What the Genetic Background of Individuals with Asthma and Obesity Can Reveal: Is β 2-Adrenergic Receptor Gene Polymorphism Important?

Hanna Danielewicz, PhD, MD

The goal of this review was to evaluate the association of β 2-adrenergic receptor (*ADRB2*) gene polymorphisms with asthma and obesity. Asthma is the most common pediatric inflammatory disorder. The prevalence, severity, and hospitalization index for asthma have increased markedly in the last several decades. Interestingly, asthma is often diagnosed along with obesity. Genetic factors are essential for both conditions, and some of the candidate pleiotropic genes thought to be involved in the development of these diseases are *ADRB2*, vitamin D receptor (*VDR*), leptin (*LEP*), protein kinase C alpha (*PRKCA*), and tumor necrosis factor alpha (*TNF α*). The *ADRB2* has been studied in multiple populations and more than 80 polymorphisms, mainly single-nucleotide polymorphisms, have been identified. For nonsynonymous Arg16Gly, Gln27Glu, and Thr164Ile, functional effects have been shown. *In vivo*, these polymorphisms have been evaluated to determine their association with both obesity and asthma, but the results are inconsistent and depend on the population studied or how the disease was defined. Currently, there are only few reports describing the genetic background for the comorbidity of asthma and obesity.

Introduction

IN THE LAST TWO DECADES, the prevalence of respiratory and circulatory disorders has markedly increased. While medical professionals have managed to treat serious infectious diseases for most part, lifestyle changes have caused a substantial increase in the so-called civilisation disorders, such as asthma and obesity. Numerous epidemiological studies have revealed the parallel increase in morbidity. Additionally, a trend is observed to comorbidity of these disorders. The nature of this relationship is not completely understood. Obesity is a known risk factor for asthma. This could be related to both the proinflammatory effects of cytokines, which are released in obese individuals, or due to mechanical effects that cause impaired ventilation in obese individuals.¹

Obesity is highly correlated with oxidative stress in tissues. Macrophage infiltration in fat tissue corresponds with the area undergoing hypoxia, suggesting that hypoxia initiates cell death, which further stimulates the expression of proinflammatory cytokines, such as tumor necrosis factor alpha (*TNF α*) and IL-6. Later, these cytokines are spread by blood and affect the whole body together with the lung and bronchi. In obese individuals, functional residual capacity is significantly reduced due to changes in the elastic properties of the chest wall. Breathing at a low lung volume further

increases the airway responsiveness. Small airway closure is an additional mechanism leading to mechanical impairment of ventilation.^{2,3}

There is an evolutionary-based hypothesis that common disorders, such as asthma, hypertension, and obesity, are wide spread among populations because the susceptibility alleles were selected during human evolution and has become unfavourable nowadays due to the changes in environmental conditions and lifestyle. Thus, it is plausible that, based on selective patterns, the ancestral *ADRB2* variants were beneficial with regard to energy storage, ascariasis resistance, and vascular reactivity. There is also evidence of favorable selection of *ADRB2* variants due to the effect on *Plasmodium falciparum* infection, which has strong selective pressures on humans.⁴

Genetic factors are essential for both asthma and obesity. Family and twin studies confirmed that body-mass index (BMI) is heritable in 40%–70% of individuals.⁵ For asthma, this proportion was determined to be similar.⁶ For at least 10 years, shared genetic background for asthma and obesity has been investigated, summarized elsewhere.⁷ Between commonly shared genes, the most biologically plausible are those that are pleiotropic, including β 2-adrenergic receptor (*ADRB2*), vitamin D receptor gene (*VDR*), leptin (*LEP*), protein kinase C alpha (*PRKCA*), and tumor necrosis factor α (*TNF α*).^{8–12} Polymorphisms within *ADRB2* were described in

1st Department of Pediatrics, Allergy and Cardiology, Wrocław Medical University, Wrocław, Poland.

association with different disorders, including not only asthma and obesity but also hypertension,¹³ autism,¹⁴ cerebral palsy,¹⁵ susceptibility to parasite infestation,¹⁶ and rheumatoid arthritis.¹⁷

