High-altitude pulmonary edema (HAPE), a potentially life-threatening complication of acute mountain sickness, is postulated to be a noncardiogenic permeability edema caused by acute pulmonary arteriolar vasoconstriction and resultant pulmonary hypertension in response to the hypoxia of rapid ascent to high altitudes.\textsuperscript{1-4} HAPE typically occurs unexpectedly in young, otherwise healthy mountainers. A constitutional susceptibility has been noted for some time\textsuperscript{5,6}, the disease tends to recur in the same individuals on reexposure to high altitude, whereas others appear not to be susceptible at all. The basis for this predisposition to HAPE, whether genetic or environmental, and its underlying pathophysiology remain poorly understood.

High-Altitude Pulmonary Edema
An Immunogenetically Mediated Disease?

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In this issue of \textit{Circulation}, Hanaoka and colleagues\textsuperscript{7} present interesting new evidence that certain human leukocyte antigen (HLA) are increased in Japanese patients with HAPE, especially those with recurrent disease. HLA-DR6 and/or HLA-DQ4 were found to occur significantly more often in Japanese patients with HAPE than in a large number of normal Japanese control subjects. Moreover, the HLA-DR6-positive patients with HAPE had significantly higher pulmonary arterial pressures than did their HLA-DR6-negative counterparts with HAPE. The authors speculate that at least some cases of HAPE are immunogenetically mediated, perhaps through an inherent HLA-associated susceptibility to pulmonary hypertension. They cite several recent studies reporting HLA associations, specifically HLA-DR6, with pulmonary hypertension complicating other diseases, namely scleroderma and human immunodeficiency virus (HIV) infection.\textsuperscript{8,9}

What is implied by the finding of an HLA association with a disease? First, HLA antigens are cell surface molecules encoded by a cluster of highly polymorphic linked genes located on human chromosome 6 termed the major histocompatibility complex, or MHC (Figure).\textsuperscript{10} A significant correlation between one or more HLA antigens (or alleles) and a disease means that there is a significant genetic contribution to disease susceptibility. A large number of human diseases have been associated with different alleles (or HLA antigens) of the MHC\textsuperscript{11} (Figure). Many of these diseases are considered to be “autoimmune” in origin, but, increasingly MHC influences on host responses to infectious and neoplastic diseases are being recognized. Such disease associations are not surprising given that MHC alleles are specific immune response genes, and one’s inherited MHC repertoire largely dictates how the immune system interacts with a hostile environment. Increasingly, however, it is becoming apparent that MHC genes alone cannot account for the genetic susceptibility to the diseases with which they are associated. Most of these disorders appear to be complex genetic traits where the MHC is only one of several (or many) interacting genes, which along with environmental stimuli, ultimately lead to a pathological condition.\textsuperscript{12} The genetic complexity of such diseases as insulin-dependent diabetes mellitus, multiple sclerosis, and systemic lupus erythematosus, to name but a few, is increasingly being recognized as human genome-wide scans for susceptibility genes are being conducted.\textsuperscript{13-15} For most of the complex disorders recently studied, it appears that the MHC contribution to risk constitutes less than 50% of the overall genetic liability. Thus if there is genetic susceptibility to HAPE, HLA is likely to be only part of the genetic equation. Of potential interest in this regard is a recent report of the genetic mapping of a locus on human chromosome 2 predisposing to familial primary pulmonary hypertension.\textsuperscript{16}

