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Genetic Biomarkers of Health-Related Quality of Life in Pediatric Asthma

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Abstract

Objectives—To determine the relationship between single nucleotide polymorphisms (SNPs) in candidate genes associated with multiple asthma phenotypes and HRQOL (HRQOL).

Study design—A cross-sectional study was conducted with 275 school-aged children diagnosed with asthma and their caregiver receiving care at a pediatric hospital. Genomic DNA was obtained from children, and caregivers completed a measure of their child's HRQOL. ANOVA was used to investigate the association between SNPs and HRQOL.

Results—Children homozygous for the major variant at *IL-4RA* rs 1805010 evidenced significantly better HRQOL than their counterparts. Significant associations with pulmonary function were not observed.

Conclusion—Genes associated with asthma phenotype can be associated with HRQOL at least partly independently from pulmonary function.

Children and adolescents with asthma experience substantial morbidity as defined by functional impairment, decrements in health-related quality of life (HRQOL), and healthcare utilization (1-3). The recent NHLBI guidelines for the clinical management of pediatric asthma emphasize the goal of improving children's health-related quality of life as a cornerstone of clinical care (4). For this reason, study of the influences on HRQOL in pediatric asthma assumes special importance. Studies have documented the relationship between factors such as family functioning, children's psychological symptoms, and asthma severity on HRQOL (5-7) and assessed the association of HRQOL with a wide range of environmental and asthma- specific risk factors.

Genetic factors are a potentially important, but poorly understood influence on children with pediatric asthma. Links between asthma-related genotype and various clinical outcomes

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have been documented, (8), and recent research indicates that variability in genotype contributes significantly to the heterogeneity of asthma phenotype and morbidity (9). Several genes have been implicated in increased risk for asthma, with outcome variables including bronchial hyperresponsiveness, atopy, and IgE (10). Some of the most replicated genes are located in the 5q region and have demonstrated associations with not only asthma and atopy phenotype, but also response to drug therapy (11).

Although objective measures of asthma severity are typically used in the management of childhood asthma, pulmonary function tests are not always reliable markers of asthma or severity (12-14) In contrast, HRQOL assesses the functional impact of asthma symptoms independent of disease severity across multiple clinically relevant domains. Guidelines for the care of asthma recommend routine assessment of HRQOL (15). Biological processes have been shown to influence perceptions of the impact of pediatric asthma (16), with genes influencing sensitivity to and interpretation of stressful events (17). Consequently, HRQOL may be a more sensitive descriptor of disease activity and therefore, a relevant outcome variable in the investigation of genetic factors and asthma phenotype.

Despite the fact that HRQOL is emphasized in the new guidelines as a critical endpoint in clinical care, to our knowledge, no study has elucidated the role of specific genotypes on the effects of asthma on children's HRQOL (4). To address this need, this study sought to provide the first evidence of the utility of HRQOL as phenotype in genetic studies of childhood asthma. We focused on known single nucleotide polymorphisms (SNPs) in candidate genes associated with multiple asthma phenotypes in more than ten studies (11), including IL-4RA, IL-4, CD14, and GSTP1. Given their highly replicated relationships with other asthma outcomes, we hypothesized that the association of these SNPs with HRQOL would be significant.

Methods

Children with asthma (n=275) and their caregiver were recruited sequentially from the Pulmonary, Allergy and Immunology outpatient clinics at Cincinnati Children's Hospital. Asthma was diagnosed in accordance with American Thoracic Society (ATS) criteria (18-19). This study was approved by the IRB at Cincinnati Children's Hospital Medical Center and participants provided written informed consent and assent.

Children's Health Survey for Asthma (CHSA) is a 48 item condition-specific, parent proxy-report of functional health for school-aged children with chronic asthma that was developed and validated in samples of children with asthma from a range of socio-economic circumstances (20-21). The instrument includes a broad spectrum of child- and family-focused items divided into five scales (physical health, 15 items; activity [child], 5 items; activity [family], 6 items; emotional health [child], 5 items; and emotional health [family], 17 items). A total score comprised of the mean score across all 48 items is also included. Participants respond using a 5-point Likert scale and raw mean scale scores were computed (range= 1-5), with higher scores indicating better functioning. The internal consistency, reliability, and test-re-test reliability of the CHSA in heterogeneous samples are good to excellent. The CHSA demonstrates validity to distinguish among levels of asthma severity (22).

