RESEARCH ARTICLE

THE GENETICS OF SYSTEMIC LUPUSERYTHEMATOSUSIN SAUDI ARABIA

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Abstract

Systemic Lupus Erythematosus (SLE) is a complex multisystem autoimmune disorder. It is characterized by the production of autoantibodies that react against its own tissues, which may lead to immune-complex mediated end organ involvement. There are more than 30 genetic loci in different ethnic backgrounds that have been associated with the risk of developing this disease. The high level of consanguinity in the Saudi population is a risk factor for developing the disease. On the other hand, it provides an opportunity to identify the genetic variations that are associated with the disease. Applying Genome Wide Association Studies (GWAS) and exome sequencing would help to identify these variations. This review provides an opportunity to outline the genetics of Systemic Lupus Erythematosus in the Saudi population.

Introduction:

Systemic Lupus Erythematosus (SLE) is a complex multisystem autoimmune disorder. It is characterized by the production of autoantibodies that react against its own tissues, which may lead to immune-complex mediated end organ involvement. SLE can affect almost any part of the body and it can range from mild to severe. The most common clinical features are kidney diseases, thrombotic problems and skin diseases. SLE is associated with a wide range of autoantibodies, which could help in the diagnosis and monitoring the progress of the disease. The complexity of this autoimmune disease with the diverse clinical manifestations makes the progress of understanding the pathogenesis of SLE quite challenging. Despite these challenges, it has been reported that there are several factors that have roles in the development of SLE such as genetic susceptibility, gender, age, hormonal and environmental factors. (Hersh et al., 2016; O’Neill & Cervera, 2010; Smith & Gordon, 2010)

Based on many epidemiological studies, there are marked differences in the incidence of SLE, which mainly based on the features of the studied populations. (Pons-Estel, Alarcon, Scofield, Reinlib, & Cooper, 2010) In Europe, it is estimated to be 2.2 cases per 100,000 per year while in the US it is estimated to be 7.6 per 100,000 cases per year. (Lopez, Mozó, Gutierrez, & Suarez, 2003) The worldwide prevalence ranges from 10 to 150 per 100,000 per year. (Cervera et al., 1999; Fessel, 1974) These variations are due to the difference in the ethnic groups, as it appears to be higher and more severe in the non-European ancestry. (Borchers, Naguwa, Shoenfeld, & Gershwin, 2010; Sanchez et al., 2012) These differences among ethnic groups are due to the variation in the genetic components that is related to the ethnicity, which leads to the variation in the phenotypic expression of SLE among the individuals who have different genetic background.
For the past few years, significant progress has been done to understand the role of genetics in the pathogenesis of the disease. These studies investigated the mechanism of the disease, the occurrence, the inflammatory process and the reversible organ damage. Despite these studies, there are still significant gaps to understand the pathogenesis of the disease. (Pons-Estel et al., 2010) One of the best methods to understand the genetic roles in the development of the disease is using familial aggregation, which has been reported in many studies in SLE patients.

In Saudi Arabia, many studies emphasize the prevalence of SLE in the Saudi population. The largest study included 624 patients, 551 of these patients have Saudi genetic background. The overall of the clinical and the laboratory investigations were similar to the other populations such as the European population. However, the average age of onset was relatively lower comparing to the age of onset in different groups, which is often associated with a higher risk of genetic role in the development of the disease. (Al Arfaj & Khalil, 2009; Heller, Ahmed, Siddiqqi, Wallrauch, & Bahlas, 2007; Qari, 2002)

The aim of this review is to outline the predisposing factors of SLE in the Saudi population, and to highlight the relationship between the high level of consanguinity and its role in increasing the risk of the development of SLE. In addition, it will provide an overview of the genetic diagnostic methods applied to increase the efficacy of determining the high-risk variations.

**Genetic Pathogenesis of Systemic Lupus Erythematosus:**

The autoantibodies in SLE are directed against the nucleic antigens. It occurs due to abnormalities in the innate immune system, which includes the toll-like receptors beside the malfunctioning of the T-helper, IgG autoantibodies and the gene expression pattern of type-1 interferon. All these elements would have a critical role in developing the production of the autoimmune response. Another studies emphasized the apoptosis process in the pathogenesis of the current disease. (Moulton, Lo, & Tsokos, 2012; Shin, Lee, & Kang, 2011; Tsokos, 2011)

Based on the findings of many studies, there is strong evidence that Lupus is a non-Mendelian complex inheritance and that there is a main role of the polygenic contribution to its pathogenesis. For the past few years, over 30 genetic loci have been identified in different ethnic backgrounds that have been associated with the risk of developing the disease. (Gateva et al., 2009; Guerra, Vyse, & Cunningham Hame Graham, 2012; Harley et al., 2008; Hom et al., 2008; Moser, Kelly, Lessard, & Harley, 2009; Ramos et al., 2011; Yang et al., 2010) Some of these genes have important roles in the immune system including T-cell regulations, B-cell differentiation and production of antibodies and dendritic cells in the antigen presentation process. Some of these genes are identified by certain Single Nucleotide Polymorphisms, SNP’s that are located in certain genes. For example; the IRF5 gene, which is mainly, involved in the expression of type 1 interferon. (Graham et al., 2006; Guthridge et al., 2012) The STATA4 gene, which is an important transcription factor that has a role in the TH1, or TH17 which are associated with the autoimmunity. (Remmers et al., 2007; Shin et al., 2011) Although, some of these genes are common with autoimmunity disorders, they appear to be more specific with the Lupus especially with certain genetic variations located in these determined genes. (Ramos et al., 2011)

