composition is altered due to SLC6A14 presence or absence and thus biome effects remain plausible obstruction modifiers.

1. Background

Genetic association studies identify relationships between genomic variants and measurable phenotypes, providing insight into physiologic mechanisms not found by traditional hypothesis testing. Genome-wide and linkage association studies (GWAS) [1,2] have identified several loci with variants associating with the cystic fibrosis (CF) neonatal intestinal obstruction phenotype, meconium ileus, and suggested candidate genes proximate to the variants. The most significant associations suggested by GWAS were *SLC26A9, SLC6A14, ATP12A* and *MSRA* by linkage analysis [3]. These associations lack mechanistic information, such as whether the protective allele confers greater or lower activity than the risk allele. Expression correlations with SNPs (GTEx) can predict direction of effect, but those associations may or may not be carried out in disease-relevant tissues or from individuals affected by a disease that may influence gene expression. Consequently, empiric data are necessary to verify modifying effects and to elucidate how a modifying gene exerts its effects. Mouse models may allow us to address direction of effect by examining alleles of candidate modifier orthologs for effects on CF phenotypes. *MSRA*, a gene suggested by genetic linkage studies to modify incidence of meconium ileus, was examined in CF mouse models for its effect on obstruction. It reduced the incidence of lethal obstructions in CF mice by its absence [3], supporting its modifying role. In contrast, if a null allele were deleterious, the effect may not be detectable in severe CF models, necessitating the use of both mild and severe versions of CF to determine phenotypic direction of effect.

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There are precedents for some of these loci to influence human physiology. For example, variants in or near *SLC6A14*, encoding the neutral and basic amino acid transporter X-linked solute carrier family 6 member 14, have been linked to other disorders as well [4–7]. A *Slc6a14* null allele was created [8] and crossed with an FVB-background CF mouse to create a mixed strain background mouse lacking functional SLC6A14. While altered arginine transport was identified as an intestinal modifying mechanism of action [9], other mechanistic hypotheses including osmotic, bacterial, or inflammatory changes could not be excluded. *Slc6a14* mRNA increases in the ileum and colon of CF mice [10] but decreases following antibiotic use, indicating that gene expression associations may be disease state-specific, and also that microbiome differences between CF and non-CF mice contribute to host responses.

Gastrointestinal obstructions are the predominant cause of mortality in CF mice and our husbandry evolved to include acidified water treated with low level osmotic laxative to increase survival of CF animals [11]. Murine chows with defined composition were chosen to test whether *Slc6a14* ablation would also influence survival of CF mice with and without functional SLC6A14 when reared without laxative. This systematic approach to vetting a putative modifier gene and elucidating its role in disease pathophysiology could greatly aid in translating genetic association to mechanistic understanding and hopefully facilitate clinical application.

Murine F508del CFTR (*Cftr*^{tm1Eur}) leads to a very mild phenotype [12], compared to the commonly used F508del model (*Cftr*^{tm1Kth}) carrying a selectable marker that reduces *Cftr* mRNA levels akin to a *Cftr*-null [13,14]. The severe G542X model [15] and a mild F508del model described here provide severely and mildly affected CF mice in which to test the effects of SLC6A14 absence on the mouse gut. To minimize the genomic variation between mice used in this study, CRISPR/Cas9 was used to generate a “scarless” F508del *Cftr* allele directly in C57BL/6 J, matching the genetic background of all mice used in this study.

This study supports a role for SLC6A14 as a modifier of CF intestinal obstructions and examines the native gene expression of both *Cftr* and *Slc6a14* in intestinal tissue of C57BL/6 J mice during development and postnatally and evaluates the effects of the *Slc6a14* null allele in two models of CF severity. It evaluates how murine GI physiology is altered in mice of a uniform genetic background and fed a defined high fat diet (HFD). This approach for *SLC6A14* and its mouse ortholog *Slc6a14* provides an example for how other modifier candidates might be evaluated.

2. Methods

2.1. Mice

Mice absent functional *Slc6a14,* generated by NORCOMM Consortium and provided to the Cystic Fibrosis Mouse Resource Center, were backcrossed >10 generations to the C57BL/6 J background to match the reposited CF strains, such as G542X [15]. Mice were genotyped day (D)5 postnatally. The F508del allele was generated by CRISPR and homology-directed repair in single-cell embryos. Because the *Slc6a14* gene is located on the X-chromosome, homozygous females (-/-) or hemizygous males (-/y) were crossed with F508del homozygous mice or G542X heterozygous mice to generate the “double mutants”. All mice were maintained post-weaning on either standard chow (Teklad 7904) or 45% HFD (Research Diets D12451i) and acidified water rather than laxative. Mice were weighed every 5 days from D5 to D50 and survival tracked throughout.

2.2. Genotyping

Genomic DNA was isolated from tissue samples of D0 or D5 mouse pups. *Slc6a14* genotyping was performed as previously described [9] (wildtype product 225 bases, mutant product 386 bases). PCR was performed with Invitrogen Platinum™ Taq DNA Polymerase (10,966, 026) on Applied Biosystems™ Veriti™ Thermal Cycler for 40 cycles. See Supplemental Table for primers.

