

GENETIC BACKGROUND OF PSORIASIS

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Abstract

Psoriasis is a common autoimmune disease that affects the skin. The main cause of psoriasis is still not known, although along with some environmental factors genetics plays crucial role in development of disease. Many genes are susceptible in development of psoriasis like TNF α , IL 23, IL12, HLA-Cw6, IL12B, IL23R, and LCE3B/3C. The prevalence of psoriasis is 2-3% worldwide. Psoriasis is a chronic inflammatory disease which was having bad or worst effect on health. The environmental factors that trigger the immune system are stress, low humidity, drugs (beta-blockers, lithium, antimalarial agents, and interferon), smoking, and obesity. However some studies showed that males are more affected as compared with female. In India, the prevalence rate is about 0.44-2.8%. There are plenty of genes which plays crucial role developing body's immune system among these, CARD14 gene gives instruction for proteins which turn on or off nuclear factor- kappa- β (NF- κ B). NF- κ B regulates the activity of multiple genes, including gene that control the body's immune responses and inflammatory reactions. One of the major genes like CARD14 found in body tissue and also in skin tissue whose activity is under control of NF- κ B. Hence, mutation in CARD14 having broad spectrum influence on developing disease. Recent report showed that CARD 14 gene was the first gene which directly link to the most common form of developing psoriasis. Among all the psoriatic diseases plaque, nail & guttate psoriasis has emerged the major health problem worldwide. In the present review article, we describe the impending role of genetics in increasing psoriatic disease, & their molecular pathway of pathogenic inflammation.

Keywords: Psoriasis, Genetics, CARD14, HLA, Autoimmune

1.1. Introduction

Psoriasis is a skin disease which was immune mediated, genetically determined common dermatological and chronic inflammatory skin disease. The chronic disease results of few scattered red & scaly plaques all over the body surface (Hani A. AlShobaili et. al., 2010). The main cause of psoriasis is still not known, although along with some environmental factors genetics plays crucial role in development of disease (Rocio Prieto-Pérez et. al., 2013). This chronic non-communicable, painful, disfiguring & disabling disease is still not having permanent cure (WHO Library).

The prevalence rate of psoriasis is about 2-3% world-wide (Rocio Prieto-Pérez et. al., 2013). Psoriasis is autoimmune disease affects skin lesion, mostly to nails & elbow (Hani A. AlShobaili et. al., 2010). Psoriatic patients are at high risk of cardiovascular disease along with NCDs (WHO Library). One-third of population based studies shown that it is genetic disorder, with majority of MHC and T cell genes involvement. Psoriasis is strongly a hereditary disease some gene loci have been associated with it but how those gene work together is still under research. Genetic studies regarding psoriasis are very much important to identify their molecular mechanism and to design the potential drug (Nestle FO, Kaplan DH, Barker J, 2009). Nine different loci on chromosomes have been identified of having association with psoriasis. Mutation in these loci leads to psoriasis along with some autoimmune disease and they named as psoriasis susceptibility 1 through 9 (PSORS1 through PSORS9). PSORS1 and PSORS 2 are the two main loci on chromosomes which plays crucial role in developing psoriasis. Mutation in one of these locus causes association of different genes with psoriasis. Genes like, IL 23, IL12, HLA-Cw6, IL 23R, IL12B, LCE3B/3C and TNF α , are associated with PSORS1 loci (Nestle F O., Kaplan D., Barker J, 2009).

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the major determinant, which accounts for about 35–50% of psoriasis heritability. It encodes the skin protein which controls genes that affect the immune system or overabundant with psoriasis (Smith et al., 2016). Genes like *HLA-C* variant *HLA-Cw6*, which encodes an MHC class I protein; *CCHCR1* are having strong association with psoriasis vulgaris and these are located in *PSORS1* locus (47). *CARD14* gene gives instruction for proteins which turn on or off nuclear factor- κ -B (NF- κ B). NF- κ B regulates the activity of multiple genes, including gene that control the body's immune responses and inflammatory reactions. One of the major genes like *CARD14* found in body tissue and also in skin tissue whose activity is under control of NF- κ B. Hence, mutation in *CARD14* having broad spectrum influence on developing disease. Recent report showed that *CARD14* gene was the first gene which directly link to the most common form of developing psoriasis. The *CARD14* gene is located in the *PSORS2* locus. A rare mutation in the gene encoding for the *CARD14* causes plaque psoriasis (the most common form of psoriasis) (Nestle F.O., Kaplan D.H., Barker, 2009). Five different types of psoriasis have been reported namely plaque, guttate, inverse, postural, and erythrodermic (WHO Library). The environmental factors that trigger the immune system are stress, low humidity, drugs (beta-blockers, lithium, antimalarial agents, and interferon), smoking, and obesity. However some studies showed that males are more affected as compared with female. In India, the prevalence rate is about 0.44-2.8% (Devinder Mohan Thappa and Malathi Munisamy, 2017). Global report shows that prevalence rate of psoriasis is 0.09%- 11.4% (WHO Library).