The *ADRB2* Gene

The gene encoding *ADRB2* was cloned by Kobilka et al.¹⁸ and is localized to chromosome 5q31-q32, a region that has been linked to asthma. *ADRB2* consists of a single 2015 nucleotide exon that encodes a protein that is 413 amino acids in length. This gene is highly polymorphic and the allele prevalence differs among different ethnic groups. It has been studied in multiple populations and more than 80 polymorphisms have been identified.^{19,20} Four known single-nucleotide polymorphisms (SNPs) are nonsynonymous polymorphisms: Val34-Met, Arg16Gly, Gln27Glu, and Thr164Ile. Two of these SNPs (Arg16Gly and Gln27Glu) are common with minor allele frequencies (MAF) of 40%–50%.^{21,22} Thr164Ile occurs with MAF of 1%–3%. The rarely occurring Val34Met has MAF of less than 1%.²³ The genetic analysis also showed that the 3' UTR of the gene contains a poly-C repeat of variable length that is interrupted by 2 polymorphisms.¹⁹ It was suggested that these polymorphisms could be responsible for the variable response to beta-adrenergic therapy. However, a clinical study concerning therapy with a long-acting beta-agonist (LABA) plus inhaled corticosteroid did not show any association with this genotype.²⁴

Genetic Polymorphisms of *ADRB2*

Arg16Gly and Gln27Glu encode the amino acids localized in the extracellular part of the receptor. Both affect the downregulation and internalization of the receptors *in vitro*. The Gly16 allele was reported to be associated with enhanced agonist-related sensitivity, while the Glu27 allele was associated with its decreased downregulation.²⁵ The Ile164 allele has been shown to associate with impaired receptor binding and decreased basal and epinephrine-stimulated adenylyl cyclase activity. The Ile164 isoform has been revealed to be 3–4 times less responsive to agonist-induced stimulation.²⁶ Cys19 polymorphisms in the promoter region of the gene have been revealed to be related to the gene transcription. Carriers of Cys19 show a 72% higher expression of *ADRB2* together with increased activity of adenylyl cyclase.²⁷

ADRB2 polymorphisms are in linkage disequilibrium. According to the study by Wang et al.,²⁸ the most common haplotypes are Arg19/Gly16/Glu27, Cys19/Gly16/Gln27, and Cys19/Arg16/Gln27. In a study by Cagliani et al.,⁴ dominant clades were identified: Gly16/Gln27 Ha, Arg16Gln27 Hb, Arg16Gln27 Hc1, and Gly16/Glu27 Hc2. In a HuGE²⁹ review, Arg16/Gln27 was the most common haplotype in both the control and asthma group. Drysdale et al.³⁰ described 12 haplotypes and 5 pairs of haplotypes. These haplotypes have been shown to be responsible for genetic variability in 90% of the population studied. While any effect was observed for single polymorphisms in this study, only haplotype analysis brought some conclusion.

Function of *ADRB2*

The beta-adrenergic receptors are members of the G protein-coupled receptor superfamily (GPCR), which have 7

transmembrane domains. They make up an integral part of the sympathetic nervous system and are responsible for the response to catecholamine in different tissues. There are 3 types of *ADRB* (*ADRB1*, *ADRB2*, and *ADRB3*), which share 65%–70% homology. *ADRB2* are crucial for the functioning of the respiratory and circulatory systems and they play an important role in the immune and metabolic processes. They are also key factors in thermogenesis and energy balance and, therefore, can affect obesity and glucose intolerance. *ADRB2* are localized mainly to smooth muscles of the bronchi, but is also found on the surface of inflammatory cells, in adipose tissue, on cardiac myocytes, and on vascular smooth muscle cells. Additionally, *ADRB2* have recently been described in endothelial cells, neuron axon processes, mast cells, kidney, and hepatocytes.^{31–33} Intracellular signaling upon *ADRB2* begins with the activation of stimulatory G proteins, which in turn stimulates adenylyl cyclase with the conversion of ATP to second messenger cAMP. cAMP further activates cAMP-dependent protein kinase (PKA), which causes phosphorylation of a variety of substrates, among which are phospholipase C and *ADRB2* itself. Phosphorylated *ADRB2* is uncoupled from the G protein and binds units beta and gamma of G inhibitory protein, which leads to termination of the signal and stimulates binding to beta arrestin and internalization of the receptor.^{34,35} The extent of the downregulation is genotype dependent. Expression of the *ADRB2* gene is also related to the glucocorticosteroid activity since the *ADRB2* gene activity is positively regulated by glucocorticosteroids GKS.²² *ADRB2* plays a crucial role in asthma pathogenesis. Apart from bronchodilatation, it was shown that beta2-adrenergic receptor stimulation inhibits the release of proinflammatory mediators from mast cells, influences T-cell growth and functions, and affects eosinophil survival and function. *ADRB2* stimulation could induce IgE production by human B lymphocytes and expression of the soluble low-affinity IgE receptor sCD23.^{36,37}

