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Research paper

De-regulation of diabetic regulatory genes in psoriasis: Deciphering the unsolved riddle

Suad AlFadhli [a,*], Alaa A.M. Al-Zufairi [a], Rasheeba Nizam [a], Huda A. AlSaffar [b], Nawaf Al-Mutairi [c]

[a] Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University, Kuwait
[b] Asad AlHamad Dermatology Centre, Sabah Hospital, Kuwait
[c] Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

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ABSTRACT

The purpose of our study was to identify the currently lacking molecular mechanism that accounts for the co-occurrence of two seemingly disparate diseases: psoriasis and type II diabetes. We aimed to investigate a panel of 84 genes related to the diabetic regulatory network in psoriasis (Ps), psoriasis type II diabetes (Ps-T2D), type II diabetes (T2D) and healthy control (HC). We hypothesize that such attempts would provide novel diagnostic markers and/or insights into pathogenesis of the disease. A quantitative Real Time-PCR Human Diabetes RT^2 Profiler PCR Array was chosen to explore the expression profile 84 diabetic genes in study subjects. Statistical analysis was carried out using appropriate software. The analysis revealed three candidate genes *GSK3B*, *PTPN1*, *STX4* that are differentially expressed in study subjects. *GSK3B* was highly significant in Ps-T2D ($P = 0.00018$, FR $= -26.6$), followed by Ps ($P = 0.0028$, FR $= -14.5$) and T2D groups ($P = 0.032$, FR $= -5.9$). *PTPN1* showed significant association only with PS-T2D ($P = 0.00027$, FR $= -8.5$). *STX4* showed significant association with both Ps ($P = 0.0002$, FR $= -20$) and Ps-T2D ($P = 0.0016$, FR $= -11.2$). *ACE* represents an additional marker that showed suggestive association with Ps ($P = 0.0079$, FR $= -9.37$). Our study highlights the complex genetics of Ps-T2D and present biomarkers for the development of T2D in Ps cases.

1. Introduction

Psoriasis (Ps) is a chronic heterogeneous inflammatory skin disease characterised by the hyper proliferation and aberrant differentiation of keratinocytes leading to scaly plaques. It affects about 2–3% of the world wide population and occurs equally in men and women. A compelling evidence for the involvement of genes in the development of Ps is provided by increased concordance rate of Ps among monozygotic twins (65–72%) compared to fraternal (15–30%) (Bowcock and Cookson, 2004). functioning of both innate and adaptive immune system also tends to contribute to the pathogenesis of Ps (Conrad and Nestle, 2006; Lande et al., 2007). The involvement of T-cells in the pathogenesis of Ps has been evidenced by bone marrow transplantation, where Ps was transferred from the donor to the healthy recipient (Eedy et al., 1990). Proliferation and migration of auto reactive T-cells to epidermis is one of the key events in the pathogenesis of Ps, which in turn is facilitated by the expression of alpha beta integrin on So far, 15 locations (loci) on different chromosomes have been associated with Ps and they are named as Ps susceptibility 1–15 (PSORS1 through PSORS15). Inappropriate effector T-cells (Conrad et al., 2007).

Systemic inflammation makes Ps patients vulnerable to other chronic and serious medical co-morbidities (Pearce et al., 2005). It is estimated that up to 30% of Ps patients may develop psoriatic arthritis, 58% are more likely to have a major cardiac event, 46% may develop type 2 diabetes, 43% stroke and one fourth of patient's may have depression (www.Psoriais.org, 2016). Recently, increased numbers of publications has been spotted evaluating the risk of type II diabetes (T2D) among Ps patients. T2D, also known as noninsulin-dependent diabetes, is the most common form that comprises 90% of people with diabetes around the world (World Health Organization, 2016). In contrast to type 1 diabetes mellitus which is caused by an absolute lack of insulin due to breakdown of islet cells in pancreas, T2D is characterised by insulin resistance and relative insulin deficiency.

Several retrospective and cross sectional studies have been found in the literature investigation the association of Ps with T2D. In a case-control study from Israel, the risk of diabetes was reported to be significantly higher in Ps patients (Shapiro et al., 2014). In yet another study

Abbreviations: Ps, psoriasis; Ps-T2D, psoriasis type II diabetes; T2D, type II diabetes; HC, healthy controls; *B2M*, beta-2-microglobuli; *HPRT1*, hypoxanthine phosphoribosyl transferase; *RPL13A*, ribosomal protein L13a; *GAPDH*, glyceraldehyde-3-phosphate dehydrogenase; *ACTB*, b-actin; STX4, Syntaxin 4; GSK3B, glycogen synthase kinase 3 beta; PTPN1, protein tyrosine phosphatase, non-receptor type 1; ACE, angiotensin I converting enzyme (peptidyl-dipeptidase A) 1; PWBC, peripheral white blood cells.

