MITOCHONDRIAL HAPLOGROUP REVEALS THE
GENETIC BASIS OF DIABETES MELLITUS TYPE 2
COMORBIDITY IN PSORIASIS

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Abstract
Objective: Published data show a clear link between psoriasis (Ps) and the increasing prevalence of comorbid conditions, such as diabetes mellitus type 2 (DM2). The role of the mitochondrial genomic haplogroup in the potential coexistence of Ps and DM2 comorbidity is the subject of this study.

Material and Methods: Ninety-eight Kuwaiti individuals were recruited in 4 cohorts (20 healthy controls, 15 with DM2, 34 with Ps, and 29 with Ps and diabetes mellitus). An Ion Torrent S5XL was used to sequence mitochondrial DNA (mtDNA). χ² test was used to assess differences in the distribution of each haplogroup between cases and controls (p < 0.05). The Bonferroni correction was applied (p < 0.004). The mtDNA haplogroups were analyzed by HaploGrep. Results: Haplogroups R0, U, J, T, N, L3, M, H, X, HV, R, and K were detected in the studied population. Haplogroup M had a high risk for Ps (odds ratio (OR) 4.0, p = 0.003). Haplogroup R0 and J had decreased the risk of DM2 (OR 0.28, p = 0.007).

Conclusion: Our results indicated that mtDNA haplogroups have a potential contribution to the pathogenesis of Ps and DM2 comorbidity. We show for the first time that the comorbidity of diabetes in Ps may be related to mitochondrial dysfunction.

Keywords
Psoriasis · Diabetes mellitus type 2 · Mitochondrial haplogroups · Mitochondria

Introduction
Human mitochondrial DNA (mtDNA) is a small circular double-stranded DNA molecule of 16,569 bp in length, located in all nucleated cells. It contains 37 genes which encode 13 essential polypeptides of the oxidative phosphorylation system and the 12 and 16S rRNA and 22 tRNAs [1]. Moreover, the control region (D-loop) contains regulatory sequences controlling both replication and transcription of mtDNA that is highly susceptible to mutations because of its continuous exposure to high lev-

Highlights of the Study
- Patients with psoriasis (Ps) have the potential risk of comorbidity of diabetes mellitus type 2
- Haplogroup M may increase the risk of Ps
- Haplogroups R0 and J may decrease the risk of diabetes mellitus
- Diabetes comorbidity in patients with Ps is related to mitochondrial dysfunction
els of reactive oxygen species (ROS) generated during oxidative phosphorylation. The rate of mtDNA mutation has been estimated to be 5–10 times higher than nuclear DNA due to ROS generation and lack of protective histones. Accumulative studies have reported that specific mtDNA variants have contributed to mitochondrial pathogenicity [1].

During evolution, several mutations have accumulated and scattered in the mtDNA. These mutations have subdivided the human population into several discrete, region-specific mitochondrial clades or haplogroups. Emerging evidence suggests that different mitochondrial haplogroups have a role in mitochondrial function and mitochondria-mediated signaling pathways [2,3]. Therefore, it has been linked to a series of metabolic diseases such as obesity, diabetes mellitus type 2 (DM2), and DM2-associated complications [4–6]. Recently, haplogroup N9a has been associated with an increased risk of DM2 and significantly associated with the incidence of diabetic nephropathy [3]. Several studies have linked mtDNA haplogroups to specific diseases such as cancer [7] and late-onset neurodegenerative disease [5].

Recently, the association between microbiome and mitochondrial function and mtDNA haplogroups has been reported. Mitochondria and microbiome both have a maternal inheritance and a circular genome. It has been shown that patients with mitochondrial diseases are more susceptible to develop bacterial infections [8]. In addition, the gut microbiota metabolites such as short-chain fatty acids may modify mitochondria activity that can activate AMP kinase and lead to mitochondrial genesis. Also, it contributes to host energy production, ROS, and inflammation modulation. Thus, mtDNA variants have a critical role in regulating the gut microbiota activity, mostly effecting intestinal barrier function and mucosal immune responses [8]. Ma et al. [9] reported that a high mutation rate of mtDNA linked with mtDNA haplogroups may influence microbiome through a potential selective and different inflammatory response to different levels of ROS activity. Also, they showed a significant association between mtDNA haplogroups and specific microbiota community [9].