DNA isolation and Genotyping

Genomic DNA was isolated from buccal swabs using Puregene Genomic DNA Purification Kit (Gentra Systems, Minneapolis, MN) per the manufacturers instructions. Genotyping was performed by melting-curve analysis. Primers and probes were designed using LightCycler Probe Design Software 2.0 (Roche Diagnostics GmbH, Mannheim, Germany) and

synthesized by Proligo (Proligo LLC, Boulder, CO) as indicated in Table I (available at www.jpeds.com). Cycling was performed in a Px2 or PxE Thermal Cycler (Thermo Electron Corporation, Milford, MA) with LightTyper 384 reagents (Roche Diagnostics, Indianapolis, IN). Melting curve analysis was done in a LightTyper 96 Instrument (Roche Diagnostics GmbH, Mannheim, Germany). Error rates, as determined by re-sampling a minimum of ten percent of the samples analyzed, were found to be less than five percent for each SNP.

Statistical Analyses

Statistical analyses were conducted in a three-stage process. First, associations between HRQOL scores and potential covariates were examined. Specifically, body mass index (BMI) and mean respiratory symptom scores (RSS) were included as previous research suggests each is associated with asthma severity (23-25). Mean RSS measure average frequency of asthma symptoms and were adapted from the National Institutes of Health guidelines for the diagnosis and management of asthma to assess asthma severity (24). Mean RSS was calculated by averaging parent-reported symptom scores for child cough, wheeze, shortness of breath, and chest tightness (where 1= less than once per week, 2= 1-2 times per week, 3= 3-5 times per week, and 4= 6-7 times per week for each symptom with higher scores indicating greater severity. Mean RSS was 1.55 (SD= .95). Correlations between HRQOL total and subscale scores and BMI, as well as mean RSS were non-significant and not included in multivariate analyses. Second, one-way analysis of variance (ANOVA) was used to determine associations between individual genes and HRQOL scores. Finally, genotypes were combined and one-way ANOVAs were used to examine associations with HRQOL. A Bonferroni correction was implemented to account for the number of analyses conducted and $p < .006$ was considered significant for all analyses.

Results

Children with asthma (n=861) and their caregivers were included in a database documenting asthma symptoms. Of those families, 275 completed the CHSA in clinic and were included in this study (non-participants were administered the CHSA but did not return a completed form). Participants were 49.8% White with a mean age of 9.32 years (SD= 3.12; Table II). Additionally, more than half (54.5%) were male and the mean BMI score was 1.98 kg/m^2 (SD= 6.06 kg/m^2). The majority of participants did not have a member of the household who smoked (77.1%). Mean FEV1 percent predicted value was 98.7% (SD= 15.38). The CHSA total scale evidenced a Cronbach alpha of .95._Individual subscales' reliability were also high: physical health (alpha= .92), activity (child; alpha= .92), activity (family; alpha= . 76), emotional health (child; alpha= .95), and emotional health (family; alpha= .91). Chi-squared analyses revealed no significant differences between participants and non-participants on race, family income or medical variables.

Association of individual SNPs with HRQOL

Each SNP was examined for association with HRQOL. ANOVA analysis revealed differences for *IL4RA* rs 1805010, rs 1805012, *GSTP1* rs 1695, and *IL4* [rs 2243250].

Differences in the HRQOL total score were associated with *IL4RA* rs 1805010 (Table III). Specifically, children homozygous for the major allele had better total HRQOL scores than children with a heterozygous genotype or those with two variant alleles. This differences remained significant after Bonferroni correction ($p = .005$).

Differences for the physical health domain of HRQOL were associated with *IL4RA* rs 1805012 such that homozygosity for the major allele was related to significantly greater Physical Health than the heterozygous genotype ($p = .002$). Homozygosity for the major

allele at *IL4RA* rs 1805010 was associated with significantly greater family emotional health than the heterozygous configuration ($p < .006$). However, no significant differences in the emotional child health, child activity, or family activity were found for any of the genetic variants.

Analysis of relationship between individual SNPs and pulmonary function

As summarized above, our data revealed several significant associations of individual SNPs with HRQOL domains. It was possible that these observed associations were driven by associations with disease severity. In order to address whether the findings were mediated by illness severity, ANOVAs were conducted to compare differences in pulmonary function based upon genotype at each gene. In addition, in order to determine potential gene-dose effects, ANOVA with contrasts were conducted to compare differences in pulmonary function between children with no variant alleles versus those carrying one or two variant alleles. All results were non-significant. Effects of gene-gene interactions on HRQOL and pulmonary function were not conducted due to inadequate power in the sample.

