caused by the change of the E-to-K substitution at amino acid 254. This SNP in the *5-LO*, which changes the charge from negative to positive, may affect the stability of the 5-lipoxygenase. Therefore, this SNP is induced to inhibit the synthesis of cys-LTs.

In order to clarify the functional effect of E254K, we analyzed the structural model of 5-lipoxygenase. The human 5-lipoxygenase structural model consisted of the N-terminal ß-barrel domain, thought to interact with lipids, and the C-terminal catalytic domain containing the active site that is the iron-binding site and the substrate-binding cleft. Our new finding is that the substitution of *5-LO*, E254K, existed at the surface edge of the C-terminal catalytic domain, but this site was far from the active site of that enzyme. However, part of glutamine acid 254 and lysine 254 had side chains, which are obviously exposed to the solvent in these structural models. Also, the E-to-K substitution changed the charge of the side chain from negative to positive, and it has been reported that this type of change can induce certain diseases (17,18). A previous report showed that some of the other cellular proteins interact with 5-lipoxygenase using the yeast two-hybrid screening method (19). Glutamine acid 254 might influence 5-lipoxygenase to interact with some other cellular proteins but not with FLAP or with the substrate of this enzyme (20-25). Pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to therapy (26). Further studies may be necessary to define the relationship between these 4 SNPs and patients' response to therapy.

In conclusion, our study suggested that the c.760 G>A polymorphism, E254K, in the 5-lipoxygenase gene, is associated with bronchial asthma, and our findings can contribute to the evaluation of one of the genetic risk factors for this disease.

Acknowledgements

This study was supported by Health and Labour Science Research Grants for Research on Allergic Disease and Immunology from Ministry of Health, Labour and Welfare.

References

1. Bochner BS and Busse WW: Allergy and asthma. J Allergy Clin Immunol 115: 953-959, 2005.
2. Sanak M: Genetic variance of 5-lipoxygenase metabolic pathway in bronchial asthma. Int Rev Asthma 4: 70-80, 2002.
3. Chen XS, Sheller JR, Johnson EN and Funk CD: Role of leukotrienes revealed by targeted disruption of the 5-lipoxygenase gene. Nature 372: 179-182, 1994.
4. Samuelsson B: Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. Science 220: 568-575, 1983.
5. Samuelsson B, Dahlen SE, Lindgren JA, Rouzer CA and Serhan CN: Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science 1237: 1171-1176, 1987.
6. Lewis RA, Austen KF and Soberman RJ: Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. N Engl J Med 323: 645-655, 1990.
7. Funk CD, Hoshiko S, Matsumoto T, Radmark O and Samuelsson B: Characterization of the human 5-lipoxygenase gene. Proc Natl Acad Sci USA 86: 2587-2591, 1989.
8. Drazen JM and Silverman ES: Genetic determinants of 5-lipoxygenase transcription. Int Arch Allergy Immunol 118: 275-278, 1999.
9. Silverman ES and Drazen JM: Genetic variations in the 5-lipoxygenase core promoter. Am J Respir Crit Care Med 161: 77-80, 2000.
10. Koshino T, Takano S, Kitani S, *et al*: Novel polymorphism of the 5-lipoxygenase activating protein (FLAP) promoter gene associated with asthma. Mol Cell Biol Res Commun 2: 32-35, 1999.
11. Koshino T, Takano S, Houjo T, *et al*: Expression of 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP) mRNAs in the peripheral blood leukocytes of asthma. Biochem Biophys Res Commun 247: 510-513, 1998.
12. Helgadottir A, Manolescu A, Thorleifsson G, *et al*: The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. Nat Genet 36: 233-239, 2004.
13. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real time quantitative PCR and the $2^{-\Delta\Delta Ct}$ method. Methods 25: 402-408, 2001.
14. Caterina RD and Zampolli A: From asthma to atherosclerosis - 5-lipoxygenase, leukotrienes, and inflammation. N Engl J Med 350: 4-7, 2004.
15. Shibata A, Katsunuma T, Tomikawa M, Tan A, Yuki K, Akashi K and Eto Y: Increased leukotriene E4 in the exhaled breath condensate of children with mild asthma. Chest 130: 1718-1722, 2006.
16. In K-H, Silverman ES, Asano K, *et al*: Mutations in the human 5-lipoxygenase gene. Clin Rev Allergy Immunol 17: 59-69, 1999.
17. Yuen PH, Ryan EA, Devroe E and Wong PKY: A single Glu (62)-to-Lys (62) mutation in the Mos residues of the R7Delta447Gag-tMos protein causes the mutant virus to induce brain lesions. Oncogene 20: 692-703, 2001.
18. Berretta F, Butler RH, Diaz G, *et al*: Detailed analysis of the effects of Glu/Lys ß69 human leukocyte antigen-DP polymorphism on peptide-binding specificity. Tissue Antigens 62: 459-471, 2003.
19. Provost P, Samuelsson B and Radmark O: Interaction of 5-lipoxygenase with cellular proteins. Biochemistry 96: 1881-1885, 1999.
20. Manev H and Tolga UZ: Primary cultures of rat cerebellar granule cells as a model to study neuronal 5-lipoxygenase and FLAP gene expression. Ann NY Acad Sci 890: 183-190, 1999.
21. Zimmer JS, Dyckes DF, Bernlohr DA and Murphy RC: Fatty acid binding proteins stabilize leukotriene A4: competition with arachidonic acid but not other lipoxygenase products. J Lipid Res 45: 2138-2144, 2004.
22. Voelkel NF, Tuder RM, Wade K, *et al*: Inhibition of 5-lipoxygenase-activating protein (FLAP) reduces pulmonary vascular reactivity and pulmonary hypertension in hypoxic rats. J Clin Invest 97: 2491-2498, 1996.
23. Lepley RA, Muskardin DT and Fitzpatrick FA: Tyrosine kinase activity modulates catalysis and translocation of cellular 5-lipoxygenase. J Biol Chem 271: 6179-6184, 1996.
24. Abramovitz M, Wong E, Cox ME, Richardson CD, Li C and Vickers PJ: 5-Lipoxygenase-activating protein stimulates the utilization of arachidonic acid by 5-lipoxygenase. Eur J Biochem 215: 105-111, 1993.
25. In KH, Asano K, Beier D, *et al*: Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. J Clin Invest 99: 1130-1137, 1997.
26. Israel E: Genetics and the variability of treatment response in asthma. J Allergy Clin Immunol 115: 532-538, 2005.