Perspectives in psoriasis, psoriatic arthritis, non-alcoholic fatty liver disease and atherosclerosis in psoriasis

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ABSTRACT

Psoriasis is a disease of chronic systemic inflammation that involves not only the skin, but also internal organs. The frequency of non-alcoholic fatty liver disease was found to be significantly greater in psoriasis patients with increased risk of atherosclerosis and cardiovascular disease. A large number of immune cells are found in psoriatic skin and this immune produce chemokine's, cytokine and inflammatory molecules. The exact role of genetics in psoriasis is still unclear and an overlap between some psoriasis loci and those identified in other autoimmune or inflammatory diseases has been reported.

Key words: Psoriasis; Genetics; Arthritis; Fatty liver; Atherosclerosis; Obesity

INTRODUCTION

Psoriasis affects 2–3% of the European population. It is common found less in an individual of Asian descent (0.1% or less) and is exceedingly rare in Africa [1]. Large number of immune cells are found in psoriatic skin and this immune produce chemokine’s, cytokine and inflammatory molecules. The genetics basis of psoriasis has been unclear yet, whether they reflect defects of the immune system or of the skin. It has been reveal by Genome-Wide association that genetic susceptibility factors which play a role in the formation of immune cell found in psoriasis or in the proliferation epidermal and skin barrier formation. Furthermore, as many as 10-30% of patient with psoriasis develop an inflammatory arthritis which cause the destruction of joints if it is not properly treated in aggressive manner. It is now universally acknowledged that psoriasis and Psoriatic arthritis are consistent with a multifactorial pattern of inheritance.

Pre-Genome Wide Association Studies in Psoriasis Genetics

The earliest genetic studies revealed association with human leukocyte antigen (HLA) class I alleles, and the strongest association was with the HLA-C allele. Approximately 10 genome-wide linkage scans, primarily with polymorphic microsatellites, lead to the identification of over 20 possible linked regions. Some of which are: PSORS1 on 6p21.3 [2], PSORS2 on 17q [3], PSORS3 on 4q [4], PSORS4 on 1cenq21 [5], PSORS5 on 3q21 [6], PSORS6 on 19p [7], PSORS7 on 1p [8], and PSORS9 on 4q31 [9].

Psoriasis genetic associations

Inflammatory genes

GWAS studies have been performed primarily in populations of European and Asian till date, and the most highly significant associations that are found in both population are with SNPs from the MHC class I region that encodes the HLA molecules HLAA, HLAB and HLAC. The psoriasis-associated with SNPs are nearly to the gene encoding HLAC [10-12] and this have form several risk Gene that are HLAC [10-12], IL12B [13], IL23RA, IL23RB, TNFAIP3, TNIP1 [11], IL22 [10], SLG12A8 [14], ZNF313 [5], HBD [15] and LCE [12]. Additional two independent MHC locihave also confer the risk of psoriasis in both European and Chinese populations. One of the Mhc
loci is found within the chromosome 6 open reading frame 10 (c6orf10), and the second locus is 30kb in size centromeric of HLAB and 16 kb telomeric of the MHC class I polypeptide related sequence A gene, MICA [16].

**Barrier development genes**
There is a new evidence that skin barrier functions may also plays a role in susceptibility to develop psoriasis. The Epidermal Differentiation Complex lies on human chromosome 1q21, spans 2 Mb and encodes at least 45 genes that play a role in the generation or maintenance of the epidermis. Many genes of the Epidermal Differentiation Complex are upregulated in psoriatic lesions suggesting the underlying alterations in coordinate regulation of genes of this complex [17,18].

