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Determinants of Psoriasis in Thi-Qar: Genetic Study of a Case-Control Design

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Abstract— Background: psoriasis is a multifactorial disease, where the genetic predisposition has a big role in the disease development. **Rationale:**few studies try to prove that null GSTM1 and GSTT1 associated with psoriasis development. **Aim:** to evaluate the role of null GSTM1 and GSTT1 on psoriasis development as a genetic risk factor. **Material and method:** diagnostic case-control study evaluate the availability and the role of polymorphic genotyping of GTMS1 & GTTS1in development of psoriasis, done in Thi-Qar University research unites , extended all-over the 2017. Equal number of well crossly matched psoriatic patients and control (100) of each group. Family history, smoking status , stressful event assessment and co-infection had been assessed well. Ethical consideration had been optimally taken from the ethical committee, ethical approval accomplished by verbal consents from all participants, P value < 0.05 consider as significant comparative cut.GSTT1, GSTM1and albumin genes had fully assessed by fully automated PCR, Deletion occurring when only albumin gene present without GSTM1or GSTT1. **Result:**among psoriatic patient the value of genotypes of GSTM1, GSTT1 and combined was present in a percent of (37,66 and 27%) while in control group (51,80 and 40%), that show significant difference, and role of protection was obvious, where the strength of association that expressed by odd's ratios that were less than one in all state of comparison. **Conclusion:** Null genotype states of GSTT1 and GSTM1 polymorphic genes and or both might had a role in development of psoriasis.

Key word: gene polymorphism, Glutathione, psoriasis, ThiQar

Introduction:

Psoriasis is one of the main ,chronic proliferative inflammatory, skin disease, with not well understood causes, i e non comprehended causes[1]. Two percent of the population world-wide affected by different types of psoriasis[2]. Any age can be a target of psoriasis, but the peak age of incidence(o three quarters of patients) is that of less than forty years. [3].Even-though direct causes remain ambiguous, but the genetic, immunological and environmental factors consider as the main attributers and risk factors for the disease development, where the foundation of genetics for psoriasis is a complex and sophisticated matter, and many genes had been proved to play a role in psoriasis pathogenesis. more than three quarters (60-90%) of psoriatic patients link to heritability. Psoriasis proved to be one of the genetic disease of a multifactorial pattern.[4,5]. If both mother and father had a psoriatic disease their progeny had the chance of 50% to getting the illness(proved by many family studies), while if one of them only had the disease the risk will reduce to 16%. This risk will reduced to 8% only , if her or his parents are free from disease. Gender difference of transmitting the disease also had been noticed where female show lower tendency for transmitting the disease than males to her offspring [6].

Recent studied proved that the oxidative stress had a role in disease development and as a risk factor for psoriasis[7].

Oxidants resulting in disturb signals of redox very small damages to skin, which consider as a target for oxidants, UV radiation exposure in addition to other stressor of environmental generating reactive oxygen speciesthat symbols as (ROS) [8]. ROS including a biological molecules in a large number that causingperoxidation of lipid, modulation of DNA, and inflammatory cytokines excretion [9]. Under special conditions and circumstances, skin cells (might be all) express the empirical isoform of NOS (NOS II). That liberate subsequent radiation of ultraviolet, which plays big role in erythema, melano-genesis & immunosuppression [10]. The universal defense mechanism of skin antioxidant is a critical protector ROS[11]. Enzymatic system is one of the essential line for the defense by making superoxidedismutase , glutathione-peroxidase and catalase that decreasing the harmful oxidants concentration [12].

Epidermal toxicity by foreign molecules can be prevented by antioxidants, if the system was insufficient leading the antioxidant aggregate reduction.[13].low antioxidant concentration or high ROS causing oxidative stress, which have a role in many dermal lesions, Psoriasis an example of.[14].