Obesity and *ADRB2* Polymorphisms

While it has been estimated that genetics explains 40% of population variability in the prevalence of obesity, conflicting results exist for the association of the *ADRB2* Arg16 polymorphism and obesity. Several studies reported that increased BMI was associated with the Arg16 isoform, while other studies have revealed the opposite results. The Glu27 variant has been shown to be associated with obesity, but not all of the results have been replicated unambiguously in all studies.^{38–40}

In the Park et al. survey,⁴¹ a group of adolescents was studied to determine the relationship between the *ADRB2* gene polymorphism and obesity. This study included 329 unrelated children. The authors considered different phenotypes that are related to obesity: BMI, % fat content, LEP serum concentration, insulin concentration, serum glucose, and lipid profile. Three *ADRB2* variants were considered: Arg16Gly, Gln27Glu, and Thr164Ile. The conclusion in the study was that *ADRB2* and *ADRB3* polymorphisms explain 4.3% and 10.1%, respectively, of the population variability with regard to BMI. When gene interactions were considered, these polymorphisms together explain 18.3% BMI diversity. In the study by Lima et al.,⁴² the frequency of genotypes Cys19Arg, Gly16Arg, Glu27Gln and haplotypes

Cys19/Arg16/Gln2, Cys19/Gly16/Gln2, Arg19/Gly16/Glu27 was estimated. A positive association was revealed for Glu27. Carriers of this allele, in addition to being obese, showed a reduced lipolytic activity.

What is quite interesting is that the presence of a polymorphism within the *ADRB2* gene could predict the effect of weight loss in a slimming program. In a study of obese Spanish women, only carriers of Glu27 benefitted from increased physical activity and a slimming diet.^{43,44} Similarly, in another survey, an interaction was described between changes in fat mass and abdominal adiposity during a training program and *ADRB3* polymorphism—Trp64Arg and *ADRB2* polymorphism—Arg16Gly.⁴⁵ In a study by Tsunekawa et al.,⁴⁶ significant differences were observed between combinations of the *ADRB3* polymorphisms Trp64Arg, *ADRB2* Arg16Gly, and uncoupling protein 1 UCP1-3826 A/G (mitochondrial, proton carrier) and hip/waist ratio.

In the year 2008, a meta-analysis was performed to examine the obesity risk with respect to Arg16Gly and Gln27Glu. This report included together 41 studies and genotyping results for more than 20,000 subjects. The risk for obesity in relation to both genotypes in general analysis was statistically insignificant. However, subsequent analysis restricted to the Asian, Pacific Island, and native South American populations showed a statistically significant association between the 27Glu genotype and obesity.⁴⁷

Previous studies on individual *ADRB2* genotypes (Arg16Gly and Gln27Glu) in groups divided based on age, sex, and race revealed rather inconsistent results with respect to the risk of obesity, glucose intolerance, insulin resistance, and type II diabetes mellitus. A possible explanation could be that the risk is associated with both genotype and gender or lifestyle factors, such as diet and physical activity. The goal of Prior et al.⁴⁸ study was to evaluate the hypothesis that the *ADRB2* Arg16Gly-Gln27Glu haplotype is associated with the degree of obesity, glucose tolerance, and insulin sensitivity in obese postmenopausal women. The data showed an association between specific haplotypes and maximal oxygen consumption during an exercise test, body composition and an independent association between haplotypes and glucose metabolism, which persisted after controlling for fitness. Recent analysis from Lee et al.⁴⁹ also revealed a possible gene–environment interaction for the Arg16Gly polymorphism. Carriers of Arg16 allele smoking and overeating were much more likely to be obese than noncarriers.