**Psoriasis risk factors shared by other autoimmune or inflammatory diseases**
To date only one genome-wide scan has been completed in psoriatic arthritis (PsA), and this study localized a candidate region on chromosome 16q. Association of psoriasis and PsA with alleles in the MHC region has been recognized for over three decades, and presently there are plethora of association studies for both of these disorders with HLA alleles. Overlap between some psoriasis loci and those identified in other autoimmune or inflammatory diseases has been reported. The same variant of IL23R is associated with Crohn’s disease, PsA, and ankylosing spondylitis [10,19,20]. This is consistent with the role of IL23R in Th17 cell activation and with the fact that these cells have a pathogenic role in several other inflammatory diseases including Crohn’s disease and multiple sclerosis [21].

**Genetics of Psoriatic Arthritis**
Approximately 25% of patients also develop psoriatic arthritis (PsA), a common, debilitating auto-immune disease belonging to the family of spondyloarthritides [22]. HLA alleles have been associated with both psoriasis and PsA [23]. HLA-B13, -B16, and its splits -B38 and -B39, B17 and Cw6 were described as being psoriasis associated arthristis or not [24]. The possible biologic significance that are associated with psoriasis is recognize to be nine genes and this genes include HLA-B, HLA-C, PSORS1G3, OTF3, HCR, SPR1, SEEK1, corneodesmosin (CDSN), and TNF-α [25-31]. Genomic DNA sequences and recombinant haplotypes suggested that HLA-Cw*0602 is the allele diseases at PSOR1. It has been noted that gene within this region have been investigated with PsA [32]. A study from a metaphysis shows that there is an association between TNF-α -238 polymorphism and PsA [33]. Therefore, susceptibility locus for PsA may lie more centromeric to that of psoriasis and these is closer to HLA-B. PsA associated studies has recognized that a numbers of genes outside the chromosome 6p are IL-23R, IL-1, and killer-cell immunoglobulin like receptor genes [33,35,36]. The study of GWAS on PsA has not been formally shown. However GWAS on psoriasis subjects of European ethnicity, there were three loci that is associated with PsA when compared to normal controls (HLA-C, IL-12B, and TNIP1). It has been shown that between PsA and psoriasis alone, there is a statistical significant differences at three loci (HLA-C, IL-12B and IL-23R). The loci that more strongly associated with psoriasis alone are HLA-C and IL-23R, and IL-12B with PsA [11]. Another GWAS identified a novel PsA locus on chromosome 4q27 that harbors the interleukin 2 (IL-2) and interleukin 21 (IL-21) genes [10].

**Psoriasis, Non-alcoholic Fatty Liver Disease and Obesity**
Obesity is a significant and growing problem worldwide and it has also been linked to the onset of psoriasis. In the Nurses’ Health Study II, increased body mass index (BMI) correlated with an increased incident rate of psoriasis, and hip circumference and waist-
to-hip ratio were all associated with a higher risk of incident psoriasis [37]. The psoriasis that are associated with metabolic syndrome and increase risk of cardiovascular disease are non-alcoholic fatty liver disease (NAFLD) and chronic plague. NAFLD is the hepatic manifestation of metabolic syndrome, with its key component being visceral obesity [38]. The prevalence of NAFLD is 10–24% of the general population worldwide, increasing to 57.5–74% in obese individuals. The mortality was increased in patients with NAFLD compared with the general population and in the National Health and Nutrition Examination Survey (NHANES III) study, the NAFLD cohort had both increased overall mortality and liver-related mortality compared with individuals without liver disease [39]. While in most patients, NAFLD does not progress beyond simple steatosis, it may progress to Non-Alcoholic Steato-Hepatitis (NASH). The prevalence of NASH also correlates with obesity, with waist-to-hip ratio and abdominal obesity reported to be predictors of NASH. Diagnosing patients with NAFLD and identifying those with NASH is challenging, as they are generally asymptomatic. Clinical presentation and current radiological modalities may not be reliably to diagnose NASH, while non-invasive biomarkers remain to be fully established. The frequency of NAFLD was found to be significantly greater in psoriasis patients (47%) vs. matched controls (28%). Indeed, the relationship strengthened with increasing psoriasis severity [40]. Collectively, these observations support the early recognition of NAFLD in psoriasis patients, the results of which may dictate treatment regimens to avoid potentially liver toxic therapies, such as methotrexate. Positive correlations have been reported among cumulative methotrexate dose, risk factors (e.g. obesity) and progression of NAFLD. Gram for gram, psoriasis patients are also twice as likely to develop hepatic complications from methotrexate as a patients with rheumatoid arthritis (RA). The prevalence of obesity and being overweight are increasing in Saudi Arabia reaching 35.5% [41]. Thus, reduction of weight are of considerable importance to public health [42].