2.3. RNAscope

Embryonic timepoints were generated via plug breeding and sacrificed at appropriate ages. Intestines were dissected and elongated, and indicated segments fixed in 10% neutral buffered formalin for 24 h at 4 °C. Tissues were embedded in paraffin and serial sectioned at 5 μm. Tissues were hybridized using ACDbio RNAscope Multiplex Fluorescent Detection Kit v2 with mouse probes for C3 Slc6a14 (536,831-C3) and C1 Cftr (483,011- C1) and visualized with Akoya Biosciences Opal 570 and 690 at 1:1000 dilution on Zeiss Axio Observer 7.

2.4. RT-PCR

Bulk RNA from C57BL/6 J wildtype (WT) tissue was extracted using Qiagen RNeasy Mini. One microgram of total RNA was reverse transcribed using VWR QScript cDNA kit. Controls without reverse transcriptase were included. 2 uL of cDNA was assessed with TaqMan for *Slc6a14* (Thermo Fisher Mm00451433_m1) to generate an initial expression profile with Applied Biosystems StepOnePlus Real Time PCR.

2.5. Bulk RNAseq

Three-inch segments of duodenum, jejunum, and ileum were collected from 8-week-old G542X and WT mice. Tissue segments were flushed with PBS and a longitudinal third of the opened tissue was directly saved for whole tissue RNA and two-thirds processed for crypt isolation. Part of the isolated crypts were differentiated into organoids [15] and the remainder was isolated as the crypt population. RNA from each extracted via Qiagen RNeasy Mini Kit. Libraries were created following TruSeq stranded Total RNA Ribo-Zero mouse gold kit (Illumina, San Diego, CA) and pooled for sequencing on Ilumina NovaSeq X. RNA-sequencing was performed as described [16].

2.6. Spatial transcriptomics

Whole intestinal Swiss rolls were provided to 10X Genomics for spatial transcriptomics on the Xenium platform of 11-week-old WT mice. Approximately 5000 genes including *Slc6a14* and *Cftr* were probed.

2.7. Transit

Eight-week-old mice were overnight fasted with water available ad libitum. 100 μL of 10% 1.0 μm Nile Red fluorescent (535/575) FluoSpheres™ (Invitrogen F8819) and 2.5% blue food coloring solution in water was administered via oral gavage. Mice were allowed ad libitum feeding during 25-minute transit, prior to sacrifice. Intestines were isolated, elongated and transit metrics measured. Fluorescence images taken for 330 ms and colorimetric images taken for 33 ms on a Biorad ChemiDoc.

2.8. 16S rRNA gene sequencing and analysis

Fecal pellets were directly collected from 8-week-old mice raised on either standard chow (Teklad 7904) or 45% HFD (Research Diets D12451i). DNA was isolated from fecal pellets with Qiagen QIAamp Fast DNA Stool Kit (51,604), and libraries were prepared and sequenced with MiSeq Illumina. Sequences were analyzed following QIIME 2 pathway (https://use.qiime2.org/en/latest/).

2.9. Statistics

Statistics were performed in Graphpad Prism, using one-way ANOVA for goblet cell counts and transit metrics and two-way ANOVA was used for gene expression experiments.

3. Results

The "scarless" F508del mutation (*Cftr*^{F508del} or *Cftr*^{em1Cwr}) was created in the C57BL/6 J inbred mouse line through CRISPR-mediated mutagenesis (Fig. 1A) and compared to C57BL/6 J mice with WT *Cftr* and severely affected G542X (*Cftr*^{em3Cwr}) mice. Unlike G542X mice, which show high mortality across the first four weeks, nearly all deaths in F508del mice occurred within the first 10 days of life (Fig. 1B). Weights ranged but on average F508del mice were intermediate to WT and G542X mice (Fig. 1C). Although milder, these F508del mice clearly displayed CF phenotypes. Histological investigation of intestinal segments through serial SI Swiss rolls showed the composition of acidic Alcian Blue (AB) and neutral Periodic Acid-Schiff (PAS) staining mucins and demonstrate an increase in colonic goblet cells in both, but slightly more in F508del mice than G542X animals (Fig. 1D,1E). F508del animals had less muscle thickening than G542X mice but greater than WT. Swiss rolls showed an increase in circular and longitudinal smooth muscle thickness, as demonstrated by others (Fig. 1F) and an increase in SI crypt depth and villus length (Fig. 1G).

