Section: Skin & VD

Original Research Article

GENETIC ASSOCIATION WITH ENDOPLASMIC RETICULUM AMINOPEPTIDASE1 (ERAP1) IN PSORIASIS PATIENTS: A CASE CONTROL STUDY IN A TERTIARY CARE CENTRE IN MITHILANCHAL, INDIA

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Abstract

Background: This work reveals striking genetic heterogeneity among patients with early-onset psoriasis and stresses the importance of detailed stratification in future genetic studies in psoriasis. **Materials and Methods:** A total of 123 patients with PsV (Psoriasis Vulgaris) were recruited from Darbhanga Medical College and Hospital, laheriasarai, Darbhanga from January 2022 to December 2023. Healthy individuals without systemic autoimmune disorders and skin lesions were enrolled as control group. Current study was approved by the Ethic committee of the Hospital. Informed consent was signed by each participant. The PCR primers for ERAP1 gene rs26653 and rs27524 polymorphisms were design educing Primer Premier 5.0 (Table1). ERAP1 gene polymorphisms were amplified through PCR and sequenced adopting direct sequencing method. All of the calculations were performed with PASW18.0. All the tests were 2-tailed, and P-values <.05 were considered as statistical significance. **Result:** Characteristics of subjects Age and gender showed no significant difference between case and control groups. As for the age of onset, it was below 40 years in 105 (85.71%) patient s(EO-PsV) and over 40 in 18(14.59%). The frequencies of the GG, GC, and CC genotypes of rs26653 SNP were 21.57%, 55.15%, 27.38% in patients with PsV, and 39.40%, 43.82%, 17.88% in healthy controls. Besides, the CC genotype and C allele were significantly more frequent in patients with PsV than in healthy controls, indicating that they could significantly increase PsV susceptibility. **Conclusion:** Rs26653 SNP may be positively correlated with PsV susceptibility Indian population. Several limitations in present study should be stated.

INTRODUCTION

Psoriasis is a chronic skin disease of unclear aetiology and pathogenesis which is characterized by an inflammatory infiltration in dermis and epidermis, proliferation of epidermal cells – keratinocytes which clinically manifests with the formation of erythematosquamose papules, and is often accompanied by the engagement of joints and nails in the process of inflammation (Hartmane I. 2004; Bowcock A. M. et al. 2005; Lowes M. A. et al. 2007; Albanesi C. et al. 2004; Van de Kerkhof P. C. et al. 1996; Luba K. M. et al. 2006).[1-6] The results of multiple studies and the efficiency of certain treatment methods show that the development of a psoriatic process in the skin is more likely to be linked with the abnormalities in functions of T lymphocytes and the inflammation mediators excreted by them rather than with a primary epidermal pathology (Dong C. et al. 2001; Santamaria-Babí. L. F. 2004; Vissers W. H. et al. 2004; Woods A. C. et al. 2006; Nickloff B. J. et al. 1999).[7-11] The prevailing Th1 lymphocyte subpopulation of the inflammatory infiltrate secrete the number of cytokines which then induces the proliferation of keratinocytes and activates dermal endothelium and other inflammatory cells – macrophage, neutrophil and cytotoxic T lymphocyte in the skin (Romagnani S. T. et al. 2006; Nestle F. O. et al. 1994).[12,13] TGF-β1 and EGF dictate the proliferative processes in the skin and participate in the regulation of immune responses. The role of these growth factors in the pathogenesis of psoriasis is still not fully explored but diametrically opposed data on their effect on the development of psoriasis are often found in scientific literature (Li A. G. et al.

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2004; Kane C. J. et al. 1990; Pasonen Seppänen S. et al. 2003; Kobayashi T. et al. 1998; Neirinckx R. D. et al. 2006).[14-18] TGF- 6 β1 and EGF were determined in the serum of 200 psoriasis patients and their concentration changes before and after 2 weeks treatment were compared. A recent genome-wide association study reported evidence for a genetic interaction between the HLA-C and endoplasmic reticulum amino peptidase 1(ERAP1) genes (combined P¼6.95_10_6), with the ERAP1-associated synonymous single-nucleotide polymorphism (SNP) (rs27524) affecting psoriasis susceptibility only in individuals carrying the HLA-C risk allele (Strange et al.,2010).[19] ERAP1 has an important role in MHC class I peptide processing in the endoplasmic reticulum and has also been shown to be involved in shedding of pro inflammatory cytokine receptors, altogether suggestive of a potential involvement in the pathogenesis of psoriasis (Cui et al., 2003a; Hearn et al., 2009; Haroon and Inman, 2010).

