Promoter Polymorphism G-50T of a Human *CYP2J2* Epoxygenase Gene Is Associated With Common Susceptibility to Asthma*

Alexey V. Polonikov, MD, PhD; Vladimir P. Ivanov, MD, PhD; Mariya A. Solodilova, PhD; Irina V. Khoroshaya, PhD; Mikhail A. Kozhuhov, PhD; and Valery I. Panfilov, PhD

Background: **Cytochrome P-450 2J2 (*CYP2J2*) has recently been shown to be an important enzyme in the metabolism of epoxygenase-derived eicosanoids that play important functional roles in pulmonary physiology and may contribute to the pathogenesis of asthma.**

Study objective: **The focus of our pilot study was to evaluate whether common polymorphism G-50T within the proximal promoter of human *CYP2J2* gene is associated with the susceptibility to bronchial asthma.**

Design and participants: **A total of 429 unrelated Russian subjects were recruited in this case-control study, including 215 sex-matched and age-matched patients with asthma and 214 healthy control subjects. The blood samples were analyzed for genetic polymorphism G-50T in the *CYP2J2* gene by polymerase chain reaction followed by restriction fragment length polymorphism analysis.**

Results: **The frequency of variant allele −50T of the *CYP2J2* gene was significantly higher in asthmatic patients than in healthy subjects (odds ratio [OR], 5.04; 95% confidence interval [CI], 1.99 to 12.77; p = 0.0003). In addition, the heterozygous genotype −50GT of the *CYP2J2* gene was found to be significantly associated with susceptibility to allergic asthma (OR, 5.40; 95% CI, 2.05 to 14.26; p = 0.0003) as well as nonallergic asthma (OR, 5.77; 95% CI, 1.84 to 18.10; p = 0.004). The associations of the *CYP2J2* gene G-50T polymorphism with asthma remained significant after adjustment for age and gender using multiple logistic regression analysis.**

Conclusions: **Our data demonstrate for the first time that the *CYP2J2* gene might be considered as a novel candidate gene for common susceptibility to asthma and highlight the importance of the P-450 epoxygenase pathway of metabolism of arachidonic acid in the pathogenesis of the disease.**

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Key words: arachidonic acids metabolism; asthma; case-control studies; cytochrome p-450 *CYP2J2* genetics; single-nucleotide polymorphism

Abbreviations: bp = base pair; CI = confidence interval; *CYP2J2* = cytochrome P450 2J2; EET = epoxyeicosatrienoic acid; NF = nuclear factor; OR = odds ratio; PCR = polymerase chain reaction; SNP = single-nucleotide polymorphism

Bronchial asthma is an inflammatory lung disease that is characterized by reversible airflow obstruction, airway inflammation, bronchial hyperresponsiveness, epithelial damage, and airway smooth-muscle hypertrophy.[1,2] It is widely accepted that

*From the Department of Medical Biology, Genetics, and Ecology (Drs. Polonikov, Ivanov, Solodilova, and Khoroshaya), Kursk State Medical University, Kursk, Russia; and the Department of Pulmonology (Drs. Kozhuhov and Panfilov), Kursk Regional Clinical Hospital, Kursk, Russia.

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Correspondence to: Alexey V. Polonikov, MD, PhD, Kursk State Medical University, Karl Marx St, 3, Kursk, Russia 305041; e-mail: polonikov@rambler.ru

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asthma is a complex disease that is determined by both genetic and nongenetic factors, and that multiple genes are involved in the pathogenesis of this disease.[3] Despite the discovery of a number of potential environmental factors that have been found to both trigger and/or modulate allergic asthma responses, the genetic components of the disease that underlie the susceptibility to nonatopic asthma are not yet well characterized.

Genetic Studies on Arachidonic Acid Pathways and Asthma

The advancing availability of molecular biology tools to exploit sequence variation to identify genetic polymorphisms contributing to complex disease susceptibility creates new opportunities for progress in asthma research. The literature review has now addressed the hypothesis that variations in the genetics of the inflammatory system, especially in the metabolic pathways of arachidonic acid, may increase the risk of bronchial asthma. The majority of the research has been focused on genetic studies of both cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism in patients with aspirin-intolerant asthma.[4–8] However, no genetic studies have been performed on the epoxygenase pathway of arachidonic acid metabolism in other pathogenetic variants of asthma. It is important to note that genes involved in the epoxygenase pathway of arachidonic acid metabolism are attractive candidate genes for establishing not only the inflammatory component of asthma but also the regulation of bronchomotor tone, the control of the composition and secretion of airway lining fluid, and other pathogenetically relevant components determining the asthmatic phenotype.[9–11]

Cytochrome P-450 2J2 Is One of the Major Enzymes of Arachidonic Acid Epoxygenase Pathway

The cytochrome P-450 epoxygenase pathway, which produces midchain and 11ω-terminal hydroxyeicosatetraenoic acids and *cis*-epoxyeicosatrienoic acids (EETs), is one of three major metabolic pathways of arachidonic acid.[9,11,12] Cytochrome P-450 2J2 (CYP2J2) has been found to be one of the major enzymes involved in the formation of EETs in extrahepatic tissue in humans.[11] The human *CYP2J2* gene is shown to be constitutively expressed in a number of organs, including the heart and vascular tissue,[13,14] the kidney,[13] the liver,[15] the pancreas and GI tract,[16] and the lung.[17] Immunohistochemical and biochemical studies have demonstrated that *CYP2J* gene expression and epoxygenase-derived eicosanoid metabolites are localized to both ciliated and nonciliated airway epithelial cells, bronchial and vascular smooth muscle cells, the endothelium, and alveolar macrophages, and also have been shown to be present in BAL fluid.[10,17,18]

Genetic Variations in *CYP2J2* Gene

A large degree of interindividual variation in *CYP2J2* gene expression has been observed.[13] Some data[13,19] have demonstrated that the human *CYP2J2* gene is highly polymorphic and that several of the coding single-nucleotide polymorphisms (SNPs) result in altered catalytic function of the enzyme. Nineteen SNPs were identified within the human *CYP2J2* gene, and 5 uncommon SNPs were found to change amino acids (Thr143Ala, Arg158Cys, Ile192Asn, Asp342Asn, and Asn404Tyr) in the peptide and to reduce activity toward arachidonic and linoleic acids.[13] One common SNP (G-50T) was identified within a proximal promoter of the human *CYP2J2* gene, which is present in approximately 8 to 17% of the population depending on racial/ethnic background.[19] This common polymorphism leads to a decrease in the gene expression and results in an altered epoxygenase-dependent arachidonic acid metabolism of eicosanoids that possess important biological functions in the lung and airways, making the *CYP2J2* gene an attractive candidate gene in patients with asthma.[20] Our pilot study was designed to determine whether the functionally relevant polymorphism G-50T of the *CYP2J2* gene is associated with susceptibility to bronchial asthma.

Materials and Methods

Study Population

A total of 429 unrelated subjects were recruited into this study, including 215 patients with asthma and 214 sex-matched and age-matched healthy subjects. The mean age of the asthmatic patients was 43.3 years (range, 16 to 67 years), the mean age of the healthy subjects was 41.3 years (range, 17 to 84 years). The study subjects were of Russian origin (from central Russia). The present study was performed in keeping with the principles of the Helsinki Declaration, and informed consent was obtained from all subjects after a detailed explanation of the aims of the study. The Kursk State Medical University Ethical Review Committee approved the study protocol.

Diagnosis of Asthma

All patients were examined at the Department of Pulmonology (Kursk Regional Clinical Hospital). Asthma was diagnosed in all patients by the presence of characteristic symptoms (*ie*, recurrent