Analysis of potential gene-dose effects

In order to determine potential gene-dose effects, ANOVA with contrasts were conducted to compare differences in asthma-related QOL between children with no variant alleles versus those carrying one or two variant alleles in any of the examined genes. Comparisons were made across all HRQOL and domains. Several differences were observed, including *IL4RA* rs 1805010, as well as with *IL4* rs 2243250. Results are reported in Table IV along with effect sizes. Here, Pearson r^2 was included as a commonly used measure of effect size. ANOVA is considered a parametric test that is based on correlation and thus, it yields effect sizes analogous to Pearson's r^2 (24).

Notably, *IL4RA* rs 1805010 was associated with overall HRQOL and impact of asthma on emotional health. Specifically, children carrying 1 or 2 copies of the minor variant allele had significantly worse overall HRQOL (M= 3.68, SD= .76 versus M= 4.05, SD= .67; $p = .002$) and family emotional health (M= 3.63, SD= .88 versus M= 4.06, SD= .71; $p = .001$).

Finally, *IL4* rs 2243250 was associated with impact of asthma on children's emotional health. Specifically, youth homozygous for the major allele had better Emotional health (M= 3.80, SD= 1.67 versus M= 3.30, SD= 1.44; $p = .009$). This difference remained significant after Bonferroni correction. Differences for other domains were not significant. Results were non-significant for all other SNPs examined.

Discussion

Although asthma management guidelines emphasize the importance of assessing HRQOL (4), the impact of asthma genetics on HRQOL have not been described. The genetic variants examined in this study were among some of the most highly replicated within the asthma literature, demonstrating associations with PFT, asthma symptoms, and IgE (10,11). We sought to extend scientific knowledge by determining whether the same association between previously implicated genes and asthma symptoms could be shown with HRQOL.

Results from this study identified key differences in child HRQOL, with the following individual SNPs evidencing significant variations: *IL-4RA* rs 1805010 and *IL-4* rs 2243250. Specifically, children homozygous for the major variant at each of the aforementioned SNPs evidenced significantly better HRQOL than their counterparts. Moreover, when variants were combined and contrasted (i.e., children homozygous for major variants were compared with children carrying either one or two minor variant alleles), children homozygous for major variant alleles continued to demonstrate better HRQOL. Because significant

associations with pulmonary function were not observed, results from this study suggest that genes can be associated with asthma HRQOL independent of pulmonary function.

The most likely explanation for these observations is that the same genes that influence pediatric asthma symptoms and severity influence HRQOL, but that HRQOL may be a more sensitive outcome for asthma genetic studies than lung function. An alternative explanation is that genes have a role in child and maternal perceptions of HRQOL. The idea that genes influence individuals' sensitivity to and interpretation of stressful events and mood reflects a bio-behavioral approach to adjustment (26). Even though behavioral genetic analysis of parent and child perceptions was not specifically measured here, previous studies provide support for the unique influence of genetics on childhood psychological and behavioral factors (27-28).

Results of this study should be viewed in light of several limitations. First, some differences are statistically significant, but may be less clinically meaningful due to relatively similar mean values. Second, gene-gene interaction effects were not conducted for HRQOL or pulmonary functioning due to low sample power. Moreover, the effect of asthma therapy on HRQOL was not considered in this analysis. It may be that particular SNPs predispose children to better response to asthma treatment, thereby rendering better HRQOL. Alternatively, children not receiving the preferred treatment or those with genetic profiles that are not responsive to the preferred treatment could be expected to evidence worse HRQOL. Previous research in the area of pharmacogenetics suggests that airway symptoms for adults and children alike do respond to asthma medication treatments differently based on genotype (29). Differential response to asthma treatment could likely mean a differential impact of asthma symptoms on quality of life.

Finally, the current study utilized parent-reported HRQOL for children. Prior research indicates parent and child reports of HRQOL may be discordant (30-31) possibly owing to differences in the way that parents and children interpret events or respond to Likert scales (i.e., endorsing very high or very low scores versus moderate; (32-33). Moreover, parents may be more accurate in describing behavioral or family impact of illness, and children and adolescents may be more accurate in describing effects on mood (34). Additional research incorporating child self-report is needed to substantiate this study's initial findings.

Maintenance of patients' functional well-being is a primary goal for medical practitioners and one that requires on-going, comprehensive assessment (35). Everyday, patients and families make decisions about medical treatment based on an array of factors, only some of which relate to their health status. Factors such as medication side effects, forgetfulness, peer perceptions, and family functioning can all influence decisions about treatment, and conceivably, perceptions of health status (36-38). Information gained from a comprehensive assessment of how children with asthma are feeling and functioning is vital to enabling clinicians and families to better manage the clinical visit, address therapeutic options, and accurately assess treatment efficacy. To this end, HRQOL assessment, including not only a discussion of asthma symptoms but their perceived functional impact, supports clinicians in determining best course of care and outcome.