The HLA antigens associated with HAPE in this study are MHC class II alleles (Figure). What clues to the underlying pathophysiology of HAPE or pulmonary hypertension might this information provide? MHC class II molecules (HLA-DR, DQ, and DP) are normally expressed on antigen presenting cells, such as macrophages and B lymphocytes, although many other cell types, including endothelial cells, can be induced by various stimuli to express class II MHC molecules.\textsuperscript{17,18} The major function of class II MHC molecules is to present intracellularly processed exogenous or self-peptides to CD4 positive helper or inducer T lymphocytes, thus initiating a specific immune response to those peptides recognized by the T cell as being foreign. Each HLA molecule, on the basis of its polymorphic amino acid composition, possesses its own unique “peptide-binding motif” configured into a groove at the most external end of the molecule.\textsuperscript{17} Only peptides composed of amino acids meeting specific requirements in size and charge can be bound by a specific HLA molecule for presentation to a T cell. Once such an MHC–T-cell–mediated immune response is initiated, it is amplified by the release of a cascade of various cytokines, growth factors, and other inflammatory mediators.\textsuperscript{18}
Might such an immunologic reaction be occurring in the pulmonary arterioles of patients with HAPE, perhaps as a result of the upregulation and expression of HLA-DR6 and/or DQ4 molecules on endothelial cells as a response to hypoxia? Might such a scenario not produce an inflammatory response and/or endothelial proliferation leading to pulmonary hypertension? The authors of this report raise such possibilities, which are certainly viable and testable hypotheses. On the other hand, the HLA associations described here could simply be markers of another non-HLA gene tightly linked to the MHC that plays a role in pulmonary hypertension. After all, hemochromatosis, a genetic disease caused by increased gut absorption of iron and not believed to be immunologic in origin, is linked to the MHC.19

There are many potential pathogenetic implications raised by this study that should lead to new investigations and insight into HAPE specifically and perhaps into other disorders in which pulmonary hypertension plays a central role, such as scleroderma or primary pulmonary hypertension. First, however, these results need to be confirmed, especially in additional populations. There are many vagaries to HLA and disease association studies, especially in the selection of cases and controls, which could lead to false-positive results. No such problems are obvious in this study; however, the Japanese population is, relatively speaking, a genetic isolate with a more restricted pool of HLA alleles than many other ethnic groups. Proven MHC associations with other diseases tend to cross ethnic lines. For some diseases, the same HLA antigen (allele) association is found in many populations, the best example being HLA-B27 and ankylosing spondylitis; but for other disorders, different HLA correlations have been found in various ethnic groups. In the latter situation, the different disease-associated HLA alleles have been found to share similar polymorphic sequences in the antigen-binding cleft (the shared epitope hypothesis).20 Thus it will be of interest to see whether these or other investigators find the same or different HLA alleles associated with HAPE in other ethnic groups.

In addition, a limitation of this study is the use of serological methods to detect HLA antigens. More accurate DNA typing is available for MHC class II alleles that can reveal more specific molecular information about the alleles associated with HAPE. In fact, 60 different HLA-DR6 alleles, which have been redesignated as HLA-DR13 or DR14 alleles on the basis of molecular structure, and two DQ4 alleles are now recognized, each having its own unique sequence and peptide-binding motif, and, importantly, population frequency. Some of these HLA alleles are relatively unique to the Japanese population, whereas others are more ubiquitous in their ethnic distributions. Thus it would be useful for this group of investigators to perform molecular MHC class II typing of their HAPE cases and control subjects, so as to define better the specific alleles that confer susceptibility. Equally interesting would be a comparison of HLA alleles in persons who have developed HAPE versus mountain climbers who have proven not to be susceptible to this disorder. In other HLA-associated diseases, most notably insulin-dependent diabetes mellitus, some HLA alleles show decreased frequencies and have proven to be “protective,” whereas others are increased and tend to be “promotive” of disease expression.20 From a clinical viewpoint, it even might be possible by HLA typing to determine which individuals are at risk for HAPE before they are exposed, so as to provide them the appropriate counseling and/or preventive measures if they choose to ascend to high altitudes.

This interesting study raises more questions than it answers. If subsequent investigations confirm a link between susceptibility to HAPE and MHC alleles, a new dimension will have been opened in the exploration for mechanisms underlying this seemingly nonimmunologic disease as well as potentially other forms of pulmonary hypertension.

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References


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