

Genes-4U

Leukotriene C4 Synthase A -444 C

Leukotriene C4 Synthase is the first committed enzyme in the pathway leading from Leukotriene A4 to the Sulfido-Leukotrienes C4, D4 and E4, formerly known as „Slow Reacting Substances of Anaphylaxis (SRS-A)“. Leukotrienes C4, D4 and E4 are potent stimulators of smooth muscle constriction and strong chemoattractants for inflammatory cells and play a major pathogenetic role in inflammation, particularly Acute Allergy, Pseudoallergy, Anaphylaxis and Anaphylactic shock.

Recently, the A-444C promoter variant of the Leukotriene C4 Synthase gene has been described (1). This variant promoter (-444C) interacts more efficiently with transcription factors and thus leads to overexpression of active enzyme and to enhanced Leukotriene C4 synthesis in vivo (2). Clinically, an association with Aspirin-induced asthma has been described (1,3). Importantly, Variant LTC(4) synthase allele apparently modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to the anti-asthma drug zafirlukast, a cysteinyl-leukotriene-receptor-antagonist (4).

(1) Sanak M, Simon HU, Szczeklik A. Leukotriene C4 synthase promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997 Nov 29;350(9091):1599-600

(2) Sanak M, Pierzchalska M, Bazan-Socha S, Szczeklik A. Enhanced expression of the leukotriene C(4) synthase due to overactive transcription of an allelic variant associated with aspirin-intolerant asthma. *Am J Respir Cell Mol Biol* 2000 Sep;23(3):290-6

(3) Penrose JF, Baldasaro MH. Leukotriene C4 synthase: a candidate gene for the aspirin-intolerant asthmatic phenotype. *Allergy Asthma Proc* 1999 Nov-Dec;20(6):353-60

(4) Sampson AP, Siddiqui S, Buchanan D, Howarth PH, Holgate ST, Holloway JW, Sayers I. Variant LTC(4) synthase allele modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to zafirlukast. *Thorax* 2000 Oct;55 Suppl 2:S28-31