Psoriasis (Ps) is a common chronic immunologically mediated inflammatory skin disease affecting approximately 2–4% of the population [10]. It plays an important role in driving insulin resistance and metabolic syndrome (MetS) [10]. The association of Ps with metabolic diseases has been studied in several populations, and previous studies have found an association between Ps and DM2 [11–13]. A meta-analysis done by Juan et al. [14] suggested that Ps patients are susceptible to diabetes with odds ratio (OR) = 1.42. In another study, the same association found the OR was 1.76 [11]. In a study conducted by Mala et al. [13], fasting and postprandial blood glucose, as well as glycated hemoglobin percentage (HbA1C), were significantly higher among psoriatic patients. Another study correlated the association between Ps and DM2 and atherosclerosis, reporting that the proportion of DM2 and atherosclerosis was significantly higher in the Ps group with OR = 1.27 and 1.28, respectively. Also, the association was prominent in patients between 35 and 55 years of age [12]. However, the nature of the association between Ps and DM2 is still obscure.

Many studies have focused on the correlation between Ps and DM2 based on the examination of nuclear DNA mutation in certain susceptibility loci and investigate shared pathogenesis between these 2 diseases. In China, 89 reported diabetes susceptibility loci were genotyped in 4,456 Ps patients, and PTPN22, ST6GAL1, and JAZF1 were suggested as Ps risk genes shared pathogenesis between Ps and diabetes [15]. In another study, they evaluated the selected cardiovascular and metabolic SNPs for association with Ps. This study suggested that patients with Ps are enriched for certain common genetic variants (HLA, FUT2, UBE2L3, and SH2B3) that predispose to increased risk of MetS [16]. Polic et al. [17] evaluated the possible association between polymorphisms in the vitamin D receptor gene and the tendency for the development of Ps vulgaris and diabetes mellitus. He concluded that none of the analyzed polymorphisms individually was associated with the risk of development of Ps, diabetes, or combined phenotype [17].

Interestingly, none of the studies linked the mtDNA haplogroups with Ps comorbidity with DM2. Two studies investigated the association of European mtDNA haplogroups with patients of Ps and psoriasis arthritis (PsA). One of the studies concluded that haplogroup J was significantly less frequent among PsA patients, suggesting a protective effect, while the other one concluded that the subclades of the haplogroup U (U4a2 and U5) associated with increased risk of Ps [18, 19]. In the current study, the genetic link between Ps and DM2 based on mtDNA haplogroups association has been examined.

**Material and Methods**

A total of 98 unrelated Kuwaiti subjects were recruited for this study. Patient groups consisted of 15 DM2, 34 Ps, and 29 psoriasis and diabetes mellitus type 2 (PsDM2) patients, and 20 unrelated healthy Kuwaiti subjects were included without any dermatologi-
Genomic DNA was extracted from whole blood using a QIAamp DNA Blood Mini Kit (Qiagen, Venlo, The Netherlands) according to the manufacturer’s instructions. Each DNA sample was checked for purity using a NanoDrop 1000 system (Thermo Fisher Scientific) and for concentration using a Qubit 3.0 Fluorometer (Thermo Fisher Scientific). The concentration of input DNA was then adjusted to 1 ng/μL. mtDNA whole genome sequence was done by Ion Torrent S5XL according to precision ID mtDNA panels with the HID Ion S5™/HID Ion Gene Studio™ S5 System application guide. Raw signal data from sequencing runs from the Ion Torrent S5XL were automatically transferred to the Torrent Server Hosting the Torrent Suite Software that processed the raw voltage semiconductor sequencing data into DNA base calls. The pipeline included signaling processing, base calling, quality score assignment, adapter trimming, read mapping to 19 reference human genomes, quality control of mapping quality, coverage analysis with down sampling, and variant calling. The identification of variants was performed by the Ion Torrent Variant Caller plug-in and Ion Reporter Software v5.2 (Life Technologies). Torrent Variant Caller v5.2 was used for alignment and variant detection according to the revised Cambridge Reference Sequence of humans [20]. Samples were multiplexed and sequenced on an Ion 520 chip (3–6 megabase throughput). The average throughput of Ion 520 chip was 3.5 Mb. The average coverage depth was 24,625.2× and the mean read length was 144 bp. However, the average total reads were 3,359,441.

SPSS 15.0 software (SPSS Inc., Chicago, IL, USA) package was used for the statistical analysis. The demographic comparison of groups was performed using the t test. Pearson’s χ² test was used to assess differences in the distribution of each haplogroup between cases and controls. The results were evaluated with 95% CIs and p value <0.05 was considered as significant. Because of the multiple comparisons of mtDNA haplogroups, the Bonferroni correction was applied. We examined 12 haplogroups (R0, U, J, T, N, L3, M, H, X, HV, R, and K) and divided 0.05 by 12 to give 0.004. Thus, a p value of <0.004 was considered statistically significant. We used the HaploGrep program to annotate the mtDNA haplogroup for the cases and controls; however, the haplogroup quality scores reported by HaploGrep was 95% [21].

