Gene-Environment Interactions in Early Childhood Caries

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ADAMS SCHOOL OF DENTISTRY

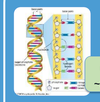
INTRODUCTION

Early childhood caries (ECC) is a multifactorial disease

Genes + **Environmental factors**
- Fluoride
- Sugar
- Oral Hygiene
- Socio-economic factors
- Saliva
- Microbiome, etc.

= Early Childhood Caries

OBJECTIVE: To identify ECC-associated interactions between two strong ECC risk factors [sugary snacks/beverage consumption frequency and sub-optimal fluoride exposure in home water] and human genetic polymorphisms.

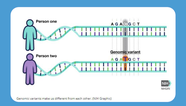


Genome (G) ~144 million markers

ECC (n=6,075)

Novel genetic loci

Environment (E)
1) Sugar-containing snacks & beverages
2) Fluoride "exposure"

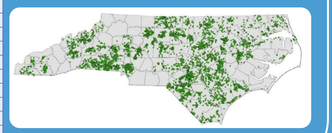


GWA: Genome-wide Association, ECC: Early childhood caries

Study population

3-5-year-olds enrolled in Head Start centers in North Carolina **(N=6,144)**

Variable	Mean (SD) or (%)
Age (months)	53 (7)
Female	3069 (50%)
Race/Ethnicity	
Non-Hispanic African American	48%
Hispanic American	20%
Non-Hispanic white	18%
American Indian/Alaskan Native	2%
More than 1 race	10%
Other (includes Asian/NHOPI)	2%



*Abbreviations: SD: Standard Deviation; NHOPI: Native Hawaiian and other Pacific Islanders

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In relation to this presentation, I declare that there are no conflicts of interest.

METHODS & MATERIALS

Genotyping approach

CIDR Center for Inherited Disease Research, Johns Hopkins University

NIH National Heart, Lung, and Blood Institute | BioData CATALYST | TOPMed Imputation Server

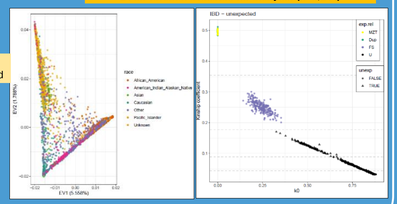
307M variants in reference

144M variants available for analysis (n=6,144)

1.4M variants directly measured

Assisted saliva collection

Illumina Global Diversity Array

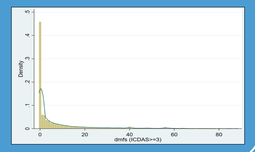


PHENOTYPE: Cavitated decay (ECC)

"cavitated decay" or $d_{3\text{-}6}$mfs, (ICDAS≥3)

Pearson Residuals (adjusted for age, sex and race/ethnicity)

Zero-inflated Negative Binomial model



Statistical analysis

Generalized linear mixed model

Phenotype | Controlling for ancestry | Controlling for relatedness

Residuals (ECC) = SNP + 8 PCs* + Kinship + *e*

Approach 1: Joint 2-degree-of-freedom (2DF) test: H_0: $\beta_G = \beta_{GE} = 0$

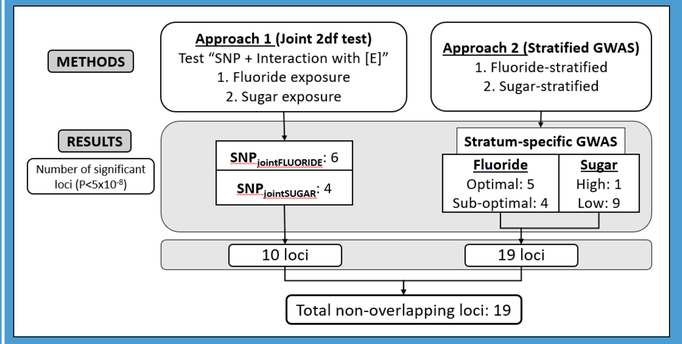
Approach 2: Stratified analysis models

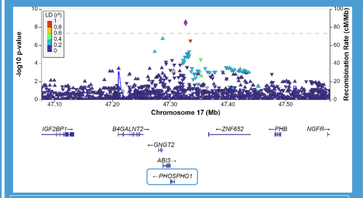
1. $Exposed: Y = \beta_0^{(1)} + \beta_G^{(1)} \times SNP + \beta_C^{(1)} \times covariates + e$