Absence of *Slc6a14* alone had no significant effect on mortality or growth reared on the standard diet, although *Slc6a14*-mutant mice trended slightly smaller (Fig. 2A, $P > 0.05$). The *Slc6a14*-null allele was crossed onto both the G542X and F508del lines, producing severe and mild double mutants to determine if CF-modifying effects were detectable. In both models of reduced CFTR function, absence of *Slc6a14* caused a shift in survival, delaying mortality in the G542X mice by 2–3 weeks and reducing overall mortality of F508del mice (Fig. 2B). However, it did not increase survival in the first week as the percentage of

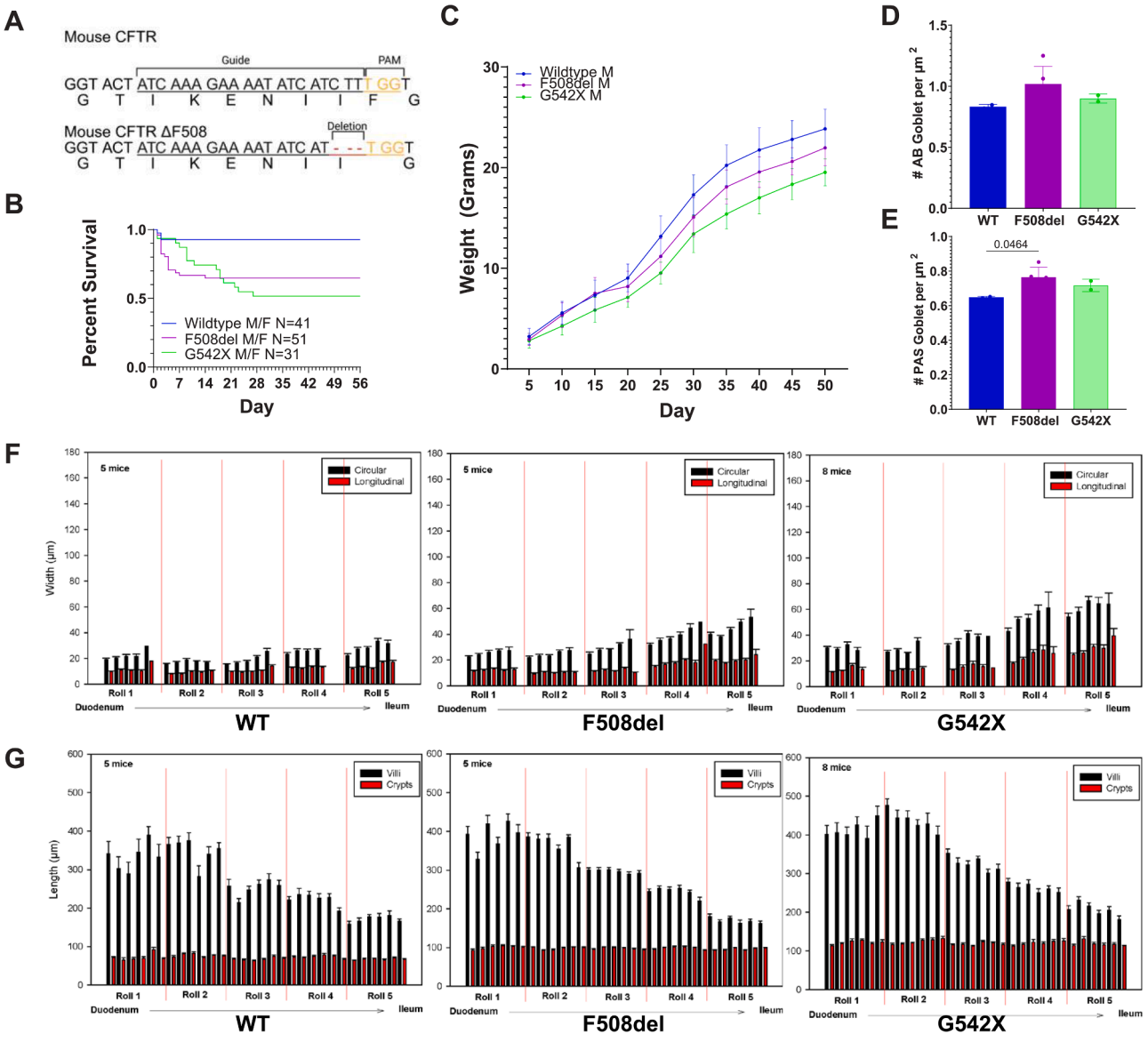


Fig. 1. (A) F508del mutation was introduced directly into mouse embryo of C56BL/6 J using CRISPR/Cas9. (B) Survival of CF mice carrying F508del and G542X mutations were assessed compared to wildtype. F508del mice fatalities occurred near exclusively in the first week, compared to the first month in G542X animals. (C) Beginning D5, mice were weighed every 5 days to D50. Intestinal characteristics were assessed through Alcian blue stain for acidic (D) and PAS stain for neutral mucins (E) to quantify colonic goblet cells. Excised intestines were divided into 5 Swiss Rolls and fixed. Rolls were divided into regions, with left closest to center and right furthest from center. (F) Circular and longitudinal muscle increased with distal progression, and higher in CF animals. (G) Similarly, crypt depth and villi length increased in CF compared to WT.