### Results

**MtDNA Haplogroup Distribution**

Using Ion Torrent S5XL next-generation sequencing, mtDNA haplogroups were analyzed in 98 individuals from the Kuwaiti population subdivided into 4 cohorts: 15 DM2, or 34 Ps, 29 PsDM2, and 20 healthy controls (HCs). Table 1 shows the demographic parameters of the cohort groups. There were no significant differences between the age of females and males among the study groups.

Twelve haplogroups were detected in the 4 cohorts (R0, U, J, T, N, L3, M, H, X, HV, R, and K). The frequencies of the haplogroups found in the various cohorts are summarized in Table 2. The absence of mitochondrial

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**Table 1. Demographic parameters of cohort groups**

| Gender | Ps | DM2 | PsDM2 | HC  |
|--------|----|-----|-------|-----|
| Male, %| 58 | 46  | 58    | 50  |
| Age (mean ± SD) | 43±18 | 50±18 | 57±9 | 33±10 |
| Female, %| 41 | 53  | 41    | 50  |
| Age (mean ± SD) | 40±10 | 47±7 | 51±8 | 28±5 |

SD, standard deviation; Ps, psoriasis; DM2, diabetes mellitus type 2; PsDM2, psoriasis diabetes mellitus type 2; HC, healthy control. *t* test (*p* < 0.05).

**Table 2. Distribution of mtDNA haplogroups among the studied cohort groups**

| Haplogroups | Frequency, % |
|-------------|--------------|
|             | HC (n = 20) | Ps (n = 34) | DM2 (n = 15) | PsDM2 (n = 29) |
| R0          | 20           | 9            | 7            | 10            |
| U           | 20           | 9            | 27           | 24            |
| J           | 20           | 15           | 7            | 14            |
| T           | 10           | 6            | 20           | 3             |
| N           | 5            | 3            | 0            | 0             |
| L3          | 10           | 18           | 20           | 14            |
| M           | 5            | 18           | 0            | 10            |
| H           | 0            | 12           | 13           | 7             |
| X           | 0            | 0            | 7            | 3             |
| HV          | 0            | 3            | 0            | 3             |
| R           | 0            | 6            | 0            | 7             |
| K           | 10           | 3            | 0            | 3             |

Ps, psoriasis; DM2, diabetes mellitus type 2; PsDM2, psoriasis diabetes mellitus type 2; HC, healthy control; mtDNA, mitochondrial DNA.
haplogroup H in HCs compared to Ps (12%), PsDM2 (7%), and DM2 (13%) suggests that haplogroup H is a risk factor of Ps and DM2. The presence of haplogroup X in groups PsDM2 and DM2 (3 and 7%, respectively) and absence in HC and Ps groups suggested that the haplogroup X may be associated with DM2 disease. Conversely, the absence of haplogroups HV and R in HC and DM2 groups and its presence in PsDM2 and Ps groups (7 and 6%, respectively, and HV = 3% in both) suggested that haplogroups HV and R may associate with Ps (Table 2). The small sample size of haplogroup X, HV, and R in the study groups may affect the significance of statistical analysis. Therefore, it needs to be investigated with a larger sample size.

While comparing the frequency of haplogroups found in Ps patients against healthy control, our results show that the frequency of haplogroups R0 and U had the same effect (9 vs. 20%, OR = 0.36, 95% CI = 0.1–0.9, with \( p = 0.02 \) and risk ratio [RR] = 0.4) and was significantly higher in healthy controls than Ps patients. Following the same trend, haplogroup K was significantly higher in HCs than in Ps (10 vs. 3%, OR = 0.3, 95% CI = 0.07–1, with \( p = 0.04 \) and RR = 0.3). Haplogroup M had an opposite effect, where the frequency was (18 vs. 5%, OR = 4.0, 95% CI = 1.2–2.8, with \( p = 0.003 \) and RR = 3) significantly lower in the healthy controls than the Ps group (Table 3a).

When comparing the frequency of haplogroups found in DM2 patients against healthy controls, our results also show that the frequency of haplogroups R0 and J but not U (7 vs. 20%, OR = 0.2, 95% CI = 0.1–0.7, with \( p = 0.007 \) and RR = 0.3) was significantly higher in the healthy controls than DM2 patients. In contrast, haplogroup T had an opposite effect where the frequency of haplogroups T (20 vs. 10%, OR = 2, 95% CI = 0.6–2.7, with \( p = 0.04 \) and RR = 2) was significantly lower in healthy controls than DM2 (Table 3b). For further analysis, the cluster of haplogroup JT of DM2 was analyzed. The frequency of haplogroup JT was 26 and 30% in DM2 and healthy controls, respectively, with \( p = 0.5 \).