Types of Psoriasis

Globally five different types of psoriasis have been reported. Based on type of skin lesion, location, the age on onset and course of disease psoriasis disorder mainly classified in to five different types (Fig.No1.) (WHO Library).

Plaque Psoriasis- Plaque psoriasis is the most common type of psoriasis, cases 90% to other types of psoriasis. It is also called as psoriasis vulgaris. Silvery scaly plaques covers coalesces and larger area of skin. Common symptoms include trunks, Scalp & exterior surface of limbs (Fig.No1.) (11).

Guttate Psoriasis- Guttate psoriasis most commonly seen in children or adolescents with characteristic future of small erythematous plaques. Often triggered by group A streptococcal infections of tonsils (Fig.No1.) (Ortonne J et. al., 2009).

Inverse Psoriasis- It affects intertriginous location of skin and also called as flexural psoriasis (Fig.No1.) (Ko H.C et. al., 2010).

Pustular Psoriasis- Pustular psoriasis is either localized or generalized with characteristic future of multiple coalescing sterile pustules. Localized phenotype can be described as psoriasis pustulosa palmoplantaris (PPP) and acrodermatitis continua of Hallopeau. Both of them affect the hands and feet; PPP is restricted to the palms and soles. Generalized Pustular psoriasis presents with an acute and rapidly progressive course (Fig.No1.) (Navarini A.A et. al., 2017).

Erythrodermic psoriasis- 90% of total body surface is covered in erythrodermic type of psoriasis with acute condition having immediate treatment (Fig.No1.) (Ortonne J et. al., 2009).

Psoriasis typically affects the body surface, but may also affect the joints and has been associated with number of other diseases (Sommer D.M. et.al., 2006).

1.2. Burden of Psoriatic Disease

Psoriasis occurs worldwide. It affects men as well as female at any age. According to the recent literature of review it has been estimated that, the prevalence of psoriasis is varies worldwide. The prevalence of psoriasis in Canada was 4.7% while in USA it was estimated to be around 4.6%. Data from Europe show less variation in countries with a range from 1.4% (Norway), 1.55% (Croatia) and 1.6% (UK). In East Africa, the figure was 0.7% and in the Henan district of China only 0.7% was found affected (Dogra S, Yadav S. 2010). It has been estimated that more than 125 million people worldwide affected by psoriasis. In India men are more affected as compared with that of

female with prevalence percent of about 0.44-2.8%, followed by age group in between 20-39 (Dogra S, Yadav S. 2010). It has been pointed out in the WHO's recent Global Report on Psoriasis that there are many unmet research gaps in psoriasis addressing various aspects such as epidemiology, aetiology, association with comorbidities, treatment and ways to improve healthcare services (Devinder Mohan Thappa and Malathi Munisamy 2017). Okhandi *et al.*, stated that Dibrugarh, Calcutta, Patna, Darbhanga, Lucknow, New Delhi and Amritsar are having high rate of prevalence followed by 0.44 and 2.2%, with overall incidence of 1.02%. They noted that the incidence in Amritsar (2.2%) was higher as compared to other centers in Eastern India (Dogra S, Yadav S. 2010). Recent report stated that patients suffering with psoriasis disorders can also showed increased risk of hyperlipidemia, hypertension, coronary artery disease, type 2 diabetes, and increased body mass index (7). Psoriatic arthritis results of inflammation of psoriasis, however some studies shown that prevalence of diabetes and cardiovascular disease correlating with the severity of psoriasis (Gelfand J.M *et al.*, 2009, Stern R.S. 2010). Patient with psoriatic disease independently showed high risk of myocardial infarction, stroke and cardiovascular disease (Kimball A.B *et al.*, 2010). It has been recommended that therapeutic researches should focus on options which can be applicable globally, on a large scale (Devinder Mohan Thappa and Malathi Munisamy 2017).