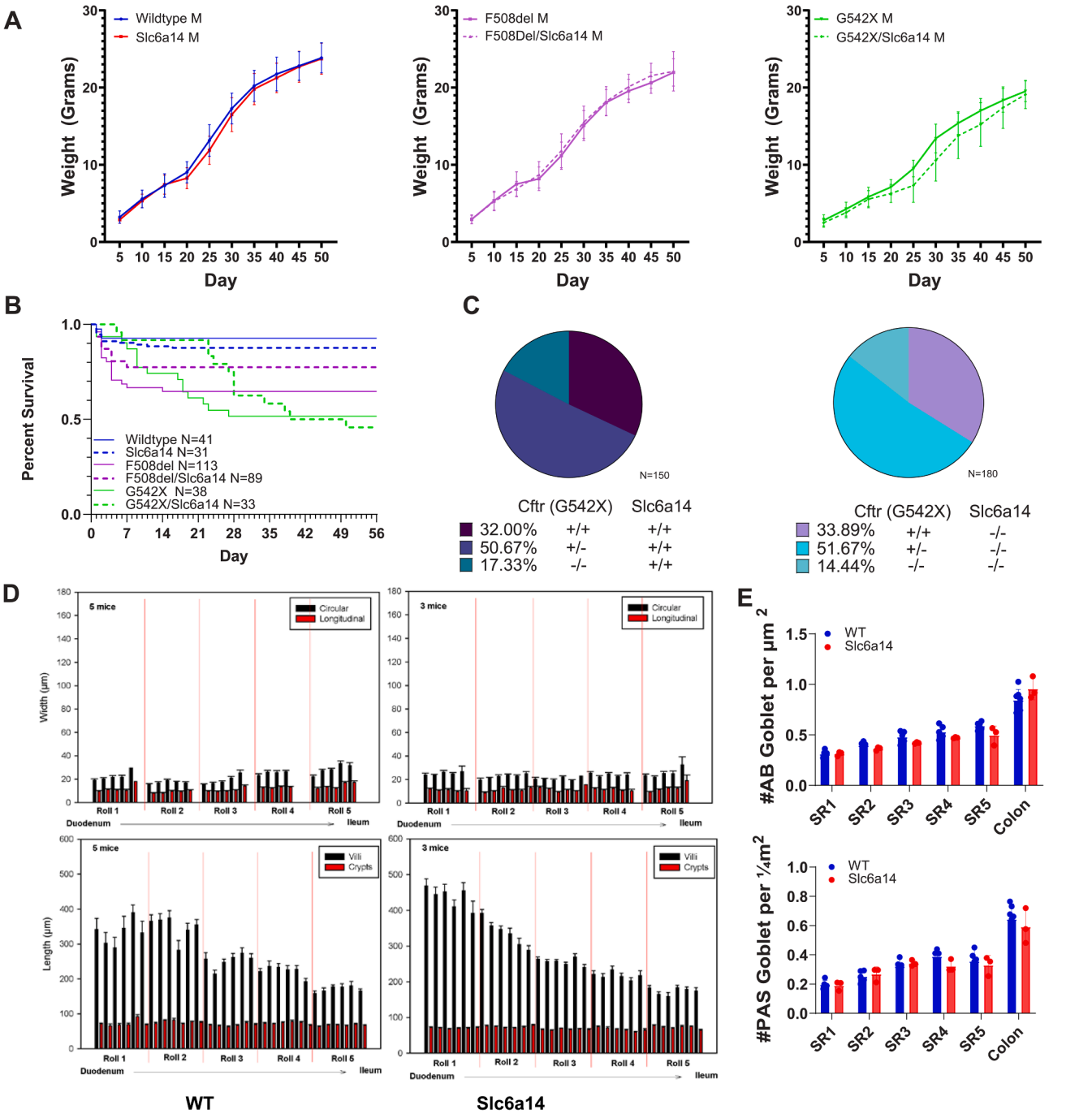


Fig. 2. (A) Comparative growth showing no effect on weight through Slc6a14 mutation and improved survival (B) of single and double mutant animals. (C) Observed distribution of genotypes from heterozygous crosses for both G542X and G542X/Slc6a14 animals is nonmendelian. (D) Villi and Crypt depth and muscle profile for Slc6a14 animals compared to wildtype (E) Slc6a14 intestinal Swiss Rolls including colon, stained with Alcian Blue and PAS-stained goblet cells.

offspring surviving to genotyping at D5 had similar distributions, showing decreased survival in mice carrying the G542X allele. Altered Mendelian ratios persisted when the *Slc6a14* mutation was added, suggesting the effect is driven by the *Cftr* allele (Single mutant X^2 (2, $N = 150$) = 6.48, $p < 0.0392$, Double mutant X^2 (2, $N = 180$) = 13.81, $p < 0.001$) (Fig. 2C). Morphologically, we observed a duodenal villi increase in *Slc6a14* mutants compared to wildtype but otherwise typical villi and crypt lengths. No deviation from observed wildtype smooth muscle thickness was observed (Fig. 2D). We observed the expected increase in both PAS and AB positive goblet cells in the colon but observed no difference between wildtype and *Slc6a14* lines (Fig. 2E). The lack of morphological differences from wildtype intestine were not unexpected, as the expected function of *Slc6a14* was not predicted to change SI characteristics.