A super family multi-genes expressed in form of(GSTs) glutathione S-transferases. Glutathione coupled to substrate that are electrophilic in nature by enzymatic stimulation that produced by these genes. These enzymes interact with DNA (as a cellular molecule) and had a role in endo& exogenous electrophiles detoxification[15]. Eightgenes isoforms possessed by family, these are: kappa (GSTK), omicron, (GSTO), sigma,(GSTS), tau (GSTZ), theta,(GSTT), pi (GSTP), mu (GSTM) and alpha(GSTA)[16]. The GSTM1 and GSTT1 greatest predominant various form is homozygous deletion of the genes (null,geno-type), that related to lack of activity of enzyme and increased cytogenetic damage sensitivity increment[17].GSTM1genes location on 1p13.3 chromosome, that codes the enzymes mu class[18]. While GSTT1 located on 22q11.23 chromosome codes the theta enzyme class [19]. Susceptibility for many dermatological diseases such vetiligo due to lack of certain enzyme activities in genes of Glutathions (ST1,& STT1)[20,21,22] and for SLE[23,24]. Even-though they are few but prove that psoriasis development associated with absence or null GSTM1 and GSTT1 [25].
Aim: to evaluate the role of null GSTM1 and GSTT1 on psoriasis development as a genetic risk factor.

Material and method:
A diagnostic case-control study evaluate the availability (presence) polymorphic genotyping of GTMS1 & GTTS1, this study done in Thiqar University research unites (college of medicine and Mazaya university college- unites of research) extended all-over the 2017. Equal number of cases and control (100) of each group had enrolled in this study, well crossly matched regarding age, residence and gender. Age was unlimited and subtyped into 5 groups (10 years interval). Family history, smoking status , stressful event assessment and co-infection had been assessed well. Ethical consideration had been optimally taken from the ethical committee in the management offices of the both college of medicine and Mazaya university college, where the ethical approval accomplished by taken as a verbal consents from all participants in both Psoriatic group and control group.**Work in field:** Tools of the study: including 1-Questionnaire forma that filled by the researcher regarding the full identity of psoriatic patients and control. Duration of the disease (age of onset psoriasis only), family history, stress , viral and bacterial infection and smoking status also had been registered.2-About 2.5-3 cc of venous blood is drown from all studied population collectedby EDTA tubes and kept under listed optimum criteria of investigation, until genomic extraction of DNA.

DNA extracted from WBC by using of Mini kit of gSYNC^{TM}DNA, GSTT1 and GSTM1 genes were amplification by using polymerase, chain reaction of multiplex type (,PCR,) using a in which albumin gene as an internal control was utilized. Forward and reverse primers of GSTM1 gene amplification were as follow

GSTT1 gene	5\-GAG GAA CTC CCT GAA AAG CTA AAG-3/(forward)
	5\- CTC AAA TAT ACG GTG GAG GTC AAG-3(reverse).
GSTM1	5/-TTC CTT ACT GGT CCT CAC ATC TC-3\(forward)
	5\-TCA CCG GAT CAT GGC CAG CA-3/(reverse).
albumin gene primers	5/- GCC CTC TGC TAA CAA GTC CTA C -3/(forward)
	5/- GCC CTA AAA AGA AAA TCG CCA ATC -3/ (reverse).

PCR amplification (25 µl)DNA template5 µl +5 µlmaster mix+, 9 µl DWand 1 µl of each primers of GSTM1, GSTT1 and albumin genes. PCR procedurestarted by 5 minutes**initial denaturation (95 °C**)then**denaturation** (94°C - 35 cycles of - 1 minute), then **anneling**(58°C- 1 minute), **extension** (72°C-1 minute), lastly**extension**(72°C- 10 minutes). Products of PCR **migrated electrophoretically** on a 2% agarose gel (by recolored 0.5 µlethidium bromide). The GSTT1at (480 bp), GSTM1at (216 bp) and albumin genes appeared bands at 350 bpon respective way.Deletion occurring when only albumin gene present without GSTM1or GSTT1.**Statistical and epidemiological analysis** was done by using version 21 of SPSS through which estimations of frequencies and percentages and estimation of difference by chi-square, ANOVA and Fissure exact test and accordingly P value ue assessed at critical level of 0.05(95%) , odd's ratio as a measure of strength of association between presence and absence of studied genes with their confidence interval

Results:
The study include 100 psoriatic patient with mean age 29.08 years and 24.9 year mean age control group with similar number(100 also)presented in nearly similar pattern of distribution according to age group categories (10 years intervals), with no significant differences in distribution according to age groups As shown in figure1. The time of diagnosis a an age of onset was differ in distribution, where by most of the cases presented at the age of 11-30 years (49%) As shown in figure 2 , Gender distribution

of both study group was non significantly differ between the studied group, whereby male is higher to very low extent than female, with a ratio of 1.04: 1 cases among cases, while in control group was 1.5:1. As shown in figure 3.