1.3. Risk Factors

The chronic inflammatory skin disease can be cause at any age, prevalence rate is varies with the country. Along with low and high secretions of hormones, Ethnicity, genetic background, and environmental factors affect the onset of psoriasis. Genetic factors play a significant role in the pathogenesis of psoriasis (Koji *et al.*). In India prevalence rate is high. Koji *et al.*, summarized the risk factors of psoriasis in two groups namely Extrinsic and Intrinsic factors which are responsible for onset of developing disease.

The major risk factors for psoriasis includes-

Extrinsic factors

Mechanical Stress

Mechanical stress like Radiotherapy, Ultraviolet (UV) B will increase the formation of skin lesions. Type, depth, site and degree of trauma may affect the formation of lesion. Patient with psoriatic disease shows these lesions only after various injuries this phenomenon is called as Koebner phenomenon (Alolabi, N., White, C.P., Cin, A.D. 2011, -Morais, P., Oliveira, M., Matos, J. Striae, 2013). Keratinocyte is one of the most important proteins for growth of hairs will affect by Nerve Growth Factor (NGF) and increases the production of psoriatic keratinocyte. However NGF also associated with Koebner phenomenon (Raychaudhuri, S.P., Jiang, W.Y., Raychaudhuri, S.K. (2008). Type 1 interferon's (IFNs), such as IFN α and IFN β have been suggested to play an indispensable role in initiating psoriasis during skin injury. Skin injury rapidly induces IFN β from keratinocyte and IFN α from dermal plasmacytoid dendritic cells through distinct mechanisms (Zhang, L.J. 2019).

Air Pollutants and Sun Exposure

Air pollutants such as, volatile organic compounds, oxides, particulate matter, ozone, polycyclic aromatic hydrocarbons, heavy metals and UV damage the skin by inducing oxidative stress followed by increasing rate of skin diseases (Puri, P., Nandar, S.K., Kathuria, S., Ramesh, V. 2017). Psoriatic patient having higher blood cadmium, compared with normal peoples. However, Cadmium is one of the air pollutants which affect the pathogenesis of psoriasis (Liaw, F.Y *et al.* 2017). Some studies suggested that environmental exposure to cadmium may compromise immunity, and micro environmental perturbation can predispose one to the worsening of psoriasis (Zhang, P. and Wu, M.X. 2018). Now days, phototherapy has been widely used to treat psoriasis. As we know that UV radiation that reaches the earth's surface is divided into two subtypes: more than 95% UVA (315-400 nm) and 1%-5% UVB (280-315 nm). Both the UVA and UVB have been used to treat

psoriasis but patients family history of psoriasis, having strong HLA-Cw*0602 association and in a certain group, psoriasis can develop after UV exposure (Rutter, K.J, et. al., 2009).

Drugs

Drug-related psoriasis would evident as plaque psoriasis, palmoplantar psoriasis, nail psoriasis, scalp psoriasis, Pustular psoriasis, and erythrodermic psoriasis. Drug-related psoriasis is recognized as the onset and exacerbation of psoriasis which is associated with certain drugs. It is often difficult to identify drug-related causes of psoriasis in clinical situations, because the latency period between the start of the medication and the onset of psoriatic skin lesions can vary considerably between drugs (Balak D.M. and Hajdarbegovic, E.2017). However, drugs like β -blockers, lithium, anti-malarial drugs, interferon's, imiquimod, angiotensin-converting enzyme inhibitors, terbinafine, tetracycline, nonsteroidal anti-inflammatory drugs, and fibrate, have been known to affect keratinocyte hyper proliferation and the IL-23/IL-17 axis (Balak D.M. and Hajdarbegovic, E.2017). The mechanisms of drug-related psoriasis still remain to be fully elucidated and the molecular mechanisms are complicated.

