Jpn. J. Infect. Dis., 57, 2004

Genomic Variations in Myeloperoxidase Gene in the Japanese Population

Yosuke Kameoka*, Amanda S. Persad[2] and Kazuo Suzuki[1]

Division of Genetic Resources and [1]Department of Bioactive Molecules, National Institute of Infectious Diseases, Tokyo, Japan; [2]Burdock Group, Florida, USA

SUMMARY: Myeloperoxidase (MPO; EC 1.11.1.7) is a lysosomal hemeprotein that plays an important role in the host defense mechanism against microbial diseases. This neutrophil disorder, characterized by the lack of MPO, may result in a weakened defense activity. Complete MPO deficiency has been postulated to be to originate from genomic mutation. Recently, two Japanese patients were reported with MPO deficiency. Both had base substitutions in the exon 9 region of the MPO gene; a region in close proximity functionally important residue, His502. Genomic DNA from 387 Japanese individuals was examined to determine the prevalence of these recently discovered base substitutions. None of these DNA samples possessed the mutations found in the MPO deficient cases, though two synonymous and one non-synonymous mutation were found. The frequency of mutation in the exon 9 coding region was estimated to be one heterozygote in 129, thus the homozygote of such mutations would be revealed one in 16,000 in the Japanese population.

Myeloperoxidase (MPO) is a lysosomal hemeprotein located in azurophilic granules of neutrophils and monocytes. MPO is part of the host defense system and is responsible for microbicidal activity against a wide range of organisms. A deficiency in MPO is speculated to be associated with a decreased level of immunity (4). Aratani et al. (1) has described the association with this deficiency and continuous infection of *Candida albicans* in MPO knock-out mice.

In the human population, the prevalence of complete MPO deficiency in Japan is estimated to be 1.75/100,000, a value 14- to 28-fold lower than that of the United States and Europe, respectively (8). Three allelic mutations related to MPO deficiency have been previously reported: R569W (5), Y173C (3), and M251T (7). MPO research is now making headway with the genetic analysis of patients with complete and partial MPO deficiency.

Research conducted over the past year entailed identifying mutations found in cases afflicted with MPO deficiency and estimating the prevalence of these mutations in a control cohort. Two novel non-synonymous mutations were researched during this time period; a glycine to serine substitution (G501S) and an arginine to cysteine substitution (R499C), both found on the exon 9 region of the MPO gene. The G501S mutation, first reported in the Japanese population, (6) was found originally in a patient with complete MPO deficiency. Neutrophil function analysis revealed that MPO activity was significantly diminished with slightly elevated superoxide production.

*Corresponding author: E-mail: ykameoka@nih.go.jp

Another patient was later identified with complete MPO deficiency. As with the first case, MPO activity was diminished with increased superoxide production. In this case, a new mutation was also found in the region responsible for coding MPO: a point mutation in exon 9 region that resulted in an arginine to cysteine substitution (R499C) (Persad, in preparation). Primer sets used in the recognition of mutations found in both patients are described in (6).

A total of 387 DNA samples served as a comparison cohort in the investigation of a possible link between these identified mutations and the presence of MPO deficiency. Due to difficulties in obtaining samples from a large number of healthy individuals, the control group used consisted of DNA from rheumatoid arthritis samples (21%), hepatitis C samples (41%) and healthy blood donors (38%), none of which had information on levels of MPO activity or superoxide production. Among these samples, three isolated point mutations were found in exon 9, all of which were heterozygous, with two of the mutations being synonymous in nature (1434 G/A, 1478 C/A; the numbers indicate the base position from Adenine of first ATG in mRNA). The third isolated mutation (1464 T/C) would result in an amino acid substitution from isoleucine to threonine. This mutation has not been confirm nor is MPO activity available for this DNA sample. All 387 samples did not possess the non-synonymous mutations found in the MPO deficient cases, thus drawing a more defined postulation that G501S and R499C may be associated with complete MPO deficiency.

Complete MPO deficiency is hereditary and requires the possession of two recessive alleles. This knowledge, coupled with population dynamics in Japan, produced a scenario in which cases with this type of deficiency can serve as sentinels in the detection of clusters of individuals that are heterozygous for these novel mutations.

Both novel mutations, G501S and R499C, have thus far been only found Japanese individuals. An interesting phenomenon, unlike previously identified mutations, is the proximity of these mutations to each other as well as to the histidine at codon 502 that is pivitol to heme binding (2). Based on this research, it is speculated that mechanism of action of these mutations to induce MPO deficiency is via the interruption of heme binding due to the amino acid substitution caused.

ACKNOWLEDGMENTS

This study is supported in part by a grant of Ministry of Health, Labour and Welfare, Japan.

REFERENCES

1. Aratani, Y., Kura, F., Watanabe, H., Akagawa, H., Takano, Y., Suzuki, K., Maeda, N. and Koyama, H. (2000): Differential host susceptibility to pulmonary infections with bacteria and fungi in mice deficient in myeloperoxidase. J. Infect. Dis., 182, 1276-1279.
2. Davey, C. A. and Fenna, R. E (1996): 2.3 A resolution X-ray crystal structure of the bisubstrate analogue inhibitor salicylhydroxamic acid bound to human myeloperoxidase: a model for a prereaction complex with hydrogen peroxide. Biochemistry, 35, 10967-10973.
3. DeLeo, F. R., Goedken, M., McCormick, S. J. and Nauseef, W. M. (1998): A novel form of hereditary myeloperoxidase deficiency linked to endoplasmic reticulum/proteasome degradation. J. Clin. Invest., 101, 2900-2909.
4. Lanza, F. (1998): Clinical manifestation of myeloperoxidase deficiency. J. Mol. Med., 76, 676-681.
5. Nauseef, W. M., Cogley, M. and McCormick, S. (1996): Effect of the R569W missense mutation on the biosynthesis of myeloperoxidase. J. Biol. Chem., 271, 9546-9549.
6. Ohashi ,Y. Y., Kameoka, Y., Persad, A. S., Koi, F., Yamagoe, S., Hashimoto, K. and Suzuki, K. (2004): Novel missense mutation found in a Japanese patient with myeloperoxidase deficiency. Gene, 327, 195-200.
7. Romano, M., Dri, P., Dadalt, L., Patriarca, P. and Baralle, F. E (1997): Biochemical and molecular characterization of hereditary myeloproliferative deficiency. Blood, 90, 4126-4134.
8. Nunoi, H., Kohi, F., Kajiwara, H. and Suzuki, K. (2003): Prevalence of inherited myeloperoxidase deficiency in Japan. Microbiol. Immunol., 47, 527-531.