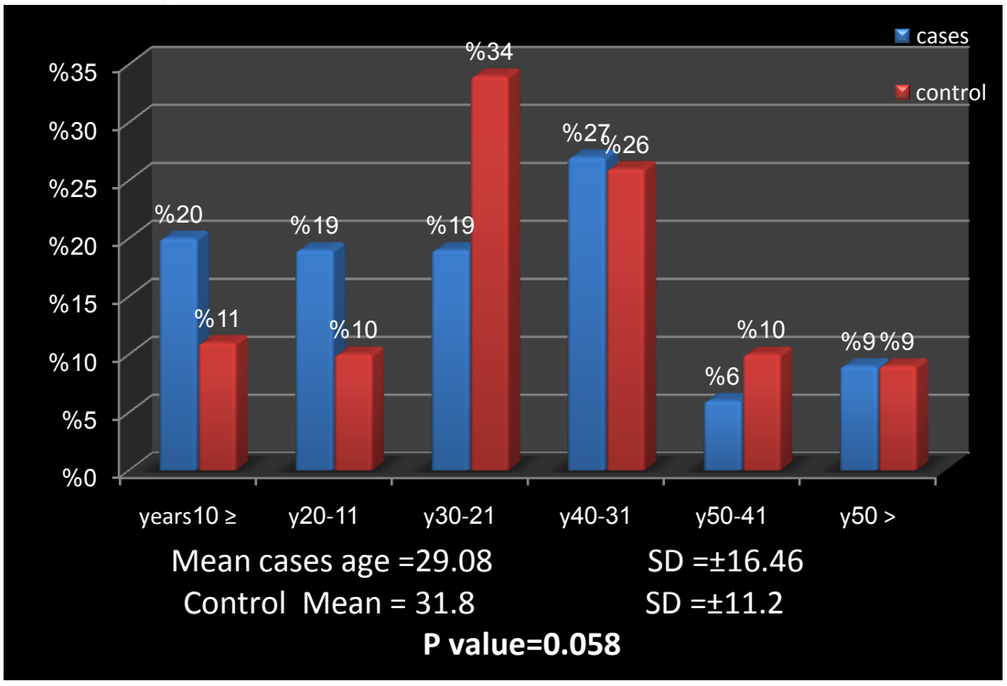


Figure 1: Age distribution of studied groups

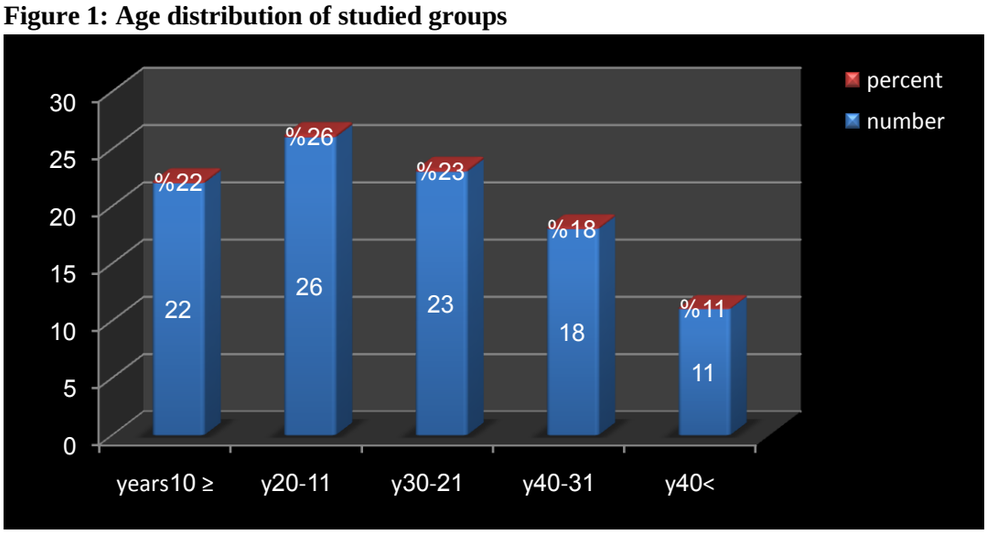


Figure 2: Age distribution of psoriatic groups according to the time of diagnosis.