Vaccination

Vaccines like Bacillus Calmette–Guerin (BCG) which is a live attenuated strain of *Mycobacterium bovine*, used for the prevention of tuberculosis. Followed by TB treatment it is also used as local immunotherapy for bladder cancer, and in case of erythrodermic Pustular psoriasis. Psoriasis can be triggered by BCG and other vaccines such as tetanus–diphtheria vaccination and pneumococcal polysaccharide vaccination. However the incidence of psoriasis induced by vaccination is very low; rather, vaccination is therapeutically effective in patients with psoriasis (Luca, S. and Mihaescu, T. ,2013).

Infection

Streptococcal spp. infection has been largely associated with psoriasis. Guttate psoriasis is the result of *streptococcal* infection (Telfer N.R et. al., 1992). In human body *Candida spp.* is usually present but patients with psoriatic symptoms show high regulation of *Candida* either on skin lesion or in the mucosal membrane (Pietrzak et. al., 2018). Upto 60% of psoriasis is the result of *Staphylococcus (S.) aureus* infection. Dysregulation of skin microbiota and colonization of *S. aureus* in psoriatic lesion will be most frequently found. Moreover, psoriasis severity will be correlated with that of the *Enterotoxin spp* (Tomi et. al., 2005). Other viruses such as HIV, papilloma viruses, retroviruses, and endogenous retroviruses have also been implicated in psoriasis (Lee et. al., 2018). However, it is important to note that psoriasis is the condition where other normal skin flora also plays important role in development of lesion.

Life Style

Psoriasis is strongly associated with that of consumption of alcohol and smoking. One of the systematic review and meta-analysis revealed that patients with psoriasis are more likely to be current or former smokers (Armstrong et. al., 2014). Smoking is associated with an increased risk of developing psoriasis (Li et.al., 2012). In addition, smoking is strongly associated with pustular lesions of psoriasis (Naldi et. al., 2005). On the other hand consumption of alcohol also increases the risk of developing psoriasis. But however limited research have been done to accomplish that relationship between psoriasis and alcohol consumption is complex and multifactorial, alcohol abuse positively correlates with psoriasis severity and reduced treatment efficacy (Murzaku et. al., 2014). Dietary modifications such as supplementation with polyunsaturated fatty acids, folic acid, vitamin D, and antioxidants can also be considered as adjuncts in the management of psoriasis. To date, randomized controlled trials have produced conflicting results. Diet is a complex combination of foods from various groups; nutrients and the rich diversity of such foods may contribute to its protective effects against psoriasis (Naldi et. al., 2005).

Intrinsic Risk Factors

Most likely the genetic factors came under intrinsic risk factors, there is a strong correlation between genetic and psoriasis because, one-third of psoriatic people have been reported with family history. Followed by genetics some epigenetic factors like weather and climatic conditions are also affects the psoriasis. Some research says that people living in cold, dry climates are at much greater risk of developing psoriasis than people living in temperate or warm climates. In fact, warm, humid weather helps to heal psoriasis symptoms (Debra 2020).

Skin Color

Skin color is the important factor in developing psoriasis disease. One research study stated that people with white skin are at high rate of psoriasis as compared to black skin, followed by prevalence rate 1.3 percent in black patients compared to 2.5 percent in white patients. The difference in prevalence is likely due to genetics but can also be affected by a lack of proper diagnosis in patients of color. Because black skin has high melanin content than white skin, this can affect the way that certain skin conditions appear, including psoriasis (Debra 2020).

Diabetes Mellitus (DM)

DM broadly divided into two main categories Type 1 and Type 2 diabetes. Patient with psoriasis have high risk Type 2 DM. However it is unclear that which comes first as DM 2 or psoriasis but psoriasis is a marker for developing DM. Thus, obesity and type 2 DM are directly correlated with psoriasis and type 1 DM may not directly contribute to the pathogenesis of psoriasis. Type 1 DM is a chronic disease characterized by insulin deficiency due to autoimmune destruction of insulin producing pancreatic β cells, leading to hyperglycemia and included proinflammation of TNF α along with both Th1 and Th17 cells may also contribute to the onset of type 1 DM. As we know that TNF α / IL-23 / IL-17 are correlated with psoriasis so as Type 1 DM cannot play directly crucial role in pathogenesis of psoriasis.