Furthermore, the haplogroups were clustered into macro-haplogroup (L3, M, and N) according to the phylogenetic tree [22]. The statistical analysis of haplogroup L3 and M were mentioned previously. Macro-haplogroup N was significantly higher in healthy controls than in Ps

### Table 3. Multivariate statistical analysis for the various haplogroups in the disease cohorts versus healthy controls

| Haplogroups | \( p \) value\(^{a} \) | OR (RR) (95% CI) |
|-------------|-----------------|-----------------|
| a. Ps group |                 |                 |
| R0          | 0.02            | 0.36 (0.4) (0.1–0.9) |
| U           | 0.02            | 0.36 (0.4) (0.1–0.9) |
| J           | 0.46            |                 |
| T           | 0.3             |                 |
| L3          | 0.15            |                 |
| M           | 0.003           | 4 (3) (1.2–2.8)   |
| K           | 0.04            | 0.3 (0.3) (0.07–1) |
| b. DM2 group|                 |                 |
| R0          | 0.007           | 0.2 (0.3) (0.1–0.7) |
| U           | 0.32            |                 |
| J           | 0.007           | 0.2 (0.3) (0.1–0.7) |
| T           | 0.04            | 2 (2) (0.6–2.7)   |
| L3          | 0.05            |                 |
| c. PsDM2    |                 |                 |
| R0          | 0.04            | 0.4 (0.8) (0.1–1) |
| U           | 0.61            |                 |
| J           | 0.34            |                 |
| T           | 0.04            | 0.2 (0.3) (0.07–1) |
| L3          | 0.51            |                 |
| M           | 0.28            |                 |
| K           | 0.04            | 0.2 (0.3) (0.07–1) |
| d. Ps and PsDM2 groups | | |
| R0          | 0.04            | 0.4 (0.8) (0.1–1) |
| U           | 0.4             |                 |
| J           | 0.2             |                 |
| T           | 0.2             |                 |
| N           | 0.09            |                 |
| L3          | 0.2             |                 |
| M           | 0.02            | 3 (1.1) (1–1.2) |
| K           | 0.04            | 0.4 (0.8) (0.1–1) |

OR, odds ratio; RR, risk ratio; Ps, psoriasis; DM2, diabetes mellitus type 2; PsDM2, psoriasis diabetes mellitus type 2. \(^{a} \chi^{2} \) test (\( p \) value <0.05).
and PsDM2 groups as well as the combination of these groups \( (p = 0.0006; 0.07 \text{ and } 0.007, \text{ respectively}) \). These results, after the Bonferroni correction (setting at \( p < 0.004 \)), showed a significant relationship between the generation of Ps and subjects carrying mitochondrial haplogroup M (Table 3a), while a protective effect of macrohaplogroup N against Ps and also a borderline protective effect of haplogroup R0 and J against DM2 (Table 3b).

**Discussion**

In the present study, frequencies of mtDNA haplogroups were determined in patients with Ps and Ps patients who develop DM2 comorbidity during the interval of the disease. In addition, this study reveals the mtDNA genetic basis of DM2 comorbidity in psoriatic patients. Our data show an association of mtDNA haplogroups with Ps, diabetes mellitus, and combined Ps with DM2.

This study suggests that haplogroup M was significantly more frequent in Ps than in controls and may increase the risk of Ps. Haplogroup M is defined by 263, 489, 10,400, 14,783, and 15,043 mutations motif (www.snpedia.com/index.php/MtDNA_haplogroup). There is a G15043A variant located in the \( MT-CYB \) gene. This gene encodes the protein cytochrome b which plays a role in the function of the complex III of the mitochondrial respiratory chain. The G15043A variant correlated with metabolic and psychiatric diseases in a different study [23]. Because of the G15043A variant associated with the metabolic disease [24], its effect may be associated with Ps. According to the literature, we know of only 2 studies that investigated the association of common European mtDNA haplogroups with Ps, diabetes mellitus, and combined Ps with DM2.