Previous research indicates that including an assessment and discussion of HRQOL in clinical care is not only feasible, but preferred by patients. Wagner et al found that the majority of patients with epilepsy who took part in a randomized controlled trial regarding the routine use of HRQOL assessment in clinical care wanted their clinician to ask about emotional and physical functioning and reported a willingness to complete a brief questionnaire at each visit to facilitate the assessment process (39). These findings were irrespective of whether or not patients were part of the intervention. Moreover, clinicians

rated the availability of health status assessment as most helpful in treating patients with poorer functioning. More recent research found that including HRQOL in regular clinic visits was associated with higher patient- reported satisfaction and resulted in improved self-reported HRQOL (40).

The current study's findings suggest that clinical efforts to improve health outcomes in pediatric asthma should target those most at-risk for poor HRQOL. Our data support that genetic biomarkers may help distinguish this group in childhood asthma. Thus, there is potential for genetic tests to inform personalized medicine not only in terms of asthma risk, but also HRQOL. Additional research is needed to help clarify the impact of genes on asthma treatment responsiveness and health functioning to better inform pediatric personalized medicine and improve children's HRQOL.

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List of Abbreviations

ANOVA	(analysis of variance)
ATS	(American Thoracic Society)
BMI	(body mass index)
FEV1	(forced expiratory volume in 1 second)
HRQOL	(health related quality of life)
RSS	(respiratory symptom score)
SNP	(single nucleotide polymorphisms)

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Table1

Primers and probes used to genotype Single Nucleotide Polymorphisms (SNP)

SNP		Primer or Probe sequence (5-prime to 3-prime)	Allele *
IL4RA	Forward	CCCAGCCAGCCTACA	
rs1805010	Reverse	CAGCCCACAGGTCCA	Major-A
	Sensor	LC Red 640-TGTTCTCAGGGACACACGT-Phosphate	**Minor-G**
	Anchor	GCACCCCGCGCCTCC-Fluorescein	
IL4RA	Forward	GCTCGGAGAGGAGAAT	
rs1805012	Reverse	TGTGCAAGTCAGGTTGT	**Major-T**
	Sensor	LC Red 640-CCGAAGGTGGAAGAAGGCATGA-Phosphate	Minor-C
	Anchor	GGGCATGTGAGCACTCGTACT-Fluorescein	
IL4RA	Forward	CAGATCCTCCGCCGAA	
rs1801275	Reverse	GAGGTCTTGGAAAGGCTTATAC	Major-A
	Sensor	LC Red 640-TACAAACTCCCGATAGCCACTGG-Phosphate	**Minor-G**
	Anchor	CCACCCTGCTCCACCGCA-Fluorescein	
CD14	Forward	CATTCACCGCCTGGG	
rs2569190	Reverse	CCTCTCTTCCTCCGAGC	**Major-C**
	Sensor	LC Red 640-TTCCTGTTACGGCCCCCCT-Phosphate	Minor-T
	Anchor	ACACAGAACCCTAGATGCCCTGCAGAAT-Fluorescein	
IL4	Forward	GGCCTCACCTGATACGA	
rs2243250	Reverse	TTGGAAACTGTCCTGTCAT	**Major-C**
	Sensor	AACATTGTCCCCCAGTGC-Fluorescein	Minor-T
	Anchor	LC Red 640-GGGTAGGAGAGTCTGCCTGTTATTCT-Phosphate	
IL13	Forward	TAACCCTCCTTCCCGCCTA	
rs20541	Reverse	GAGGTGGCCCAGTTTGT	**Major-C**
	Sensor	LC Red 640-AAGTTTCAGTTGAACCGTCCCTC-Phosphate	Minor-T
	Anchor	AGGTCCTGTCTCTGCAAATAATGATGCTTT-Fluorescein	
GST-P1	Forward	TGGACATGGTGAATGACGGCG	
rs1695	Reverse	GGTCAGCCCAAGCCACCT	**Major-A**
	Sensor	LC Red 640-AGGGAGACGTATTTGCAGCGGAGG-Phosphate	Minor-G
	Anchor	ACCCTGGTGCAGATGCTCACATAGTTGGTGTAGA-Fluorescein	