Slc6a14 was reported as a CF GI modifier based on adult tissues [9]. A more physiologically relevant period would be before the appearance of obstructions. This would be the prenatal period in humans and peri-natal to weaning in mice. To provide spatial and temporal characterization, *Slc6a14* mRNA expression was surveyed across WT intestine and other tissues at multiple timepoints before and after weaning, when obstruction typically occurs (Fig. 3A). As previously reported in post-weaning animals [9], there was high *Slc6a14* expression in the colon and cecum, whereas throughout the SI very low levels of *Slc6a14* mRNA were detected. RNAScope revealed distinct bands of *Cftr* and

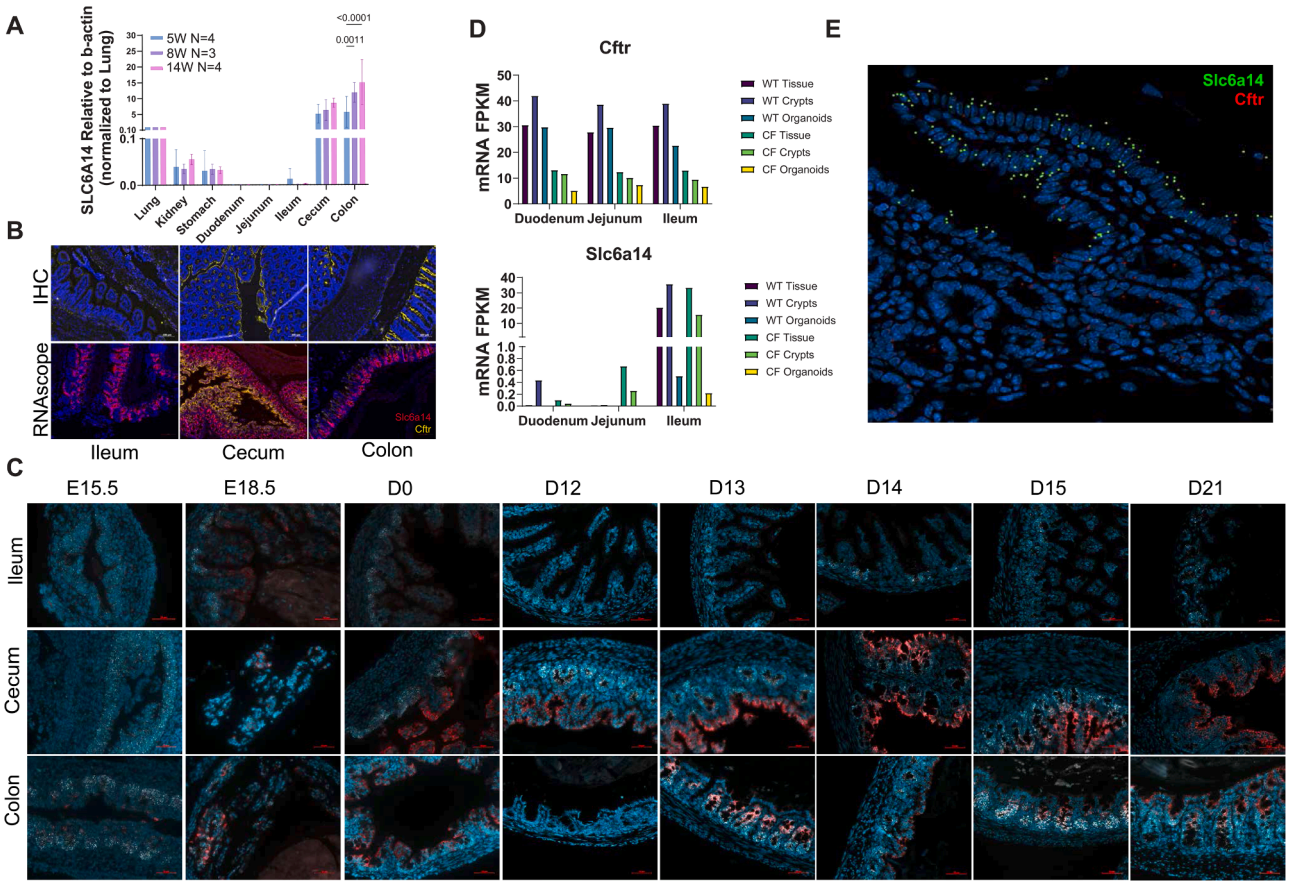


Fig. 3. (A) RT-PCR profile of Slc6a14 in 5, 8, and 14-week-old WT mice. (B)Slc6a14 immunohistochemistry and corresponding Slc6a14 (yellow) and Cftr (red) RNAscope of 8-week-old tissue (C) RNAscope of Slc6a14(red) and Cftr (white) in ileum, cecum, and colon during development (D) Bulk RNAseq of Slc6a14 and Cftr in bulk tissue, crypts, and cultured organoids. (E) 10X Xenium spatial expression of Cftr (red) and Slc6a14 (green) in ileum.

Slc6a14 mRNA expression in cecum and colon with a small area of overlap (Fig. 3B). Embryonic and neonatal ileum, cecum, and colon were surveyed for *Slc6a14* and *Cftr* expression in wildtype fetuses and pups. Large intestine *Slc6a14* expression was detectable by E15.5 and persisted through all subsequent time points, while ileum only showed strong expression right before birth, before fading to fewer cells (Fig. 3C). Bulk RNAseq and spatial transcriptomics were used to complement spatial localization. Eight-week-old duodenum, jejunum, and ileum were divided into whole tissue, isolated crypts, and crypt-derived organoids from G542X and wildtype animals. *Slc6a14* was only identified in the ileum, while *Cftr* was expressed throughout (Fig. 3D). Organoids did not show detectable *Slc6a14* expression, although *Cftr* expression was present. Spatial transcriptomics data concurred with RNAscope data (Fig. 3E).

