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POSTER ABSTRACTS

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Development of a Genetic Risk Score for Albuminuria in Pediatric Patients with Sickle Cell Anemia

Rima Zahr, DO[1], *Guolian Kang, PhDMS*[2], *Sara Rashkin, PhD*[3], *Yutaka Yasui*[4], *Csaba Kovesdy*[1], *Clifford M Takemoto, MD*[5], *Jeffrey D. Lebensburger, DO*[6], *Mitchell Weiss, MD PhD*[7], *Santosh L. Saraf, MD*[8], *Kenneth I. Ataga, MD*[9]

[1] University of Tennessee Health Science Center, Memphis, TN
[2] Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN
[3] St. Jude Children's Research Hospital, MEMPHIS, TN
[4] St. Jude Children's Research Hospital, Department of Epidemiology and Cancer Control, Memphis, TN
[5] Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN
[6] University of Alabama at Birmingham, Birmingham, AL
[7] St. Jude Children's Research Hospital, Memphis, TN
[8] Department of Medicine, University of Illinois College of Medicine, Willowbrook, IL
[9] University of Tennessee Health Sciences Center, Memphis, Nashville, TN

Introduction

Sickle cell anemia (SCA) causes progressive, age-dependent, kidney damage. Albuminuria is an early clinical biomarker for chronic kidney disease (CKD) and is associated with progressive glomerular injury. Identifying patients at risk for albuminuria is critical for early institution of renoprotective interventions to prevent progressive kidney injury. Developing a genetic risk score (GRS) to predict albuminuria is one approach to identifying high risk patients. Our prior data demonstrates that Apolipoprotein-L1 (*APOL1 G1/G2*) is associated with early development of albuminuria in children with SCA (PMID:30890594). However, this gene variant does not account for all kidney disease progression. Multiple other gene variants that modify SCA-severity have been associated with CKD in adults with SCA. We hypothesized that developing a genetic risk score (GRS) will allow for identification of pediatric patients at increased risk for development and progression of kidney disease. We aimed to develop a novel pediatric GRS that can identify pediatric SCA patients at high risk for albuminuria.

Methods

Gene allele variants in *APOL1 G1/G2, HMOX1, BCL11A* and α-thalassemia ($\alpha^{-3.7}$ allele), were identified in 324 African American patients with SCA (HbSS or HbS ^{0}-thalassemia genotypes) enrolled in the Sickle Cell Clinical Research and Intervention Program (NCT02098863), a lifespan, longitudinal cohort study. The first urine albumin to creatinine ratio (ACR) collected after birth was analyzed as a continuous variable and dichotomized by a threshold of ACR $\geq$30mg/g creatinine as albuminuria. We defined a GRS ^{3} based on established risk alleles in three genes: *APOL1* (G1/G2), *BCL11A (*rs1427407), and $\alpha^{-3.7}$(PMID:27658436). High risk was defined as patients with APOL1 (G1/G1, G2/G2 or G1/G2), without $\alpha^{-3.7}$ and with wildtype *BCL11A* (G/G); low-risk was defined as patients negative for *APOL1* G1/G2 and with $\alpha^{-3.7}$ (either $\alpha^{-3.7}/\alpha\alpha$ or $\alpha^{-3.7}/\alpha^{-3.7}$) and the *BCL11A* T allele (either G/T or T/T). All other combinations were defined as intermediate risk. By adding *HMOX1 (*rs743811), C allele (TT/TC vs CC), we further refined GRS ^{3} as GRS ^{4} using the summation of the number of high-risk alleles of kidney outcomes for four variants and created four risk categories. The generalized linear regression model was used to associate additive dose-effect models for GRS ^{3} and GRS ^{4} with continuous ACR and albuminuria, adjusted for age, sex, hydroxyurea treatment, 5 principal components, and, if significant, the age-genotype interaction. ACR was log-transformed to approximate normality. As we included variants with known associations, we used a one-sided p-value for testing associations of individual variants, GRS ^{3}, and two-sided p-values for GRS ^{4}. P-values <0.05 were considered significant.

Results

In 324 individuals with SCA, those with albuminuria (34, 10.5%) appeared to be older than those without albuminuria (290, 89.5%) (mean 9.8 years [standard deviation ±4.4 years] vs. 8.6 [± 4.0], p=0.053). There were no significant differences between these groups by sex (female 58% vs. 49%, p=0.37), proportion on hydroxyurea (62% vs. 59%, p=0.85) or fetal hemoglobin (15.6 [± 10.61] vs. 14.8% [± 10.0], p= 0.81). All four individual genetic variants were associated with the first ACR (all p $\leq$ 0.028) and albuminuria (all p$\leq$ 0.03). GRS ^{3} was significantly associated with the first ACR (estimate=1.4, standard error [SE]=0.5, p=0.0035)

and albuminuria (odds ratio [OR]=3.0, 95% CI: 1.2-7.5, p= 0.008). After adding *HMOX1* to GRS ^{3}, GRS ^{4} was more significantly associated with the first ACR (estimate=0.9, SE=0.3, p=0.0005) and albuminuria (OR=2.0, 95% CI: 1.2-3.4, p=0.003).