Another possible susceptible haplogroup is T, which was significantly more frequent in DM2. Haplogroup T is defined by 709, 1,888, 4,917, 8,697, 10,463, 13,368, 14,905, 15,607, 15,928, and 16,294 mutations motif (www.snpedia.com/index.php/MtDNA_haplogroup). There is an A4917G variant located in the \( MT-ND2 \) gene. MT-ND2 (NADH dehydrogenase 2) is a core subunit of the mitochondrial NADH dehydrogenase (complex I) that catalyzes the transfer of electrons from NADH to ubiquinone by pumping protons through the mitochondrial membrane complexes to provide energy for the generation of ATP.

Mutations within the NADH dehydrogenase 2 mitochondrial gene have been found in patients with the mitochondrial type of Alzheimer disease, Leber hereditary optic neuropathy and DM2 [25,26]. Crispim et al. [27] studied the mtDNA m.4216T > C and m.4917A > G variants, which are European-specific mitochondrial cluster J/T in the development of type 2 diabetes mellitus in Caucasian-Brazilian patients. He found that the frequency of these variants is higher in diabetic patients than in control subjects. Moreover, haplogroups J, defined by the presence of the m.4216T > C variant only, and T, defined by the presence of both m.4216T > C and m.4917A > G variants, are more frequent in the diabetic group than in the control group [27]. In this study, the haplogroup JT was not significantly associated with DM2, while haplogroup T was significantly linked to DM2 but not haplogroup J.

In Taiwan, haplogroup B was associated with an increased risk of diabetes generation, whereas those harboring mitochondrial haplogroup D were found to have a resistance to the development of DM2 [4]. However, mtDNA haplogroup N9a was associated with an increased occurrence of MD2 and significantly associated with diabetic nephropathy incidence [3]. Also, Kofler et al. [28] has reported that mtDNA haplogroup T is associated with coronary artery disease and diabetic retinopathy.

The frequency of haplogroup X for DM2 and PsDM2 groups was 7 and 3%, respectively, while the frequency of HC and Ps groups was 0%, suggesting that haplogroup X may be a risk factor of DM2 and for developing diabetes in Ps patients for the duration of the disease. This result may need to confirm with a large sample size as the low frequency of haplogroup X in study groups may obscure the rational distribution.

Haplogroup X is defined by 73, 7,028, 11,719, 12,705, 14,766, 16,189, 16,223, and 16,278 mutations motif (www.snpedia.com/index.php/MtDNA_haplogroup). There is a T > C transition in the 16,189-bp position of the non-coding control region of mtDNA that has been associated in several studies with DM2, MetS, and obesity [6]. This variant resides in the first hypervariable segment of the control region of mtDNA, containing a homopolymeric tract of cytosines, which is interrupted by a thymidine at nucleotide position 16,189. T to C substitution at position 16,189 creates an uninterrupted tract of 8–12 cytosines (poly-C tract) [29]. The T16189C variant has been associated with thinness at birth and impaired glucose tolerance [30]. Poulton et al. [31] reported a significant association of T16189C with higher fasting insulin levels and insulin resistance. Likewise, Liou et al. [32] concluded that the
T16189 C variant can impact the development of DM2 in combination with high BMI. A similar association with MetS has been confirmed by another study of Chinese population [33].

There are at least 25 mitochondrial variants that have been associated with DM2. Most of these variants are rare and are associated with additional traits such as neurological symptoms or myopathy. One common variant, T16189C, has been reported to be associated with DM2, a higher fasting insulin level and lower body mass in infants [34]. Interestingly, in this study, haplogroup T was susceptible to DM2, while there was also a protective effect with PsDM2. This suggests that the DM2 comorbidity in Ps patients may be related to mitochondrial dysfunction.

This is the first study to correlate mtDNA haplogroups with Ps comorbidity with DM2 and investigate the mtDNA haplogroups of Ps patients in Kuwaiti population. The limitation of this study was the small sample size of study groups that may weaken the statistical analysis.

Conclusion

This study suggests that mtDNA haplogroups have a potential contribution to the pathogenesis of Ps as a disease and DM2 as a comorbidity of Ps which is related to mitochondrial dysfunction. This study showed the potential risk of haplogroup M and the protective effect of macro-haplogroup N in Ps.

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Statement of Ethics

A written permission was obtained from each participant under the protocols approved by the joint Committee for the Protection of Human Subjects in Research in Kuwait (KIMS). This research was confirmed by the Health Science Center Ethics Committee at Kuwait University and Health and Medical Research Committee in the Ministry of Health and registered on No. 2016/496.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization: Materah Salem Alwehaidah and Suad Al-Fadhli; data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, project administration, and writing original draft: Materah Salem Alwehaidah; and supervision: Materah Salem Alwehaidah, and Moiz Bakhiet.

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