To understand how absence of SLC6A14 might reduce or delay obstructions, intestinal transit metrics were collected from overnight-fasted mice and measured fluorescently following oral gavage (Fig. 4). Absolute distance transited after 25 min was modestly reduced by the HFD relative to the standard diet but the greatest effect on transit was due to *Cftr* genotype, demonstrating CFTR function is the primary driver of transit changes in both males and females on the standard maintenance diet. Although one cannot rule out an effect of SLC6A14 on intestinal transit, it is at best modest compared to CFTR.

To determine effects that might be conferred by an amino acid transporter on the gut biome, fecal pellet DNA was isolated and sequenced for microbial composition. Genera under 1% were grouped for visual clarity, as were unknown genera. Genera found in each mouse line on standard diet (Fig. 5A) compared to HFD (Fig. 5B) shows changes in microbiome by both genotype and diet. No alpha diversity Shannon Index genotype comparison by sex reached significance, but all Shannon q-values comparing by diet were significant (3.94E-2 – 1.57E-7). Comparisons of alpha diversity by genotype show that most significant changes were driven by absence of G542X (Fig. 5C). Emperor plots showing beta diversity for sex (Fig. 5D) shows no separation, but clearly defined groups are visible when comparing genotype (Fig. 5E) and diet (Fig. 5F). Certain strains including Bacteroides exhibited suggestive population changes, but further microbiome substitution or addition experiments are beyond the scope of this work.

4. Discussion

Genomic variants associating with phenotypic variation suggest a proximate gene's involvement with a phenotype. *SLC6A14* is reported to function as an amino acid transporter, but how such a function would influence intestinal obstruction is speculative. Integrating GWAS with gene expression (GTEx;eQTL expression database), the risk allele for MI is associated with higher *SLC6A14* mRNA in tissue from non-CF individuals [1,2,17], suggesting lower expression is protective in CF. This is concordant with the data presented here showing absence of SLC6A14 improves survival of CF mice (Fig. 2). Others reported that absence of SLC6A14 in CF mice impairs fluid secretion and increases incidence of obstruction [9]. These observations appear to be contradictory and whether they reflect differences in husbandry, or other explanation remains unclear. While the two CF models used here had dams of different genotypes, both models showed improved survival of CF animals when SLC6A14 was absent.

We observed no detectable transit improvement of CF mice lacking SLC6A14 (Fig. 4), a likely mechanism for modifying intestinal