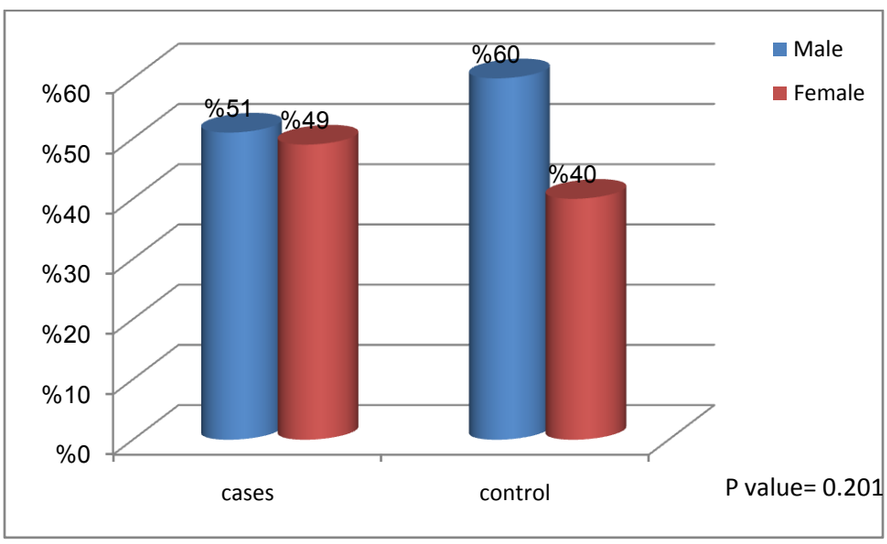


Figure 3: Gender distribution of studied groups

The smoker psoriatic was represent the 20% only , which not differ statistically from control As shown in figure 4, figure five also prove that, there was no significant statistical difference in the living sites where most of the cases living in urban areas