* Corresponding author at: Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University, PO Box 31470, Sulaibekhat, Kuwait.
E-mail addresses: s.alfadhli@hsc.edu.kw, suadq8@yahoo.com (S. AlFadhli).

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Table 1
Characteristics of study subjects.

Characteristics	Ps (n = 16)	Ps-T2D (n = 16)	T2D (n = 8)	HC (n = 8)
Gender	8F 8M	6F 10M	4F 4M	4F 4M
Ethnic	14K 2A	14K 2A	4K 4A	4K 4A
Age (years)	33.6 ± 5.6*	41.5 ± 13*	47.25 ± 0.96*	27.5 ± 6.5
Age of onset	13.8 ± 4.9	6.4 ± 7.8	11 ± 6.481	Nil
Smoking & habits	8S	4S	2S	2S
BMI (kg/m^2)	30 ± 3.8*	31 ± 5.5*	28.59 ± 5.47	25 ± 1.2
Waist circumference (cm)	85.4 ± 38	93.5 ± 27	90.5 ± 10.34	84.5 ± 8.3
PASI score	4.6 ± 6.6	5.3 ± 3.3	Nil	Nil
Diabetes type II	Nil	Positive	Positive	Nil
Blood pressure (mm Hg)	128*/86* ±13/±7	130/83* ±18/±9	116/78 ±4.9/±5	117/73 ±5/4.8
Inflammatory profile	4 + ve	ANA negative	Nil	Nil
Glucose profile (mmol/L)	5.3 ± 0.59	8.2 ± 1.9*	10.8 ± 2.6*	5.2 ± 0.3
Lipid profile				
CHOL (mmol/L)	4.8 ± 0.74	4.6 ± 0.81	4.5 ± 0.9	5.0 ± 0.62
TG (mmol/L)	1.95 ± 2.22	1.67 ± 1.55	1.63 ± 1.41	1.2 ± 0.54
Hematological profile				
Hb (g/dL)	13.7 ± 2.35	14.1 ± 1.1	14.3 ± 1.76	14.6 ± 1.88
RBC (10^6/μL)	5.0 ± 0.32	4.8 ± 0.26*	5.1 ± 0.67	5.2 ± 0.6
PLT (10^3/μL)	266 ± 91	222 ± 25*	198 ± 10.5*	287 ± 43.9
WBC (10^9/L)	7.6 ± 1.32	7.6 ± 1.08	8.4 ± 1.2*	7.2 ± 0.7

F - female, M - male, K - Kuwaiti Arab, A - non-Kuwaiti Arab, Nil - not in list or zero, + ve - positive, ANA - antinuclear antibody, cm-centimeter, kg/m^2 - kilogram/square meter, mm Hg - millimeters of mercury, mmol/L - millimole per liter, g/dL - gram per deciliter, μL - microliter, L - liter, Ps - psoriasis, Ps-T2D - psoriasis type II diabetes, T2D type II diabetes.
* Denotes significant difference between the test group and the healthy control by *t*-test ($P \leq 0.05$).

from Italy, diabetes was reported to be more frequent in psoriatic patients with <50 years of age (Binazzi et al., 1975). Similarly, several cross sectional studies have reported an increased risk of diabetes among Ps patients ranging from 1.27–2.48 (Shapiro et al., 2014; Binazzi et al., 1975; Brownstein, 1996; Gibson and Perry, 1956; Mallbris et al., 2006; Hollendorff-Curth, 1996; Reeds et al., 1964). A recent meta-analysis on 27 studies has reported that patients with mild Ps are 1.5 times more likely to develop diabetes than the general population while those suffering from severe Ps are twice as likely (Armstrong et al., 2013).Yet, the prospective factor that underlies the increased risk of diabetes among Ps patient remains unclear.

In this study, we aim to identify the genes involved in the development of diabetes in Ps by comparative expression profiling of psoriasis (Ps), psoriatic type II diabetes (Ps-T2D), type II diabetes (T2D) patients and carefully selected healthy controls (HC) on a diabetes array containing 84 genes related to the onset, development and progression of diabetes.