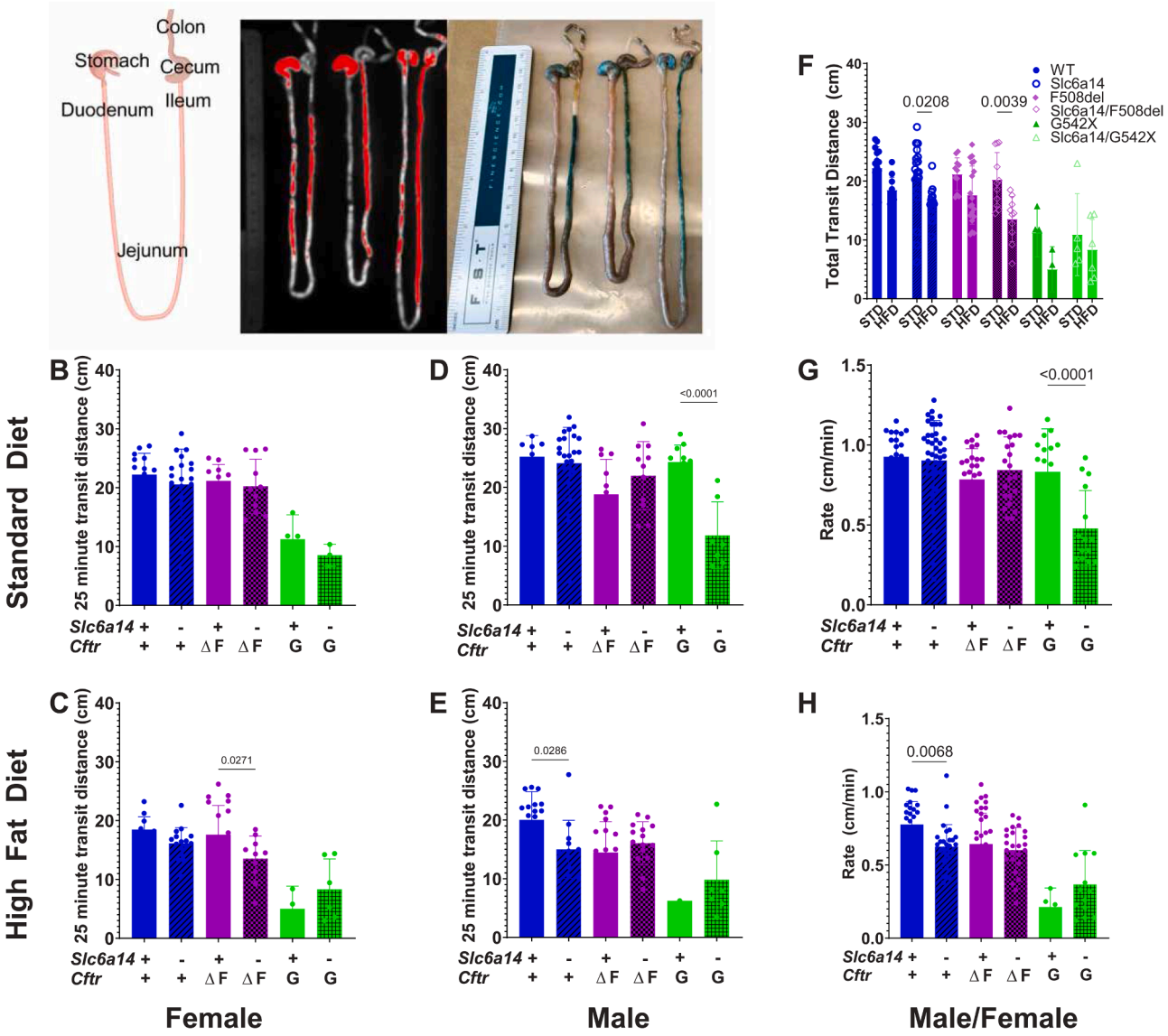


Fig. 4. (A) Diagram of intestinal imaging layout with fluorescent and visible light comparison. Total intestinal distance on standard diet for female (B) and male (C) or 45% high fat diet for female (D) and male (E). Combined transit rate for standard diet (F) and high fat diet (G). (H) Total distance comparison by genotype on standard and high fat diet. F = F508del, G = G542X.

obstruction, but did observe increased survival of CF mice lacking SLC6A14. While HFD drastically slows transit, absence of SLC6A14 did not. We established spatial and temporal relationships of intestinal cells expressing *Cftr* and *Slc6a14* mRNAs and showed they are found in crypts and villi, respectively, implying that modifying effects are most likely through intercellular, rather than intracellular interactions. We also see the most intense expression of *Slc6a14* in the cecum, initiating at birth and continuing through later ages. As obstructions occur proximal to the cecum, the expression of *Slc6a14* coincides spatially and temporally with obstructions (Figs. 2B and 3C). However, brief strong expression of Slc6a14 in the ileum restricted to the time around birth is also intriguing. Meconium ileus develops *in utero,* while obstructions in CF mice characteristically occur weeks after birth. It has long been held that the fetal intestines are germ-free until birth, but the advent of non-culture based bacterial identification techniques have contested this, and precipitated debates on *in utero* colonization [18,19], thus leaving the biome as a potential contributor to obstructions.

We investigated the effect altering nutritional sources might have on the gut biome. Our studies show that SLC6A14 presence or absence changes microbiome composition and thus biome effects remain plausible modifiers of obstruction. Furthermore, both *Cftr* and *Slc6a14* influence the intestinal microbiome, and their absence together results in a unique microbiome composition. Transcriptomic changes in response to SLC6A14 changes should be considered through additional profiling studies (RNAseq, single-cell analyses) to generate robust hypotheses. Various papers have reported on *Slc6a14's* role in responding to foreign entities, although the speculative mechanisms seem pathogen dependent [7,20–24]. In the airway, *SLC6A14* is upregulated in response to P. aeruginosa flagellin, also attributed to an arginine response [22]. Yet porcine dietary arginine supplementation did not affect *Slc6a14* transcript abundance [25], suggesting *Slc6a14* upregulation is related to pathogen response rather than dietary changes. The mRNA localization data presented here shows *Slc6a14* is present from the distal ileum to the proximal colon. Lack of *Slc6a14* in the jejunum suggests the deficit is not likely nutrient uptake though further experiments are needed to label and track amino acids.

The risk haplotype implicating SLC6A14 as an obstruction modifier associated with increased SLC6A14 mRNA in pancreas (not intestines), and while we observed no pancreatic expression of Slc6a14, this supports the concept that cascading changes from other intestinal regions