The rare Thr164Ile polymorphism has recently been described as being associated with a risk for obesity, but not with BMI.⁵⁰ These findings are especially important because the Thr164Ile polymorphism has profound functional consequences on receptor functions.

Asthma and *ADRB2* Polymorphisms

Asthma has a polygenic nature due to the interactions between genetic and environmental factors. Additionally, the variability in treatment response is related to genetic susceptibility. Numerous genes have been described as asthma susceptibility genes, however, not much conclusion was done due to indicating a single foothold for predicting asthma natural history or early prevention in susceptible individuals.⁵¹ Early studies suggested that polymorphism

within the *ADRB2* gene could be related to some asthma phenotypes.²¹ There are also 3 meta-analyses from previous years of the Arg16Gly and Glu27Gln associations that confirm that these polymorphisms are not associated with asthma *per se*, but may associate with nocturnal asthma or asthma severity.^{29,52,53} It is currently believed that Arg16Gly and Glu27Gln are not disease-causing variants, but they predetermine the response to agonists and antagonists.^{54,55}

However, the results surrounding these hypotheses are inconsistent. In a study by Carroll et al.,⁵⁶ Gln27 was associated with a significantly shorter stay in the Intensive Care Unit, ICU, due to asthma exacerbation, while the Arg16/Gln27 haplotype was related to the longest stay. In the study by Manoharan et al.,⁵⁷ no differences were found for BHR with respect to both polymorphisms and haplotypes. In a report by Torjussen et al.,⁵⁸ Arg16Gly was revealed to associate with lung functions in children.

Numerous studies have investigated the relationship between polymorphisms within the *ADRB2* gene and treatment with beta-adrenergics. This relationship seems to be associated with increased downregulation of the receptors and resistance to the bronchodilatory effect of these drugs. In a meta-analysis, including all studies that used a bronchodilator test and genotyping for SNPs of Arg16Gly or Gln27Glu until November 2008, an association was found for the therapeutic effect of beta-adrenergic therapy and Arg16Arg genotype. This effect was strongly expressed in Afro Americans. Such relationship neither was nor pronounced for beta-adrenergic response and Glu27Gln variants. The authors concluded that the lack of efficacy in beta-agonist therapy could be associated with the Arg16Gly polymorphism.⁵⁹ In another study, a protocol was designed to determine the effect of LABA on spirometric parameters in relation to Arg16Gly genotypes.⁶⁰ After 18 weeks of corticosteroid therapy with LABA, the medium peak expiratory flow was higher in groups of patients who received active treatment in comparison with the placebo group (inhaled corticosteroid alone), regardless of genotype. However, when considering the metacholine reactivity in Gly/Gly patients, the provocative concentration of metacholine that causes a 20% decline in forced expiratory volume in first second (FEV1) (PC20) was 2.4 times higher when LABA was included. In the Arg/Arg genotype group, there were no differences in metacholine responsiveness according to the therapy group. Another study included asthma pediatric patients who were genotyped for *ADRB2* polymorphisms. The mean value of FEV1 was associated with corresponding haplotypes and was lowest for Gly16/Gln27. Moreover, the index of drug intake, number of hospitalizations, and asthma exacerbations were lower in Gln/Glu carriers in comparison to Gln/Gln carriers, which suggest strong clinical implications for this polymorphism.⁶¹ In contrast to previous findings, a recent study conducted in asthmatic and nonasthmatic children in Colombia did not reveal any differences between genotypes and haplotypes according to disease status, spirometric parameters, demographics, and clinical variables. Additionally, there were not any differences in the *ADRB2* gene expression according to the genotypes and treatment with beta-agonist plus inhaled corticosteroids.⁶² However, a recent survey concerning combined therapy with the LABA—PACMAN cohort study revealed that Arg16 increases the risk of exacerbations in children when they are treated with a combination of inhaled steroids and LABA.⁶³ In another study from the previous year, any *ADRB2* genotype effect was revealed in relation to loss of salmeterol bronchoprotection against exercise.⁶⁴

There are only few studies concerning the rare Thr164Ile polymorphism. In a Hall et al.⁶⁵ study, the authors did not reveal any effect from this variant on prognostic factors in asthma and wheezing phenotypes.

