# 5-Lipoxygenase Activating Protein (ALOX5AP): Association with Cardiovascular Infarction and Stroke

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Polygenic and multifactorial diseases such as stroke, asthma and others are tough nuts to decipher. Since each genetic variation that contributes to the symptom may do so only by a small percentage, it is difficult to map and identify the genetic components that contain the at-risk composition. Yet this is the challenge of the post-genome era. Leading research in this field is carried out by the Icelandic company deCODE Genetics, which takes advantage of the special genetic structure of the Icelandic population, a population that has been isolated for many generations. At the beginning of February the company reported the identification of the first gene associated with a higher risk of both heart attacks and strokes – diseases that result in the death of most people in developed countries [1]

Two variants of the *ALOX5AP* gene, encoding the arachinodate 5-lipoxygenase-activating protein (FLAP), have been identified as associated with the diseases. One variant (HapA) is predominant in the Icelandic population whereas the other (HapB) is predominant in the British population.

The ALOX5AP gene product, FLAP, has been implicated as playing a role in regulating the production of substances that trigger inflammation – such as leukotrienes, which are potent vasoconstrictors of coronary arteries [2]. It is proposed that increased FLAP activity may lead to the accumulation of leukotrienes on fatty deposits on the arterial wall. The subsequent breakdown of these deposits by the immune system may then lead to the development of blood clots and an increased risk of heart attack. The authors found that individuals with a past history of myocardial infarction had greater activity of the 5-lypoxygenase (5-LO) pathway than the controls. This was estimated by following the production of leukotriene $B_4$ ($LTB_4$), a key product of the 5-LO pathway, in blood neutrophils isolated from Icelandic individuals with myocardial infarction as compared to controls.

Leukotrienes are a family of paracrine hormones derived from the oxidative metabolism of arachidonic acid (reviewed by Haeggstrom and Wetterholm, 2002 [3]). These lipid mediators are recognized as important signal molecules in a variety of inflammatory and allergic conditions affecting the skin, joints, and gastrointestinal and respiratory systems, in particular asthma. Such conditions are typified by local pain, tissue edema, hyperemia, and functional losses. In the tissues, immunocompetent cells accumulate at the site of injury and contribute to tissue damage and perpetuation of the disease process. Leukotrienes can elicit most, if not all, of these signs and symptoms. Thus, leukotriene $B_4$ is one of the most powerful chemotactic agents known to date and participates in the recruitment of leukocytes. The cysteinyl leukotrienes, on the other hand, contract smooth muscles, particularly in peripheral airways and microcirculation.

Leukotriene synthesis results from the action of 5-lipoxygenase on arachidonic acid [Figure 1]. This enzyme cannot metabolize free arachidonic acid; instead, it must be bound to the membrane-bound protein, FLAP. The interaction of arachidonic acid, FLAP and 5-lipoxygenase leads to the production of the unstable compound

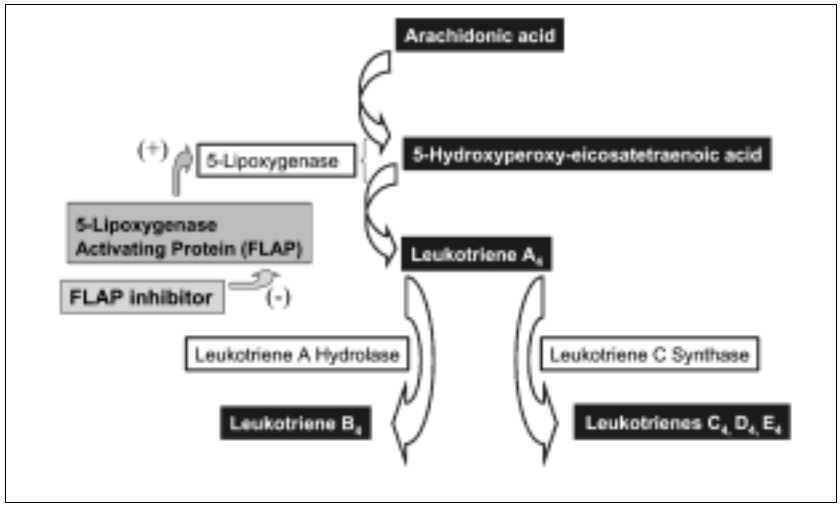


**Figure 1.** The leukotriene synthesis pathway. The substrates/products are marked by the boxes with white letters, the enzymes by the boxes and arrows with white background. Leukotriene biosynthesis inhibitors may act on either 5-lipoxygenase or its activating protein. The new drug specifically inhibits the *ALOX5AP* gene product, FLAP.

5-hydroxyperoxy-eiocosatetraenoic acid (5-HPETE), which is either reduced or converted to leukotriene $A_4$. Leukotriene $A_4$ is then converted by a hydrolase to leukotriene $B_4$ or by a synthase (glutathione-S-transferase) to leukotriene $C_4$. The leukotrienes are excreted to the extracellular milieu by a carrier-mediated mechanism [4].

Drugs that block the formation and action of leukotrienes were recently introduced as a novel anti-asthmatic medication. The German pharmaceutical company Bayer has created a drug that inhibits the enzyme produced by the gene *ALOX5AP*. Bayer believed the gene might contribute to the lung inflammation of asthma. It tested the drug in 2,000 asthma patients and found that it was safe but ineffective for asthma.

DeCode Genetics has licensed the drug from Bayer and hopes to start testing it in humans for its effect on cardiovascular inflammation. Testing will begin almost immediately since the required safety testing has been completed. If the clinical trial is successful, one can imagine the size of the market for this drug.

However, there is one reservation regarding the important findings described above. Since the genetic markers that were studied are associated with only a twofold-increased risk of incurring a heart attack, this work is just the first step toward the goal of unraveling the complex interplay of genes with significant environmental factors such as diet and exercise.

## References


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