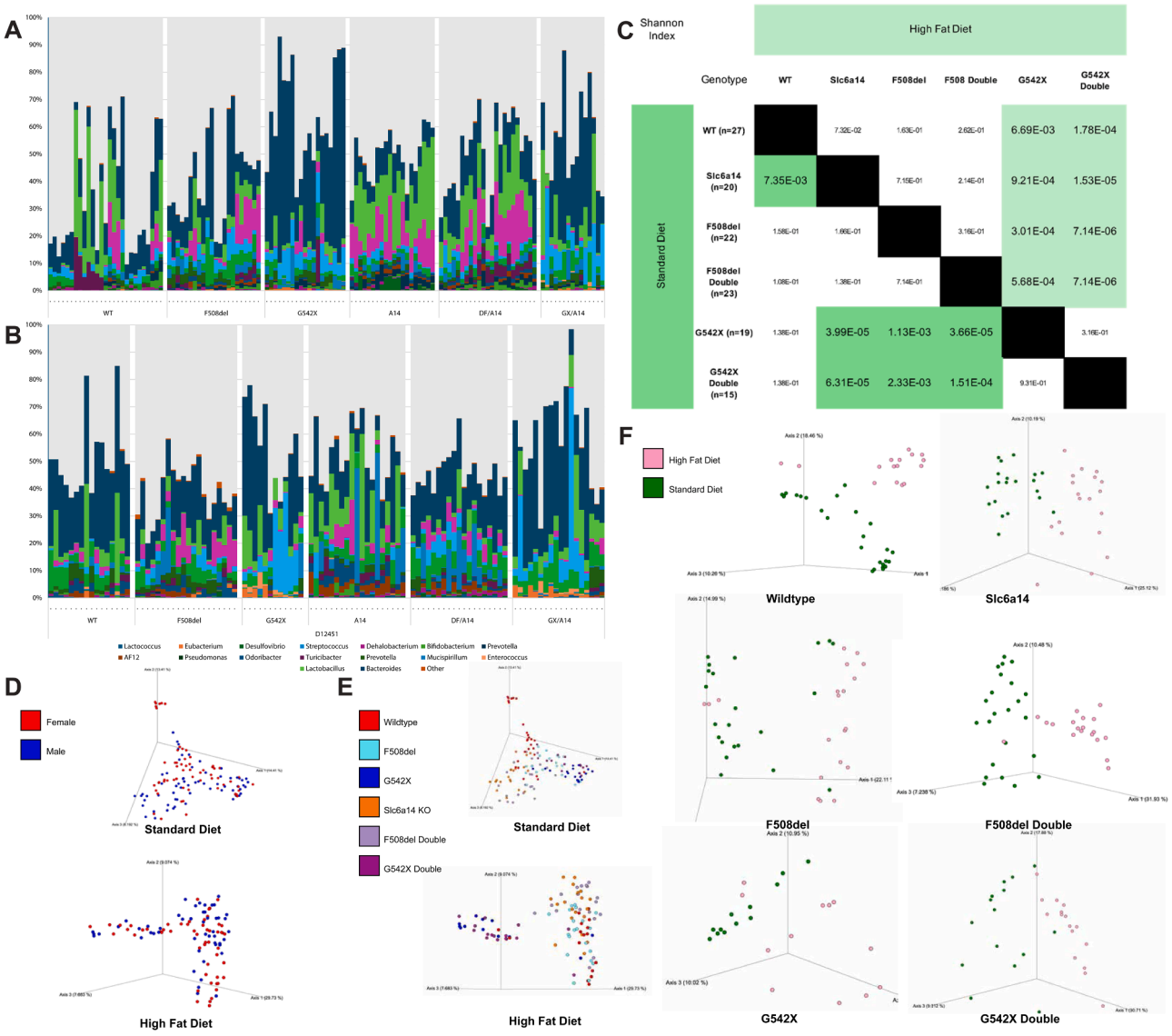


Fig. 5. Fecal samples were analyzed through 16S percent population at the genus level. The proportion of taxa at the genus level are shown for standard (A) and high fat (B) diet by genotype. Other genera with maximum proportions less than 1% were grouped together. Unknown genera combined for clarity. Comparative alpha diversity by genotypes (C) shows certain G542X mutation is the main driver of difference between genotypes. Fecal samples were further analyzed for significant beta diversity differences by sex (D), genotype (E), and diet (F) by Bray Curtis.

like the colon or even other organs might contribute indirectly, even when the primary MI phenotype is SI obstruction. Prior functional studies, which implied reduced SLC6A14 function is deleterious and decreases survival [9], used a transgene and thus is prone to artifacts from overexpression and lack of endogenous control.

In colon cancer, upregulated *SLC6A14,* hijacked by cancerous cells, is an ongoing therapeutic target [23]. CF patients are known to have a 5–10x increased risk of colorectal cancer [26] and *Slc6a14* upregulation has been linked with progression of colorectal cancer [27]. Stressful conditions, like methionine deprivation, increases *SLC6A14* expression [24] and CF-induced intestinal changes may create environments for *Slc6a14* to become similarly dysregulated. Preliminary RNASeq data suggest *Slc6a14* is upregulated compared to wildtype in the ileum and that higher mast cell counts may be present but further work is needed for other tissues.

We have shown here in two independent CF mouse models that SLC6A14 absence has a beneficial modifying effect on intestinal obstruction-mediated mortality. We also show the spatial and temporal expression patterns of *Slc6a14* during intestinal development and postnatally when obstructions occur. While mortality differs depending on SLC6A14 presence or absence, we do not find clear evidence of an effect of SLC6A14 on intestinal transit, except perhaps in CF males on the standard diet. However, we did find differences in each model's established microbiome in response to dietary changes and nutrient availability. Further work is needed to examine the differential species and assess functions of bacterial byproducts.

Ethics declaration

This study was conducted in accordance with the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines. This study was approved by the CWRU IACUC.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2026.11.008.

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