Also, many recent studies have shown that the high frequencies in certain genetic variations that are specific in genetic populations are associated with lupus phenotype. For example; certain genetic variations in the ETS1 and WDFY4 genes were found to be specific in the East Asian populations but not in the European populations. (Alarcon et al., 1999; Alarcon et al., 2002; Chung et al., 2009; Richman et al., 2010; Richman et al., 2012; Yang et al., 2010)

**Consanguinity and the development of lupus:**

Generally, it appears that populations with high rate of consanguinity are more susceptible to genetic diseases. Consanguinity increases the overall frequency of inherited diseases including many complex phenotypic diseases such as SLE. The decrease in the heterozygosity due to the impact of the consanguineous marriages leads to increase in the uncommon genetic variations relatively to the other populations groups. (Bittles & Black, 2010; Rudan et al., 2003) In Saudi Arabia, it has been estimated that the prevalence of consanguinity is 52 % with 39.3 % are in first cousin marriages. (al-Abdulkaareem & Ballal, 1998; El-Mouzan, Al-Salloum, Al-Herbish, Qurachi, & Al-Omar, 2007) Another important factor is high inbreeding coefficient due to polygamy, which is common in the Saudipopulation. In one of my published studies, using data from the Human Genome Diversity Panel (HGDP), the inbreeding coefficient was very high ($F_{st}$ = 0.038) comparing to the other population groups. (al-Abdulkaareem & Ballal, 1998; Tian et al., 2009) Also, there are two different studies in Kuwait and Qatar that investigated the genetic substructure of the population of the Arabian Peninsula. The results of these two studies support our findings that the
Saudi population has a very small west-African contribution similar to the HGDP. (Hunter-Zinck et al., 2010; Mohammad, Xue, Evison, & Tyler-Smith, 2009; Nassir et al., 2009) For the reasons stated above, especially the findings in Qatar, it is extremely important to consider the genetic variation in the subgroups as it play a critical role in the development of the genetic diseases such as SLE.

Genetics and Molecular Diagnosis:-
Genome Wide Association Studies (GWAS) method has successfully identified many of the risk alleles for many complex genetic diseases. Basically, this method assesses the association between the genetic variations and the phenotype of interest such as lupus. The challenge for this method requires a large well-characterized sample for the disease, advanced genotyping technology and advanced data managing system. (Guerra et al., 2012; Iwamoto & Niewold, 2016)

For the past few years, the success of exome-sequencing technology has achieved an important advancement. Exome sequencing is highly effective in the process of the high-throughput genetic analysis. This is accomplished by using a set of “exome capture” techniques that specifically target all the exons in the genome. This is due to the nature of the DNA and the coding regions in the human genome, which represents about 1% of the whole genome. This would allow us to approach and determine the genetic variations very easily in a coast effective approach comparing to the whole genome sequencing. (Do, Kathiresan, & Abecasis, 2012; Manolio et al., 2009)

In complex genetic disease such as SLE, determining the genetic susceptibility is quite challenging due to the rare variants with the large genotyping effects. GWAS has successfully identified multiple susceptible genes. However, these genes do not provide any valuable insights to the pathogenesis of the disease other than the additive proportion of the hereditary risk. Therefore, it is important to consider other methods in determining the rare variant that have a significant association with the complex genetic diseases. (Fernandez et al., 2007; Iwamoto & Niewold, 2016; Mohan & Putterman, 2015; Williams et al., 2016)

In SLE, it is extremely important to consider rare variants for the genetic studies for many reasons. First, there are several family studies that have determined that there are certain deficiencies in the complement system (C1q, C2 and C4) that are linked to the SLE phenotype. Another study reported a mutation in the FAS ligand gene that is associated with the SLE. Also, there is another study that has reported a rare mutation in the TREX1 gene that is highly associated with the SLE development. Lately, a recent study in the Saudi population reported that there is a rare loss-of-function mutation in the DNASEI L3 gene that is associated with the recessive familial form of SLE. The later mutation was identified in several families using an autozygome analysis. (Al-Mayouf et al., 2011; Hannema et al., 1984; Lee-Kirsch et al., 2007; Meyer, Hauptmann, Tappeiner, Ochs, & Mascart-Lemone, 1985; Rynes, 1982; Wu et al., 1996)

Therefore, it is extremely important to consider each genetic variation in a population especially for complex genetic diseases such as SLE. Also, it is crucial to consider the social behavior that has an effect in the genetic modifications such as the high rate of consanguinity in the Saudi population. Such information would help to understand the pathogenesis of the disease overall and in the Saudi population in particular. It would help to provide new methods for therapies in addition to stratifying the populations based on the genetic variations for more effective therapeutic interventions.

References:-