Summary

We developed a GRS ^{3} based on three genetic variants associated with albuminuria in pediatric patients with SCA and stratified patients into different risk categories. Addition of a fourth genetic variant to create GRS ^{4}improved the model. Our findings will need to be validated in larger longitudinal studies to further examine the association between GRS ^{4} and development of albuminuria and chronic kidney disease. Genetic prediction strategies using GRS has the potential to identify high risk SCA patients for whom renoprotective measures could prevent the development of albuminuria.

Disclosures Kovesdy: *Abbott:* Honoraria; *Abbvie:* Honoraria; *Akebia:* Honoraria; *AstraZeneca:* Honoraria; *Bayer:* Honoraria; *Boehringer Ingelheim:* Honoraria; *Cara Therapeutics:* Honoraria; *CSL Vifor:* Honoraria; *GSK:* Honoraria; *Pharmacosmos:* Honoraria; *ProKidney:* Honoraria; *Takeda:* Honoraria. **Weiss:** *Cellarity:* Current equity holder in private company; *Novartis Inc.:* Consultancy; *Vertex Pharmaceuticals:* Consultancy; *GlaxoSmithKline:* Consultancy; *bluebird bio:* Consultancy. **Saraf:** *Agios:* Consultancy, Other: Advisory board; *BEAM Therapeutics:* Consultancy, Other: Advisory board; *Novartis:* Consultancy, Other: Advisory board, Research Funding; *Forma Therapeutics:* Consultancy, Other: Advisory board, Research Funding; *GBT/Pfizer:* Consultancy, Other: Advisory board, Research Funding, Speakers Bureau. **Ataga:** *Hillhurst Biopharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *FDA:* Research Funding; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Agios Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Roche:* Consultancy, Honoraria; *Biomarin:* Consultancy, Honoraria; *Fulcrum Therapeutics:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Vertex:* Other: Data Monitoring Committee; *NHLBI:* Research Funding; *Novo Nordisk:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Takeda Pharmaceuticals:* Research Funding.

Figure A and B. The association of genetic risk score (GRS^4) based on four genes of *APOL1 G1/G2, HMOX1, BCL11A*, and α-thalassemia ($\alpha^{-3.7}$ allele) with ACR and albuminuria in patients with SCA. GRS^4 is defined as ≤2, 3, 4, and ≥5 of the summation of the number of risk alleles and was analyzed as an additive dose-effect model. P-values were calculated using the generalized linear regression model, adjusting for age, sex, hydroxyurea treatment, and 5 principal components. ACR was log-transformed to approximate normality. OR=odds ratio. ACR = albumin-creatinine-ratio.

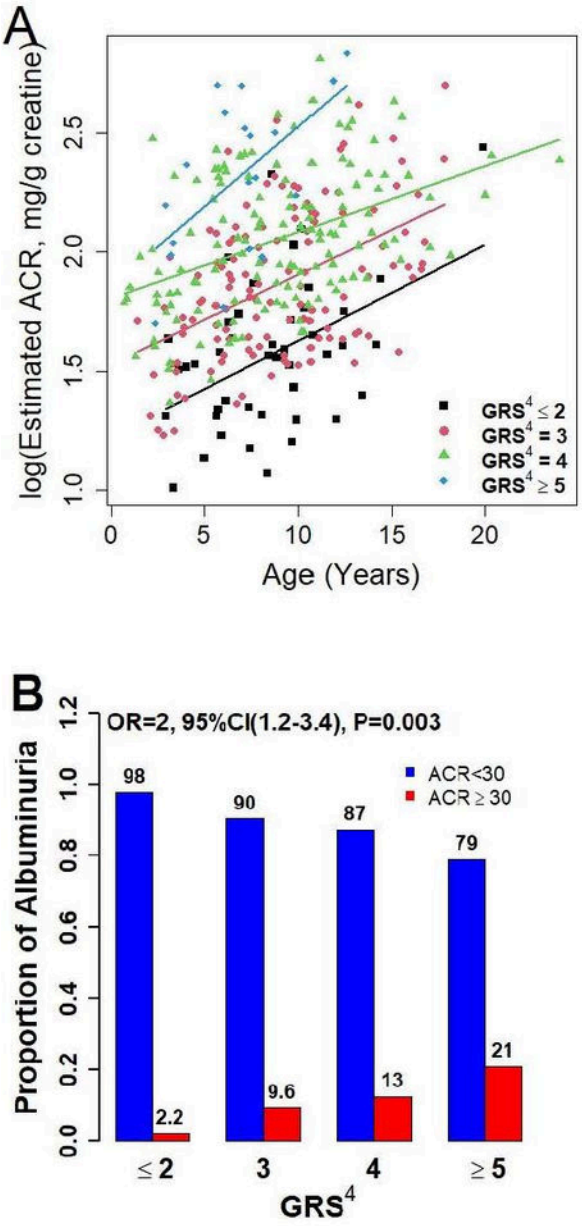

Figure 1

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