Table 2

Participant characteristics

Characteristic	%	Mean	SD
Age (in years)		9.32	3.12
Sex (male)	54.5		
Race/Ethnicity			
Caucasian	49.8		
African-American	34.2		
Hispanic	.7		
Asian	1.8		
Other	5.7		
BMI		1.98	6.06
Mean RSS		1.55	.95
Household smoker (no)	77.1		
CHSA scores			
Total		3.78	.75
Physical health		3.67	.89
Emotional health		3.50	1.36
Activity		3.95	1.04
Family emotional health		3.74	.85
Family activity		4.20	1.02
FEV1%		98.69	15.38

Table 3

Health related quality of life for each SNP

Variable	M (SD)	R	F	P
CHSA-Total				
IL-4Ra [rs1805010]		.15	5.55	.005*
0 vs. 1	4.05 (.67) vs. 3.65 (.75)			.003*
0 vs. 2	4.05 (.67) vs. 3.77 (.76)			.19
1 vs. 2	3.65 (.75) vs. 3.77 (.76)			.68
IL-4Ra [rs1805011]		.11	1.67	.19
0 vs. 1	3.81 (.75) vs. 3.74 (.79)			.87
0 vs. 2	3.81 (.75) vs. 3.41 (.83)			.17
1 vs. 2	3.74 (.79) vs. 3.41 (.83)			.31
IL-4Ra [rs1805012]		.43	6.18	.02
0 vs. 1	4.04 (.71) vs. 3.10 (1.22)			
2 not available				
IL-4Ra [rs1801275]		.08	.63	.53
0 vs. 1	3.72 (.76) vs. 3.84 (.77)			.62
0 vs. 2	3.72 (.76) vs. 3.86 (.62)			.63
1 vs. 2	3.84 (.77) vs. 3.86 (.62)			.99
IL-13 [rs20541]		.05	.32	.72
0 vs. 1	3.76 (.76) vs. 3.66 (.80)			.70
0 vs. 2	3.76 (.76) vs. 3.73 (.76)			.99
1 vs. 2	3.66 (.80) vs. 3.73 (.76)			.96
CD14 [rs2569190]		.06	.89	.41
0 vs. 1	3.85 (.73) vs. 3.67 (.78)			.38
0 vs. 2	3.85 (.73) vs. 3.76 (.77)			.82
1 vs. 2	3.67 (.78) vs, 3.76 (.77)			.85
GSTP1 [rs1695]		.10	1.01	.37
0 vs. 1	3.83 (.78) vs. 3.80 (.70)			.97
0 vs. 2	3.83 (.78) vs. 3.59 (.80)			.35
1 vs. 2	3.80 (.70) vs. 3.59 (.80)			.44
IL-4 [rs2243250]		.15	2.16	.12
0 vs. 1	3.88 (.73) vs. 3.69 (.78)			.29
0 vs. 2	3.88 (.73) vs. 3.61 (.80)			.15
1 vs. 2	3.69 (.78) vs. 3.61 (.80)			.87
IL-13 [rs1800925]		.04	.88	.42
0 vs. 1	3.76 (.75) vs. 3.81 (.74)			.91

Variable	M (SD)	R	F	P
CHSA-Total				
0 vs. 2	3.76 (.74) vs. 3.54 (.95)			.51
1 vs. 2	3.81 (.74) vs. 3.54 (.95)			.38

* denotes significance after Bonferroni correction

0= no variant alleles

1= one variant allele

2= two variant alleles

Table 4

Effect of genotype on QOL

Variable				**SNP**					
	IL-4Ra [rs1805010]	**IL-4Ra [rs1805011]**	**IL-4Ra [rs1805012]**	**IL-4Ra [rs1801275]**	**IL-13 [rs20541]**	**CD14 [rs2569190]**	**GSTP1 [rs1695]**	**IL-4 [rs2243250]**	**IL-13 [rs1800925]**
CHSA Total	0 vs. 1/2combined P= .002* r^2= .22	NS P= .27 r^2= .08	0 vs. 1/2combined P= .02 r^2=.43	NS P= .26 r^2= .08	NS P= .42 r^2= .06	NS P= .23 r^2= .10	NS P= .42 r^2= .06	0 vs. 1/2combined P= .04 r^2= .15	NS P= .97 r^2= .003
FEV1%	NS P= .38 r^2= .12	NS P= .73 r^2= .05	NS P= .15 r^2= .61	NS P= .39 r^2= .004	NS P= .97 r^2= .06	NS P= .42 r^2= .14	NS P= .90 r^2= .09	NS P=.35 r^2= .02	NS P=.14 r^2= .003

* denotes significance; NS= not significant

0= no variant alleles

1/2combined= 1 or 2 variant alleles