Psoriasis Inflammation and Endothelial Dysfunction

Psoriasis inflammation may act independently in promoting an accelerated atherosclerosis by eliciting endothelial dysfunction and oxidative stress similarly to other chronic inflammatory systemic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Crohn’s disease [43]. Psoriasis inflammation is characterized by high levels of TNF-α, IFN-α, IFN-γ, IL-1, IL-6, and IL-17, which are released by keratinocytes and inflammatory cells infiltrating skin and joint tissues [44]. These cytokines could also boost several proatherogenic functions of the liver, adipose tissue, and skeletal muscle, including liver production of C-reactive protein (CRP), dyslipidemia, production of proinflammatory adipokines, and insulin resistance, generating lipid abnormalities and culminate in the development of NAFLD and resulting in endothelial dysfunction. Cytokines can also mediate several metabolic effects that can in short term result to inappropriate response to injury or infection, but on a chronic basis, its prove detrimental by accelerating the development of atherosclerosis and predisposing to thrombosis. Endothelial dysfunction is the critical early step in the process of atherogenesis, and it is commonly investigated by measuring arterial stiffness. Arterial stiffness has been found increased in psoriasis patients independently of the other cardiovascular risk factors [45,46].

NAFLD and Cardiovascular Disease

Giving the fact that NAFLD is usually an asymptomatic disorder, it is often unrecognized in everyday clinical practice. Therefore, patient with NAFLD have no symptoms, and aminotransferase levels which are used as a marker of liver damage, are within normal values in almost half of all patients. Type 2 diabetes (T2DM) is strongly associated with NAFLD and has been linked to increased cardiovascular disease (CVD) risk. It is characterized by insulin resistance and mitochondrial dysfunction. Indeed, there is a gradual increase in the severity of insulin resistance in the range of NAFLD which may contribute to the evolution of liver damage. Also, it is associated with an increased risk of kidney disease in subjects with multiple CVD risk factors and tends to be considered as an independent CVD marker [47]. Diabetes, dyslipidemia, hypertension and CVD coexist more frequently in individuals with NAFLD [48]. Hepatic steatosis has been linked to visceral adiposity, low serum HDL, high serum triglycerides, and pro-inflammatory biomarkers such as CRP and has been shown to be associated with an increased risk of cardiovascular events independent of these other variables in diabetic patients [49].