Dyslipidemia

Elevation in the levels of plasma cholesterol, triglycerides (TGs) or a low HDL cholesterol level contributes to the development dyslipidemia. Psoriatic patient having higher prevalence of dyslipidemia vice versa it also increases the risk of developing psoriasis. Some study stated that cyclosporine can also lead to Dyslipidemia although dyslipidemia is associated with immunological abnormalities and it's still unclear whether dyslipidemia affects the onset and exacerbation of psoriasis or not (Pietrzak et. al., 2010).

Hypertension

Psoriasis is associated with hypertension. One of the study conducted on 2210 patients reveled that upto 26% of psoriasis is due to the hypertension. This Meta-analysis revealed that sever psoriasis is related with greater prevalence of hypertension. However the mechanism behind the correlation between hypertension and psoriasis was still not know but conversely psoriasis shows the greater prevalence to hypertension (Phan et.al., 2016).

Mental Stress

Studies conducted in America and Denmark showed that 2.6% of people are having psoriasis due to mental health disorders, including depression, anxiety, and bipolar disorder. Koji et al., conducted 39 studies (32,537 patients) of that 46% of patients believed their disease was stress reactive and 54% recalled preceding stressful event. High level secretion of genes like pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1 β , and IL-6 are observed in both the conditions, like in psoriasis as well as in mental stress. So it is believe that mental stress is commonly regarded as a well-established trigger of psoriasis. However there are no fruitfully studies have been done which remarkably proves that the stress was strongly associated

with the onset and exacerbation of psoriasis. So it is necessary to conduct a broad spectrum studies to revile the association between mental stress and psoriasis.

Obesity

Obesity is a major risk factor for develop in psoriasis. Jensen et al., conducted a study on 159,200 Sweden individuals who were followed up over a 10-year period shows high prevalence to psoriasis and obesity and so on also shows weight reduction may improve the severity of psoriasis in overweight individuals. Excess body fat may interfere with the medical treatment used in psoriasis and adds other cardiovascular risk profile in these patients, which underscores the importance of effective weight control regimens. Henseler and Christopher's in 1995 conducted a large population based study which included 42,461 individuals of whom 2,941 (7%) had psoriasis and found higher prevalence of obesity in patients with psoriasis. There has been numerous mechanisms are involved which explains the link between psoriasis and obesity. Psoriatic patients may have a higher risk of poor eating habits, depression, decreased physical activity, mental stress and increased alcohol consumption and smoking habit so on. Along with these one of the study showed that patients with psoriasis consumed significantly more fat, saturated fat, and alcohol compared to normal people (Devinder Mohan Thappa and Malathi Munisamy 2017). Expansion of white adipose tissue and increased rate of free fatty acid from white adipocytes which in turn leads to high serum fatty acid levels is nothing but obesity. Adipose tissue is the most effective lipid storage organ in the body besides providing mechanical protection and insulation (Morais et. al., 2013). Recent report stated that white adipose tissue is a central site in the formation of pro-inflammatory adipokines which include the classical cytokines such as IL-6, TNF- α , and the specific molecules leptin, adiponectin, and adipocytes. Over secretion of leptin and adipocytes downregulates the synthesis of testosterone, glucocorticoids, and starvation and up regulated by inflammatory mediators (TNF- α , IL-1 β), insulin, and ovarian sex hormones (Phan et. al., 2016). Resistin increase with obesity and, although controversial, high circulating levels have been associated with increased obesity, type 2 diabetes and insulin resistance. Apart from this, induction in the levels of T-helper 17 cells (Th17) are due to increased level of adipocytes. As we know that Th17 cells plays crucial role in secretion of IL-17 and also recognized in the pathogenesis of autoimmune diseases including psoriasis (Peter et.al. 2016, Murray et.al., 2009). Proliferation of Th1, Th17, and Th22 cells resulting in the production of the pro-inflammatory mediator like interferon- γ , TNF- α , IL-6, and IL-22 all these contributes the development of psoriasis. High levels of leptin and resistin were observed in obese as well as in psoriatic individual and the plasma concentrate ions also correlated with the severity of psoriasis (Peter et.al. 2016). So it is clear that obesity is correlated with psoriasis. Because over production of TNF, adipose tissue blocks the pathways of cell signaling molecules which makes type 2 DM and cardiovascular patients at high risk in developing psoriasis. Thus, evidence is strongly suggested that obesity plays crucial role in both the occurrence and severity of psoriasis.