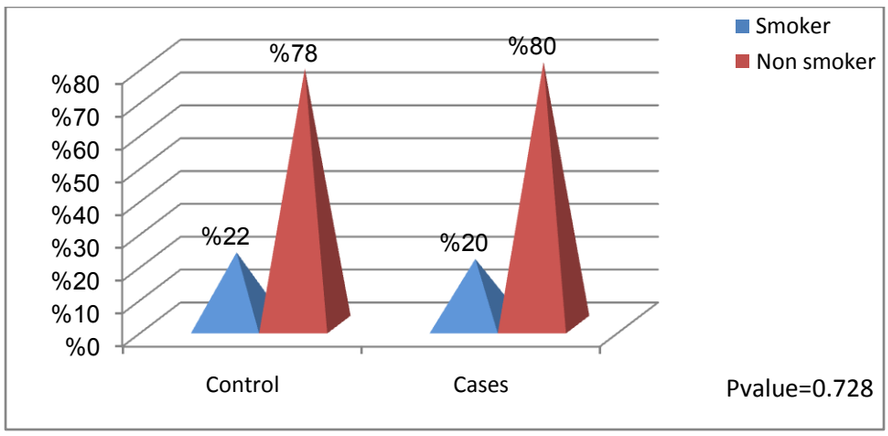


Figure 4: Smoking status of the cases and control

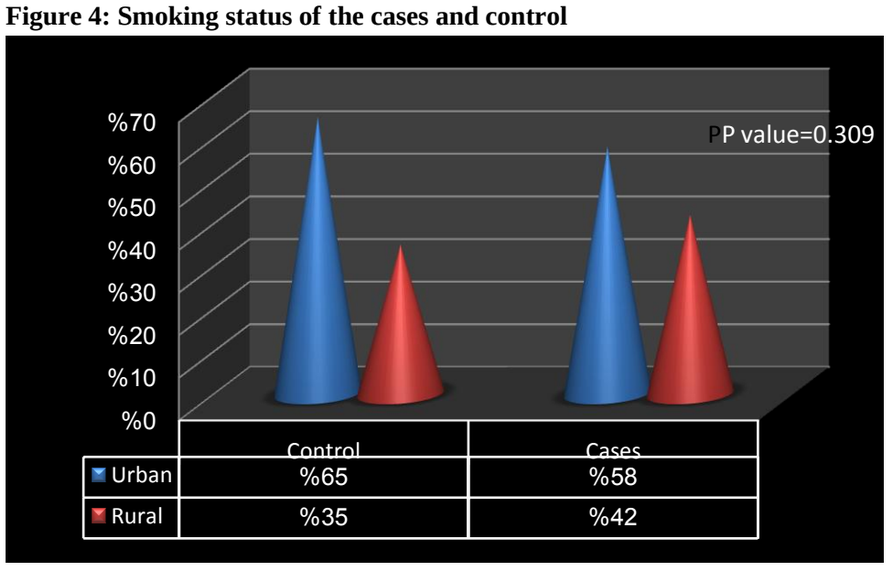


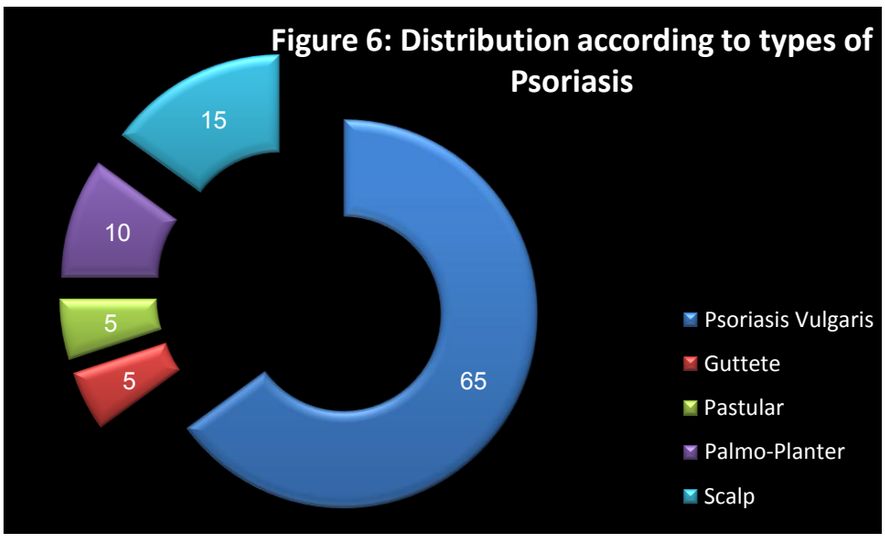
Figure 5: Studied group according to their residence

Table one: Difference in Psoriasis triggers criteria

	No	Percent	P value
Family history	**Number**	**Percent**	
Positive	**13**	**13%**	**<0.05**
Negative	**87**	**87%**	
Stress			
Yes	**56**	**56%**	**N.S**
No	**44**	**44%**	
Viral or bacterial infection			
Yes	**5**	**5%**	**<0.05**
No	**95**	**95%**	
Total	**100**	**100%**	

According to th types Psoriasis found to be arranged in (65%, 15%, 10%, 5% and 5%), as a psoriasis vulgaris, scalp palmo plantar, psoriasis Guttate and Pustular respectively As shown in table 1.

According to triggers only 13% positive family psoriasis history , while lifestyle stress sufferer 56% psoriatic patient were answering of positive scores of stress, only five patients were with microbes (viral or bacterial type of infection) As shown in figure6.



Presence and absence of GSTM1& GSTT1 polymorphic genotypes between studied group had been illustrated in table 2, among Psoriatic patient the value of genotypes of GSTM1, GSTT1 and combined was present in a percent of (37,66 and 27%) while in control group (51, 80 and 40%), that show significant difference, and role of protection was obvious, where the strength of association that expressed by odd's ratios that were less than one in all state of comparison

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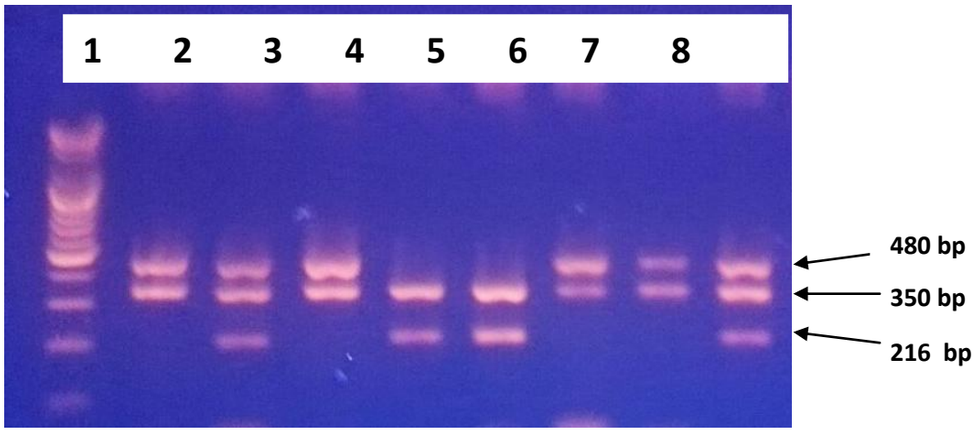

