ARIC Manuscript Proposal # 814

PC Reviewed: 08/23/01 **Status: _A__** **Priority: __2_**
SC Reviewed: 09/06/01 **Status: __A__** **Priority: ___2_**

1.a. Full title: Association of beta2-adrenergic receptor polymorphisms with asthma and obesity in the Atherosclerosis Risk in Communities Study

1.b. Abbreviated title: ADRB2, asthma and obesity

2. Writing group:

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3. Time line:

Measurement of the ADRB2 polymorphisms will be completed in the ARIC cohort by August 2001. Analysis of the data on obesity, asthma and genotype will be completed by December 2001. A draft manuscript will be distributed for internal circulation by February 2002.

4. Rationale:

Asthma and Obesity

Asthma and obesity are complex phenotypes resulting from the combined effects of genes, environment, behavior and their interactions. The prevalence of both asthma and obesity in the US has increased dramatically in recent years. Researchers are beginning to question the possibility of a link between the two and have even hypothesized that asthma may be another comorbid risk associated with obesity. At least two studies have shown that increasing body mass index was associated with the risk of developing asthma in females (1, 2). And a recent study found that severe obesity was a significant risk factor for asthma, wheeze and medication use (3). Asthma and obesity may be linked at the molecular level and could result from a genetic susceptibility to both conditions. One gene where this hypothesis might be explored is the $\exists_2$-adrenergic receptor gene that has been shown to be associated with both asthma and obesity.

The $\exists_2$-adrenergic receptor gene has a large number of polymorphic variants. Three variants within the coding region of the gene appear to be functionally relevant but only two are functionally relevant and common: Arg16→Gly16 and Gln27→Glu 27 (4). Cells expressing the Glu27 form of the receptor show attenuated downregulation following $\exists_2$–agonist exposure. Cells expressing the Gly 16 form of the receptor show enhanced receptor downregulation.

Genotype prevalence

Estimates of genotype prevalence are limited. In a study by Ramsey et al. (5) genotypes were determined for three hundred and thirty-two subjects from 76 families in Perth, Australia. The majority of the population was Caucasian (97%). Allele frequencies in the human population have been reported as: Gly16 (60%); Arg16 (40%); Gln27 (53%); Glu27 (47%).

Gene-Disease association

$\exists_2$-adrenergic receptor and asthma

The $\exists_2$-adrenergic receptor plays an important role in airway responses. The $\exists_2$-adrenergic receptors are present on bronchial smooth muscle cells in the lungs where they act to dilate the airways in response to stimulation by circulating catecholamines or exogenous $\exists_2$-agonists. The beta-2-adrenergic receptor agonists are the most widely used agents in the treatment of asthma. Variants of $\exists_2$-AR that alter airway behavior could predispose individuals to develop an asthmatic phenotype (5). Studies in this area have looked at whether $\exists_2$-AR polymorphisms were associated with asthma or its intermediate phenotypes; and whether treatment responses or asthma severity were associated with $\exists_2$-AR polymorphisms. Although the effects seen in most studies to date are small, there does appear to be a reasonable consistent association with IgE levels, bronchial hyperresponsiveness, and treatment response (see table below). An association between $\exists_2$-AR polymorphisms and the development of asthma is less certain.

$\exists_2$-adrenergic receptor and obesity

The adrenergic system plays a role in the regulation of energy balance. Human adipocytes contain adrenergic receptors that can stimulate or inhibit lipolysis. The beta-2 adrenergic receptor is a major lipolytic receptor in human fat cells and may play a pathogenic role in essential hypertension. Increased surface $\exists_2$-adreneric receptor density in lymphocytes has been reported in hypertensive subjects (6). In subjects with abdominal obesity, the $\exists_2$-adreneric receptors in abdominal subcutaneous fat cells display a 10-fold decrease in lipolytic noradrenaline sensitivity (7). Associations between $\exists_2$-adreneric receptors and obesity from the published literature are
summarized in the table below.

Polymorphism	Association	Study Ref
Glu 27	decreased airway reactivity	8
Glu27	Reduc response to histamine	5
Glu27	Type II diabetes	9
Gln 27	elevated serum IgE	10
Gln27	childhood asthma	11
Gln 27	asthma severity	12
Gln27Glu	plasma cholesterol concentration	13
Gln27Glu	obesity in women	14
Gln27Glu	Obesity	9
Gly 16	asthma severity	15
Gly 16	nocturnal phenotype	16
Gly 16	incr bronchial hyperreactivity	17
Gly16	incr bronchodilator desensit after chronic dosing with formoterol	18
Gly16	Incr agonist sensitivity	14
Gly16 homozy	lower freq in obese women	9
Gly16/Gln27 haplotype	asthma severity	12
Arg16	incr wheeze with a cold	5
Arg16Gly	obesity in men	13
Arg16Gly	plasma cholesterol concentration	13
Arg16Gly	incr waist-to-hip ratio and systolic blood pressure in men	19
Arg16 homozy	deterior in pulmonary function assoc with reg albuterol use	20
Arg16 homozy	adverse effects of treatment with salbutamol	21

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5. Main Issues/Hypotheses to be addressed:

a. Influence of the ADRB2 Arg16→Gly16 and Gln27→Glu 27 polymorphisms on asthma and lung function. Univariate and multivariate analysis will be done. Traditional risk factors (age, race/ethnicity, gender, and smoking) will be controlled.
b. Influence of the ADRB2 Arg16→Gly16 and Gln27→Glu 27 polymorphisms on obesity status. Univariate and multivariate analysis will be done. Traditional risk factors (age, race/ethnicity, gender, smoking, hypertension, diabetes, and total cholesterol) will be controlled.
c. Tests of interaction between the ADRB2 polymorphisms and obesity in the occurrence of asthma in multivariate models that include traditional risk factors (age, race/ethnicity, gender and smoking).

6. Data (variables, time window, source, inclusions/exclusions):

Asthma – ever had asthma, confirmed by a doctor, age at onset (Respiratory Symptoms Physical Activity Form) and pulmonary function measures
Obesity status and body size measures - BMI, waist circumference, hip circumference, waist/hip ratio, percent body fat
$\exists_2$-adrenergic receptor genotoypes

7.a. Will the data be used for non-CVD analysis in this manuscript? __X_ Yes ___ No

7.b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __X_ Yes ____ No
(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _X_ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X_ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:
http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html __X__ Yes ____ No