1.4. Conclusion

On the basis of the review of literature provided, it can be stated that a cluster of factors associated with developing psoriasis disease. There is also an affirmation that one or more of the genes may be associated with psoriasis. The genes associated with psoriasis and mutation in these genes may increase the susceptibility to the disease. Incident and prevalence of psoriasis have increased in recent year. Due to lack of information on the epidemiology of psoriasis about Eighty one per cent of countries are not aware about how psoriasis occurs and what the risk factors behind that are. The genes that are susceptible to psoriasis in one population may not be necessarily being susceptible in another set of population. It is very apparent that individual suffering from psoriasis usually because of having high cholesterol level, type 1 diabetes or may be due to the radioactive exposure etc. The prolonged incidence of psoriasis in an individual increases the risk of secondary complications such as mental retardation and stress, cardiovascular diseases, Diabetes. Considering the prevalence of the disease, every first person is diabetic and second person is suffering from

psoriasis disorders. Present review, explains the both extrinsic and intrinsic or Genetic and Epigenetic factors for the development of psoriasis in detailed. However, genetics plays crucial role in developing psoriasis disorder so on biologics have dramatically changed the treatment of psoriasis. Psoriasis shows significant association with some metabolic syndromes, obesity, dyslipidemia, and hypertension. On set of disease also depends on the patient's age, lifestyle, and concomitant diseases vary among individuals. Hence, it is apparent that psoriasis is a predominant compared with other disease. The genes which plays important role in development of cardiovascular diseases, diabetes may also have major role in developing psoriasis. With the available literature, it can be safely assumed that *PSORS1* and *PSORS2* are the two main loci on chromosomes which plays crucial role in developing psoriasis and mutation in these loci causes impairment in TNF α , IL 23, IL12, HLA-Cw6, IL12B, IL23R, LCE3B/3C, CARD14 gene and NF- κ β have which leads to the development of psoriasis. Susceptibility of these genes to psoriasis varies depending on geographical regions. So, it is important to conduct the work on different population to screen which gene is highly susceptible to psoriasis. However, there is limited research that has been done on the association of the psoriasis in India as compared with other countries. The disease occurs more frequently in adults than in children. However, various factors interact with each other and can affect the pathogenesis of psoriasis directly and/or indirectly. The risk factors of psoriasis are not fully understood and future studies need to successfully establish preventive approaches for psoriasis. Therefore, it is not confirmed that which gene was more susceptible to the psoriasis disorders. So for further research it is important to screening of the genes in Indian population as well.

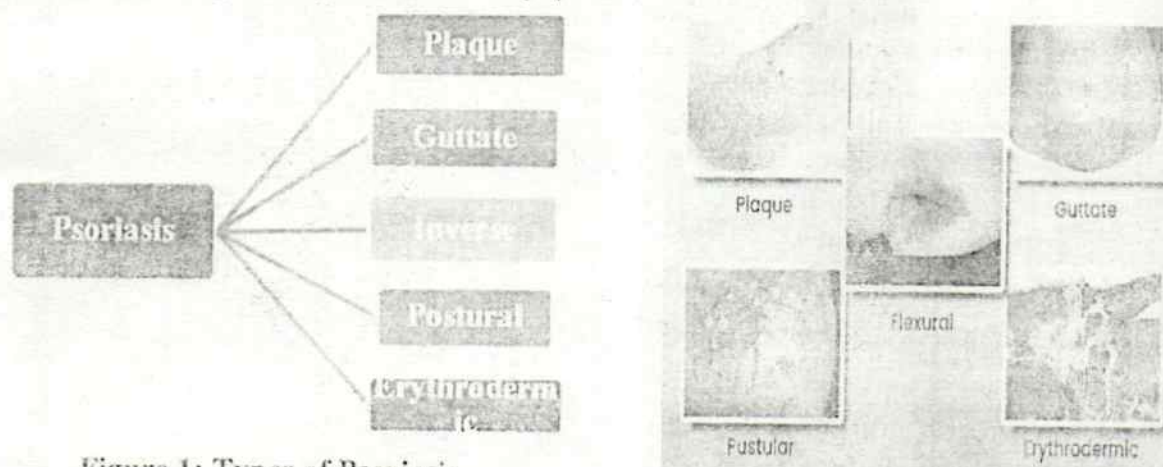


Figure 1: Types of Psoriasis

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