Genetic Modifiers of Nutritional Status in CF Are Both Unique to CF and Shared with the General Population

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Cystic Fibrosis Genome Project

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Background

Persons with cystic fibrosis (PwCF) often struggle to maintain good nutritional status, and this contributes to lung disease and mortality. Paradoxically, some with CF have obesity. After accounting for *CFTR* genotype severity, variation in nutritional status (e.g. body mass index, BMI) is largely determined by genes other than CFTR (genetic modifiers). We report an initial genome-wide association (GWAS) study for BMI on >4000 individuals with CF in the **CF** **G**enome **P**roject (CFGP).

Methods

CFGP:

- Initiated in 2018 including **5** cohorts from 3 groups
- Goals:
  1. Study genetic modifiers of CF traits using whole genome sequencing on > 5000 PwCF
  2. Develop a protected resource for the research community

Table 1: Characteristics of CFGP participants by study group

	JHU (n = 1,886)	UNC (n = 1,783)	UW (n = 1,389)	Total (N = 5,058*)
Age at last PFT^(mean ± SD)	23 ± 11	31 ± 11	14 ± 4	23 ± 11
% alive as of 2017	87%	72%	98%	85%
Sex as determined by WGS (% females)	52%	56%	51%	53%
Race from registration (% White)	95.8%	96.7%	95.2%	96%
Pancreatic insufficient (%)	86.8%	99.6%	91.3%	92.6%
F508del homozygous	76.6%	88.5%	76.8%	80.8%

JHU: CF Twin and Sibling Study (**TSS**) & CF-Related Diabetes Study (**CFRD**)
UNC: Genetic Modifier Study (**GMS**) & Genetic Modifier Study of Severe CF Liver Disease (**CFLD**)
UW: Early Pseudomonas Infection Control Observational Study (**EPIC Obs**)

Study samples:

- 4409 including PI^ and PS: 4101 PI only (93%)
- 96% European ancestry

Phenotype data: all age AvgBMIz score

- Average of per-quarter average BMI z score
- Excluded data: year of death, after 1st solid organ transplantation or modulator use

Genetic data:

- ~10M Bi-allelic SNV w/MAF > 0.5% (4065 maxUnrelated)

Statistical Analysis:

1. Genetic association analysis
   - Model: linear mixed effect
   - Fixed effect: study site, birth cohort, G-tube use, PI/PS status
   - Random effect: GRM (genetic relationship matrix)
2. PRS
   - Derived from 941 SNPs from a meta-analysis of BMI GWAS[1] after excluding SNPs from FTO
   - Weighted on log(OR)

Table2: Fixed effects from null model in 4409 samples

	Est Beta	SE	P-value
(Intercept)	-0.40	0.04	4.58E-25
Site_UNC	-0.088	0.035	0.013*
Site_UW	0.17	0.033	1.73E-07*
Birth cohort	0.11	0.011	1.14E-23*
PI/PS status (ref: PI)	0.38	0.051	1.55E-13*
G-tube use	-0.70	0.028	7.12E-136*
PC1	-0.27	0.42	0.527
PC2	1.83	0.49	2.14E-4*
PC3	-1.38	1.64	0.40
PC4	0.073	1.12	0.95

Note: G tube use has the strongest effect on AvgBMIz.

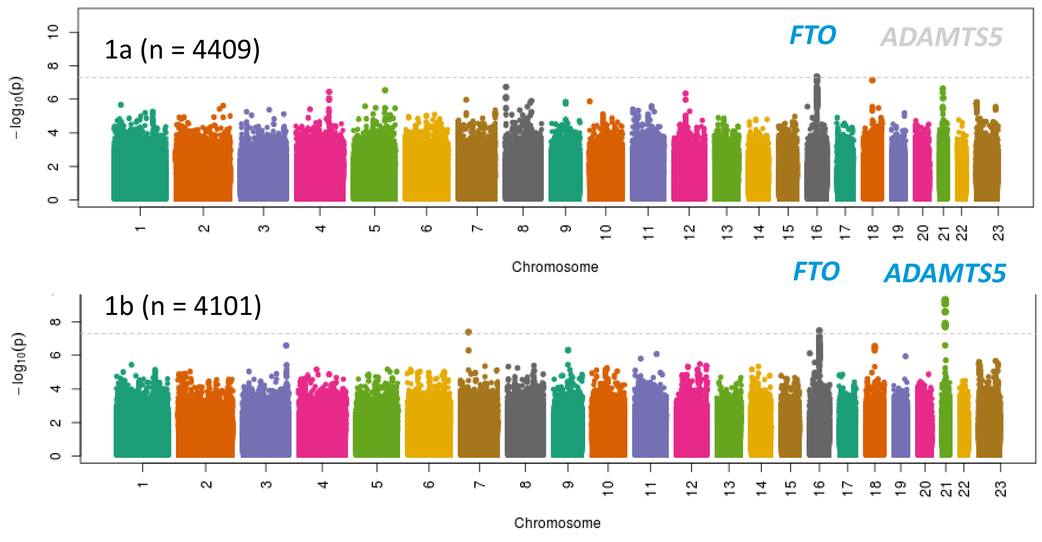
^ **PI/PS**: Pancreatic insufficiency/Pancreatic sufficiency

Reference

1. Yengo (2018): PMID: 30124842
2. Bauters (2018): PMID: 29293679
3. Bauters (2017): PMID: 28702327
4. Bauters (2016): PMID: 27254774
5. Bauters (2016): PMID: 27383908

Results

Figure 1: Manhattan plot for AvgBMIz for both PI/PS (1a) & PI only (1b)



Note: The signal on *ADAMTS5* gene became more extreme after limiting analysis to PI only suggesting the signal was driven by PI only samples (**Fig 1**).