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Lane one : DNA Ladder=2000 pb	**Lane two, four, seven& eight** : GSTM1 null genotype
Lane five and six: GSTT1 null genotype	**Lane three and nine:** normal-both gene

Figure 7: polymerase chain reaction product (2% AgaroseGell-analysis)

Polymorphism	Cases		Controls		Odds Ratio	95%Confidence Interval
	Number	percent	No.	percent		
GSTM1						
Present*(88)	37	42	51	58	0.56 (< 1)***	0.32-0.99-
Absent(112)**	63	56.25	49	43.75		
GSTT1						
Present(144)	66	45.2	80	54.8	0.48 (< 1)***	0.25-0.92
Absent (54)	34	63	20	37		
GSTM1/GSTT1						
Present /Present(67)	27	40.3	40	59.7	0.55(<1)***	0.20-1.51
Absent / Absent(56)	11	55	9	45		
Total	100		100*=(+)	**=(-)	***OR (< 1)=protective.	

Discussion

Iraq suffer from scarcity of genetic data, but there are some of epidemiological data are available regarding psoriasis, that encourage us to do this type of study. Even though it was high cost and expensive but an expected nice result had been found. In the current study age distribution was comparable Solak B et al and Mikrani JA studies [25,26] with mean age of 29±16, 31± 11years for the psoriasis and control respectively, there was no significant statistical differences(P>0.05)

Regarding gender distribution of our studied population, there was no significant statistical difference were male to female ratio was 1:1 (51%, 49%), also control was nearly the same distribution in order to avoid selection bias. P value >0.05 (0.2) in difference between psoriasis and control group, which consistent with Gao*et al*. study[27], who study the gender difference and found no significant association of gender distribution with occurrence of psoriasis, but in other hand sex difference had been noticed, where female was more predominance of getting psoriasis as in Cakmur H et al study at 2015[28].this might be attributed to the role of genetic and environmental factors that affecting the occurrence of psoriasis,

Smoking status studied well regarding its association with disease occurrence, where many of studies consider it as a triggering factor but in the current study there was no significant difference between smoker and non; regarding their distribution among cases and control (p=0.7), were most of the cases and control were non- smoker (nearly 80%). This finding was differ from other studies (Schafer T and anldi L et al) who find the smoking has a role in psoriasis, this explained by different type of study, sample size personal characters engaged with in the study and smoking status categorization (Current, Ex and non smoker).[29,30],

Leyva et al study was found no association with residence of patient P = 0.4*t*his was agree with our findingP(0.3)[31].

More than 70% of studied psoriatic patients were diagnosed at early age(less than 30 yaers), that nominated as early onset of psoriasis which was comparable Gandhi etal study [32]Where nearly 80% diagnosed as early onset psoriasis.

According to sub-types of psoriasis, our finding reveal the P. vulgaris was he commonest type (65%), which consistent with Mikrani JA etal al and Cakmur H etal studies [26,28]

Family history show significant difference, where 13% of psoriatic patients had 1st degree positive family history of psoriasis, which comparable to other studies such as Siow KY et al and Marino MG etal studies [33,34]

Regarding stress, 56% of our patients were stress sufferer a converged result was done by .Remrod*et al*[36]where they found nearly half of psoriatic patients are stress sufferer. Viral and bacterial infection was ore likely to occur among these types of patient due to lack or have a defect in one of the main defense mechanism, also comparable result had been found in Alexander E etal study [37].

oxidative stress and disease development proved by many studies such as Armstrong AW study[38].

GSTT1 and GSTM1 genes were expressed in lower percent in psoriatic patients, than control group, where they was (37%, 66%, 27 %) for GSTT1 , GSTM1 and both while in control group they were (51%, 80%, 40%), so the intergroup comparison show a significant difference and the odd's ratio at all levels had directed the association and measure its strength toward that the null states of GSTT1 and GSTM1 and or both might had a role in development of psoriasis. Our results inconsistent with Turkish - Solak et al study[25] , which might be due to the interaction of other factors as a predisposal risk for psoriasis. And also due to the differences in the personal characters.

Conclusion:

Null genotype states of GSTT1 and GSTM1 polymorphic genes and or both might had a role in development of psoriasis.

Recommendation: a genetic analysis must done for any case of psoriasis, whatever the personal characters

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