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Longitudinal assessment of Allergic Outcomes and Atopic Dermatitis Phenotypes in The Children's Respiratory and Environmental Workgroup (CREW) Birth Cohort Consortium

Amy A. Eapen

Alexandra R. Sitarik

Jocelyn Biagini

Daniel Jackson

Christine L. M Joseph

See next page for additional authors

Authors

Amy A. Eapen, Alexandra R. Sitarik, Jocelyn Biagini, Daniel Jackson, Christine L. M Joseph, Haejin Kim, Lisa Martin, Katherine Rivera-Spoljaric, Eric Schauberger, Ganesa Wegienka, James Gern, and Annie M. Singh

446 Infants with loss of function filaggrin mutations show augmented response to early life, short term skin barrier protection compared to filaggrin wild type infants; results from the STOP-AD trial.

Jonathan Hourihane, MD, MD FAAAAI[1], Claudio Nico, PhD[2], Dhanis Lad, MD[3], Gerwin Puppels, PhD[2], Carol Ni Chaoimh, PhD[4], Colin Wong, PhD[5], John Common, PhD[5], Peter Caspers, PhD[6], Alan Irvine, MD[7]; [1]Royal College of Surgeons in lreland, [2]River D international, [3]University College Cork Ireland, [4]University College Cork, Ireland, [5]A*STAR Skin Research Labs, Singapore, [6]Erasmus university Rotterdam, Netherlands, [7]Children.

RATIONALE: Loss-of-function (LoF) filaggrin (FLG)-mutations are the strongest genetic risk factor for atopic dermatitis (AD). The STOP-AD study showed early initiation of daily specialized emollient, used only until 2 months, reduces the incidence of AD in the first year of life in high-risk infants.

METHODS: 321 newborns were recruited, randomized 1:1 between intervention group (IG), receiving emollient treatment and control group (CG). FLG status was determined by Microfluidics PCR for full coverage of FLG repeat alleles.

RESULTS: 257 infants with genotyping completed the study, 119 in IG and 138 in CG. 12 month cumulative AD-incidence was 46% in the CG vs. 33% in the IG (p=0.03). 44 (17.4%, evenly split between groups) were LOF-FLG mutation carriers, who had significantly higher AD-prevalence of 56% and 59% at 6 and 12 months respectively in the CG, compared to 32% at 6m (p =0.02) and 34 at 12m % (p=0.01) in WT-FLG. In IG group the LOF-FLG babies had AD rates nearly the same as WT-FLG infants at 6 and 12m: 19% and 14% respectively compared to 15% (p=NS)and 14% (p=NS) in WT-FLG babies.

CONCLUSIONS: Daily specialized emollient use until 2 months may be especially beneficial for LoF FLG-mutation carriers, reducing their AD-prevalence and incidence to the level of the treated FLG-wildtype group. Identification of FLG status soon after birth may be beneficial in deciding which child may benefit most from targeted preventive strategies.

447 A New Algorithm Identifying Association of Staphylococcus aureus Strains with Low Expression of Filaggrin in Atopic Dermatitis

Latha Satish[1], Wan-Chi Chang[1], Arya Dahal[1], Elizabeth Johansson[1], makenna eversole[1], Matthew Schuetz[1], Brittany Grashel[1], daniel spagna[1], seth jenkins[1], veronica velasquez[1], Andrew Herr, PhD[2], Jocelyn Biagini, PhD[2], david haslam[1], Lisa Martin, PhD[2], Gurjit Khurana Hershey, MD PhD FAAAAI[1]; [1]Cincinnati Children's Hospital Medical Center, [2]Cincinnati Children.

RATIONALE: Skin colonization with *Staphylococcus aureus* (*S. aureus; Sa*) contributes to the development of atopic dermatitis (AD). AD is associated with low filaggrin (FLG) expression in the skin due to genetic mutations and inflammation. We hypothesized that in the context of low FLG, colonizing *Sa* strains may have distinct gene patterns.