Here in we present a cohort of psoriasis patients stratified for phenotype (plaque and guttate) and age at onset. The age groups were chosen in an attempt to reflect biologically significant transitions. In particular, we aimed to explore the impact of puberty. Setting the limit for puberty at 10 years represents a stringent approach (Parent et al., 2003). Here in we report a strong association of ERAP1 SNP rs26653 not restricted to HLA-C*06:02-positive individuals. Stratification for age at onset revealed that ERAP1 association was confined to cases with disease onset between 10 and 20years (odds ratio (OR) 1.59, 95% confidence interval (CI): 1.28–1.98, P¼0.00008), whereas prepubertal children with onset between 0 and 9 years lacked association (OR 1.24, 95% CI: 0.93–1.65, P¼0.4). This work reveals striking genetic heterogeneity among patients with early-onset psoriasis and stresses the importance of detailed stratification in future genetic studies in psoriasis.

MATERIALS AND METHODS

Study Subjects

A total of 123 patients with PsV (Psoriasis Vulgaris) were recruited from Darbhanga Medical College and Hospital, laheriasarai, Darbhanga from January 2022 to December 2023. Healthy individuals without systemic autoimmune disorders and skin lesions were enrolled as control group. Healthy controls were matched with the cases in both age and gender. The current study was approved by the Ethic committee of the Hospital. Informed consent was signed by each participant. Demographic and clinical characteristics were recorded through questionnaire.

Genotyping

Blood samples were collected from each subject and processed with EDTA. Then genomic DNA was extract educing DNA extraction kit (TIANGEN, Beijing, China) according to the manufacturer's specification. The PCR primers for ERAP1 gene rs26653 and rs27524 polymorphisms were design educing Primer Premier 5.0 (Table1). ERAP1 gene polymorphisms were amplified through PCR and sequenced adopting direct sequencing method.

Statistical Analysis

The conformity to Hardy–Weinberg equilibrium (HWE) was examined to detect the representativeness of the subjects. Genotype and allele frequencies were calculated through direct counting. Correlation between ERAP1 gene polymorphisms and PsV susceptibility was assessed using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All of the calculations were performed with PASW18.0. All the tests were 2-tailed, and P-values <.05 were considered as statistical significance.

RESULTS

Characteristics of subjects Age and gender showed no significant difference between case and control groups. As for the age of onset, it was below 40 years in 105 (85.71%) patient s(EO-PsV) and over 40 in 18(14.59%).

Perception of caregiver burden found in the present Cases (LO-PsV). Among the patients, the onset age and disease duration were 30.52±9.14 and 11.32±6.19 years, respectively. Only 17 patients had the family history of PsV, while none of the controls had the family history .Association of ERAP1 gene SNPs with the susceptibility to PsV Genotype distributions of ERAP1 gene rs26653 and rs27524 SNPs did not deviate from HWE in control group revealing that the controls were representative for general population. The frequencies of the GG, GC, and CC genotypes of rs26653 SNP were 21.57%, 55.15%, 27.38% in patients with PsV, and 39.40%, 43.82%, 17.88% in healthy controls. Besides, the CC genotype and C allele were significantly more frequent in patients with PsV than in healthy controls, indicating that they could significantly increase PsV susceptibility. As for rs27524 SNP, its AA genotype and A allele exhibited higher frequencies in patients with PsV than in the controls, but the difference was not significant (29.08 vs. 24.09, P=.086). While the frequencies of the GG and GA genotypes and the G allele were similar between case and control groups (P>.05 for all). So rs27524 SNP might have no significant association with PsV risk.