2. Results

A total of 48 age/gender/ethnically matched Arab subjects were recruited for this study (Table 1). Clinical and immunological profiling of all recruited subjects were carried out at Asa'd Al Hamad dermatological centre. A positive family history of Ps, Ps-T2D and T2D were observed in 75%, 12.5% and 50% of recruited cases respectively. Increased body mass index (BMI) was observed in 50% of Ps and Ps-T2D subjects. None of recruited subjects had any ocular or other immune mediated comorbidity.

A comparative analysis of gene expression profile was carried out to find biomarkers for the development of T2D in Ps patients. Three individual patient groups (Ps, Ps-T2D, T2D) and ethnically matched healthy controls were thoroughly investigated for expression of 84 genes related to diabetic network. Sample size calculation for the gene expression array is complicated by the fact that 84 different genes are simultaneously analyzed in four different study groups. A priori calculation indicates that, for a *P*-value of 0.01 and statistical power of 90%, 20 samples are required to detect a fold change of 2. Hence our study ensures that >60% of power is achieved. The scatter plot indicates the normalized expression of every diabetic gene on the array between Ps, Ps-T2D, T2D compared to healthy control (Fig. 1). Cluster analysis was carried out to find the list of co-regulated genes (Fig. 2).

Majority of diabetic network genes belongs to the category of receptors, transporters and channels. These include *ABCC8*, *ADRB3*, *AQP2*, *CCR2*, *CD28*, *CEACAM1*, *CTLA4*, *GCGR*, *GLP1R*, *ICAM1*, *IL4R*, *INSR*, *NSF*, *RAB4A*, *SELL*, *SLC2A4*, *SNAP23*, *SNAP25*, *STX4*, *STXBP1*, *STXBP2*, *TNFRSF1A*, *VAMP3* and *VAPA*. Of these genes, only *STX4* showed a significant difference in expression between Ps and healthy control ($P = 0.0002$, fold

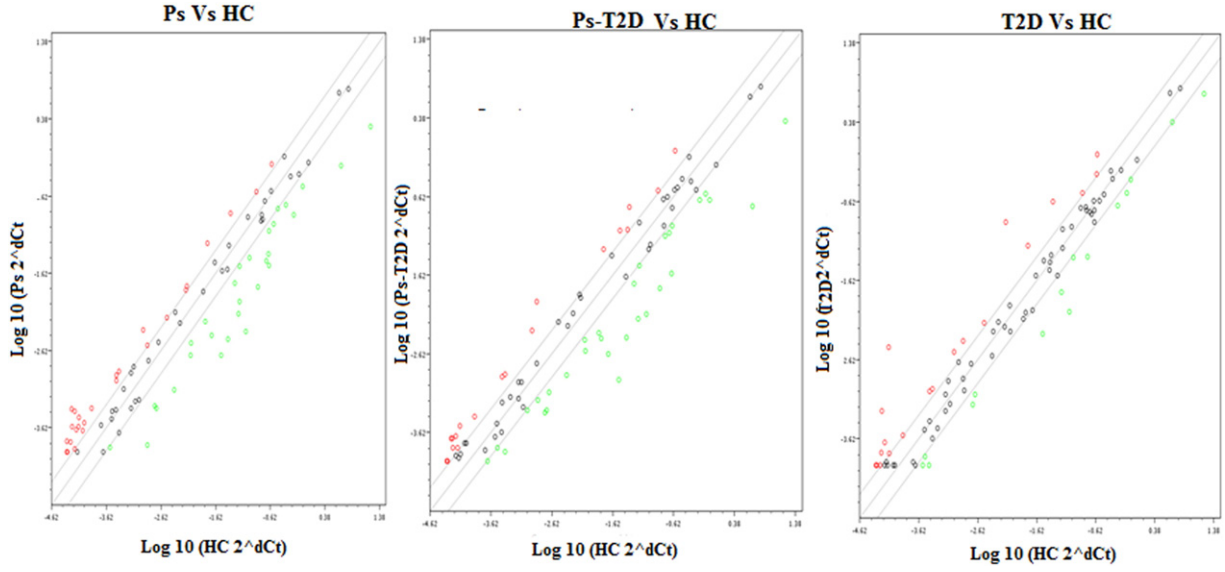

Fig. 1. The scatter plot indicates the normalized expression of every diabetic gene on the array between psoriasis (Ps), psoriasis diabetes (Ps-T2D), diabetes (T2D) and healthy control (HC). The central line indicates unchanged gene expression. The fold regulation cut-off is set to 2.