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Mutant gene susceptibility to Systemic Lupus Erythematosus affects specific ethnic populations

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Systemic Lupus Erythematosus (SLE), a relatively common but complex autoimmune disease, is characterized by the production of a variety of autoantibodies and has a substantial genetic component. SLE is a significant health problem causing about 20,000 mortality rate annually in the United States. Clinical manifestation and disease severity vary significantly among different ethnicities and populations. Recently, researchers at Oklahoma Medical Research Foundation (OMRF) have identified a novel predisposing variant of a gene referred to as Integrin Alpha M (ITGAM) which is strongly susceptibility to SLE. Using Real Time Polymerase Chain Reaction (RT PCR), a total number of 5,753 DNA samples of patients and 6,800 DNA samples of healthy individuals were genotyped with an ITGAM primer. The results depicted that ITGAM gene susceptibility to SLE is associated in multiple populations including Colombians, European Americans, British, Mexicans, Hispanic Americans, and African Americans. However Korean and Japanese populations are unaffected. The objective of this review is to analyze the association between the ITGAM gene and SLE in eight different populations.

Introduction

Systemic Lupus Erythematosus (SLE) is the most common form of lupus and has the highest array of symptoms. It can affect the skin, joints, kidneys, brain, liver, and other organs in the body (1). Symptoms of SLE are associated with prolonged inflammations and vary among individuals. The American College of Rheumatology has established a set of criteria for SLE diagnosis. The symptoms include molar rash, arthritis, dry mouth, auto-antibody production, nephritis, serositis, oral ulcer, neurological disorders, low blood count, lung disease, and photosensitivity (3). Fulfillment of four of the eleven criteria categorizes an individual as an SLE patient. SLE affects both males and females of all ages. However, women have a higher risk of contracting SLE than men (3). SLE is predominant in Asian and African populations. Approximately 1.5 million Americans are living with SLE (1). The causative agents of SLE are centered on both environmental and genetic factors. Researchers are now focused on identifying predisposing genetic variants associated with SLE susceptibility. The purpose of this microreview is to present and analyze the variations in SLE in eight different populations.

Recent Progress

OMRF researchers have identified a prominent genetic variant associated with SLE susceptibility. Hans et al. demonstrated the association between ITGAM and SLE in Hispanic American, European American, British, Colombian, African American, and Mexican populations (2). Furthermore, experimental data from Nath et al. and Sanchez et al. confirmed the strong correlation between the ITGAM and SLE in European American and African American populations (3,4). ITGAM proteins, expressed by ITGAM genes, are located predominantly on the surface of leukocytes and are involved in innate immune defenses. Mutations associated with the ITGAM gene causes the amino acid conversion of two arginines (CGU

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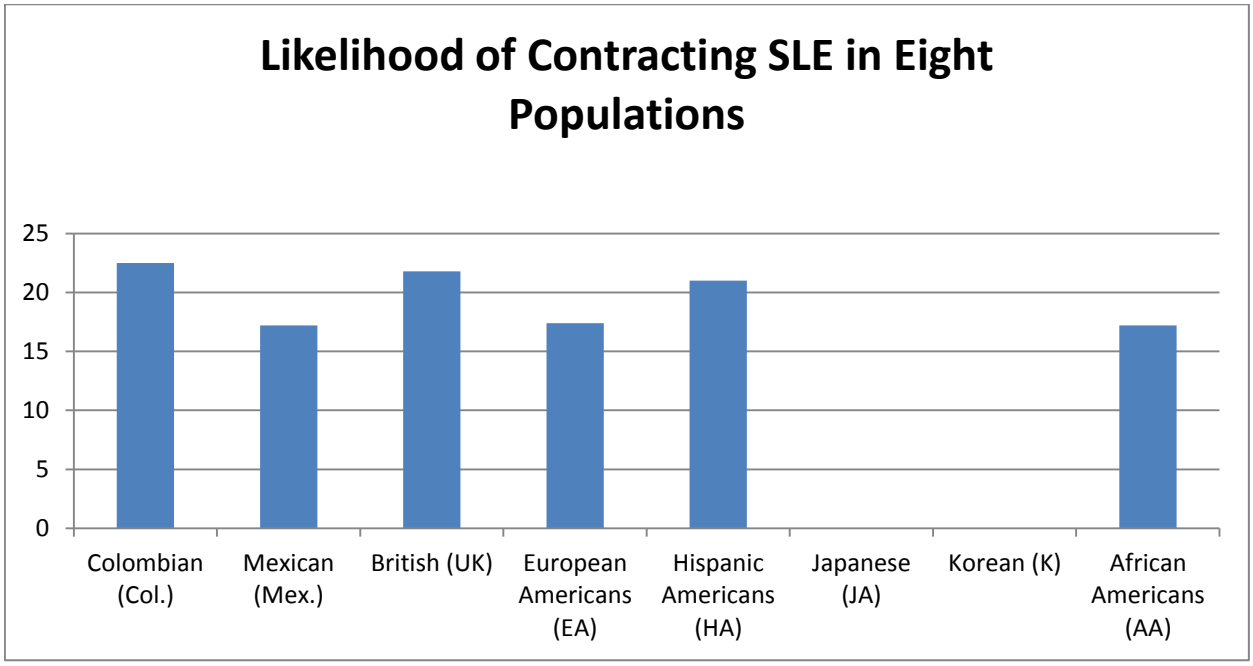

