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Severe Acute Respiratory Syndrome in Association with Human Leukocyte Antigen and Clinical Implications

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Human leukocyte antigen (HLA) is the most polymorphic genetic system in humans, with numerous alleles, and subsequently, various possible combinations [1]. These genes, the products of histocompatibility complex (MHC) [2] are located in the short arm of chromosome 6 at band p 21.3 [2] and are divided into three classes, I, II and III [1]. HLA class I is responsible for coding the molecules HLA-A, -B and -C, present in almost all somatic cells with killing of viral infected targets by class I antigens restrict cytotoxic T-cell (CD8+) function [2] while HLA class II genes code the molecules HLA-DR, -DQ and -DP [1] by presentation of exogenous antigens to T-helper cells (CD4+) or antigen presenting cells (APC) [2]. This polymorphism contributes to the differences in susceptibility to diseases among genetically distinct groups [1]. The molecules coded for by the HLA system are responsible for the antigen presentation [1]. The T lymphocytes that are linked to HLA molecules only recognize antigens by the antigen-specific cell surface receptor-antigens interaction [2], thus the HLA antigens [1] and MCH molecules [2] apparently participate in controlling susceptibility and resistance to various diseases. Some infectious diseases were considered as familial before the finding of the causative microorganism and early twin studies indicated that there was a substantial host genetic influence on susceptibility to diseases such as polio and tuberculosis (TB) [3]. At present, it has been confirmed that human genetic variation demonstrates a major influence on the course of diseases caused by several infectious microorganisms [3].

Itoyama reported that the deletion of the 287 bp *Alu* repeat (D allele) in intron 16 of the angiotensin converting enzyme 2 (*ACE 2*) gene is associated with hypoxemia and diffuse alveolar damage in patients with severe acute respiratory syndrome (SARS) [4] and may protect acute lung injury and respiratory failure [5]. Nevertheless, there may be potential confounders to a genetic association study as the following: 1) the dead patients were excluded from this study, 2) hypoxemia was defined as requiring oxygen supplementation, and 3) only 44 patients were studied [6]. Some HLA subtypes, particularly *HLA-B*0703* and *HLA-DRB1*0301* alleles have been demonstrated to be more prevalent in patients with SARS [7] and those with poorer outcomes [8]. On the other hand, the polymorphism in *ACE II* gene, coding for a functional receptor of the SARS-coronavirus, was not associated with the susceptibility or outcome of SARS [9]. A previous study revealed that *CXCL10(-938AA)* gene is always protective from SARS infection whenever it appears only jointly with either *Fg12(+158T/*)* or *HO-1 (-497A/*)*, whereas *Fg12(+158T/*)* is associated with higher SARS-infection susceptibility unless combined with CXCL10/IP-10(-938AA) which is associated with lower susceptibility [10]. Chan concluded that the *ACE I/D* polymorphism was not directly associated with increasing susceptibility to SARS-coronavirus infection and was not associated with poor outcome after SARS-coronavirus infection [6]. A recent study in Taiwan demonstrated that *HLA-Cw*1502* [11], *-DR*0301* [11], and *-A*2402* [12] alleles conferred resistance against SARS infection. CD209L homozygote individuals [13] and low-mannose-binding-lectin-producing genotypes [14] have been demonstrated to have a significantly lower risk and increased risk of SARS infection, respectively. A previous study among Vietnamese population with SARS revealed that polymorphisms of two interferon-inducible genes, *2′,5′-oligoadenylate synthetase 1 (OAS-1* (G-allele in exon 3 and the one in exon 6)) and *myxovirus resistance-A (MxA)* were associated with SARS infection [15]. The single nucleotide polymorphisms (SNPs) in *MxA* was associated with the progression of SARS [15]. The SNPs in OAS-1 were associated with SARS-coronavirus infection or SARS development [15]. The GG genotype and G-allele of G/T-SNP at position -88 in the *MxA* gene promoter were demonstrated more frequent in hypoxemic group of patients with SARS than non-hypoxemic group [15]. They may be related to the response of SARS patients to interferons (IFNs), particularly those with AA genotype of the A/G-SNP in exon 3 of *OAS-1* may respond to IFN treatment more effectively than those with AG or GG genotype [15]. If SARS re-emerges, IFN could be a promising candidate to treat patients with SARS [16-23]. These findings may contribute to the perception of IFN-induced antiviral response to SARS infection. SARS-coronavirus infection elicited both CD^{4+} and CD^{8+} T-cell responses to the M protein in recovered SARS patients that persisted for a long period of time [24]. This may have significant implications in developing SARS vaccines [24]. A previous study indicated that a *HLA-A*0201*-restricted decameric epitope P15 (S411-420, KLPDDFMGCV) derived from the S protein that was found to localized within the angiotensin-converting enzyme 2 receptor-binding region of the S1 domain could significantly enhance the expression of *HLA-A*0201* molecules on the T2 cell surface [25]. P15 then stimulated IFN-γ-producing cytotoxic-T lymphocytes (CTLs) from the peripheral blood mononuclear cells of former SARS patients and induced specific CTLs from P15-immunized *HLA-A*2.1*-transgenic mice *in vivo* [25]. Significant P15-specific CTLs then were induced by *HLA-A*2.1*-trangenic mice that was immunized by a deoxyribonucleic-acid (DNA) vaccine encoding the S protein [25]. This suggested that P15 was a naturally processed epitope [25]. Thus, P15 could be a novel SARS-associated coronavirus-specific epitope and a potential target for evaluation of candidate SARS vaccines and characterization of virus control mechanisms [25].

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