Note: Proportion of variance explained (PVE) is similar between *FTO* and *ADAMTS5* despite large difference in MAF. The total variance explained by the two loci is < 2% (**Table 3**).

Table 3: Summary of GWAS test results for the top hit of the two significant loci

SNP	Chr:Pos	MAF	Gene	Beta (p-value) *PVE^*			
				PI/PS w/G-tube as cov (n = 4409)	PI only (n = 4101)	G tube non-users (n = 3064)	G tube users (n = 1037)
rs28567725	16: 53,792,116	0.41	*FTO*	0.096 (4.52E-08) *0.0068*	0.099 (3.36E-08) *0.0075*	0.094 (3.31E-06) *0.0071*	0.130 (4.46E-04) *0.013*
rs162500	21: 26,930,764	0.005	*ADAMTS5*	-0.54 (2.35E-07) *0.0061*	-0.705 (4.92E-10) *0.0095*	-0.701 (2.81E-07) *0.0086*	-0.908 (5.67E-06) *0.021*

Table 6: Mean of AvgBMIz broken down by race and genotype of rs162500 (*ADAMTS5*)

	White	Non-White
0/0	-0.196 (3887*)	-0.190 (100)
0/1	-0.748 (28)	-0.640 (18)

*: chi-sq = 214. P-value < .00001.

Table 4: GWAS association results from GWAS Catalog in non-CF population for *FTO* & *ADAMTS5*

	# association	# studies	# traits
FTO	610 (222)	444	156 (23)
ADAMTS5	22 (2)	18	14 (1*)

(): Count related to BMI, which was defined as containing strings of "body mass|fat|obesity|BMI|body size" in the "trait label" column.
*: The only BMI-related trait that associated with *ADAMTS5* is "BMI-adjusted waist circumference".

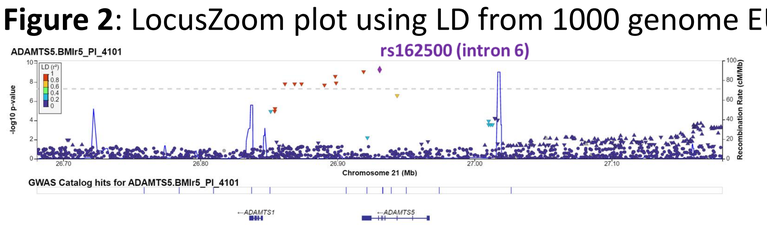
https://www.ebi.ac.uk/gwas/docs/about

- *FTO*: Unequivocally associated w/ BMI in general population.
- *ADAMTS5*: No direct association w/ BMI reported in general population.

Table 5: Allele Freq of rs162500 by population

	ALL	EUR	AFR	EAS
CFGP	0.007	0.004	0.110*	
TOPMed	0.050	--	--	--
1000 genome	0.052	0.006	0.183	0.001

Figure 2: LocusZoom plot using LD from 1000 genome EUR



The significant SNPs at *ADAMTS5* are all rare in EUR but common in AFR and were on the same haplotype after in-silico phasing, suggesting this African originated haplotype is associated with lower AvgBMIz score in CFGP. Although no direct association reported in human studies, several mouse studies suggest *ADAMTS5* plays an important role in adipogenesis and can be modified by High Fat Diet[2,3,4,5]. Bulk gene expression data show *ADAMTS5* is abundantly expressed in adipose tissues (**Fig 3**) providing additional support of its role in function related to adipose tissue.

Figure 3: Bulk gene expression for ADAMTS5 from GTEx

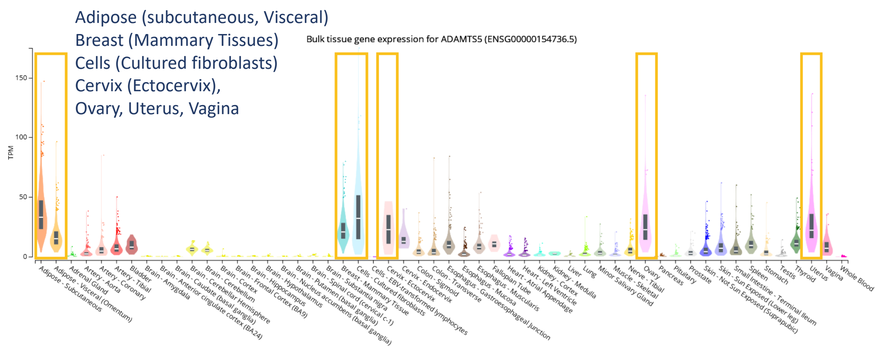
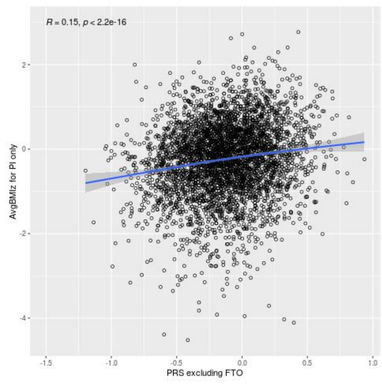


Figure 4: AvgBMIz vs PRS (no FTO) in PI only



The subtle correlation of PRS with AvgBMIz suggests modest contribution of other loci to variation of nutritional status for PwCF.

Conclusions

- Some genetic modifiers of AvgBMIz in PwCF, including *FTO*, are shared with general population.
- The association of *ADAMTS5* with AvgBMIz in PwCF is novel. Functional studies in mice suggest a role for *ADAMTS5* in adipogenesis.
- Understanding the modifier gene contributions to BMI in CF can identify mechanisms and targets independent of *CFTR* contributing to undernutrition or obesity in PwCF.

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