Figure 1 shows the % Odd Ratio to the seven populations genotyped by Hans et al.

and CGC) to two histidines (CAU and CAC) (2). These mutations are caused by the substitution of the nucleotide guanine (G) with adenine (A). This type of mutation is called Single Nucleotide Polymorphism (SNP) (3). Genetic mutations like SNPs are designated with two lower cases and seven numbers. In the case of ITGAM, the risk allele (the adenine (A) nucleotide) which is expressed on mutated proteins is designated as rs1143679. Most SNPs are located within introns. SNPs within exons are of great interest to researchers because they are likely to alter the biological function of the expressed protein (3). Experimental data from Hans et al. demonstrated that SNPs occur throughout the human genome and tend to be genetically stable. However, when SNPs are triggered by other factors like chemicals, radicals, or radiations, they instigate disease progression.

SNPs can also serve as excellent biological markers for gene identification. During genotyping, primers (ITGAM primers) and enzymes (taqman) are used to identify SNPs in mutated genes (2). Using case control analysis, Hans et al. genotyped 2,845 DNA samples of SLE patients and 3,621 DNA samples of healthy individuals from eight different populations (European American, Korean, Hispanic American, Japanese, British, Mexican, African American, and Colombian) (2). Nath et al. genotyped 1,184 DNA samples of SLE patients and 1,155 DNA samples of healthy individuals from European Americans (3). Sanchez et al. genotyped 1,724 DNA samples of SLE patients and 2,024 controls from African American population (4). All samples were genotyped with ITGAM primer and taqman enzyme using RT-PCR (Real Time Polymerase Chain Reaction) to specifically identify the SNPs within the ITGAM gene. After genotyping, data discrimination (process of counting risk allele (A) and non-risk allele (G)) was done on both patients and controls to separate risk allele (A) from non-risk allele (G). The total number of risk allele (A) and non-risk allele (G) in both patients and controls were counted in all the populations and their odd ratios were calculated (2, 3, 4).

Odd ratio is the relative measure of how likely an individual with a mutated gene (ITGAM) will develop SLE as compared to a healthy person (5). In addition to genotyping, Nath et al. studied the apoptosis (programmed cell death) level in SLE patients and controls. To do this, they stained stable cells (cells that are in the quiescent phase, G_0, of the cell cycle and are not multiplying) with antibodies (alexa-700 conjugated antibody of CD11b and annexin-PE and 7-ADD) (3). After Staining, apoptotic level in both unhealthy and healthy cells was analyzed using flow cytometry.

After data discrimination and analysis, it was shown that Korean and Japanese SLE patients had no association with ITGAM (2). Meaning, Japanese and

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Koreans with ITGAM mutations have a negligible rate of contracting SLE. On the contrary, SLE incidence was strongly correlated with Colombian, Mexican, British, European American, African American, and Hispanic American populations (2). Colombians had the highest likelihood of SLE contraction as illustrated in figure 1. Results from Nath et al. and Sanchez et al. also demonstrated 17.2% and 19.7% odd ratios in African Americans and European Americans respectively (3,4). The result of the apoptotic level in healthy and unhealthy cells also showed that mutated genes or risk allele have less apoptosis than non-risk allele (3). In other words, unhealthy cells in SLE patients tend to live longer than healthy cells in SLE patients.

Discussion

These studies are very relevant because they revealed the differences in genetic disease (SLE) in different populations. The results of these studies also suggest that SLE infection is not solely centered on genetic variations but also on some environmental factors like UV radiation, toxic chemical emissions, and smoking. This also explains the reason why people in the most industrialized areas are more susceptible to SLE than people in less industrialized areas. Also, people who live in areas that are constantly exposed to the sun radiation are more vulnerable to SLE than people who live in areas that are less exposed to the sun radiation. Nath et al. demonstrated that people in North Korea, Japanese, and Singapore had the lowest SLE rate in the world (3). The consequences in genetic disease disparity are very profound because it prevents scientist from designing a universal drug for SLE treatment. This means that, different drugs have to be developed for different populations. It also suggests that physicians need to take into consideration their patients' backgrounds before administering treatment.

It also implies that more research has to be done in different populations to identify and characterize the differences in gene mutations associated with SLE. On the issue of apoptosis, it can be deduced that genes or proteins that regulate apoptosis have been turned off due to mutations. Apoptosis is very important in the clearance of infected cells to prevent the spread of diseases to other parts of the body. If apoptosis is impeded, infection spreads uncontrollably to other parts of the body. Another problem that could arise when apoptosis is impeded is the uncontrolled inflammation and the continual production of antibodies. Research on SLE has showed that all the aforementioned side effects that accompany apoptosis inhibition are exhibited in SLE patients (3). To address this situation, extensive research into apoptosis regulation in SLE should be highly considered. Moreover, the expression of innate cells like monocytes, neutrophils, and macrophages that regulate apoptosis and inflammation should be investigated in SLE patients. Finally, on the issue of women with increased susceptibility to SLE, more research needs to be done to investigate the role of estrogen in apoptosis regulation.

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