METHODS: Whole-genome sequencing (WGS) was performed on total DNA extracted from clinical *Sa* isolates (N=66) taken from the non-lesional (NL) skin of a subset of children with AD participating in the MPAACH cohort (N=56). An algorithm was developed to determine whether a specific *Sa* gene was associated with differences in NL-FLG, NL-Trans-epidermal water loss (TEWL), and Scoring Atopic Dermatitis (SCORAD). Student's t-tests compared the mean of each parameter between isolates with and without the given gene. The magnitude of the difference in each parameter (denoted as *delta*) was calculated for genes with FDR < 0.05. The hierarchically-clustered heatmap was used to visualize the similarities across isolates according to the presence of lower-NL-FLG- associated *Sa* genes.

RESULTS: WGS identified 6,621 *Sa* genes in the 66 bacterial isolates, of which 1,574 genes were annotated and used in the analyses. We found that 63 and 1076 *Sa* genes were associated with low_{delta}FLG and $high_{delta}$FLG, respectively. Clustering analysis showed six different clusters (26 isolates) for low_{delta}FLG-associated *Sa* genes and a single cluster for $high_{delta}$FLG-associated *Sa* genes (54 isolates).

CONCLUSIONS: A novel approach identified *Sa* genes that are associated with low_{delta} FLG expression, which can serve as targets for reducing *Sa* colonization.

448 Withdrawn

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Amy Eapen, MD, MS[1], Alexandra Sitarik[1], Jocelyn Biagini, PhD[2], Daniel Jackson, MD FAAAAI[3], Christine Joseph, PhD[1], Haejin Kim, MD[1], Lisa Martin, PhD[2], Katherine Rivera-Spoljaric, MD[4], Eric Schauberger, PhD, DO[3], Ganesa Wegienka, PhD FAAAAI[1], James Gern, MD FAAAAI[3], Anne Marie Singh, MD[3]; [1]Henry Ford Health, [2]Cincinnati Children's Hospital Medical Center, [3]University of Wisconsin-Madison, [4]St. Louis Children.

RATIONALE: Atopic dermatitis (AD) is a heterogenous inflammatory skin disease often associated with other allergic diseases. We characterized AD phenotypes and associated allergic outcomes longitudinally across a multi-site consortium.

METHODS: AD expression in 11 U.S. birth cohorts from the CREW (Children's Respiratory and Environmental Workgroup) consortium was assessed in each year of life from age 0-7 years (N=7,900). Longitudinal Latent Class Analysis was performed to identify AD phenotypes. Five classes of AD were identified: Persistent AD (15.4%), Early AD with Potential Reoccurrence (2.7%), Late-Onset AD (7.0%), Transient Early AD (3.0%), and Minimal/No AD (72.0%). Serum allergen sensitization patterns and allergic clinical disease were associated with AD phenotype using multinomial logistic regression with a 3-step procedure to account for uncertainty in class membership.

RESULTS: Children with Persistent AD, Early AD with Potential Reoccurrence, and Transient Early AD were more likely to have food allergy compared to those with Minimal/No AD (OR[95% CI]=2.73[2.15, 3.45], 2.69[1.63, 4.45], 2.54[1.55, 4.16], respectively). These groups had similarly higher odds of food sensitization. Persistent AD (OR[95% CI]=1.81[1.48, 2.21]) and Early AD with Potential Reoccurrence (OR[95% CI]=3.66[1.90, 7.05]) had significantly higher odds of ever asthma relative to Minimal/No AD. At both 2-4 years and 5-7 years, persistent AD (OR [95% CI]=1.35[1.04, 1.74], 1.25[1.01, 1.53]) and Late-Onset AD (OR [95% CI]=1.68[1.13, 2.50], 2.22[1.33, 3.70]) relative to Minimal/No AD had higher odds of allergic rhinitis.

CONCLUSIONS: Longitudinal AD phenotypes had varying associations with allergic sensitization, food allergy, asthma and allergic rhinitis, demonstrating the heterogeneity of allergic comorbidity risk associated with AD.

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