2. $Unexposed: Y = \beta_0^{(2)} + \beta_G^{(2)} \times SNP + \beta_C^{(2)} \times covariates + e$

* ECC: Early childhood caries, SNP: Single nucleotide polymorphism, PC: Principal Component

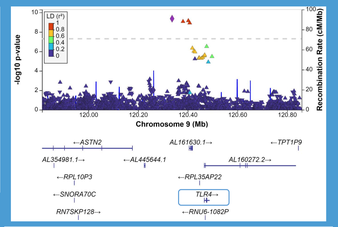
RESULTS





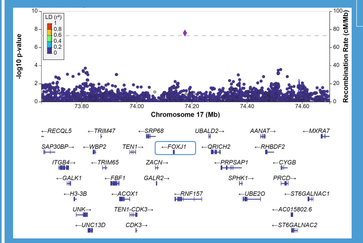
rs650314, EAF[C]: 0.86, P-value: $3.2x10^{-9}$ (Joint test - Fluoride).

PHOSPHO1: Bone and dental tissue mineralization; Associated with childhood hypophosphatasia



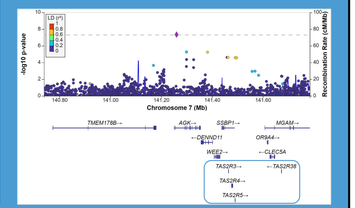
rs114565086, EAF[C]: 0.01, P-value: $4.3x10^{-10}$ (Joint test - Fluoride).

TLR4: Associated with chronic periodontitis and regulation of dental pulp stem cells. Role in tooth development.



rs117997344, EAF[T]: 0.01, P-value: $5.2x10^{-9}$ (Joint test – Sugar).

Foxj1: Role in the regulation of odontogenesis.

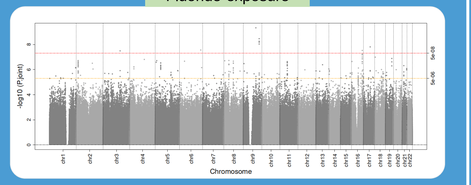


rs144438881, EAF[G]: 0.01, P-value: $4.5x10^{-8}$ (Low-sugar-GWAS).

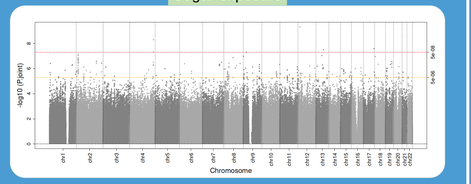
Bitter taste receptor genes (***TAS2R3, TAS2R4, TAS2R5, TAS2R38***): Associated with ECC and dental caries in adults

Approach 1 (Joint 2DF test)

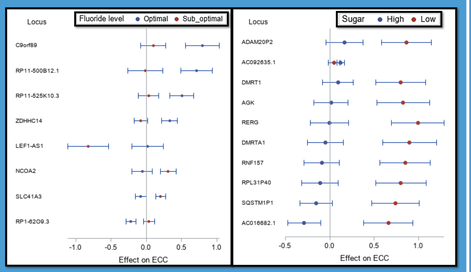
Fluoride-exposure



Sugar-exposure



Heterogeneity of Genetic Effect
1) Fluoride exposure AND 2) Sugar exposure



CONCLUSIONS

- Multi-ancestry study finding 19 novel variants with a potential role in ECC using the Gene–Environment interaction effects.
- Upon replication and validation, this advances our understanding of the biological basis of ECC
- Potential to optimize ECC prevention and management through incorporation in risk assessment and precision dentistry