**EDITORIAL COMMENT**

Beta$_2$-Adrenergic Receptor Gene Polymorphisms

Will the Important One Please Step Forward?*

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Beta$_2$-adrenergic receptors (B2ARs) contribute to the regulation of many physiological functions in, for example, blood vessels, the heart, airways, and the uterus. They also are the molecular target of clinically important drugs, particularly in the treatment of obstructive airway disease. The human gene encoding the B2AR resides on chromosome 5q31-32. However, at least 12 single nucleotide polymorphisms (SNPs) in the coding and several more in the promoter region have been identified (1). Many of these are synonymous SNPs and/or have not been well characterized at the molecular level or in clinical association studies. Most reported studies relate to the nonsynonymous polymorphisms arginine at position 16 replaced by glycine (Arg16Gly) and glutamine at position 27 replaced by glutamic acid (Gln27Glu) and, more rarely, threonine at position 164 replaced by isoleucine (Thr164Ile). Even though polymorphisms in positions 16 and 27 may be associated with altered treatment responses in some cases, association studies have not consistently implicated them alone or as part of haplotypes in the pathophysiology of cardiovascular or airway disease (1–3).

In this issue of the *Journal*, Piscione et al. (4) report that the Thr164Ile SNP of the B2AR gene is associated with coronary and peripheral artery disease. The Thr164Ile polymorphism is infrequent in the general population of various ethnicities, typically being present in <4% in its heterozygous form, and subjects homozygous for the isoleucine at position 164 (Ile164) genotype may not exist (1). Despite its limited prevalence, this SNP may be important as it has consistently been shown in transfected cells (4–6) or in native cells from genotyped subjects (7–9) that the Ile164 variant is hypofunctional: that is, it produces smaller cellular responses upon agonist stimulation. This hyporesponsiveness is not explained by altered expression levels but rather is due to an intrinsically impaired signaling capacity of the receptor variant. Accordingly, mice transgenic for the Ile164 genotype exhibit smaller adenylyl cyclase, heart rate, and inotropic responses than those transgenic for threonine at position 164 (Thr164) (10). Taken together, these data consistently establish the Ile164 variant of the B2AR as hypofunctional.

To assess the clinical relevance of the Thr164Ile polymorphism, both disease association and drug response studies have been performed. Association studies have been hampered by the low prevalence of the Thr164Ile polymorphism, which necessitates large patient groups to reach robust conclusions. With regard to arterial hypertension, Ile164 was associated with an increased risk for high blood pressure in women (but not men) of 1 large (9,185 subjects) Danish population study (11), whereas no such association between genotype at this locus and blood pressure was observed in a smaller Italian population (775 hypertensive patients) study (12), the lack of association in the latter possibly reflecting the limited statistical power of a smaller population. Piscione et al. (4) now report that Ile164 is much more prevalent in a population of coronary artery disease patients than in a control population (12% vs. 3%), and that within the patient group, Ile164 carriers exhibit a more severe pathology than those with Thr164 genotype. Similarly, a group of patients with peripheral artery disease also exhibited a high prevalence of the Ile164 genotype (7%) and a more severe clinical phenotype than those with Thr164 (4). An early report on reduced survival in patients with congestive heart failure carrying 1 Ile164 allele (13) was confirmed in 1 (14) but not 2 other studies (15,16). Thus, in line with its hypofunctional properties in vitro, the Ile164 genotype is associated with clinical phenotypes reflecting a reduced vasodilation in most studies. Although B2AR can affect cardiac function in some settings (17), this role may be insufficient to yield consistent associations of the Thr164Ile polymorphism with heart failure.

However, the Thr164Ile polymorphism may not only have pathophysiological but also therapeutic relevance. Thus, inotropy and heart rate responses to infusions of the B2AR agonist terbutaline were reduced in Ile164 carriers, and such findings were obtained in both healthy volunteers (18,19) and heart failure patients (14). Similarly, studies using the dorsal hand vein model reported impaired vasodilation in healthy Ile164 carriers; this was based on a lower agonist potency, whereas maximum dilation responses to local agonist infusion were not affected (20,21). Reduced B2AR responses of Ile164 carriers were also reported for lipolysis in isolated adipocytes (7), inhibition of histamine release from mast cells (9), and airway dilation and lympho-

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cyte cyclic adenosine monophosphate formation in cystic fibrosis patients (8). Accordingly, the B2AR were proposed to be disease-modifying genes in cystic fibrosis (22).

Taken together, the available data demonstrate that the Ile164 variant of the B2AR is hypofunctional. This appears to be associated with cardiovascular disease states in which B2AR are considered to be important. Moreover, it is consistently associated with reduced functional responses to agonist stimulation in cardiovascular and other tissues. The latter finding most likely is most important therapeutically for airway disease but has only been studied to a limited extent in such patients. In a more general sense, these data demonstrate that infrequent gene polymorphisms with major effects on the function of the associated protein may be clinically more relevant, at least in the afflicted subjects, than more frequent polymorphisms that affect gene function to a more limited extent.

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