PNPLA3 Gene polymorphism and Carotid Atherosclerosis

Identifying the underlying genetic factors for any disease locus relies intimately on data collected through
genome-wide association (GWA) initiatives. These studies survey genotypic-phenotypic associations among large population based cohorts [50]. Recent GWAs have isolated a number of single nucleotide polymorphisms (SNPs) linked to either increased hepatic fat content or elevated liver enzymes or coronary heart disease [50-52]. The patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene locus on chromosome 22 indicate one of the most investigated polymorphism in fatty liver diseases. Heterozygote carriage of the I148M minor allele in particular is associated with more hepatic triglyceride levels in 2 mixed population studies conducted in North America and Europe [51,53,54]. PNPLA3-148M homozygotes showed an even greater propensity for hepatic fat accumulation; triglyceride levels were two-fold higher in this group compared to non-carriers [1]. The variant allele surfaced most frequently in Hispanic persons, followed by those of European descent and least often in African Americans. On the contrary, a minor variant referred to as PNPLA3-S4531 was commonly detected in African Americans and furthermore associated with a lower hepatic fat burden in these individuals. The exact mechanism by which the PNPLA3-148M variant exerts its effects remains largely unknown. In humans PNPLA3 expresses most abundantly in the liver and to a larger extent in obese individuals [55]. Evidence from in vitro experiments suggests that PNPLA3 displays both lipolytic and lipogenic activity [56,57]. The PNPLA3-148M variant may promote fat accumulation by limiting triglyceride hydrolysis [55]. However, to what degree PNPLA3 participates in triglyceride hydrolysis remains controversial [55,57-59]. Targeted PNPLA3 deletion for example did not influence triglyceride hydrolysis or metabolic functions in animal models [57]. A marked up-regulation of PNPLA3 in response to feeding has led investigators to alternatively propose a function for PNPLA3 in lipid remodelling rather than catabolism [60]. Further functional studies should help assess the precise physiological role of PNPLA3 in hepatic lipid metabolism. Despite the strong association between fatty liver and both insulin resistance and glucose intolerance both studies which evaluated a Southern European population failed to find an independent association between PNPLA3-148M and features of metabolic syndrome including fasting serum insulin, HOMA-IR, triglycerides, total cholesterol, or HDL-cholesterol [14,17]. The Dallas Heart Study reported a similar finding [51].

Different lines of evidence, including cross sectional and prospective studies, showed that NAFLD patients are at high risk of cardiovascular dysfunction/events, identifying conventional cardiometabolic alterations and the extremity of liver damage as risk factors [61,62].

**GCKR Functional Gene Variants and Atherosclerosis**

Glukokinase (GCK) is the most overriding glucose enzyme (phosphorylating enzymes) that is present in the liver and Pancreatic islets, is also known as islets of Langerhans, which have small clusters of cells scattered throughout the pancreas. Pancreatic islets contain several types of cells, including beta cells that produce the hormone insulin which act as physiological glucose-sensor. This regulatory protein (Glukokinase regulatory protein) present in pancreatic islets and the liver form an inactive heterodimer. The GCKR that is 27 kb is located on chromosome 2p23 that contain encodes a 68 kDA protein 19 exons. The association study of wide genome has showed that the common functional variants of the GCKR gene are associated with insulin levels, fasting plasma glucose, and both serum triglycerides and low/high-density lipoprotein cholesterol levels, thus, single nucleotide polymorphisms [63-65]. The variant that is common in GCKR gene has been reported to be in association with increase in more CRP levels, which indicates a good atherosclerotic marker [66].

**IN CONCLUSION**

Psoriasis is a disease of chronic systemic inflammation, it therefore recommended to reduce the risk of associated comorbidities such as psoriatic arthritis, NAFLD and CVD by early recognition and diagnosis. Chronic inflammation, mediated by either proinflammatory adipokines or skin-derived cytokines, may contribute to fatty liver disease development by increasing insulin resistance which in turn promotes hepatic lipid accumulation in patients with psoriasis and CVD risk. Further studies are needed to better understand the role of genetics and inflammatory markers. It is also essential to screen for comorbidities and hepatic ones in patients with psoriasis.

**ABBREVIATIONS**

HLA: Human leukocyte antigen  
GWA: Genome-wide association  
SNP. Single nucleotide polymorphisms  
MHC: Major histocompatibility complex  
PS: Psoriasis  
PsA: psoriatic arthritis
CDSN: Corneodesmosin  
IL: Interleukin  
BMI: Body mass index  
NAFLD: Non-alcoholic fatty liver disease  
NHANES: Nutrition Examination Survey  
NASH: Non-alcoholic steatohepatitis  
CRP: C-reactive protein  
T2DM: Type 2 diabetes mellitus  
CVD: Cardiovascular disease  
HDL: High density lipoproteins  
PNPLA3: Patatin-like phospholipase domain-containing protein 3  
GCK: Glucokinase  

Statement of Human and Animal Rights  
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent  
Informed consent was obtained from all patients for being included in the study.

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