Allele of rs27524 SNP showed a tendency toward being related to EO-PsV, which might become significant in a larger sample size. Subgroup analysis based on gender revealed no significant association of rs26653 and rs27524 SNPs with PsV susceptibility, either in males or in females. Subgroup analysis based on family history showed that rs26653 CC genotype was distinctly correlated with enhanced PsV risk in the patients with family

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history, Such association was also observed for rs26653C allele (P=.029, OR=1.644, 95% CI= 1.034–2.059). No obvious association was detected between rs26653 SNP and PsV risk in patients without family history. While rs27524 SNP had no significant association with PsV risk in either of the subgroups with and without family history (P>.05).

Table 1: Primer sequences of ERAP1 gene polymorphisms

rs ID	Region	Allele	Varition	Primer sequence	Anneling (c)
rs26653	Exon2	C/G	Arg127Pro	F: 5-GAGGCAAATTGCTAGATCGGA-3	55
				R: 5-GCTGGTCGGCTTTGGTGA-3	
rs27524	30UTR	A/G	None	F: 5-GGAGAGAGGCTATCGGAAGAACCC-3	60
				R: 5-CCGAAAGATTGCCAGCATAGTGAA-3	

DISCUSSION

Disorders in immune system in regard to skin cells (especially the excessive and rapid growth of epidermal layer during wound repair) may lead to skin diseases, including PsV. Presently, PsV has been regarded as a complex and multifactorial disease, and its pathogenesis is reportedly associated with hereditary factors, immune or inflammatory factors, life style, and other environmental factors. Hyper-proliferative and infiltrating keratinocytes interact with activated immune cells and thus result in PsV onset. A variety of immune cells play important roles in PsV pathogenesis. These immune cells, moving from dermis to epidermis, secrete cytokines, and participate in different immune pathways.[10] Various immune pathways have been proved to be involved in PsV, including TH17 pathway, passive immunity pathway, and nuclear factor kappa B (NF-kB) subunit 1 and interferon signalling pathways. Immune or inflammatory genes involved in these pathways may be associated with the occurrence of PsV. The ERAP1 could regulate the link between peptides and major histocompatibility complex (MHC) class I molecules, such as HLA-C. It has been reported that mutations in ERAP1 gene are correlated with PsV susceptibility only in people harbouring certain alleles of the HLA-C.[21] GWAS and meta-analysis found that mutations in ERAP1 gene were distinctly related to the development of PsV. At the same time, the degree of increase in disease risk by its C allele was up to 1.403 times. These findings partly accorded with those from a previous study by Lysell et al which found that rs26653 was strongly correlated with psoriasis susceptibility in their studied population. Our subgroup analysis found significantly enhanced disease risk related to rs26653 CC genotype for EO-PsV, and its C allele elevated the disease susceptibility by 1.443 folds for EO-PsV. However, no significant association was observed for LO-PsV. We failed to find any significant association for ERAP1 SNPs with PsV risk, in either male or female subgroup. While the CC genotype and C allele of rs26653 SNP increased PsV risk in patients with the family history by 1.294 and 1.664 times, respectively. Besides, rs26653 was obviously associated with the response to ustekinumab therapy among patients with psoriasis. Minor allele of rs27524 SNP had higher frequency in patients with PsV than in healthy controls. There was a tendency for the relationship of ERAP1 gene rs27524 SNP with increased PsV risk, though without statistical significance. No significant association was discovered of rs27524 SNP with PsV types, genders, or with or without family history. Our findings accorded with those from a previous study by Lysell and colleagues in a Sweden population. But divergence still exists. For instance, Yang et al suggested that rs27524 SNP was distinctly associated with PsV risk. In addition, GWAS demonstrated that rs27524 A allele was significantly associated with classical Hodgkin lymphoma, another inflammatory disease.

CONCLUSION

Rs26653 SNP may be positively correlated with PsV susceptibility Indian population. Several limitations in present study should be stated. First of all, sample size was not large enough that might reduce analysis power. Secondly, only 1 ethnic group was included in our study, and this situation might limit the application range of our results. Thirdly, the results were not adjusted for potentially confounding factors. Additionally, gene–environment interactions were not taken into account in the current study. Therefore, well designed studies with enlarged sample size and ethnicity number are needed to further verify our findings in the future.

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