Conflicting results exist for many genetic studies on asthma and *ADRB2* polymorphism. This situation is probably due to false-positive and false-negative associations rather than depending on the population effect. A substantial problem is to define the disease phenotype. Usually, different study groups used different definitions. It seems to be crucial to emerge a new phenotype for further studies—the asthma and obesity phenotype.

Shared Genetic Factors for Asthma and Obesity

In the current bibliography, there are few genetic studies where the comorbidity of asthma and obesity was taken into account. One of them included children from the Childhood Asthma Management Program⁶⁶ survey, Melén et al. study.⁶⁷ The authors presumed that shared genetic factors are possibly associated with genes with pleiotropic effects, such as *ADRB2*, *VDR*, *LEP*, *PRKCA*, and *TNF α* . However, while genetic analysis did not reveal any association for these genes, together with no association for *ADRB2*, and with the comorbidity of asthma and obesity, a trend was observed for glucosamine-6-phosphate deaminase-2 (*GNPDA2*), protein tyrosine phosphatase, receptor type D (*PTPRD*), and roundabout axon guidance receptor homolog 1 (*ROBO1*), although further research is likely required. In a recent study by Melén et al.,⁶⁸ the DENN/MAD domain containing 1B (*DENND1B*), which is a protein that may play a role in clathrin-mediated endocytosis, was identified as being associated with BMI in asthmatic children, while no such relation was revealed for *ADRB2*. In another study (Tesse et al.), the authors suggested that the *TNFA* and *VDR* genes probably could be involved in pleiotropic mechanisms responsible for the comorbidity of asthma and some endocrine disorders.¹² *PRKCA*, *LEP*, and *TNF α* were studied in individual surveys and the results were promising.^{8,9,11}

Why the *ADRB2* polymorphism seems to be worth studying in the context of asthma and obesity phenotype? The same defect, which leads to a poorer response to the bronchodilator treatment, could be responsible for inadequate lipolysis and energy storage thus affecting both conditions. Moreover, the asthma–obesity phenotype is characterized as severe asthma.⁶⁹ The same is true for the association of *ADRB2* polymorphisms and asthma severity⁷⁰ or lung functions⁵⁸; however, more than a single polymorphism, a specific haplotype is conclusive.

Conclusion

Is it possible that the *ADRB2* gene is responsible for the comorbidity of asthma and obesity? It is likely not to be so simple, and there is probably more than 1 gene that has important functions in immunological and physiological alternations that are characteristic of both asthma and obesity. How should this relationship be studied? GWAS revealed some new findings, but the identified genes probably have subtle effects.^{71–74}

The polymorphisms within the *ADRB2* gene that are potentially associated with obesity and asthma include Arg16Gly and Glu27Gln, and probably to some extent

Thr164Ile, as well. The pleiotropic nature of *ADRB2* makes it a good candidate for such an association. It also has an established role in the development of both conditions separately. The underlying mechanism seems to depend on both the alternations in lung function and the metabolic effect associated with *ADRB2*. However, it could also be linked to immunological functions related to *ADRB2* expressions on leukocytes. It also seems plausible that a specific *ADRB2* haplotype was selected during evolution and became unfavourable due to changes in lifestyle. Only 2 studies were conducted on the association between *ADRB2* and the asthma–obesity phenotype (case–control and GWAS). Both failed to reveal any association with the *ADRB2* genotypes. The simple explanation may be not including gene–environment interactions in the analysis. Environmental factors like diet and exercise seem to be the most important, but exposure to tobacco smoke and industrial pollutants is also relevant in relation to the risk conferred by *ADRB2* polymorphisms, which makes these factors promising for future research.

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Address correspondence to:
Hanna Danielewicz, PhD, MD
1st Department of Pediatrics, Allergy and Cardiology
Wroclaw Medical University
ul. Chatubińskiego 2a
50-368 Wrocław
Poland

E-mail: hanna.danielewicz@umed.wroc.pl

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